NATIONALE VERSORGUNGS LEITLINIEN

Nationale VersorgungsLeitlinie

Chronische KHK

Recherchedokumentation
+ Evidenztabellen

Version 7
AWMF-Register-Nr. nvl-004

Träger:

Bundesärztekammer

Kassenärztliche Bundesvereinigung

Arbeitsgemeinschaft der Wissenschaftlichen
Medizinischen Fachgesellschaften

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1 Recherche zu KHK – Themenübergreifende Recherche

1.1 PICO-Frage

P   erwachsene Patient*innen mit chronischer KHK

I   jegliche diagnostische, medikamentöse, nicht medikamentöse Intervention

C   jeglicher diagnostische, medikamentöse, nicht medikamentöse Vergleich

O   muss in Auftaktsitzung priorisiert werden

S   systematische Übersichtsarbeiten, HTA

Z   ab 01.01.2020

Version 6.0 der NVL Chronische KHK wurde im September 2022 veröffentlicht (Gültigkeit bis 15. September 2027), Letzte Recherchen wurden im Dezember 2019 umgesetzt

1.2 Recherchestrategien

1.2.1 Datenbanken der Cochrane Library (23.11.2022)

Nr.	Suchfrage	Anzahl
#9	**#1 OR #2 OR #6 OR #7 in Cochrane Protocols; Publication date from 01/01/2020**	**9**
#8	**#1 OR #2 OR #6 OR #7 in Cochrane Reviews; Publication date from 01/01/2020**	**44**
#7	((coronary heart diseas* OR CHD OR coronary artery diseas* OR CAD OR angina pectoris OR stable angina)):ti,ab,kw	45138
#6	#3 AND #4 AND #5	7489
#5	(stable OR chronic):ti,ab,kw	215409
#4	(heart disease OR coronar* OR myocard*):ti,ab,kw	117284
#3	(ischemi* OR ischaemi* OR atheroscleros* OR arterioscleros* OR stenos* OR occlusion):ti,ab,kw	80042
#2	MeSH descriptor: [Angina Pectoris] explode all trees	4687
#1	MeSH descriptor: [Coronary Disease] explode all trees	14779

Cochrane Reviews	
• Review	44
• Protocol	9

1.2.2 NICE (03.11.2022)

Nr.	Suchfrage
Suchbegriffe	coronary heart disease
	chronic ischaemic heart disease
	coronary syndrome*
Suchzeitraum	seit 2020
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	1 + 0 + 0

Nr.	Suchfrage
Eingeschlossene Treffer	1
2. Filter	NICE advice, evidence
Treffer	0
2. Filter	NICE quality standard
Treffer	0

Quellen:

https://www.nice.org.uk/guidance/ipg732/evidence/overview-final-pdf-11186291773 - Bioresorbable stent implantation to treat coronary artery disease Interventional procedures guidance [IPG732] Published: 03 August 2022 (Rapid Review to 11-08-2021)

1.2.3   IQWiG (03.11.2022)

Nr.	Suchfrage
Filter	Projekte, Ergebnisse
Suchzeitraum	seit 01.01.2020
Suchbegriff: koronare Herzkrankheit	
Treffer	6
Eingeschlossene Treffer	6
Filter	ThemencheckMedizin - HTA
Suchzeitraum	seit 01.01.2020
Suchbegriffe: …koronare Herzkrankheit, KHK, Koronarsyndrom (Einzelsuche)	
Treffer	0
Eingeschlossene Treffer	0

Quellen:

[GA20-01] CT- oder MRT-Diagnostik bei Verdacht auf chronische koronare Herzkrankheit: eine Evidenzkartierung - https://www.iqwig.de/projekte/ga20-01.html 2020

[D06-01L] Positronen-Emissions-Tomographie (PET) bei koronarer Herzerkrankung - https://www.iqwig.de/projekte/d06-01l.html (vorläufiger Bericht) 2020 – Auftrag zurück genommen

[H20-07] Koronare Lithoplastie bei koronarer Herzkrankheit- Bewertung gemäß §137h SGB V - https://www.iqwig.de/projekte/h20-07.html 2021

[H21-06] Koronare Lithoplastie bei koronarer Herzkrankheit - Addendum zum Auftrag H20-07 - https://www.iqwig.de/projekte/h21-06.html 2021

[D22-01] Computertomographie-Koronarangiographie zur Diagnosestellung bei Patientinnen und Patienten mit Verdacht auf eine chronische koronare Herzkrankheit - https://www.iqwig.de/projekte/d22-01.html 2022 (Berichtsplan, Abschlussbericht geplant für 2023)

[V22-04] Leitliniensynopse für die Aktualisierung des DMP koronare Herzkrankheit https://www.iqwig.de/projekte/v22-04.html 2022 (Berichtsplan, Abschlussbericht geplant für 2023)

1.2.4   AHRQ (03.11.2022)

Kategorien	Suchbegriffe/ Filter (Keine Einschränkung des Zeitraums)	Treffer	Eingeschlossene Treffer
EPC Evidence-based	coronary heart disease coronary syndrome* seit 2020	12 0	6 0

Kategorien	Suchbegriffe/ Filter (Keine Einschränkung des Zeitraums)	Treffer	Eingeschlossene Treffer
Technology Assessment Program (completed)	allgemein/ abgeschlossen im Prozess, seit 2020	0	0

Quellen:

Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force

Date: August 2022 - Report Type: U.S. Preventive Services Task Force Evidence Syntheses

Affiliation: Pacific Northwest EPC—Oregon Health & Science University, Report Status: Final

Behavioral Counseling to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Systematic Review for the U.S. Preventive Services Task Force

Date: July 2022 - Report Type: U.S. Preventive Services Task Force Evidence Syntheses

Affiliation: Kaiser Permanente Research Affiliates, Report Status: Final

Vitamin, Mineral, and Multivitamin Supplementation for the Primary Prevention of Cardiovascular Disease and Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Date: June 2022 - Report Type: U.S. Preventive Services Task Force Evidence Syntheses

Affiliation: Kaiser Permanente Research Affiliates, Report Status: Final

Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: An Evidence Update for the U.S. Preventive Services Task Force

Date: April 2022 - Report Type: U.S. Preventive Services Task Force Evidence Syntheses

Affiliation: Kaiser Permanente Research Affiliates, Report Status: Final

Screening for Asymptomatic Carotid Artery Stenosis in the General Population: An Evidence Update for the U.S. Preventive Services Task Force

Date: February 2021 - Report Type: U.S. Preventive Services Task Force Evidence Syntheses

Affiliation: Kaiser Permanente Research Affiliates, Report Status: Final

Behavioral Counseling Interventions to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease Prevention in Adults With Cardiovascular Risk Factors: Updated Systematic Review for the U.S. Preventive Services

Date: November 2020 - Report Type: U.S. Preventive Services Task Force Evidence Syntheses

Affiliation: Kaiser Permanente Research Affiliates, Report Status: Final

1.2.5 Übersicht der eingeschlossenen Treffer

Aggregierte Evidenz	Anzahl
Cochrane Datenbanken	49
NICE	2
IQWIG	6
AHRQ	6

1.2.6 Zusatzinformationen Epidemiologie etc.:

1.2.6.1 www.gbe-bund.de (0 neue Treffer seit 2020)

Quellen:

https://www.gbe-bund.de/pdf/gesber2015.pdf Gesundheit in Deutschland (Bericht) [Gesundheit in Deutschland, 2015] Robert Koch-Institut (Hrsg) (2015) Gesundheit in Deutschland. Gesundheitsberichterstattung des Bundes. Gemeinsam getragen von RKI und Destatis. RKI, Berlin + Gesundheitsbericht. Gemeinsam getragen von RKI und Destatis. (bereits zitiert)

1.2.6.2 www.degs-studie.de (0 neue Treffer seit 2020)

Quellen:

https://edoc.rki.de/bitstream/handle/176904/1490/28vWvl57DzAA.pdf?sequence=1&isAllowed=y - Prävalenz von Herzinfarkt und koronarer Herzkrankheit bei Erwachsenen im Alter von 40 bis 79 Jahren in Deutschland Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsbl 2013 · 56:650–655 DOI 10.1007/s00103-013-1666-9 Online publiziert: 27. Mai 2013 (bereits zitiert)

1.2.6.3 https://covid-19.cochrane.org/ (03.11.2022)

Kategorien	Suchbegriffe/ Filter (Keine Einschränkung des Zeitraums)	Treffer	Eingeschlossene Treffer
in 179.472 studies with 191.992 references	(coronary and heart and disease) OR (chronic and ischaemic and heart and disease) and german* Filter: 01.01.2020-03.11.2022 Filter: Journal Article Study aim: Epidemilogy	4 matching studies with 7 references	2*

*Quellen:

https://covid-19.cochrane.org/studies/crs-15513321 - CORONA Germany - Clinical Outcome and Risk in Hospitalized COVID-19 Patients - A Registry From Germany

- Prognostic Impact of Acute Cardiovascular Events in COVID-19 Hospitalized Patients-Results from the CORONA Germany Study (https://pubmed.ncbi.nlm.nih.gov/34501427)

https://covid-19.cochrane.org/studies/crs-16693366 - Preventing SARS-CoV-2 In-Hospital Infections in Cardiovascular Patients and Medical Staff: an Observational Study From the German Heart Center Berlin (https://pubmed.ncbi.nlm.nih.gov/33614675)

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten):

A2 (nicht englisch/deutsch):

A3 (Conference Abstracts):

1.3 Screening

E	PICO erfüllt
P	Protokoll
Aa	PICO nicht erfüllt

Eingeschlossene Treffer insgesamt nach Ausschlüssen:

1.4   Flowchart

```
┌─────────────────────────────┐
│ Ergebnis der systematischen │
│ Literaturrecherche          │
│ n = 74                      │
│   n = 53 Cochrane           │
│   n = 21 Sonstige           │
└─────────────────────────────┘
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```
┌─────────────────────────────┐          ┌─────────────────────────────┐
│ Literatur von Experten      │          │ Ausgeschlossene             │
│ oder durch Handsuche        │──────────│ Titel/Abstracts:            │
│ n =                         │          │ n = 41                      │
└─────────────────────────────┘          └─────────────────────────────┘
```

```
┌─────────────────────────────┐
│ Eingeschlossene Titel/Abstracts: │
│ n = 33                      │
└─────────────────────────────┘
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                                          ┌─────────────────────────────┐
                                          │ Ausgeschlossene             │
                                          │ Volltexte:                  │
                                          │ n= 25                       │
                                          └─────────────────────────────┘
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```
┌─────────────────────────────┐
│ Eingeschlossene Volltexte   │
│ n = 8                       │
│   n = 3 Cochrane            │
│   n = 5 Sonstige            │
└─────────────────────────────┘
```
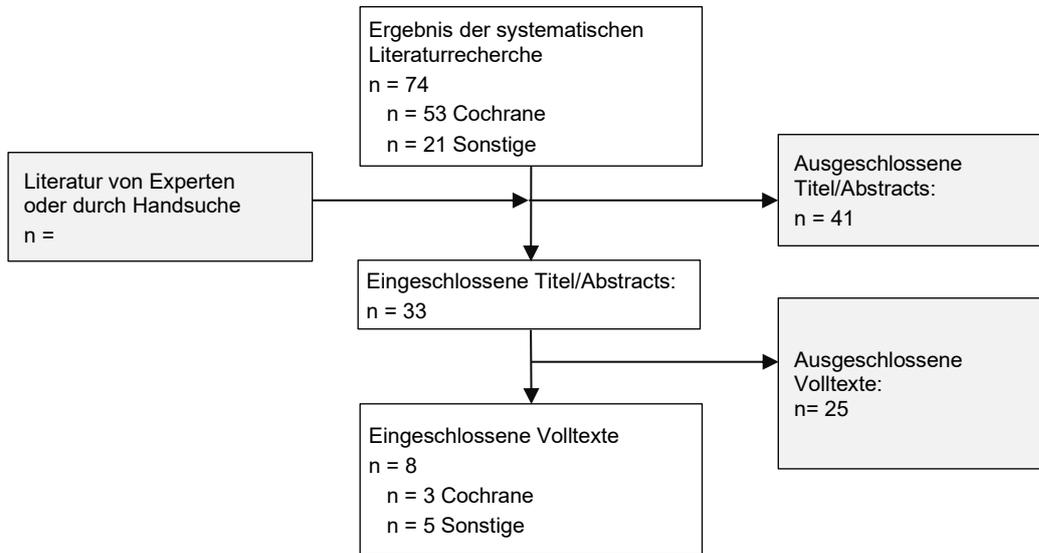
2 Recherche zu KHK – Themenübergreifende Recherche: Ergänzung

2.1 PICO-Frage

P   erwachsene Patient*innen mit chronischer KHK (ggf. auch ergänzende Themen)

I   jegliche diagnostische, medikamentöse, nicht medikamentöse Intervention

C   jegliche

O   muss in Auftaktsitzung priorisiert werden

S   Ergebnisberichte (GBA Innovationsausschuss)

2.2 Recherchen

2.2.1 GBA Innovationsausschuss – Projekte / neue Versorgungsformen

strukturierte Recherche: Ergänzung 23.01.2023, aktualisiert 30.10.2023

https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/ (Treffer: 210 gesamt/ n=27 relevant für KHK)

Nr.	Suchfrage
ABSCHaLoM Projekt laufend	Altern in Bewegung für Menschen im ländlichen Raum https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/abschalom-altern-in-bewegung-fuer-menschen-im-laendlichen-raum.500
AdAM Beschlussdatum: 23.02.2023 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF)	Anwendung digital-gestütztes Arzneimitteltherapie- und Versorgungs-Management https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/adam-anwendung-digital-gestuetztes-arzneimitteltherapie-und-versorgungs-management.71 - Ergebnisse sollen aufgrund der aus Teilergebnissen erkennbaren positiven Tendenzen an das BMG und die gematik weitergeleitet werden - Erkenntnisse sollen geprüft werden zur Verbesserung der digitalen Unterstützung der Arzneimitteltherapiesicherheit in ärztlichen Praxen, insbesondere zu den identifizierten Hürden (z. B. bislang fehlende technische Interoperabilität von Systemen zur Arzneimitteltherapie-sicherheit und Primärsystemen der Leistungserbringer) - entwickelt wurde ergänzend eine S2k-Leitlinie
BlenCon Projekt laufend	Blended Consultation – Berufsgruppenübergreifende und telemedizinische Versorgung von Pflegeheimbewohnern mit kardiologischen Erkrankungen https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/blencon-blended-consultation-berufsgruppenuebergreifende-und-telemedizinische-versorgung-von-pflegeheimbewohnern-mit-kardiologischen-erkrankungen.566
Cardiolotse Bericht in Erstellung	Entwicklung eines Versorgungsmodells zur Verbesserung der poststationären Weiterbehandlung am Beispiel kardiologischer Erkrankungen https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/cardiolotse-entwicklung-eines-versorgungsmodells-zur-verbesserung-der-poststationaeren-weiterbehandlung-am-beispiel-kardiologischer-erkrankungen.181 - Versorgungsform wird als Selektivvertrag fortgeführt bis die Auswertung der begleitenden Studie durch die Technische Universität München abgeschlossen ist und der Projektträger eine Transferentscheidung getroffen hat (vermutlich Ende des Jahres 2023)

Nr.	Suchfrage
CoCare Beschlussdatum: 12.05.2022 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF)	coordinated medical care – Erweiterte koordinierte ärztliche Pflegeheimversorgung https://innovationsfonds.g-ba.de/beschluesse/cocare-coordinated-medical-care-er-weiterte-koordinierte-aerztliche-pflegeheimversorgung.73 - GBA empfiehlt Weiterleitung an das BMG zur Prüfung der Ergebnisse mit denen themenverwandter Projekte zur Implementierung in Gesetzgebungsverfahren
Comm4Care SAN Bericht in Erstellung	Versorgung Pflegebedürftiger unter Optimierung der interprofessionellen Kommunikation https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/comm4care-san-versorgung-pflegebeduerftiger-unter-optimierung-der-interprofessionellen-kommunikation.350
DIKOM Projekt laufend	Diagnostik und Konsil im Pflegeheim mittels Mobiler Geriatrie-Unit https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/dikom-diagnos-tik-und-konsil-im-pflegeheim-mittels-mobiler-geriatrie-unit.494
EliPfad Projekt laufend	Personalisierter, interdisziplinärer Patientenpfad zur sektorenübergreifenden Versorgung multimorbider Patienten mit telemedizinischem Monitoring (RCT) https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/elipfad-perso-nalisierter-interdisziplinaerer-patientenpfad-zur-sektorenuebergreifenden-versor-gung-multimorbider-patienten-mit-telemedizinischem-monitoring.507
ERIC Beschlussdatum: 21.01.2022 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF) Dokumentation der Rückmel-dungen (PDF)	Enhanced Recovery after Intensive Care https://innovationsfonds.g-ba.de/beschluesse/eric-enhanced-recovery-after-inten-sive-care.55 - GBA empfiehlt Weiterleitung an die Gesundheitsministerien der Länder zu Prüfung einer Adaption im Bereich Intensivmedizin im jeweiligen Bundesland - Ergebnisse zur Bedarfsplanung im GBA sowie der Deutschen Krankenhaus-gesellschaft (DKG), GKV-Spitzenverband, InEK - sowie Weiterleitung an spezifische Fachgesellschaften
eRIKA Projekt laufend	eRezept als Element interprofessioneller Versorgungspfade für kontinuierliche AMTS https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/erika-erezept-als-element-interprofessioneller-versorgungspfade-fuer-kontinuierliche-amts.503
ErwiN Projekt laufend	Erweiterte Übertragung von arztentlastenden Tätigkeiten in ArztNetzen https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/erwin-erwei-terte-uebertragung-von-arztentlastenden-taetigkeiten-in-arztnetzen.564
FAMOUS Projekt laufend	Fallbezogene Versorgung multimorbider Patientinnen und Patienten in der Hausarztpraxis durch Advanced Practice Nurses (APN) https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/famous-fallbe-zogene-versorgung-multimorbider-patientinnen-und-patienten-in-der-hausarztpra-xis-durch-advanced-practice-nurses-apn.361
GeRas Projekt laufend	Geriatrische Rehabilitationserfolge nachhaltig sichern https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/geras-geriatri-sche-rehabilitationserfolge-nachhaltig-sichern.430

Nr.	Suchfrage
GeriNoVe Bericht in Erstellung	Regionales Geriatrisches Notfall-Versorgungszentrum https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/gerinove-regionales-geriatrisches-notfall-versorgungszentrum.110
GerNe Bericht in Erstellung	E-Health-basierte, sektorenübergreifende geriatrische Versorgung / Geriatrisches Netzwerk GerNe https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/gerne-e-health-basierte-sektorenuebergreifende-geriatrische-versorgung-geriatrisches-netzwerk-gerne.175
HandinHand Bericht in Erstellung	Hausarzt und Pflegeexperte Hand in Hand – ANP Center zur Zukunftssicherung der medizinischen Basisversorgung in der Region https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/handinhand-hausarzt-und-pflegeexperte-hand-in-hand-anp-center-zur-zukunftssicherung-der-medizinischen-basisversorgung-in-der-region.192
HerzEffektMV Beschlussdatum: 24.01.2023 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF)	Entwicklung und spezifischer Aufbau eines sektorenübergreifenden Care-Centers zur Versorgungsoptimierung chronischer Herzerkrankungen in MV https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/herzeffekt-mv-entwicklung-und-spezifischer-aufbau-eines-sektorenuebergreifenden-care-centers-zur-versorgungsoptimierung-chronischer-herzerkrankungen-in-mv.82 - GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)
LeIKD Beschlussdatum: 20.09.2022 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF)	Lebensstil-Intervention bei Koronarer Herzkrankheit und Diabetes https://innovationsfonds.g-ba.de/beschluesse/leikd-lebensstil-intervention-bei-koronarer-herzkrankheit-und-diabetes.105 - GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)
MAMBO Beschlussdatum: 16.12.2022 Beschlusstext (PDF) Ergebnisbericht (PDF) Anlage 48, 49 (Excel) Evaluationsbericht (PDF)	Multimorbide Menschen in der ambulanten Betreuung: Patientenzentriertes, Bedarfsorientiertes Versorgungsmanagement https://innovationsfonds.g-ba.de/beschluesse/mambo-multimorbide-menschen-in-der-ambulanten-betreuung-patientenzentriertes-bedarfsorientiertes-versorgungs-management.121 - GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)
OAV Beschlussdatum: 12.05.2023 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF)	Optimierte Arzneimittelversorgung für pflegebedürftige geriatrische Patienten https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/oav-optimierte-arzneimittelversorgung-fuer-pflegebeduerftige-geriatrische-patienten.111 - GBA spricht keine Empfehlung aus (Abschlussbericht verfügbar) - aufgrund positiver Tendenzen Weiterleitung der Ergebnisse zur Information an den Deutschen Hausärzteverband e. V., die Deutsche Gesellschaft für Geriatrie e. V., die Bundesvereinigung Deutscher Apothekerverbände e. V., den Deutschen Pflegerat e. V., die Bundesarbeitsgemeinschaft der Freien Wohlfahrtspflege e. V. und den Bundesverband privater Anbieter sozialer Dienste e. V.

Nr.	Suchfrage
PASTA Beschlussdatum: 21.01.2022 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF) Dokumentation der Rückmeldungen (PDF)	Patientenbriefe nach stationären Aufenthalten https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/pasta-patientenbriefe-nach-stationaeren-aufenthalten.113 - Empfehlung zur Überführung in die Regelversorgung - Weiterleitung an den GKV-Spitzenverband, die Kassenärztliche Bundesvereinigung, die Deutsche Krankenhausgesellschaft (Rahmenvertrag Entlassmanagement) - Ziel: automatisiert erstellte, laienverständliche Patienteninformationen als einen weiteren Baustein der routinemäßigen Dokumentation im Entlassmanagement zu etablieren (sowie weitere)
pAVK Beschlussdatum: 24.01.2023 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF)	TeGeCoach – Periphere arterielle Verschlusskrankheit (pAVK): Gesundheitscoaching und telemetrisch unterstütztes Gehtraining zur Steigerung der Lebensqualität https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/pavk-tege-coach-periphere-arterielle-verschlusskrankheit-pavk-gesundheitscoaching-und-telemetrisch-unterstuetztes-gehtraining-zur-steigerung-der-lebensqualitaet.99 - Empfehlung zur Überführung in die Regelversorgung - Weiterleitung an die Verbände der Kranken- und Pflegekassen auf Bundesebene und an die kassenärztlichen Vereinigungen (Prüfung der Umsetzung als neue Versorgungsform)
PRECOVERY Projekt laufend	Prehabilitation „Karl-Heinz" mit Schwerpunkt auf kardiale und kognitive Funktionen vor Eingriffen am Herzen: eine Analyse des Gesundheitszustands https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/precovery-prehabilitation-karl-heinz-mit-schwerpunkt-auf-cardiale-und-kognitive-funktionen-vor-eingriffen-am-herzen-eine-analyse-des-gesundheitszustands.502
PromeTheus Projekt laufend	Prävention für mehr Teilhabe im Alter https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/prometheus-praevention-fuer-mehr-teilhabe-im-alter.369
QT-Life Bericht in Erstellung	Apothekenbasierte Früherkennung der unerwünschten Arzneimittelwirkung QT-Streckenverlängerung https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/qt-life-apothekenbasierte-frueherkennung-der-unerwuenschten-arzneimittelwirkung-qt-streckenverlaengerung.373
USER Bericht in Erstellung	Umsetzung eines strukturierten Entlassmanagements mit Routinedaten https://innovationsfonds.g-ba.de/projekte/neue-versorgungsformen/user-umsetzung-eines-strukturierten-entlassmanagements-mit-routinedaten.263
VESPEERA Beschlussdatum: 20.08.2021 Beschlusstext (PDF) Ergebnisbericht (PDF) Evaluationsbericht (PDF)	Versorgungskontinuität sichern – Patientenorientiertes Einweisungs- und Entlassmanagement in Hausarztpraxen und Krankenhäusern https://innovationsfonds.g-ba.de/beschluesse/vespeera-versorgungskontinuitaet-sichern-patientenorientiertes-einweisungs-und-entlassmanagement-in-hausarztpraxen-und-krankenhaeusern.37 - GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)

2.2.2 GBA Innovationsausschuss – Projekte / Versorgungsforschung

strukturierte Recherche: Ergänzung 23.01.2023

https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/ (Treffer: 411 gesamt/ n=29 relevant für KHK)

Nr.	Suchfrage
arriba-PPI Beschlussdatum: 16.08.2023 Beschlusstext (PDF) Ergebnisbericht (PDF) Dokumentation der Rückmeldungen (PDF)	Evaluation einer patientenorientierten Absetzstrategie zur Reduktion der Überversorgung mit Protonenpumpenhemmern (PPI) / arriba-PPI https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/arriba-ppi-evaluation-einer-patientenorientierten-absetzstrategie-zur-reduktion-der-ueberversorgung-mit-protonenpumpenhemmern-ppi-arriba-ppi.142 - Ergebnisse werden weitergeleitet zur Information an die kassenärztlichen Vereinigungen und an die Verbände der Kranken- und Pflegekassen auf Bundesebene; ebenso an den Deutschen Hausärzteverband sowie die DEGAM
BEVOR Bericht in Erstellung	Patienten-relevante Auswirkungen von Behandlung im Voraus planen: cluster-randomisierte Interventionsstudie in Seniorenpflegeeinrichtungen https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/bevor-patienten-relevante-auswirkungen-von-behandlung-im-voraus-planen-cluster-randomisierte-interventionsstudie-in-seniorenpflegeeinrichtungen.204
BURDEN 2020 Beschlussdatum: 01.03.2023 Beschlusstext (PDF) Ergebnisbericht (PDF)	Die Krankheitslast in Deutschland und seinen Regionen. Grundlagen einer umfassenden Planung im Gesundheitswesen https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/burden-2020-die-krankheitslast-in-deutschland-und-seinen-regionen-grundlagen-einer-umfassenden-planung-im-gesundheitswesen.124 - Ergebnisse werden weitergeleitet an das BMG (Ziel: dauerhafte Etablierung einer nationalen Krankheitslaststudie); zudem an den Unterausschuss Bedarfsplanung des GBA (räumliche Verteilung) sowie an die Gesundheitsministerkonferenz der Länder (GMK)
CareTrans Projekt laufend	Care in Transition – Pflegeteams im Spannungsfeld von Migration und Akademisierung am Beispiel von Krankenhaus und Pflegeheim https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/caretrans-care-in-transition-pflegeteams-im-spannungsfeld-von-migration-und-akademisierung-am-beispiel-von-krankenhaus-und-pflegeheim.381
ChroMO Projekt laufend	Monitoring-Routinen bei Menschen mit chronischen Erkrankungen: Bestandsaufnahme und Fahrplan für die Zukunft https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/chromo-monitoring-routinen-bei-menschen-mit-chronischen-erkrankungen-bestandsaufnahme-und-fahrplan-fuer-die-zukunft.556
DASI Projekt laufend	Digital assistierte Informationserfassung vor der Sprechstunde https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/dasi-digital-assistierte-informationserfassung-vor-der-sprechstunde.338
DECADE Projekt laufend	Förderung des Selbstmanagements in der hausärztlichen Versorgung zur Prävention von Herz-Kreislauf-Erkrankungen https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/decade-foerderung-des-selbstmanagements-in-der-hausaerztlichen-versorgung-zur-praevention-von-herz-kreislauf-erkrankungen.312

Nr.	Suchfrage
DEMAND Bericht in Erstellung	Implementierung einer standardisierten Ersteinschätzung als Basis eines Demand Managements in der ambulanten Notfallversorgung https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/demand-implementierung-einer-standardisierten-ersteinschaetzung-als-basis-eines-demand-managements-in-der-ambulanten-notfallversorgung.136
Der nahtlose Patient - Projekt laufend	Von der präoperativen Vorbereitung zur postoperativen Rehabilitation https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/der-nahtlose-patient-von-der-praeoperativen-vorbereitung-zur-postoperativen-rehabilitation.454
EMSE Beschlussdatum: 03.04.2020 Beschlusstext (PDF) Ergebnisbericht (PDF + Anlagen)	Entwicklung von Methoden zur Nutzung von Routinedaten für ein Sektorenübergreifendes Entlassmanagement https://innovationsfonds.g-ba.de/beschluesse/emse-entwicklung-von-methoden-zur-nutzung-von-routinedaten-fuer-ein-sektorenuebergreifendes-entlassmanagement.3 - Vorprojekt zu USER (s.o.), GBA empfiehlt auf Basis der Ergebnisse zum Prozessmodell weitere Erprobung sowie als informative Ressource für Vertragsverhandlungen zwischen GKV-Spitzenverband, KBV und DKG
ENLIGHT-KHK Bericht in Erstellung	Erfassung und Optimierung der Leitlinienadhärenz im Indikationsstellungsprozess zur Koronarangiographie bei stabiler Koronarer Herzerkrankung https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/enlight-khk-erfassung-und-optimierung-der-leitlinienadhaerenz-im-indikationsstellungsprozess-zur-koronarangiographie-bei-stabiler-koronarer-herzerkrankung.128
ENQuIRE Bericht in Erstellung	Evaluierung der Qualitätsindikatoren von Notaufnahmen auf Outcome-Relevanz für den Patienten https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/enquire-evaluierung-der-qualitaetsindikatoren-von-notaufnahmen-auf-outcome-relevanz-fuer-den-patienten.122
ESC+ Beschlussdatum: 21.01.2022 Beschlusstext (PDF) Ergebnisbericht (PDF)	Evaluation des bestehenden Selektivvertrages nach § 140a SGB V – careplus https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/esc-evaluation-des-bestehenden-selektivvertrages-nach-140a-sgb-v-careplus.118 - der GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)
EVITA Beschlussdatum: 12.05.2022 Beschlusstext (PDF) Ergebnisbericht (PDF) Dokumentation der Rückmeldungen (PDF)	Evidenzbasiertes Multimedikations-Programm mit Implementierung in die Versorgungspraxis https://innovationsfonds.g-ba.de/beschluesse/evita-evidenzbasiertes-multimedikations-programm-mit-implementierung-in-die-versorgungspraxis.77 - GBA empfiehlt Weiterleitung an Verbände der Kranken- und Pflegekassen auf Bundesebene, die Bundesvereinigung Deutscher Apothekerverbände e. V. (ABDA) und den Deutschen Hausärzteverband e. V. - Zudem Hinweis auf die Veröffentlichung der im Projekt weiterentwickelten „S3-Hausärztliche Leitlinie Multimedikation" - basierend auf den Erkenntnissen des Projekts soll geprüft werden, ob weitergehende Ansätze des Projekts genutzt werden können
GenderVasc Bericht in Erstellung	Geschlechtsspezifische reale Versorgungssituation von Patienten mit arteriosclerotischen kardiovaskulären Erkrankungen in Deutschland

Nr.	Suchfrage
	https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/gendervasc-ge-schlechtsspezifische-reale-versorgungssituation-von-patienten-mit-arteriosclerotischen-kardiovaskulaeren-erkrankungen-in-deutschland.246
HeartGap Projekt laufend	Gender Health Gaps in der leitlinienorientierten stationären kardiologischen Versorgung und Implementierungsstrategien zu deren Reduktion https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/heartgap-gender-health-gaps-in-der-leitlinienorientierten-stationaeren-kardiologischen-versorgung-und-implementierungsstrategien-zu-deren-reduktion.540

INTEGRAL
 	
Beschlussdatum: 18.12.2020
    Beschlusstext (PDF)
    Ergebnisbericht (PDF)
	10-Jahres-Evaluation der populationsbezogenen integrierten Versorgung Gesundes Kinzigtal in Aufbau- und Konsolidierungsphase
	
	https://innovationsfonds.g-ba.de/beschluesse/integral-10-jahres-evaluation-der-populationsbezogenen-integrierten-versorgung-gesundes-kinzigtal-in-aufbau-und-konsolidierungsphase.10
	- GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)

ISAR-IQ Bericht in Erstellung	Integration und räumliche Analyse von regionalen, standortspezifischen und patientenindividuellen Faktoren zur Verbesserung der Versorgungsqualität bei Revaskularisation der Arteria carotis https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/isar-iq-integration-und-raeumliche-analyse-von-regionalen-standortspezifischen-und-patientenindividuellen-faktoren-zur-verbesserung-der-versorgungsqualitaet-bei-revaskularisation-der-arteria-carotis.311

KARDIO-Studie
 	
Beschlussdatum: 12.05.2022
    Beschlusstext (PDF)
    Ergebnisbericht (PDF)
    Dokumentation der
    Rückmeldungen (PDF)
	Linksherzkatheter bei Brustschmerzen und KHK: Analyse regionaler Variationen und Behandlungspfade zur Verbesserung der Indikationsqualität
	
	https://innovationsfonds.g-ba.de/beschluesse/kardio-studie-linksherzkatheter-bei-brustschmerzen-und-khk-analyse-regionaler-variationen-und-behandlungspfade-zur-verbesserung-der-indikationsqualitaet.78
	- GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)

Kardiologie-Vertrag
 	
Beschlussdatum: 25.06.2020
    Beschlusstext (PDF)
    Ergebnisbericht (PDF)
	Evaluation Kardiologie-Vertrag – Evaluation des Vertrages zur Versorgung im Fachgebiet der Kardiologie in Baden-Württemberg gemäß § 73 c SGB V (Kardiologie-Vertrag)
	
	https://innovationsfonds.g-ba.de/beschluesse/evaluation-kardiologie-vertrag-evaluation-des-vertrages-zur-versorgung-im-fachgebiet-der-kardiologie-in-baden-wuerttemberg-gemaess-73-c-sgb-v-kardiologie-vertrag.4
	- GBA spricht keine Empfehlung aus (Abschlussbericht vorhanden)

LLKVP Projekt laufend	S3-Leitlinie Hausärztliche Risikoberatung zur kardiovaskulären Prävention https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/llkvp-s3-leitlinie-hausaerztliche-risikoberatung-zur-kardiovaskulaeren-praevention.522
MIDAS-Studie Bericht in Erstellung	Einfluss eines Clinical Decision Support (CDS) Systems auf Quantität und Qualität indizierter medizinischer Bildgebung https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/midas-studie-einfluss-eines-clinical-decision-support-cds-systems-auf-quantitaet-und-qualitaet-indizierter-medizinischer-bildgebung.208
Mo2Regio Projekt laufend	Sektorenübergreifendes Monitoring und Modellierung der regionalen Gesundheitsversorgung

Nr.	Suchfrage
	https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/mo2regio-sektore-nuebergreifendes-monitoring-und-modellierung-der-regionalen-gesundheitsversor-gung.547
PARTNER Projekt laufend	Interprofessioneller Behandlungspfad zum PAtientenzentRierTeN dEpRescribing potentiell inadäquater Medikation bei älteren Patienten mit Multimedikation https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/partner-interpro-fessioneller-behandlungspfad-zum-patientenzentrierten-deprescribing-potentiell-inadaequater-medikation-bei-aelteren-patienten-mit-multimedikation.456
REVASK Bericht in Erstellung	Versorgungsanalyse zur myokardialen Revaskularisationstherapie bei chronischer KHK https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/revask-versor-gungsanalyse-zur-myokardialen-revaskularisationstherapie-bei-chronischer-khk.210
SELMA Bericht in Erstellung	Verbesserte Versorgungsstruktur für Menschen mit chronischen Herzerkrankungen mit implantierter Herzunterstützung durch curriculares Selbstmanagement https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/selma-verbes-serte-versorgungsstruktur-fuer-menschen-mit-chronischen-herzerkrankungen-mit-implantierter-herzunterstuetzung-durch-curriculares-selbstmanagement.212
Together4Trans Projekt laufend	S3-Leitlinie zur interdisziplinären, integrierten Gesundheitsversorgung für trans*, transsexuelle und nichtbinäre Menschen https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/together4trans-s3-leitlinie-zur-interdisziplinaeren-integrierten-gesundheitsversorgung-fuer-trans-trans-sexuelle-und-nichtbinaere-menschen.586
WEGE Projekt laufend	Analysen von Versorgungsverläufen bei älteren AOK Versicherten im Vorfeld einer Pflegebedürftigkeit https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/wege-analysen-von-versorgungsverlaeufen-bei-aelteren-aok-versicherten-im-vorfeld-einer-pflege-beduerftigkeit.557
ZWEIT Beschlussdatum: 16.10.2023 Beschlusstext (PDF) Ergebnisbericht (PDF)	Bestandsaufnahme und Bedarfsanalyse von medizinischen Zweitmeinungsverfah-ren in Deutschland https://innovationsfonds.g-ba.de/beschluesse/zweit-bestandsaufnahme-und-be-darfsanalyse-von-medizinischen-zweitmeinungsverfahren-in-deutschland.171 - Ergebnisse werden an den Unterausschuss Qualitätssicherung des GBA weitergeleitet (u. a. aktuelle Versorgung und Inanspruchnahme von Zweit-meinungen)

2.2.3 Übersicht der eingeschlossenen Treffer

Ergebnisse GBA Innovations-ausschuss	
• Neue Versorgungsformen	n=27 (n=10 Berichte vorliegend)
• Versorgungsforschung	n=29 (n=9 Berichte vorliegend)

3 Recherche zu KHK – Gezielte Recherche: Quell- und Referenzleitlinien

Die allgemeine systematische Recherche von 2014 zu Bildgebenden Verfahren schloss n = 41 Arbeiten ein, n = 31 zur Diagnostik sowie n = 10 zur Prognose (vgl. Anhang 2.1 des Leitlinienreports der Version 5.0 der NVL Chronische KHK); zur Koronarangiografie erfolgte eine Leitlinienrecherche (2010-2015), wobei n = 9 Leitlinien berücksichtigt wurden (vgl. Anhang 2.2 S. 44f des Leitlinienreports der Version 5.0 der NVL)

3.1 Gezielte Recherche (28.05.2014–16.05.2023)

Relevante Leitlinien (v. a. mit Evidenzaufbereitungen)

ESC

www.escardio.org/Guidelines

Topic: Coronary Artery Disease (Chronic)

- 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal (2020) 41, 407/477 doi:10.1093/eurheartj/ehz425 https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes
  - □ https://academic.oup.com/eurheartj/article/41/3/407/5556137?login=true

AWMF

www.awmf.org/leitlinien/leitlinien-suche.html

S3, Langfassung Leitlinie; Schlagworte: koronare Herzkrankheit, KHK, Angina pectoris, Brustschmerz

- S3-Leitlinie Brustschmerz - DEGAM-Leitlinie für die primärärztliche Versorgung, in Überarbeitung, geplante Fertigstellung: 30.09.2023: https://register.awmf.org/de/leitlinien/detail/053-023#anmeldung

DGK

leitlinien.dgk.org/leitlinien

Suchwort: koronare Herzkrankheit, KHK, Angina pectoris, Brustschmerz

- Rolf, A., Schmermund, A., Hell, M., et al. Positionspapier Erbringung kardialer CT-Leistungen Kardiologie 2023 · 17:81–94. https://doi.org/10.1007/s12181-023-00599-z,
  - □ https://leitlinien.dgk.org/2023/positionspapier-qualitaetskriterien-fuer-die-erbringung-kardialer-ct-leistungen/
- Perings, S., Smetak, N., Kelm, M. et al. Krieterien der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e. V. für „Brustschmerz-Ambulanzen". Kardiologe (2016) 10: 301. doi:10.1007/s12181-016-0074-4
  - □ https://leitlinien.dgk.org/2016/kriterien-der-deutschen-gesellschaft-fuer-kardiologie-herz-und-kreislaufforschung-e-v-fuer-brustschmerz-ambulanzen-update-2016/
- Update 2020: Giannitsis, E., Post, F., Haerer, W. et al. Kriterien der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung für „Chest Pain Units". Kardiologe (2020). https://doi.org/10.1007/s12181-020-00417-w
  - □ https://leitlinien.dgk.org/2020/kriterien-der-deutschen-gesellschaft-fuer-kardiologie-herz-und-kreislaufforschung-fuer-chest-pain-units-2/

- H. Reinecke, M. Braun, L. Frankenstein et al. (2015) Kriterien für die Notwendigkeit und Dauer von Kranken-hausbehandlungen bei Koronarangiografien und –Interventionen Kardiologe 2015 · 9:295–302
  - https://leitlinien.dgk.org/2015/kriterien-fuer-die-notwendigkeit-und-dauer-von-krankenhausbehandlungen-bei-koronarangiogafien-und-interventionen/

DEGAM

https://www.degam.de/leitlinien

geplante und aktuelle Leitlinien

- S3-Leitlinie Brustschmerz - DEGAM-Leitlinie für die primärärztliche Versorgung, in Überarbeitung, geplante Fertigstellung: 30.09.2023
- S3-Leitlinie Hausärztliche Risikoberatung zur kardiovaskulären Prävention, in Überarbeitung, geplante Fertig-stellung: 06.2024. www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S3-Leitlinien/053-024_Risikoberatung%20kardiovaskul.%20Praevention/oeffentlich/053-024l_Hausa%CC%88rztliche_Risikober-atung_kardivaskula%CC%88re_Praevention_29-08-2018.pdf

IQWIG (www.iqwig.de)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	05.2014 – 16.05.2023
Suchbegriff: koronare Herzkrankheit, KHK, Angina pectoris, Brustschmerz	
Treffer	29
Eingeschlossene Treffer	6

- [D22-01] Computertomographie-Koronarangiographie zur Diagnosestellung bei Patientinnen und Patienten mit Verdacht auf eine chronische koronare Herzkrankheit, Letzte Aktualisierung 17.02.2023.
- [V22-04] Leitliniensynopse für die Aktualisierung des DMP koronare Herzkrankheit, Letzte Aktualisierung 16.05.2023. https://www.iqwig.de/projekte/v22-04.html
- [GA20-01] CT- oder MRT-Diagnostik bei Verdacht auf chronische koronare Herzkrankheit: eine Evidenzkartie-rung, Letzte Aktualisierung 30.06.2020. https://www.iqwig.de/download/ga20-01_herz-ct-oder-mrt-bei-verdacht-auf-khk_arbeitspapier_v1-0.pdf
- [V16-03] Leitlinienrecherche zur Aktualisierung des DMP KHK, Letzte Aktualisierung 28.03.2018. https://www.iqwig.de/projekte/v16-03.html
- [D15-02] Messung der myokardialen fraktionellen Flussreserve (FFR-Messung) bei koronarer Herzkrankheit, Letzte Aktualisierung 09.01.2017. https://www.iqwig.de/projekte/d15-02.html
- [V15-01] Orientierende Prüfung des Überarbeitungsbedarfs des DMP koronare Herzkrankheit - Rapid Report, Letzte Aktualisierung 17.03.2016. https://www.iqwig.de/projekte/v15-01.html

NICE (www.nice.org.uk/guidance)

Nr.	Suchfrage
Suchbegriffe	coronary angiography, cardiac imaging, diagnostic imaging, coronary disease
Suchzeitraum	from 2014
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medi-cal technology guidance, safe staffing guideline, social care guideline) published
Eingeschlossene Treffer	0

Zusatzinformation:

- DG43-QAngio XA 3D QFR and CAAS vFFR imaging software for assessing coronary stenosis during invasive coronary angiography. published: 17 March 2021. https://www.nice.org.uk/guidance/dg43

- MTG32- HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. Published: 13 February 2017. Review Decision April 2021. https://www.nice.org.uk/guidance/mtg32/evidence/review-decision-april-2021-pdf-9076795165

Datenbanken der AHRQ (www.ahrq.gov/research/findings/evidence-based-reports/search.html)

Kategorien	Suchbegriffe/ Filter (Zeitraum ab November 2017 bis 10.05.2023)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	0	0
Technology Assessment Program (completed)		0	0

4 Recherche zu KHK – Gezielte Recherche: Epidemiologie

4.1 Gezielte Recherche Epidemiologie (29.09.2023)

Die themenübergreifende ergänzende Recherche zur NVL Chronische KHK vom 23.01.2023 bzw. aktualisiert vom 30.10.2023 ermittelte u. a. aus dem Innovationsausschuss des GBA (Projekte / Versorgungsforschung; Kapitel 2.2.2 GBA Innovationsausschuss – Projekte / Versorgungsforschung) den Projektbericht des Projektes BURDEN 2020 (Details siehe dort).

Der Projektbericht enthielt u. a. den Verweis auf Primärpublikationen, in denen weitere Verweise u. a. auf die Ergebnisse des Projektes BURDEN 2020 in einem Gesundheitsinformationssystem (www.daly.rki.de) sowie die Ursprungsquellen für die epidemiologischen Kennzahlen (www.krankheitslagedeutschland.de) zu finden waren.

Aus den ergänzenden Quellen (Projekthomepage) sowie der bereits zuvor durchgeführten themenbezogenen Recherche gingen weitere Quellen hervor (siehe auch dort, Kapitel 2 Recherche zu KHK – Themenübergreifende Recherche: Ergänzung).

Gezielt ausgewählt wurden (Details siehe separate Evidenztabellen):

Gezielte Recherche – Epidemiologie: ermittelte Quellen
Porst M, Lippe Ev, Leddin J, et al. The Burden of Disease in Germany at the National and Regional LevelResults in Terms of Disability–Adjusted Life Years (DALY) from the BURDEN 2020 Study. Dtsch Arztebl Int 2022; 119(46):785-792. DOI: 10.3238/arztebl.m2022.0314.http://www.ncbi.nlm.nih.gov/pubmed/36350160.
Robert Koch-Institut (2022): Ergebnisdatensatz BURDEN 2020 – Krankheitslast in Deutschland und seinen Regionen, Berlin:Zenodo. DOI: 10.5281/zenodo.7323766 www.daly.rki.de/map
Robert Koch-Institut (RKI). Gesundheitliche Lage der erwachsenen Bevölkerung in Deutschland – Ergebnisse der Studie GEDA 2019/2020- EHIS. J Health Monit 2021; 6(3).
Robert Koch-Institut, editor. Gesundheit in Deutschland. Gesundheitsberichterstattung des Bundes. Gemeinsam getragen von RKI und Destatis. Berlin: RKI; 2015. www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GesInDtld/gesundheit_in_deutschland_2015.pdf (bereits zitiert in der Version 6.0 der NVL Chronische KHK)
Wissenschaftlichen Instituts der AOK (WIdO). KrankheitslageDeutschland.de www.krankheitslage-deutschland.de
Zentralinstitut für die kassenärztliche Versorgung in der Bundesrepublik Deutschland (Zi). Versorgungsatlas – Dashboard häufige chronische Krankheiten www.versorgungsatlas.de/dashboard/#/evaluation/1005

5 Recherche Statine mittlere Dosis vs. Hohe Dosis (AkdÄ – Recherchefrage 3/4)

5.1 PICO-Frage

P   Patient*innen mit stabiler KHK

I   Statine mittlere Dosis

C   Statine hohe Dosis

O   Effektivität und Sicherheit

Studientyp: systematische Reviews, Metaanalysen, RCT

Sprache: englisch, deutsch

5.2 Recherchestrategien

Hinweis: Recherchefrage 3/4 (Statine hohe Dosis vs. niedrig-moderat) des Leitfadens der AkdÄ.

PICO-3/4: Effektivität und Sicherheit von Statinen in Hochdosis in der Primär- und Sekundärprävention (SR)

Suchzeitraum: 2012 bis 15.12.2021

Suchbegriffe: #1 AND #1A AND #1B AND #8 AND #10

#1 Statine

"hmg-coa reductase inhibitors" OR "hmg-coa reductase inhibitor" OR statin OR statins OR simvastatin OR pravastatin OR atorvastatin OR fluvastatin OR rosuvastatin OR lovastatin OR pitavastatin OR cerivastatin

#1A Moderate bis geringe Dosis

"low-dose" OR "low dose" OR "low intens*" OR "low-intens*" OR "low intensity" OR "low-intensity" OR "moderate-dose" OR "moderate dose" OR "moderate intens*" OR "moderate-intens*" OR "moderate intensity" OR "moderate-intensity" OR "mediumdose" OR "medium dose" OR "medium intens*" OR "medium-intens*" OR "medium intensity" OR "medium-intensity" OR "middle-dose" OR "middle dose" OR "middle intens*" OR "middle-intens*" OR "middle intensity" OR "middle-intensity" OR "less statin"

#1B Hochdosis

"high-dose" OR "high dose" OR "high intensity" OR "high-intensity" OR "high intens*" OR "high-intens*" OR "more statin"

#8 Klinische Endpunkte

death OR infarction OR stroke OR "coronary syndrome" OR revascularisat* OR "cardiovascular event*" OR "coronary event*" OR "cerebrovascular event*" OR "unstable angina" OR resuscitation OR bypass

#10 SR

"systematic review" OR metaanalys* OR meta-analys* OR "pooled analys*" OR network

Eingeschlossene Volltexte: n = 4 (Primärprävention, SR) sowie n = 4 (Sekundärprävention, SR)

PICO-3/4: Effektivität und Sicherheit von Statinen in Hochdosis in der Primär- und Sekundärprävention (RCT)

Suchzeitraum: 2012 bis 15.12.2021

Suchbegriffe: ##1 AND #1A AND #1B AND #8 AND #9

#1 Statine

"hmg-coa reductase inhibitors" OR "hmg-coa reductase inhibitor" OR statin OR statins OR simvastatin OR pravastatin OR atorvastatin OR fluvastatin OR rosuvastatin OR lovastatin OR pitavastatin OR cerivastatin

#1A Moderate bis geringe Dosis

"low-dose" OR "low dose" OR "low intens*" OR "low-intens*" OR "low intensity" OR "low-intensity" OR "moderate-dose" OR "moderate dose" OR "moderate intens*" OR "moderate-intens*" OR "moderate intensity" OR "moderate-intensity" OR "mediumdose" OR "medium dose" OR "medium intens*" OR "medium-intens*" OR "medium intensity" OR "medium-intensity" OR "middle-dose" OR "middle dose" OR "middle intens*" OR "middle-intens*" OR "middle intensity" OR "middle-intensity" OR "less statin"

#1B Hochdosis

"high-dose" OR "high dose" OR "high intensity" OR "high-intensity" OR "high intens*" OR "high-intens*" OR "more statin"

#8 Klinische Endpunkte

death OR infarction OR stroke OR "coronary syndrome" OR revascularisat* OR "cardiovascular event*" OR "coronary event*" OR "cerebrovascular event*" OR "unstable angina" OR resuscitation OR bypass

#9 RCT

randomized OR randomised OR "at random" OR randomly

Eingeschlossene Volltexte: n = 0 (Primärprävention, RCT) sowie n = 6 (Sekundärprävention, RCT)

Rechercheauftrag für die NVL Chronische KHK Version 7.0: Aktualisierung der Suche **ab 15.12.2021**

Hinweis: s. a. Methodenreport der Version 5.0: Anhang 8.2.5

5.2.1   Strukturierte Suche (Dezember 2021 – 11.05.2023)

IQWIG (www.iqwig.de)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	12.2021 – 11.05.2023
Suchbegriff: Statine	
Treffer	0
Eingeschlossene Treffer	0

NICE (www.nice.org.uk/guidance)

Nr.	Suchfrage
Suchbegriffe	statin, low-density lipoprotein cholesterol, LDL, coronary artery disease, lipid modification
Suchzeitraum	from Dez 2021
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE advice
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE quality standard

Nr.	Suchfrage
Treffer	0 + 1*

*im Mai 2023 veröffentlicht: https://www.nice.org.uk/guidance/cg181/evidence/c-risk-assessment-and-reduction-including-lipid-modification-pdf-13065827440

Datenbanken der AHRQ (www.ahrq.gov/research/findings/evidence-based-reports/search.html)

Kategorien	Suchbegriffe/ Filter (Zeitraum ab Dez 2021 bis 11.05.2023)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	0	0
Technology Assessment Program (completed)		0	0

Zusatzinformation (ältere Version berücksichtigt in der Evidenzaufbereitung des Leitfadens der AkdÄ):

▪ AHRQ. Final Evidence Review. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication. August 23, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/document/final-evidence-review/statin-use-in-adults-preventive-medication (Primärprävention)

5.2.2 Medline via Pubmed (www.pubmed.gov) (19. Juni 2023)

Nr.	Suchfrage	Anzahl
#12	**Search: (#6 AND #9) NOT (#10 OR #11)**	**15**
#11	**Search: (#6 AND #8) NOT #10**	**19**
#10	**Search: #6 AND #7**	**8**
#9	Search: cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]	3,311,804
#8	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,543,149
#7	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab]	656,883

Nr.	Suchfrage	Anzahl
	OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	
#6	Search: #1 AND #2 AND #3 AND #4 Filters: from 2021/12/15 - 3000/12/12	54
#5	Search: #1 AND #2 AND #3 AND #4	295
#4	Search: death[tw] OR infarction[tw] OR stroke[tw] OR "coronary syndrome"[tw] OR revascularisat*[tw] OR "cardiovascular event*"[tw] OR "coronary event*"[tw] OR "cerebrovascular event*"[tw] OR "unstable angina"[tw] OR resuscitation[tw] OR bypass[tw]	1,794,826
#3	Search: "high-dose"[tw] OR "high dose"[tw] OR "high intensity"[tw] OR "high-intensity"[tw] OR "high intens*"[tw] OR "high-intens*"[tw] OR "more statin"[tiab:~0]	157,430
#2	Search: "low-dose"[tw] OR "low dose"[tw] OR "low intens*"[tw] OR "low-intens*"[tw] OR "low intensity"[tw] OR "low-intensity"[tw] OR "moderate-dose"[tw] OR "moderate dose"[tw] OR "moderate intens*"[tw] OR "moderate-intens*"[tw] OR "moderate intensity"[tw] OR "moderate-intensity"[tw] OR "mediumdose"[tw] OR "medium dose"[tw] OR "medium intens*"[tw] OR "medium-intens*"[tw] OR "medium intensity"[tw] OR "medium-intensity"[tw] OR "middle-dose"[tw] OR "middle dose"[tw] OR "middle intens*"[tw] OR "middle-intens*"[tw] OR "middle intensity"[tw] OR "middle-intensity"[tw] OR "less statin"[tiab:~0]	149,411
#1	Search: "hmg-coa reductase inhibitors"[tw] OR "hmg-coa reductase inhibitor"[tw] OR statin[tw] OR statins[tw] OR simvastatin[tw] OR pravastatin[tw] OR atorvastatin[tw] OR fluvastatin[tw] OR rosuvastatin[tw] OR lovastatin[tw] OR pitavastatin[tw] OR cerivastatin[tw]	66,905

5.2.3 Datenbanken der Cochrane Library (19. Juni 2023)

Nr.	Suchfrage	Anzahl
#6	**(#1 AND #2 AND #3 AND #4) NOT (conference proceeding):pt in Trials, Year first published: from 2021**	**31**
#5	**(#1 AND #2 AND #3 AND #4) NOT (conference proceeding):pt in Cochrane Reviews, Cochrane Protocols**	**0**
#4	(death OR infarction OR stroke OR "coronary syndrome" OR revascularisat* OR (cardiovascular NEXT event*) OR (coronary NEXT event*) OR (cerebrovascular NEXT event*) OR "unstable angina" OR resuscitation OR bypass):ti,ab,kw	188453
#3	("high-dose" OR "high dose" OR "high intensity" OR "high-intensity" OR (high NEXT intens*) OR high-intens* OR "more statin"):ti,ab,kw	36286
#2	("low-dose" OR "low dose" OR (low NEXT intens*) OR low-intens* OR "low intensity" OR "low-intensity" OR "moderate-dose" OR "moderate dose" OR (moderate NEXT intens*) OR moderate-intens* OR "moderate intensity" OR "moderate-intensity" OR "mediumdose" OR "medium dose" OR (medium NEXT intens*) OR medium-intens* OR "medium intensity" OR "medium-intensity" OR "middle-dose" OR "middle dose" OR (middle NEXT intens*) OR middle-intens* OR "middle intensity" OR "middle-intensity" OR "less statin"):ti,ab,kw	42583
#1	("hmg-coa reductase inhibitors" OR "hmg-coa reductase inhibitor" OR statin OR statins OR simvastatin OR pravastatin OR atorvastatin OR fluvastatin OR rosuvastatin OR lovastatin OR pitavastatin OR cerivastatin):ti,ab,kw	18854

5.2.4 Epistemonikos (www.epistemonikos.org) (19. Juni 2023)

Nr.	Suchfrage	Anzahl
#1	("hmg-coa reductase inhibitors" OR "hmg-coa reductase inhibitor" OR statin OR statins OR simvastatin OR pravastatin OR atorvastatin OR fluvastatin OR rosuvastatin OR lovastatin OR pitavastatin OR cerivastatin) AND ("low-dose" OR "low dose" OR "low intens*" OR "low-intens*" OR "low intensity" OR "low-intensity" OR "moderate-dose" OR "moderate dose" OR "moderate intens*" OR "moderate-intens*" OR "moderate intensity" OR "moderate-intensity" OR "mediumdose" OR "medium dose" OR "medium intens*" OR "medium-intens*" OR "medium intensity" OR "medium-intensity" OR "middle-dose" OR "middle dose" OR "middle intens*" OR "middle-intens*" OR "middle intensity" OR "middle-intensity" OR "less statin") AND ("high-dose" OR "high dose" OR "high intensity" OR "high-intensity" OR "high intens*" OR "high-intens*" OR "more statin") AND (death OR infarction OR stroke OR "coronary syndrome" OR revascularisat* OR "cardiovascular event*" OR "coronary event*" OR "cerebrovascular event*" OR "unstable angina" OR resuscitation OR bypass) **Filter: Publication type: Systematic Review; Publication year: 2021-2023**	10

5.2.5 Übersicht der eingeschlossenen Treffer

	strukturiert	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz		8	0	10	
RCTs		19	31	-	
Sonstige Primär		15	-	-	
GESAMT		**42**	**31**	**10**	**83**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 23

A2 (nicht englisch/deutsch): -

A3 (Conference Abstracts): -

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 60

5.3   Flowchart

```
┌────────────────────────┐        ┌──────────────────────────┐      ┌──────────────────────────┐
│                        │        │ Ergebnis der systematischen│     │ Ausgeschlossene          │
│                        │        │ Literaturrecherche         │──→  │ Titel/Abstracts: n = 45  │
│ Literatur von Experten │──────→ │ n = 60                     │     │ Aa: n = 39               │
│ oder durch Handsuche   │        └──────────────────────────┘      │ Ap: n = 6                │
│ n =                    │                    │                     └──────────────────────────┘
└────────────────────────┘                    ↓
                            ┌──────────────────────────┐            ┌──────────────────────────┐
                            │ Eingeschlossene Titel/    │            │ Ausgeschlossene          │
                            │ Abstracts: n = 15         │──→         │ Volltexte: n= 14         │
                            └──────────────────────────┘            │ Aa: n = 8                │
                                         │                          │ Ap: n = 6                │
                                         ↓                          └──────────────────────────┘
                            ┌──────────────────────────┐
                            │ Eingeschlossene Volltexte │
                            │ n = 1 RCT                 │
                            │ + n = 1 SR aus der        │
                            │ strukturierten Suche      │
                            │ (Mai 2023)                │
                            └──────────────────────────┘
```
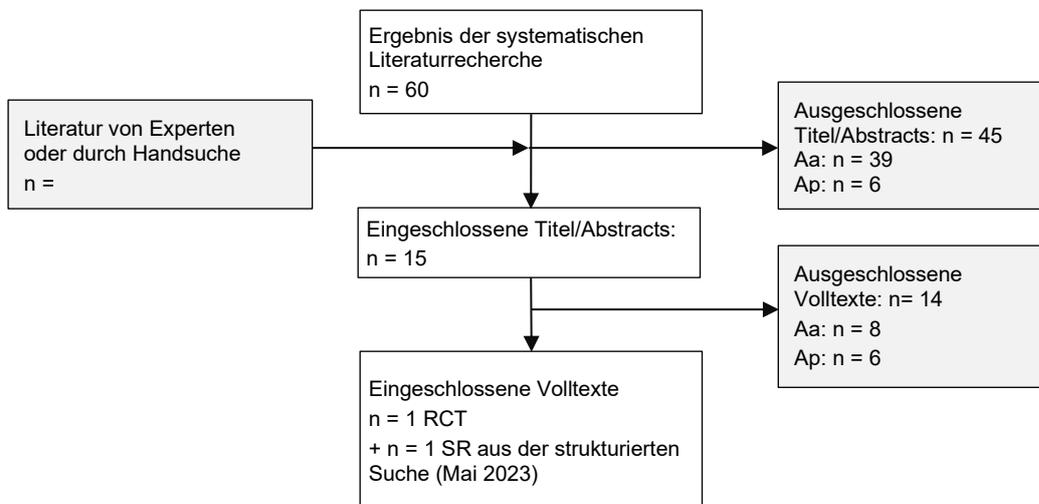
Legende

Aa   Thema nicht passend (PICO)

Ap   Studientyp nicht passend

6 Recherche Statine Zielwert vs. feste Dosis (AkdÄ - Recherche-frage5/6)

6.1 PICO-Frage

P   Patient*innen mit stabiler KHK

I   Statine zielwertgesteuert

C   Statine in fester Dosis

O   Effektivität und Sicherheit

Studientyp: systematische Reviews, Metaanalysen, RCT

Sprache: englisch, deutsch

6.2 Recherchestrategien

Hinweis: Recherchefrage 5/6 (Statine, Zielwert vs. feste Dosis) des Leitfadens der AkdÄ.

PICO-5/6: Effektivität einer Zielwert-Strategie in der Primär- und Sekundärprävention (SR)

Suchzeitraum: 2017 bis 15.12.2021

Suchbegriffe: #3A AND #3B AND #8 AND #10

#3A Zielwert

target OR trageted OR targets OR targeting OR goal OR goals OR "goal-directed"

#3B LDL

„low density lipoprotein cholesterol" OR ldl-c OR ldl OR „LDL cholesterol"

#8 Klinische Endpunkte

death OR infarction OR stroke OR "coronary syndrome" OR revascularisat* OR "cardiovascular event*" OR „coronary event*" OR „cerebrovascular event*" OR "unstable angina" OR resuscitation OR bypass

#10 SR

„systematic review" OR metaanalys* OR meta-analys* OR „pooled analys*" OR network

Eingeschlossene Volltexte: n = 0 (Sekundärprävention, SR) sowie n = 2 (Primärprävention, SR)

PICO-5/6: Effektivität einer LDL-Zielwert-Strategie in der Primär- und Sekundärprävention (RCT)

Suchzeitraum: 2017 bis 15.12.2021

Suchbegriffe: #3A AND #3B AND #8 AND #9

#3A Zielwert

target OR trageted OR targets OR targeting OR goal OR goals OR "goal-directed"

#3B LDL

„low density lipoprotein cholesterol" OR ldl-c OR ldl OR „LDL cholesterol"

#8 Klinische Endpunkte

death OR infarction OR stroke OR "coronary syndrome" OR revascularisat* OR "cardiovascular event*" OR „coronary event*" OR „cerebrovascular event*" OR "unstable angina" OR resuscitation OR bypass

#9 RCT

randomized OR randomised OR „at random" OR randomly

Eingeschlossene Volltexte: n = 3 (Sekundärprävention, RCT) sowie n = 1 (Primärprävention, RCT)

Rechercheauftrag für die NVL Chronische KHK Version 7.0: Aktualisierung der Suche **ab 15.12.2021**

Hinweis: s. a. Methodenreport der Version 5.0: Anhang 8.2.5 Strategien der Lipidsenkung: Strategie der festen Dosis (Empfehlung 7-13); Anhang 8.2.6 Strategien der Lipidsenkung: Zielwertstrategie (Empfehlung 7-14) (Expertenkonsens ohne strukturierte oder systematische Recherche)

6.2.1 Strukturierte Suche (Dezember 2021 – 11.05.2023)

IQWIG (www.iqwig.de)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	12.2021 – 11.05.2023
Suchbegriff: Statine, LDL	
Treffer	0
Eingeschlossene Treffer	0

NICE (www.nice.org.uk/guidance)

Nr.	Suchfrage
Suchbegriffe	statin, low-density lipoprotein cholesterol, LDL, treat-to-target, coronary artery disease
Suchzeitraum	from Dez 2021
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE advice
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE quality standard
Treffer	0

Zusatzinformation:

▪ Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides. Technology appraisal guidance [TA805] Published: 13 July 2022. https://www.nice.org.uk/guidance/ta805/evidence

Datenbanken der AHRQ (www.ahrq.gov/research/findings/evidence-based-reports/search.html)

Kategorien	Suchbegriffe/ Filter (Zeitraum ab Dez 2021 bis 11.05.2023)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	0	0
Technology Assessment Program (completed)		0	0

Zusatzinformation (ältere Version berücksichtigt in der Evidenzaufbereitung des Leitfadens der AkdÄ):

- AHRQ. Final Evidence Review. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication. August 23, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/document/final-evidence-review/statin-use-in-adults-preventive-medication (Primärprävention)

6.2.2 Medline via Pubmed (www.pubmed.gov) (19. Juni 2023)

Nr.	Suchfrage	Anzahl
#12	**Search: (#6 AND #9) NOT (#10 OR #11)**	**78**
#11	**Search: (#6 AND #8) NOT #10**	**40**
#10	**Search: #6 AND #7**	**25**
#9	Search: cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]	3,311,804
#8	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,543,149
#7	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	656,883
#6	Search: #3 AND #4 Filters: from 2021/12/15 - 3000/12/12	368
#5	Search: #3 AND #4	3,100
#4	Search: "death"[tw] OR "infarction"[tw] OR "stroke"[tw] OR "coronary syndrome"[tw] OR "revascularisat*"[tw] OR "cardiovascular event*"[tw] OR "coronary event*"[tw] OR "cerebrovascular event*"[tw] OR "unstable angina"[tw] OR "resuscitation"[tw] OR "bypass"[tw]	1,794,826
#3	Search: #1 AND #2	13,743
#2	Search: "target"[tw] OR "trageted"[tw] OR "targets"[tw] OR "targeting"[tw] OR "goal"[tw] OR "goals"[tw] OR "goal-directed"[tw]	2,080,433
#1	Search: "low density lipoprotein cholesterol"[tw] OR "ldl-c"[tw] OR "ldl"[tw] OR "LDL cholesterol"[tw]	126,828

6.2.3 Datenbanken der Cochrane Library (19. Juni 2023)

Nr.	Suchfrage	Anzahl
#7	**#5 NOT (conference proceeding):pt in Trials; Year first published: from 2021**	**103**
#6	**#5 NOT (conference proceeding):pt in Cochrane Reviews, Cochrane Protocols, Publication date: from 2021-12-15**	**0**
#5	#3 AND #4	954
#4	("death" OR "infarction" OR "stroke" OR "coronary syndrome" OR revascularisat* OR (cardiovascular NEXT event*) OR (coronary NEXT event*) OR (cerebrovascular NEXT event*) OR "unstable angina" OR "resuscitation" OR "bypass"):ti,ab,kw	188454
#3	#1 AND #2	3273
#2	(("target" OR "trageted" OR "targets" OR "targeting" OR "goal" OR "goals" OR "goal-directed")):ti,ab,kw	128084
#1	(("low density lipoprotein cholesterol" OR "ldl-c" OR "ldl" OR "LDL cholesterol")):ti,ab,kw	27874

Zusatzinformation (vor dem Recherchezeitraum):

- Schmidt et al. 2020. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease (Review). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011748.pub3/epdf/full

- Zhan et al. 2018. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events (Review). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012502.pub2/epdf/full

- Taylor et al. 2013 Statins for the primary prevention of cardiovascular disease (Review). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004816.pub5/full

6.2.4 Epistemonikos (www.epistemonikos.org) (19. Juni 2023)

Nr.	Suchfrage	Anzahl
#1	(title:((title:(("low density lipoprotein cholesterol" OR "ldl-c" OR "ldl" OR "LDL cholesterol")) OR abstract:(("low density lipoprotein cholesterol" OR "ldl-c" OR "ldl" OR "LDL cholesterol"))) AND (title:(("target" OR "trageted" OR "targets" OR "targeting" OR "goal" OR "goals" OR "goal-directed")) OR abstract:(("target" OR "trageted" OR "targets" OR "targeting" OR "goal" OR "goals" OR "goal-directed"))) AND (title:(("death" OR "infarction" OR "stroke" OR "coronary syndrome" OR "revascularisat*" OR "cardiovascular event*" OR "coronary event*" OR "cerebrovascular event*" OR "unstable angina" OR "resuscitation" OR "bypass")) OR abstract:(("death" OR "infarction" OR "stroke" OR "coronary syndrome" OR "revascularisat*" OR "cardiovascular event*" OR "coronary event*" OR "cerebrovascular event*" OR "unstable angina" OR "resuscitation" OR "bypass")))) OR abstract:((title:(("low density lipoprotein cholesterol" OR "ldl-c" OR "ldl" OR "LDL cholesterol")) OR abstract:(("low density lipoprotein cholesterol" OR "ldl-c" OR "ldl" OR "LDL cholesterol"))) AND (title:(("target" OR "trageted" OR "targets" OR "targeting" OR "goal" OR "goals" OR "goal-directed")) OR abstract:(("target" OR "trageted" OR "targets" OR "targeting" OR "goal" OR "goals" OR "goal-directed"))) AND (title:(("death" OR "infarction" OR "stroke" OR "coronary syndrome" OR "revascularisat*" OR "cardiovascular event*" OR "coronary event*" OR "cerebrovascular event*" OR "unstable angina" OR "resuscitation" OR "bypass")) OR abstract:(("death" OR "infarction" OR "stroke" OR "coronary syndrome" OR "revascularisat*" OR "cardiovascular event*" OR "coronary event*" OR "cerebrovascular event*" OR "unstable angina" OR "resuscitation" OR "bypass"))))) **Filter: Publication type: Systematic review; Publication year: 2021-2023**	14

6.2.5 Übersicht der eingeschlossenen Treffer

	strukturiert	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz		25	-	14	39
RCTs		40	103	-	143
Sonstige Primär		78	-	-	78
GESAMT					**260**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 32

A2 (nicht englisch/deutsch): 4

A3 (Conference Abstracts): -

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 224

6.3 Flowchart

Ergebnis der systematischen Literaturrecherche n = 229

n = 224 systematisch ermittelt

+ 5 Treffer aus der strukturierten Recherche

Literatur von Experten oder durch Handsuche n =

Ausgeschlossene Titel/Abstracts: n = 218
Aa: n = 213
Ap: n = 5

Eingeschlossene Titel/Abstracts: n = 11

Ausgeschlossene Volltexte: n= 4
Aa: n = 4
Ap: n = 0

Eingeschlossene Volltexte n = 5

+ 2 interessante Zufallsfunde der strukturierten Recherche
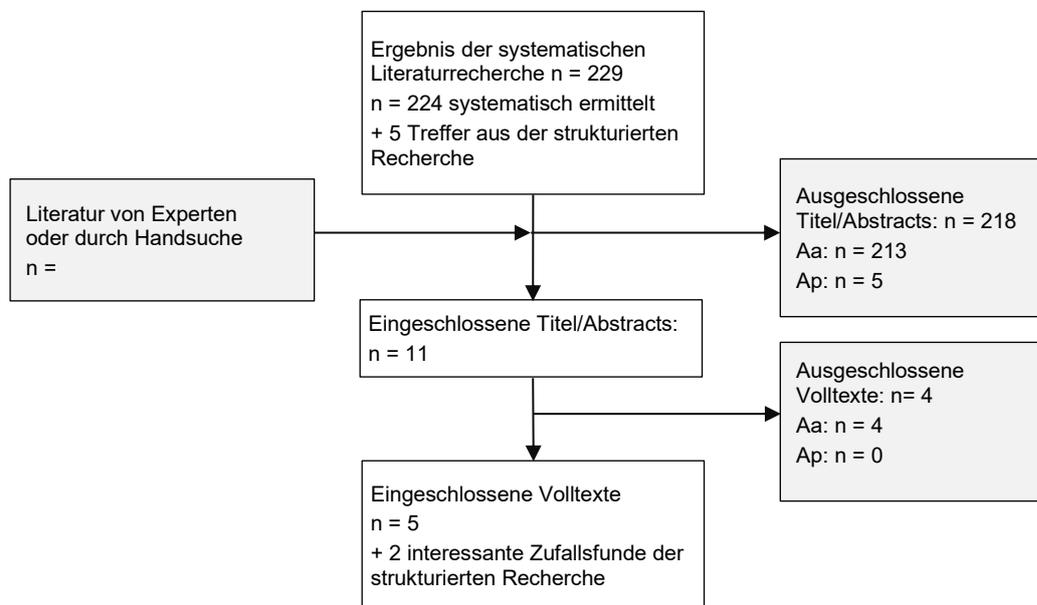
Legende

Aa   Thema nicht passend (PICO)

Ap   Studientyp nicht passend

7 Recherche zu Bempedoinsäure bei maximal verträglicher Statin-therapie (AkdÄ – Recherchefrage 25)

7.1 PICO-Frage

P   Patient*innen mit stabiler KHK nach invasivem Verfahren oder akutem Koronarsyndrom bzw. akutem kardiovaskulärem Ereignis und Indikation zur Lipidsenkung

I   Bempedoinsäure bei maximal verträglicher Statintherapie

C   Placebo oder Standartherapie

O   Effektivität und Sicherheit

Studientyp: systematische Reviews, Metaanalysen, RCT

Sprache: englisch, deutsch

7.2 Recherchestrategien

Hinweis: Recherchefragen 25 (Bempedoinsäure) des Leitfadens der AkdÄ. (AkdÄ)[1]

PICO-25: Effektivität und Sicherheit von Bempedoinsäure bei maximal verträglicher Statintherapie in der Se-kundärprävention (RCT)

Suchzeitraum: 2017 bis 15.12.2021

Suchbegriffe: #7 AND #9

#7 Bempedoinsäure

"(ATP)-citrate lyase inhibitor" OR "ATP:citrate lyase inhibitor" OR bempedoic OR ETC-1002

#9 RCT

randomized OR randomised OR „at random" OR randomly

Eingeschlossene Volltexte: n = 5

Rechercheauftrag für die NVL Chronische KHK Version 7.0: Aktualisierung der Suche **ab 15.12.2021**

7.2.1 Strukturierte Suche (Dezember 2021 – 11.05.2023)

IQWIG (www.iqwig.de)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	12.2021 – 11.05.2023
Suchbegriff: Bempedoinsäure	
Treffer	0
Eingeschlossene Treffer	0

Zusatzinformation (berücksichtigt im Recherchezeitraum in der Evidenzaufbereitung des Leitfadens der AkdÄ):

- A20-92: Version 1.0 28.01.2021. IQWiG-Berichte – Nr. 1033. Bempedoinsäure (primäre Hypercholesteri-nämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V
  https://www.iqwig.de/download/a20-92_bempedoinsaeure_nutzenbewertung-35a-sgb-v_v1-0.pdf

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[1] Evidenzaktualisierung des Leitfadens Medikamentöse Cholesterinsenkung zur Vorbeugung kardiovaskulärer Ereignisse der Bundesärztekammer / Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) – Version 1.0 März 2023 www.akdae.de/arzneimitteltherapie/lf/cholesterinsenkung

- A20-91: Version 1.0 28.01.2021. IQWiG-Berichte – Nr. 1031. Bempedoinsäure/Ezetimib (primäre Hyper-cholesterinämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V
https://www.iqwig.de/download/a20-91_bempedoinsaeure-ezetimib_nutzenbewertung-35a-sgb-v_v1-0.pdf

NICE (www.nice.org.uk/guidance)

Nr.	Suchfrage
Suchbegriffe	Bempedoic acid
Suchzeitraum	from Dez 2021
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE advice
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE quality standard
Treffer	0

Zusatzinformation (berücksichtigt im Recherchezeitraum in der Evidenzaufbereitung des Leitfadens der AkdÄ):

- Single Technology Appraisal Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515] Committee Papers. https://www.nice.org.uk/guidance/ta694/evidence/appraisal-consultation-committee-papers-pdf-9082103581

- Single Technology Appraisal Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515] Committee Papers: https://www.nice.org.uk/guidance/ta694/evidence/final-appraisal-determination-committee-papers-pdf-9082103582

- NICE Guidance: Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia https://www.nice.org.uk/guidance/ta694/resources/bempedoic-acid-with-ezetimibe-for-treating-primary-hypercholesterolaemia-or-mixed-dyslipidaemia-pdf-82609440519877

Datenbanken der AHRQ (www.ahrq.gov/research/findings/evidence-based-reports/search.html)

Kategorien	Suchbegriffe/ Filter (Zeitraum ab Dez 2021 bis 11.05.2023)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	0	0
Technology Assessment Program (completed)		0	0

7.2.2 Medline via Pubmed (www.pubmed.gov) (16. Juni 2023)

Nr.	Suchfrage	Anzahl
#10	Search: (#4 AND #7) NOT (#8 OR #9)	7
#9	Search: (#4 AND #6) NOT #8	23
#8	Search: #4 AND #5	13

Nr.	Suchfrage	Anzahl
#7	Search: cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]	3,311,046
#6	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,542,811
#5	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	656,605
#4	Search: #1 OR #2 Filters: from 2021/12/15 - 3000/12/12	130
#3	Search: #1 OR #2	323
#2	Search: 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid [Supplementary Concept]	166
#1	Search: "ATP:citrate lyase inhibitor"[Text Word] OR "ATP:citrate lyase inhibitor"[Text Word] OR "bempedoic"[Text Word] OR "ETC-1002"[Text Word]	306

Hinweis: PubMed Medline Entry Terms: bempedoic acid, nilemdo, nexletol, ETC-1002, ESP55016, ESP-55016

7.2.3 Datenbanken der Cochrane Library (16. Juni 2023)

Nr.	Suchfrage	Anzahl
#2	"(ATP)-citrate lyase inhibitor" OR "ATP:citrate lyase inhibitor" OR bempedoic OR ETC-1002 in Trials, ;from 2021	42
#1	("(ATP)-citrate lyase inhibitor" OR "ATP:citrate lyase inhibitor" OR bempedoic OR ETC-1002):ti,ab,kw in Cochrane Reviews, Cochrane Protocols	0

7.2.4 Epistemonikos (www.epistemonikos.org) (16. Juni 2023)

Nr.	Suchfrage	Anzahl
#1	(title:((title:("(ATP)-citrate lyase inhibitor" OR "ATP:citrate lyase inhibitor" OR bempedoic OR ETC-1002) OR abstract:("(ATP)-citrate lyase inhibitor" OR "ATP:citrate lyase inhibitor" OR bempedoic OR ETC-1002))) OR abstract:((title:("(ATP)-citrate lyase inhibitor" OR "ATP:citrate lyase inhibitor" OR bempedoic OR ETC-1002) OR abstract:("(ATP)-citrate ly-ase inhibitor" OR "ATP:citrate lyase inhibitor" OR bempedoic OR ETC-1002)))) **Filter: Publication type: Systematic review; Publication year: 2021-2023**	12

7.2.5 Übersicht der eingeschlossenen Treffer

	Strukturiert	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz		13	-	12	25
RCTs		23	42	-	65
Sonstige Primär		7	-	-	7
GESAMT					**97**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 22

A2 (nicht englisch/deutsch): 1

A3 (Conference Abstracts): 12

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 62

7.3 Flowchart
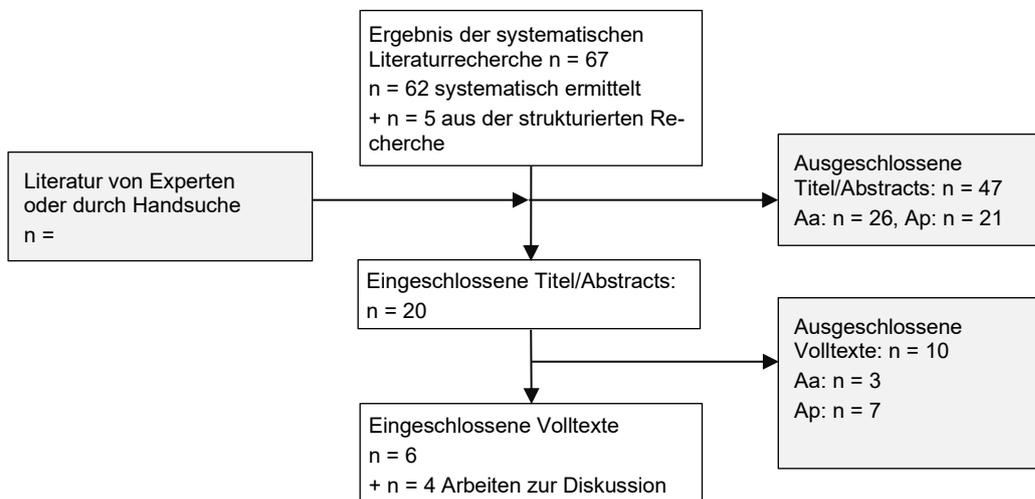
Legende

Aa   Thema nicht passend (PICO)

Ap   Studientyp nicht passend

8 Recherche zu Anhang 8.1.1 der 5. Auflage 2019 (S. 123ff) Stabile KHK: Keine Indikation zur Antikoagulation (Empfehlung 7-1 und Empfehlung 7-3)

8.1 PICO-Frage

P   Patient*innen mit stabiler KHK

I   Clopidogrel

C   ASS oder Standardmedikation

O   Gesamtmortalität, kardiovaskuläre Mortalität, Myokardinfarkt, unerwünschte Wirkungen

Studientyp: systematische Reviews, Metaanalysen

Sprache: englisch, deutsch

8.2 Recherchestrategien

Strukturierte Suche nach aggregierter Evidenz (21.11.2017 – 10.05.2023)

Hinweis: bis November 2017 n = 2 Treffer (n = 1 IQWIG Bericht (ASS vs. Clopidogrel), n = 1 Treffer NICE (ASS vs. Placebo))

- Der NICE-Review bezieht sich ausschließlich auf Patienten ohne zurückliegenden Myokardinfarkt. Zur Sekundärprävention nach Myokardinfarkt liegt zwar eine Empfehlung einer NICE-Guideline vor, bezüglich dieser Empfehlung wird jedoch keine systematische Suche berichtet. Als Evidenzgrundlage wird eine Übersichtsarbeit der Antithrombotic Trialists' (ATT) Collaboration zitiert. Wir fanden eine aktuellere Übersichtsarbeit der ATT-Collaboration, die keine neuen relevanten Studien identifiziert, jedoch ergänzende Informationen beispielsweise zu Patientencharakteristika bereitstellt. Beide Reviews der ATT-Collaboration wurden von uns methodisch bewertet und extrahiert. Da sie keine qualitative Bewertung der eingeschlossenen Studien berichten, erfolgte außerdem eine Extraktion und methodische Bewertung der Primärstudien.

- Im Rahmen der Konsultationsphase wurde die aktuell diskutierte Metaanalyse von Rothwell et al. zur Dosierung von ASS eingebracht.

bis Mai 2023 **n = 0 Treffer** (*Hinweis*: eine Zusatzinformation zur Prävention mit ASS ist weiter unten aufgeführt (AHRQ))

Systematische Suche nach aggregierter Evidenz und RCT (21.11.2017 – heute) s. u.

8.2.1 Strukturierte Suche (21. November 2017 – 10.05.2023)

IQWIG (www.iqwig.de)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	11.2017 – 10.05.2023
Suchbegriff: Clopidogrel	
Treffer	4
Eingeschlossene Treffer	0

NICE (www.nice.org.uk/guidance)

Nr.	Suchfrage
Suchbegriffe	Clopidogrel
Suchzeitraum	from November 2017

Nr.	Suchfrage
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE advice
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE quality standard
Treffer	0

Datenbanken der AHRQ (www.ahrq.gov/research/findings/evidence-based-reports/search.html)

Kategorien	Suchbegriffe/ Filter (Zeitraum ab November 2017 bis 10.05.2023)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	0	0
Technology Assessment Program (completed)		0	0

Zusatzinformation (nicht eingeschlossen)

Final Evidence Review. Aspirin Use to Prevent Cardiovascular Disease: Preventive Medication. April 26, 2022
https://www.uspreventiveservicestaskforce.org/uspstf/document/final-evidence-review/aspirin-to-prevent-cardio-vascular-disease-preventive-medication

8.2.2 Medline via Pubmed (www.pubmed.gov) (6. Juli 2023)

Nr.	Suchfrage	Anzahl
#12	**Search: (#8 AND #10) NOT #11**	**345**
#11	**Search: #8 AND #9**	**198**
#10	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,546,908
#9	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw]	660,331

Nr.	Suchfrage	Anzahl
	OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	
#8	Search: #5 AND #6 Filters: from 2017/11/21 - 3000/12/12	1,693
#7	Search: #5 AND #6	6,678
#6	Search: Clopidogrel*[tw]	16,571
#5	Search: #1 OR #2 OR #3 OR #4	318,733
#4	Search: "Coronary Thrombosis"[Mesh]	8,347
#3	Search: "Coronary Occlusion"[Mesh]	4,352
#2	Search: "Angina Pectoris"[Mesh]	44,667
#1	Search: coronary[tiab] AND (syndrome*[tiab] OR occlusion*[tiab] OR thrombosis*[tiab] OR disease*[tiab] OR (heart[tiab] AND disease*[tiab]))	285,623

Hinweis: stufenweises Vorgehen: nach Einschluss der SR, ggf. zeitliche Begrenzung der RCT

8.2.3   Datenbanken der Cochrane Library (6. Juli 2023)

Nr.	Suchfrage	Anzahl
#9	**#7 NOT (conference proceeding):pt in Trials; Year first published: from 2017**	**762**
#8	**#7 NOT (conference proceeding):pt in Cochrane Reviews, Cochrane Protocols; Publication date: from 2017-11-21**	**3**
#7	#5 AND #6	3335
#6	("clopidogrel"):ti,ab,kw	6162
#5	#1 OR #2 OR #3 OR #4	51571
#4	MeSH descriptor: [Coronary Thrombosis] explode all trees	565
#3	MeSH descriptor: [Coronary Occlusion] explode all trees	510
#2	MeSH descriptor: [Angina Pectoris] explode all trees	5570
#1	((coronary AND (syndrome* OR occlusion* OR thrombosis* OR disease* OR (heart AND disease*)))):ti,ab,kw	48766

8.2.4   Epistemonikos (www.epistemonikos.org) (6. Juli 2023)

Nr.	Suchfrage	Anzahl
	(advanced_title_en:(coronary) OR advanced_abstract_en:(coronary)) AND (advanced_title_en:(syndrome* OR occlusion* OR thrombosis* OR disease* OR (heart AND disease*)) OR advanced_abstract_en:(syndrome* OR occlusion* OR thrombosis* OR disease* OR (heart AND disease*))) AND (advanced_title_en:(clopidogrel) OR advanced_abstract_en:(clopidogrel)) [Filters: classification=systematic-review, protocol=no, min_year=2017, max_year=2023]	180

8.2.5   Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz	198	3	180	381
RCTs	345	762		1107
GESAMT				**1488**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 461

A2 (nicht englisch/deutsch): 20

A3 (Conference Abstracts):

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 1007 + n = 1 SR (strukturierte Suche)

Stufenweises Vorgehen:

- n = 204 Studienregisterpublikationen ausgeschlossen, n = 804 (SR: n = 222 +, RCT: n = 582)
- **e: n = 222 SR + n = 253 RCT (eingeschränktes RCT Screening, s. u.)**

8.3   Flowchart

```
Literatur von Experten          Ergebnis der systematischen
oder durch Handsuche            Literaturrecherche (e)
n =                             n = 475                        ──▶  Ausgeschlossene
                                (n = 222 SR; n = 253 RCT)           Titel/Abstracts:
                                      │                             n = 461
                                      ▼
                                Eingeschlossene Titel/Abstracts:
                                n = 14                         ──▶  Ausgeschlossene
                                      │                             Volltexte: n= 7
                                      ▼                             Aa: n = 3
                                Eingeschlossene Volltexte            Et: n = 4 (Transfer zu
                                n = 7                                weiterer Fragestellung)
```
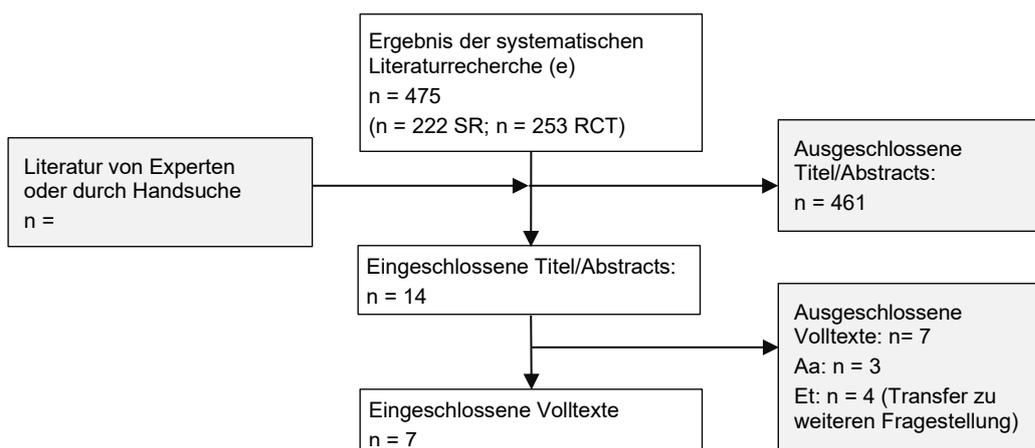
Hinweis: das Screening der aggregierten Evidenz ergab u.a. eine systematische Übersichtsarbeit aus dem Jahr 2020 (Suche im Dec 2019), die der betrachteten Fragestellung entsprach, daher wurde das Screening der weiteren Evidenz (RCT) auf den Zeitraum ab 2020 eingeschränkt (n = 253), s.o. (e = eingeschränkt)

9 Recherche zu Protonenpumpeninhibitoren

9.1 PICO-Frage

Wirksamkeit und Sicherheit von Kombinationstherapien aus NSAR+PPI bei Patient*innen mit Schmerzen.

P   Patient*innen mit Schmerzen (alle)

I   NSAR+PPI

C   alle

O   Reduktion gastrointestinaler Nebenwirkungen

       alle sicherheitsrelevanten Endpunkte (AE, SAE)

Sprache: englisch, deutsch

Studientyp: SR über RCT

Zeitraum: keine Einschränkung

Hinweis: die AG medikamentöse Therapie der NVL Chronische KHK entschied in 2023, die Recherche der NVL Kreuzschmerz aus 2022 zu verwenden, um eine erweiterte Evidenzbasis für eine Empfehlung der NVL Chronische KHK nutzbar zu machen; die TiAb-Screeningtabelle wurde in Bezug auf möglicherweise ergänzend relevante Evidenz überprüft und die Ergebnisse der NVL Kreuzschmerz übernommen, die Aktualität und Gültigkeit der Recherche wurde als gegeben gesehen (Stand: 14.12.2023)

9.2 Recherchestrategien

9.2.1 Medline via Pubmed (www.pubmed.gov) (01. August 2022)

Nr.	Suchfrage	Anzahl
#9	**Search: #7 AND #8**	**185**
#8	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	597,106
#7	Search: #3 AND #6	2,877
#6	Search: #4 OR #5	49,23

Nr.	Suchfrage	Anzahl
#5	Search: "PPI"[Title/Abstract] OR "PPIs"[Title/Abstract] OR "proton pump inhibitor*"[Title/Abstract] OR "omeprazole"[Title/Abstract] OR "esomeprazole"[Title/Abstract] OR "pantoprazole"[Title/Abstract] OR "lansoprazole"[Title/Abstract] OR "dexlansoprazole"[Title/Abstract]	45,796
#4	Search: "proton pump inhibitors/adverse effects"[MeSH Terms] OR "proton pump inhibitors/therapeutic use"[MeSH Terms] OR "omeprazole"[MeSH Terms] OR "esomeprazole"[MeSH Terms] OR "pantoprazole"[MeSH Terms] OR "dexlansoprazole"[MeSH Terms] OR "lansoprazole"[MeSH Terms]	17,580
#3	Search: #1 OR #2	188,339
#2	Search: "nsaid*"[Title/Abstract] OR "non steroidal anti inflammatory drug*"[Title/Abstract] OR "nonsteroidal anti inflammatory drug*"[Title/Abstract] OR "nonsteroidal antiinflammatory drug*"[Title/Abstract] OR "non steroidal antiinflammatory drug*"[Title/Abstract] OR "non steroidal anti inflammatory agent*"[Title/Abstract] OR "nonsteroidal anti inflammatory agent*"[Title/Abstract] OR "nonsteroidal antiinflammatory agent*"[Title/Abstract] OR "non steroidal antiinflammatory agent*"[Title/Abstract] OR "Aceclofenac"[Title/Abstract] OR "Acetaminophen"[Title/Abstract] OR "Celecoxib"[Title/Abstract] OR "Diclofenac"[Title/Abstract] OR "Ibuprofen"[Title/Abstract] OR "Indomethacin"[Title/Abstract] OR "Ketoprofen"[Title/Abstract] OR "Ketorolac"[Title/Abstract] OR "Meloxicam"[Title/Abstract] OR "Metamizole"[Title/Abstract] OR "Naproxen"[Title/Abstract] OR "Piroxicam"[Title/Abstract] OR "Pyrazolones"[Title/Abstract]	129,392
#1	Search: "anti inflammatory agents, non steroidal/adverse effects"[MeSH Terms] OR "anti inflammatory agents, non steroidal/therapeutic use"[MeSH Terms] OR "cyclooxygenase inhibitors/adverse effects"[MeSH Terms] OR "cyclooxygenase inhibitors/therapeutic use"[MeSH Terms] OR "Acetaminophen"[MeSH Terms] OR "Celecoxib"[MeSH Terms] OR "Diclofenac"[MeSH Terms] OR "Etoricoxib"[MeSH Terms] OR "Ibuprofen"[MeSH Terms] OR "Indomethacin"[MeSH Terms] OR "Ketoprofen"[MeSH Terms] OR "Ketorolac"[MeSH Terms] OR "Meloxicam"[MeSH Terms] OR "Naproxen"[MeSH Terms] OR "Piroxicam"[MeSH Terms] OR "Pyrazolones"[MeSH Terms]	134,169

9.2.2 Datenbanken der Cochrane Library (01. August 2022)

Nr.	Suchfrage	Anzahl
#22	**#16 AND #21 in Cochrane Reviews, Cochrane Protocols**	**12**
#21	#17 OR #18 OR #19 OR #20	17318
#20	(PPI OR PPIs OR proton pump inhibitor* OR omeprazole OR esomeprazole OR pantoprazole OR lansoprazole OR dexlansoprazole):ti,ab,kw (Word variations have been searched)	10793
#19	MeSH descriptor: [Omeprazole] explode all trees	3121
#18	MeSH descriptor: [Gastrointestinal Agents] explode all trees	8329
#17	MeSH descriptor: [Proton Pump Inhibitors] explode all trees	1563
#16	#1 OR #14 OR #15	36435
#15	("nsaid*" OR "non steroidal anti inflammatory drug*" OR "nonsteroidal anti inflammatory drug*" OR "nonsteroidal antiinflammatory drug*" OR "nonsteroidal anti inflammatory drug*" OR "non steroidal anti inflammatory agent*" OR "nonsteroidal anti inflammatory agent*" OR "nonsteroidal antiinflammatory agent*" OR "non steroidal antiinflammatory agent *" OR Aceclofenac OR Acetaminophen OR Celecoxib OR Diclofenac OR Etoricoxib OR Ibuprofen OR Indomethacin OR Ketoprofen OR Ketorolac OR Meloxicam OR Metamizole OR Naproxen OR Piroxicam):ti,ab,kw (Word variations have been searched)	33505
#14	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	12653

Nr.	Suchfrage	Anzahl
#13	MeSH descriptor: [Pyrazolones] explode all trees	861
#12	MeSH descriptor: [Piroxicam] explode all trees	663
#11	MeSH descriptor: [Naproxen] explode all trees	1180
#10	MeSH descriptor: [Meloxicam] explode all trees	245
#9	MeSH descriptor: [Ketorolac] explode all trees	964
#8	MeSH descriptor: [Ketoprofen] explode all trees	583
#7	MeSH descriptor: [Indomethacin] explode all trees	2753
#6	MeSH descriptor: [Ibuprofen] explode all trees	2142
#5	MeSH descriptor: [Etoricoxib] explode all trees	242
#4	MeSH descriptor: [Diclofenac] explode all trees	2002
#3	MeSH descriptor: [Celecoxib] explode all trees	1015
#2	MeSH descriptor: [Acetaminophen] explode all trees	3482
#1	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees	7923

9.2.3 Epistemonikos (www.epistemonikos.org) (01. August 2022)

Nr.	Suchfrage	Anzahl
#1	[Title/Abstract]: ((NSAID*) OR (non steroidal anti inflammatory drug*) OR (nonsteroidal antiinflammatory drug*) OR (nonsteroidal anti inflammatory drug*) OR (nonsteroidal anti inflammatory drug*) OR (Aceclofenac) OR (Acetaminophen) OR (Celecoxib) OR (Diclofenac) OR (Etoricoxib) OR (Ibuprofen) OR (Indomethacin) OR (Ketoprofen) OR (Ketorolac) OR (Meloxicam) OR (Metamizole) OR (Naproxen) OR (Piroxicam)) AND ((proton pump inhibitor*) OR (PPI*) OR omeprazole OR esomeprazole OR pantoprazole OR lansoprazole OR dexlansoprazole) **(Publication type: Systematic review)**	66

9.2.4 Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz	185	12	66	**263**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 51

A2 (nicht englisch/deutsch): 21

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 191

9.3 Flowchart

```
┌─────────────────────┐      ┌──────────────────────────────┐
│ Literatur von       │      │ Ergebnis der systematischen  │
│ Experten            │─────▶│ Literaturrecherche           │
│ oder durch Handsuche│      │ n = 191                      │
│ n =                 │      └──────────────────────────────┘
└─────────────────────┘                  │
                                          │          ┌──────────────────────────┐
                                          │─────────▶│ Ausgeschlossene          │
                                          ▼          │ Titel/Abstracts:         │
                              ┌──────────────────────┐│ n = 181                  │
                              │ Eingeschlossene      │└──────────────────────────┘
                              │ Titel/Abstracts:     │
                              │ n = 10*              │
                              └──────────────────────┘
                                          │          ┌──────────────────────────┐
                                          │─────────▶│ Ausgeschlossene          │
                                          ▼          │ Volltexte: n= 4          │
                              ┌──────────────────────┐│ Ap: n =  4               │
                              │ Eingeschlossene      │└──────────────────────────┘
                              │ Volltexte            │
                              │ n = 6*               │
                              └──────────────────────┘
```
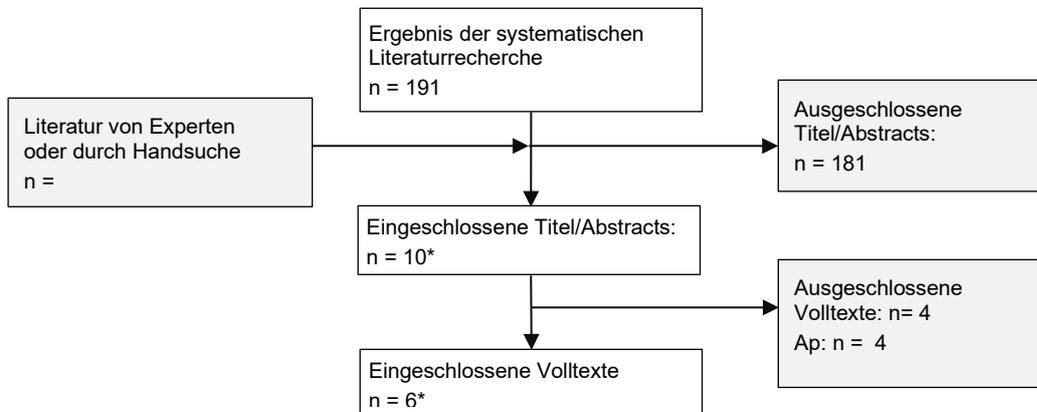
*n = 1 Protokoll (zum Zeitpunkt der Recherche bzw. des Screenings für die NVL Chronische KHK noch keine Publikation verfügbar:

Garegnani L. Proton pump inhibitors for the prevention of non-steroidal anti-inflammatory drug-induced ulcers and dyspepsia. Cochrane Database of Systematic Reviews 2022; 2022(5):357. dx.doi.org/10.1002/14651858.CD014585.

(von den n = 6 eingeschlossenen Volltexten wurden n = 3 direkt herangezogen und ein weiterer unterstützend für den Hintergrundtext; der Cochrane Review diente zum Abgleich als indirekte Evidenz für die Diskussion)

10 Recherche zu Anhang 8.1.4, 8.1.5 und 8.1.6 der 5. Auflage 2019 (S. 124ff) Z.n. elektiver PCI bei stabiler KHK: Clopidogrel oder Prasugrel oder Ticagrelor plus ASS nach elektiver PCI (Empfehlung 7-5) bzw. nach akutem Koronarsyndrom (Kapitel 7.1.4)

10.1 PICO-Frage

Fragestellung 1

P   Patient*innen mit elektiver PCI (Stentimplantation) oder nach akutem Koronarsyndrom

I   Clopidogrel plus ASS

C   Placebo oder OAK oder ADP-Rezeptor-Antagonist, jeweils plus ASS

O   Gesamtmortalität, kardiovaskuläre Mortalität, Myokardinfarkt, unerwünschte Wirkungen

Studientyp: systematische Reviews, Metaanalysen

Sprache: englisch, deutsch

Fragestellung 2 und 3

P   Patienten nach elektiver Stentimplantation oder nach akutem Koronarsyndrom

I   Ticagrelor plus ASS oder Prasugrel plus ASS

C   Clopidogrel plus ASS

O   Gesamtmortalität, kardiovaskuläre Mortalität, Myokardinfarkt, unerwünschte Wirkungen

Studientyp: RCT, systematische Reviews, Metaanalysen

Sprache: englisch, deutsch

10.2 Recherchestrategien

Strukturierte Suche nach aggregierter Evidenz (21.07.2017 – 10.05.2023)

Hinweis: bis November 2017 keine Treffer für SR Clopidogrel + ASS; bis Juli 2017 n = 2 Treffer SR (n = 1 IQWIG Bericht sowie n = 1 NICE Evidenzbericht, beide nach akutem Koronarsyndrom)

Systematische Suche nach aggregierter Evidenz und RCT (21.07.2017 – heute), ggf. ergänzende Suche nach Langzeitbetrachtungen ab Juli 2017, insbesondere zu unerwünschten Wirkungen, s. u.

Hinweis: bis Juli 2017 n = 10 Treffer RCT (Ticagrelor plus ASS nach akutem Koronarsyndrom) + n = 6 Treffer RCT: n = 3 Treffer RCT (Prasugrel plus ASS nach elektiver PCI) und n = 3 Treffer RCT (Prasugrel plus ASS nach akutem Koronarsyndrom)

bis Mai 2023 n = 1 Treffer (IQWIG Rapid Report, Clopidogrel, Prasugrel, Ticagrelor bei akutem Koronarsyndrom)

Systematische Suche nach aggregierter Evidenz und RCT (21.07.2017 – heute) s. u.

10.2.1 Strukturierte Suche (21. Juli 2017 – 10.05.2023)

IQWIG (www.iqwig.de)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	07.2017 – 10.05.2023
Suchbegriff: Clopidogrel, Prasugrel, Ticagrelor	
Treffer	4 bzw. 3 bzw. 5

Nr.	Suchfrage
Eingeschlossene Treffer	1

A21-41 Clopidogrel, Prasugrel und Ticagrelor zur Prävention atherothrombotischer Ereignisse bei akutem Koronar-syndrom (22.02.2023) – Rapid Report, https://www.iqwig.de/download/a21-41_clopidogrel-prasugrel-und-ticag-relor-beim-akuten-koronarsyndrom_rapid-report_v1-0.pdf

NICE (www.nice.org.uk/guidance)

Nr.	Suchfrage
Suchbegriffe	**Clopidogrel, Prasugrel, Ticagrelor**
Suchzeitraum	from July 2017
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medi-cal technology guidance, safe staffing guideline, social care guideline) published
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE advice
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE quality standard
Treffer	0

Datenbanken der AHRQ (www.ahrq.gov/research/findings/evidence-based-reports/search.html)

Kategorien	Suchbegriffe/ Filter (Zeitraum ab July 2017 bis 10.05.2023)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Ein-gabe von Suchbegriffen	0	0
Technology Assessment Program (completed)		0	0

10.2.2   Medline via Pubmed (www.pubmed.gov) (12. Juli 2023)

Nr.	Suchfrage	Anzahl
#27	**Search: (#21 AND #24) NOT (#25 OR #26)**	**748**
#26	**Search: (#21 AND #23) NOT #25**	**808**
#25	**Search: #21 AND #22**	**322**
#24	Search: cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective stud-ies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retro-spective[TIAB]	3,332,239
#23	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,550,402
#22	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative re-view [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw]	663,420

Nr.	Suchfrage	Anzahl
	OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	
#21	Search: #18 AND #19 Filters: from 2017/7/21 – 3000/12/12	3,231
#20	Search: #18 AND #19	10,522
#19	Search: Clopidogrel*[tw] OR Prasugrel*[tw] OR Ticagrelor*[tw]	18,641
#18	Search: #11 OR #17	461,529
#17	Search: #12 OR #13 OR #14 OR #15 OR #16	187,691
#16	Search: "Percutaneous Coronary Intervention"[Mesh]	64,853
#15	Search: bare-metal stent*[tiab] OR bare metal stent*[tiab] OR BMS[tiab]	11,095
#14	Search: drug-eluting stent*[tiab] OR drug eluting stent*[tiab] OR drug-coated stent*[tiab] OR drug coated stent*[tiab] OR DES[tiab]	39,495
#13	Search: PCI[tiab]	34,230
#12	Search: (percutaneous[tiab] OR coronary[tiab]) AND (intervention*[tiab] OR revascularization*[tiab])	119,174
#11	Search: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	347,769
#10	Search: "Coronary Thrombosis"[Mesh]	8,349
#9	Search: "Coronary Occlusion"[Mesh]	4,360
#8	Search: acute[tiab] AND coronary[tiab] AND syndrome*[tiab]	44,349
#7	Search: coronary[tiab] AND thrombosis*[tiab]	18,318
#6	Search: "Myocardial Infarction"[Mesh]	193,633
#5	Search: "Angina, Unstable"[Mesh]	11,324
#4	Search: "Acute Coronary Syndrome"[Mesh]	20,086
#3	Search: coronary[tiab] AND occlusion*[tiab]	28,768
#2	Search: myocardial infarct*[tiab] OR heart attack*[tiab] OR post-myocardial[tiab]	233,813
#1	Search: unstable[tiab] AND angina[tiab]	14,779

Hinweis: stufenweises Vorgehen: nach Einschluss der SR, ggf. zeitliche Begrenzung der RCT

10.2.3 Datenbanken der Cochrane Library (12. Juli 2023)

Nr.	Suchfrage	Anzahl
#21	**(#18 and #19) NOT (conference proceeding):pt in Trials; Year first published: from 2017**	**1419**
#20	**#18 and #19 in Cochrane Reviews, Cochrane Protocols; Publication date: from 2017/07/21**	**5**
#19	(Clopidogrel or Prasugrel or Ticagrelor):ti,ab,kw	7289
#18	#11 or #17	70743
#17	#12 or #13 or #14 or #15 or #16	43658
#16	MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees	8417
#15	(bare-metal stent* or bare metal stent* or BMS):ti,ab,kw	4241
#14	(drug-eluting stent* or drug eluting stent* or drug-coated stent* or drug coated stent* or DES):ti,ab,kw	8234
#13	(PCI):ti,ab,kw	10148
#12	((percutaneous or coronary) and (intervention* or revascularization*)):ti,ab,kw	33817
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	47208
#10	MeSH descriptor: [Coronary Thrombosis] explode all trees	565
#9	MeSH descriptor: [Coronary Occlusion] explode all trees	510
#8	(acute coronary syndrome*):ti,ab,kw	8865
#7	(coronary thrombosis*):ti,ab,kw	5062
#6	MeSH descriptor: [Myocardial Infarction] explode all trees	13934
#5	MeSH descriptor: [Angina, Unstable] explode all trees	1335
#4	MeSH descriptor: [Acute Coronary Syndrome] explode all trees	3286
#3	(coronary occlusion*):ti,ab,kw	3166
#2	(myocardial infarct* OR heart attack* OR post-myocardial):ti,ab,kw	38730
#1	(unstable angina):ti,ab,kw	4742

10.2.4 Epistemonikos (www.epistemonikos.org) (12. Juli 2023)

Nr.	Suchfrage	Anzahl
#1	(advanced_title_en:(((((percutaneous OR coronary) AND (intervention* OR revascularization*) OR PCI OR (drug-eluting stent* OR drug eluting stent* OR drug-coated stent* OR drug coated stent* OR DES) OR (bare-metal stent* OR bare metal stent* OR BMS) OR (acute AND coronary AND syndrome*) OR (coronary AND (thrombosis* OR occlusion*)) OR (unstable AND angina)) AND (Clopidogrel OR Prasugrel OR Ticagrelor)))) OR advanced_abstract_en:(((((percutaneous OR coronary) AND (intervention* OR revascularization*) OR PCI OR (drug-eluting stent* OR drug eluting stent* OR drug-coated stent* OR drug coated stent* OR DES) OR (bare-metal stent* OR bare metal stent* OR BMS) OR (acute AND coronary AND syndrome*) OR (coronary AND (thrombosis* OR occlusion*)) OR (unstable AND angina)) AND (Clopidogrel OR Prasugrel OR Ticagrelor))))) [Filters: classification=systematic-review, protocol=no, min_year=2017, max_year=2023]	248

10.2.5 Übersicht der eingeschlossenen Treffer

	strukturiert	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz		322	5	248	566
RCTs		808	1419		2214
Langzeitstudien		748			732
GESAMT		**1878**	**1424**	**248**	**3550**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 996

A2 (nicht englisch/deutsch): 30

A3 (Conference Abstracts): 2

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 2522 + n = 1 SR aus der strukturierten Recherche

Stufenweises Vorgehen

n = 369 Studienregistereinträge ausgeschlossen; n = 2154

- SR n = 360; RCT = 163; Langzeitbetrachtungen n = 731

- **e: SR: n = 360; RCT n = 332 (ab 2021, eingeschränktes Screening); Langzeitbetrachtungen n = 52 (in 2023, eingeschränktes Screening) → n = 744**

10.3 Flowchart
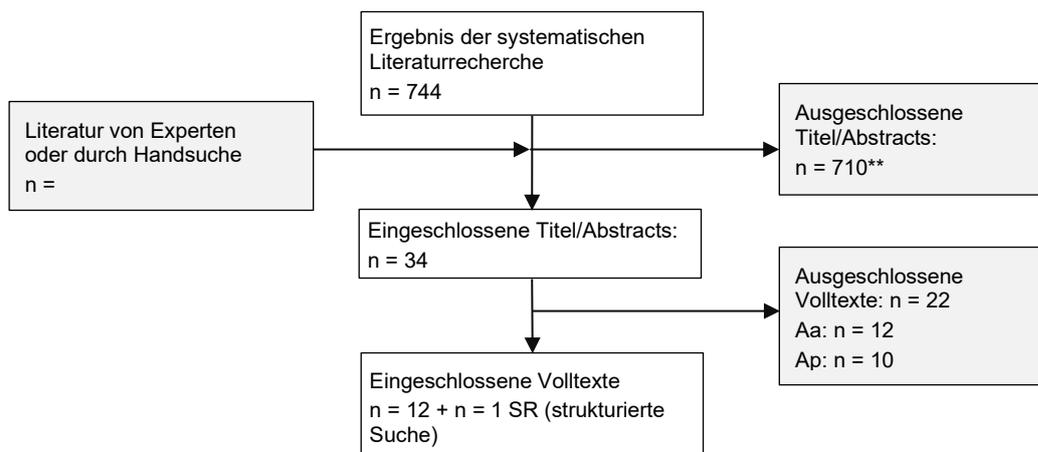
TiAb: SR n = 17*, RCT n = 15, Langzeitbetrachtungen n = 2

**Hinweis*: unter Ei (n = 86) zurückgestellt wurden SR, die interessant für die Wirksamkeit und Sicherheit im Vergleich der Wirkstoffe untereinander wären, allerdings auf Grund der Vielzahl der SR, NMA sowie Subgruppenanalysen (Mehrfachpublikation einzelner Studien) hier nicht betrachtet wurden; Auswahl s. Zusammenfassung

*aus der Recherche ergaben sich aktuelle systematische Übersichtsarbeiten zur Fragestellung, weshalb das RCT Screening eingeschränkt wurde auf den Zeitraum ab 2021; ergänzend wurden Langzeitbetrachtungen aus 2023 berücksichtigt

SR z. B.
Gelbenegger G. Optimal duration and combination of antiplatelet therapies following percutaneous coronary intervention: A meta-analysis. Vascul Pharmacol 2021; 138:106858. https://www.ncbi.nlm.nih.gov/pubmed/33753284.

11 Recherche zu Anhang 8.1.7 der 5. Auflage 2019 (S. 124ff) Z.n. elektiver PCI bei stabiler KHK: Elektive PCI und Indikation zur OAK (Empfehlung 7-6 und Empfehlung 7-7)

11.1 PICO-Frage

P   Patient*innen mit stabiler KHK, Z.n. elektiver PCI und Indikation zur OAK

I   Duale Therapie (OAK plus ein Thrombozytenaggregationshemmer)

C   Triple Therapie (OAK plus zwei Thrombozytenaggregationshemmer)

O   Gesamtmortalität, kardiovaskuläre Mortalität, Myokardinfarkt, unerwünschte Wirkungen (v.a. Blutungen)

Studientyp: RCT, Metaanalysen, systematische Reviews

Sprache: englisch, deutsch

11.2 Recherchestrategien

Strukturierte Suche nach aggregierter Evidenz (03.05.2018 – 10.05.2023)

Hinweis: bis Mai 2018 n = 1 Treffer nach SR (Auf die Extraktion und Bewertung der älteren Reviews wurde aus Gründen der Redundanz verzichtet.)

Systematische Suche nach aggregierter Evidenz und RCT (11.01.2018 – heute)

Hinweis: bis Januar 2023 n = 3 Treffer

11.2.1 Strukturierte Suche (Mai 2018 – 10.05.2023)

IQWIG (www.iqwig.de)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	05.2018 – 10.05.2023
Suchbegriff: Antikoagulantien, Antikoagulanzien, Antikoagulation, Acetylsalicylsäure, Thrombozytenaggregation	
Treffer	4
Eingeschlossene Treffer	0

NICE (www.nice.org.uk/guidance)

Nr.	Suchfrage
Suchbegriffe	dual therapy, triple therapy, anticoagulants, Apixaban, Dabigatran, Edoxaban, Rivaroxaban, acetylsalicylic acid
Suchzeitraum	from May 2018
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	7
Eingeschlossene Treffer	1
2. Filter	NICE advice
Treffer	1
Eingeschlossene Treffer	0

Nr.	Suchfrage
2. Filter	NICE quality standard
Treffer	0

Eingeschlossen:

- NICE-ER: Single Technology Appraisal Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397] Committee Papers. 17. Oktober 2019 https://www.nice.org.uk/guidance/ta607/evidence/committee-papers-pdf-6955673437

Interessante Zusatzinformation (nicht eingeschlossen):

- NICE Advice: DOAC Dipstick for detecting direct oral anticoagulants https://www.nice.org.uk/advice/mib248

- NICE Guidance: Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. 12. Mai 2021 https://www.nice.org.uk/guidance/ta697

Datenbanken der AHRQ (www.ahrq.gov/research/findings/evidence-based-reports/search.html)

Kategorien	Suchbegriffe/ Filter (Zeitraum ab Mai 2018 bis 10.05.2023)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	0	0
Technology Assessment Program (completed)		0	0

11.2.2 Medline via Pubmed (www.pubmed.gov) (10. Juli 2023)

Nr.	Suchfrage	Anzahl
#24	**Search: (#20 AND #22) NOT #23**	**104**
#23	**Search: #20 AND #21**	**78**
#22	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,547,553
#21	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab]	660,920

Nr.	Suchfrage	Anzahl
	OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	
#20	Search: #6 AND #12 AND #17 AND #18 Filters: from 2018/1/11 - 3000/12/12	451
#19	Search: #6 AND #12 AND #17 AND #18	837
#18	Search: Triple therapy[tiab] OR triple-therapy[tiab] OR double therapy[tiab] OR double-therapy[tiab] OR double antiplatelet therapy[tiab] OR dual therapy[tiab] OR dual-therapy[tiab] OR dual antiplatelet therapy[tiab]	15,189
#17	Search: #13 OR #14 OR #15 OR #16	167,583
#16	Search: "Anticoagulants"[Mesh]	96,269
#15	Search: Phenprocoumon[tiab] OR Warfarin[tiab] OR Dabigatran[tiab] OR Rivaroxaban[tiab] OR Apixaban[tiab] OR Edoxaban[tiab]	36,717
#14	Search: vitamin K antagonist*[tiab] OR non-vitamin K antagonist*[tiab] OR NOAC*[tiab] OR VKA[tiab]	10,015
#13	Search: anticoagulant*[tiab] OR anticoagulation[tiab]	114,959
#12	Search: #7 OR #8 OR #9 OR #10 OR #11	209,879
#11	Search: antiplatelet*[tiab]	39,073
#10	Search: antithrombotic*[tiab]	24,099
#9	Search: clopidogrel[tiab] OR ticagrelor[tiab] OR prasugrel[tiab]	16,543
#8	Search: aspirin*[tiab]	56,456
#7	Search: "Platelet Aggregation Inhibitors" [Pharmacological Action]	154,241
#6	Search: #1 OR #2 OR #3 OR #4 OR #5	187,309
#5	Search: "Percutaneous Coronary Intervention"[Mesh]	64,774
#4	Search: bare-metal stent*[tiab] OR bare metal stent*[tiab] OR BMS[tiab]	11,073
#3	Search: drug-eluting stent*[tiab] OR drug eluting stent*[tiab] OR drug-coated stent*[tiab] OR drug coated stent*[tiab] OR DES[tiab]	39,409
#2	Search: PCI[tiab]	34,141
#1	Search: (percutaneous[tiab] OR coronary[tiab]) AND (intervention*[tiab] OR revascularization*[tiab])	118,905

11.2.3   Datenbanken der Cochrane Library (10. Juli 2023)

Nr.	Suchfrage	Anzahl
#20	**#6 and #12 and #17 and #18 in Trials; Year first published: from 2018**	**160**
#19	**#6 and #12 and #17 and #18 in Cochrane Reviews, Cochrane Protocols**	**0**
#18	(Triple therapy or triple-therapy or double therapy or double-therapy or double antiplatelet therapy or dual therapy or dual-therapy or dual antiplatelet therapy):ti,ab,kw	223529
#17	#13 or #14 or #15 or #16	20338
#16	MeSH descriptor: [Anticoagulants] explode all trees	6152
#15	(Phenprocoumon or Warfarin or Dabigatran or Rivaroxaban or Apixaban or Edoxaban):ti,ab,kw	8350
#14	(vitamin K antagonist* or non-vitamin K antagonist* or NOAC* or VKA*):ti,ab,kw	1652

Nr.	Suchfrage	Anzahl
#13	(anticoagulant* or anticoagulation):ti,ab,kw	16440
#12	#7 or #8 or #9 or #10 or #11	25623
#11	(antiplatelet*):ti,ab,kw	7811
#10	(antithrombotic*):ti,ab,kw	3187
#9	(clopidogrel or ticagrelor or prasugrel):ti,ab,kw	7289
#8	(aspirin*):ti,ab,kw	15840
#7	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees	5106
#6	#1 or #2 or #3 or #4 or #5	43658
#5	MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees	8417
#4	(bare-metal stent* or bare metal stent* or BMS):ti,ab,kw	4241
#3	(drug-eluting stent* or drug eluting stent* or drug-coated stent* or drug coated stent* or DES):ti,ab,kw	8234
#2	(PCI):ti,ab,kw	10148
#1	(((percutaneous or coronary) and (intervention* or revascularization*))):ti,ab,kw	33817

11.2.4 Epistemonikos (www.epistemonikos.org) (10. Juli 2023)

Nr.	Suchfrage	Anzahl
#1	(title:((title:(percutaneous OR coronar) OR abstract:(percutaneous OR coronar))) OR abstract:((title:(percutaneous OR coronar) OR abstract:(percutaneous OR coronar)))) AND (title:((intervention* OR revascularization*) OR PCI OR (drug-eluting stent* OR drug eluting stent* OR drug-coated stent* OR drug coated stent* OR DES OR bare-metal stent* OR bare metal stent* OR BMS)) OR abstract:((intervention* OR revascularization*) OR PCI OR (drug-eluting stent* OR drug eluting stent* OR drug-coated stent* OR drug coated stent* OR DES OR bare-metal stent* OR bare metal stent* OR BMS))) AND (title:(aspirin* OR clopidogrel OR ticagrelor OR prasugrel OR antithrombotic* OR antiplatelet* OR anticoagulant* OR vitamin K antagonist* OR non-vitamin K antagonist* OR NOAC* OR VKA* OR Phenprocoumon OR Warfarin OR Dabigatran OR Rivaroxaban OR Apixaban OR Edoxaban) OR abstract:(aspirin* OR clopidogrel OR ticagrelor OR prasugrel OR antithrombotic* OR antiplatelet* OR anticoagulant* OR vitamin K antagonist* OR non-vitamin K antagonist* OR NOAC* OR VKA* OR Phenprocoumon OR Warfarin OR Dabigatran OR Rivaroxaban OR Apixaban OR Edoxaban)) AND (title:(Triple therapy OR triple-therapy OR double therapy OR double-therapy OR double antiplatelet therapy OR dual therapy OR dual-therapy OR dual antiplatelet therapy) OR abstract:(Triple therapy OR triple-therapy OR double therapy OR double-therapy OR double antiplatelet therapy OR dual therapy OR dual-therapy OR dual antiplatelet therapy)) **Publication type: Systematic review** **Publication year: 2018-2023**	15

11.2.5 Übersicht der eingeschlossenen Treffer

	strukturiert	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz		78	0	15	93
RCTs		104	160		264
GESAMT					**357**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 58

A2 (nicht englisch/deutsch): 5

A3 (Conference Abstracts):

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 294

11.3 Flowchart
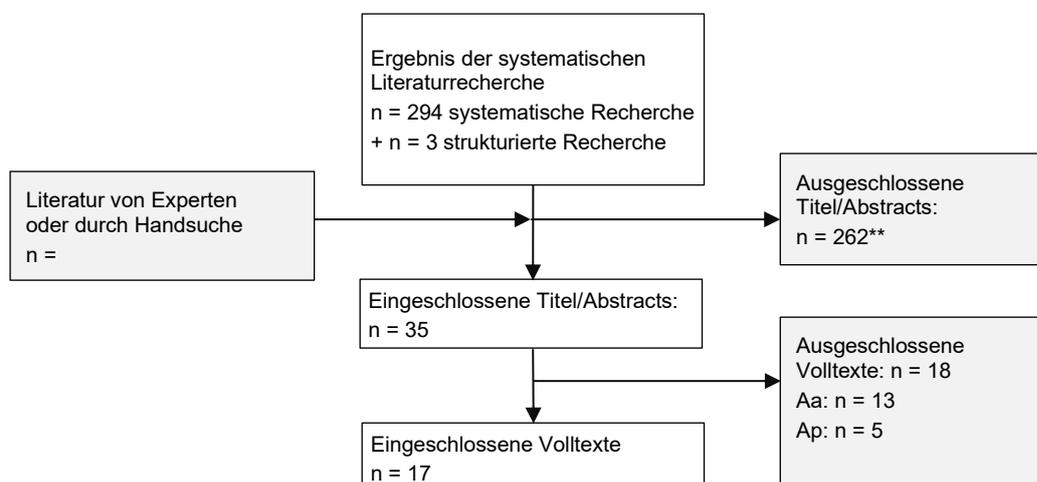
TiAb: n = 14 SR*, n = 19 RCT + n = 2 Sonstige (gesamt n = 35)

**Hinweis: unter Ei (n = 49) zurückgestellt wurden SR und RCT, die interessant für die Wirksamkeit und Sicherheit wären, insbesondere zu AF, allerdings auf Grund der Vielzahl der SR, NMA sowie Subgruppenanalysen (Mehrfachpublikation einzelner Studien) hier nicht betrachtet wurden; Auswahl s. Zusammenfassung

*u. a. n = 1 für die Frage Dauer Triple aus 2019

E7-7 Shah R. Short-term versus long-term triple antithrombotic therapy for patients with coronary stents and requiring oral anticoagulation: A meta-analysis of randomized clinical trials. Coron Artery Dis 2019; 30(2):116–23. https://www.ncbi.nlm.nih.gov/pubmed/30589646.

n = 2 für die Frage Dauer Dual aus 2023

E7-5 Costa F. Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding risk: A meta-analysis of randomized trials. Eur Heart J 2023; 44(11):954–68. https://www.ncbi.nlm.nih.gov/pubmed/36477292.

E7-6 Montalto C. Dual antiplatelet therapy duration after percutaneous coronary intervention in patients with indication to oral anticoagulant therapy. A systematic review and meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother 2023; 9(3):220–30. https://www.ncbi.nlm.nih.gov/pubmed/36427063.

12 Evidenztabellen

12.1 Kapitel Epidemiologie

Porst et al. 2022 Krankheitslast in Deutschland

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Porst M, Lippe Ev, Leddin J, et al. The Burden of Disease in Germany at the National and Regional Level- Results in Terms of Disability–Adjusted Life Years (DALY) from the BURDEN 2020 Study. Dtsch Arztebl Int 2022; 119(46):785-792. DOI: 10.3238/arztebl.m2022.0314. http://www.ncbi.nlm.nih.gov/pubmed/36350160. [1]	**Objective** Das Projekt BURDEN 2020 zielte darauf ab, auf Grundlage nationaler Daten eine eigenständige Krankheitslaststudie für Deutschland mit kleinräumigen Schätzungen als Pilotprojekt durchzuführen. **Methods** - Public Health Surveillance - Bewertung der Krankheitslast der Bevölkerung - Global-Burden-of-Disease(GBD)-Studie - Datenquellen: v. a. Todesursachenstatistik, Befragungsdaten und Krankenkassenroutinedaten (alters-, geschlechts- und zumeist morbiditätsadjustiert) - DALY (Summe aus „durch Sterblichkeit verlorene Lebensjahre" („years of life lost due to death" [YLL]) und „mit gesundheitlichen Einschränkungen oder in Krankheit verbrachte Lebensjahre" („years lived with disability" [YLD])	für Deutschland (2017) gesamt - 12,1 Millionen DALY (UI 11,9; 13,1) - Frauen 6,0 Millionen DALY (UI 5,9; 6,8) - Männer 6,1 Millionen DALY (UI 6,0; 6,6) - 14 584 DALY je 100 000 Einwohner (EW) - Frauen 14 303 DALY je 100 000 EW - Männer 14 872 DALY je 100 000 EW KHK (koronare Herzkrankheit) trug am meisten zur Krankheitslast bei - 2 321 DALY je 100 000 EW - Frauen 1 690 DALY je 100 000 EW - Männer 2 969 DALY je 100 000 EW - zu den Anteilen (YLD, YLL) vgl. Grafik 2 der Publikation (bei der KHK v. a. beeinflusst durch Todesfälle (YLL)): - Anteil der YLD (Morbidität) an der Krankheitslast - gesamt ~ 10 % - Frauen ~ 13 % - Männer ~ 7 % - Anteil der YLL (Mortalität) an der Krankheitslast - gesamt ~ 90 % - Frauen ~ 87 % - Männer ~ 93 % - mit dem Alter stieg die Krankheitslast für einen Teil der Erkrankungen, einschließlich der kardiovaskulären Erkrankungen - KHK – DALY je 100 000 EW im Altersverlauf - 25-29 Jahre: 43 - 30-34 Jahre: 92	n. a. Limitationen - Auswahl an Erkrankungen im Pilotprojekt - Vielzahl an Datengrundlagen (diese sollten eine hohe Validität und räumliche Auflösung aufweisen) – hier sind spezifische Limitationen zu beachten - Ausgleichsmechanismen: z. B. morbiditätsadjustiertes Hochrechnungsverfahren sowie Plausibilitätsprüfungen - eingeschränkte Altersgruppen, da Prävalenzschätzungen für Kinder und Jugendliche nicht möglich waren	Ergebnisse deuten auf alters- und geschlechtsspezifische Präventions- sowie kleinräumige Versorgungsbedarfe hin die Publikation enthält Grafiken z. B. zur räumlichen Verteilung der Krankheitslast in Deutschlad (gesamt und krankheitsspezifisch) – Grafik 3 S. 790 Ergebnisse des Projektes BURDEN 2020 gehen in ein Gesundheitsinformationssystem ein (www.daly.rki.de) die auf Krankenkassenroutinedaten basierenden epidemiologischen Kennzahlen, wie zum Beispiel Prävalenzen, nach Alter, Geschlecht und Region entstam-

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- YLL Abstand zwischen Todesalter und fernerer Lebenserwartung
	- YLD Jahre, die mit gesundheitlichen Einschränkungen verbracht werden
	
	Outcome
	- DALY „disability-adjusted life years" (DALY) (Summe der Krankheitslast aus Mortalität („years of life lost due to death" [YLL]) und Morbidität („years lived with disability" [YLD]) (95-%-Unsicherheitsintervalle [UI])
	- absolute Werte sowie rohe und altersstandardisierte Raten je 100 000 Einwohner (EW) im Jahr 2017 berichtet (europäische Standardbevölkerung 2013
		o 35-39 Jahre: 224
		o 40-44 Jahre: 485
		o 45-49 Jahre: 854
		o 50-54 Jahre: 1 350
		o 55-59 Jahre: 2 138
		o 60-64 Jahre: 3 092
		o 65-69 Jahre: 4 215
		o 70-74 Jahre: 5 406
		o 75-79 Jahre: 7 367
		o 80-84 Jahre: 11 162
		o 85-89 Jahre: 16 308
		o 90-94 Jahre: 21 215
		o 95+ Jahre: 24 962
		
		- teilweise zeigte die Krankheitslast unterschiedliche regionale Verteilungen (96 Raumordnungsregionen (kurz ROR)); vgl. Grafik 3 der Publikation
		  o für Deutschland gesamt (altersstandardisiert je 100 000 EW)
		    ▪ Regionen Emscher-Lippe (Nordrhein-Westfalen) und Bremerhaven mit der höchsten Krankheitslast im Bereich von 10 492 bis 11 460 DALY je 100 000 EW
		    ▪ Auch Sachsen-Anhalt und Teile von Thüringen und Mecklenburg-Vorpommern sowie das Saarland befinden sich in diesem Klassifikationsbereich
		  o KHK (altersstandardisiert je 100 000 EW)
		    ▪ im Osten Deutschlands höhere Krankheitslast
		    ▪ z. B. Sachsen-Anhalt im Bereich von 2 601 bis 2 977 DALY pro 100 000 EW (altersstandardisiert)
				men dem Wissenschaftlichen Instituts der AOK (WIdO) (www.krankheitslage-deutschland.de)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		▪ z. B. Mecklenburg Vorpommern im Bereich von 2 308 bis 2 601 DALY je 100 000 EW (altersstandardisiert)		

Robert Koch-Institut 2022 Ergebnisdatensatz BURDEN 2020

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Robert Koch-Institut (2022): Ergebnisdatensatz BURDEN 2020 – Krankheitslast in Deutschland und seinen Regionen, Berlin:Zenodo. DOI: 10.5281/zenodo.7323766 www.daly.rki.de/map [z. g. 29.09.2023] [2]	s. o. Porst et al. 2022 Krankheitslast in Deutschland	Krankheitslast KHK Regionaler Vergleich; [z. g. 29.09.2023] (Länder, DALY (je 100 000 EW), Level 3, Alle Geschlechter, Altersstandardisiert, gesamt, Koronare Herzkrankheit) - Baden-Württemberg 1 788 - Bayern 1 956 - Berlin 1 934 - Brandenburg 2 448 - Bremen 2 291 - Hamburg 1 704 - Hessen 2 001 - Mecklenburg-Vorpommern 2 509 - Niedersachsen 2 123 - Nordrhein-Westfalen 1 947 - Rheinland-Pfalz 2 164 - Saarland 2 410 - Sachsen 2 319 - Sachsen-Anhalt 2 900 - Schleswig-Holstein 2 136 - Thüringen 2 501		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		DALY – Karte Robert Koch-Institut (2022): Ergebnisdatensatz BURDEN 2020 – Krankheitslast in Deutschland und seinen Regionen, Berlin:Zenodo. DOI: 10.5281/zenodo.7323766 https://www.daly.rki.de/map [z. g. 29.09.2023]		
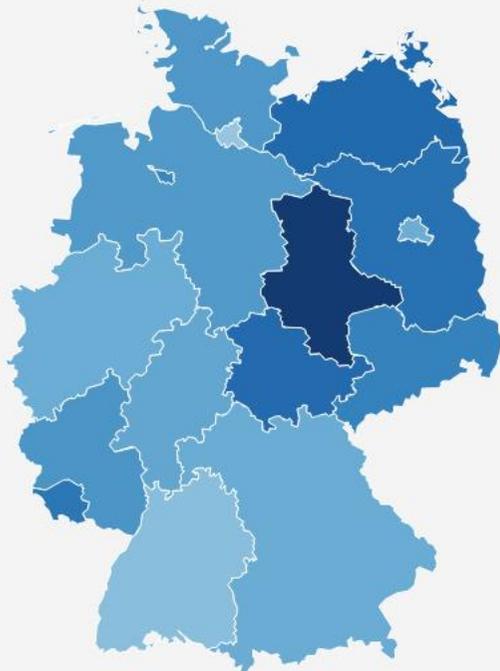
Robert Koch-Institut 2021 Ergebnisse GEDA 2019/2020-EHIS

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Robert Koch-Institut (RKI). Gesundheitliche Lage der erwachsenen Bevölkerung in Deutschland – Ergebnisse der Studie GEDA 2019/2020-EHIS. J Health Monit 2021; 6(3). [3]	**Ziel**
	- Darstellung der gesundheitlichen Lage in Deutschland
	- Ableitung der Public-health Relevanz sowie des Einflusses auf den Versorgungsbedarf
	
	Methodik
	- bundesweite Befragungsstudie Gesundheit in Deutschland (GEDA 2019/2020-EHIS)
	- April 2019 und September 2020
	- ausgewählte Indikatoren
	- Erwachsene Bevölkerung ab 18 Jahre (n = 22 708)
	- ab dem mittleren Erwachsenenalter (ab 45 Jahre) schrittweiser Prävalenzanstieg chronischer Erkrankungen
	
	Ereignisse (u.a.)
	- Betehen einer KHK (d. h. eines Herzinfarktes, chronischer Beschwerden infolge eines Herzinfarktes, einer koronaren Herzerkrankung oder einer Angina pectoris)
		Kardiometabolische Erkrankungen
		- Bestehen einer KHK: 5,8% (95% KI 5,4; 6,3%) in den letzten 12 Monaten
		  o Frauen 5,1% (95% KI 4,5; 5,7)
		  o Männer 6,6% (95% KI 5,9; 7,4)
		- Frauen
		- Altersgruppe (in % (95% KI))
		  o 18 – 29 Jahre 0,8 (0,5 – 1,4)
		  o 30 – 44 Jahre -
		  o 45 – 64 Jahre 3,6 (2,7 – 4,6)
		  o 65 – 79 Jahre 9,2 (7,8 – 10,9))
		  o ≥ 80 Jahre 18,9 (15,3 – 23,1)
		- Bildungsstatus (in % (95% KI))
		  o Untere Bildungsgruppe 9,8 (7,7 – 12,4)
		  o Mittlere Bildungsgruppe 4,3 (3,7 – 5,0)
		  o Obere Bildungsgruppe 2,3 (1,9 – 2,8)
		- Männer
		- Altersgruppe (in % (95% KI))
		  o 18 – 29 Jahre 0,4 (0,2 – 0,8)
		  o 30 – 44 Jahre -
		  o 45 – 64 Jahre 6,4 (5,2 – 7,7)
		  o 65 – 79 Jahre 16,5 (14,2 – 19,1))
		  o ≥ 80 Jahre 21,9 (17,7 – 26,8)
		- Bildungsstatus (in % (95% KI))
		  o Untere Bildungsgruppe 6,5 (4,3 – 9,6)
		  o Mittlere Bildungsgruppe 7,1 (6,1 – 8,2)
		  o Obere Bildungsgruppe 5,8 (5,2 – 6,5)
			n. a.	

RKI Gesundheit in Deutschland 2015 (Todesursachenstatistik)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Robert Koch-Institut, editor. Gesundheit in Deutschland. Gesundheitsberichterstattung des Bundes. Ge-meinsam getragen von RKI und Destatis. Berlin: RKI; 2015. www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GesInDtld/gesundheit_in_deutschland_2015.pdf [4]	**Ziel** Bericht soll die evidenzbasierte Entscheidungen für mehr Gesundheit in Deutschland unterstützen **Hintergrund** elf Kapitel, die einen Überblick über den Stand und die Entwicklung der Gesundheit der Menschen in Deutschland im Jahr 2015 geben breite Datenbasis zum Erkrankungsspektrum, der Verteilung von Risikofaktoren, die Inanspruchnahme von Prävention und Gesundheitsversorgung größter Einfluss durch die demografischen Veränderungen sozialen Lage Qualitätssicherung der Kapitel (u. a. durch die Kommission »Gesundheitsberichterstattung und Gesundheitsmonitoring« (GBEMON)) **Quellen/Datengrundlage** aus u. a. regelmäßigen großen bevölkerungsbezogene Gesundheitserhebungen werden bevölkerungsrepräsentative Querschnittsanalysen zu einem breiten Themenspektrum ermöglicht; darüber hinaus Trendauswertungen und längsschnittliche Analysen KiGGS (»Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland«, Basiserhebung und Welle 1),	2.1.3 Todesursachenstatistik (S. 24ff) Altersstruktur der Verstorbenen und Todesursachen (nach ICD-10) in 2013 84,4% der Gestorbenen ≥ 65 Jahre alt 64,9% der gestorbenen Frauen und 39,9% der gestorbenen Männer waren ≥ 85 Jahre alt 0,3% der Verstorbenen waren jünger als 1 Jahr (n = 982 Mädchen, n = 1.268 Jungen) Frauen vs. Männer: häufiger an Herz-Kreislauf-Erkrankungen (43,3 % bzw. 35,7 %), seltener an bösartigen Neubildungen (25,8 % bzw. 29,1 %) sowie an Verletzungen oder Vergiftungen (3,0 % bzw. 4,8 %) bei Krankheiten von Atmungs- oder Verdauungssystem ist die Differenz gering Veränderung im Stellenwert verschiedener Todesursachen im gesamten Sterbegeschehen (altersstandardisierte Sterberaten), Referenzpopulation = Bevölkerung der Bundesrepublik Deutschland im Jahr 1987 zwischen 1993 und 2013 hat sich die altersstandardisierte Sterberate für Herz- und Kreislauf-Erkrankungen (ICD-10: I00 – I99) nahezu halbiert bei Frauen von 561 auf 298 und bei Männern von 456 auf 228 je 100.000 Einwohner es sank der Anteil der Herz- und Kreislauf-Erkrankungen an den Todesursachen von 53,4 % auf 43,3 % bei Frauen und von 44,2 % auf 35,7 % bei Männern steigende Sterberaten gab es bei einigen selteneren Todesursachen wie Psychischen Störungen und Verhaltensstörungen (ICD-10: F00 – F99), bedingt v.a . durch die häufigere Angabe von Demenz als Todesursache, Infektiösen und parasitären Krankheiten (ICD-10: A00 – B99) sowie Krankheiten des Urogenitalsystems (ICD-10: N00 – N99) (< 28 Verstorbene je 100.000 Einwohner)	n. a.	elektronische Informationssystem der GBE: www.gbe-bund.de dritter bundesweiter Gesundheitsbericht für Deutschland (Vorversionen aus 1998 und 2006); der Bericht aus 2015 wurde nicht mehr aktualisiert in der Online-Version gibt es Verknüpfungen zu den jeweils aktuellen Daten des Statistischen Bundesamtes und anderer Datenhalter (Deep Links); Feedback zum Bericht kann gegeben warden unter: gbe@rki.de gesundheitliche Entwicklung über 20 Jahre sowie Weiterentwicklung in der Gesundheitsberichterstattung abgebildet (lernfähiger Entwicklungsprozess; flexibel und offen für Veränderungen)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	DEGS1 (»Studie zur Gesundheit Erwachsener in Deutschland«) und GEDA (»Gesundheit in Deutschland aktuell« 2009, 2010, 2012), auch europaweit durchgeführte European Health Interview Survey integriert (GEDA 2014/2015-EHIS) weitere Gesundheitssurveys und epidemiologische Studien, Daten von Krankheitsregistern (zum Beispiel Krebs-, Herzinfarktund Schlaganfallregister), Routinedaten der Sozialversicherungsträger (etwa der gesetzlichen Krankenkassen und der Deutschen Rentenversicherung Bund), amtliche Statistiken (wie die Todesursachenstatistik oder die Krankenhausdiagnosestatistik) und sozialwissenschaftliche Erhebungen (darunter das Sozio-oekonomische Panel) auch das vom Statistischen Bundesamt koordinierte elektronische Informationssystem der GBE (www.gbe-bund.de) gehört zur GBE; für bestimmte Fragestellungen hat das Statistische Bundesamt Sonderauswertungen erstellt *Hinweis*: in der amtliche Bevölkerungsstatistik (z. B. Erkrankungs- oder Sterberaten) gab es einen Wechsel in der Datengrundlage: Ab 2011 erfolgt die Bevölkerungsfortschreibung auf Basis von aktuellen	39,7% der Sterbefälle Krankheiten des Kreislaufsystems (ICD-10: I00-I99) 25,0% Krebserkrankungen (ICD-10: C00-C97) 7,3 % Krankheiten des Atmungssystems (ICD-10: J00 – J99) 4,5 % Krankheiten des Verdauungssystems (ICD-10: K00 – K93) 3,8% Verletzungen und Vergiftungen (ICD-10: S00 – T98) übrigen 19,7 % andere Krankheiten 10 häufigste Diagnosen unter den Todesursachen (2013, nach Statistisches Bundesamt (2014) Todesursachenstatistik ab 1998. Sterbefälle, Sterbeziffern (je 100.000 Einwohner, altersstandardisiert) www.gbe-bund.de (Stand: 15.04.2015)) Frauen, Anteil in % Ischämische Herzkrankheiten (I20-I25) 13,3% Zerebrovaskuläre Krankheiten (I60-I69) 7,6% Herzinsuffizienz (I50) 6,5% Alzheimer-Krankheit und andere Demenz (F01, F03, G30) 5,2% Hypertensive Herzkrankheit / Herz- und Nierenkrankheit (I11, I13) 4,6% Brustkrebs (C50) 3,8% Lungenkrebs (C33-C34) 3,3% Chronische Krankheiten der unteren Atemwege (J40-J47) 3,2% Diabetes mellitus (E10-E14) 3,0% Darmkrebs (C18-C21) 2,6% Summe 53% Männer Ischämischen Herzkrankheiten (I20-I25) 15,6% Lungenkrebs (C33-C34) 6,9% Zerebrovaskuläre Krankheiten (I60-I69) 5,4% Chronische Krankheiten der unteren Atemwege (J40-J47) 4,2% Herzinsuffizienz (I50) 3,7% Darmkrebs (C18-C21) 3,2% Prostatakrebs (C61) 3,1% Unfälle (V01-X59) 2,6%		im Gesundheitsbericht aus 2015 ist die soziale Differenzierung sowohl auf individueller als auch auf regionaler Ebene ein durchgehender Aspekt, die Unterscheidung zwischen alten und neuen Ländern kommt kaum noch vor es erfolgt ein Hinweis darauf, dass die Zuwanderung zukünftig Einfluss auf die Altersstrukturen haben kann (Zuwanderung von Menschen unter 40 Jahren und Kindern) neben dme Anstieg der Lebenserwartung in den vergangenen 20 Jahren auch ein allgemeiner Rückgang der todesursachenspezifischen Sterberaten vieler bedeutender Krankheiten

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	Zensusdaten, deshalb ist die Vergleichbarkeit zu den Vorjahren eingeschränkt)	Alzheimer-Krankheit und andere Demenz (F01, F03, G30) 2,5% Diabetes mellitus (E10-E14) 2,4% Summe 49,6%		
	Definition (wichtige Indikatoren): **Prävalenz:** Krankheitsverbreitung, Anteil der Personen in einer Bevölkerung, die beispielsweise an einem Stichtag (Punktprävalenz), innerhalb eines Jahres (12-Monats-Prävalenz) oder im Verlauf ihres bisherigen Lebens (Lebenszeitprävalenz) unter einer bestimmten Krankheit leiden **Inzidenz:** Häufigkeit von Neuerkrankungen in einem bestimmten Zeitraum (z. B. ein Jahr), Anzahl der Neuerkrankungen oder als Anzahl der Neuerkrankungen pro 100.000 Personen (Neuerkrankungsrate) **Mortalität:** Sterblichkeit in einem bestimmten Zeitraum (z. B. ein Jahr), Anzahl der Sterbefälle oder als Anzahl der Sterbefälle pro 100.000 Personen (Sterberate) (Gesamtsterblichkeit oder krankehitsbezogen; meist altersstandardisiert) **Altersstandardisierte Raten:** Altersstandardisierung wird verwendet, um Erkrankungs- und Sterbehäufigkeiten von Bevölkerungsgruppen mit unterschiedlicher	Einflussfaktoren (vorzeitige Sterblichkeit) Bezug auf Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) für die Jahre 1990 und 2010: Ernährung, Übergewicht, Bluthochdruck Rauchen 2.3 Herz-Kreislauf-Erkrankungen (ICD-10: I00-I99) (S. 38ff) die häufigste Todesursache bei Frauen und Männern in Deutschland höchsten Kosten: 2008 wurden 14,5 % der direkten Krankheitskosten (rund 37 Milliarden Euro) verursacht durch Herz-Kreislauf-Erkrankungen größte Rolle spielen dabei die koronare Herzkrankheit (KHK) und der Schlaganfall insgesamt stetiger Rückgang der Sterberaten für Herz-Kreislauf-Erkrankungen (Fortschritt in Prävention und Therapie) als Risikofaktoren für Herz-Kreislauf-Erkrankungen angegeben: Rauchen, Adipositas, Bewegungsarmut, Fettstoffwechselstörungen, Bluthochdruck und Diabetes **Prävalenz (GEDA, 2009-2010):** KORONARE HERZKRANKHEIT (ICD-10: I20 – I25) UND AKUTER HERZINFARKT (ICD-10: I21 – I22) Durchblutungsstörung am Herzen oder ein Herzinfarkt (durch Arzt diagnostiziert) bei 6,6 % der Frauen und 9,6 % der Männer		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	Altersstruktur zu vergleichen; auch bei Zeitvergleichen (auf eine Standardbevölkerung mit einer festgelegten Altersverteilung übertragen; hier überwiegend die sogenannte »alte Europastandard-bevölkerung«, so lässt sich bspw. die Entwicklung von Erkrankungen und Todesursachen im Zeitverlauf beurteilen, ohne dass demografi-sche Veränderungen wie ein zu-nehmender Anteil älterer Menschen das Geschehen überlagern) **Sterblichkeit** Sterblichkeitsverhältnisse werden in Sterbetafeln abgebildet; basieren auf dem nach Alter und Geschlecht differenzierten Verhältnis zwischen den registrierten Sterbefällen und dem Bevölkerungsstand (ermittelt durch das Statistische Bundesamt auf Ba-sis von Volkszählungen) **Todesursachen** Todesursachenstatistik gibt Auf-schluss über die wichtigsten Todes-ursachen und ihre zeitliche Ent-wicklung; Daten stamen aus der Auswertung der ärztlichen Todes-bescheinigungen; auf Basis der Be-stattungsgesetze der Länder für alle Verstorbenen sowie für Totge-borene ab einem Geburtsgewicht von 500 g ausgestellt	Ende 2010 2.481.000 Frauen und 3.349.000 Männer an ei-ner koronaren Herzkrankheit erkrankt **Sterblichkeit** koronare Herzkrankheit (KHK) bei Frauen und Männern die häufigste Todesursache in 2013 starben in Deutschland laut amtlicher Todesursa-chenstatistik insgesamt 61.633 Frauen und 67.175 Männer an einer KHK entspricht 13,3 % aller Todesfälle bei Frauen und 15,6 % aller Todesfälle bei Männern davon verstarben 23.916 Frauen und 30.622 Männer (5,2 % bzw. 7,1 % aller Todesfälle) an einem Herzinfarkt im Zeitraum von 1998 bis 2013 zeigt sich ein kontinuierli-cher Rückgang der altersstandardisierten Sterberaten auf-grund einer KHK – wie auch in anderen hochentwickelten Ländern Westeuropas, in Australien und in den USA in Deutschland sank die Sterberate durch KHK insgesamt zwischen 1998 und 2013 bei Frauen von 102,5 auf 51,4 und bei Männern von 197,2 auf 105,0 je 100.000 Einwoh-ner (Sterberaten standardisiert auf die alte Europastandardbevölkerung) regionale Unterschiede begründend für die geringere Sterblichkeit angegeben wer-den u. a. "kombinierte Effekte von verändertem Gesundheitsverhal-ten und zunehmend leitliniengerechter Behandlung" Veränderungen in der Therapie: "Langzeitbehandlung von Personen mit kardiovaskulären Risikofaktoren oder bereits bestehenden arterioskleroti-schen Gefäßerkrankungen wird zunehmend an das indivi-duelle Risiko für das Auftreten eines Herzinfarktes oder Schlaganfalls angepasst" "In der Akutbehandlung von Herzinfarkt und Schlaganfall werden invasive und medikamentöse Maßnahmen zur Wiederherstellung der Durchblutung des Herzens bezie-hungsweise des Gehirns mit messbaren Erfolgen einge-setzt."		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		"Eine zeitgemäße Akutversorgung geschieht heute in spezialisierten Einheiten" *Hinweis:* zitiert werden hier v. a. die Leitlinien der ESC		

Wissenschaftlichen Instituts der AOK (WIdO). Krankheitslage-Deutschland.de

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Wissenschaftlichen Instituts der AOK (WIdO). Krankheitslage-Deutschland.de
www.krankheitslage-deutschland.de
[z. g. 29.09.2023]
[5]
 	
(Überblicksartikel:
Breitkreuz et al. Krankheitslastbestimmung mit Prävalenzen und Schweregraden auf Routinedatenbasis. GGW 2021. Jg. 21, Heft 1 (Januar), 24–34
	Objective
	Transparenz zur gesundheitlichen Beeinträchtigung bei ausgewählten Krankheiten unter allen Einwohnern in den Regionen Deutschlands
	- Ermittlung der gesundheitlichen Beeinträchtigung der Bevölkerung im Rahmen einer Krankheitslastberechnung
	
	Methods
	- Wissenschaftliche Institut der AOK (WIdO)
	- Robert Koch-Institut
	- Umweltbundesamt
	- Forschungsprojekt BURDEN 2020
	- „Global Burden of Disease" (GBD)-Studie
	- Todesursachenstatistik, Befragungsdaten, Umweltdaten, Routinedaten
	- etabliertes methodisches Instrumentarium aus drei Säulen:
	   o Abrechnungsdaten der > 27 Millionen AOK-Versicherten
	   o Prävalenzkonzepts, das die
		1-Jahresprävalenz (Berichtsjahr 2017)
		Anzahl bundesweit (Deutschland):
		4,91 Mio aus 82,7 Mio Menschen absolut (5,94%)
		- Baden-Württemberg (BW) 528 Tsd. (Prävalenz 4,80%)
		- Bayern (BY) 661 Tsd. (Prävalenz 5,10%)
		- Berlin (BE) 183 Tsd. (Prävalenz 5,09%)
		- Brandenburg (BR) 200 Tsd. (Prävalenz 7,98%)
		- Bremen (HB) 35,3 Tsd. (Prävalenz 5,19%)
		- Hamburg (HH) 83,4 Tsd. (4,58%)
		- Hessen (HE) 330 Tsd. (5,30%)
		- Mecklenburg-Vorpommern (MV) 126 Tsd. (Prävalenz 7,81%)
		- Niedersachsen (NI) 454 Tsd. (Prävalenz 5,71%)
		- Nordrhein-Westfalen (NW) 1,11 Mio (Prävalenz 6,22%)
		- Rheinland-Pfalz (RP) 246 Tsd. (Prävalenz 6,05%)
		- Saarland (SL) 71,8 Tsd. (Prävalenz 7,21%)
		- Sachsen (SN) 204 Tsd. (Prävalenz 7,45%)
		- Sachsen-Anhalt (ST) 226 Tsd. (Prävalenz 10,2%)
		- Schleswig-Holstein (SH) 166 Tsd. (Prävalenz 5,75%)
		- Thüringen (TH) 183 Tsd. (Prävalenz 8,47%)
		
		Anzahl bundesweit (Deutschland)
		Frauen 2,10 Mio aus 41,9 Mio gesamt (5,01%)
		Männer 2,81 Mio aus 40,8 Mio gesamt (6,90%)
		
		nach Alter
		- 20-44 Jahre 70,5 Tsd. (Prävalenz 0,281%)
		   o Frauen 25,8 Tsd. (Prävalenz 0,21%)
		   o Männer 44,7 Tsd. (Prävalenz 0,35%)
			n. a.	Methodendokument online verfügbar:
				https://krankheitslage-deutschland.de/dokumente/Methodendokumentation.pdf

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	Herausforderung beim Umgang mit einer dynamischen, offenen Kohorte berücksichtigt
	
	    o alters-, geschlechts- und morbiditätsadjustierendes Hochrechnungsverfahren, das Aussagen über alle Einwohner in den Regionen Deutschlands erlaubt
	- Berichtsjahr 2017
	- Schweregrade bzw. Folgezustände sind als BURDEN 2020-spezifische Schweregrade im Sinne der Krankheitslastberechnung und nicht als klinische Schweregrade
	- da einige BURDEN-Schweregrad-Zustände selten vorliegen, wird ausschließlich eine bundesweite Hochrechnung nach Alter und Geschlecht – ohne Anwendung des morbiditätsadjustierenden Verfahrens und ohne regionale Differenzierung - umgesetzt
	
	Outcomes
		- 45-59 Jahre 608 Tsd. (Prävalenz 3,13%)
		  o Frauen 185 Tsd. (Prävalenz 1,92%)
		  o Männer 422 Tsd. (Prävalenz 4,33%)
		- 60-69 Jahre 993 Tsd. (Prävalenz 9,96%)
		  o Frauen 343 Tsd. (Prävalenz 6,67%)
		  o Männer 649 Tsd. (Prävalenz 13,5%)
		- 70-74 Jahre 625 Tsd. (Prävalenz 17,2%)
		  o Frauen 238 Tsd. (Prävalenz 12,3%)
		  o Männer 387 Tsd. (22,8%)
		- 75-79 Jahre 994 Tsd. (Prävalenz 23,2%)
		  o Frauen 423 Tsd. (Prävalenz 17,7%)
		  o Männer 571 Tsd. (Prävalenz 30,0%)
		- 80-84 Jahre 849 Tsd. (Prävalenz 30,4%)
		  o Frauen 415 Tsd. (Prävalenz 25,2%)
		  o Männer 433 Tsd. (Prävalenz 37,9%)
		- 85+ Jahre 773 Tsd. (Prävalenz 35,2%)
		  o Frauen 467 Tsd. (Prävalenz 30,1%)
		  o Männer 306 Tsd. (Prävalenz 43,2%)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- Berechnung der Krankheitsprävalenzen zur Bestimmung der Krankheitslage in Deutschland			

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Zentralinstitut für die kassenärztliche Versorgung (Zi) – Versorgungsatlas – Dashboard – Koronare Herzkrankheit (2021)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Zentralinstitut für die kassenärztliche Versorgung in der Bundesrepublik Deutschland (Zi). Versorgungsatlas – Dashboard häufige chronische Krankheiten www.versorgungsatlas.de/dashboard/#/evaluation/1005 [z. g. 29.09.2023] [6]	Hintergrundinformation: www.versorgungsatlas.de//filead-min/pdf/Dashboard/Versorgungsat-las-Dashboard_ID-1005_KHK1.pdf **Quelle** - Dashboard - basierend auf bundeswei-ten pseudonymisierten, krankenkassenübergrei-fenden vertragsärztlichen Abrechnungsdaten gemäß § 295 SGB V - 2015-2021 - Grundlage ärztlicher Diag-nosecode (ICD-10-GM) - Prävalente Fälle (mind. 2 Quartale im Beobach-tungsjahr mit Zusatzkenn-zeichen („gesichert"): o für KHK: I20. , I21. , I22. , I23. , I24. , I25 - rohe und alters- bzw. ge-schlechsstandardisiert	Berichtszeitraum 2021 4 321,618 absolut standardisierte Diagnoseprävalen (Koronare Herzkrankheit) 5,72 % - Frauen: 3,87 % - Männer: 8,20 % - Verhältnis Männer : Frauen (2021): 1,52 - Veränderung seit 20215: -105 316 (-2,4 %)	n. a.	weitere Details s. a. Holstiege J, Akmatov MK, Steffen A, Bätzing J. Die ischämische Herzerkrankung in der vertragsärztlichen Ver-sorgung – Zeitliche Trends und regionale Variationen. Zentra-linstitut für die kassen-ärztliche Versorgung in Deutsch land (Zi). Versorgungs-atlas Bericht Nr. 20/04. Berlin 2020. URL: https://doi.org/10.20364/VA 20.04

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

		Diagnoseprävalenz (%) pro KV-Bereich, Kassenärztliche Vereinigung (2021)
		
		Roh **Standardisiert**
		
		0 — Diagnoseprävalenz (%) — 8
		
		Diagnoseprävalenz nach Alters- und Geschlechtsgruppen (2021)
		- 0-14 Jahre
		   o Frauen 0,00%
		   o Männer 0,00%		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

		- 15-19 Jahr
		    o Frauen 0,01%
		    o Männer 0,01%
		- 20-29 Jahre
		    o Frauen 0,03%
		    o Männer 0,04%
		- 30-39 Jahre
		    o Frauen 0,11%
		    o Männer 0,22%
		- 40-49 Jahre
		    o Frauen 0,52%
		    o Männer 1,45%
		- 50-59 Jahre
		    o Frauen 1,97%
		    o Männer 6,01%
		- 60-69 Jahre
		    o Frauen 5,73%
		    o Männer 15,05%
		- 70-79 Jahre
		    o Frauen 12,74%
		    o Männer 26,60%
		- 80-89 Jahre
		    o Frauen 21,93%
		    o Männer 37,70%
		- ≥90 Jahre
		    o Frauen 27,62%
		    o Männer 42,77%
		
		Diagnoseprävalenz nach KV-Bereich (2021)
		Baden-Württemberg 4,86%
		Hamburg 5,20%
		Bayern 5,21%
		Bremen 5,25%
		Hessen 5,46%
		Niedersachsen 5,47%
		Westfalen-Lippe 5,70%
		Sachsen 5,71%
		Berlin 5,79%
		Rheinland-Pfalz 5,84%		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Schleswig-Holstein 5,86% Nordrhein 6,18% Brandenburg 6,54% Mecklenburg-Vorpommern 6,67% Thüringen 6,68% Saarland 6,69% Sachsen-Anhalt 8,00%		

12.2 Kapitel Diagnostik

Risikoeinschätzung

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
33523	Evidenzbericht 2023 zur: S3-Leitlinie Brustschmerz - DEGAM-Leitlinie für die primärärztliche Versorgung, in Überarbeitung, geplante Fertigstellung: 30.09.2023: https://register.awmf.org/de/leitlinien/detail/053-023#anmeldung [7,8]	2023	**Fragestellung** unterschiedliche Fragestellungen aktualisiert bzw. untersucht, von besonderer Relevanz K1: Welche diagnostische Aussagekraft haben klinische Vorhersageregeln (gegebenenfalls einzelne Symptome, Zeichen und Risikofaktoren) hinsichtlich der Diagnose einer Koronaren Herzkrankheit (KHK) bei Patienten mit Brustschmerz in der Primärversorgung? **Studientyp** Leitlinie bzw. Evidenzberichte zur Leitlinie, in der Aktualisierung, Update der Evidenz u. a. zum Marburger Herz-Score (Evidenzberichte vgl. Anhang zur LL bzw. zum LL-Report) systematische Recherche in Medline, Embase März 2008 bzw. Juni 2009 sowie Literaturlistensuche; Update nach	**Fragestellung K1:** ursprügliche Recherche bereits veröffentlicht (n = 4 Arbeiten eingeschlossen für den hausärztlichen Versorgungsbereich) n = 3 SR neu berücksichtigt - identifizierten klinische Vorhersageregeln - INTERCHEST Rule, - Sox Rule; - Gencer Rule, - Marburg Heart Score, - aus den letzten drei war die diagnostische Aussagekraft für die hausärztliche Versorgungsebene evaluiert worden, n = 3 SR (vgl. a. S. 42ff) aus diesen SR gingen n = 6 Primärstudien hervor; ergänzend ermittelt wurde eine weitere Publikation (gesamt: n =	AMSTAR 2 moderate y-py-y-y-y-n-py-y-y-n-y-y-y (basierend u. a. auf der Vorversion, vorbehaltlich der Veröffentlichung)	E	basierend auf einem Evidenzbericht der S3-Leitlinie Brustschmerz - DEGAM-Leitlinie für die primärärztliche Versorgung, in Überarbeitung, geplante Fertigstellung: 30.09.2023: https://register.awmf.org/de/leitlinien/detail/053-023#anmeldung insbesondere für für die NVL Empfehlungen 4-2 und 4-3 der Version 6.0 der NVL Chronische KHK relevante Evidenzaktualisierung; (vgl. Fragestellung K1 im Evidenzbericht zudem Ergebnisse zur Fragestellung im Kapitel 4.2.1 (Seite 41ff)); es ergeben sich keine inhaltlichen

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
			SR und Primärstudien (01.10.2008 - 01.10.2021) **Qualitätsbewertung** Graduierung mittels SIGN-Schema (modifizierte Version); Bewertung der internen und externen Validität (Verzerrungsrisiko und Übertragbarkeit); QUADAS 2 für diagnostische Studien, AMSTAR für systematische Übersichtsarbeiten **Ein- und Ausschlusskriterien** Für die erste Version der Leitlinie Studien eingeschlossen, die - die diagnostische Aussagekraft von klinischen Vorhersageregeln bzw. von einzelnen Zeichen und Symptomen - bei Patient*innen mit Brustschmerz - für die Diagnose einer KHK bzw. eines ACS - in verschiedenen Versorgungsebenen untersucht hatten Für das Update der Recherche wurden Studien eingeschlossen, die - die diagnostische Aussagekraft von klinischen Vorhersageregeln (Zeichen, Symptome, keine Laborbefunde) bzw. von einzelnen Zeichen und Symptomen - bei Patient*innen mit Brustschmerz - für die Diagnose einer KHK bzw. eines ACS untersuchten. In **Suche 1 (**Aggregierte Evidenz) zusätzlich (gezielte Suche): - Studientyp: Meta-Analyse/ systematisches Review	7), Tabelle 15, erster Teil im Bericht (S. 60ff) *Hinweis:* eine der neu eingeschlossenen SR (Quelle 25 Harskamp et al BMJ open 2019) berichtete den aktuellesten Suchzeitraum, die breiteste Suche sowie Angaben zur diagnostischen Güte der Vorhersageregeln); Bewertung gute Übertragbarkeit; SIGN 2++ **Ergebnisse:** Marburg Heart Score, n = 1 SR (Quelle 25) sensitivity (86%–91%) specificity (61%–81%) positive predictive value (PPV) (23%–35%) negative predictive value (NPV) (97%–98%) AUC 0.90 (95% CI 0.87–0.93), n = 1 Studie (n = 672 Patient*innen) sowie AUC 0.84 (95% CI = 0.80 - 0.88), n = 1 weitere Studie (n = 844 Patient*innen) zur Validierung), deutscher Versorgungskontext - der Marburger Herz-Score n = 2 externe Validierungsstudien guter methodischer Qualität - Marburg Heart Score more sensitive in detecting coronary disease than the clinical judgement of the general practitioner; n = 1 SR - recommended for rule out of CAD in low-risk general practice populations with intermittent-type chest pain (level of evidence of 2 ; definitions of the			Änderungen/Einflüsse auf die Empfehlungen; allerdings sollte die Evidenz im Hintergrundtext aktualisiert werden

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Risikoeinschätzung							

			- Versorgungsebene: keine Einschränkung
			
			In **Suche 2** (Primärstudien)
			
			zusätzlich (gezielte Suche):
			- Studientyp: diagnostische Primärstudie
			- Setting: hausärztliche Versorgungsebene
			- Studie berichtet die unabhängige Aussagekraft einzelner Zeichen und Symptome (d.h. nach multivariater Adjustierung)
			
			Outcome
			diagnostische Aussagekraft Sensitivität/Spezifität, PPV, NPV
				Mount Sinai Evidence-Based Medicine Working group)
				
				diagnostic performance of Gencer rule
				PPV : 20%–34%, NPV : 95%–99%)
				and
				INTERCHEST
				PPV: 35%–43%, NPV : 96%–98%
				appear comparable, but requires further validation
				
				- ergänzend werden Hinweise berichtet, die den Einsatz des MHS mit einer besseren klinischen Einschätzung der Hausärzt*innen in Verbindung bringen (zusätzlich als klinische Hinweise angegeben: Transparenz, leichte Anwendbarkeit, Augenscheinvalidität)
				- Mehrheit der Patient*innen mit stabiler KHK, daher Aussagekraft für ACS eingeschränkt (n = 1 SR berichtet, dass: In general practice, there is currently no clinical decision aid that can safely rule out ACS):
				- Grijseels rule
				  - sensitivity : 91%,
				  - specificity : 37%,
				  - PPV : 57%,
				  - NPV : 82%)
				
				Bruins Slot
				  - sensitivity : 97%,
				  - specificity : 10%,
				  - PPV : 23%,
				  - NPV : 92%) (Quelle 25 aus 2019)			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
				- eine ergänzende Primärstudie aus 2020 liefert hier weitere Daten (auch zum MHS) zu MACE (major adverse cardiac events), welche die Aussage bestätigt, allerdings den INTERCHEST score als am besten diskriminierend beschreibt (mit guter Sensitivität und Spezifität); im Vergleich zur ärztlichen Einschätzung ohne Score-Unterstützung gibt es vergleichbare Werte für die Sensitivität, Spezifität und einen Hinweis auf eine bessere Vorhersage bei Anwendung des Cut-off von 2 Punkten in Bezug auf MACE, ACS (vgl. S. 69) **zudem interessant:** Wie häufig ist das Symptom „Brustschmerz" Beratungsanlass in der allgemeinärztlichen Praxis? - Häufigkeit des Symptoms „**Thoraxschmerz**" im allgemeinmedizinischen, primärärztlichen Setting: 0,68 – 3,0% (6–11) (Häufigkeit der Patientenkontakte mit Thoraxschmerz bezogen auf Patientenkontakte gesamt) bzw. 15,5 - 67,4 Patient*innen mit Thoraxschmerz/ 1000 Patient*innen und Jahr (7, 12–14) - Heterogenität beschrieben (Grund: u. a. Unterschiede in den Gesundheitssystemen sowie untersuchten Zeiträumen) - in Studien mit guter methodischer Qualität/ Übertragbarkeit: Häufigkeit des Beratungsanlasses 1-3% (2++), n = 3 Arbeiten			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
				Welche Erkrankungen sind in welcher Häufigkeit Ursache für das Symptom „Brustschmerz" in der allgemeinärztlichen Praxis? - systematische Literaturübersicht mit geringem Verzerrungspotential: für die KHK (chronische KHK und ACS) eine Häufigkeit von 9,7-14,8% - häufigste Ursache mit 24,5-49,8 %: Brustwandsyndrom (BWS) (2++), n = 1 Arbeit Tabelle 6: Ursachen des Brustschmerzes aus ausgewählten Studien. (SIGN 2++) vgl. S. 23 Evidenzbericht Ursache des Brustschmerzes Prozent, Häufigkeit Chronische KHK 8-11% 75/672 (15) 135/1212 (9) 71/868 (22) Akutes Koronarsyndrom 2-4% 10/672 (15) 44/1212 (9) 21/868 (22) Brustwandsyndrom 43-47% 287/672 (15) 565/1212 (9) Psychogene Ursachen 10-12% 77/672 (15) 115/1212 (9) Erkrankungen der Atemwege 10-12% 69/672 (15)			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
				146/1212 (9)			
				Ösophageale Ursachen 4-7% 48/672 (15) 42/1212 (9)			
				Hypertensive Krise 1-4% 5/672 (15) 48/1212 (9)			
				Arrhythmien 1-2% 10/672 (15) 10/1212 *			
				Lungenembolie < 0,5% 2/672 (15) 1/1212 *			
				Aortenstenose < 0,5% 1/672 (15)			
				Myo-/Perikarditis < 0,5% 3/1212 *			
				Kardiomyopathie < 0,5% 4/672 (15)			
				Aortendissektion 0/672 (15) < 0,1% 0/1212 * < 0,1% * Nicht publizierte Daten der Studie von Bösner et al. 2009 (9)			
33573	Harskamp RE, Laeven SC, Himmelreich JC, Lucassen WAM, van Weert HCPM. Chest pain in general practice: a systematic review of prediction rules. BMJ Open 2019; 9(2):e027081. doi: 10.1136/bmjopen-	2019	**Fragestellung** aim to identify and assess the performance of existing clinical decision aids/rules for stable angina and/or acute coronary syndrome in patients with chest pain that are applicable and	n = 8 studies included which evaluated n = 5 different clinical decision rules (CDR)) for rule out CAD: - Gencer rule - the Marburg Heart Score - INTERCHEST	AMSTAR 2 low y-py-n-y-y-n-y-y-n-y-y keine Metaanalyse eine kritische Domäne wurde nicht erfüllt (keine Angabe	E	Literaturlistensuche basierend auf einem Evidenzbericht der S3-Leitlinie Brustschmerz - DEGAM-Leitlinie für die

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
	2018-027081. https://pub-med.ncbi.nlm.nih.gov/30819715/ [9]		have been validated in low-resource general practice or equivalent settings **Studientyp** systematic review (following the PRISMA-Guidelines); PubMed, Embase, CINAHL and Google Scholar (up to 17 October 2018) **Ein- und Ausschlusskriterien** - original studies in adults (≥18 years of age) - enrolement in primary care setting - patients with chest pain - suspected coronary artery disease, acute coronary syndrome - in general practice, primary care practice - language of publication: English, Dutch or German - studies with a retrospective study design were excluded - in-hospital, emergency department (ED) and/or preselected outpatient populations were not eligible **Qualitätsbewertung** QUADAS-2 tool (online supplement) assessed whether a clinical decision rule (CDR) was ready for application in clinical practice (level of evidence for each rule using the definitions of the Mount Sinai Evidence-Based Medicine Working group) **Intervention** prediction rule, decision model or decision aid (may include items from history taking, physical examination, laboratory	for rule out ACS - Grijseels rule - Bruins Slot rule overall quality of the studies was moderate (QUADAS 2) - n = 6 studies with high risk of bias in reference standard (assesor not blinded to the index test results) - CDRs have been developed based on readily available clinical information - Marburg Heart Score was most extensively tested with good overall discrimination - (C-statistic of 0.84–0.90) - sensitivity of 86%–89%, - specificity of 64%–81%, - PPV of 23%–40% - NPV of 97%–98% - diagnostic properties illustrating its consistent diagnostic performance in terms of sensitivity and specificity - sensitivity (+8.0%) and specificity (+5.8%) were higher as unaided clinical judgement - the level of evidence is 2 for the Marburg Heart Score, which implicates that this rule can be used in a general practice setting of low-risk patients with intermittent chest pain with confidence in its accuracy - INTERCHEST rule has a number of quality concerns (not validated) - C-statistic of 0.84, - sensitivity 82%–88%, - specificity 74%–82%,	einer Liste der ausgeschlossenen Studien mit dem Ausschlussgrund)		primärärztliche Versorgung, in Überarbeitung, geplante Fertigstellung: 30.09.2023: https://register.awmf.org/de/leitlinien/detail/053-023#anmeldung authors noted that during office hours, 1.5% of all consultations and 4% of all new episodes are related to chest pain additionally, highest frequency of chest pain consultations is in the age category 45 to 64 years, with notable differences between men and women in its presentation

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
			and electrocardiographic data) **Referenz** clinical outcomes that we used as reference diagnosis were (1) any form of coronary artery disease (CAD) or coronary heart disease; or (2) a more restricted form including unstable angina or myocardial infarction (referred to as acute coronary syndrome) in patients with acute chest pain **Outcome** diagnostic test characteristics of included rules, including: sensitivity, specificity, negative and positive prediction values	- PPV of 35%–43% - NPV of 96%–98% - Gencer rule has limited evidence (validated only in one study, lower specificity (42%-71) - C-statistic: 0.75–0.95, - sensitivity 87%–98%, - specificity 42%–71%			
33571	Juarez-Orozco et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. Eur Heart J Cardiovasc Imaging. 2019 Nov 1;20(11):1198-1207. doi: 10.1093/ehjci/jez054. https://pub-med.ncbi.nlm.nih.gov/30982851/ [10]	2019	**Fragestellung** to provide a pooled estimation of contemporary PTPs of significant CAD across traditionally considered clinical patient categories, and to re-evaluate the utility of application of exercise ECG, ICA, CCTA, PET, stress CMR, and SPECT according to such contemporary PTPs, while exploring novel progressive ruling-out thresholds **Studientyp** Übersichtsarbeit (since last operational estimations by Genders et al. was performed),search and cross-referencing, other sources (search string is avalable within an online-supplement) **Ein- und Ausschlusskriterien** (i) demonstrated consistency of methods for identification of significant CAD and	n = 3 trials - Foldyna et al. – PROMISE - Reeh et al. - Cheng et al. - CONFIRM)* n = 15 815 patients (mean age 59 ± 11 years) - significant CAD as any luminal narrowing of >50% - overall prevalence of significant CAD in the pooled population ranged from 1 to 52% (mean of 14.9%) - corresponds to about a 66% decrease in average from the values defined by Genders et al. 2011 used in the 2013 ESC guidelines across all patient categories. updated pooled PTPs of obstructive CAD across the clinical patient categories: Table 2 Pre-test probabilities of obstructive CAD in symptomatic patients	n. a.	E	Literaturlistensuche (basierend auf der ESC 2019); European Heart Journal (2020) 41, 407/477 https://pub-med.ncbi.nlm.nih.gov/31504439/ 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal (2020) 41, 407/477) s. a. **Figure 2** Utility of non-invasive techniques for detection of significant CAD (ICA, FFR)* * Updated diagnostic technique selection tool for all patient categories based

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
			(ii) stratified their PTP estimates according to sex, age, and type of chest pain as established in current guidelines. **Intervention** exercise ECG, ICA, CCTA, PET, stress CMR, and SPECT **Kontrolle** i. e. ICA and fractional flow reserve (FFR) **Outcomes** continuous baseline variables from the included reports CAD prevalence data	according to age, gender, and the nature of symptoms (pooled analysis of n = 3 studies) (Men / Women)			on sex, age, and type of chest pain, considering both ICA (upper panel) and FFR (lower panel) as the reference standard. The colour gradients inform the confidence with which a negative result can rule-out disease (i.e. by driving the post-test probability below 15, 10, or 5). CAD is directly rule-out with a PTP <_5. a The categories corresponding to dyspnoea as the predominant or only symptom; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single photon emission computed tomography. Adapted from Knuuti et al.

Age (years)	Typical (%)	Atypical (%)	Non-anginal (%)	Dyspnoea (%)
30-39	3 / 5	4 / 3	1 / 1	0 / 3
40-49	22 / 10	10 / 6	3 / 2	12 / 3
50-59	32 / 13	17 / 6	11 / 3	20 / 9
60-69	44 / 16	26 / 11	22 7 6	27 / 14
70+	52 / 27	34 / 19	24 / 10	32 / 12

aIn addition to the classic Diamond and Forrester classes, patients with dyspnoea only or dyspnoea as primary symptom are included. The dark green shaded regions denote the groups in which non-invasive testing is most beneficial (pre-test probability >15%). The light green shaded regions denote the groups with pre-test probability of CAD between 5 and 15% in which the testing for diagnosis may be considered based on clinical judgement.

pooled estimate
CAD cases (n) 2350
CAD prevalence (%) 14.9
men (n (%)) 7573 (48)
women (n (%)) 8222 (52)
BMI (kg/m2 (SD)) 28.2 (5.5)
arterial hypertension (n (%)) 8691 (55)
diabetes mellitus (n (%)) 2485 (16)
dyslipidaemis (n (%)) 9432 (60)
smokers (n (%)) 5494 (35)

- groups of participant subjects:
atypical angina (59%)

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
				non-anginal pain (25%) typical angina (16%) - overall prevalence of significant CAD: 1 to 52% (mean of 14.9%) (pooled population), which corresponds to about a 66% decrease in average from the values defined by Genders et al. 2011 used in the 2013 ESC guidelines across all patient categories (former average PTP = 44.5%) - patients with significant CAD: atypical angina (58%) typical angina (29%) non-anginal pain (14%) - patients with significant CAD were older and more often male - PTP ranges in which it is possible to rule-out the disease by driving the post-test probability below the following thresholds of post-test probability: <15, <10, and <5% - The ruling-out capabilities of the included techniques were remarkable in ruling-out CAD across all clinical patient categories with a post-test probability of at least <15% - ICA demonstrated the most restricted profile for ruling-out FFR-significant CAD, particularly, in clinical groups that convey the highest PTP estimates (males with typical anginal above 50 years old)			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
				- a clear nonlinear function linking the PTP with the rate of false positive and negative findings at each extreme of PTP			
	Haase et al. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data. BMJ. 2019 Jun 12;365:l1945. doi: 10.1136/bmj.l1945. https://pubmed.ncbi.nlm.nih.gov/31189617/ [11]	2019	**Fragestellung** to determine whether coronary computed tomography angiography (CTA) should be performed in patients with any clinical probability of coronary artery disease (CAD), and whether the diagnostic performance differs between subgroups of patients **Studientyp** Prospectively designed meta-analysis of individual patient data from prospective diagnostic accuracy studies Medline, Embase, and Web of Science for published studies; unpublished studies via contact with investigators (COME-CCT), protocol, registered at PROSPERO Schuetz GM, Schlattmann P, Achenbach S, et al. Individual patient data meta-analysis for the clinical assessment of coronary computed tomography angiography: protocol of the Collaborative Meta-Analysis of Cardiac CT (CoMe-CCT). Syst Rev 2013;2:13. doi:10.1186/2046-4053-2-13 **Qualitätsbewertung** Risk of Bias Tool, QUADAS-2 tool **Ein- und Ausschlusskriterien** - prospective diagnostic accuracy studies - compared coronary CTA with coronary angiography	Individual patient data from 5 332 patients (n = 65 prospective diagnostic accuracy studies) n = 63 published and two unpublished risk of bias was low for all items in most studies, and applicability concerns were not present in any of the included studies assessed by the QUADAS-2 tool patient baseline characteristics vgl. Tabelle 1 pretest probability range of 7-67%, treat threshold of more than 50% and the no-treat threshold of less than 15% post-test probability were obtained using CTA a pretest probability of 7% (95%CI): - PPV of CTA 50.9% (43.3% to 57.7%) - NPV of CTA 97.8% (96.4% to 98.7%) pretest probability of 67%: - PPV 82.7% (78.3% to 86.2%) - NPV 85.0% (80.2% to 88.9%) overall (CTA): - sensitivity 95.2% (92.6% to 96.9%) - specificity 79.2% (74.9% to 82.9%)	AMSTAR-2 low Y-Y-N-Y-Y-N-Y-Y-Y-Y-Y-Y-Y-Y eine kritische Domäne wurde nicht erfüllt (keine Angabe einer Liste der ausgeschlossenen Studien mit dem Ausschlussgrund)	Ei	Literaturlistensuche (geeignete Prätestwahrscheinlichkeitsspanne für die CT-Koronarangiographie, welche der Publikation der DISCHARGE Group (supplement zu NEJM 2022) zugrunde liegt (CCTA vs. ICA; eine Publikation die unter den n = 4 Publikationen eingeschlossen wurde)

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							

			- using at least a 50% diameter reduction as a cutoff value for obstructive CAD
			- patients needed to have a clinical indication for coronary angiography due to suspected CAD
			- both tests had to be performed in all patients
			
			angina pectoris was classified as typical angina, atypical angina, non-anginal chest pain, or other chest discomfort according to Diamond and Forrester
			Intervention
			coronary CTA
			Kontrolle
			coronary angiography (ICA)
			Outcome
			primary:
			- positive predictive value (PPV)
			- negative predictive value (NPV)
			of CTA as a function of clinical pretest probability of obstructive CAD, analysed by a generalised linear mixed model
			secondary:
			- sensitivity and specificity
			
			no-treat/treat threshold model was used (based on obtained post-test probabilities of less than 15% in case of negative CTA and above 50% in case of positive CTA. Sex, angina pectoris
				CTA using more than 64 detector rows vs. CTA using up to 64 rows
				- empirical sensitivity (93.4% vs. 86.5%, P=0.002)
				- specificity (84.4% vs. 72.6%, P<0.001).
				- AUC for CTA was 0.897 (0.889 to 0.906)
				
				- diagnostic performance of CTA slightly lower in women than in men (AUC 0.874 (0.858 to 0.890) vs. 0.907 (0.897 to 0.916), P<0.001)
				- diagnostic performance of CTA was slightly lower in patients older than 75 (0.864 (0.834 to 0.894), P=0.018 v all other age groups)
				- patients older than 75:
				  o sensitivity 93.2% (88.6% to 96.0%)
				  o specificity 73.6% (65.7% to 80.2%)
				- diagnostic performance was not significantly influenced by angina pectoris type (typical angina 0.895 (0.873 to 0.917), atypical angina 0.898 (0.884 to 0.913), non-anginal chest pain 0.884 (0.870 to 0.899), other chest discomfort 0.915 (0.897 to 0.934))			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
Risikoeinschätzung							
			type, age, and number of computed to-mography detector rows)				

CT-Koronarangiografie

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
33569 33640	[D22-01] Computertomographie-Koronarangiographie zur Diagnosestellung bei Patientinnen und Patienten mit Verdacht auf eine chronische koronare Herzkrankheit, Letzte Aktualisierung 17.02.2023. [D22-01] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Computertomographie-Koronarangiografie mit oder ohne funktionelle Beurteilung zur Diagnose einer chronischen koronaren Herzkrankheit. Abschlussbericht. Projekt: D22-01. Version 1.1. 2023 (IQWiG-Berichte; 1570) [cited: 2023-07-03]. https://www.iqwig.de/projekte/d22-01.html., Stand 20.06.2023. [12,13]	2023	**Fragestellung** Fragestellung 1: Nutzenbewertung von diagnostischen Strategien mit Anwendung einer kontrastverstärkten Computertomografie-Koronarangiografie (CCTA) vs. diagnostische Strategien der gleichen Zielsetzung ohne Anwendung einer CCTA **Studientyp** systematische Übersichtsarbeit zu SR aus RCT sowie RCT (Medline, HTA Database, NICE, AHRQ, Vorarbeiten des IQWIG sowie Embase, Cochrane, Studienregister, Herstelleranfragen, Referenzlisten), letzte Suche Frage 1 20.09.2022 **Ein- und Ausschlusskriterien** P: Patient*innen mit Verdacht auf eine chronische koronare Herzkrankheit, bei denen nach Durchführung der Basisdiagnostik die Indikation zur weiterführenden nicht invasiven Diagnostik besteht Randomisierte kontrollierte Studien (RCT), Systematische Übersichtsarbeiten zur Identifizierung von Primärstudien	Fragestellung 1 gesamt: n = 1 systematische Übersichtsarbeit, n = 15 RCT kontrastverstärkten Computertomografie-Koronarangiografie (CCTA) vs. funktionelle Verfahren (fV): n = 11 Studien (CAPP [10], CARE-CCTA [11], CATCH [12], CT-STAT [13], Goldstein 2007 [14], IAEA-SPECT/CTA [15], Min 2012 [16], Nabi 2016 [17], PERFECT [18], PROMISE [19] und SCOT-HEART [20]) kontrastverstärkten Computertomografie-Koronarangiografie (CCTA) vs. invasiver Koronarangiografie (ICA): n = 4 Studien (CAD-MAN [21], CONSERVE [22], DISCHARGE [23] und Reis 2022 [24]) n = 3 geplante sowie n = 3 laufende Studien u. a. aus Registern sowie n = 3 Studien mit unklarem Status Charakteristika der Studien vgl. S. 8-12 im Bericht sowie S. 81-103 im Bericht	*AMSTAR 2: high* *y-y-y-y-y-n-y-y-py-y-y-y-y-y-y* *Hinweis zu den RCT:* **CCTA vs. fV** niedriges Verzerrungspotential endpunktübergreifend für n = 4 Studien hohes Verzerrungspotential endpunktübergreifend für n = 7 Studien (u. a. unklare Erzeugung der Randomisierungsfrequenz) --> für diese 7 Studien keine weitergehende endpunktspezifische Bewertung **CCTA vs. direkte ICA** niedriges Verzerrungspotential endpunktübergreifend für n = 3 Studien hohes Verzerrungspotential endpunktübergreifen für n = 1 Studie (unklare Verdeckung der Gruppenzuteilung)	E	Sachverständige haben wissenschaftliche Forschungsaufträge für das Institut bearbeitet; Vorbericht ist eine vorläufige Nutzenbewertung es wird angeführt, dass bei Ausschluss eines ACS und anderer Ursachen bei pektangiöser Beschwerden, mittels Elektrokardiogramm (EKG) und Laborbestimmung plus Anamnese und körperlicher Untersuchung, je nach Vortestwahrscheinlichkeit, unterschiedliche bildgebende nicht invasive und invasive Verfahren zur Verfügung stehen, um eine stabile stenosierende KHK als wahrscheinlichste Verdachtsdiagnose zu bestätigen (vgl. NVL Chronische KHK Version 6.0) starke Negativempfehlung

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
			Qualitätsbewertung qualitative Ergebnissicherheit wurde endpunktübergreifend und endpunktspezifisch des Verzerrungspotenzials bewertet; Metaanalysen und Sensitivitätsanalysen wurden durchgeführt sowie Effektmodifikatoren untersucht; endpunktübergreifende Bewertung des Nutzens und Schadens **Intervention** diagnostische Strategien mit Anwendung einer CCTA **Kontrolle** diagnostische Strategien der gleichen Zielsetzung ohne Anwendung einer CCTA **Endpunkte** Mortalität Morbidität gesundheitsbezogene Lebensqualität Nebenwirkungen (zur Morbidität berichtet (mit unterschiedlicher Verteilung zwischen den Studien) u. a. Myokardinfarkt, Schlaganfall, instabile Angina pectoris, Angina pectoris, unnötige invasive Diagnostik)	3 Auswertungszeiträume definiert - bis 30 Tage nach Untersuchung = periprozedural - 6-24 Monate = mittelfristig - 2-5 Jahre = langfristig **Ergebnisse Fragestellung 1 CCTA vs. funktionelle Verfahren** **Gesamtmortalität** niedriges Verzerrungspotential n = 4 Studien hohes Verzerrungspotential n = 6 Studien periprozedural – mittelfristig OR 0,77 (95 % KI 0,40; 1,50), (hohe Ergebnissicherheit), n = 4 Studien (CATCH, IAEA-SPECT/CTA, PROMISE und SCOT-HEART) gesamt - langfristig OR 0,99 (95 % KI 0,77; 1,28), n = 2 Studien (SCOT-HEART und PROMISE) gesamt (n / N) 117 / 7 069 vs. 118 / 7 080 **kardiovaskuläre Mortalität** niedriges Verzerrungspotential n = 2 Studien hohes Verzerrungspotential n = 5 Studien	**Lebensqualität** verwertbare Angaben zur Lebensqualität allgemein wurden für die CCTA vs. fV ausschließlich aus n = 2 Studie berichtet (CATCH; SCOT-HEART); für die CCTA vs. ICA zu n = 1 Studie (DISCHARGE); für die krankheitsbezogene Lebensqualität konnte nur ein Teil der vorliegenden Daten verwendet werden (aus n = 1 Studie (SCOT-HEART) zu CCTA vs. fV und n = 0 zu CCTA vs. ICA)		gegen die ICA bei niedriger und mittlerer Vortestwahrscheinlichkeit, aber Zunahme an ICAs in Deutschland (im Jahr 2019 ca. 510 000 ICAs; dabei lag bei etwa 30 % der Indikationen, die zu einer ICA geführt haben, kein pathologischer Befund vor [NVL, IQTIG]; möglicher Grund: CCTA zählt – im Gegensatz zur ICA (mit und ohne Messung der fraktionellen Flussreserve) – nicht zum Leistungsumfang der GKV) **Abschlussbericht im Vergleich zum Vorbericht** Neben redaktionellen Änderungen ergaben sich folgende Spezifizierungen oder Änderungen im Abschlussbericht: ▪ Studie PROTECCT (im Vorbericht als Studie mit unklarem Status) wurde aufgrund neuer Daten (Publikation) ausgeschlossen ▪ Studie TARGET (im Vorbericht als Studie mit unklarem Status) wurde berücksichtigt

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				periprozedural – mittelfristig OR 0,53 (0,17; 1,66), (hohe Ergebnissicherheit); n = 2 Studien (CATCH, SCOT-HEART) gesamt – langfristig - **Myokardinfarkt** niedriges Verzerrungspotential n = 3 Studien hohes Verzerrungspotential n = 6 Studien periprozedural – mittelfristig gesamt - CATCH OR 0,29 (95 % KI 0,06; 1,39), (hohe Ergebnissicherheit), (n / N) 2 / 285 vs. 7 / 291 PROMISE OR 0,67 (95 % KI 0,37; 1,21), (hohe Ergebnissicherheit), (n / N) 18 / 4996 vs. 27 / 5007 SCOT-Heart OR 0,62 (95 % KI 0,37; 1,07), (hohe Ergebnissicherheit), (n / N) 22 / 2073 vs. 35 / 2073 (qualitative Bewertung, da die beiden gewählten statistischen Verfahren (random effect modell nach Knapp und Hartung + Sensitivitätsanalyse nach			und ergänzend dargestellt (Publikation) • Begriff für das Krankheitsbild der nicht obstruktiven KHK wurde in Kapitel 1 ergänzt • in Kapitel 1 wurde klarer dargestellt, dass bei dem CCS (in Abgrenzung zum ACS) die Ischämie nur unter Belastung auftritt • Charakterisierung der Intervention im CCTA-Arm der Studie DISCHARGE wurde im Bericht im Abschnitt 4.2.1 und in Tabelle 18 angepasst • für die ergänzend dargestellte Studie PRECISE wurde ein Manuskript eingereicht, aus welchem zusätzliche Daten zur Verfügung standen (Folge: Überarbeitung der Verzerrungspotenzialbewertung und Berücksichtigung von 2 weiteren Endpunkten (kardiovaskuläre Mortalität, instabile Angina Pectoris) • Daten zum Endpunkt krankheitsspezifische Lebensqualität, gemessen anhand des Gesamtscore des SAQ-7 aus der Studie

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				DerSimonian) nicht statistisch signifikant waren (vgl. Bericht S. 23); zudem wurde eine ergänzende Auswertung aller Studien mit hoher und mäßiger Ergebnissicherheit durchgeführt: OR = 0,61 (95 % KI 0,41; 0,89), (hohe und mäßige Ergebnissicherheit), n = 8 Studien (CAPP, CARE-CCTA, CATCH, CT-STAT, Goldstein 2007, PERFECT, PROMISE, SCOT-HEART) sowie ein 95 % Prädiktionsintervall (0,41; 0,89) angegeben (neueres Verfahren zur Abschätzung der Sicherheit des Effektschätzers) langfristig OR 0,65 (95 % KI 0,48; 0,87), (hohe Ergebnissicherheit), n = 2 Studien (PROMISE, SCOT-HEART) gesamt (n / N) 74 / 7069 vs. 113 / 7080 **Schlaganfall** niedriges Verzerrungspotential n = 2 Studien hohes Verzerrungspotential n = 1 Studie periprozedural - mittelfristig OR 0,71 (0,23; 2,25), (hohe Ergebnissicherheit), n = 1 Studie (SCOT-HEART) (n / N) 5 / 2 073 vs. 7 / 2 073 langfristig - **instabile Angina pectoris**			FORECAST wurden ergänzt ■ in Kapitel 5 wurde ein Abschnitt zum Wert der Diagnose einer nicht obstruktiven KHK eingefügt ■ Nutzenaussage zu Fragestellung 2 wurde geändert, siehe Abschnitt 4.4 ■ im Vorbericht war im Ergebnisabschnitt 4.3.4.8 dargestellt, dass die Ergebnisse der Studie PRECISE nur ergänzend berichtet werden; jetzt im vorangehenden Abschnitt 4.3.1 zu den Studiencharakteristika dieses Vorgehen begründet und in allen Tabellen, die Daten zur Studie PRECISE enthalten, jeweils anhand einer Fußnote auf die rein ergänzende Darstellung der Studie verwiesen ■ bei der nur ergänzend berichteten Studie PRECISE wurde (wie bei der Studie TARGET) auf die Darstellung der Bewertung des Verzerrungspotenzials und der Ergebnisse zu End-

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				niedriges Verzerrungspotential n = 2 Studien hohes Verzerrungspotential n = 5 Studien periprozedural - mittelfristig OR 1,34 (0,88; 2,04), (hohe Ergebnissicherheit), n = 2 Studien (CATCH, PROMISE) gesamt - langfristig - **Angina pectoris** niedriges Verzerrungspotential n = 1 Studie hohes Verzerrungspotential n = 1 Studie periprozedural - mittelfristig - Einzelstudien gesamt - CAPP OR 0,20 (0,08; 0,50), n = 1 Studie (n / N) 6 / 243 vs. 27 / 245 SCOT-HEART OR 1,11 (0,79; 1,54), n = 1 Studie (n / N) 76 / 2 073 vs. 69 / 2 073 langfristig - **Gesundheitszustand (EQ-5D VAS)** niedriges Verzerrungspotential –			punkten in den Abschnitten 4.3.3 und 4.3.4 verzichtet (Daten in den Abschnitten A3.3.1.2 und A3.3.2.) **Abschlussbericht Version 1.1 im Vergleich zum Abschlussbericht Version 1.0** ▪ Abschnitt A1.2 ein fehlerhafter Verweis nun auf Kapitel 5 korrigiert und an gleicher Stelle eine formale Anpassung durch Ergänzung eines Aufzählungspunkts vorgenommen ▪ Abschnitt A1.2 wurde ein Aufzählungspunkt zur nun deutlicher gekennzeichneten ergänzenden Darstellung der Studie PRECISE hinzugefügt

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				hohes Verzerrungspotential n = 2 periprozedural – mittelfristig Mittelwertdifferenz (MWD) -0,70 (95 % KI -1,50; 0,10), n = 2 Studien (CARE-CCTA, PROMISE) MW (SD) Studienbeginn vs. Studienende CCTA 65,0 (14,5) vs. 69,0 (13,8) gegenüber SPECT 65,1 (12,4) vs. 69,7 (11,9) (n) 441 vs. 424 CCTA 72,0 (19,5) vs. 74,7 (20,3) gegenüber fV 72,4 (19,8) vs. 74,9 (21,2) (n) 2679 vs. 2525 langfristig - **unnötige invasive Diagnostik** niedriges Verzerrungspotential n = 2 Studien hohes Verzerrungspotential n = 2 Studien OR 0,77 (95 % KI 0,64; 0,94), (hohe Ergebnissicherheit), n = 2 Studien (CATCH, PROMISE) gesamt – (n / N) 14 / 285 vs. 23 / 291, n = 1 Studie (n / N) 170 / 4996 vs. 213 / 5007, n = 1 Studie			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				gesundheitsbezogene Lebensqualität niedriges Verzerrungspotential – hohes Verzerrungspotential n = 2 periprozedural - mittelfristig SF-12 oder SF-36 körperlicher Summenscore MWD -0,07 (95 % KI -0,13; 0,00), n = 2 Studien (CATCH, SCOT-HEART) MW (SD) Studienbeginn vs. Studienende CCTA 44,2 (0,2) vs. 45,0 (0,3) gegenüber fV 44,0 (0,2) vs. 46,0 (0,3) (n) 1777 vs. 1705 SF-12 oder SF-36 psychischer Summenscore MWD -0,05 (95 % KI -0,12; 0,02), n = 2 Studien (CATCH, SCOT-HEART) MW (SD) Studienbeginn vs. Studienende CCTA 46,1 (0,3) vs. 47,8 (0,3) gegenüber fV 46,7 (0,3) vs. 48,6 (0,3) (n) 1777 vs. 1705 langfristig - **unerwünschte Ereignisse** niedriges Verzerrungsrisiko n = 2 hohes Verzerrungsrisiko n = 2 es lagen kaum verwertbare Daten vor			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				periprozedural (bis 30 Tage nach Untersuchung) in beiden Gruppen nach Untersuchung keine Komplikationen, n = 1 Studien n = 3 Patient*innen mit schweren Blutungen vs. n = 3 Patient*innen mit schweren Blutungen sowie n = 9 SUE (u.a. ventrikuläre Tachykardien), n = 1 Studie mittelfristig (6-24 Monate) in beiden Gruppen nach Untersuchung keine Komplikationen, n = 2 Studien keine SUE, n = 1 Studie langfristig - **CCTA vs. direkte ICA** **Gesamtmortalität** niedriges Verzerrungspotential n = 2 Studien hohes Verzerrungspotential n = 2 Studien periprozedural – mittelfristig Peto-OR 1,79 (95 % KI 0,19; 17,27); n = 1 Studie (CONVERSE) gesamt (n / N) 2 / 784 vs. 1 / 719 langfristig - **kardiovaskuläre Mortalität** niedriges Verzerrungspotential n = 2 Studien			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				hohes Verzerrungspotential n = 1 Studie			
				periprozedural –			
				mittelfristig -			
				langfristig OR 0,47 (0,19; 1,12), n = 2 Studien (CAD-MAN, DISCHARGE) gesamt (n / N) 7 / 1 975 vs. 15 / 1 915			
				Myokardinfarkt niedriges Verzerrungspotential n = 2 Studien hohes Verzerrungspotential n = 2 Studien			
				periprocedural OR 0,41 (0,14; 1,25), n = 2 Studien (CAD-MAN, DISCHARGE) gesamt (n / N) 4 / 1 975 vs. 10 / 1 915			
				mittelfristig OR 0,66 (0,13; 3,38), n = 2 Studien (CONDERVE, Reis 2022) gesamt (n / N) 2 / 893 vs. 3 / 824			
				langfristig OR 1,16 (0,64; 2,09), n = 2 Studien (CAD-MAN, DISCHARGE) gesamt (n / N) 24 / 1 975 vs. 20 / 1 915			
				Schlaganfall niedriges Verzerrungspotential n = 2 Studien			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				hohes Verzerrungspotential n = 2 Studien periprozedural - mittelfristig OR 0,65 (95 % KI 0,13; 3,32), n = 2 Studien (CONSERVE, Reis 2022) gesamt (n / N) 2 / 899 vs. 3 / 824 langfristig OR 0,47 (95 % KI 0,22; 0,99), n = 2 Studien (CAD-MAN, DISCHARGE) gesamt (n / N) 10 / 1975 vs. 21 / 1915 **instabile Angina pectoris** niedriges Verzerrungspotential n = 1 Studie hohes Verzerrungspotential n = 2 Studien periprozedural - mittelfristig OR 1,13 (0,47; 2,74), n = 2 Studien (CONSERVE, Reis 2022) gesamt (n / N) 11 / 893 vs. 9 / 824 langfristig - **Angina pectoris** niedriges Verzerrungspotential - hohes Verzerrungspotential n = 2 Studien periprozedural –			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				mittelfristig OR 1,21 (0,98; 1,50), n = 2 Studien gesamt (n / N) 210 / 1 893 vs. 171 / 1 829 langfristig - **Gesundheitszustand (EQ-5D VAS)** niedriges Verzerrungspotential – hohes verzerrungspotential n = 1 periprozedural – mittelfristig MWD -0,20 (95 % KI -1,25; 0,87), n = 1 Studie (DISCHARGE) MW (SD) Studienbeginn vs. Studienende CCTA 67,8 (17,4) vs. 70,4 (18,6) gegenüber ICA 66,5 (17,5) vs. 69,9 (18,1) (n) 1592 vs. 1521 langfristig MWD 0,31 (95 % KI -0,76; 1,38), n = 1 Studie (DISCHARGE) MW (SD) Studienbeginn vs. Studienende CCTA 67,8 (17,4) vs. 71,8 (16,4) gegenüber ICA 66,5 (17,5) vs. 71,1 (16,7) (n) 1395 vs. 1313 **unnötige invasive Diagnostik** niedriges Verzerrungspotential n = 2 Studien			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				hohes Verzerrungspotential n = 2 Studien			
				CAD-MAN OR 0,01 (0,00; 0,02), (hohe Ergebnissicherheit) (n / N) 6 / 167 vs. 137 / 162 DISCHARGE OR 0,03 (0,02; 0,03), (hohe Ergebnissicherheit) (n / N) 111 / 1808 vs. 1260 / 1753			
				gesundheitsbezogene Lebensqualität niedriges Verzerrungspotential – hohes Verzerrungspotential n = 1			
				periprozedural –			
				mittelfristig SF-12 körperlicher Summenscore MWD 0,12 (95 % KI -0,37; 0,61) MW (SD) Studienbeginn vs. Studienende CCTA 44,1 (9,1) vs. 46,7 (8,9) gegenüber ICA 43,4 (9,3) vs. 46,1 (9,1) (n) 1551 vs. 1489			
				langfristig SF-12 körperlicher Summenscore MWD 0,26 (95 % KI -0,27; 0,78) MW (SD) Studienbeginn vs. Studienende CCTA 44,1 (9,1) vs. 48,4 (8,7) gegenüber			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				ICA 43,4 (9,3) vs. 47,8 (8,7) (n) 1392 vs. 1310 **unerwünschte Ereignisse** niedriges Verzerrungsrisiko n = 2 hohes Verzerrungsrisiko n = 1 periprozedural (bis 30 Tage nach Untersuchung) in beiden Behandlungsgruppen keine SUE, n = 1 Studie n = 6 Patient*innen mit SUE vs. n = 22 SUE (u. a. Arrythmie, Herzstillstand, kardiale Tamponade) OR 0,26 (95 % KI 0,11; 0,64), n = 1 Studie mittelfristig (6-24 Monate) keine SUE vs. n = 2 Patient*innen mit schweren Blutungen, n = 1 Studie			
33569	[D22-01] Computertomographie-Koronarangiographie zur Diagnosestellung bei Patientinnen und Patienten mit Verdacht auf eine chronische koronare Herzkrankheit, Letzte Aktualisierung 17.02.2023. [12]	2023	**Fragestellung 2:** Nutzenbewertung von diagnostischen Strategien mit Anwendung einer kontrastverstärkten Computertomografie-Koronarangiografie (CCTA) mit der Option einer anschließenden CT-basierten funktionellen Beurteilung vs. diagnostische Strategien der gleichen Zielsetzung ohne die Option einer CT-basierten funktionellen Beurteilung (iIm Falle eines mindestens vergleichbaren Nutzens der CCTA gemäß Fragestellung 1 können die diagnostischen Vergleichsstrategien zudem die CCTA beinhalten) Einschlusskriterien s. Fragestellung 1	Fragestellung 2 n = 0 systematische Übersichtsarbeiten, n = 5 RCT CCTA mit Option einer CT-basierten funktionellen Beurteilung vs. Strategien ohne Option einer CT-basierten funktionellen Beurteilung: n = 4 Studien (mit 2 verschiedenen Verfahren zur funktionellen Beurteilung als Ergänzung zur CCTA: - Computertomografie(CT)-basierte Messung der fraktionellen Flussreserve (FFR), kurz (CT-FFR) (FORECAST, PRECISE, TARGET), wobei PRECISE und TARGET nicht	Verzerrungspotential endpunktübergreifend für die CATCH-2 Studie und FORCAST als niedrig eingestuft, für die Studie Yu 2020 als hoch (adäquate Erzeugung der Randomisierungsfrequenz sowie verdeckte Gruppenzuteilung mit unklar klassifiziert) daher für Yu 2020 für alle Endpunkte hohes Verzerrungspotential für die beiden anderen Studien alle Endpunkte mit niedrigem Verzerrungspotential		**Abschlussbericht im Vergleich zum Vorbericht** Neben redaktionellen Änderungen ergaben sich folgende Spezifizierungen oder Änderungen im Abschlussbericht: ▪ Studie PROTECCT (im Vorbericht als Studie mit unklarem Status) wurde aufgrund neuer Daten (Publikation) ausgeschlossen

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				ausreichend den Einschlusskriterien entsprachen – Ausschluss aus der Bewertung, ergänzend descriptiv dargestellt - CT-basierte Messung der myokardialen Perfusion (CTP) (CATCH-2, Yu 2020) beide Verfahren sind technisch nicht vergleichbar, daher sind zusammenfassende Metaanalysen nicht sinnvoll n = 2 laufende Studien sowie n = 1 Studien mit unklarem Status **Ergebnisse** nach Auswertungszeitpunkten - von bis zu 30 Tagen nach der Untersuchung dem periprozeduralen Auswertungszeitraum, - von 6 bis 24 Monaten dem mittelfristigen Auswertungszeitraum und - von 2 bis 5 Jahren dem langfristigen Auswertungszeitraum zugeordnet es lagen nur Daten zum mittelfristigen Zeitpunkt vor **Fragestellung 2** Gesamtmortalität CATCH-2, 18 Monate - n = 3/300 (1,0%) vs. n =3/300 (1,0%)	bewertet, Ausnahme die Lebensqualität (SAQ-7 (aus FORECAST): hohes Verzerrungspotential durch fehlende Verblindung und subjektive Erhebung		▪ Studie TARGET (im Vorbericht als Studie mit unklarem Status) wurde berücksichtigt und ergänzend dargestellt (Publikation) ▪ Begriff für das Krankheitsbild der nicht obstruktiven KHK wurde in Kapitel 1 ergänzt ▪ in Kapitel 1 wurde klarer dargestellt, dass bei dem CCS (in Abgrenzung zum ACS) die Ischämie nur unter Belastung auftritt ▪ Charakterisierung der Intervention im CCTA-Arm der Studie DISCHARGE wurde im Bericht im Abschnitt 4.2.1 und in Tabelle 18 angepasst ▪ für die ergänzend dargestellte Studie PRECISE wurde ein Manuskript eingereicht, aus welchem zusätzliche Daten zur Verfügung standen (Folge: Überarbeitung der Verzerrungspotenzialbewertung und Berücksichtigung von 2 weiteren Endpunkten (kardiovaskuläre Mortalität, instabile Angina Pectoris) ▪ Daten zum Endpunkt krankheitsspezifische

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				- Peto-OR 1,00 [0,20; 4,99], p >0,999, hohe Ergebnisqualität FORECAST, 9 Monate - n = 2/699 (0,3%) vs. n = 0/700 (0%) - OR 5,02 [0,24; 104,78], p = 0,171, hohe Ergebnisqualität PRECISE, 11,8 Monate - n = 5/1057 (0,5%) vs. n = 7/1046 (0,7%) - HR 0,74 [0,24; 2,35], p = k. A. Yu 2020, 12 Monate - n = 0/120 (0%) vs. n = 0/120 (0%), mäßige Ergebnisqualität - k. A. kardiovaskuläre Mortalität CATCH-2, 18 Monate - n = 0 / 300 vs. 0 / 300, hohe Ergebnissicherheit - k. A. PRECISE, 11,8 Monate - n = 1/1057 (0,1%) vs. n = 2/1046 (0,2%) - k. A. TARGET, 12,2 Monate - n = 2/587 (0,3%) vs. n = 1/589 (0,2%) - OR 0,96 (0,20; 18,85), p = 0,60 Yu 2020 - n = 0 / 120 (0%) vs.n = 0 / 120 (0%), mäßige qualitative Ergebnissicherheit - k. A.			Lebensqualität, gemessen anhand des Gesamtscore des SAQ-7 aus der Studie FORECAST wurden ergänzt • in Kapitel 5 wurde ein Abschnitt zum Wert der Diagnose einer nicht obstruktiven KHK eingefügt • Nutzenaussage zu Fragestellung 2 wurde geändert, siehe Abschnitt 4.4 • im Vorbericht war im Ergebnisabschnitt 4.3.4.8 dargestellt, dass die Ergebnisse der Studie PRECISE nur ergänzend berichtet werden; jetzt im vorangehenden Abschnitt 4.3.1 zu den Studiencharakteristika dieses Vorgehen begründet und in allen Tabellen, die Daten zur Studie PRECISE enthalten, jeweils anhand einer Fußnote auf die rein ergänzende Darstellung der Studie verwiesen • bei der nur ergänzend berichteten Studie PRECISE wurde (wie bei der Studie TARGET) auf die Darstellung der Bewertung

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				MACE PRECISE, 11,8 Monate - n =18/1057 (1,7%) vs. n = 12/1046 (1,1%) - HR 1,57 (0,76; 3,27), p = k.A. Herzinfarkt CATCH-2, 18 Monate - n =1/300 (0,3%) vs. 2/300 (0,7%) - Peto-OR 0,51 (0,05; 4,94), p = 0,683, hohe Ergebnissicherheit FORECAST, 9 Monate - n = 9/699 (1,3%) vs. 3/700 (0,4%) - OR 3,03 (0,82; 11,24), p = 0,084, hohe Ergebnissicherheit PRECISE, 11,8 Monate - n = 13/1057 (1,2%) vs. 5/1046 (0,5%) - HR 2,67 (0,94; 7,52), p = k. A. TARGET, 12,2 Monate - n = 7/587 (1,2%) vs. n = 9/589 (1,5%) - OR 0,78 (0,29; 2,10), p = 0,683 Yu 2020, 12 Monate - n = 0/120 (0%) vs. 0/120 (0%)			des Verzerrungspotenzials und der Ergebnisse zu Endpunkten in den Abschnitten 4.3.3 und 4.3.4 verzichtet (Daten in den Abschnitten A3.3.1.2 und A3.3.2.) **Abschlussbericht Version 1.1 im Vergleich zum Abschlussbericht Version 1.0** ▪ Abschnitt A1.2 ein fehlerhafter Verweis nun auf Kapitel 5 korrigiert und an gleicher Stelle eine formale Anpassung durch Ergänzung eines Aufzählungspunkts vorgenommen Abschnitt A1.2 wurde ein Aufzählungspunkt zur nun deutlicher gekennzeichneten ergänzenden Darstellung der Studie PRECISE hinzugefügt

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				- k. A., mäßige Ergebnissicherheit Schlaganfall FORCAST, 9 Monate - n = 0/699 (0%) vs. 1/700 (0,1%) - OR 0,33 (0,01; 8,20), p = 0,530 instabile Angina pectoris CATCH-2, 18 Monate - n =1/300 (0,3%) vs. n =1/300 (0,3%) - Peto-OR 1,00 (0,06; 16,02), p > 0,999 PRECISE, 11,8 Monate - n = 9/1057 (0,9%) vs. n = 5/1046 (0,5%) - k. A. TARGET, 12,2 Monate - n = 39/587 (6,6%) vs. n = 44/589 (7,5%) - OR 0,88 (0,56; 1,38), p = 0,683 Angina Pectoris CATCH-2, 18 Monate - n = 18/300 (6,0%) vs. n = 24/300 (8,0%) - OR 0,73 (0,39; 1,38), p = 0,530 Vermeidung unnötiger invasiver Diagnostik CATCH-2			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				- n = 15/300 (4,3%) vs. n = 35/300 (11,7%) - OR 0,34 (0,18; 0,66), p > 0,001, hohe Ergebnissicherheit FORCAST - n = 30/699 (4,3%) vs. n = 62/700 (8,9%) - OR 0,46 (95 % KI 0,29; 0,72), p < 0,001, hohe Ergebnissicherheit PRECISE - n = 27/1057 (2,6%) vs. n = 107/1046 (10,2%) - HR 0,18 (95 % KI 0,12; 0,30), p < 0,001 TARGET - n = 88/608 (14,5%) vs. n = 184/608 (30,3%) - OR 0,39 (95 % KI 0,29; 0,52), p < 0,001 krankheitsspezifische Lebensqualität, FORECAST (SAQ-7), 9 Monate - MWD: −1,9; 95 %-KI: [−4,93; 1,13]; p = 0,22, mäßige Ergebnissicherheit TARGET (SAQ-7), 12,2 Monate - MWD: -0,8 (-1,99; 0,39), p = 0,15 **unerwünschten Ereignisse** es lagen keine Daten vor			
33570	[GA20-01] CT- oder MRT-Diagnostik bei Verdacht auf chronische koronare Herzkrankheit: eine Evidenzkartierung, Letzte Aktualisierung 30.06.2020.	2020	**Fragestellung** Kartierung der Evidenz zu nicht invasiven diagnostischen Verfahren mittels computertomografischer Koronarangiografie und Magnetresonanztomografie	n = 24 systematische Übersichtsarbeiten (SR) relevant, n = 9 SR eingeschlossen (n = 4 zu RCT und n = 5 zur diagnostischen	n.a.	E	Dieser Bericht wurde ohne die Beteiligung externer Sachverständiger erstellt. Für die eingeschlossenen

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
	www.iqwig.de/download/ga20-01_herz-ct-oder-mrt-bei-verdacht-auf-khk_arbeitspapier_v1-0.pdf [14]		**Studientyp** Systematische Übersichtsarbeit auf Basis randomisierter kontrollierter Studien Basis von Studien zur diagnostischen Güte (MEDLINE, NICE, AHRQ, ab 2015) **Ein- und Ausschlusskriterien** P: Personen mit Verdacht auf chronische koronare Herzkrankheit *selektierten Populationen mit Vor-erkrankungen wie Mitralklappeninsuffizienz, Diabetes oder einer Nierenerkrankung wurden nicht eingeschlossen, ebenso Personen, die bereits eine perkutane Koronarintervention in Form eines Stents erhielten, eine Bypassoperation erhielten oder infolge einer Restenose erneut behandelt werden **Intervention** computertomografischer Koronarangiografie (CTA) und Magnetresonanztomografie (Stress-MRT) (*Mehrschicht-Spiral-CT, Stress-Perfusions-MRT und Dobutamin-Stress-MRT) **Kontrolle** invasive Koronarangiografie (ICA) ggf. mit Messung der fraktionellen Flussreserve (FFR) sowie zu den nicht invasiven Verfahren (Myokard-Perfusions-Single-Photonen-Emissions-Computer-Tomografie, Stress-Echokardiografie,	Güte) sowie n = 3 Leitlinien zu Test-strategien zur Diagnose einer chronischen KHK Charakteristika der eingeschlossenen Arbeiten s. Tabelle 4 (RCT), S.14 sowie Tabelle 11 ab S. 23 (diagnostische Güte) im Bericht; SR zu RCT schlossen 3-6 Primärstudien ein, SR zur diagnostischen Güte 10-65 (CTA) sowie 4-67 (Stress-MRT) PROMISE mit n = 10 003 und SCOT-HEART mit n = 4146 waren die beiden größten Studien aus den n = 4 SR zu RCT zur CTA Ergebnisse: CTA-basiert vs. ICA Gesamtmortalität kein Effekt Myokardinfarkt: , n = 3 SR Notwendigkeit einer nachgeschalteten ICA, n = 1 SR MRT-basiert Gesamtmortalität - unzureichende Datenlage Myokardinfarkt - unzureichende Datenlage Notwendigkeit einer nachgeschalteten ICA, n = 1 SR			systematischen Übersichten und Leitlinien wurde keine detaillierte Prüfung in Form einer Bewertung ihrer Qualität vorgenommen. Für RCT sollte die Randomisierungsfrequenz sowie Gruppenzuteilung geprüft werden. Grund: Evidenzkartierung war das Ziel Zum Nutzen und Schaden nicht invasiver CTA- und Stress-MRT-Diagnostik bei Personen mit Verdacht auf KHK liegt aussagekräftige Evidenz vor (RCT/SR). Daher wäre eine Nutzenbewertung eines der beiden oder beider Verfahren sinnvoll möglich. Die 3 ausgewählten evidenzbasierten Leitlinien empfehlen übereinstimmend nicht invasive Verfahren als 1. Test zur Diagnose einer KHK. (vgl. S. 33ff) Tabelle 6 beschreibt, dass der Einsatz der CTA im Vergleich zur ICA zu einer statistisch signifikant geringeren Häufigkeit von Myokardinfarkten führte; dennoch wird aus den Arbeiten berichtet, dass trotz

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
			Belastungs-Elektrokardiogramm und computertomografische Messung der fraktionellen Flussreserve) oder invasiven Koronarangiografie ggf. mit Messung der fraktionellen Flussreserve oder mit der klinischen Nachbeobachtung als Referenztest **Outcome** Gesamtmortalität (S. 17 bzw. S. 20) Myokardinfarkt (S. 18 bzw. S. 21) Notwendigkeit einer nachgeschalteten ICA (S. 19 bzw. S. 21) ergänzend diagnostische Güte: Sensitivität und Spezifität				bereits erfolgter CTA teilweise eine ICA im Anschluss (mit unterschiedlicher Häufigkeit) notwendig ist (mit Hinweis auf die Bildqualität) - Abhängigkeit von der Strategie zur Diagnose und damit dem Versorgungskontext; es wird von 490 000 isolierten ICA in Deutschland im Jahr 2018 berichtet Hintergrund: Morphologische Verfahren dienen dem direkten Nachweis von Stenosen, wohingegen die funktionellen Verfahren die Folgen von Stenosen für die Durchblutung des Herzmuskelgewebes nachweisen. Weitere nicht invasive Verfahren in der Versorgung sind neben der Stress-Perfusions-MRT und der Dobutamin-Stress-MRT die 3 ebenfalls funktionellen Verfahren Myokard-Perfusions-Single-Photonen-Emissions-Computer-Tomografie (SPECT), Stress-Echokardiografie und Belastungs-Elektrokardiogramm (EKG)
ergänzende/weiterführende Information							
33518	Rolf, A. et al. Positionspapier Erbringung kardialer CT-Leistungen Kardiologie 2023 · 17:81–94.	2023	**Hintergrund** Nationale Herz-Kreislauf-Strategie in Deutschland	es werden u. a. die Indikation sowie Mindestanforderungen an die Befun-	n. a.	Ei	Auto*innen schlussfolgern, dass ein kooperatives He-

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
	https://doi.org/10.1007/s12181-023-00599-z, https://leitlinien.dgk.org/2023/positionspapier-qualitaetskriterien-fuer-die-erbringung-kardialer-ct-leistungen/ [15]		kardiale Computertomografie ein bildgebendes Verfahren mit definierter Indikation für die Diagnostik und Therapievorbereitung **Ziel des Positionspapies der DGK** Indikationen und Qualitätskriterien für die Durchführung, Befundung und Interpretation der kardialen CT aus Sicht der kardiologischen Fachgesellschaft (Leitfaden Heart-Team-Modell) **Intervention** CT-Koronarangiografie - Untersuchungsablauf (stabile Herzfrequenz <60/min ist anzustreben, um die Wahrscheinlichkeit von Artefakten zu minimieren und die Anwendung von Verfahren zur Reduktion der Strahlenexposition zu erlauben, ohne die Bildqualität negativ zu beeinflussen) Alle der folgenden Kriterien müssen gewährleistet sein – Vor Untersuchungsbeginn Beurteilung von Herzrhythmus und -frequenz anhand zumindest 1-Kanal EKG in tiefer Inspiration – Medikamentöse Senkung der Herzfrequenz bei Ruhefrequenz >65/min durch die Gabe von Betablockern oral (genügend zeitlicher Vorlauf: zumindest 45 min vor der Untersuchung) oder Ivabradin (Vorlauf zumindest 24 h vor der Untersuchung) und zusätzlich ggf. β-Blockern i.v. (Metoprolol bis 40mg)	dung beschrieben sowie Anforderungen an die Untersuchung sowie klinischen Angaben und die technischen Qualitätskriterien sowie Logistische und organisatorische Qualitätskriterien; ergänzt um Kriterien zur Qualitätskontrolle - es wird angegeben, dass etwa 200 Kardiologen aktuell die **Qualifikation** im Level II und III für die kardiale CT besitzen (s. u.) sowie rund 350 für Level II und III für die kardiale MRT - ergänzt um die Angabe von 294 Radiologen mit analogem Level Q2 sowie 195 mit analogem Level Q3 der radiologischen Zertifizierungsprogramme (allerdings sind CT und MRT hier kombiniert angegeben für eine Qualifikation) - geforderte Mindestanforderung: Qualifikation auf Level II bzw. Q2 **gemeinsame Kompetenzen (für jeden Schritt von Indikation bis Therapieempfehlung)**: diagnostischer Pfad mit Selektion des angemessenen Verfahrens (patientenindividuelle Beschwerden und Risikoprofil zu berücksichtigen) sowie lokale Verfügbarkeit und Expertise nur die Patient*innen sollen Zugang zur Methode bekommen, die a) davon wirklich profitieren, b) bei denen eine Leitlinienindikation vorliegt, und c) sichergestellt ist, dass der Befund zu			art-Team-Modell mit gemeinsamer Erbringung der Leistung durch Radiologen und Kardiologen ist am besten geeignet erscheint, die Qualitätsziele zu erreichen und eine nicht evidenzbasierte, Zusatzleistungen provozierende und damit das Gesundheitssystem zusätzlich signifikant belastende Leistungsausweitung zu vermeiden. es wird auf eine sich stetig weiterentwickelnde Evidenzlage hingewiesen Abb 1 auf S. 90 zeigt die Pfade und Qualitätskriterien des kooperativen Modells für die CCTA (ambulant und stationär) im Überblick **ältere Versionen:** Update 2020: Giannitsis, E., Post, F., Haerer, W. et al. Kriterien der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung für „Chest Pain Units". Kardiologe (2020). https://doi.org/10.1007/s12181-020-00417-w https://leitlinien.dgk.org/2020/kriterien-der-deutschen-gesellschaft-fuer-kardiologie-

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
			– Gabe von Nitraten zur Koronardilata-tion, abgesehen von Patientinnen/Pati-enten mit Kontraindikationen – Kontrastmittelflussrate ≥5ml/s Nachsorge: Bei der CCTA-Überwa-chung für zumindest 30 min nach Gabe blutdruck- und herzfrequenzwirksamer Medikamente Während der Prämedikation ist auf eine ausreichende Überwachung der Patien-tinnen/Patienten zu achten. In Notfallmedizin geschultes ärztliches und Assistenzpersonal muss unmittel-bar verfügbar sein, umauf Bradykardie oder Hypotonie reagieren zu können.	einer unmittelbaren klinischen Konse-quenz führt, ohne eine Kette weiterer (für die Patient*innen belastende und das Gesundheitssystem kostenintensive) Folgeuntersuchungen mit nichtinvasiver Diagnostik und nach-folgend eventuell dann doch invasiver Diagnostik zur Absicherung nach sich zu ziehen geforderte Angaben zur Untersuchung sind: 1. Symptomatik des Patienten, 2. kardiovaskulären Risikofaktoren, 3. Vortestwahrscheinlichkeit für eine KHK und 4. relevanten Vorerkrankungen (insbe-sondere Vorbefunde aus der Echokardiographie oder anderen bildgebenden Verfahren sind zu dokumentieren) Für die CCTA sind Kontraindikationen zur medikamentösen Senkung der Herzfrequenz (z.B. AV-Block, Vormedi-kation mit Kalziumantagonisten vom Nicht-Dihyd-ropyridin-Typ) und zur Gabe von Nitra-ten (z. B. hypertroph-obstruktive Kardi-omyopathie, Aortenklappenstenose, PDE-5-Hemmer-Einnahme) bezüglich der Indi-kationsstellung zu beachten und in der Anforderung zu dokumentieren. technischen Parameter des eingesetz-			herz-und-kreislaufforschung-fuer-chest-pain-units-2/ Perings, S., Smetak, N., Kelm, M. et al. Krieterien der Deutschen Gesell-schaft für Kardiologie – Herz- und Kreislauffor-schung e. V. für „Brust-schmerz-Ambulanzen". Kardiologe (2016) 10: 301. doi:10.1007/s12181-016-0074-4 https://leitli-nien.dgk.org/2016/krite-rien-der-deutschen-gesell-schaft-fuer-kardiologie-herz-und-kreislauffor-schung-e-v-fuer-brust-schmerz-ambulanzen-up-date-2016/ H. Reinecke, M. Braun, L. Frankenstein et al. (2015) Kriterien für die Notwen-digkeit und Dauer von Krankenhausbehandlun-gen bei Koronarangiogra-fien und –Interventionen Kardiologe 2015 · 9:295–302 https://leitli-nien.dgk.org/2015/krite-rien-fuer-die-notwendig-keit-und-dauer-von-kran-kenhausbehandlungen-bei-koronarangiogafien-und-interventionen/

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				ten CT-Gerätes und das Untersuchungsprotokoll beeinflussen Bildqualität und Strahlenexposition bei CT-Untersuchungen des Herzens in maßgeblicher Weise - empfohlen werden hier CT-Systeme, die sowohl über die Möglichkeit zur Spiral/Helikal-Akquisition mit retrospektiv EKG-synchronisierter Bildrekonstruktion als auch zur axialen Akquisition mit prospektiver EKG-Triggerung verfügen - Für CT-Untersuchungen des Herzens außerhalb der Koronararterien mit geringerer Ortsauflösung sind ggf. geringere Anforderungen ausreichend - die DGK hat zudem 3 Kompetenzebenen definiert, die es dem Programmkandidaten ermöglichen, diese Qualifikation in konsekutiven Schritten zu erwerben und die Weiterbildung zum Kardiologen um spezielle Inhalte zu erweitern, Level 1 zur Stellung der richtigen Indikation, Level II zur selbstständigen Planung, Durchführung und Befundung (beinhaltet Praxisanwendungen), Level III (über 12-Monate Praxiseinsatz mit mind. 300 Befundungen + vertiefende Ausbildung im Katheterlabor) (u. a. mindestens 3-jährige Grundausbildung in allgemeiner Kardiologie sowie Erfahrungen inder Echokardiographie und im Katheterlabor)			

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
33519	Sieren et al. Current Status of Cardiovascular Imaging in Germany: Structured Data from the National Certification Program, ESCR Registry, and Survey among Radiologists. Rofo. 2022 Feb;194(2):181-191. doi: 10.1055/a-1554-9236. Epub 2021 Aug 12. https://pub-med.ncbi.nlm.nih.gov/34384112/ [16]	2022	**Fragestellung** Überblick über die in radiologischen Einrichtungen in Deutschland angebotenen kardiovaskulären Bildgebungen (KVB) **Studientyp** Registerstudie, - Datenbank des nationalen Zertifizierungsprogramms der Deutschen Röntgengesellschaft (DRG) von 2015-2021 - bundesweite online-Umfrage aus 2019 (ambulant und stationär) aus n = 18 Fragen - Daten aus dem Register der European Society of Cardiovascular Radiology (ESCR) **Endpunkte** Anzahl der für die KVB zertifizierten Zentren und Personen Anzahl durchgeführter kardialer CT- und MRT-Untersuchungen Befundgewohnheiten Teilnahme am ESCR-Register *certification levels: Q1 (basic knowledge) to Q3 (comprehensive knowledge, instructor)	n = 71 Zentren und n = 1278 Personen waren für KVB zertifiziert - Q1 n = 902 (71 %), Q2 n = 227 (18 %), Q3 n = 149 (12 %) - Cardiovascular Imaging Working Group (WG CVI) mit n = 1612 registrierten Mitgliedern in 2021 - deutlicher Anstieg seit 2015 - Teilnahmequote am ESCR-Register: bei 48 % Umfrage: n = 184 Teilnehmende bzw. Rückmeldungen (n = 30 aus Universitätskliniken, n = 76 aus Kliniken, n = 78 aus privaten Praxen) (Umfrageteilnehmende: n = 262 (38 %) aus Universitätskliniken, n = 289 (42 %) aus Kliniken und n = 144 (21%) aus privaten Praxen) - n = 69 286 CT-Untersuchungen / Jahr --- n = 30 682 (44 %) in Universitätskliniken --- n = 27 521 (40 %) in Kliniken --- n = 11 083 (16 %) in privaten Praxen - n = 64 281 MRT-Untersuchungen / Jahr --- n = 22 630 (33 %) in Universitätskliniken --- n = 28 151 (40 %) in Kliniken --- n = 13 500 (20 %) in privaten Praxen - von den 99 PLZ-Regionen in Deutschland haben n = 56 (57 %) einen direkten Zugang zu zertifizierten Zentren	n. a.	Ei	Autor*innen leiten flächendeckende Verfügbarkeit der KVB durch Radiologen ab; regionale Cluster werden beschrieben sowohl ambulant als auch stationär hochqualifizierte Expertise Versorgungssicherstellung und wirtschaftliche Nachhaltigkeit werden als Herausforderungen beschrieben es wir ergänzend das Zertifizierungsprogramm der DRG beschrieben, das u. a. ein Online-Angebot zur Weiterqualifizierung enthält (CONRAD)

Nr.	Referenz	Jahr	Charakteristika	Ergebnisse	Methodische Qualität	A/E	Kommentar
CT-Coronarangiografie							
				Umfrage und ESCR-Register: - Befunde zumeist durch Radiologen, in geringem Maße in gemeinsamen Konsensus-Meetings mit nichtradiologischen Fachdisziplinen durchgeführt - n = 88 (48 %) der Institutionen dokumentieren ihre Ergebnisse in ESCR Registern --- n = 181 deutsche Präsenzen berichten kardiale MR und n = 160 kardiale CT Fälle im Register			

12.3 Kapitel Therapieplanung und gemeinsame Entscheidungsfindung

IQWIG ThemenCheck Medizin – Behandlungsgespräche (gemeinsame Entscheidungsfindung)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Behandlungsgespräche: Führt eine gemeinsame Entscheidungsfindung von Arzt und Patient bei der Therapiewahl zu besseren Ergebnissen? HT22-01. www.iqwig.de/sich-ein-bringen/themencheck-medizin/berichte/ht22-01.html Stand: 04.09.2023 (vorläufiger Bericht) [17]	**Fragestellungen** Ziele sind - die Nutzenbewertung verschiedener Interventionen (oder Kombination) zur Unterstützung der gemeinsamen Entscheidungsfindung von Ärzt*innen/Leistungserbringer*innen und Betroffenen (Shared Decision Making) - im Vergleich oder zum Standardvorgehen ohne Shared Decision Making	n = 9 SR bewertet (AMSTAR-II), n = 2 mit nidrig bis kritisch eingestuft, daher aus der Nutzenbewertung ausgeschlossen n = 7 SR mit hoher bis moderater AMSTAR-II-Bewertung (n = 252 RCT) [4,8,9,13,25-27] (Seite 34) - n = 3 fokussierten auf „Entscheidungshilfen für Patientinnen und Patienten" (Scalia 2019 [28], Stacey 2017 [13], Yen 2021 [27]) - n = 4 fokussierten auf Interventionen bei Betroffenen, Leistungserbringer*innen oder beiden im Vergleich zum Standard (Jull 2021 [25], Legaré 2018 [4], NICE A 2021 [8] und NICE B 2021 [9])	n.a. Evidenzqualität für die berichteten statistisch signifikanten Ergebnisse aus Meta-Analysen wurde durch die Autor*innen mit niedrig bis hoch bewertet (Herabstufung teils wegen schwerer Design-Mängel, Verzerrungsrisiko, Heterogenität, indirekter Evidenz, unzureichender Präzision); tlw. geprüft durch Sensitivitätsanalysen insbesondere bei der SDM-Intervention "Entscheidungshilfen" war die	Hinweis: Dieser Bericht wurde durch externe Sachverständige erstellt. Der vorläufige HTA-Bericht wird zur Anhörung gestellt. die Autor*innen schlussfolgern, dass für die patientenrelevanten Endpunkte Mortalität, Morbidität und Lebensqualität

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- Bestimmung der Kosten (Interventionskosten) - Bewertung der Kosteneffektivität verschiedener Interventionen - die Aufarbeitung ethischer, sozialer, rechtlicher und organisatorischer Aspekte Die Themenvorschlagende interessiert sich für die Frage, ob Maßnahmen wie die gemeinsame bzw. partizipative Entscheidungsfindung von Ärztin und Arzt und Patientin und Patient Einfluss auf das Behandlungsergebnis und die Patientenzufriedenheit haben können. **Methodik** HTA-Bericht; u. a. systematische Übersichtsarbeit zu SR (fokussierte Informationsbeschaffung ab 2010) in MEDLINE, HTA Database, Referenzlisten SR, zudem bei NICE, Agency of Healthcare Reseacrh and Quality (AHRQ) - letzte Suche am 07.11.2022 (Suchzeitraum ab 2017) zur gesundheitsökonomischen Bewertung sowie ethischen, sozialen und rechtlichen Betrachtung vgl. Bericht ab S. 31; zudem wurden Interviews mt Betroffenen duchgeführt **Ein- und Ausschlusskriterien**	Fokus: o (a) zur Vorbereitung auf ein Gespräch, o (b) zur Verbesserung der Gesundheitskompetenz der Betroffenen, o (c) zur Präferenzerhebung, o (d) zur Patienten-Aktivierung, o (e) zur Unterstützung der Betroffenen durch Dritte, o (f) zur Dokumentation der Versorgung, o (g) Kombinationen der genannten Interventionen - Studien wurden in sehr unterschiedlichen Indikationen, Ländern und Settings (ambulant und/oder stationär) durchgeführt - meisten RCT aus den USA oder Europa - häufig im Bereich des Screenings oder - der Behandlung von onkologischen, Herz-Kreislauf- und psychischen Erkrankungen n = 5 Evidenzberichte des NICE zum Nutzen und Schaden von SDM-Interventionen (seit 2015), in 2021 veröffentlichte Leitlinie des NICE zum Thema (Quelle s. u.) werden eingangs im Bericht beschrieben **Ergebnisse** Übersicht: Tabelle 1 (PROMs), Tabelle 2 (SDM-bezogene) und Tabelle 3 (weitere Endpunkte) des Berichts für die folgenden Vergleiche wurden Endpunkte berichtet: 1) Entscheidungshilfen vs. Standardversorgung 2) SDM-Interventionen bei Betroffenen vs. Standardversorgung bzw. andere SDM-Interventionen bei Betroffenen 3) SDM-Interventionen bei Leistungser*innen vs. Standardversorgung bzw. andere SDM-Interventionen bei Leistungserbringer*innen 4) SDM-Interventionen bei beiden vs. Standardversorgung bzw. andere SDM-Interventionen bei beiden	Interpretation der Ergebnisse erschwert durch eine fehlende Einordnung der Effektgröße bzw. Relevanz (eingeschränktes Vertrauen in die Ergebnisse), eine Bewertung und Diskussion der Ergebnisse wird gewünscht für andere SDM-Interventionen wurden die Evidenzqualität als zu niedrig bzw. die Aussagesicherheit als unzureichend bewertet (u. a. schwache Effektschätzer) hohe klinische und inhaltliche Heterogenität wird berichtet (Indikation, Population, Intervention, Vergleiche, Endpunkte (Operationalisierung)), zeigt sich auch in einer statistischen Heterogenität (nur wenige Studien konnten zusammengefasst werden) eigene, zusätzliche MA wurden daher nicht durchgeführt eine grobe Kosten(Aufwands-)schätzung war möglich, für die Regelversorgung konnten aber keine verbindlichen Angaben gegeben warden - die gesundheitsökonomische Auswertung wird durch die Autor*innen mit einer Vermutung gegeben, dass für bestimmte Indikationen und Populationen im Vergleich zum Standard kosteneffektiv	kein Nutzen oder Schaden von SDM-Interventionen im Vergleich zur Standardversorgung ohne SDM bzw. Im Vergleich zu anderen SDM-Interventionen abgeleitet warden kann für die Intervention "Entscheidungshilfen" wurden 6 von 17 untersuchte SDM-bezogene Endpunkte mit einem Vorteil im Vergleich zur Standardversorgung ohne SDM bewertet: ▪ „Umsetzung von SDM/ Einbindung des Patienten", ▪ „Arzt-Patient-Kommunikation", ▪ „Wissen", ▪ „richtige Einschätzung von Risiken", ▪ „Übereinstimmung zwischen informierter Präferenz und Entscheidung" ▪ „Entscheidungskonflikt" Nachteile wurden für keine der SDM-Interventionen und Vergleiche gefunden

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- erwachsene (> 18 Jahre) und einwilligungsfähige Betroffene - keine Beschränkung auf bestimmtes Krankheitsbild - Leistungserbringer*innen - SR, RCT (Ergebnisse aus nicht-RCT wurden nicht berücksichtigt) - SR vor 2010 wurden nicht herangezogen (da erst ab da eine systematische Aufbereitung in Studien erfolgte, dort wurden verbindliche Standards definiert) **Qualitätsbewertung** AMSTAR-II, keine eigene Bewertung der in SR eingeschlossenen RCT, Qualitätsbewertung der SR wurde übernommen (Evidenzqualität, hoch, moderat, niedrig und sehr niedrig; abweichend von den Bezeichnungen des IQWiG („Ergebnissicherheit") und des Cochrane Netzwerks („Aussagesicherheit")) **Intervention** Zur Unterstützung einer gemeinsamen Entscheidungsfindung (SDM-Interventionen): - SDM-Schulung von Ärzt*innen oder anderen an der Behandlung beteiligten Personen (z. B. anhand von Fallbeispielen) - Decision Coaching von Betroffenen durch bspw.	Ergebnisse zu den patientenrelevanten Endpunkten in Tabelle 8, Tabelle 9, Tabelle 10 und Tabelle 11 (Matrix Tabelle 1, S. 37) zeigen die Landkarte der Beleglage für die jeweiligen SDM-Interventionen und Vergleiche (Matrix s. a. Tabelle 2 und 3, S. 38): z. B. kein Anhaltspunkt, Hinweis oder Beleg für einen Nutzen/Schaden für die Endpunkte: • HRQoL für 1), 2), 3) und 4) • Angst, Depression, andere psychische Belastung für 1) und 2) keinen der patientenrelevanten Endpunkte (Mortalität, Morbidität und gesundheitsbezogene Lebensqualität) erbrachten Nutzennachweise (es fehlte hochwertige Evidenz zu diesen Endpunkten, in den RCT entweder gar nicht oder als sekundäre Endpunkte erhoben), Fokus überwiegend auf SDM-bezogenen Endpunkten: Matrix der ermittelten Daten in Tabelle 1, S. 37 (keine berichteten Daten zur Gesamtmortalität, in n = 4 SR Angaben zur Mortalität (Gesundheitszustand/Symtome aus Einzelstudien), in n = 7 SR Angaben zu Nebenwirkungen (u. a. Angst/Depression) – darunter in n = 4 aus Metaanalysen, in n = 5 SR Angaben zur Lebensqualität – darunter in n = 1 SR aus Metaanalysen) Endpunkt Nutzen-Aussage (aus Perspektive der SDM-Intervention, im Vergleich zur Standardversorgung oder vergleichbarer Intervention) Entscheidungshilfen - Gesamtmortalität keine Daten berichtet - Morbidität (Gesundheitszustand/ Symptome aus Einzelstudien) ○ Einzelstudienauswertung (n = 1 SR): keine Gruppenunterschiede - HRQoL	oder gar kosteneinsparend sein könnten	es wird als plausible eingeschätzt, dass ein Mehr an Wissen, Umsetzung der SDM, Einbindung der Betroffenen, bessere Kommunikation und eine Verringerung von Entscheidungskonflikten die gemeinsame Entscheidungsfindung im Versorgungsalltag fördern können SDM-Interventionen seien geeignet, die Autonomie der Betroffenen zu stützen (Recht auf Selbstbestimmung) und zudem die Erfüllung der Anforderungen aus dem Patientenrechtegesetz zu unterstützen soziale Sicht: für die Implementierung von SDM-Interventionen ist es wichtig, dass sie auf die Bedarfe aller sozialen Gruppen angepasst und gut zugänglich gemacht werden als hindernde Faktoren beschrieben werden u. a. Zeitmangel

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	qualifizierte Pflegefach-personen (Entscheidungs-begleitung)
	- evidenzbasierte Entschei-dungshilfen oder Patien-teninformationen
	- Maßnahmen zur Aktivie-rung bzw. Motivation von Betroffenen (bspw. zur Kommunikation oder akti-ven Beteiligung am Ent-scheidungsprozess) – Leitfaden 3 Fragen (Wel-che Möglichkeiten?, Vor-/Nachteile?, Wahrschein-lichkeit, dass Vor-/Nach-teile eintreten?)
	Allein oder in Kombination
	
	Vergleich
	Standard ohne SDM-Intervention oder
	andere SDM-Intervention
	
	Endpunkte
	patientenrelevante Endpunkte
	- Mortalität,
	- Morbidität,
	- Nebenwirkungen wie Angst, Depression,
	- Unerwünschte Ereignisse,
	- gesundheitsbezogene Le-bensqualität
	
	Aussage zur Beleglage des (höhe-ren) Nutzens und (höheren) Scha-dens in 4 Abstufungen:
	- ein Beleg (höchste Aus-sagesicherheit),
		○ Einzelstudienauswertung (n = 1 SR): keine Gruppenunterschiede
		Betroffene
		- Gesamtmortalität keine Daten berichtet
		- Morbidität (Gesundheitszustand/ Symptome aus Einzelstudien)
		   ○ Einzelstudienauswertung (n = 3 SR): keine Gruppenunterschiede
		- HRQoL
		   ○ Einzelstudienauswertung (n = 4 SR): keine Gruppenunterschiede
		Leistungserbringer*in
		- Gesamtmortalität keine Daten berichchtet
		- Morbidität (Gesundheitszustand/ Symptome aus Einzelstudien) /
		- HRQoL
		   ○ Einzelstudienauswertung (n = 1 SR): keine Gruppenunterschiede
		   ○ Meta-Analyse (n = 1 SR) vs. Standard: SMD: 0 (-0,06; 0,06), p = 0,94 (2 Stu-dien)
		Betroffene und Leistungserbringer*in
		- Gesamtmortalität keine Daten berichtet
		
		- Morbidität (Gesundheitszustand/ Symptome aus Einzelstudien) /
		- HRQoL
		   ○ Einzelstudienauswertung (n = 1 SR): keine Gruppenunterschiede
		   ○ Meta-Analyse (n = 1 SR) vs. Standard: SMD 0,20 (-0,03; 0,43), p = 0,09 (3 Studien) (physisch)
		SMD 0,21 (-0,01; 0,44), p = 0,07 (3 Studien) (psychisch)
		
		Nebenwirkungen (u. a. Angst, Depression)
		Entscheidungshilfen
		- Einzelstudienauswertung (n = 1 SR): keine Grup-penunterschiede
				(z. B. im Kranken-haus) oder wirtschaftli-che Fehlanreize
				
				die Autor*innen be-werten die gemein-same Entscheidungs-findung aus ethischer und rechtlicher Sicht als geboten, sozial er-wünscht und organisa-torisch umsetzbar
				
				RCT werden gefor-dert, die die Heteroge-nität der Endpunkte und deren Operationa-lisierung reduzieren und auf validierten und konsentierten Erhe-bungs-Methoden und Instrumenten basieren
				
				neben den patienten-relevanten Endpunk-ten erfolgt ein Hinweis auf versorgerrelevante Endpunkte (z. B. die Berufszufriedenheit oder die Zufriedenheit mit der Kommunika-tion und der Behand-lung) (hier nicht ge-messen bzw. berich-tet)

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	- ein Hinweis (mittlere Aussagesicherheit),
	- ein Anhaltspunkt (schwächste Aussagesicherheit)
	- keine dieser 3 Situationen (z. B. keine Daten)
	
	SDM-bezogene Endpunkte (patienten- oder beobachter- bzw. versorgerberichtet, PROMs/OBOMs/CROMs), u. a.:
	- Vorbereitung auf die Entscheidung von Betroffenen
	- Bedauern der Entscheidung (decision regret) von Betroffenen
	- Umsetzung von SDM / Einbindung von Betroffenen (patienten- und beobachterberichtet)
	- Wissen / richtige Einschätzung von Risiken durch Betroffene
	- Entscheidungskonflikt (decisional conflict) von Betroffenen
	- Selbstwirksamkeit (self-efficacy) in der Behandlungsentscheidung von Betroffenen
	- Arzt-Patient-Beziehung und -Kommunikation
	- Zufriedenheit von Betroffenen
	- Empowerment von Betroffenen
	- Übereinstimmung zwischen gewünschter und
		- Angst (n = 2 SR):
		    ○ SMD -0,03 (-0,27; 0,22), p = 0,83 (4 Studien), n = 1 SR
		    ○ SMD 0,02 (-0,22; 0,26], p-Wert nicht berichtet (4 Studien), n = 1 SR
		
		Betroffene
		- Einzelstudienauswertung (n = 1 SR): keine Gruppenunterschiede
		- Meta-Analysen (n = 2 SR)
		vs. Standard:
		    ○ SMD: 0,02 (-0,33; 0,37), p = 0,91 (2 Studien), n = 1 SR
		    ○ SMD: 0,02 (-0,33; 0,37), p = 0,91 (2 Studien), n = 1 SR
		vs. andere Intervention:
		    ○ SMD: -0,11 (-0,27; 0,05), p = 0,17 (2 Studien), n = 1 SR
		    ○ SMD: -0,11 (-0,27; 0,05), p = 0,17 (2 Studien), n = 1 SR
		- Einzelstudienauswertung (n = 1 SR): Depression scheint häufiger bei niedriger Evidenzqualität
		
		Leistungserbringer*innen: /
		Betroffene und Leistungserbringer*innen: /
		
		(weitere) unerwünschte Wirkungen
		Entscheidungshilfen: /
		Betroffene: /
		Leistungserbringer*innen: /
		Betroffene und Leistungserbringer*innen: /
		
		SDM-bezogene Endpunkte finden sich in Tabelle 12, Tabelle 13, Tabelle 14 und Tabelle 15 des Berichts (S. 56-68), Matrix der berichteten Endpunkte vgl. auch Tabelle 2/3 (insgesamt n = 17 betrachtete SDM-bezogene Endpukte)
		
		z. B. richtige Einschätzung von Risiken:		

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	tatsächlicher Einbindung in die Entscheidung
	- Übereinstimmung zwischen gewünschter Option und getroffener Entscheidung
	
	Hinweis:
	Gemeinsame Entscheidungsfindung (shared decision making, SDM) ist Prozess zwischen Betroffenen und Angehörigen der Gesundheitsberufe, im Gespräch treten die Beteiligten miteinander in eine Beziehung, wobei beide eine aktive Rolle haben; es werden für die Krankheit sowie Behandlung relevante Aspekte besprochen und Informationen ausgetauscht, Zusammenhänge sowie Behandlungsmöglichkeiten werden mit Vor- und Nachteilen vorgestellt und auf das Verständnis der Inhalte überprüft; es ist Raum für Fragen und ggf. Betrachtung der und Bezug zu Lebensumstände(n), Präferenzen und Werten der Betroffenen, eine gemeinsame Zieldefinition (fundamental, funktional und symptom-spezifisch) wird angestrebt sowie eine gemeinsame Entscheidungsfindung zur Behandlung oder auch gegen eine Behandlung
	
	Prozess der gemeinsamen Entscheidungsfindung wird als komplex und auf verschiedenen Ebenen von Bedeutung beschrieben: auf der Mikro-, Meso- und Makroebene
		- RR 2,10 (95% KI 1,66; 2,66), p < 0,001, n = 1 SR (Entscheidungshilfen für Betroffene), n = 17 Studien, moderate Evidenzqualität
		
		Zudem sind von S. 69-71 Übersichten zu den Vor/Nachteilen SDM-bezogene Endpunkte dargestellt (Tabelle 16-19)
		
		z. B. Entscheidungshilfen (Tabelle 12, S. 56ff, Matrix Tabelle 16, S. 69):
		Vorteile für
		- die Umsetzung von SDM/Einbindung der Betroffenen:
		  o SDM patientenberichtet (n = 1 SR):
		    ▪ patientengesteuert RR: 1,28 [1,05; 1,55], p = 0,01 (15 Studien, Evidenzqualität moderat)
		    ▪ arztgesteuert RR: 0,68 [0,55; 0,83], p = 0 (16 Studien, Evidenzqualität moderat)
		    ▪ durch beide gesteuert RR: 0,95 [0,83; 1,10]; p=0,52
		  o SDM beobachterberichtet (n = 1 SR):
		    ▪ SMD: 0,94 [0,40; 1,48], p = 0,0007 (9 Studien), großer Effekt
		  o Einzelstudienauswertung (n = 1 SR):
		    ▪ keine Gruppenunterschiede
		    ▪
		    ▪ Bei Auswertung zusammen mit anderen SDM-Interventionene,f: SMD: 0,23 [0,05; 0,42], p-Wert nicht berichtet
		- das Wissen:
		  o MD: 13,27 [11,32; 15,23], p = 0,0001 (Effekt unabhängig vom Zeitpunkt der Intervention: im/vor Gespräch) (52 Studien, Evidenzqualität hoch), n = 1 SR		

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	(Mikroebene steht im Bericht zur Nutzenbewertung im Fokus; Gesundheitsökonomie, Ethik, Recht und sozialer Einfluss v. a. für die Meso- und Makroebene)	- SMD: 0,50 [0,33; 0,67] p < 0,00001 (18 Studien), mittlerer Effekt (n = 1 SR) - MD: 13,91 [9,01; 18,82], p-Wert nicht berichtet (11 Studien), n = 1 SR - die richtige Einschätzung von Risiken: - RR: 2,10 [1,66; 2,66], p < 0,0001 (Effekt unabhängig vom Zeitpunkt der Intervention: im/vor Gespräch) (17 Studien, Evidenzqualität moderat), n = 1 SR - Vermeidung von Entscheidungskonflikten: - MD: -7,22 [-9,12; -5,31], p = 0,0001 (38 Studien, Evidenzqualität hoch), n = 1 SR - SMD: -0,33 [-0,56; -0,09], p = 0,007 (15 Studien), mittlerer Effekt (n = 1 SR) - SMD: -0,41 [-0,83; 0,02], p-Wert nicht berichtet (7 Studien), n = 1 SR - Bei Auswertung zusammen mit anderen - SDM-Interventionene: Low Literacy Scale: MD: -9,59 [-18,94; -0,24] (5 Studien), n = 1 SR - die Arzt-Patient-Kommunikation: - Einzelstudienauswertung: Arzt-Patient Kommunikation scheint besser bei unklarer Evidenzqualität (n = 1 SR) - RR: 1,62 [1,42; 1,84], p-Wert nicht berichtet (3 Studien), n = 1 SR - die informierte Übereinstimmung der Präferenz/Entscheidung: - RR: 2,06 [1,46; 2,91], p < 0,0001 (10 Studien, Evidenzqualität niedrig) Für (fast) alle anderen Parameter und Interventionen sind in der Übersicht keine Vor- oder Nachteile festgestellt worden. u. a. gesundheitsökonomische Betrachtungen ab S. 73		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Quellen: **4. Legare F, Adekpedjou R, Stacey D et al. Interventions for increasing the use of shared decision making by healthcare professionals. Cochrane Database Syst Rev 2018; 7: CD006732. https://dx.doi.org/10.1002/14651858.CD006732.pub4.** 7. NICE. National Institute for Health and Care Excellence: Clinical Guidelines. In: Shared decision making. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2021.; 2021. **8. NICE. NICE Evidence Reviews Collection. Evidence review for effectiveness of approaches and activities to increase engagement in shared decision making and the barriers and facilitators to engagement: Shared decision making: Evidence review A. . In: Shared decision making. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2021.; 2021.** **9. NICE. NICE Evidence Reviews Collection. Evidence review for interventions to support effective shared decision making: Shared decision making: Evidence review B. In: Shared Decision Making. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2021.; 2021.** 10. NICE. NICE Evidence Reviews Collection. Evidence review for decision aids for people facing health treatment or screening decisions: Shared decision making: Evidence review C. In: Shared Decision Making. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2021.; 2021. 11. NICE. NICE Evidence Reviews Collection. Evidence review for risk communication: Shared decision making: Evidence review D. . In: Shared decision making. London: National Institute for Health and Care Excellence Copyright © NICE 2021.; 2021. 12. NICE. NICE Evidence Reviews Collection. Evidence review for effective approaches and activities to normalise shared decision making in the healthcare system: Shared decision making: Evidence review E. . In: Shared decision making. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2021.; 2021		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		13. Stacey D, Legare F, Lewis K et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2017; 4: CD001431. https://dx.doi.org/10.1002/14651858.CD001431.pub5. - Aktualisierung des Cochrane-Reviews von Stacey 2017, auf Anfrage der Autorengruppe des HTA-Berichts wurde mitgeteilt, dass die Aktualisierung des Cochrane-Reviews die Ergebnisse des Reviews aus 2017 bestätigt. Die Aktualisierung wird voraussichtlich Mitte/Ende des Jahres 2023 veröffentlicht. Sie schließt 104 zusätzliche Primärstudien ein. **25. Jull J, Kopke S, Smith M et al. Decision coaching for people making healthcare decisions. Cochrane Database Syst Rev 2021; 11: CD013385.** https://dx.doi.org/10.1002/14651858.CD013385.pub2. **26. Scalia P, Durand MA, Berkowitz JL et al. The impact and utility of encounter patient decision aids: Systematic review, meta-analysis and narrative synthesis. Patient Educ Couns 2019; 102(5): 817-841.** https://dx.doi.org/10.1016/j.pec.2018.12.020. **27. Yen RW, Smith J, Engel J et al. A Systematic Review and Meta-Analysis of Patient Decision Aids for Socially Disadvantaged Populations: Update from the International Patient Decision Aid Standards (IDPAS). Med Decis Making 2021; 41(7): 870-896.** https://dx.doi.org/10.1177/0272989x211020317.		

12.4 Kapitel medikamentöse Therapie - Lipidsenker

12.4.1 Statine mittlere vs. hohe Dosis (Empfehlung 7-13)

NICE (Evidence Review, statins, 2023)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Cardiovascular disease: risk assessment and reduction, including lipid modification [C] Evidence review for statins: efficacy and adverse effects NICE guideline CG181 Evidence review underpinning recommendations 1.4.11 to 1.4.43 and research recommendations in the NICE guideline May 2023 https://www.nice.org.uk/guidance/cg181/evidence/c-risk-assessment-and-reduction-including-lipid-modification-pdf-13065827440 [18]	**Objective** aim of this review is to update the evidence on the clinical and cost effectiveness and safety of different statin intensities in people with and without established cardiovascular disease (CVD) **Search** the following databases (from November 2013) will be searched: - Cochrane Central Register of Controlled Trials (CENTRAL) - Cochrane Database of Systematic Reviews (CDSR) - Embase - MEDLINE - Epistemonikos lists of systematic reviews[2] **Inclusion and exclusion criteria** - SR of RCT, RCT, NMA, IPD - primary and secondary prevention of CVD - adults	updated Version of 2014; changes: - outcome of non-fatal stroke was changed to non-fatal ischaemic stroke - composite outcome of combined major adverse cardiovascular events was added - no stratification by populations was planned; pre-specified subgroup analyses were performed if heterogeneity was observed **background information** statin intensity classification based on the percentage reduction in low-density lipoprotein (LDL) cholesterol they can produce Intensity / LDL-cholesterol reduction (%) / Statin and dose Low intensity / (20% to 30%) - Fluvastatin 20 or 40 mg - Pravastatin 5, 10, 20 or 40 mg - Simvastatin 10 mg Medium intensity / (31% to 40%) - Atorvastatin 10 mg - Fluvastatin 80 mg - Rosuvastatin 5 mg - Simvastatin 20 or 40 mg High intensity / (Greater than 40%) - Atorvastatin 20, 40 or 80 mg - Rosuvastatin 10, 20 or 40 mg	AMSTAR-II high authors noted that for the head-to-head comparisons (studies comparing statins of different intensities or comparing different high intensity statin regimens), the majority of the efficacy evidence was of low or very low quality, with the most common reason for downgrading being imprecision (smaller number of trials and smaller pooled sample size)	authors noted that statins are recognised as the first-choice lipid modification therapy to reduce CVD events and were first appraised by NICE in 2006 authorse noted that in 2014, the guideline recommended that when prescribing a statin, a statin of high intensity should be used (recently, clinical and epidemiological evidence on the benefits of lipid lowering has increased) authors noted that n = 6 relevant Cochrane reviews were identified but could not be included; because they

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[2] Key papers: Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. (2016) Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. New England Journal of Medicine 374(21):2021–31 (#95); Feinstein MJ, Jhund P, Kang J, Ning H, Maggioni A, Wikstrand J, et al. Do statins reduce the risk of myocardial infarction in patients with heart failure? A pooled individual-level reanalysis of CORONA and GISSI-HF. European Journal of Heart Failure 17(4):434–41 (#87)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- studies with follow-up < 1 year were excluded
	- cross-over RCT, non-randomized trials, conference abstracts were excluded
	- trials of statins with aims other than CVD prevention or lipid lowering were also excluded
	
	Intervention
	statins (assume class effect)
	
	Comperator
	placebo, usual care, no treatment
	- different intensities
	- high intensity vs. other high intensity drug/dose
	
	Quality assessment
	Risk of bias (ROBIS, RoB 2.0)
	GRADEpro (quality of evidence)
	
	Outcome
	primary (critical)
	- all-cause mortality (time-to-event)
		Note: Simvastatin 80 mg is no longer used because of risk of myopathy and muscle symptoms and so will not be included in the update. Any existing data on this drug dose will be removed from the analyses.
		
		n = 7 trials were added, n = 43 previously included studies were also retained in the analysis
		- placebo controlled
		  o n = 38 trials
		    ▪ n = 16 primary prevention
		    ▪ n = 20 secondary prevention[3]
		    ▪ ect.
		  o n = 20 trials reported final LDL-cholesterol value for both arms
		- head-to-head statin comparisons
		  o n = 14 trials
		    ▪ n = 2 primary prevention
		    ▪ n = 12 secondary prevention[4]
		    ▪ ect.
		  o n = 10 trials reported final LDL-cholesterol values for both arms
		- adverse effect evidence (additional research question): n = 7 new RCT (n = 10 publications) and n = 24 previously included studies; n = 2 SR
		  o placebo-controlled studies
		  o (n = 16 for primary prevention, n = 12 for secondary prevention; etc.)
				did not include any outcomes relevant to the protocol and 1 because all relevant studies were already included in the 2014 update of this guideline (all studies included in the reviews were cross-checked for inclusion in this review)
				
				authors presented that effect estimate for most comparisons and outcomes did not change sufficiently to change the conclusions from those outlined in the previous update
				
				(authors summary placebo-control: all outcomes showed a direction of effect favouring the use of statins to reduce the risk of fatal and non-

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[3] Quellen Sekundärprävention (placebo-controlled)

9, 24, 33, 75, 94, 101, 112, 137, 139, 143, 144, 151, 154, 164, 167, 170, 176, 189-191

Amarenco 2006[9](SPARCL), Athyros 2002[24](GREACE), Byington 1995[33](PLAC II), Hosomi 2015[75](J-STARS), Koren 2004[94](ALLIANCE), Lemos 2003[101](LIPS), Meade 1999[112](HPS), Pitt 1995[137](PLAC I), Anon 1998[139](LIPID), Anon 1994[143](4S), Anon 2000[144](GISSI), Riegger 1999[151], Sacks 1996[154](CARE), Shepherd 2002[164](PROSPER), Shukla 2005[167], Sola 2006[170], Teo 2000[176](SCAT), Yakusevich 2012[189], Yamada 2007[190], Yokoi 2005[191]

[4] Quellen Sekundärprävention (head-to-head)

34, 52, 54, 78, **99**, 105, 127, 129, **134**, **159, 195**, 196

Cannon 2004[34](PROVE IT TIMI 22), Deedwania 2007[52], Egede 2013[54](VIRHISTAMI), Im 2018[78], Larosa 2005[99](TNT), Liu 2016[105], Nicholls 2011[127](SATURN), Nissen 2005[128,129](REVERSAL), Pedersen 2005[134](IDEAL), Schmermund et al. 2006[159], Zhao 2014[195](CHILLAS), Zou 2003[196]

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- cardiovascular mortality (time-to-event) - non-fatal myocardial infarction (time-to-event) - non-fatal ischaemic stroke (time-to-event) - combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) - quality of life, any validated measure (continuous) - time points - the minimum follow-up is 1 year - the longest available follow-up will be used for each trial, and all these timepoints will be pooled (Cholesterol levels will not be included as a surrogate outcome for CVD risk because it is whether or	o see also Appendix C, Appendix D, forest plots Appendix E and GRADE tables Appendix F o active-control studies: were not included in the review because no harm was found in terms of clinically important differences based on the absolute risk difference in the primary analysis of any statin versus placebo (s. b.) o note: studies with simvastatin 80 mg were excluded from analyses (different from the previous review of 2014) The comparisons available were as follows: • High versus low intensity (3 studies) [34, 52, 78] • **High versus medium intensity (4 studies)** [99, 134, 159, 195] • High versus high intensity (2 studies) [105, 127] • Medium versus low intensity (1 study) [196] note: combined outcome of major adverse cardiovascular events is defined differently across the literature[5] **Results** - Table 7: Clinical evidence summary: statins vs. placebo stratified by statin intensity (page 19 ff)		fatal cardiovascular (CV) events with benefit greatest for non-fatal MI for both relative and absolute risk estimates; an increasing benefit in terms of the relative risk of events with increasing statin intensity was noted for the outcomes of CV mortality and non-fatal MI, which supports the recommendation of high intensity statins as the most effective option; this effect was supported by the newly added composite outcome of MACE, with limited confidence in this evidence (inconsistency of definition))

[5] Definitions that incorporate any of the following events were excluded from the analysis for being too indirect:
- all-cause mortality
- transient ischaemic attack
- peripheral vascular disorder
- peripheral artery bypass graft
- amputation because of atherosclerotic disease
• Definitions that omit fatal or non-fatal stroke were excluded from the analysis for being too indirect.
• Definitions that included the following terms, which fall within the cardiovascular death component, were not excluded nor downgraded for indirectness:
- Resuscitation after cardiac arrest
- Sudden cardiac death
• Definitions that included the following terms, which fall within the cardiovascular death component, were not excluded nor downgraded for indirectness:
- Coronary intervention procedure
- Recanalisation

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	not a CVD event occurs that is important to patients and data on this will be available)	- all-cause mortality
		    ■ low intensity vs placebo, RR 0.89 (0.84 to 0.94), (n = 13 RCT (n = 50,425 participants, high certainty of evidence)
		    ■ medium intensity vs placebo, RR 0.85 (0.80 to 0.90), (n = 9 RCT (n = 43,021 participants, high certainty of evidence)
		    ■ high intensity vs placebo, RR 0.91 (0.83 to 0.99), (n = 8 RCT (n = 43,371 participants, high certainty of evidence)
		    ■ etc.
		- Table 8: Time-to-event results for statins versus placebo (stratified by statin intensity) (page 21f)
		    ○ All-cause mortality
		      ■ Low dose vs. placebo, HR 0.85 (0.78,0.92), n = 5 trials
		      ■ Medium dose vs. placebo, HR 0.77 (0.68, 0.87), n = 3 trials
		      ■ High dose vs. placebo, HR 0.89 (0.79, 1.00), n = 3 trials
		      ■ etc.
		forest plots for placebo comparisons see also Appendix E page 377-385
		
		forest plots for high vs. low intensity statin comparisons see Appendix E page 386-387
		
		forest plot for high vs. high intensity statin comparisons see Appendix E page 390-391
		
		forest plots for medium vs. low intensity statin comparisons see Appendix E page 391		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		High versus medium intensity (forest plots for high vs. medium intensity statin comparisons see also page 388-390) Table 11: Clinical evidence summary: High versus medium intensity statin (page 23f) all-cause mortality - RR 0.99 (0.89 to 1.10), (n = 2 RCT (n = 18,889 participants, low certainty of evidence) cardiovascular mortality - RR 0.92 (0.72 to 1.17), (n = 2 RCT (n = 18,889 participants, very low certainty of evidence) non-fatal myocardial infarction - RR 0.81 (0.72 to 0.91), (n = 3 RCT (n = 19,356 participants, low certainty of evidence) stroke - RR 0.87 (0.70 to 1.08), (n = 2 RCT (n = 9355 participants, low certainty of evidence) major adverse cardiovascular events (MACE) - RR 0.86 (0.75 to 1.00), (n = 3 RCT (n = 20,244 participants, very low certainty of evidence) Table 12: Time-to-event results for medium versus high intensity statin (note opposite direction of effect due to comparison reported in studies) (page 24) - all-cause mortality, HR 0.94 (0.75, 1.19), n = 3 trials - CV mortality, HR 1.09 (0.94, 1.28), n = 2 trials - Non-fatal MI, HR 1.24 (1.11, 1.40), n = 2 trials - Non-fatal stroke - - MACE, HR 1.17 (1.01, 1.36), n = 3 trials **adverse events**		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Table 18: Clinical evidence summary: statins versus placebo (page 34 f) - rhabdomyolysis ('myopathy' from IPD analysis), OR 2.12 (1.20 to 3.73), (n = 13 RCT (n = 103,020 participants, moderate certainty of evidence) - myalgia ('Any muscle pain' from IPD analysis), RR 1.02 (1.01 to 1.04), (n = 13 RCT (n = 103,020 participants, high certainty of evidence) comparator planned (review protocol): primary analysis: - All statins versus placebo/usual care/no treatment - If harm is found for all statins compared with control, then analyse by - Intensity categories (as defined above) - Individual agents within each intensity class committee discussion: "As for the efficacy review, the committee agreed that the updated evidence review for adverse effects was largely supportive of the recommendations from the previous iteration of the guideline." (page 52) "Since no clinically important harms were observed when comparing all statin intensities with placebo, as stated in the review protocol, no analysis was performed to assess specific statin intensity subgroups for the adverse event outcomes." (page 54) note: studies with simvastatin 80 mg were excluded from analyses (different from the previous review of 2014) Table 32 Clinical evidence profile: statins vs. placebo (page 405ff) Rhabdomyolysis (myopathy from IPD analysis) - 33/51554 (0.1%) vs. 15/51466 (0.0%) - OR 2.12 (1.20; 3.73), n = 13 studies - moderate certainty of evidence		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Rhabdomyolysis from studies not in IPD analysis - 4/5133 (0.1%) vs. 5/4715 (0.1%) - not estimable, n = 9 studies - low certainty of evidence Myalgia (Any muscle pain from IPD analysis) - 13928/51554 (27.0%) vs. 13595/51466 (26.4%) - RR 1.02 (1.01; 1.04), n = 13 studies - high certainty of evidence Myalgia from studies not in IPD analysis - 113/1239 (9.1%) vs. 62/613 (10.1%) - RR 0.95 (0.70; 1.28), n = 3 studies - very low certainty of evidence Liver adverse events - 406/51761 (0.8%) vs. 235/51101 (0.5%) - OR 1.70 (1.46; 1.99), n = 20 studies - moderate certainty of evidence New onset diabetes - 2244/47637 (4.7%) vs. 2030/47680 (4.3%) - RR 1.11 (1.04; 1.17), n = 14 studies - high certainty of evidence Worsening of diabetes - 1/414 (0.2%) vs. 0/207 (0.0%) - OR 4.48 (0.07; 286.49), n = 1 study - Very low certainty of evidence Haemorrhagic stroke - 139/33983 (0.4%) vs. 119/34067 (0.3%) - RR 1.17 (0.92; 1.49), n = 6 studies - Moderate certainty of evidence Dementia - 43/11076 (0.4%) vs. 39/11086 (0.4%) - RR 1.11 (0.72; 1.70), n = 2 studies - Very low certainty of evidence Cognitive decline or dementia (high intensity vs. placebo), decrease of at least 5 points on DSST, 2 points on mMoCA and 10% on TMT-B - 597/807 (74.0%) vs. 599/819 (73.1%) - RR 1.01 (0.95; 1.07) - Low certainty of evidnece		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Cognitive decline or dementia (high intensity vs. placebo), based on changes in MMS or DSE score - 39/366 (10.7%) vs. 68/366 (18.6%) - RR 0.57 (0.40; 0.83), n = 1 study - moderate certainty of evidence Cognitive decline or dementia (medium intensity vs. placebo), cognitive impairment - 35/5101 (0.6%) vs. 32/5079 (0.6%) - RR 0.96 (0.59; 1.58) - very low certainty of evidnece Cognitive decline (change from baseline) – Low intensity vs. placebo: Mini mental state examination (scale 0-30 – higher is better) - 2891 vs. 2913 - - - MD 0.06 points higher (0.04 lower to 0.16 higher) - low certainty of evidence		

Chehrevar et al. (RCT, high or moderate intensity Rosuvastatin, 2022)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Chehrevar M. Effects of High- or Moderate-intensity Rosuvastatin on 1-year Major Adverse Cardiovascular Events Post-percutaneous Coronary Intervention. Interv Cardiol 2022; 17:e20. https://www.ncbi.nlm.nih.gov/pubmed/36890806 [19]	**Aim** to determine the effective dose of statin to prevent major adverse cardiovascular events (MACEs), such as acute coronary syndrome, stroke, myocardial infarction, revascularisation and cardiac death, after PCI in patients with chronic coronary syndrome **Methods** - randomised, double-blind clinical trial - patients with chronic coronary syndrome - recent history of PCI	n = 582 eligible patients - group 1: 5 mg rosuvastatin (n=295) - mean age 63.09 ± 10.08 years - group 2: 40 mg rosuvastatin (n=287) - mean age and 62.19 ± 10.15 years **Results** MACE - n = 24 patients in the 5 mg rosuvastatin group - n = 17 patients in the 40 mg rosuvastatin group - difference during the 1-year follow-up (p=0.66) separately (see also supplement Table 4) 5 mg vs. 40 mg - non-fatal MI n = 4 vs. n = 3 (p=0.64) - revascularisation n = 3 vs. n = 2 (p=0.641)	**Selection bias** randomization: low concealment and unpredictability: high **Performance bias** blinding of participants and staff: unclear **Detection bias** blinding of evaluation: unclear **Attrition bias** lost to follow-up: low ITT-analysis:	authors investigated recommendations for pre- and post-PCI statin doses

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- exclusion criteria: patients with ACS, primary LDL >190 mg/dl, patients who developed statin-induced myopathy or rhabdomyolysis, persistent increase in hepatic enzyme levels or hepatic failure, pregnancy and breastfeeding, statin hypersensitivity, a history of multiple atherosclerotic events, and a history of receiving highintensity statins before the study enrolment **Intervention** high-dose rosuvastatin (40 mg daily) (high intensity) **Control** after 1 month* high dose rosuvastatin over the next year rosuvastatin 5 mg daily (moderate intensity) **Outcomes** - high-sensitivity C-reactive protein - MACE (defined as any hospitalisation due to acute coronary syndrome (ACS), stroke, MI, unplanned revascularisation or cardiac death) *median of 28 days (range 24–37 days)	- coronary artery bypass grafting n = 1 vs. n = 1 (p=0.87) - cerebrovascular accident n = 3 vs. n = 1 (p=0.59) - ACS n = 8 vs. n = 6 (p=0.62) - cardiac death n = 5 vs. n = 4 (p=0.63) mean values of high-sensitivity C-reactive protein, LDL, HDL, Cholesterol, Triglyceride in the first hospitalisation and after 1 year see Table 2 within the publication safety 40 mg rosuvastatin group - n = 8 patients (2.78%): a rise in fasting blood sugar (at the level of impaired fasting glucose corrected by lifestyle modifications) - n = 9 patients (3.13%): an increase in alanine transaminase (ALT) - n = 15 patients (5.22%): with myalgia and myopathy - those with rising ALT levels or significant myopathy were shifted to 5 mg rosuvastatin (analyses ITT) 5 mg rosuvastatin group - n = 5 patients (1.69%): a rises in fasting blood sugar (at the level of impaired fasting glucose, corrected by lifestyle modifications) - n = 5 patients (1.69%): an increase in ALT - n = 7 patients (2.37%): with myalgia and myopathy - rosuvastatin was discontinued in those with significant ALT elevation or myopathy (analyses ITT)	low **Reporting bias** selective result presentation: unclear **Other bias** methods were described rarely within the publication sample size calculation not described paired t-test was used	

12.4.2 Statine Zielwert vs. feste Dosis (Empfehlung 7-14)

Hong et al. 2023 (RCT, non-inferiority design, South Korea)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Hong S-J, Lee Y-J, Lee S-J, et al. Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease: A Randomized Clinical Trial. JAMA 2023; 329(13):1078–87. DOI: 10.1001/jama.2023.2487. http://www.ncbi.nlm.nih.gov/pubmed/36877807. [20]	**Objective** to assess whether a treat-to-target strategy is noninferior to a strategy of high-intensity statins for long-term clinical outcomes in patients with coronary artery disease (LODESTAR Trial)
	
	Methods
	- randomized, multicenter, noninferiority trial
	- open-label
	- patients with a coronary disease diagnosis (including stable ischemic heart disease or acute coronary syndrome (unstable angina, acute myocardial infarction)
	- treated at 12 centers in South Korea
	- enrollment: September 9, 2016, through November 27, 2019; final follow-up: October 26, 2022
	
	Intervention LDL-C target strategy, with an LDL-C level between 50 and 70mg/dL as the target[6]
		n = 4400 patients (n = 2200 in both groups)
		n = 4341 patients (98.7%) completed the trial
		n = 2200 vs. n = 2200 (as-randomized, ITT)
		n = 2108 vs. n = 2106 (per-protocol, PP)
		- n = 16 vs. n = 14 withdrew consent
		- n = 14 vs. n = 11 lost to follow up
		- n = 92 vs. n = 94 did not meet protocol
		
		- mean [SD] age, 65.1 [9.9] years
		- n = 1228 females [27.9%])
		- mean weight 67 kg (SD 11)
		- mean high 164 bzw. 165 cm (SD 8)
		- hypertension 67 % (n = 1473 bzw. 1464)
		- previous PCI 55-57 % (n = 1243 bzw. 1214)
		- > 1y after unstable angina or revaskularization: 40-41 % (n = 919 bzw. 874)
		- Lipid-lowering therapy before randomization:
		  o moderate intensity: 56-58 % (n = 1284 bzw. n = 1240)
		  o high and low intensity see Table 1
		  o none: 16 % (n = 334)
		  o ezetimibe: 10-12 % (n = 253 bzw. 226)
		- treat-to-target group (n = 2200), 6449 person-years of follow-up (moderate-intensity and high-intensity dosing were used in 43% and 54%)
		- high-intensity statin therapy group (n = 2200), 6461 person-years
		- ezetimibe was used more in the treat-to-target group than in the high-intensity statin therapy group
		- mean (SD) LDL-C level for 3 years:
		  o treat-to-target: 69.1 (17.8)mg/dL
			Selection bias randomization: low
			concealment and unpredictability: low
			Performance bias blinding of participants and staff: high (open-label)
			Detection bias blinding of evaluation: unclear (independent committee blinded to therapy assignment adjudicated all clinical events and assessed the clinical end points)
			Attrition bias lost to follow-up: low (ITT and PP analyses were performed, missing data were censored) ITT-analysis: low
			Reporting bias selective result presentation: low
			Other bias lower event rates than anticipated were observed (underpowered)	

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[6] intensity of statin treatment was divided into high or moderate intensity according to the 2013 American College of Cardiology/American Heart Association guideline for the treatment of blood cholesterol.5 Patients were treated with rosuvastatin, 10 mg, or atorvastatin, 20 mg, for the moderate-intensity statin therapy and rosuvastatin, 20 mg, or atorvastatin, 40 mg, for the high-intensity statin therapy (for statin-naïve patients, moderate-intensity statin therapy was initiated and uptitrated if necessary)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	Comperator high-intensity statin treatment, which consisted of rosuvastatin, 20mg, or atorvastatin, 40mg **Outcomes** primary - 3-year composite (MACE) of death, myocardial infarction, stroke, or coronary revascularization - with a noninferiority margin of 3.0 percentage points secondary - new-onset diabetes - hospitalization due to heart failure - deep vein thrombosis or pulmonary thromboembolism - endovascular revacularization for peripheral artery disease - aortic intervention or surgery - end-stage kidney disease - discontinuation of study drugs due to intolerance - cataract operation - composit of laboratory abnormalities nonstatin add-on therapy was not recommended strongly to avoid confounding	○ high-intensity statin group : 68.4 (20.1)mg/dL ○ p = 0.21 **results** primary end point (treat-to-target vs. high-intensity statin) - n = 177 (8.1%) vs. n = 190 (8.7%) patients - absolute difference, −0.6 percentage points [upper boundary of the 1-sided 97.5%CI, 1.1 percentage points]; P < .001 for noninferiority) all-cause death - n = 54 (2.5%) vs. n = 54 (2.5%) - absolute difference, <0.1% (95%CI, −0.9%; 0.9%); p = 0.99 myocardial infarction - n = 34 (1.6%) vs. n = 26 (1.2%) - absolute difference, 0.4% (95%CI,−0.3%; 1.1%); p = 0.23. stroke - n = 17 (0.8%) vs. n = 27 (1.3%) - absolute difference, −0.5% (95%CI, −1.1%; 0.1%); p = 0.13 coronary revacularization - n = 112 (5.2%) vs. n = 150 (7.0%) - absolute difference, −0.1 (95 % CI −1.4; 1.2), p = 0.89 authors noted that no prespecified secondary end points differed statistically between the groups (Table 2) "[…] authors noted that no prespecified secondary end points differed statistically between the groups (Table 2)" Ergänzung: **secondary end points** (treat-to-target (n = 2200) vs. high-intensity (n = 2200), absolute difference (%, 95% CI), p-value new-onset diabetes	(authors note: latest guideline at the time of trial design and several randomized trials demonstrating the superiority of fixed-dose high-intensity statin therapy to fixed-dose moderate-intensity statin therapy in patients with CAD - standard; treat-to-target strategy had not been evaluated in RCT for this population – experimental; noninferiority was investigated, sample size calculation based on other studies)	

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- n = 121 (5.6%) vs. n = 150 (7.0%) - absolute difference -1.3 (-2.8; 0.1), p = 0.07 (initiation of antidiabetic drug: n = 73 vs. n = 105) hospitalization due to heart failure - n = 13 (0.6%) vs. n = 7 (0.3%) - absolute difference 0.3 (-0.1; 0.7), p = 0.17 deep vein thrombosis or pulmonary thromboembolism - n = 4 (0.2%) vs. n = 5 (0.2%) - absolute difference <0.1 (-0.3; 0.2), p = 0.74 (deep vein thrombosis n = 2 vs. n = 5 Pulmonary embolism n = 3 vs. n = 0) endovascular revacularization for peripheral artery disease - n = 12 (0.6%) vs. n = 17 (0.8%) - absolute difference -0.2 (-0.8; 0.3), p = 0.35 aortic intervention or surgery - n = 2 (0.1%) vs. n = 3 (0.1%) - absolute difference not reported (endovascular therapy n = 1 vs. n = 2 surgical therapy n = 1 vs. n = 1) end-stage kidney disease - n = 3 (0.1%) vs. n = 10 (0.5%) - absolute difference -0.3 (-0.7; 0.0), p = 0.05 discontinuation of statin therapy - n = 31 (1.5%) vs. n = 46 (2.2%) - absolute difference -0.7 (-1.5; 0.1), p = 0.09 cataract operation - n = 43 (2.0%) vs. n = 42 (1.9%)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- absolute difference 0.1 (-0.8; 0.9), p = 0.90 composit of laboratory abnormalities - n = 18 (0.8%) vs. n = 30 (1.3%) - absolute difference – 0.5 (-1.1; 0.1), p = 0.11 (aminotransferase elevation n = 8 vs. n = 12 creatinine kinase elevation n = 3 vs. n = 8 creatinine elevation n = 7 vs. n = 11) (composite of new-onset diabetes, aminotransferase or creatine kinase elevation, or end-stage kidney disease (post hoc) - n = 132 (6.1%) vs. n = 177 (8.2%) - absolute difference −2.1 (−3.6; −0.5), p = 0.009)		

Kaldal et al. 2021 (RCT, komplexe Intervention ("hospital-based vs. primary care"), Norway)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Kaldal A, Tonstad S, Jortveit J. Long-term hospital-based secondary prevention of coronary artery disease: A randomized controlled trial. BMC Cardiovasc Disord 2021; 21(1):600. DOI: 10.1186/s12872-021-02426-3. http://www.ncbi.nlm.nih.gov/pubmed/34915839. [21]	**Objective** to compare long-term hospital-based treatment with follow-up at primary health care regarding new cardiovascular events and achievement of treatment targets ("secondary prevention") **Methods** - randomized controlled trial (open) - at Sørlandet Hospital, Norway 2007–2021 - patients hospitalized due to myocardial infarction (MI) (n = 760) or after scheduled percutaneous coronary intervention (PCI)	n = 1613 participants randomized - hospital-based follow-up 1 year n = 788 - no hospital-based follow-up 1 year n = 752 - 2 years n = 745 vs. n = 703 - 5 years n = 582 vs. n = 537 - 10 years n = 211 vs. n = 151 - mean age: 62 years (SD 10) vs. 64 years (SD 9) - women: n = 178 (23%) vs. 159 (21%) - high education: n = 205 (28%) vs. n = 201 (29%) - history of prior MI: n = 205 (13%) - prior PCI: n = 209 (14%) - prior CABG: n = 91 (6%) - experienced a stroke: n = 73 (5%) **Results** primary mean follow-up 5.9 (SD 2.8) years vs. 5.3 (SD 2.8) years	**Selection bias** randomization: low concealment and unpredictability: unclear **Performance bias** blinding of participants and staff: high (open; hospital-based follow-up vs. primary health care) **Detection bias** blinding of evaluation: unclear **Attrition bias** lost to follow-up: unclear ITT-analysis:	secondary preventive treatment targets • No smoking • Blood pressure < 140/90 mmHg • LDL-cholesterol < 1.8 mmol/l (< 2.5 mmol/l until 2017, < 1.4 mmol/l from 2020) • HbA1c < 53 mmol/mol (7%) • BMI < 25 kg/m2 • Daily use of statins • Daily use of acetylsalicylic acid • Physical activity of moderate intensity ≥ 150 min weekly or of

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	(n = 677) or coronary artery bypass grafting (CABG) (n = 103)
	- aged 18-80 years
	- exclusion criteria were lack of ability to cooperate, known alcohol or drug-abuse, use of narcotics, pregnancy or breastfeeding, serious comorbidity with a life expectancy less than 2 years, or participation in other secondary prevention studies
	
	Intervention
	- hospital-based secondary preventive care with consultations 2 weeks, 3 months, 6 months and 1 year after the index event and annually for up to 5 years (specially trained nurses, supervised by cardiologists)
	
	Comperator
	- follow-up at primary health care (patients not randomized to the intervention arm were, after 1 year, formally asked to participate as controls)
	
	final data collected after 10 years
	
	Outcomes
	primary
	- all-cause mortality
		all-cause mortality
		- n = 33 (4%) vs. n = 32 (4%), p = 0.86
		- ageadjusted HR 0.96, 95% CI 0.59–1.56
		new PCI
		- n = 144 (18%) vs. n = 179 (24%), p = 0.002
		- aHR 0.71, 95% CI 0.57–0.88
		MI
		- n = 38 (5%) vs. n = 39 (5%), p = 0,56
		- aHR 0.87, 95% CI 0.56–1.37
		CABG
		- n = 11 (1%) vs. n = 12 (2%), p = 0.71
		- aHR 0.85, 95% CI 0.38–1.95
		stroke
		- n = 33 (4%) vs. n = 30 (4%), p = 0,95
		- aHR 0.98, 95% CI 0.60–1.62
		
		composite endpoint-free survival
		- n = 214 (27%) vs. n = 235 (31%), p = 0.02
		- age-adjusted HR 0.80, 95% CI 0.66–0.96
		- due to a lower rate of PCI
		
		secondary outcomes:
		- supplemental material
		
		- mean blood pressure levels were significantly lower in the intervention group compared to the control group in the first 5 years of follow-up; no significant differences after 10 years (data not shown)
		- abstract: at 1 year,
		  o systolic blood pressure 132 [SD 16] versus 142 [SD 20] mm/Hg; p < 0.001
		  o the differences remained significant during the first 5 years
		- LDL-cholesterol levels were significantly lower in the hospital-based follow-up group until annual consultations ceased (data not shown)
		- abstract: at 1 year,
			low
			Reporting bias
			selective result presentation: low
			
			work was supported by National Association for Public Health and Sørlandet Hospital HF, Arendal, Norway (funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript)
				vigorous intensity ≥ 75 min weekly

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- a composite of all-cause mortality, PCI, CABG, non-fatal stroke or non-fatal MI (first event) secondary - proportion of participants who attained the secondary preventive treatment targets	o LDL-cholesterol 2.1 [SD 0.7] vs. 2.3 [SD 0.8] mmol/l; p < 0.001 o the differences remained significant during the first 5 years - significantly higher proportion of patients in the hospital-based follow-up group received statins during the first 2 years, as well as ezetimibe (20% vs. 7 %) (data not shown) - other secondary preventive measures (smoking cessation, physical activity, body weight, glucose control, drug adherence) did not differ (data not shown)		

Ersboll et al. 2023 (Register, Dänemark)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Ersbøll AK, Kristensen MS, Nybo M, et al. Trends in low-density lipoprotein cholesterol goal achievement and changes in lipid-lowering therapy after incident atherosclerotic cardiovascular disease: Danish cohort study. PloS one 2023; 18(5):e0286376. DOI: 10.1371/journal.pone.0286376. http://www.ncbi.nlm.nih.gov/pubmed/37256879. [22]	**Objective**
	to investigate trends in low-density lipoprotein cholesterol (LDL-C) goal achievement (LDL-C<1.8 mmol/L, equivalent to 70 mg/dL), initiation of lipid-lowering therapy (LLT) and changes in LLT intensity in individuals with atherosclerotic cardiovascular disease (ASCVD) at very high risk of recurrent cardiovascular disease
	
	Source
	- residents of Funen Island, Denmark
	- national, population-based registers (patient, prescription, income, laboratory)
	- individual-level linkage of data (unique personal identification number)
		n = 11,997 individuals included
		(discharged alive and with an LDL-C≥1.8 mmol/L (70 mg/dL) before or during ASCVD hospitalization)
		- mean age 68.2 years
		- 59.7% males
		- 56.0% cohabitants
		- 94.5% ethnic Danes
		- 79.6% of ASCVD events (acute myocardial infarction, ischemic stroke and stable angina pectoris)
		- 14.8% with a history of diabetes
		- 3.7% with a history of chronic kidney disease
		- 62.8% (n=7533) no treatment (lipid-modifying, LLT)
		- 34.3% (n=4114) moderate LLT, 2.9% (n=350) intensive LLT
		    o 36% (n=4313) with statins
		    o 0.6% (n=74) with Ezitimibe
		    o 0.4% (n=49) with other non-statins
		    o 0.2% (n=28) with combination therapy
		at inclusion:
		- 37.2% LLT (initiation of lipid-lowering therapy)
		- 7.8% (n=350) had an intensive LLT
			n. a.	epidemiological data
				
				high risk population (for cardiovascular events) – high precision for this population
				
				authors noted that data are reliable and validated (completeness)
				
				complete follow-up (individual-level up to two years)
				
				limitations: data not documented (e.g. reasons for a suboptimal LLT), health behaviour (i. e. diet, physical activity), adherence

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	study was approved by the Danish Data Protection Agency and the Danish Health and Medicines Authority
	
	Methods
	- cohort study
	- individuals with incident ASCVD[7]
	- index date was defined as date of hospitalization with a qualifying ASCVD diagnosis
	- LDL-C ≥ 1.8 mmol/L
	- 2010-2015
	- follow-up 2 years
	
	Outcomes
	primary
	- lipid measurements included LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol and triglycerides
	- lipid-lowering therapy (LLT) - statins, ezetimibe, other non-statins, and combination therapies
	secondary
	- sociodemographic and clinical characteristics were examined as associations
	
	intensive LLT:
		- mean LDL-C: 3.1 mmol/L (120 mg/dL), before or during ASCVD hospitalization
		- mean HDL-C 1.4 mmol/L
		- total cholesterol 5.2 mmol/L
		- triglycerides 1.8 mmol/L
		
		Results:
		primary
		- LDL-C goal achievement in the first two years
		  o from 40.5% (in 2010) to 50.6% (in 2015), (p<0.001)
		- LLT initiation within the first 90 days
		  o from 48.6% (in 2010) to 56.0% (in 2015), (p<0.001)
		- initiation of intensive LLT
		  o from 9.6% (in 2010) to 32.8% (in 2015)
		- proportion of individuals in intensive LLT before index date
		  o from 2.4% (in 2010) to 3.6% (in 2015), (p<0.001)
		
		- proportion of individuals in LLT (i.e., at least one LLT prescription redemption) before index date did not change during the study period (19.2–22.3% in LLT, p = 0.36)
		- 33.3% to 39.4% did not initiate LLT within 365 days after index date
		
		secondary
		sociodemographic and clinical characteristics associations
		- initiation of LLT therapy (moderate or intensive)
		  o individuals with AMI or IS at index date AMI: OR = 10.84 (95% CI: 9.41; 12.48) IS: OR = 8.77 (95% CI: 7.65; 10.05))
		  o younger age (<40 years): OR = 3.95 (95% CI: 2.48; 6.28); 40–49 years: OR
				authors noted, that a much larger proportion of individuals with UA, SA, PAD, or coronary revascularization (e.g., PCI and CABG) should initiate LLT
				
				authors noted that a focus on individuals at older age and individuals with comorbidities (CKD, DM) is needed

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[7] ASCVD included acute myocardial infarction (AMI), ischemic stroke (IS), unstable angina pectoris (UA) together with a procedure of coronary angiography (CAG), stable angina pectoris (SA) together with a procedure of CAG or computerized tomography coronary angiography (CT-CAG), and peripheral artery disease (PAD) (included diagnoses (ICD 8/10 and procedure codes) see S1 Table in S1 File – supplement)

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	- a minimum of two prescription redemptions of one combinational drug
	- minimum of two prescription redemptions of statins (80 mg Simvastatin, 40–80 mg Atorvastatin or 20–40 mg Rosuvastatin)
	- a minimum of two prescription redemptions of statins (all doses and types) and one ezetimibe prescription redemption or
	- a minimum of two prescription redemptions of statins (all doses and types) and one other non-statin prescription redemption (i.e. not ezetimibe)
	
	a logistic regression model was used for LDL-C goal achievement and initiating LLT therapy
		= 2.85 (95% CI: 2.38; 3.41); 50–59 years: OR = 1.51 (95% CI: 1.34; 1.71))
		  o without comorbidity (not diabetes: OR = 3.12 (95% CI: 2.75; 3.53); not CKD: OR = 2.29 (95% CI: 1.78; 2.94))
		  o no LDL-C measurements before admission (OR = 13.17 (95% CI: 11.18; 15.51))
		- Odds for initiation of LLT was high for individuals with a moderate to high LDL-C measurement (LDL-C at 2.4–3.8: OR = 6.99 (95% CI: 6.13; 7.96) and LDL-C>3.8: OR = 18.38 (95% CI: 15.73; 21.46)), and with a moderate to high total cholesterol, TC (TC at 4.4–59: OR = 4.14 (95% CI: 3.69; 4.65) and TC>5.9: OR = 9.75 (95% CI: 8.50; 11.18))
		
		trends in initiation of LLT therapy stratified by type of ASCVD (AMI and IS vs. remaining diagnoses and/or procedures)
		- a higher proportion of individuals with AMI or IS initiated LLT therapy between admission and 90 days after discharge (data not shown)
		- among individuals with AMI or IS, the proportion initiating LLT between admission and 90 days after discharge increased during the study period from 67.4% to 74.6%
		- among individuals with other ASCVD diagnoses or procedures (SA, UA, PAD, CABG, PCI), the proportion initiating LLT between admission and 90 days after discharge increased during the study period from 23.1% to 25.0%		

Homeniuk et al. 2023 (Register, Irland)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Homeniuk R, Stanley F, Gallagher J, et al. Heartwatch: An Irish cardiovascular secondary prevention programme in primary care, a secondary analysis of patient outcomes. BMJ open 2023; 13(1):e063811. DOI: 10.1136/bmjopen-2022-063811. http://www.ncbi.nlm.nih.gov/pubmed/36599635. [23]	**Objective** to investigate patient follow-up data from Heartwatch: Ireland's secondary prevention programme for cardiovascular disease delivered in general practice
	
	Source
	- based on secondary analysis of routinely collected data from Heartwatch
	- a national structured programme led by Irish GPs
	- standard protocol for the continuing care
	- each area employed a regional GP coordinator and nurse facilitator to assist with the deployment of Heartwatch care protocol
	- Heartwatch targeted 20% of general practices in Ireland and recruited 475 general practitioners across 325 practices
	- over 16 000 patients entered the programme
	- programme was designed using WHO and European Society of Cardiology guidelines on secondary prevention
	
	there is a data management committee (aggregated, anonymous version of the collected data)
	
	Methods
		Heartwatch overview: 2003–2020
		Jan 2003-March 2020
		- 300 practices
		- 16,000 patients
		- 350 000 visits
		- mean follow-up 7 years
		- > 7 000 (45%) patients have been in the programme for 8 years or more
		- mean 3 visits per year
		- male (76%) participants
		- median age 67 (range: 63–67)
		- female group were typically older, with a median age of 70 compared with 65 for males
		- sign up in the program with
		  o 27% aged <60 years old
		  o 33% of all participants aged between 60 and 69 years
		- AMI (40%)
		- PTCAs (35%)
		- CABGs (25%)
		- enrollment
		  o 18% of patients within 1 year of the qualifying event (QE)
		  o 32% of patients between 1 and 2 years after QE
		  o 25% between 3 and 6 years
		  o 26% more than 6 years after their QE
		
		the 8-year cohort (2003 to 2023)
		n = 5 700 patients
		- a minimum of one visit per year for 8 years
		- 38% PTCA as QE
		- 26% CABG as QE
		- 34% with a median QE-interval of 2 years
		- 77% male
		- median age at signup 65 years
		
		Results
			n. a.	epidemiological data
				
				the Strengthening the Reporting of Observational studies in Epidemiology cohort reporting guidelines were used
				
				Heartwatch was developed in collaboration with the Irish Heart Foundation Irish a national heart and stroke charity which supports and advocates for people who have been affected by heart and stroke
				
				authors noted that data come from an active clinical programme and there is no comparative or control group
				
				LDLc (Low-density Lipoprotein cholesterol) guideline targets changed during the programme; they noted that they have underestimated the number achieving the desired active target prior to 2016

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	- retrospective descriptive study - 2003-2020 (extracted in Dec 2021) - patient population included people with a history of acute myocardial infarction (AMI), percutaneous transluminal coronary angioplasty (PTCA) or a coronary artery bypass graft (CABG) - cohort of 5700 patients with at least 8 years in the programme **Interventions** - standard protocol for continuing care of patients for the secondary prevention of cardiovascular disease - administered by general practices **Outcome** primary - Continuing Care (CCare) score out of eight (calculated based on programme targets for well-known cardiovascular risk factors: exercise, systolic blood pressure, LDL cholesterol, optimally controlled glucose, smoking status, and pharmacological treatment) - (based on EUROASPIRE studies)	CCare score after 1 year: - median score 5 - 5 (33% of patients) - <5 (30% of patients) - > 5 (37% of patients) CCare score after 4 years: - median score 5 - 37% of patients had individual-level improvements in their score - 36% of scores had not changed - 27% of scores decreased - >5 (44% of patients) CCare score after 8 years: - median score 5 - 36% with higher scores - 32% with same scores - 32% with lower scores - ≥6 (40% of patients) within the target for SBP - at the start of the first year: 64% of patient - after 4 years: 70% of patients - after 8 years: 67% of patients LDL cholesterol < 1.8 mmol/L - at year 1: 21% of patients - after 4 years: 26% of patients - after 8 years: 30% of patients moderate exercise >210 min/min - at year 1: 37% of patients - after 4 years: 41% of patients - after 8 years: 35% of patients non-smoking - at year 1: 88% of patients		(2016, the target level for lipoprotein cholesterol (LDLc) for very high-risk patients was changed to 1.8 mmol/L (from 3.0 mmol/L)) authors documented a survivor bias on the available long-term information, as those with worse scores may have exited the programme earlier than 8 years Heartwatch does not collect outcome information such as mortality or further cardiac events, nor does it collect patient-reported outcomes

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		- after 4 years: 90% of patients
		- after 8 years: 92% of patients
		
		the rate of waist circumference within target did not change much through follow-up (waist circumference of <80cm (female) ans <94cm (male)): ~ 27 % of participants
		
		prescribed anticoagulant/antiplatelet and lipid lowering agents
		- at year 1 88% of patients
		- after 4 years: 94% of patients
		- after 8 years: 92% of patients
		
		associations with the CCare score
		- patient sex was predictive of better scores
		   o male patients had almost a half-point advantage on females (0.432, 99% CI: 0.335 to 0.509)
		   o female patients had lower CCare scores across all 8 years of follow-up, 26% had scores >5 in year 1, which rose to a maximum of 33% in year 4 and fell again to 28% in year 8, which was 15% points lower than the equivalent in male patients (41%, 47%–44%, respectively)
		- patient's age at signup does not appear to predict CCare scores
		- more younger patients had a CCare score >5 at signup (<60: 42%) compared with older patients (60–69: 38%, 70+: 34%)
		- patients who had a CABG as a QE
		   o were predicted to have better scores than patients qualifying from an AMI (0.106, CI: 0.028 to 0.183, p<0.0001)
		- patients qualifying from a PTCA events
		   o do not differ much from AMI (0.038, CI: −0.045 to 0.121, p=0.234)
		- number of Heartwatch visits per year		

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		○ was predictive of higher CCare scores (0.109, CI: 0.051 to 0.168, p<0.0001		

Kerneis et al. 2022 (Register, ESC-EORP-CICD-LT)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Kerneis M, Cosentino F, Ferrari R, et al. Impact of chronic coronary syndromes on cardiovascular hospi-tali-zation and mortality: The ESC-EORP CICD-LT registry. Eur J Prev Cardiol 2022; 29(15):1945–54. DOI: 10.1093/eurjpc/zwac089. http://www.ncbi.nlm.nih.gov/pub-med/35653582. [24]	**Objective** to investigate clinical events at one-year follow-up from the ESC EORP CICD-LT Registry **Source** European Society of Cardiology (ESC) EORP CICD-LT registry (a prospective European registry, de-signed to describe the profile, man-agement and outcomes of patients with CCS across the ESC countries) independent Executive Committee; Steering Committee; National coordi-nators; approvals of national or re-gional ethics committees or Institu-tional Review Boards; Data Manage-ment teams **Methods** - observational, longitudinal study - patients with chronic coro-nary syndrome (CCS[8], identified by means of a routine ambulatory visit or	overall: n = 9 174 patients enrolled (across 154 centers from 20 countries) – May 2015 – July 2018) n = 6 655 participants with one-year follow-up (72.5%) - median age 67 years - 73 % men - 23.9% hypertension - 40.4% hypercholesterolemia - 30.2% diabetes mellitus - 19.6% previous non-urgent coronary revasculari-zation - 36.5% previous ST-segment elevation myocardial infarction (STEMI) **Results** at 1 year all-cause mortality n = 168 (2.5 %) all-cause rehospitalization n = 1 606 (27.1%) CV mortality n = 97 (1.5%) CV rehospitalization n = 1 220 (20.6%) - CAD related hospitalization n=661 (11.2%) - heart failure n=276 (4.7%) - vascular causes n=117 (2.0%) Cox model identified 7 variables independently associated with an increased risk of cardiovascular events:	n. a.	epidemiological data authors noted: that selection of cen-ters was made on a voluntary basis (center bias cannot be ex-cluded) outcomes were not ad-judicated; ICD codes were not used (varia-tion of definition cannot be excluded) important number of missing data (one in three patients (2519, 27.4%) having an 'un-known status' (includ-ing loss of follow-up)) pharmaceutical compa-nies have supported the programme authors 'One-sentence Summary': Patients

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[8] defined as previous myocardial infarction, previous coronary revascularization or other CCS (effort-induced angina or rest angina with documented myocardial ischaemia detected by exercise or any stress imaging test or documented >50% stenosis in at least one major coronary artery on coronary angiography or asymptomatic ischaemia with a documented >50% stenosis in at least one major coronary artery on coronary angiography; Patients were excluded if they had experienced an acute coronary syndrome (ACS) in the previous 30 days)

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	an elective coronary revascularization procedure) - aged ≥ 18 years - one year follow-up - 20 countries **Outcomes** at one year primary - composite endpoint of cardiovascular death or cardiovascular rehospitalization secondary - all-cause death - cardiovascular and non-cardiac death - all cause of rehospitalization - cardiovascular, coronary artery disease (CAD) related, heart failure related, vascular related, non-cardiovascular rehospitalization	- age (by 10 years, HR=1.08, confidence interval (CI) [1.02-1.16]) - atrial fibrillation (HR=1.23, CI [1.05-1.44]) - stroke/TIA (HR=1.60, CI[1.32-1.95]) - severe liver disease (HR=1.70, CI[1.12-2.58] - COPD/asthma (HR=1.33, CI[1.08-1.64]) - elevated serum creatinine (per ten mmol/l, HR=1.02, CI[1.01-1.04]) - impaired left ventricular function (left ventricular ejection fraction [LVEF] <40%), HR=1.85, CI[1.58-2.16]) authors noted: - northern Europe had the lowest cardiovascular mortality rate, southern Europe the highest (0.5% vs 2.0%, p value = 0.04) - women had a significantly higher rate of cardiovascular mortality compared to men (2.0% vs 1.3%, p value 0.02) - recommended treatment, including the number of lipid lowering agents (n = 6045 (95.4%) vs. n = 5816 (91.8%), p<0.001), decreased between baseline and one year - among the population with measured LDL-cholesterol level at one-year, 1434 patients (66.5%) were above the recommended target - 83.3% (n=2226) of the follow-up population with complete information on cardiovascular risk factors had at least one modifiable risk factor not at target according to current guidelines, including glycemia > 7mmol/l or low-density lipoprotein-cholesterol (LDL-C) 4 > 1.81 mM/l or blood pressure above 140/90 mmHg		with CCS enrolled in the CICD registry were at high risk of rehospitalization for CV causes, suggesting that the early identification of comorbidities associated with this risk (impaired left ventricular function, atrial fibrillation, previous stroke, liver, kidney and pulmonary diseases) may represent an opportunity for enhanced care and better outcomes.

12.4.3   Bempedoinsäure (neu 2023)

PICO Frage 25 der AkdÄ (Bempedoinsäure), Recherche bis Dez 2021

Zur Therapie mit Bempedoinsäure (bei maximal verträglicher Statintherapie) in der Sekundärprävention ermittelte ein Evidenzbericht der AkdÄ fünf Studien (Bempedoinsäure in Kombination mit Statinen und oder Ezetimib bzw. mit der Angabe eines Placebos ohne lipidenkende Begleittherapie gegenüber der (Therapie)-strategie ohne Bempedoinsäure) [25]. Die Studienaufbereitung wurde an anderer Stelle dokumentiert (Goldberg 2019 [26] (CLEAR Wisdom), Ray 2019 [27] (CLEAR Harmony), Ballantyne 2018 [28] (CLEAR Tranqulity), Laufs 2019 [29] (CLEAR Serenity), Ballantyne 2020 [30]. Die zweite Version des Berichts ergänzt klinische Überlegungen zur Statinintoleranz (Primärprävention) [31,32].

Sayed et al. 2023 (SR, n =11 Studien, Primär- und Sekundärprävention)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Sayed A. The Clinical Efficacy and Safety of Bempedoic Acid in Patients at Elevated Risk of Cardiovascular Disease: A Meta-Analysis of Randomized Clinical Trials. Cardiovasc Drugs Ther 2023. https://www.ncbi.nlm.nih.gov/pubmed/37261676. [33]	**Objective** to summarize the latest evidence for the clinical efficacy and safety of bempedoic acid (BA) **Methods** - prospectively registered on PROSPERO - (CRD: 42023404231) - searching Pubmed, the Cochrane Central Register of Controlled Trials, and Clinicaltrials.gov (March 2023) - randomized clinical trials (RCTs) of bempedoic acid (BA) - patients at an elevated risk for atherosclerotic cardiovascular disease (ASCVD) - history of one or more risk factors for ASCVD (primary prevention) - or had a pre-existing history of ASCVD (secondary prevention)	n = 11 RCT [7–17 see below] (18,496 patients) - n = 9,959 bempedoic acid - n = 8,537 control - weighted median follow-up of 40.6 months (Nissen et al. 2023); follow up varied by 2 to 12 months for the other RCT - average age 65.3 years (BA: 65.2; control: 65.4) - 45.6% were females - prevalence of diabetes 42.5% - prevalence of hypertension 78.4% overall risk of bias was low 7 of 11 trials, with 4 trials being assessed as having a moderate risk of bias **Results** efficacy bempedoic acid vs. control (placebo) all-cause mortality - RR: 1.05; 95% CI: 0.92 to 1.19 - ARD: 0.24 (95% CI -0.39; 0.96) MACE - RR: 0.87; 95% CI: 0.80 to 0.95 - ARD: -1.63% (95% CI -2.51; -0.68); NNT: 62 (95% CI 40; 147) cardiovascular mortality - RR: 1.05; 95% CI 0.89 to 1.24 - ARD: 0.16 (95% CI -0.33; 0.75)	AMSTAR-II low authors noted: overall risk of bias was low 7 of 11 trials, with 4 trials being assessed as having a moderate risk of bias possibility of subgroup analysis was limited by the lack of access to patient-level data follow-up duration was generally less than what might be seen in clinical practice, where use of lipid-lowering treatments can span decades safety outcome myalgia was reported by all studies (no evidence of publication bias, funnel plot)	authors noted that results contrast with those of the most recent metaanalysis assessing clinical outcomes (differences are likely attributable to a lack of statistical power and imprecise estimates as the largest outcomesbased trial, CLEAR Outcomes, had not yet been published at the time of the previous meta-analyses but is included in our meta-analysis) authors noted that ezetimibe is the oldest drug (compared to evolocumab etc.) and is available in generic form; the high cost of evolocumab and bempedoic acid are significant barriers to

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	Quality assemssment Risk of Bias 2 (RoBII) tool **Outcome** - all-cause mortality and major adverse cardiovascular events (MACE) - MACE consisted of cardiovascular mortality, myocardial infarction, stroke, unstable angina hospitalization, and revascularization, which were analysed both separately and as a 5-component composite endpoint - safety endpoints included gout, myalgia, renal impairment, cholelithiasis, and new-onset or worsening of diabetes mellitus (DM) Mantel-Haenszel method to pool estimates; relative risks (RR), absolute risk differences (ARD), and number needed to treat/harm (NNTB/H)	myocardial infarction - RR: 0.76; 95% CI: 0.66 to 0.89 - ARD: -1.03% (95% CI -1.50; -0.49); NNT: 98 (95% CI 67; 207) stroke - RR: 0.87; 95% CI 0.69 to 1.08 - ARD: -0.27 (95% CI -0.61; 0.17) unstable angina hospitalization - RR: 0.70; 95%: CI: 0.55 to 0.89 - ARD: -0.57% (95% KI -0.85; -0.21); NNT: 177 (95% CI 119; 484) revascularization - RR: 0.81; 95% CI: 0.72 to 0.91 - ARD: -1.31% (95% CI -1.94; -0.60); NNT: 77 (95% CI 52; 167) safety risk of gout - RR: 1.56; 95% CI: 1.27 to 1.91 - ARD: 0.99%; NNH: 101 myalgia - RR: 0.85; 95% CI: 0.75 to 0.95 - ARD: -0.99%; NNT: 102 renal impairment - RR: 1.35; 95% CI: 1.22 to 1.49 - ARD: 2.54%; NNH: 40 cholelithiasis - RR: 1.87; 95% CI: 1.43 to 2.44 - ARD: 1.01%; NNH: 100 new/worsening DM - RR: 0.91; 95% CI 0.83 to 1.00 - ARD: -1.24 (95% CI -2.42; 0.06) (forest plots for all outcomes presented within a supplement) **Included studies** 7. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in statin-		widespread adoption in these settings authors additionally noted one trial in the context of statin-associated myalgias, (SAMSON trial), which showed that most statin-associated myalgias are due to the nocebo effect (statins have by far the greatest body of evidence on clinical safety and efficacy)

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		intolerant patients. N Engl J Med. 2023. https://doi.org/10.1056/NEJMoa2215024. [32] *(CLEAR Outcomes; primary and secondary prevention)* 8. Bays HE, Baum SJ, Brinton EA, et al. Effect of bempedoic acid plus ezetimibe fixed-dose combination vs ezetimibe or placebo on low-density lipoprotein cholesterol in patients with type 2 diabetes and hypercholesterolemia not treated with statins. Am J Prev Cardiol. 2021;8:100278. https://doi.org/10.1016/j. ajpc.2021.100278. *(Typ 2 Diabetes mellitus; Subgruppenanalyse, primary prevention)* 9. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at High Risk for Cardiovascular Disease: the CLEAR Wisdom Randomized Clinical Trial. JAMA. 2019;322(18):1780–8. https://doi.org/10.1001/ jama.2019.16585. [26] *(CLEAR WISDOM; primary and secondary prevention)* 10. Lalwani ND, Hanselman JC, MacDougall DE, Sterling LR, Cramer CT. Complementary low-density lipoprotein-cholesterol lowering and pharmacokinetics of adding bempedoic acid (ETC- 1002) to high-dose atorvastatin background therapy in hypercholesterolemic patients: a randomized placebo-controlled trial. J Clin Lipidol. 2019;13(4):568–79. https://doi.org/10.1016/j. jacl.2019.05.003. *(Charakterisierung Bempedoinsäure und Studienvorbereitun; primary prevention)* 11. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of Bempedoic Acid in patients with hypercholesterolemia and statin intolerance. J Am Heart		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Assoc. 2019;8(7):e011662. https://doi.org/10.1161/JAHA.118.011662. [29] *(CLEAR SERENITY; primary and secondary prevention)* 12. Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to reduce LDL cholesterol. N Engl J Med. 2019;380(11):1022–32. https://doi.org/10.1056/ NEJMoa1803917. [27] *(CLEAR HARMONY; primary and secondary prevention)* 13. Rubino J, MacDougall DE, Sterling LR, et al. Lipid lowering with bempedoic acid added to a proprotein convertase subtilisin/ kexin type 9 inhibitor therapy: a randomized, controlled trial. J Clin Lipidol. 2021;15(4):593–601. https://doi.org/10.1016/j.jacl.2021.05.002. *(Bempedoinsäure + proprotein convertase subtilisin/ kexin type 9 inhibitor therapy; primary prevention)* 14. Ballantyne CM, Davidson MH, Macdougall DE, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. J Am Coll Cardiol. 2013;62(13):1154–62. https://doi. org/10.1016/j.jacc.2013.05.050. *(primary prevention; Ballantyne 2018 (CLEAR Tranqulity) sowie 2020 vorhanden)* 15. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis. 2018;277:195–203. https://doi. org/10.1016/j.atherosclerosis.2018.06.002. [28]		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		(CLEAR Tranqulity; primary prevention) 16. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol. 2020;27(6):593–603. https://doi.org/10.1177/2047487319864671. [30] *(primary and secondary prevention)* 17. Thompson PD, MacDougall DE, Newton RS, et al. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. J Clin Lipidol. 2016;10(3):556–67. https://doi.org/10.1016/j.jacl.2015.12.025. *(Studiencharakterisierung; primary and/or secondary prevention (?))*		

Krishna Mohan et al. 2023 (SR, n = 3 Studien, Primärprävention, Statinintoleranz bzw. max. tolerierte Statintherapie)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Krishna Mohan GV. Efficacy and Safety of Bempedoic Acid to Prevent Cardiovascular Events in Individuals at Risk of Cardiovascular Diseases: A Meta-Analysis of Randomized-Control Trials. Cureus 2023; 15(5):e38662. https://www.ncbi.nlm.nih.gov/pubmed/37288183. [34]	**Objective** to evaluate the effectiveness and safety of bempedoic acid in preventing cardiovascular events among high-risk patients of cardiovascular diseases **Methods** - meta-analysis of RCT following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines	n = 3 Studien (n = 16 978 patients) - n = 9 001 bempedoic acid - n = 7 977 placebo - sample size range 779 to 13 970 - follow-up range 12 to 60 months - Goldberg et al 2019 (max. tolerated statins: bempedoic acid vs. placebo) - Ray et al. 2019 (max. tolerated statins: bempedoic acid vs. placebo) - Nissen et al. 2023 (statin intolerant patients: bempedoic acid vs. placebo) **Results** (n = 3 studies, bempedoic acid vs. placebo)	AMSTAR-II low risk of bias was rated as low for most domains (selective reporting was noted) heterogeneity in study co-medications, such as no statin versus maximally tolerated statin and additional ezetimibe was reported as limitation	

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- database Medline, the Cochrane Library of Clinical Trials, and EMBASE until April 15, 2023 - cardiovascular outcomes between patients receiving bempedoic acid (alone or in combination with other drugs or interventions) and those receiving a placebo - RCT - follow-up at least 12 months - studies that did not report the primary outcome (MACE) were excluded **Quality assessment** Cochrane risk of bias tool (7 domains) **Outcome** primary - major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization secondary - LDL-C - Safety (adverse events and serious adverse events)	primary MACE - incidence 11,5% - RR 0.86 (95% CI: 0.80-0.94) cardiovascular death - RR 1.05 (95% CI 0.89-1.24) myocardial infarction - RR 0.76 (95% CI 0.65-0.89) stroke - RR 0.98 (95% CI 0.78-1.24) coronary revascularization - RR 0.81 (95% CI 0.72-0.91) hospitalization due to instable angina - RR 0.69 (95% CI 0.54-0.88) secondary LDL-C (heterogeneity reported) - MD -17.47 (95% CI: -21.13, -13.81) adverse events - RR 1.01 (95% CI: 1.00-1.03) risk of SAE - RR: 1.02 (95% CI: 0.96-1.08) **Included studies** Goldberg 2019 [26] (CLEAR Wisdom) Ray 2019 [27] (CLEAR Harmony) Nissen 2013 [32] (CLEAR Outcome)		

Lin et al. 2022 (SR, n = 6 Studien, Primär- und Sekundärprävention)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Lin Y. Clinical efficacy and safety outcomes of bempedoic acid for LDL-C lowering therapy in patients at high cardiovascular risk: A systematic review and meta-analysis. BMJ Open 2022; 12(2):e048893. https://www.ncbi.nlm.nih.gov/pubmed/35210334. [35]	**Objectives** to assess efficacy and safety of bempedoic acid (BA) for clinical outcomes in high cardiovascular (CV) risk patients **Methods** - sources: MEDLINE, Cochrane Central Register of Controlled Trials, Google Scholar, Embase, ClinicalTrials.gov, Clinical Trial Results and the American College of Cardiology web site - randomised controlled trials (RCT) of BA vs placebo in high CV risk patients reporting clinical outcomes were included **Quality assessment** Risk of Bias; GRADE **Outcomes** primary - major adverse cardiovascular events (MACE), - all-cause mortality, - CV mortality and - non-fatal myocardial infarction (MI) safety - new onset or worsening of diabetes mellitus (DM), - muscular disorders,	n = 6 studies (n = 3,956 patients), n = 5 phase 3 and n = 1 phase 2 studies - n = 3 studies with patients treated with max. tolerated statin therapy - n = 3 studies with statin intolerance or after discontinuation of lipid-lowering therapy - patients between 55 and 67 years old - suffered from a considerable CV risk profile (high rates of ASCVD, DM, HeFH or chronic kidney disease (CKD)) - and insufficient control of serum lipid levels - follow-up: ranged from 4 to 52 weeks **Results** MACE - 4,7% (BA) vs. 5,5% (placebo) - OR 0.84, 95% CI 0.61 to 1.15; p=0.27, n = 4 studies (n = 3413 patients) all-cause mortality - 0.7% (BA) vs. 0.3% (placebo) - OR 2.37; 95% CI 0.80 to 6.99; p=0.12, n = 5 studies (n = 3895 patients) CV mortality - 0.4% (BA) vs. 0.3% (placebo) - OR 1.66; CI 0.45 to 6.04; p=0.44, n = 3 studies (n = 3353 patients) non-fatal MI - 1.1% (BA) vs. 2.0% (placebo) - OR 0.57; 95% CI 0.32 to 0.99; p = 0.05 (borderline-significant trend), n = 4 studies (n = 3413 patients) coronary revascularisation - OR 0.82; 95% CI 0.55 to 1.22; p=0.32 (supplement) non-fatal stroke	AMSTAR-II low (eine kritische Domaine konnte nicht erfüllt werden: Darlegung der ausgeschlossenen Volltexte mit Ausschlussgrund) authors noted: low event rates within limited follow-ups may cause imprecise effect estimates heterogeneity in length of follow-up and background lipid-lowering therapy prespecified sensitivity analyses did not change the overall effect GRADE: low certainty of evidence for MACE and all-cause mortality moderate certainty of evidence for CV mortality and non-fatal MI	patients with high cardiovascular risk and in those with established atherosclerotic cardiovascular disease

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- gout and - worsening of renal function	- OR 1.26, 95% CI 0.42 to 3.76; p=0.68 (supplement) hospitalisation for heart failure - OR 2.33; 95% CI 0.67 to 8.11; p=0.19 (supplement) hospitalisation for unstable angina - OR 0.94; 95% CI 0.51 to 1.74; p=0.84 (supplement) safety risk of new-onset or worsening of DM - 3.8% (BA) vs. 5.5% (placebo) - OR 0.68; 95% CI 0.49 to 0.94; p = 0.02, n = 3 studies (n = 3622 patients) risk of gout - 1.5% (BA) vs. 0.5% (placebo) - OR 3.29; 95% CI 1.28 to 8.46; p=0.01 serum uric acid - 5.1% (BA) vs. 2.0% (placebo) - OR 2.60; 95% CI 1.15 to 5.91; p=0.02 (supplement) risk of muscular disorders - 10.9% (BA) vs. 9.1% (placebo) - OR 2.60; 95% CI 1.15 to 5.91; p=0.06 worsening of renal function - 0.7% (BA) vs. 0.1% (placebo) - OR 4.24; 95% CI 0.98 to 18.39; p =0.05 serum creatinine levels - 0.8% (BA) vs 0.4% (placebo) - OR 2.01; 95% CI 0.67 to 6.02; p=0.21 (supplement) upper respiratory tract infection - OR 0.82; 95% CI 0.63 to 1.06; p=0.13 (supplement) urinary tract infection - OR 0.84, 95% CI 0.62 to 1.14; p=0.25 (supplement) neurocongnitive disorders		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- OR 1.00, 95% CI 0.58 to 1.74; p=0.99 (supplement) nasopharyngitis - OR 0.88; 95% CI 0.68 to 1.14; p=0.33 (supplement) LDL-C level - MD in LDL-C levels from baseline: o −19.93% (95% CI −21.55 to −18.31); p<0.01 (BA vs. placebo) total cholesterol - MD −12.43%; 95% CI −13.42 to −11.43, p<0.01 non-high density lipoprotein cholesterol (non-HDL-C) - MD −15.27%; 95% CI −16.59 to −13.95, p<0.01 apolipoprotein B (apoB) - MD −13.20%; 95% CI −14.47 to −11.93, p<0.01 high-densitiy lipoprotein cholesterol levels - MD −7.5%, 95% CI −8.30 to −6.61, p<0.01 triglyceride levels - MD 3.35%, 95% CI −1.78 to 8.49, p=0.20 **Included studies** 6 Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis 2018;277:195–203. [28] 7 Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol 2020;27:2047487319864671. [30]		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		8 Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the clear wisdom randomized clinical trial. JAMA 2019;322:1780–8. [26] 9 Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of Bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc 2019;8:e011662. [29] 10 Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of Bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019;380:1022–32. [27] 11 Gutierrez MJ, Rosenberg NL, Macdougall DE, et al. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 2014;34:676–83.		

Dai et al. 2021 (SR, n = 10 Studien, Primär- und Sekundärprävention)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Dai L. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: A systematic review and meta-analysis of randomized controlled trials. Eur J Prev Cardiol 2021; 28(8):825–33. https://www.ncbi.nlm.nih.gov/pubmed/34298558. [36]	**Objective** to conduct a meta-analysis to quantitatively appraise the efficacy and safety of bempedoic acid **Methods** - preferred reporting items for systematic review and meta analyses guidelines were used	n = 10 studies (n = 4 142 patients) - n = 2 736 BA - n = 1 368 placebo - duration of intervention: 4 – 52 weeks - range of participants: 56 to 2 230 - n = 3 studies patients with hypercholesterolemia ans statin-intolerance - n = 1 study patients with hypercholesterolemia and typ 2 diabetes mellitus **Results**	AMSTAR-II low (eine kritische Domaine konnte nicht erfüllt werden: Darlegung der ausgeschlossenen Volltexte mit Ausschlussgrund) authors noted that all included studies were associated with low risk of performance bias, detection bias and reporting bias	

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- PubMed, Embase, Web of Science and Scopus; reference lists - from inception to 30 January 2020 - randomized controlled trials - compared the efficacy and safety of bempedoic acid (ETC-1002) with placebo - patients with hypercholesterolemia **Quality assessment** - risk of bias (Cochrane Collaborations tool) and heterogeneity were assessed **Outcomes** efficacy and safety parameters related to the treatment	**data from week 12 or less** BA vs. placebo, n = 10 studies LDL-C levels MD –23.16%, 95% CI –26.92% to –19.04%; p < 0.00001 non-HDL-C level MD –18.30%, 95% CI –21.65% to –14.95%; p < 0.00001 total cholesterol level MD –14.62%, 95% CI –17.08% to –12.16%; p < 0.00001 apoB level MD –14.77%, 95% CI –16.85% to –12.70%; p < 0.00001 HDL-C level MD –3.80%, 95% CI –5.54% to –2.06%; p < 0.00001 triglycerides MD 1.09%, 95% CI –4.94% to 7.12%; p = 0.72 safety risk of overall adverse events OR 1.02, 95% CI 0.88; 1.18; p = 0.82 serious adverse events OR 1.07, 95% CI 0.87 to 1.30; p = 0.54 muscle-related adverse events OR 1.21, 95% CI 0.97 to 1.51; p = 0.09 study drug-related adverse events OR 1.36, 95% CI 1.05 to 1.76; p = 0.05 adverse events leading to discontinuation OR 1.44, 95% CI 1.14 to 1.82; p = 0.002 pain in extremity OR 1.68, 95% CI 1.06 to 2.65; p = 0.03	risk of bias in allocation concealment was generally unclear apart from two studies one study was rated as high risk of bias because there were some differences in baseline characteristics among the treatment groups considerable heterogeneity was reportet for LDL-C authors noted possible publication bias; probably, some outcomes are vulnerable for incompleteness or different definition/measurement (e. g. laboratory data) as well as affected by duration and study situation (e. g. adverse events)	

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		gout OR 2.70, 95% CI 1.08 to 6.75; p = 0.03 uric acid levels more than placebo MD 0.74mg/dl, 95% CI 0.50 to 0.99; p < 0.00001 creatinine levels MD 0.04 mg/dl, 95% CI 0.03 to 0.05; p < 0.00001 **subgroups** (1) (n=6) patients with hypercholesterolemia LDL-C level −18.31% 95% CI −19.85% to −16.76%; p< 0.00001 (n = 5 studies: enrolled patients at high risk for CVD receiving maximally tolerated statins or high-dose statins, who were randomized to treatment with bempedoic acid (180mg) or placebo) (2) (n=3) patients with hypercholesterolemia and statin-intolerance LDL-C level −24.87% 95% CI −27.66% to −22.08%; p < 0.00001 (3) (n=1) patients with hypercholesterolemia and type 2 diabetes mellitus (T2DM) LDL-C level −38.09% 95% CI −45.97% to −31.83%; p < 0.00001 **data from week 24** BA vs. placebo, n = 3 studies LDL-C level MD −16.42%, 95% CI −18.16% to −14.69%; p < 0.00001 non-HDL-C MD −14.97%, 95% CI −19.38% to −10.57%; p < 0.00001		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		TC MD –12.69%, 95% CI –16.31% to –9.06%; p < 0.00001 apoB MD –14.70%, 95% CI –17.42% to –11.98%; p < 0.00001 HDL-C MD –5.18%, 95% CI –6.19% to –4.16%; p < 0.00001 triglycerides MD 0.96%, 95% CI –4.08% to 6.01%; p < 0.00001		

IQWIG Bericht 2021 (Bempedoinsäure, Primär- und Sekundärprävention)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
A20 -92: Version 1.0 28.01.2021. IQWiG-Berichte – Nr. 1033. Bempedoinsäure (primäre Hypercholesterinämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V [37]	**Fragestellung** Ziel des Berichts ist die Bewertung des Zusatznutzens von Bempedoinsäure zusätzlich zu diätetischer Therapie und ggf. anderen lipidsenkenden Medikamenten im Vergleich zur zweckmäßigen Vergleichstherapie bei erwachsenen Patientinnen und Patienten mit primärer Hypercholesterinämie (heterozygot familiär und nicht familiär) oder gemischter Dyslipidämie **Methodik** Die Bewertung erfolgte auf Basis eines Dossiers des pharmazeutischen Unternehmers (pU). Das Dossier wurde dem IQWiG am 30.10.2020 übermittelt. NCT02666664, NCT02988115, NCT02991118	**Ergebnisse** **Fragestellung 1:** Patient*innen, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung nicht ausgeschöpft worden sind - Informationsbeschaffung des pU: RCT CLEAR HARMONY [27] (im Folgenden als Studie HARMONY benannt), CLEAR WISDOM [26] (im Folgenden als Studie WISDOM benannt) und CLEAR SERENITY [29] (im Folgenden als Studie SERENITY benannt) - zur Ableitung des Zusatznutzens (durch pU): HARMONY und WISDOM - Studie SERENITY wird ergänzend dargestellt (u. a. Studiendauer von 24 Wochen) - Vorgehen wird als sachgerecht bewertet - Das IQWIG bewertet die vom pU eingeschlossenen Studien HARMONY und WISDOM für die Bewertung des Zusatznutzens von Bempedoinsäure als nicht geeignet	AMSTAR-II critically low (Hinweis: die vorgelegten Studien entstammen dem Dossier des pharmazeutischen Unternehmers und wurden durch dessen Informationsbeschaffung dokumentiert; eine genaue Angabe der Methodik/Recherche erfolgte nicht, ausschließlich eine Zusammenfassung) eine formale Risk-of-Bias Bewertung ist nicht ersichtlich, allerdings eine Darstellung der Limitationen der Studien; eine Liste ausgeschlossener Volltexte ist nicht verfügbar	die Bewertung wurde unter Einbindung externer Sachverständiger

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	Indikation 1) Erwachsene mit primärer Hypercholesterinämie (heterozygot familiär und nicht familiär) oder gemischter Dyslipidämie, bei denen medikamentöse und diätetische Optionen zur Lipidsenkung nicht ausgeschöpft worden sind 2) Erwachsene mit primärer Hypercholesterinämie (heterozygot familiär und nicht familiär) oder gemischter Dyslipidämie, bei denen medikamentöse (außer Evolocumab) und diätetische Optionen zur Lipidsenkung ausgeschöpft worden sind **Zweckmäßige Vergleichstherapie** 1) maximal tolerierte medikamentöse Therapie nach Maßgabe des Arztes unter Berücksichtigung von Statinen, Cholesterinresorptionshemmern und Anionenaustauschern 2) Evolocumabc oder LDL-Apherese (als „ultima ratio" bei therapierefraktären Verläufen)d ggf. mit begleitender medikamentöser lipidsenkender Therapie	- Begründung: HARMONY und WISDOM sind randomisierte, doppelblinde, multizentrische Studien zum Vergleich von Bempedoinsäure mit Placebo, jeweils in Kombination mit einer lipidsenkenden Hintergrundtherapie; eingeschlossen wurden erwachsene Patient*innen mit hohem kardiovaskulärem Risiko (definiert als atherosklerotische kardiovaskuläre Erkrankung [ASCVD] oder heterozygoter familiärer Hypercholesterinämie [HeFH]), deren Low-Density-Lipoprotein-Cholesterin(LDL-C)-Wert unter bestehender lipidsenkender Therapie nicht ausreichend kontrolliert war - HARMONY und WISDOM sind nicht geeignet, um Aussagen zum Zusatznutzen von Bempedoinsäure abzuleiten, da die zweckmäßige Vergleichstherapie gemäß Festlegung des G-BA nicht umgesetzt ist (während bei den Patient*innen im Interventionsarm in beiden Studien eine Therapieeskalation durch die Verabreichung von Bempedoinsäure erfolgte, führten die Patient*innen im Vergleichsarm ihre unzureichende lipidsenkende Hintergrundtherapie fort. Erst ab Woche 24 war unter der Voraussetzung, dass definierte LDL-C-Schwellenwerte (> 170 mg/dl und ≥ 25 % erhöht gegenüber Studienbeginn) überschritten wurden, eine Anpassung der Hintergrundtherapie möglich) - nach Randomisierung wurde im Vergleichsarm bei lediglich 9 % (Studie WISDOM) bzw. 10 % (Studie HARMONY) der Patient*innen eine Anpassung der lipidsenkenden Therapie vorgenommen **Fragestellung 2:** Patient*innen, bei denen medikamentöse (außer Evolocumab) und diätetische Optionen zur Lipidsenkung ausgeschöpft worden sind - Informationsbeschaffung des pU: für erwachsene Patient*innen mit primärer Hypercholesterinämie		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		(heterozygot familiär und nicht familiär) oder gemischter Dyslipidämie, bei denen medikamentöse (außer Evolocumab) und diätetische Optionen zur Lipidsenkung ausgeschöpft worden sind o keine Daten zur Bewertung des Zusatznutzens von Bempedoinsäure gegenüber der zweckmäßigen Vergleichstherapie vom pU wird die Anzahl der GKV-Patient*innen in der Zielpopulation mit insgesamt 262 154 für die Fragestellung 1 sowie eine Spanne von 15 145 bis 16 971 Patient*innen der GKV-Zielpopulation angegeben (Einflussfaktoren könnten hier die Anpassung der Prävalenz sowie geändertes Verhalten in Bezug auf den Lebensstil sein) geschätzte Jahrestherapiekosten (GKV): - Bempedoinsäure allein oder in Kombination mit lipidsenkenden Therapien: 1 659,71 – 4 253,55 € - maximal tolerierte medikamentöse Therapie nach Maßgabe des Arztes unter Berücksichtigung von Statinen, Cholesterinresorptionshemmern und Anionenaustauschern: 26,37 – 2 593,84 € - Evolocumabe oder LDL-Apherese (als „ultima ratio bei therapierefraktären Verläufen) ggf. mit begleitender medikamentöser lipidsenkender Therapie: 5 857,36 – 69 913,04 € **Eingeschlossene Studien** Goldberg 2019 [26] (CLEAR Wisdom) Ray 2019 [27] (CLEAR Harmony) Laufs 2019 [29] (CLEAR Serenity) Charakteristika der eingeschlossenen Studien vgl. Anhang A ab S. 38 im Bericht		

NICE Single Technology Appraisal 2020 (Bempedoinsäure, Primär- und Sekundärprävention)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Single Technology Appraisal Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1515] Committee Papers. [38]	**Objective** to identify efficacy and safety studies of bempedoic acid and its comparator treatments for patients with primary hypercholesterolaemia or mixed dyslipidaemia when optimised lipid-lowering therapy including statins does not appropriately control LDL-C or when statins are contraindicated or not tolerated **Methods** - systematic literature review (May 2019, a pre-specified protocol) - databases (MEDLINE, MEDLINE In-Process, Embase, BIOSIS and The Cochrane Library) - addition of bibliographies of systematic reviews and key articles - methodologies were critically appraised according to NICE requirements - patients with primary hypercholesterolaemia or mixed dyslipidaemia when optimised lipid-lowering therapy including statins does not appropriately control LDL-C or when statins are contraindicated or not tolerated **Intervention**	clinical development programme for bempedoic acid evaluated the efficacy of bempedoic acid in reducing LDL-C as an add-on therapy to other lipid-modifying therapies (LMTs), including maximally tolerated statins (which may mean no or low statin dose) or ezetimibe or PCSK9 inhibitors, for the treatment of patients whose LDL-C levels are not currently controlled with current standard of care for dyslipidemia n = 15 studies (phase 1), n = 10 studies (phase 2), n = 5 RCT (phase 3): (CLEAR Harmony, Wisdom, Serenity, Tranquility, and Study 1002FDC-053) - bempedoic acid 180 mg either as monotherapy or in combination with stable background LMT (lipid-modifying therapy) for 12 to 52 weeks - efficacy evaluated in n = 16 trials (phase 2 and 3) - pooled meta-analysis (n = 4 studies, n = 3,623 patients, phase 3 studies) - phase 3 bempedoic acid programme evaluated >3,600 unique patients including >3,000 high-risk patients with LDL-C ≥ 70 mg/dL (1.8 mmol/L) who had ASCVD and/or heterozygous familial hypercholesterolemia (HeFH), or presence of other CVD risk factors, and were receiving maximally tolerated statin therapy - additionaly n = 614 patients were included with hypercholesterolaemia who had a history of statin intolerance with a broader range of risk factors for CV events - ongoing open label extension (OLE) study (1002-050) for safety, enrolled patients who received bempedoic acid 180 mg QD for 78 weeks after completion of the 52-week CLEAR-HARMONY study (the parent 1002-040 study) - further phase 3 global, CV outcomes trial is ongoing (CLEAR CVOT, 1002-043), primary outcome MACE (composite endpoint of CV death, non-fatal	AMSTAR-II high	(der gesamte Bericht umfasst etwa 900 Seiten) Table 3 page 20 major atherosclerotic cardiovascular disease risk factors Table 4 page 22 cardiovascular risk categories (ESC) Table 6 page 33 High-risk and very high-risk patients included in 2019 ESC/EAS dyslipidaemia guidelines epidemiology in UK: ~15% in adult UK population affected by hypercholesterolaemia; often associated with comorbidities such as diabetes or CV disease study of 200 cohorts and more than 2 million participants demonstrated that there is a dose-depent log-linear association between LDL-C burden and risk of ASCV (Ference et al. (2017), page 21 (fig 1) dyslipidaemia charactertised by elevated

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	▪ Bempedoic acid, alone or with a statin, with or without other lipid-lowering therapy Bempedoic acid in an FDC with ezetimibe, alone or with a statin
	
	Comperator
	When statins are contraindicated or not tolerated:
	▪ Ezetimibe
	▪ Evolocumab (with or without another lipidlowering therapy)
	▪ Alirocumab (with or without another lipidlowering therapy)
	
	When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C:
	▪ Ezetimibe (when evolocumab and alirocumab are not appropriate)
	▪ Evolocumab (with or without another lipidlowering therapy)
	▪ Alirocumab (with or without another lipidlowering therapy)
	
	When maximally tolerated statin dose does not appropriately control LDL-C:
	▪ Ezetimibe with a statin
	▪ Evolocumab with a statin (with or without another lipid-lowering therapy)
	▪ Alirocumab with a statin (with or without another lipid-lowering therapy)
		myocardial infarction (MI), non-fatal stroke, and coronary revascularisation) – CLEAR Outcomes study
		- phase 2 studies (1002-008 and 1002-009) investigated LDL-C level
		- characteristics of included studies presendend from page 40 to 44, page 48 to 54, page 57 to 61, page 72ff
		- for baseline characteristics see page 62 to 70 and 75ff
		
		Results
		- LS mean difference from placebo in percentage change from baseline to week 12 in LDL-C
		  o ranged from −15.7% to −38.0% (P < 0.001) (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019c; Laufs et al., 2019; Ray et al., 2019b)
		- patients receiving maximally tolerated statin, LS mean reduction from baseline in LDL-C for bempedoic acid compared with placebo
		  o −15.1% vs 2.4% (in CLEAR Wisdom)
		  o −16.5% vs −1.6% (in CLEAR Harmony)
		  o −17.2% vs +1.8% (in 1002FDC-053 (Ballantyne et al., 2019a; Esperion Therapeutics data on file, 2019c; Laufs et al., 2019; Ray et al., 2019b)
		  o −23.6% vs −1.3% (in CLEAR Serenity)
		  o −23.5% vs +5% (Ballantyne et al., 2018)
		  o mean change in LDL-C of −28.5% (CLEAR Tranquility)
		
		summary clinical effectiveness (NICE), see also Table 27, page 100f and Table 28, page 108
		bempedoic acid trials
		- n = 4 completed phase 3 trials (n = 3,623 patients) (CLEAR Harmony, CLEAR Wisdom, CLEAR Serenity, CLEAR Tranquility) n = 2 phase 2 RCT
				LDL-C and triglycerides (< 1.7 mmol/L) and/or reduced or elevated high-density lipoprotein cholesterol (HDL-C) (Carroll et al., 2017), page 19
				
				consistent evidence from multiple types of clinical and genetic studies that clearly establish that LDL-C is a causal factor of atherosclerotic cardiovascular disease (ASCVD) and that cumulative LDL burden is a determinant for initiation and progression of ASCVD (Agabiti Rosei and Salvetti, 2016; Ciccarelli et al., 2018; Ference et al., 2017; Graham et al., 2012; Herrington et al., 2016)
				
				authors noted, that lowering of LDL-C is associated with a reduction in the incidence of major coronary events, ischaemic strokes, and revascularisations (citation Baigent et al., 2011)
				
				therapy generally maintained for life with LDL targets of < 135 mg/dL

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	When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C:
	▪ Ezetimibe with a statin (when evolocumab and alirocumab are not appropriate)
	▪ Evolocumab with a statin (with or without another lipid-lowering therapy)
	▪ Alirocumab with a statin (with or without another lipid-lowering therapy)
	
	Quality assessment
	Tables Quality assessment of phase 2 study 1002-008 and -009, page 90 to 92 (checklist)
	Tables Quality assessment of phase 3 studies, page 93 to 99 (checklist)
	
	(goal of the **clinical development programme** for bempedoic acid was to evaluate the efficacy of bempedoic acid in reducing LDL-C as an add-on therapy to other LMTs, including maximally tolerated statins (which may also mean no statin at all) or ezetimibe, for the treatment of adults with primary hyperlipidaemia who require additional lowering of LDL-C)
	
	Outcomes
	▪ Plasma lipid and lipoprotein levels, including LDL-C, non–HDL-C, apolipoprotein B and lipoprotein a
	▪ Requirement of procedures including LDL apheresis and revascularisation
		(bempedoic acid 180 mg at 12 weeks (Study 1002-008 and Study 1002-009):
		○ treatment with bempedoic acid resulted in significant LDL-C reductions at 12 weeks vs. placebo in patients with hypercholesterolaemia on maximally tolerated statin dose or with statin intolerance
		○ reductions were observed at the first post-baseline study visit (week 4) and were maintained throughout the duration of the studies
		
		○ LS mean percentage change in LDL-C from baseline to week 12, n = 2 studies (CLEAR Harmony, CLEAR Wisdom):
		  ▪ −16.0 for bempedoic acid
		  ▪ 1.8 for placebo
		  ▪ between-group difference [95% CI], −17.8 [−19.5, −16.0]; P < 0.001)
		○ absolute mean reduction from baseline to week 12 in LDL-C (greater in patients treated with bempedoic acid vs placebo)
		  ▪ bempedoic acid, −19.8 mg/dL;
		  ▪ placebo, 0.3 mg/dL
		○ significantly greater percentage of patients in the bempedoic acid group achieved LDL-C < 70 mg/dL at week 12 compared with placebo (28.9% vs 8.0%; P < 0.001)
		
		○ LS mean percentage change in LDLC from baseline to week 12, n = 2 studien (CLEAR Serenity and CLEAR Tranquility):
		  ▪ −23.0 for bempedoic acid
		  ▪ 1.5 for placebo
				in children and < 55-70 mg/dL in adults depending on CV risk level (55 mg/dL is the target for very high-risk patients) (Mach et al., 2019; Volpe et al., 2017).
				
				in UK, statins and ezetimibe are currently the most common pharmacological treatments for lowering LDL-C levels
				
				Bempedoic acid (BA) Bempedoic acid fixed-dose combination with ezetimibe (180mg/10mg)
				(BA = adenosine tri-phosphate (ATP) citrate lyase (ACL) inhibitor)
				(Ezetimibe = NPC1L1 (sterol transporter) inhibitor)
				
				BA and statins both inhibit cholesterol synthesis in the liver; BA is inactive in skeletal muscle
				Ezetimibe inhibits gastrointestinal cholesterol absorption and upregulates LDL receptors

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	- Fatal and non-fatal cardiovascular events - Mortality - Adverse effects of treatment - Health-related quality of life	▪ between-group difference [95% CI], –24.5 [–27.8, –21.1]; P < 0.001)
		 ○ absolute mean reduction from baseline to week 12 in LDL-C (greater in patients treated with bempedoic acid vs placebo)
		   ▪ bempedoic acid, –36.5 mg/dL
		   ▪ placebo, 0.6 mg/dL
		
		- bempedoic acid lowered LDL-C levels similarly across subgroups in the phase 3 trials (patients treated with maximally tolerated statins received additional LDL-C reductions with the addition of bempedoic acid, while larger reductions in LDL-C were observed in patients not taking statins); in post-hoc subgroup analyses by ezetimibe use at baseline, the treatment effect of bempedoic acid was similar in patients with and without ezetimibe)
		
		- compared with placebo, treatment with bempedoic acid added to background lipid-lowering therapy significantly reduced levels of apolipoprotein (apo B), non–HDL-C, and total cholesterol (TC)
		
		fixed dose combination (FDC) (NICE), see also Table 29, page 111
		- FDC of bempedoic acid and ezetimibe has been studied in one, double-blind phase3 study (1002FDC-053) with adult patients at high risk of CVD due to ASCVD, HeFH, or multiple CVD risk factors receiving maximally tolerated statin therapy; teatment with FDC resulted in significant reductions in LDL-C at week 12 from baseline compared with placebo
		- FDC lowered LDL-C levels similarly across subgroups
		- supporting evidence for FDC in statin-intolerant patients is available from the CLEAR Tranquility study which investigated bempedoic acid and
				To note, two technologies are covered: bempedoic acid and bempedoic acid fixed-dose combination with ezetimibe.
				
				EMA (centralized procedure) marketing authorisation in March and April 2020)
				
				The proposed positions in the treatment pathway are as follows:
				- when statins are contraindicated or not tolerated, and ezetimibe does not appropriately control low-density lipoprotein cholesterol (LDL-C)
				- when maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C

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		ezetimibe given as separate tablets; pharmacokinetic studies have shown the two presentations to be equivalent (Esperion Therapeutics data on file, 2019e; Esperion Therapeutics data on file, 2019f)
		
		- LS mean reduction from baseline in LDL-C:
		   o −36.2% for FDC vs
		   o (increase of) 1.8% for placebo
		   o difference vs placebo for LS means was −38% (Ballantyne et al., 2019a; Ballantyne et al., 2019b)
		
		adverse reactions
		overview analysis of safety (phase 3 and phase 2)
		- frequent adverse events slightly higher rates with bempedoic acid than with placebo
		- small changes in laboratory parameters (creatinine increases, uric acid increases, haemoglobin decreases, and liver function test elevations), some occurred more frequently with bempedoic acid
		- increased creatinine, hepatic enzyme elevations, decreased haemoglobin, and anaemia are considered to represent adverse reactions
		- uric acid increased was an adverse reaction (incidence of gout)
		- discontinuation of therapy was reported (e. g. for musculoskeletal disordes)
		- (data not show, blackened)
		
		pathways
		Figure 2 Current NICE pathway and recommendations for LDL-C lowering (page 28)
		- entry: persons at high risk of cardiovascular disease
		- pathway: a) before offering treatment (information and advice), b) treatments not to use, c) lifestyle changes		

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		- pathway a) primary prevention (statin, ezetimibe if statin is contraindicated), secondary prevention (statin, ezetimibe if statin is contraindicated)
		    o statin intolerance (follow-up and monitoring)
		    o intolerance (1) or insufficient response to lipid-lowering therapy (2)
		    o for (1) ezetimibe (first), PCSK9 (second, if appropriate, as dual-combination)
		    o for (2) ezetimibe + statin (first), PCSK9 (second, if appropriate, as triple-combination)
		
		Figure 3 Current NICE pathway and recommendations and proposed placement of bempedoic acid and fixed dose combination FDC (page 36f)
		- same as figure 2, except special recommendations were given within an added table for different situations
		
		Indication for bempedoic acid (EMA):
		Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
		▪ in combination with a statin or a statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
		▪ alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated.
		
		Indication for bempedoic acid and ezetimibe FDC (EMA):
		Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
		▪ in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe,		

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		- alone in patients who are either statin intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone, - in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin **recommendations (NICE)**
		patients at risk of CVD and with FH (familial hypercholesterolaemia) be treated with **statins of high intensity** and low cost (NICE, 2016a; NICE, 2016b; NICE, 2016c; NICE, 2017)
		- for primary prevention: atorvastatin 20 mg
		- for secondary prevention: atorvastatin 80 mg
		- intolerant to high-intensity statins: treatement with the
		- maximum tolerated dose
		
		patients who do not reach therapeutic targets on statin therapy after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy, **combination therapy with ezetimibe** is recommended (Menzin et al., 2017; Volpe et al., 2017)
		
		proprotein convertase subtilisin/kexin type 9 (**PCSK9**) inhibitors (subcutaneous injection and indicated for patients with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet)
		- PCSK9 inhibitors alirocumab and evolocumab (NICE, 2017; Volpe et al., 2017):
		  ■ Patients with primary heterozygous-familial hypercholesterolaemia and LDL-C persistently above 5.0 mmol/L, or 3.5 mmol/L if patients have a high or very high risk of CVD
		  ■ Patients with primary non-familial hypercholesterolaemia and LDL-C persistently above 4.0 mmol/L if patients have a high risk for CVD, or 3.5 mmol/L if patients have a very high risk of CVD		

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		although a range of effective therapies are available, there are **certain patient groups with high unmet need**, particularly the following: ▪ statin therapy is contraindicated or not tolerated and ezetimibe does not adequately control LDL-C, particularly where alirocumab and evolocumab are not appropriate ▪ maximally tolerated statin dose with ezetimibe does not adequately control LDL-C, particularly where alirocumab and evolocumab are not appropriate for previous recommendations see also page 33f **Included studies** Goldberg 2019 [26] (CLEAR Wisdom) Ray 2019 [27] (CLEAR Harmony) Ballantyne 2018 [28] (CLEAR Tranqulity) Laufs 2019 [29] (CLEAR Serenity) Ballantyne 2020 [30]. other studies n = 10 Phase 2 n = 15 Phase 1 Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD) also available [39]		

Nissen et al. 2023 (RCT, Primär- und Sekundärprävention; 50% KHK, 23% Statintherapie)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Nissen SE. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med 2023; 388(15):1353–64.	**Objective** to determine the effects of bempedoic acid on adverse cardiovascular events in a mixed population of	n = 13 970 patients (randomized between Dec 2016 and Aug 2019) - n = 6 992 bempedoic acid - n = 6 978 placebo - mean age 65.5 ± (SD 9.0)	**Selection bias** randomization: low concealment and unpredictability:	authors noted at 6 months after randomization, the central laboratory began to

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https://www.ncbi.nlm.nih.gov/pubmed/36876740. [32]
 	
Nicholls S. Rationale and design of the CLEAR-outcomes trial: Evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. Am Heart J 2021; 235:104–12. https://www.ncbi.nlm.nih.gov/pubmed/33470195. [40]
	patients for whom primary or secondary prevention is clinically indicated but who were unable or unwilling to take guideline-recommended doses of statins
	
	Methods
	CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes trial
	- double-blind, randomized, placebo-controlled trial
	- patients at 1250 sites in 32 countries
	- 18 to 85 years of age
	- patients met either of two criteria for increased cardiovascular risk:
	   o a previous cardiovascular event (secondary-prevention patients)
	   o or clinical features that placed them at high risk for a cardiovascular event (primary-prevention patients)
	- patients report being unable or unwilling to receive statins owing to an adverse effect that had started or increased during statin therapy and resolved or improved after statin therapy was discontinued ("statin-intolerant" patients)
	- other lipid-lowering therapies were permitted, such
		- female 48.2% (n = 6 740)
		- diabetes n = 6 373 (45.6%)
		- previous cardiovascular event n = 9764 (69.9%)
		- primary prevention n = 2 100 (30.0%) vs. 2 106 (30.2%)
		- secondary prevention n = 4892 (70.0%) vs. n = 4872 (69.8%)
		   o coronary artery disease: n = 3 574 (51,1%) vs. n = 3536 (50.7%)
		   o other: peripheral arterial disease, cerebrovascular atherosclerotic disease
		- statin n = 3174 (22.7%)
		- ezetimibe n = 1612 (11.5%)
		- mean LDL-cholesterol: 139.0 mg per decilitre (3.59 mmol per liter)
		- mean high-density lipoprotein cholesterol: 49.5 mg per decilitre (1.28 mmol per liter)
		- median triglyceride:159.0 mg per deciliter (1.80 mmol per liter)
		- median high-sensitivity C-reactive protein (CRP): 2.3 mg per liter
		- median follow-up 40.6 months
		
		- premature discontinuation of the trial occurred in 2035 patients (29.1%) BA and in 2212 patients (31.7%) in the placebo group
		- complete assessment of the primary end point was available for 13,313 patients (95.3%), and vital status was available for 13,886 (99.4%)
		- data on the key efficacy end points at the trial sites in Ukraine were censored after the start of the conflict on February 24, 2022
		
		Results
		primary
		four-component MACE
		- n = 819 (11.7%) vs. n = 927 (13.3%)
		- HR 0.87 (95% CI 0.79; 0.96), p = 0.004
		
		secondary
			low
			
			Performance bias
			blinding of participants and staff: low
			
			Detection bias
			blinding of evaluation: low
			(independent committee blinded to therapy assignment adjudicated all clinical events and assessed the clinical end points)
			
			Attrition bias
			lost to follow-up: unclear
			(ITT, missing data (trial sites in Ukraine on Feb 2022) were censored), authors noted that data are reported without imputation unless otherwise noted
			ITT-analysis: low
			Reporting bias
			selective result presentation: low
			
			(only patients who had reported that they were unable or unwilling to take statins, a factor that resulted in a high mean LDL cholesterol level at baseline)
				notify the investigator, who remained unaware of the trial-group assignments and laboratory values, if the LDL cholesterol level in a patient was 25% or higher than the baseline level; patients were counseled on healthy dietary guidelines and reminded to take all lipid-regulating medications; if repeat testing confirmed that the LDL cholesterol level exceeded the threshold, the iinvestigator could adjust the lipid-lowering regimen according to the standard of care and local guidelines
				
				authors noted that trial enrolled a mixture of patients for whom primary or secondary prevention of cardiovascular disease is clinically indicated
				
				although the incidence of a primary end-point event was higher among the patients with pre-existing cardiovascular disease, the

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	as ezetimibe, niacin, bile acid resins, fibrates, or proprotein convertase sub-tilisin–kexin type 9 (PCSK9) inhibitors, admin-istered as monotherapy or in combinations - 4-week run-in period dur-ing which they received single-blind placebo **Intrevention** bempedoic acid at a daily oral dose of 180 mg **Controll** matching placebo **Outcomes** primary - four-component composite of major adverse cardio-vascular events, defined as death from cardiovas-cular causes, nonfatal my-ocardial infarction, nonfatal stroke, or coronary revas-cularization secondary - hierarchical order, included a three-component compo-site of death from cardio-vascular causes, nonfatal stroke, or nonfatal myocar-dial infarction; fatal or non-fatal myocardial infarction; coronary revascularization; fatal or nonfatal stroke; death from cardiovascular	three-component MACE - n = 575 (8.2%) vs. n = 663 (9.5%) - HR 0.85 (95 % CI 0.76 to 0.96), p = 0.006 fatal or nonfatal myocardial infarction - n = 261 (3.7%) vs. n = 334 (4.8%) - HR 0.77 (95% CI 0.66 to 0.91), p = 0.002 coronary revscularization - n = 435 (6.2%) vs. n = 529 (7.6%) - HR 0.81 (95% CI 0.72 to 0.92), p = 0.001 fatal or nonfatal stroke - n = 135 (1.9%) vs. n = 158 (2.3%) - HR 0.85 (95% CI 0.67 to 1.07), p = 0.16 death from cardiovascular causes - n = 269 (3.8%) vs. n = 257 (3.7%) - HR 1.04 (95% CI 0.88 to 1.24) death from any cause - n = 434 (6.2%) vs. n = 420 (6.0%) - HR 1.03 (95% CI 0.90 to 1.18) hospitalisation for unstable angina - n = 91 (1.3%) vs. n = 137 (2.0%) - HR 0.66 (95% CI 0.50 to 0.86) new-onset type 2 diabetes mellitus - n/N = 429/3848 (11.1%) vs. n/N = 433/3749 (11.5%) - HR 0.95 (95% CI 0.83 to 1.09) change from baseline in secondary lipid and biomarker mean percent change in mean LDL cholesterol level at 6 mo (95% CI) −21.1 (−21.6 to −20.5) vs. −0.8 (−1.4 to −0.2)		hazard ratio in the pri-mary-prevention sub-group was lower than that in the secondary prevention population

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	causes; and death from any cause	difference −20.3 (95% CI −21.1 to −19.5) median percent change in high-sensitivity CRP level at 6 mo (95% CI) −22.2 (−23.5 to −20.8) vs. 2.4 (0.0 to 4.2) difference −21.6 (95% CI −23.7 to −19.6) mean percentage-point change in glycated hemoglobin level at 12 mo in patients with inadequately controlled type 2 diabetes mellitus (95% CI) −0.04 (−0.12 to 0.03) vs. −0.01 (−0.09 to 0.06) difference −0.03 (95% CI −0.14 to 0.08) adverse events any adverse event that started or worsened after the first dose of a trial agent — no. (%) - 6040 (86.3) vs. 5919 (85.0) serious adverse event that started or worsened after the first dose of a trial agent — no. (%) - 1767 (25.2) vs. 1733 (24.9) adverse event leading to discontinuation of the trial regimen — no. (%) - 759 (10.8) vs. 722 (10.4) prespecified adverse events of special interest Myalgia — no. (%) - 393 (5.6) vs. 471 (6.8) Discontinuation of the trial regimen because of myalgia — no. (%) - 124 (1.8) vs. 129 (1.9) New-onset diabetes in patients without diabetes at baseline — no./total no. (%) - 621/3856 (16.1) vs. 640/3740 (17.1) New-onset diabetes in patients with prediabetes at baseline — no./total no. (%) - 569/2918 (19.5) vs. 586/2877 (20.4)		

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		New-onset diabetes in patients with normoglycemia at baseline — no./total no. (%) - 52/938 (5.5) vs. 54/863 (6.3) Worsening hyperglycemia — no./total no. (%) - 713/3145 (22.7) vs. 746/3224 (23.1) Hypoglycemia — no. (%) - 304 (4.3) vs. 267 (3.8) Metabolic acidosis — no. (%) - 13 (0.2) vs. 11 (0.2) Elevated hepatic-enzyme level — no. (%) - 317 (4.5) vs. 209 (3.0) Renal impairment — no. (%) - 802 (11.5) vs. 599 (8.6) Neurocognitive disorders — no. (%) - 58 (0.8) vs. 69 (1.0) Atrial fibrillation — no. (%) - 229 (3.3) vs. 246 (3.5) Adjudicated tendon rupture — no. (%) - 86 (1.2) vs. 66 (0.9) Tendinopathies — no. (%) - 118 (1.7) vs. 128 (1.8) Malignant conditions — no. (%) - 321 (4.6) vs. 341 (4.9) Other adverse events — no. (%) Hyperuricemia 763 (10.9) vs. 393 (5.6) Gout 215 (3.1) vs. 143 (2.1) Cholelithiasis 152 (2.2) vs. 81 (1.2) Laboratory results after 6 mo — mg/dl Change from baseline in uric acid level 0.76±1.2 vs. −0.03±1.0 Change from baseline in creatinine level 0.05±0.2 vs. 0.01±0.2 Laboratory results after 12 mo Change from baseline in glycated hemoglobin level — %		

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		0.04±0.74 vs. 0.06±0.70		

Laufs et al. 2022 (RCT-Subgruppenanalyse, Bempedoinsäure ohne Statintherapie, Patient*innencharakteristika)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Laufs U. Efficacy and safety of bempedoic acid in patients not receiving statins in phase 3 clinical trials. J Clin Lipidol 2022; 16(3):286–97. https://www.ncbi.nlm.nih.gov/pubmed/35346603. [41]	**Objective** to assess the LDL-C lowering effect of bempedoic acid in patients not taking statins (who were previously unable to tolerate any statin dose) as well as evaluating a phase 3 study investigating bempedoic acid plus ezetimibe FDC **Methods** - post hoc analysis - pooled analysis of data - patients enrolled in four phase 3 bempedoic acid studies (12 to 52 weeks in duration) - patients not taking concomitant statins (Phase 3 No Statin Cohort) - patients could still be receiving other stable lipid-lowering therapy, such as ezetimibe - patients in bempedoic acid plus ezetimibe FDC study who were not receiving statins were also assessed as the (BA + EZE FDC No Statin Cohort) **Outcome**	1) Phase 3 No Statin Cohort (n = 586 patients) BA (n = 394) vs. Placebo (n = 192) - mean age 64.9 (9.9) years - 12.8% with a history of ASCD - 24.1% with diabetes mellitus - 67,1% with hypertension mean (SD) baseline LDL-C: 148.7 (40.6) mg/dL median (Q1, Q3) baseline hsCRP: 2.4 (1.1, 4.5) mg/L 58.0% of patients received nonstatin background lipid-lowering therapy, primarily ezetimibe muscle symptoms were the reason for stopping prior statin therapy for 514 (87.7%) patients 2) BA+EZE FDC (n = 106 patients) FDC (n = 33), BA (n = 27), Ezetimibe (n = 32), Placebo (n = 14) mean baseline LDL-C: 168.6 mg/dL **Results** at week 12 Phase 3 No Statin Cohort LDL-C levels: −26.6% vs −0.1%; P < 0.001 placebo-corrected least squares mean difference −26.5% (95% CI, −29.7% to −23.2%); P < 0.001 absolute mean (SD) reduction in LDL-C level 41.0 (32.6) mg/dL vs. 1.2 (24.7) mg/dL fixed-dose combination of bempedoic acid with ezetimibe LDL-C levels: −38.8% vs 0.4%	n. a.	

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	- percent change from base-line to week 12 in LDL-C levels
	- safety and tolerability were assessed by laboratory values and adverse events
		mean difference
		–39.2% (95% CI, –51.7% to –26.7%); P < 0.001
		absolute mean (SD) reduction in LDL-C level
		8.3 (44.1) mg/dL vs. 0.0 (25.6) mg/dL
		
		safety
		Phase 3 No Statin Cohort
		adverse events
		   - incidence rate 137.0 vs. 117.0 per 100 person years
		serious adverse events
		   - incidence rate 14.8 vs. 13.8 per 100 person years
		treatment- emergent AEs leading to discontinuation
		   - incidence rate 32.8 vs. 24.3 per 100 person years
		   - most common reason: myalgia (5.8 vs. 10.6 per 100 person years)
		
		adverse events of special interest
		muscle-related disorders
		   - incidence rate 26.4 vs. 28.6 per 100 person-years
		myalgia
		   - incidence rate 9.5 vs. 14.8 per 100 person years
		pain in the extremity
		   - incidence rate 6.9 vs. 4.2 per 100 person years
		gout
		   - incidence rate 3.2 vs. 1.1 per 100 person years
		blood uric acid increased
		   - incidence rate 11.1 vs. 3.2 per 100 person years
		hepatic enzyme elevation
		   - incidence rate 8.5 vs. 2.1 per 100 person years
		new-onset diabetes/hyperglycemia
		   - incidence rate 4.8 vs. 5.3 per 100 person years
		renal disorders
		   - incidence rate 4.2 vs. 3.2 per 100 person years
		
		Bempedoic Acid Plus Ezetimibe FDC No Statin Cohort
		(BA+ezetimibe, BA, Ezetimib vs. placebo)		

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		adverse events - incidence rate 75.8, 77.8, 68.8 vs. 42.9 per 100 person years serious adverse events - incidence rate 3.0, 11.1, 9.4 vs. 7.1 per 100 person years reatment- emergent AEs leading to discontinuation - incidence rate 9.1, 11.1, 12.5 vs. 0 per 100 person years adverse events of special interest muscle-related disorders - incidence rate 6.1, 11.1, 12.5 vs. 7.1 per 100 person years **Included studies** CLEAR Harmony (NCT02666664) CLEAR Wisdom (NCT02991118) CLEAR Serenity (NCT02988115) CLEAR Tranquility (NCT03001076) BA plus ezetimibe FDC study (NCT03337308), Ballantyne 2020		

Ballantyne et al. 2022 (RCT-open-label extension, CLEAR-Harmony, Patient*innencharakteristika)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Ballantyne CM. Long-Term Safety and Efficacy of Bempedoic Acid in Patients With Atherosclerotic Cardiovascular Disease and/or Heterozygous Familial Hypercholesterolemia (from the CLEAR Harmony Open-Label Extension Study). The American journal of cardiology 2022; 174:1–11.	**Objective** CLEAR Harmony open-label extension (OLE) study was conducted to build on findings from the CLEAR Harmony parent study and evaluate the long-term safety and efficacy of bempedoic acid for up to 130 weeks **Methods**	n = 1 462 patients (BA) open-label extension (OLE) - n = 970 (66%) from patients from BA (CLEAR Harmony) - n = 492 (34%) from placebo (CLEAR Harmony) - mean age 66.9 ± 8.7 years - male 73.9% (n = 1 081) - white (race) 96.5% (n = 1 411) - ASCV 96.3% (n = 1 408) - history of diabetes n = 409 (28.0%)	n. a. single-arm design study focused on patients with established ASCVD and/or HeFH, most received BA in combination with moderate or high intensity statin therapy	authors noted that data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedures

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

https://www.ncbi.nlm.nih.gov/pubmed/35483979. [42]	- phase 3, multicenter, OLE study (NCT03067441)
	- all protocols were appoved by institutional review board
	- between Feb 2017 and Nov 2019
	- open-label for 78 weeks
	- 4-week follow-up
	- patients with atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH)
	- completed the CLEAR Harmony parent study
	- tolerated the study drug (bempedoic acid or placebo)
	- patients who had received placebo and switched to bempedoic acid treatment in the OLE study received up to 78 weeks of bempedoic acid treatment
	
	- patients were ineligible if
	  o had a medical condition that could affect study assessments or required adjustments to background lipid-modifying therapies during the first 12 weeks
		- history of hypertension n = 1161 (79.4%)
		- baseline LDL-C (mg/dL) 101.6 ± 28.2
		- baseline statin only n = 1215 (83.1%)
		- baseline statin intensity
		  o low n = 88 (6.0%)
		  o moderate n = 562 (38.4%)
		  o high n = 812 (55.5%)
		- baseline ezetimibe n 132 (9.0%)
		- all enrolled patients received at least 1 dose of the study drug during the OLE
		- most patients completed 78 weeks of OLE (86%-87%)
		- mean exposure (BA) 1.4 (±0.3) years
		
		Results
		primary
		treatment-emergent adverse events (TEAEs)
		- overall incidence (regardless of causality)
		  o overall OLE 78.2% (n = 1 143)
		  o up to 130 weeks 78.1% (n = 758)
		  o up to 78 weeks 78.3% (n = 492)
		
		serious TEAEs
		- overall incidence (regardless of causality)
		  o overall OLE 20.5% (n = 299)
		  o up to 130 weeks 20.8% (n = 202)
		  o up to 78 weeks 19.7% (n = 97)
		
		TEAEs leading to discontinuation
		- overall incidence (regardless of causality)
		  o overall OLE 7.8% (n = 114)
		  o up to 130 weeks 7.1% (n = 69)
		  o up to 78 weeks 9.1% (n = 45)
		- most common:
		  o myalgia n = 9 (0.6%)
		  o muscle spasms n = 8 (0.5%)
		- incidence did not increase with a longer duration
		
		fatal outcomes		

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	o had a known sensitivity to bempedoic acid
	o were receiving other investigational drugs during the parent study
	o were female, of child-bearing age, and pregnant, lactating, or unwilling to use an accepted method of birth control during the study
	
	Outcomes
	primary
	- long-term safety
	  o treatment-emergent adverse events (TEAEs), serious TEAEs, and
	  o adverse events of special interest (AESIs)
	secondary
	- effectiveness
	  o LDL-C, total cholesterol (TC), non−high-density lipoprotein cholesterol (non−HDL-C), HDL-C, triglycerides, apolipoprotein B (Apo B),
		- overall incidence (regardless of causality)
		  o overall OLE 0.9% (n = 13)
		  o up to 130 weeks 1.0% (n = 10)
		  o up to 78 weeks 0.6% (n = 3)
		
		most common (>0.5%) (study drug-related):
		- muscle spasms 1.7% (n = 25)
		- myalgia 1.4% (n = 21)
		- pain in extremity 0.7% (n = 10)
		- arthralgia 0.6% (n = 9)
		- dizziness 0.6% (n = 9)
		
		adverse events of special interest (OLE, gesamt - n = 1462)
		- muscular disorders n = 124 (8.5%)
		  o muscle spasms n = 48 (3.3%)
		  o myalgia pain in extremity n = 41 (2.8%)
		  o muscular weakness n = 41 (2.8%)
		- creatinine kinase elevation n = 27 (1.8%)
		- new-onset or worsening diabetes mellitus n = 81 (5.5%)
		- renal disorders n = 41 (2.8%)
		- gout n = 38 (2.6%)
		- hypoglycaemia n = 18 (1.2%)
		- neurodegenerative disorders n = 13 (0.9%)
		
		exposure-adjusted incidence per 100 person years (PY)
		- 3.9 for new-onset or worsening diabetes mellitus
		- 6.1 for muscular disorders
		- 1.9 for renal disorders
		- 1.8 for gout
		- 1.3 for creatine kinase elevations
		- 1.4 for hepatic enzyme elevations
		- 0.9 for hypoglycaemia
		- 0.6 for neurocognitive disorders
		
		authors noted that
		- prespecified AESIs were reported during the OLE study at a similar rate as that reported in the parent study (e. g. incidence of gout was 2.6%, and		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	and high-sensitivity C-reactive protein (hsCRP)	the incidence of new-onset or worsening of diabetes was 5.5%) - laboratory abnormalities observed during the OLE study also followed similar patterns as those observed in the parent study and did not worsen with a longer duration of bempedoic acid exposure - no new safety signals were identified - patients with a history of diabetes were more likely to have fasting glucose levels ≥126 mg/dl and haemoglobin A1c levels ≥6.5% after 78 weeks of treatment in the OLE study (48.7% and 58.9%) than patients without a history of diabetes (4.6% and 5.3%) secondary LDL-C from parent study baseline to week 78 of the OLE study - mean change o -14.2 % (± 0.9%) o -16.0 mg/dl (±1.0 mg/dl) adjudicated cardiovascular events n = 108 (7.4%) MACE - CV death n = 6 (0.4%) - Nonfatal myocardial infarction n = 23 (1.6%) - Nonfatal stroke n = 14 /1.0%) - Coronary revascularization n = 53 (3.6%) - Hospitalization for UA n = 20 (1.4%) Non-MACE - Non-CV death n = 3 (0.2%) - Non coronary revascularization n = 24 (1.6%) - Hospitalization for heart failure n = 9 (0.6%) authors documented also laboratory abnormalities (see Table 4)		

12.4.4 Zusatzinformation Ezetimib (Empfehlung 7-15)

Zhan et al. Ezetimib (SR, 2018)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Zhan et al. 2018. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events (Review). https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012502.pub2/epdf/full [43]	**Objectives** to assess the efficacy and safety of ezetimibe for the prevention of cardiovascular disease (CVD) and all-cause mortality
	
	Search methods searched CENTRAL, MEDLINE, Embase and Web of Science on 27 June 2018, and two clinical trial registry platforms on 11 July 2018; checked reference lists
	
	Selection criteria
	- randomised controlled trials (RCTs) that compared ezetimibe versus placebo or ezetimibe plus other lipid-modifying drugs versus other lipid-modifying drugs alone
	- follow-up at least 12 months
	- adults with or without CVD
	- cluster RCT, cross-over trials and non-randomized trials were excluded
	
	Quality assessment Cochrane risk of bias tool (Higgins 2011); GRADE (quality of evidence)
	
	Intervention ezetimibe or ezetimibe + other lipid-modifying drug(s)
		n = 26 RCT (108 records) (n = 23,499 participants)
		- n = 26 trials for ezetimibe + other lipid-modifying drugs vs. other lipid-modifying drugs (alone or + placebo)
		- ezetimibe dose: 10 mg/day
		- lipid-modifying drug:
		  ○ n = 25 trials statine (simvastatin, atorvastatin, rosuvastatin, pitavastatin, fluvastatin)
		  ○ n = 1 trial fenofibrate
		- statin dose was the same initial dose in n = 18 studies (I vs. C)
		- statin dose was a double-dose for comperator in n = 7 studies (usual dose for I)
		- n = 0 trials for ezetimibe vs. placebo
		- number of participants randomized 18 to 18,144
		- mean age 46 – 84 years
		- n = 10 studies with mostly male participants
		
		- analyses driven by two large studies (IMPROVE-IT 2015 and HIJ-PROPER 2017), findings were driven by the largest study (IMPROVE-IT; weights in the MA 41.5% to 98.4%)
		- n = 3 studies with three intervention arms
		- follow-up 1 – 6 years
		- n = 14 studies with participants with existing atherosclerotic CVD (e. g. n = 4 studies with acute coronary syndrome, n = 6 studies with coronary heart disease); other studies recruited participants with e. g. hypercholesterolaemia (at risk)
		
		- n = 21 studies included in meta-analyses
		
		- n = 3 ongoing studies and n = 4 awaiting classifications were reported
			AMSTAR-II high
			
			authors accepted conference abstracts, if primary publications were available
			
			funnel plot did not indicate a strong possibility of publication bias
			
			autors grades the quality of evidence for major adverse cardiovascular events as moderate (mainly due to potential bias) and for all-cause mortality as high
				authors documented that the effect of ezetimibe monotherapy in preventing CVD and all-cause mortality remain uncertain (included studies presented results for ezetimibe combined with lipid-modifying drugs)
				
				authors noted that none of the included studies reported quality of life
				
				authors cited n = 5 previous published reviews

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	Controll placebo or active treatment **Outcome** primary - major adverse cardiovascular events (MACE), defined as a composite outcome of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalisation for unstable angina, or coronary revascularisation procedures - all-cause mortality secondary - myocardial infarction (MI) (fatal and non-fatal) - ischaemic stroke (fatal and non-fatal) - cardiovascular mortality - coronary revascularisation - adverse events (AEs) including hepatopathy, myopathy, rhabdomyolysis, cancer, gallbladder-related disease and discontinuation due to AEs - lipid parameters (total cholesterol, LDL-C, HDL-C, triglycerides) - health-related quality of life (using any well-validated scale)	n = 5 studies specified composite of cardiovascular events as primary outcome (HIJ-PROPER 2017; IMPROVE-IT 2015; Kouvelos 2013; Liu 2017; Wang 2016) n = 5 studies specified serum lipid parameters as primary outcome n = 10 of included studies specified MACE as an outcome (definition of MACE was not consistent) n = 3 studies specified all-cause mortality as an outcome (HIJ-PROPER 2017; IMPROVE-IT 2015; PRECISE-IVUS 2015) incomplete or unclear data were reported for n = 13 studies, other domains of the risk of bias tool were often classified as unclear **Outcomes** ezetimibe plus statins vs. statins alone primary major adverse cardiovascular events - risk ratio (RR) 0.94, 95% confidence interval (CI) 0.90 to 0.98 (decrease from 284/1000 to 267/1000, 95% CI 256 to 278; 21,727 participants; 10 studies; moderate-quality evidence) (secondary non-fatal myocardial infarction (MI) - RR 0.88, 95% CI 0.81 to 0.95 (decrease from 105/1000 to 92/1000, 95% CI 85 to 100; 21,145 participants; 6 studies; moderate-quality evidence) non-fatal stroke - RR 0.83, 95% CI 0.71 to 0.97 (decrease 32/1000 to 27/1000, 95% CI 23 to 31; 21,205 participants; 6 studies; moderate-quality evidence)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		need for coronary revascularisation - RR 0.94, 95% CI 0.89 to 0.99 (decrease from 196/1000 to 184/1000, 95% 175 to 194; 21,323 participants; 7 studies)) safety risk of hepatopathy - RR 1.14, 95% CI 0.96 to 1.35; (20,687 participants; 4 studies; low-quality evidence) risk of myopathy - RR 1.31, 95% CI 0.72 to 2.38; (20,581 participants; 3 studies; very low-quality evidence) risk of rhabdomyolysis wide CIs and low event rate risk of cancer, gallbladder-related disease and discontinuation due to adverse events little or no differences ezetimibe plus statins or fenofibrate vs. statins or fenofibrate alone primary all-cause mortality - RR 0.98, 95% CI 0.91 to 1.05; (21,222 participants; 8 studies; high-quality evidence) (secondary cardiovascular mortality - RR 1.00, 95% CI 0.89 to 1.12; (19457 participants; 6 studies; moderate-quality evidence) serum lipids might further reduce the low-density lipoprotein cholesterol (LDL-C), total cholesterol and triglyceride levels and likely increase the high-density lipoprotein cholesterol levels (substantial heterogeneity))		

12.4.5 Zusatzinformation PCSK9 (Empfehlung 7-16)

Schmidt et al. PCSK9 (SR, Primär- und Sekundärprävention, 2020)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Schmidt et al. 2020. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease (Review). https://www.cochrane-library.com/cdsr/doi/10.1002/14651858.CD011748.pub3/epdf/full [44]	**Objectives**
	Primary
	to quantify the effects of PCSK9 inhibitors on CVD, all-cause mortality, myocardial infarction, and stroke, compared to placebo or active treatment(s) for primary and secondary prevention
	Secondary
	to quantify the safety of PCSK9 inhibitors, with specific focus on the incidence of influenza, hypertension, type 2 diabetes, and cancer, compared to placebo or active treatment(s) for primary and secondary prevention
	
	Search methods
	searching CENTRAL, MEDLINE, Embase, and Web of Science in December 2019; ClinicalTrials.gov and the International Clinical Trials Registry Platform in August 2020 and screened the reference lists of included studies
	
	This is an update of the review first published in 2017.
	
	Selection criteria
	- parallel-group and factorial randomised controlled trials (RCTs)
	- follow-up of at least 24 weeks
		updated Version
		- bococuzumab and RG7652 were removed
		- n = 7 additional trials evaluating alirocumab or evolocumab were included
		
		study charakteristics
		- n = 24 studies (n = 34 references) (data on 60,997 participants)
		- n = 18 trials (n = 26,583 participants) alirocumab
		- n = 6 trials (n = 34,435 participants) evolocumab
		- placebo controlled:
		  o n = 12 trials (alirocumab)
		  o n = 3 trials (evolocumab)
		- active treatment:
		  o n = 6 trials (alirocumab)
		  o n = 3 trials (evolocumab)
		- ~29% (n = 7721) female
		- ~ 10% (n = 4590) had no history of CVD
		- most of available studies preferentially enrolled people with either established CVD or at a high risk already
		- outpatient care settings
		- all participants received background lipid-lowering treatment or lifestyle counselling
		- follow-up 6 to 36 months (vs. placebo)
		- follow-up 6 to 12 months (vs. active treatment)
		- authors calculated two weeks' equivalence dosage
		
		- evidence in low- to medium-risk settings is minimal
		
		- n = 4 ongoing trials were identified
			AMSTAR-II moderate
			
			authors accepted conference abstracts, if primary publications were available
			
			asymmetry for the funnel plot war reported and explained by smaller studies
			
			authors noted that most trials were at low risk of bias; note: the domains blinding and incomplete outcome data were classified as high or unclear risk of bias for some studies
			
			analytics like multiple imputation or mixed-effects models were used
			
			authors classified clinical outcomes for PCSK9 inhibitors vs. placebo as high certainty of evidence and vs. active treatment as (very) low certainty of evidence
			
			downgrading of evidence was explained by a lack of precision and small sample size, open-label design
				authors noted that data on quality of life were unavailable for all studies
				
				authors cited two previous systematic reviews and three meta-analyses (relation to other published evidence)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- adult participants with or without a history of CVD - compared PCSK9 inhibitors alirocumab or evolocumab to placebo or active treatments such as statins, ezetimibe, or a combination of these - cluster RCT, cross-over trials and non-randomized trials were excluded **Quality assessment** Cochrane Risk of bias tool (Higgins 2011); certainty of evidence (GRADE) **Intervention** alirocumab or evolocumab **Control** placebo or active treatment (e.g. statins, ezetimibe or combinations) **Outcomes** primary - composite of CVD, defined as urgent coronary revascularisation, unstable angina pectoris, non-fatal and fatal myocardial infarction (MI), non-fatal and fatal stroke, and CHD death - all-cause mortality - MI - stroke secondary - Adverse events, specifically:	incomplete or unclear outcome data were reported for n = 11 trials; for some studies the domaine blinding was rated as high risk of bias (e. g. open-label design) **outcomes** primary alirocumab vs. placebo risk of CVD events - absolute risk difference (RD) –2% - odds ratio (OR) 0.87, 95% confidence interval (CI) 0.80 to 0.94; 10 studies, 23,868 participants; high-certainty evidence) risk of mortality - RD –1% - OR 0.83, 95% CI 0.72 to 0.96; 12 studies, 24,797 participants; high-certainty evidence) risk of MI - RD –2% - OR 0.86, 95% CI 0.79 to 0.94; 9 studies, 23,352 participants; high-certainty evidence) risk of stroke - RD 0% - OR 0.73, 95% CI 0.58 to 0.91; 8 studies, 22,835 participants; high-certainty evidence). alirocumab vs. ezetimibe and statins risk of CVD - RD 1% - OR 1.37, 95% CI 0.65 to 2.87; 3 studies, 1379 participants; low-certainty evidence) risk for mortality - RD was –1% - OR 0.51, 95% CI 0.18 to 1.40; 5 studies, 1333 participants; low-certainty evidence)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	o influenza o T2DM o cancer o hypertension	risk for MI - RD was 1% - OR 1.45, 95% CI 0.64 to 3.28, 5 studies, 1734 participants; low-certainty evidence) risk for stroke - RD less than 1% - OR 0.85, 95% CI 0.13 to 5.61; 5 studies, 1734 participants; low-certainty evidence) evolocumab vs. placebo risk for CVD - RD –2% - OR 0.84, 95% CI 0.78 to 0.91; 3 studies, 29,432 participants; high-certainty evidence) risk for mortality - RD less than 1% - OR 1.04, 95% CI 0.91 to 1.19; 3 studies, 29,432 participants; high-certainty evidence) risk for MI - RD –1% - OR 0.72, 95% CI 0.64 to 0.82; 3 studies, 29,432 participants; high-certainty evidence) risk for stroke - RD less than –1% - OR 0.79, 95% CI 0.65 to 0.94; 2 studies, 28,531 participants; high-certainty evidence) evolocumab vs. ezetimibe and statins risk for CVD events - RD less than –1% - OR 0.66, 95% CI 0.14 to 3.04; 1 study, 218 participants; very low-certainty evidence)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		risk for all-cause mortality - RD less than 1% - OR 0.43, 95% CI 0.14 to 1.30; 3 studies, 5223 participants; very low-certainty evidence) risk and for MI - RD less than 1% - OR 0.66, 95% CI 0.23 to 1.85; 3 studies, 5003 participants; very low-certainty evidence) insufficient data on any stroke forest plots for adverse events see Appendix page 64 ff (wide confidence intervals and non satistic significant results)		

12.4.6   Zusatzinformation Statinintoleranz

Meza-Contreras et al. 2023. Statin intolerance management (SR)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Meza-Contreras et al. Endocrine. 2023. Statin intolerance management: a systematic review. 2023 https://pub-med.ncbi.nlm.nih.gov/36459335/
 	
[45]
	Objective
	to characterize the range of expert recommendations about the care of patients with statin intolerance
	
	Search
	PubMed, EMBASE, Scopus, Cochrane, online textbooks, SR, guidelines (published in the past 5 years) (search on April, 1 2022)
	
	- registered in PROSPERO
	- protocol was modified (an explicit definition of statin intolerance was removed as inclusion criterion)
		n = 26 articles
		- n = 1 was added post hoc
		- n = 14 (54%) with definition of statin intolerance
		- n = 24 (92%) suggested a sequenced approach (management of statin intolerance) with n = 12 different approaches (konsensbasiert)
		
		statin intolerance definition
		- n = 14 (54%)
		- most offered own definitions
		- simple definition (n = 3):
		  o "statin therapy discontinued because of symptoms attributed to taking statins"
		- other definitions
		  o "required intolerance to ≥ 2 different statins" (n = 7)
			AMSTAR-II critically low (u. a. keine Liste der ausgeschlossenen Studien mit Ausschlussgrund verfügbar; keine Risk-of-Bias- bzw. Qualitätsbewertung der Artikel, ausschließlich Bewertung, ob systematisch gesucht wurde)
			
			Limitations mostly, narrative reviews of the last 5 years were included
			
			none of the included articles described a systematic process to identify, review and synthesize the research evidence
				Selektiv ermittelter Artikel aus der AG Arbeit; zur Diskussion, da die Definition sowie die Strategien zum (zumeist schrittweisen) Umgang aus Empfehlungen aus (zumeist narrative) Übersichten innerhalb der vergangenen 5 Jahre zusammengefasst wurden, die Frage für die NVL nicht priorisiert, aber für die Diskussion als relevant eingestuft wurde

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	Inclusion and exclusion criteria
	- articles offered recommendations for the management of statin intolerance
	- expert narrative reviews, systematic reviews, or clinical practice guidelines
	- published in the last 5 years
	- described the clinical situation as statin intolerance or as discontinuation (or threat of discontinuation) of statins due to adverse effects attributed to statins
	- offered a management strategy to address this problem in adults at
	- any level of risk for ASCVD (atherosclerotic cardiovascular disease)
	
	Outcome
	definition and described statin intolerance
	
	problem definitions, goals, steps, sequence, and supportive evidence of supposed strategies
	
	(e.g., stop statin, offer same statin, offer alternative statin, offer other lipid lowering agent, calculate ASCVD risk, engage in shared decision making, measure creatine kinase) their type (e.g., education, communication, decision making, diagnostic, intervention, referral) and sequence
		o "abnormal test results" (n = 6)
		o "muscle-related symptoms" (n = 3)
		o "a broader range of symptoms" (n = 11)
		
		- n = 12 (46%) used a definition that required resolution of symptoms or laboratory abnormalities after statin discontinuation (n = 11)
		
		management strategies
		- n = 24 (92%): stepwise approach for the management of statin intolerance with
		  o n = 12 different strategies
		  o 1st step (n = 23)
		    ▪ exclusion of other causes (n = 9)
		    ▪ recalculating CV risk (n = 7)
		    ▪ creatinine kinase level (n = 3)
		    ▪ rechallenge (n = 1)
		    ▪ other (n = 3)
		  o 2nd step (n = 22)
		    ▪ exclusion of other causes (n = 7)
		    ▪ creatinine kinase level (n = 5)
		    ▪ rechallenge (n = 4)
		    ▪ recalculating CV risk (n = 2)
		    ▪ other (n = 4)
		  o 3rd step (n = 19)
		    ▪ rechallenge (n = 6)
		    ▪ creatinine kinase level (n = 5)
		    ▪ exclusion of other causes (n = 2)
		    ▪ recalculating CV risk (n = 3)
		    ▪ other (n = 3)
		  o 4th step (n = 12)
		    ▪ rechallenge (n = 9)
		    ▪ other (n = 1)
		  o 5th step (n = 1)
		    ▪ rechallenge (n = 1)
		
		other causes for muscle symptoms:
			only one of the included articles described a process for the development and grading of their recommendations	(nicht empfehlungsbegründend)
				
				large variation in definition and strategies without structured processes used to develop these recommendations and evidence to support the recommended strategies
				
				most common early step in strategies: 39% exclusion of other causes
				
				next common step: recalculating CV risk and quantification of CK levels
				
				determinants to decide whether statin therapy
				• could be continued,
				• changed to a lower dose or
				• to a different statin, or
				• stopped (e.g., large elevations consistent with rhabdomyolysis)
				
				non considered reducing ASCVD risk

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	(e.g., before everything else, key branching step, next step)	- experts recommended excluding vitamin D deficiency, drug-drug interactions, intense exercise, hypothyroidism, and dermato- or polymyositis and other myopathies either as a primary cause of muscle symptoms or as factors that could increase the risk of statin-associated muscle symptoms rechallenging - implemented, after a washout period of 2 to 6 weeks (wash out duration was not required - or not reported in 13 (50%)) - using low-dose statin (25 (96%)), - taking long-acting statins on alternate - days (20 (77%)), - switching to another statin (24 (92%)), or - taking a generic statin (1 (4%)) definitions and proposed strategies n (%) - Offer a definition of statin intolerance 14 (54) - Offer a stepwise strategy 24 (92) Strategies - Exclusion of other causes of symptoms 23 (88) - Measure creatine kinase levels 16 (62) - Measure alanine transaminase levels 3 (12) - Supplement creatine 1 (4) - Measure vitamin D levels 10 (38) - Estimate symptom scores or use the SAMS-CI instrument 6 (23) - Recalculate ASCVD risk 14 (54) - Evaluate symptom severity 10 (38) - Stop statins 25 (96) - Maintain statins 7 (27) - Rechallenge with statins 26 (100) - Measure coronary artery calcium 1 (4) Stop/maintain then: - Use a lower dose 25 (96) - Administer on alternate days 20 (77) - Switch to another statin 24 (92)		through nonlipid pathways no article reported on the safety and efficacy of their management algorithm 58% recommended patient education

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- Use a generic statin 1 (4) - Use same statin and dose 4 (15) Switch to non-statin 15 (58) - Ezetimibe 15 (58) - Fibrates 4 (15) - PCSK-9 inhibitor 13 (50) - Bile acid sequestrant 5 (19) - Nutraceuticals 3 (12) - Bempedoic acid 2 (8) - Ion exchange resin 1 (4) Adding non-statin drug 26 (100) - Ezetimibe 25 (96) - Fibrates 2 (8) - PCSK-9 inhibitor 23 (88) - Bile acid sequestrant 8 (31) - Bempedoic acid 5 (19) - Nutraceuticals 4 (15) - Coenzyme Q10 3 (12) - Phytosterols 1 (4) - Ion exchange resin 1 (4) - Patient education 15 (58) - Shared decision making 0 (0) *ASCVD atherosclerotic cardiovascular disease, PCSK-9 proprotein convertase subtilisin/kexin type 9, SAMS-CI Statin-Associated Muscle Symptom Clinical Index*		

12.5 Kapitel medikamentöse Therapie – Thrombozytenaggregationshemmer

12.5.1 Zusatzinformation Protonenpumpenhemmer bei (Risiko für) gastrointestinale Blutungen

Hinweis: die Recherche wurde aus der NVL Kreuzschmerz übernommen (Suche am 01. August 2022); die TiAb-Screeningtabelle wurde in Bezug auf möglicherweise ergänzend relevante Evidenz überprüft und die Ergebnisse der NVL Kreuzschmerz übernommen, die Aktualität und Gültigkeit der Recherche wurde als gegeben gesehen (Stand: 14.12.2023)

12.5.1.1 PPI bei NSAR-Anwendung (tlw. indirekte Evidenz)

Rostom et al. 2021 Prevention of gastroduodenal ulcers (NSAID-induced), SR

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Rostom A. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database of Systematic Reviews 2021; 2021(10):195. dx.doi.org/10.1002/14651858.CD002296. [46] *Protokoll (noch keine Publikation vorhanden (15.12.2023)):* Garegnani L. Proton pump inhibitors for the prevention of non-steroidal anti-inflammatory drug-induced ulcers and dyspepsia. Cochrane Database of Systematic Reviews 2022; 2022(5):357. dx.doi.org/10.1002/14651858.CD014585. [47]	**Objective** to review the effectiveness of the prostaglandin analogue (PA) misoprostol, H2-receptor antagonists (H2RA), and proton pump inhibitors (PPI) for the prevention of NSAID induced upper GI toxicity, among patients requiring chronic NSAID use secondary to review effect on NSAID induced GI symptoms **Search** SR and meta-analysis MEDLINE from 1966 to May 2009, Current Contents for six months prior to May 2009, EMBASE to May 2009, and the Cochrane Controlled Trials Register from 1973 to May 2009; recent conference proceedings were reviewed; search strategy was used to supplement the Canadian NSAID consensus conference (2007-2008) **Inclusion and exclusion criteria** - RCT - NSAID > 3 weeks - prophylaxis of NSAID-induced ulcer - prostaglandin analogues (PA),	n = 41 RCTs n = 39 RCT included (n=23 misoprostol, n = 12 H2RA, n = 9 PPI) - some studies considered more than one active intervention - seven studies were used for head to head comparisons - for PPI: six direct; five head to head - all included studies were RCT in participants with arthritis who were taking traditional NSAID in an outpatient setting **Results** note: only results for PPI were extracted PPI vs. placebo (prevention of NSAID induced upper GI toxicity) - n = 6 RCT (n = 1259 participants) - (Graham 2002; Bianchi Porro 2000; Hawkey 1998; Ekstrom 1996; Cullen 1998; Lai 2003) 4 to 11 week study (n =1, Lai 2023) endoscopic gastric ulcer - n = 1study (n = 43 participants) - n = 1/22 vs. n = 7/21 - Risk Ratio (M-H, Fixed, 95% CI) 0.14 [0.02, 1.02] endoscopic duodenal ulcer - n = 1 study (n = 43 participants) - n = 1/22 vs. n = 2/21 - Risk Ratio (M-H, Fixed, 95% CI) 0.48 [0.05, 4.88] total endoscopic ulcers - n = 1 (n = 43 participants)	AMSTAR-II high majority of the studies were of reasonable quality with a Jadad score of three or greater (20 studies - Q3; ten studies - Q4; two studies Q5) nine studies received a Jadad Score of two or less publication bias was documented for PPI no significant differences were observed by quality	arthritic and inflammatory conditions were addressed included were participants with arthritis common side effects of NSAID such as nausea and dyspepsia correlate poorly with serious adverse GI event authors noted endoscopic ulcers in up to 40% of chronic NSAID users serious NSAID induced GI complications such as haemorrhage, perforation or death are much less common, occurring collectively with an incidence of about 1.5% per year authors concluded that PPI are effective at reducing the risk of endoscopic gastric and duodenal NSAID induced ulcers

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- H2-receptor antagonists (H2RA) or - proton pump inhibitors - (PPI) - prevention of chronic NSAID induced upper GI toxicity **Intervention** H2-antagonists, Proton pump inhibitors and misoprostol (each used for the prophylaxis of NSAID induced gastroduodenal ulcers) **Comperator** placebo or vs. another **Quality assessment** validated quality instrument (Jadad 1996) **Outcome** primary - endoscopic ulcers (gastric, duodenal and gastroduodenal) - clinical ulcer complications (haemorrhage, perforation, pyloric obstruction or death) secondary - symptoms - drop-outs	- n = 2/22 vs. n = 9/21 - Risk Ratio (M-H, Fixed, 95% CI) 0.21 [0.05, 0.87] clinical ulcer (POB) - n = 1 study (n = 43 participants) - n = 0/22 vs. n = 4/21 - Risk Ratio (M-H, Fixed, 95% CI) 0.11 [0.01, 1.86] clinical ulcer - PUB (POB + symptomatic ulcer) - n = 1 study (n = 43 participants) - n = 1/22 vs. n = 9/21 - Odds Ratio (M-H, Fixed, 95% CI) 0.06 [0.01, 0.56] 8 weeks or longer studies (n =6) endoscopic gastric ulcer - n = 6 studies (n =1230 participants) - n = 93/744 vs. n = 131/486 - Risk Ratio (M-H, Fixed, 95% CI) 0.39 [0.31, 0.50] endoscopic duodenal ulcer - n = 5 studies (n = 883 participants) - n = 10/508 vs. n = 38/375 - RR 0.20; 95% CI 0.10 to 0.39 total endoscopic ulcer - n = 6 studies (n = 1259 participants) - n = 108/766 vs. n =177/493 - RR 0.34; 95% CI 0.28 to 0.42 12 weeks or longer studies endoscopic gastric ulcer - n = 5 studies (n = 1187 participants) - n = 92/722 vs. n = 124/465 - Risk Ratio (M-H, Fixed, 95% CI) 0.40 [0.32, 0.51] endoscopic duodenal ulcer - n = 4 studies (n = 840 participants) - n = 9/486 vs. n = 36/354 - Risk Ratio (M-H, Fixed, 95% CI) 0.19 [0.09, 0.37] total endoscopic ulcers - n = 5 studies (n = 1216 participants) - n = 106/744 vs. n =168/472 - Risk Ratio (M-H, Fixed, 95% CI) 0.35 [0.28, 0.43]		authors noted that: several factors influence the risk of NSAID related upper GI toxicity: - increasing age (>65) - previous peptic ulcer disease - co-morbid medical illnesses - type of NSAID - use of multiple NSAID - combined use of NSAID and corticosteroids (Fries 1991; Bollini 1992; Gabriel 1991; Silverstein 1995; Hallas 1995; Hansen 1996; Laporte 1991; Rodriguez 1997; Hochain 1995) younger patients without co-morbidities or previous GI NSAID complications can be

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		clinical ulcers - small studies in high risk participants suggest that PPI can reduce the risk of clinically important ulcer complications - a small 8 week study found that PPI reduce the risk of endoscopic ulcers but there were also fewer bleeds or symptomatic ulcers in the PPI group compared to placebo (Lai 2003) symptoms - n = 4 omeprazole trials (Cullen 1998; Ekstrom 1996; Hawkey 1998; Yeomans 1998) - omeprazole significantly reduced "dyspeptic symptoms" as defined by the authors - in the combined analysis, drop-outs overall and drop-outs due to side effects were not different from placebo - results supported by a recent study by Hawkey et al that reported statistically significant improvement in dyspeptic symptoms in NSAID participants taking esomeprazole compared to placebo (Hawkey 2005) toxicity dropouts overall - n = 2 studies (n = 833 participants) - n = 66/544 vs. n = 39/289 - Risk Ratio (M-H, Fixed, 95% CI) 0.89 [0.62, 1.29] dropouts due to side effects - n = 4 studies (n = 1113 participants) - n = 32/699 vs. n =15/414 - Risk Ratio (M-H, Fixed, 95% CI) 1.20 [0.66, 2.15] 13.3 diarrhea - n = 2 studies (n = 832 participants) - n = 34/544 vs. n = 11/288 - Risk Ratio (M-H, Fixed, 95% CI) 1.66 [0.85, 3.22] abdominal pain		treated with a traditional NSAID alone (Rostom 2009; Maetzel 1998)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- n = 2 studies (n = 832 participants) - n = 14/544 vs. n =9/288 - Risk Ratio (M-H, Fixed, 95% CI) 0.88 [0.39, 1.98] flatulence - n = 1 study (n = 430 participants) - n = 7/275 vs. n = 5/155 - Risk Ratio (M-H, Fixed, 95% CI) 0.79 [0.25, 2.44] dyspepsia - n = 2 studies (n = 345 paticipants) - n = 19/169 vs. n = 40/176 - Risk Ratio (M-H, Fixed, 95% CI) 0.50 [0.30, 0.82]		

Scally et al. 2018 Prevention and treatment of peptic ulcer disease, SR

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Scally B. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: A meta-analysis of randomised trials. Lancet Gastroenterol Hepatol 2018; 3(4):231–41. https://www.ncbi.nlm.nih.gov/pubmed/29475806. [48]	**Objective** to examine the effects of proton-pump inhibitors (PPIs), prostaglandin analogues, and histamine-2 receptor antagonists (H2RAs) in different clinical circumstances by doing meta-analyses of tabular data from all relevant unconfounded randomised trials of gastroprotectant drugs **Search** MEDLINE and Embase from Jan 1, 1950, to Dec 31, 2015 **Inclusion and exclusion criteria** - RCT - people with no ulcer at baseline - people with a non-bleeding ulcer at baseline	n = 849 trials (142 485 participants) - n = 580 prevention trials (110 626 participants), - n = 233 healing trials (24 033 participants), and - n = 36 trials for the treatment of acute upper gastrointestinal bleeding (7826 participants) - comparisons of one gastroprotectant drug vs. another available in 345 trials (64 905 participants) o n = 160 prevention trials (32 959 participants), o n = 167 healing trials (28 306 participants), and o n = 18 trials for treatment of acute upper gastrointestinal bleeding (3640 participants) - median number of patients in each trial o n = 78 (IQR 44·0–210·5) - median duration o 1·4 months (0·9–2·8) **results** gastroprotectants vs. placebo	AMSTAR-II low (eine Liste der ausgeschlossen Studien ist nicht verfügbar; allerdings eine sehr detaillierte Aufbereitung der großen Anzahl eingeschlossener Studien sowie Analysen zu publication bias) they did exploratory analyses according to drug dose; NSAID use at randomisation network meta-analysis approach was used small study bias was reported	authors noted that in the context of peptic ulcer disease, gastroprotectants—and in particular PPIs—are effective in ulcer prevention, ulcer healing, and in reducing rebleeding additionally, authors noted a large ongoing COMPASS trial of pantoprazole versus placebo in 17 000 patients with stable cardiovascular disease that might provide useful safety information, and could also help to determine the true size of any beneficial effects

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- people presenting with upper gastrointestinal bleeding at baseline
	- with or without confirmed diagnosis of peptic ulcer disease
	- gastroprotectant drug
	- studies with participants with non-peptic upper gastrointestinal bleeding (eg, from varices) were excluded
	
	Intervention
	PPI, prostaglandin analogue, or H2RA
	
	Comperator
	placebo or vs. another
	
	Outcome
	primary
	- ulcer development,
	- bleeding, and
	- mortality overall
		prevention trials, gastroprotectant drugs
		- development of endoscopic ulcers
		  o n = 152 studies
		  o 1889/18042 (10%) vs. 3502/13255 (26%)
		  o odds ratio [OR] 0·27, 95% CI 0·25–0·29; p<0·0001
		  o PPI
		    ▪ OR 0.20 (0.17; 0.23)
		    ▪ 314/6541 (5%) vs. 937/4912 (19%), n = 29 studies
		- symptomatic ulcers
		  o n = 51 studies
		  o 523/9857 (5%) vs. 1136/9444 (12%)
		  o 0·25, 0·22–0·29; p<0·0001
		  o PPI
		    ▪ OR 0.15 (0.09; 0.23)
		    ▪ 28/2585 (1%) vs. 152/2587 (6%), n = 8 studies
		- mortality
		  o n = 51 studies
		  o 574/15844 (3%) vs. 496/13063 (4%)
		  o 0·85, 0·69–1·04; p=0·11
		  o PPI
		    ▪ OR 1.01 (0.50; 2.05)
		    ▪ 37/7471 (>1%) vs. 31/5352 (1%), n = 18 studies
		- upper gastrointestinal bleeding
		  o n = 49 studies
		  o 90/14139 (1%) vs. 221/12130 (2%)
		  o 0·40, 0·32–0·50; p<0·0001
		
		- larger proportional reductions in upper gastrointestinal bleeding were observed for PPIs than for other gastroprotectant drugs
		  o PPIs 0·21, 99% CI 0·12–0·36;
		  o prostaglandin analogues 0·63, 0·35–1·12;
		  o H2RAs 0·49, 0·30–0·80; phet=0·0005
				as most frequent cause of peptic ulcer disease Helicobacter pylori infection and the use of NSAID (non-steroidal anti-inflammatory drug), including ASS, were reported

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

		- gastroprotectant drugs were effective in preventing bleeding irrespective of the use of non-steroidal anti-inflammatory drugs (phet=0·56)
		
		- PPIs were effective in prevention of endoscopic and symptomatic ulcers irrespective of the use of NSAIDs, although for endoscopic ulcers the
		- proportional odds reduction appeared to be greater in those not taking NSAIDs at trial entry (appendix)
		
		healing trials, gastroprotectants
		- endoscopic ulcer healing
		   o 3·49, 95% CI 3·28–3·72; p<0·0001
		- with PPIs more effective (5·22, 99% CI 4·00–6·80) than prostaglandin analogues (2·27, 1·91–2·70) and H2RAs (3·80, 3·44–4·20; phet<0·0001)
		
		- weitere Daten vgl. Publikation sowie Appendix
		
		trials among patients with acute bleeding, gastroprotectants
		- further bleeding
		   o OR 0·68, 95% CI 0·60–0·78; p<0·0001
		- blood transfusion
		   o 0·75, 0·65–0·88; p=0·0003
		- further endoscopic intervention
		   o 0·56, 0·45–0·70; p<0·0001
		- surgery
		   o 0·72, 0·61–0·84; p<0·0001
		- mortality
		   o OR 0·90, 0·72–1·11; p=0·31
		- PPIs had larger protective effects than did H2RAs for further bleeding (phet=0·0107) and blood transfusion (phet=0·0130)
		
		- Weitere Daten vgl. Publikation und Appendix
		
		they found no clear evidence that any individual PPI or prostaglandin analogue was more effective for the prevention of		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		symptomatic ulcer than any other of the same class (appendix) found no evidence that individual PPIs differed in their effects on bleeding (phet=0·48; appendix)		

Mo et al. 2015 PPI in prevention of low-dose ASS-associated upper GI injuries, SR

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Mo C. Proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries. World J Gastroenterol 2015; 21(17):5382–92. https://www.ncbi.nlm.nih.gov/pubmed/25954113. [49]	**Objective**
	to determine the preventive effect and safety of proton pump inhibitors (PPIs) in low-dose acetylsalicylic acid (ASS) (LDA)-associated gastrointestinal (GI) ulcers and bleeding
	
	Search
	- systematic review and meta-analysis
	- Medline, Embase, Cochrane Trial regigster (to December 2013), conference abstracts
	
	Inclusion and exclusion criteria
	- RCT
	- age ≥ 18 years
	- patients taking low-dose ASS (LDA) for at least 2 continous weeks
	- regardless of the combined
	- medication used, medical condition, and comorbidities in the patients
	- non-RCT, cohort studies, case-control studies, pharmacokinetic experiments,
		n = 10 trials (n = 8780 participants)
		- published in US or Japan between 2002 and 2012
		- participants ranged from 62 to 1876 (intervention) vs. 61 to 1885 (control)
		- duration ranged from 4 to 52 weeks
		- used PPI: esomeprazole, pantoprazole, omeprazole, rabeprazole, lansoprazole
		  o dose ranged from 10 to 40 mg/d
		- used control: placebo, cytoprotective
		- agents (gefarnate 100 mg/d) and H2RA (famotidine 20-80 mg/d)
		- population varied (all had a high risk of gastrointestinal bleeding)
		  o n = 4 RCT with patients with ulcer/erosion or with a history of peptic ulcer,
		  o n = 3 RCT with Helicobacter pylori (H. pylori)-negative patients or patients whose infection had been eradicated,
		  o n = 4 RCT with hierarchical analysis according to the infection status of H. pylori,
		  o n = 4 RCT with patients with acute coronary syndrome and myocardial infarction who were treated with dual antiplatelet therapy (LDA+clopidogrel) and PPI,
		  o n = 4 RCT performed endoscopy in the patients before and after treatment,
			AMSTAR-II low
			
			(keine Liste der ausgeschlossenen Studien verfügbar)
			
			authors classified risk of bias mostly as low risk of bias, some studies showed unclear risk of bias in selection bias and/or detection bias (allocation concealment was rate das unclear risk of bias in 75% oft he studies); high risk of bias was reported for one study in the category of other bias (not excluded from meta-analysis)
			
			funnel plot indicated an asymmetric distribution that suggested the presence of publication bias
			
			authors included studies published in english language (only)
				authors noted that with the use of low-dose acetylsalicylic acid for primary and secondary prevention the incidenece of LDA-associated upper gastrointestinal (GI) injuries has been increased
				
				authors disussed available evidence (including evidence from cohort studies) and concluded that the research question probably could be extendet (this publication focused on preventive effect of PPI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	case reports were excluded - studies with short-term - or intermittent use of LDA were excluded **Intervention** oral proton pump inhibitors (PPI) **Comperator** - placebo, - a cytoprotective agent, - or an H2 receptor antagonist (H2RA) **Quality assessment** Cochrane Risk of Bias Tool **Outcome** primary - adverse GI events (hemorrhage, ulcer, perforation, or obstruction) - incidence of LDA-related peptic ulcer and upper gastrointestinal bleeding - incidence of major adverse cardiovascular events (MACE) and diarrhea	○ n = 4 RCT only conducted endoscopy after treatment - n = 5 compared preventive effect of PPI with placebo - n = 2 compared PPI with gefarnate - n = 3 compared PPI with famotidine **Results** risk of LDA-associated upper GI ulcers PPI vs. control (placebo, gefarnate and H2RA) - n = 46/4684 vs. n = 179/3781 - OR = 0.16; 95%CI: 0.12-0.23, n = 8 studies PPI vs. placebo - n = 30/4045 vs. n = 95/3248 - OR = 0.20; 95%CI: 0.13-0.30, n = 4 studies LDA-associated GI bleeding PPI vs. control (placebo, gefarnate and H2RA) - n = 19/4834 vs. n = 71/3932 - OR = 0.27; 95%CI: 0.16-0.43, n = 10 studies PPI vs. placebo - n = 11/4140 vs. 43/3334 - OR = 0.26; 95%CI: 0.14-0.49, n = 5 studies patients with dual anti-platelet therapy of LDA and clopidogrel LDA-associated GI bleeding PPI vs. control (placebo, gefarnate and H2RA) - n = 14/2190 vs. n = 41/2184 - OR = 0.36; 95%CI: 0.15-0.87, n = 4 studies risk of major adverse cardiovascular events (MACE) PPI vs. control (placebo, gefarnate and H2RA) - n = 92/2190 vs. n = 92/2184 - OR = 1.00; 95%CI: 0.76-1.31, n = 4 studies		

12.5.1.2 Häufigkeit von Blutungsereignissen bei geringen Dosen von ASS

García Rodríguez et al. 2016 Blutungsrisiko bei geringer Dosierung von ASS (SR, Beobachtungsstudien)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

García Rodríguez LA. Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies. PLoS One 2016; 11(8):e0160046. https://www.ncbi.nlm.nih.gov/pub-med/27490468. [50]	**Objective**
	to determine the risks of the most clinically relevant adverse effect, GI bleeding, and the serious but rare event, ICH, in patients taking low-dose aspirin in real-world settings; the influence of risk factors was also assessed
	
	Search
	- Medline, Embase (up to March 2015)
	- no published protocol
	
	Inclusion and exclusion criteria
	- observational studies
	- epidemiology, ASS and ASS safety (long-term, low dose)
	- reviews, editorials, comments, clinical trials and pediatric studies were excluded
	- studies using only aspirin doses higher than 325 mg per day were excluded
	
	Intervention
	low-dose aspirin (75–325 mg per day)
	
	Outcome
	primary
		n = 39 articles
		- n = 23 case-control studies (one case-crossover study) (some were nested in well-defined cohorts)
		- n = 16 cohort studies (one long-term, post-trial follow-up of a RCT)
		- n = 23 from Europe (n = 7 from Spain, n = 7 from UK), n = 9 from USA
		- duration of ASS use: 1 month to > 20 years
		- reported follow-up: 4-14 years
		- maximum time period between stopping ass use and the study index date ranged from 7 to 90 days
		
		Results
		low-dose ass vs. non-use
		all gastrointestinal bleeding
		(n = 8 studies with n = 5 cohorts)
		- n = 2 studies (cohorts): no increase in the risk of GI bleeding
		- n = 6 studies with statistically significant increased risk
		- RR 0.99–4.64, with most studies reporting values between 0.99 and 1.6
		- pooled estimates:
		  o RR 1.4 (95% CI: 1.2–1.7), overall, n = 8 studies
		  o RR 1.7 (95% CI: 1.2–2.5) for case–control studies (n = 3) and
		  o RR 1.3 (95% CI: 1.0–1.7) for cohort studies (n = 5)
		  o significant heterogeneity was reported, especially for cohort studies
		- highest risk reported in Japanese patients (LDA for CVD for > 1 year, wide confidence intervals)
		
		- overall incidence (as cases per 1000 person-years), Fig 3
			AMSTAR-II critically low
			
			(keine Liste der ausgeschlossenen Studien verfügbar; ein Instrument zur Bewertung des Risk-of-Bias ist nicht beschrieben, allerdings erfolgt eine Bewertung in der Diskussion, die Prüfung eines Publication Bias wird nicht angegeben)
			
			(Hinweis: das Instrument ist nur eingeschränkt anwendbar, da u. a. Beobachtungsstudien gesucht wurden und die Limitationen u. a. dieses Publikationstyps in der Diskussion beschrieben sind)
			
			Supplement online verfügbar; Download nur als Word-File etc. verfügbar
			
			observational studies are more prone to bias from confounding factors than RCT
			
			they identified between-study heterogeneity (e. g. differences in design, bleeding definition)
				authors noted that In the secondary prevention of cardiovascular disease (CVD), the absolute benefits of aspirin far outweigh the absolute risks of major bleeding events
				
				bleeding risk associated with low-dose aspirin use should be identified by factors that influence the risk of bleeding with ass therapy and the magnitudes of these effects on the risk (e. g. taking concomitant medications with increased risk of GI bleeding: including anticoagulants, other antiplatelet agents, and non-steroidal anti-inflammatory drugs (NSAID))
				
				authors noted that the majority of studies reported increased RR of GI bleeding, which is consistent with findings from previous MA of RCT (range 1.31–1.96)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- incidences of GI bleeding and ICH (intracranial (including intracerebral) hemorrhage) and measures of their association
	
	secondary:
	- factors with potential predictive effects on the risk of bleeding, such as age, history of peptic ulcer, and H. pylori infection
	- effects of medications taken concomitantly with low-dose ass (including proton pump inhibitors [PPIs], clopidogrel, and non-steroidal anti-inflammatory drugs [NSAIDs]) on the risk of bleeding were also documented
		o n = 2 cohort studies (USA),
		o one involved only men
		    ▪ 1.39 events per 1000 person-years
		o the other involved only women
		    ▪ 1.67 events per 1000 person-years
		
		upper gastrointestinal bleeding (UGIB)
		(n = 24 studies, with n = 7 cohort studies)
		- statistically significant increase in risk on UGIB in most studies
		o RR 2.3 (95% CI: 2.0–2.6), overall, n = 24 studies
		o RR range 1.4–4.0 and pooled estimate RR 2.3 (95% CI: 2.0–2.7) for case-control studies (n = 17)
		o RR range (1.2–4.5) and pooled estimate RR 2.0 (95% CI: 1.5–2.7) for cohort studies (n = 7 studies)
		o significant heterogeneity was reported
		o n = 1 study reported LDA in primary and secondary prevention of CVD: RR for UGIB was higher in primary prevention:
		    ▪ adjusted RR [95% CI]:
		    ▪ 1.90 [1.59–2.26] and 1.40 [1.14–1.72], respectively
		    ▪ baseline absolute risk of
		    ▪ UGIB was higher in the secondary than in the primary prevention cohort (patients were older and more likely to have a history of ulcers and concomitant medication use (e. g. NSAID, clopidogrel, oral anticoagulants)
		    ▪ absolute increase in risk of UGIB was higher in secondary prevention cohort
				cohort studies showed increased risk of UGIB with more frequent dosing; a possible correlation between dose and risk of bleeding did not find any consistent effects

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- n = 8 studies analysed effect of ass dose or dosing regimen: - n = 2 with increase in the risk of UGIB with increasing frequency of doses - n = 1 with a clear dose-dependency for UGIB - n = 4 with little difference in RR for different low-dose aspirin regimens - n = 2 studies suggested that the duration of continuous low-dose aspirin treatment up to 10 or 20 years has little effect on the RR of UGIB, when adjusted for treatment dose - n = 2 studies shown that the risk of UGIB with low-dose aspirin is greatest - during the first 2 months of therapy, and decreases with increasing treatment duration - overall incidence (as cases per 1000 person-years), Fig 3 - n = 4 studies (USA, UK, Danish cohort) - range 0.70–3.64 cases per 1000 person-years lower gastrointestinal bleeding (s. within the publication page 9): overall incidence 0.48–0.74 cases per 1000 person-years (n = 3 studies), Fig 3 risk of intracranial hemorrhage (ICH, s. within the publication page 9 ff), n = 7 studies (n = 3 cohorts, n = 3 case-control studies, n = 1 case-crossover study) - RR 0.82–1.71 across the studies, - for most studies the 95% CI included 1.0 - pooled estimates - RR 1.4 (95% CI 1.2–1.7) overall, n = 7 studies		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		○ RR 1.0 (95% CI: 0.8–1.2) for case–control studies (n = 4) and ○ RR 1.5 (95% CI: 1.4–1.7) for cohort studies (n = 3) ○ high heterogeneity was reported for case-control studies - overall incidence (n = 1 study, cohort of patients with non-valvular atrial fibrillation) ○ 8.0 cases per 1000 person-years **potential predictive factors** - age (S2, S3 and S4 Fig) ○ n = 4 studies (with increasing age and increased incidence of major bleedings) ○ n = 8 studies (with no clear evidence that the RR of bleeding with low-dose ○ aspirin increases with increasing age) ○ incidence generally higher in men than in women ○ increase of 3.24 cases per 1000 person-years in men aged ≥ 70 years compared with men aged 16–59 years, n = 1 study ○ increase of 2.22 cases per 1000 person-years in men aged ≥ 80 years compared with men aged 40–59 years, n = 1 study - (history of) peptic ulcer and Helicobacter pylori infection (S2 Table) ○ association with increased UGIB - concomitant medication (S3 Table) ○ association with increased UGIB ○ NSAID (high dose) ○ Clopidogrel + ASS ○ Selective serotonin reuptake inhibitors (SSRI) - effects of PPI on risk of major bleeding events (+ low-dose ASS) ○ available for n = 6 studies (S3 Table)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

		o major bleeding:
		    ▪ PPI vs. no PPI: adjusted RR 0.84 (95% CI 0.80; 0.88), n = 1 study
		o UGIB: PPI vs. no PPI:
		    ▪ OR 0.97 (0.65; 1.44), n = 1
		    ▪ OR 0.6 (0.5; 0.8), n = 1
		    ▪ OR 0.4 (0.3; 0.5), n = 1
		    ▪ OR 0.62 (0.35; 1.08), n = 1
		    ▪ OR 0.37 (0.18; 0.75), n = 1
		    ▪ OR 0.2 (0.1; 0.9), n = 1
		
		overall:
		the incidence of GI bleeding with low-dose ASS was 0.48–3.64 cases per 1000 personyears
		
		for upper and lower GI bleeding, the RR with low-dose ASS were 2.3 (2.0–2.6) and 1.8 (1.1–3.0), respectively
		
		neither ASS dose nor duration of use had consistent effects on RR for upper GI bleeding
		
		the estimated RR for ICH with low-dose ASS was 1.4 (1.2–1.7) overall
		
		ASS was associated with increased bleeding risks when combined with non-steroidal anti-inflammatory drugs, clopidogrel and selective serotonin reuptake inhibitors compared with monotherapy
		
		by contrast, concomitant use of proton pump inhibitors decreased upper GI bleeding risks relative to ASS monotherapy		

12.5.1.3 Langzeittherapie mit PPI

Freedberg et al. 2017 Langzeittherapie mit PPI, Risiken und Vorteile (Übersichtsartikel)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Freedberg DE. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology 2017; 152(4):706–15. https://www.ncbi.nlm.nih.gov/pubmed/28257716. [51]	**Objective** To evaluate the risks associated with long-term use of proton pump inhibitors (PPI) **Methods** - recommendations based on expert opinion - search in Pubmed, Embase, Cochrane library (through July 2016), clinical Trials **Inclusion and exclusion criteria** - Gastroesophageal reflux disease (GERD) - Barrets esophagus (BE) - Non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis **Intervention** Proton pump inhibitors (PPI) **Quality assessment** GRADE **Outcome** primary - adverse effects	Table 1. Summary of Evidence for Potential PPI-Associated Adverse Effects Potential adverse effect Types of studies Threats to validity Overall quality of evidence Kidney disease - Observational only - Modest effect size - Residual confounding would bias towards harm - Absence of dose-response effect - Very low Dementia - Observational only - Modest effect size - Residual confounding would bias towards harm - Very low Bone fracture - Observational only - Inconsistent results - Modest effect size - Residual confounding would bias towards harm - Low or very low Myocardial infarction - Observational - RCT - Results differ between RCTs and observational studies - Secondary analysis of RCT data - Modest effect size - Residual confounding would bias towards harm - Very low Small intestinal bacterial overgrowth - Observational	n. a. (Überblicksartikel; Methodik nicht bzw. unzureichend beschrieben)	Artikel zur Diskussion; konsensbasierte Empfehlungen

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- Crossover - Sparse data - Residual confounding would bias towards harm - Protopathic bias - Low Spontaneous bacterial peritonitis - Observational only - Modest effect size - Residual confounding would bias towards harm - Very low Clostridium difficile infection - Observational only - Modest effect size - Residual confounding would bias towards harm - Low Pneumonia - Observational - RCT - Results differ between RCTs and observational studies - Secondary analysis of RCT data - Modest effect size - Absence of dose-response effect - Residual confounding would bias towards harm - Protopathic bias - Very low Micronutrient deficiencies - Observational only - Inconsistent results - Modest effect size - Absence of dose-response effect - Residual confounding would bias towards harm - Low or very low Gastrointestinal malignancies - Observational - RCT - Results differ between RCTs and observational studies - RCTs use surrogate outcomes		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

		- Modest effect size
		- Residual confounding would bias towards harm
		- Confounding by indication and protopathic bias
		- Very low
		
		Note: Assessments regarding the quality of evidence are based on the methodology of the GRADE Working Group (see inset)
		
		Table 2 absolute (% per patient/year) and relative risks (% increase) for adverse events associated with long-term PPI (je n = 1 study)
		- Chronic kidney disease
		   o 0.1%-0.3% per patient/year
		   o 10-20% increase
		- Dementia
		   o 0.07%-1.5% per patient/year
		   o 4-80% increase
		- Bone fracture
		   o 0.1%-0.5% per patient/year
		   o 30% to 4-fold increase
		- Myocardial infarction
		   o –
		   o no association in RCT
		- Small intestinal bacterial overgrowth
		   o unable to calculate
		   o 2-fold to 8-fold increase
		- Campylobacter or salmonella infection
		   o 0.03%-0.2% per patient/year
		   o 2-fold to 6-fold increase
		- Spontaneous bacterial peritonitis
		   o 3%-16% per patient/year
		   o 50% to 3-fold increase
		- Clostridium difficile infection
		   o 0%-0.09% per patient/year
		   o No risk to 3-fold increase
		- Pneumonia
		   o –
		   o No association in RCT
		- Micronutrient deficiencies		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		0.3%-0.4% per patient/year 60-70% increase - Gastrointestinal malignancies – - No association in RCT **Best Practice Recommendations** Best Practice Advice 1: Patients with GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture) should take a PPI for short-term healing and for long-term symptom control. *Rationale:* PPIs are highly effective in healing esophagitis and for GERD symptom control, and this benefit is likely to outweigh PPI-related risks. There is no evidence for or against PPIs in asymptomatic patients with healed esophagitis or for PPIs beyond 12 months. Best Practice Advice 2: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia). *Rationale:* Short-term PPIs are highly effective for uncomplicated GERD. Most patients with uncomplicated GERD respond to short-term PPIs and are subsequently able to reduce PPIs to less than daily dosing. Because patients who cannot reduce PPIs face lifelong therapy, we would consider testing for an acid-related disorder in this situation. However, there is no high-quality evidence on which to base this recommendation. Best Practice Advice 3: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Rationale: PPIs have a clear symptomatic benefit and a possible benefit in slowing progression of Barrett's. There is likely to be a net benefit for long-term PPIs in these patients. Best Practice Advice 4: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI. *Rationale:* The evidence that PPIs slow progression of Barrett's is low in quality but the evidence of PPI adverse effects is also low in quality. Because there is no high quality evidence on either side of this question, this is a weak recommendation and this decision should be individualized with patients. Best Practice Advice 5: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs. *Rationale*: PPIs are highly effective in preventing ulcer-related bleeding in appropriately selected patients who take NSAIDs, and this benefit is likely to outweigh PPI-related risks. Best Practice Advice 6: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition. *Rationale:* Long-term PPI users often receive PPIs at doses higher than necessary to manage their condition. Since PPI reduction is often successful, it is logical to periodically reevaluate PPI dosing so that the minimum necessary dose is prescribed. Best Practice Advice 7: Long-term PPI users should not routinely use probiotics to prevent infection. *Rationale:* There is no evidence for or against probiotics to prevent infections in long-term users of PPIs. Best Practice Advice 8: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the Recommended Dietary Allowance (RDA).		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Rationale: There is no evidence for or against use of vitamins or supplements beyond the RDA in long-term users of PPIs. Many adults fall below the RDA in several vitamins or minerals and, in these adults, it is reasonable to raise intake to meet the RDA regardless of PPI use. Best Practice Advice 9: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12. *Rationale:* There is no evidence for or against dedicated testing for patients taking long-term PPIs. Such screening (eg, for iron or vitamin B12 deficiency) can be offered but is of no proven benefit. Best Practice Advice 10: Specific PPI formulations should not be selected based on potential risks. *Rationale:* There is no convincing evidence to rank PPI formulations by risk.		

12.5.2 Empfehlung 7-3 Clopidogrel vs. ASS (Stellenwert in der Monotherapie)

Tan et al. 2023 Clopidogrel oder ASS - Monotherapie (SR, nach 6-12 Monaten dualer Therapie, nach PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Tan BE-X. Clopidogrel vs Aspirin Monotherapy Following Dual Antiplatelet Therapy After Percutaneous Coronary Intervention: A Systematic Review and Meta-analysis. Curr Probl Cardiol 2023; 48(8):101174. https://www.ncbi.nlm.nih.gov/pubmed/35341798. [52]	**Objective**
	to assess the efficacy and safety of clopidogrel vs. ASS in post-PCI population after completing DAPT (duale antiplatet therapy)
	
	Methods
	- Systematic review and meta-analysis according to the PRISMA guidelines
		n = 5 articles (n = 13,850 patients)
		- n = 5,601 (40.4%) Clopidogrel
		- n = 8,249 (59.6%) ASS
		- mean age 64.1 years
		- high prevalence of comorbidities (hypertension 45-83%, dyslipidemia 13-80%, diabetes 21-42%, chronic kidney disease 8-40%)
		- all patients with drug-eluting stent
		- no patient received bare-metal stenst
		- n = 1 RCT, n = 4 observational cohort studies
		  o clopidogrel vs. ASS
		  o following completion of DAPT after PCI
			AMSTAR-II moderate
			
			Subgruppenanalysen und Sensitivitätsanalysen wurden präspezifiziert (u. a. um ein Risiko für Bias oder geringe Studienqualität zu berücksichtigen)
				HOST EXAM 2021 enthalten in der Metaanalyse
				
				Autor*innen berichten, dass die Analysen durch diese Studie geleitet wurden (Einfluss auf das Ergebnis u.a. durch Studiengröße, statistische Power; in

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- Registration in PROS-PERO (CRD42022301139)
	- PubMed (Ovid), Cochrane, CINAHL, Google Scholar (through Feb 2022)
	- medical librian involved
	
	Inclusion and exclusion criteria
	- trials and observational studies
	- adult patients (≥18 years)
	- patients after PCI
	- after completition of DAPT for a minimum of 1 month
	- other P2Y12 inhibitors were excluded (ticagrelor, prasugrel)
	
	Quality assessment
	Cochrane Risk-of-Bias tool
	instrument of national institute of health (NIH) for observational studies
	
	Intervention
	clopidogrel monotherapy*
	
	Comperator
	ASS monotherapy*
	
	*following completion of dual therapy (DAPT)
	
	Outcomes
	- major adverse cardiac events (MACE)
	- cardiac death
	- all-cause death
	- major bleeding
		- mean follow-up 12 to 36 months
		  o n = 2 studies follow-up from day of PCI
		  o n = 3 studies follow-up from day of monotherapy
		  o duration of DAPT before monotherapy 1-18 months
		n = 3 studies were rated as fair quality, n = 1 observational study as poor quality, n =1 studie as low risk of bias
		
		Results
		clopidogrel vs. ASS (monotherapy, after DAPT)
		MACE
		- n = 205 (3.6%) vs. n = 341 (4.2%)
		- risk ratio (RR) 0.77 (95% confidence interval (CI) 0.65-0.91), P=0.003, n = 5 studies
		all-cause death
		- n = 97 (1.8%) vs. n = 150 (1.9%)
		- RR 1.06 (95% CI 0.81-1.39), P=0.66, n = 4 studies
		cardiac death
		- n = 48 (0.9%) vs. n = 61 (1.2%)
		- RR 0.87 (95% CI 0.53-1.41), P=0.56, n = 4 studies
		major bleeding
		- n = 47 (0.8%) vs. n = 80 (1.1%)
		- RR 0.74 (95% CI 0.42-1.30), P=0.29, n = 5 studies
		MI
		- n = 73 (1.3%) vs. n = 102 (1.3%)
		- RR 1.01 (95% CI 0.64-1.60), P=0.95, n = 5 studies
		repeat revascularization
		- n = 154 (3.3%) vs. n = 108 (3.1%)
		- RR 0.88 (95% CI 0.71-1.09), P=0.23, n = 3 studies
		target vessel revascularization
		- n = 42 (1.2%) vs. n = 68 (1.3%)
		- RR 0.76 (95% CI 0.52-1.13), P=0.18, n = 3 studies
			duration of DAPT following PCI varied between studies (possible heterogeneity), results of sensitivity analysis were stable for all outcomes
			
			HOST EXAM was rated as low risk of bias for all criteria except for performance bias due to the open-label design; observational studies as fair (3) or poor (1)
			
			limited external validity due to all studies comprised of the East Asian population (authors noted that clopidogrel hypo-responsiveness is known to be greater in the East Asian population than in Caucasians (CYP2C19 polymorphism) and that thrombotic events are lower in Eat Asian patients compared with Caucasian patients receiving clopidogrel (citation: Kang et al. Korean Circ J 2018 https://pubmed.ncbi.nlm.nih.gov/29968428/: "East Asian patients have a unique ischemic and bleeding risk profile"; "revious data suggested that East Asian patients have unique features with regard to the response to antiplatelet agents. On comparing Western and East Asian patients, it was found that East Asian patients have a lower rate of ischemic events and higher rate of bleeding events after PCI, despite a higher on-treatment platelet reactivity, which is referred to as the "East Asian paradox.")
				Subruppenanalysen nicht statistisch signifikant, nach Ausschluss der Studie, Tendenz aber ähnlich)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- myocardial infarction (MI) - stroke prespecified subgroup analyses were planed (e. g. related to study type)	stent thrombosis - n = 18 (0.3%) vs. n = 27 (0.3%) - RR 0.96 (95% CI 0.35-2.59), P=0.93, n = 4 studies any stroke - n = 34 (0.7%) vs. n = 95 (1.5%) - RR 0.51 (95% CI 0.35-0.76), P=0.0008, n = 3 studies ischemic stroke - n = 21 (0.4%) vs. n = 37 (0.7%) - RR 0.55 (95% CI 0.32-0.94), P=0.03, n = 3 studies hemorrhagic stroke - n = 4 (0.0%) vs. n = 18 (0.4%) - RR 0.24 (95% CI 0.09-0.68), P=0.007, n = 2 studies		

Gragnano et al. 2023 P2Y12 Hemmer oder ASS - Monotherapie (SR, Sekundärprävention, duale Vortherapie war möglich)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Gragnano F. P2Y12 Inhibitor or Aspirin Monotherapy for Secondary Prevention of Coronary Events. J Am Coll Cardiol 2023; 82(2):89–105. https://www.ncbi.nlm.nih.gov/pubmed/37407118.
[53]
	Objective
	to compare P2Y12-inhibitor monotherapy vs. ASS in patients with CAD
	
	Methods
	- PRISMA guided
	- PANTHER collaborative initiative (CRD42021290774)
	- systematic review and patient-level meta-analysis
	- RCT
	- patients with established CAD
	- prevention of cardiovascular events (secondary prevention)
		n = 7 RCT (n = 24 325 individual patients)
		(ASCET, CADET, CAPRIE, DACAB, GLASSY, HOST-EXAM, TiCAB)
		- n = 12 178 (P2Y12)
		  o n = 7 545 (62.0%) clopidogrel
		  o 4 633 (38.0%) ticagrelor
		- n = 12 147 (ASS)
		- mean age 64.3 years
		- female 21.7 %
		- ACS ~ 60.6 %
		- CCS ~ 39.4 %
		- hypertension ~ 60 %
		- hypercholesterolemia ~ 60 %
		- previous myocardial infarction ~ 56 %
		- diabetes mellitus ~ 25 %
		- PCI ~ 54 %
		- CABG ~10.6 %
		- no revascularization ~ 30 %
			AMSAR-II low
			
			(keine Liste der ausgeschlossenen Volltexte mit Ausschlussgrund vorhanden)
			
			Limitations (authors note)
			- open-label design (n = 4 studies)
			- no correction for multiple testing was performed
			- results not generalizable to patients with prasugrel monotherapy
			- duration of treatment varied (6-36 months)	

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- initial DAPT phase after randomization was allowed - studies with oral anticoagulation or other antithrombotic agents were excluded **Intervention** P2Y12-inhibitor monotherapy **Comperator** ASS monotherapy **Quality assessment** Cochrane Risk-of Bias tool **Outcome** primary - composite of cardiovascular death, myocardial infarction, stroke secondary - major bleeding (BARC type 3 or 5) - adverse clinical events (defined as composite of primary outcome and major bleeding)	- statins ~ 89 % - ASS high dose (primary study population) ~ 19 % - ASS low dose (primary study population) ~ 30 % - median treatment duration 557 days (IQR 369-734 days) n = 2 trials classified as low risk of bias, n = 5 trials classified with some concerns **Results** primary at median follow up of 493 days (P2Y12-inhibitors vs. ASS) - n = 675 (3.58%) vs. n = 765 (4.07%) - HR 0.88 (95% CI 0.79; 0.97), P=0.012, n = 24 325 patients - Number-needed to treat 121 over 2 years secondary all-cause death - n = 404 (2.10%) vs. n = 386 (2.00%) - HR 1.04 (95% CI 0.91; 1.20), P=0.56, n = 24 325 patients cardiovascular death - n = 280 (1.45%) vs. n = 273 (1.42%) - HR 1.02 (95% CI 0.86; 1.20), P=0.82, n = 24 325 patients myocardial infarction - n = 283 (1.49%) vs. n = 366 (1.93%) - HR 0.77 (95% CI 0.66; 0.90), P<0.001, n = 24 325 patients - NNT 136 stroke - n = 202 (1.06%) vs. n =239 (1.25%) - HR 0.84 (95% CI 0.70; 1.02), P=0.076, n = 24 325 patients stent thrombosis - n = 8 (0.09%) vs. n = 19 (0.21%) - HR 0.42 (95% CI 0.19; 0.97), P=0.041, n = 12 503		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		major bleeding - n = 146 (0.76%) vs. n = 167 (0.87%) - HR 0.87 (95% CI 0.70; 1.09), P=0.23, n = 24 325 patients any bleeding - n = 646 (3.54%) vs. n = 587 (3.22%) - HR 1.10 (0.98; 1.23), P=0.10, n = 24 325 patients adverse clinical events - n = 785 (4.19%) vs. n = 874 (4.68%) - HR 0.89 (95% CI 0.81; 0.98), P=0.020, n = 24 325 patients treatment effect was consistent across all prespecified subgroups associations: geographical regions (Asian may derive enhanced benefit from P2Y12 inhibitors)		

Chiarito et al. 2020 P2Y12 Hemmer oder ASS - Monotherapie (SR, Sekundärprävention, Langzeittherapie)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Chiarito M. Monotherapy with a P2Y12 inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: A systematic review and meta-analysis. Lancet 2020; 395(10235):1487–95. https://www.ncbi.nlm.nih.gov/pubmed/32386592. [54]	**Objective** to compare monotherapy with a P2Y12 inhibitor versus aspirin for secondary prevention **Methods** - systematic review and meta-analysis - of randomised trials - study registered in PROSPERO (CRD42018115037) - PRISMA guidelines were used - monotherapy for secondary prevention	n = 9 studies (n = 42 108 patients) (TASS, CAPRIE, STAMI, AAASPS, CADET, ASCET, SOCRATES, DACAB, TiCAB) - year of publication 1989-2019 - coronary artery disease: n = 5 studies (STAMI, CADET, ASCET, DACAB, TiCAB) - cerebrovascular disease: n = 3 studies (TASS, AAASPS, SOCRATES) - n = 1 studie (cerebrovascular, coronary, and peripeheral artery disease) - n = 21 043 (P2Y$_{12}$-inhibitors) - n = 21 065 (ASS) - n = 24 508 patients after a cerebrovascular event - n = 7956 patients after a myocardial infarction - n = 3192 patients with the presence of stable coronary artery disease	AMSTAR-II low (keine Liste der ausgeschlossenen Volltexte mit Ausschlussgrund vorhanden) n = 3 studies were rate das low risk of bias, n = 6 studies with some concerns pre-specified subgroup and sensitivity analyses were performed post-hoc estimated stratified analysis to assess the effect of the estimated risk of bias	authors first excluded the GLOBAL LEADERS trial due to the design, but noted that 1 year after randomisation the patients received ticagrelor monotherapy or aspirin monotherapy for the subsequent year, with no significant differences between the two treatment strategies

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- patients with cerebrovascular, coronary, or peripheral artery disease (established atherosclerosis) - searched PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register of Controlled Trials (on Dec 18, 2019) - reviewed references from identified articles; searched abstracts from 2017 to 2019 presented at relevant scientific meetings - studies comparing dual vs. single antiplatelet therapy, studies assessing antithrombotic agents different from aspirin or P2Y12 inhibitors, and studies not reporting clinical outcomes were excluded - studies with less than 1 months of active comparison were excluded **Intervention** P2Y12 inhibitor **Comperator** aspirin **Quality assessment** Cochrane risk-of-bias tool (RoB 2) **Outcomes** co-primary endpoints	- n = 6452 patients with the presence of peripheral artery disease - mean age 59.2 – 66.7 years - follow-up 3 months to 3 years - patients lost to follow up 0.35%-0.36% - hypertension 39.2-89.9% - dyslipidaemia 36.0-81.7% - chronic coronary syndromes 14.0 (CAPRIE) - 100% (ASCET) - prior myocardial infarction 4.1-100% - PAD 4.0-38.0% - diabetes 14.9-42.7% **results** P2Y12 inhibitor vs. ASS monotherapy (only studies that reported outcomes are included) all cause death - 887/21 040 vs. 903/21 068 - odds ratio [OR] 0.98 (95% CI 0.89; 1.08), n = 9 studies vascular death - 574/20 447 vs. 595/20 476 - OR 0.97 (0.86; 1.09), n = 7 studies stroke - 1137/20 949 vs. 1235/20 975 - OR 0.92 (0.82; 1.06), n = 8 studies myocardial infarction - 357/19 514 vs. 437/19 525 - OR 0.81 (0.66; 0.99), n = 8 studies - number needed to treat 244 any bleeding - 1293/20949 vs. 1259/20975 - OR 1.08 (0.91; 1.29), n = 8 studies, p=0.37 major bleeding - 213/18613 vs. 237/18657 - OR 0.90 (0.74; 1.10), n = 7 studies, p=0.30 fatal bleeding - 33/18019 vs. 32/18026 - OR 1.05 (0.59; 1.85), n = 5 studies, p=0.85	effect modifiers ere assessed studies for prasugrel not reported authors noted limitations (e. g.): - stratified analyses might not have sufficient power to detect significant differences between groups - different bleeding definitions (limited reliability)	they added a extended analysis by including the outcomes of the GLOBAL LEADERS trial beyond the first year of follow-up, contributing to the post-hoc analysis with an additional 15 729 patients; results were were consistent with the primary analysis (appendix) authors noted that costeffectiveness should be thoroughly evaluated in different health-care systems b efore any changes are made in current recommendations on antithrombotic secondary prevention strategies (risk profiles should be recognised) *pathways*: authors added that atherosclerosis progression and subsequent ischaemic events share the same common pathophysiological pathway in different arterial territories guidelines recommended long-term treatment with ASS

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- myocardial infarction and stroke (ischaemic) secondary endpoints - all-cause death and vascular death - safety: bleeding and major bleeding	intracranial bleeding - 56/18619 vs. 76/18636 - OR 0.74 (0.52; 1.04), n = 5 studies, p=0.084 gastrointestinal bleeding - 202/12932 vs. 288/12933 - OR 0.59 (0.39; 0.89), n = 5 studies, p=0.012 **additional information** - stratified analysis of ischaemic outcomes according to type of P2Y12 inhibitor used (ie, ticlopidine, clopidogrel, or ticagrelor) showed findings consistent with the primary analysis (figure 3 within the publication) - meta-regression analysis: type of P2Y12 inhibitor had no apparent effect - ischaemic outcomes stratified by type of qualifying disease were consistent with the primary analysis - meta-regression analysis did not show any significant interaction between qualifying disease and treatment effects **authors conclusion/discussion** - P2Y12 inhibitor monotherapy vs. ASS monotherapy: associated with comparable risks of all-cause death, vascular death, and stroke, and a marginal risk reduction for myocardial infarction in the setting of secondary prevention - high number needed to treat and the absence of any major effect on death questions the clinical relevance of the marginally lower risk of myocardial infarction observed with P2Y12 inhibitors compared with ASS		over clopidogrel or others for secondary prevention (cardiovascular and cerebrovascular) an clopidogrel for PAD profound platelet inhibition with dual antiplatelet therapy (independent mechanisms for platelet activation) has been shown to reduce the risk of ischaemic events, but at the cost of an increase in the risk of major bleeding – ASS + P2Y12 inhibitors

Yuan et al. 2019 Clopidogrel oder ASS - Monotherapie (SR, Sekundärprävention, stabile CAD)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Yuan J. Aspirin Versus Clopidogrel Monotherapy for the Treatment of Patients with Stable Coronary Artery Disease: A Systematic Review and Meta-Analysis. Adv Ther 2019; 36(8):2062–71. https://www.ncbi.nlm.nih.gov/pubmed/31154631. [55]	**Objective** to systematically compare ASS versus clopidogrel monotherapy for the treatment of patients with stable coronary artery disease (CAD) **Methods** - Cochrane Central, EMBASE, MEDLINE, Google Scholar - PRISMA guideline - monotherapy - patients with CAD - patients with cardiovascular disease - patients with percutaneous coronary intervention **Intervention** clopidogrel monotherapy **Comperator** ASS monotherapy **Quality assessment** Cochrane Collaboration for the randomized controlled trials Newcastle–Ottawa Scale (NOS) for the observational studies **Outcomes** - composite outcomes: combination of cardiovascular death, myocardial infarction (MI), and stroke - all-cause mortality - cardiac death	n = 3 studies (CAPRIE, CORONOR, Park et al. 2016) - n = 2 observational studies - n = 1 sub-study of a RCT - n = 5 497 ASS - n = 2 544 clopidogrel - mean age 62 to 68.2 years - men 72-78% - comorbidities: hypertension (51-65%), dyslipidemia 28-41%), diabetes mellitus (20-42%), and smoking (11-30%) **results** clopidogrel vs. ASS (follow-up 2-3 years) composite endpoint - 65/1544 vs. 179/4497 - OR 0.99 [0.47–2.10] p=0.98, n = 2 studies all-cause death - 104/2544 vs. 226/5497 - OR 1.05 [0.82–1.33] p=0.71, n = 3 studies cardiac death - 28/1544 vs. 68/4497 - OR 0.89 [0.17–4.74] p=0.89 , n = 2 studies myocardial infarction - 22/1544 vs. 74/4497 - OR 0.84 [0.52–1.36] p=0.48, n = 2 studies stroke - 22/1544 vs. 56/4497 - OR 1.26 [0.39–4.06] p=0.70 , n = 2 studies BARC-defined bleeding - 22/1544 vs. 52/4497 - OR 1.28 [0.78–2.12] p=0.33, n = 2 studies	AMSTAR-II moderate moderate risk of bias (RCT), low bias risk (observational studies) sensitivity analyses were carried out funnel plot: there was little to moderate evidence of publication bias limitations (authors note) total number of participants was not sufficient to reach a significant conclusion other bleeding outcomes and stent thrombosis were unfortunately not assessed	authors noted that guidelines recommend treatment with DAPT (ass + clopidogrel) following coronary angioplasty with DES clopidogrel is used for only 6 months to 1 year, whereas aspirin is continually used throughout in CAD patients with high risk of bleeding, the use of clopidogrel is a relative contraindication ASA is used as a single antiplatelet agent patients with chronic gastritis, especially nonsteroidal anti-inflammatory drug-induced gastritis, ASA is often avoided, and therefore, those patients rely only on clopidogrel as a single antiplatelet drug

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- myocardial infarction - stroke - bleeding (BARC grade 3 or above) mean follow-up period ranging from 2 to 3 years			

Kang et al. 2023 ASS vs. Clopidogrel Monotherapie (RCT-Kohorte, nach 12 Monaten dualer Therapie, nach PCI, 5 Jahres-Daten)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Kang J. Aspirin Versus Clopidogrel for Long-Term Maintenance Monotherapy After Percutaneous Coronary Intervention: The HOST-EXAM Extended Study. Circulation 2023; 147(2):108–17.
https://www.ncbi.nlm.nih.gov/pubmed/36342475.
[56]
	Objective
	to perform a posttrial extended follow-up of the patients enrolled in the HOST-EXAM trial to compare the longer-term outcomes between clopidogrel and ASS monotherapy
	
	Methods
	- HOST-EXAM Extended study (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy)
	- cohort study of:
	  o investigator-initiated
	  o randomized, open-labeled, trial (Korea)
	- in March 2020, an extended follow-up was planned (extended); original study was terminated before initiation
	- HOSTEXAM in-trial period and posttrial follow-up period
		n = 5 438 patients
		- event-free for 6 to 18 months after PCI and duale therapy between 2014 and 2018
		- n = 9 patients of the total population withdrew
		- n = 618 used different antiplatelet regimen
		- n = 94 lost to follow up
		- PP (per protocol):
		  o n = 4717 patients
		  o n = 2431 patients (clopidogrel)
		  o n = 2286 patients (ASS)
		- median follow-up: 5.8 years (interquartile range, 4.8–6.2 years)
		- mean age 63.3±10.7 years
		- 69.5-70.6% dyslipedemia
		- 61.4% hypertension
		- 33.8% diabetes mellitus
		- 12.4% chronic kidney disease
		- 71.9% ACS as clinical diagnosis at the time of PCI
		- discontinuation rate:
		  o clopidogrel 8.0% [216 of 2648 patients]
		  o ASS 13.5% [367 of 2710 patients]; P<0.001
		
		Results
		primary (Clopidogrel vs. ASS)
		composite
		- n = 311 (12.8%) vs. n = 387 (16.9%)
		- hazard ratio, 0.74 (95% CI, 0.63–0.86); P<0.001
			n. a.
			
			extended follow-up of a randomized clinical trial (open-label)
			
			per protocol analysis was performed
			
			authors noted that the trial was not powered to evaluate the impact of antiplatelet therapy on mortality
				authors noted that because the original HOST-EXAM trial mandated the allocated antiplatelet therapy up to 24 months after enrollment, the posttrial follow-up antiplatelet prescription was at the discretion of the treating physician
				
				hypothesis was superiority of clopidogrel as long-term maintenance monotherapy agent (no additional sample size calculation was performed after termination of the original study)
				
				analyses od the 5 year follow-up; continuing follow-up for up to 10 years

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- randomized after termination of the original study **Inclusion and exclusion criteria** - patients ≥ 20 years - underwent PCI with drug-eluting stents - maintained dual antiplatelet therapy without any clinical events during 12±6 months after PCI - no restriction on the clinical diagnosis at the index PCI period, stenosis location, length, or number of lesions/vessels at the time of PCI **Intervention** clopidogrel monotherapy* (75 mg once daily) **Comperator** ASS monotherapy* (100 mg once daily) **Outcomes** primary - composite of all-cause death, nonfatal MI, stroke, readmission attributable to ACS, and major bleeding complications (defined as Bleeding Academic Research Consortium (BARC) type 3 or greater bleeding) secondary	- absolute risk reduction 4.1% (95% CI, 2.1%–6.2%) - number needed to treat 24 secondary thrombotic composite - n = 196 patients (8.1%) vs. n = 273 (11.9%) - HR, 0.66 [95% CI, 0.55–0.79]; P<0.001 any bleeding (BARC type 2 or greater) - n = 110 patients (4.5%) vs. n = 140 patients (6.1%) - HR, 0.74 [95% CI, 0.57–0.94]; P=0.016 all-cause death - n = 150 (6.2%) vs. n = 136 (6.0%) - HR 1.04 (95% CI, 0.82–1.31); P=0.742 cardiovascular death - n = 69 (2.8) vs. n = 71 (3.1) - HR 0.92 (0.66–1.28), P= 0.602 nonfatal MI - n = 40 (1.6) vs. n = 53 (2.3) - HR 0.71 (0.47–1.07), P= 0.102 Stroke - n = 37 (1.5) vs. n = 66 (2.9) - HR 0.53 (0.35–0.79), P= 0.002 Ischemic stroke - n = 27 (1.1) vs. n = 42 (1.8) - HR 0.61 (0.37–0.98), P=0.041 Hemorrhagic stroke - n = 10 (0.4) vs. n = 24 (1.1) - HR 0.39 (0.19–0.82), P=0.013 Readmission attributable to ACS - n = 111 (4.6) vs. n = 176 (7.7) - HR 0.59 (0.47–0.75), p <0.001 Major bleeding (BARC type 3 or greater) - n = 62 (2.6) vs. n = 90 (3.9)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- composite end points included the thrombotic composite end point (defined as cardiac death, nonfatal MI, ischemic stroke, readmission attributable to ACS, and definite or probable stent thrombosis) and any bleeding (defined as BARC type 2 or greater bleeding) *note*: methods described in: Lee et al; HOST-EXAM Investigators. A randomized clinical trial comparing long-term clopidogrel vs aspirin monotherapy beyond dual antiplatelet therapy after drug-eluting coronary stent implantation: design and rationale of the Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM) trial. Am Heart J. 2017;185:17–25. doi: 10.1016/j.ahj.2016.12.001 HOST-EXAM Extended study had a separate study protocol, approved by the institutional review board	- HR 0.65 (0.47–0.90), p=0.008 Any revascularization - n = 129 (5.3) vs. n = 157 (6.9) - HR 0.77 (0.61–0.98), p = 0.030 Target lesion revascularization - n = 53 (2.2) vs. n = 68 (3.0) - HR 0.73 (0.51–1.05), p=0.089 Target vessel revascularization - n = 76 (3.1) vs. n = 98 (4.3) - HR 0.73 (0.54–0.98), p = 0.039 Definite or probable stent thrombosis - n = 12 (0.5) vs. n = 17 (0.7) - HR 0.67 (0.32–1.39), p=0.280 analysis at 2 years showed consistent effects throughout the follow-up period		

Rhee et al. 2023 ASS vs. Clopidogrel Monotherapie (RCT-Kohorte, nach 12 Monaten dualer Therapie, nach PCI, Diabetes mellitus, post-hoc Analyse, 2 Jahre)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Rhee T-M. Aspirin vs Clopidogrel for Long-term Maintenance After Coronary Stenting in Patients With Diabetes: A Post Hoc Analysis of the HOST-EXAM Trial. JAMA Cardiol 2023; 8(6):535–44. https://www.ncbi.nlm.nih.gov/pubmed/37043192. [57]	**Objective** post hoc subgroup analysis of HOST-EXAM trial sought to investigate the association of diabetes with the risk of clinical outcomes at 24 months and compare outcomes between clopidogrel and ASS monotherapy
	
	Methods - HOST-EXAM trial was an investigator-initiated, prospective, randomized controlled trial - open-label, Korea
	
	Inclusion and exclusion criteria - patients maintained DAPT without clinical events for 6 to 18 months after PCI (drug-eluting stents) - enrolled between March 2014 to May 2018 - presence of diabetes (treatment or diagnosis)
	
	Intervention clopidogrel monotherapy for 24 months
	
	Comperator ASS monotherapy for 24 months
	
	Outcome primary
		at 24 months follow-up n = 5438 patients
		- mean age 63,5 years
		- n = 2661 patients (clopidogrel) vs. n = 2677 (ASS)
		- without diabetes: n = 1785 vs. 1793
		- with diabetes: n = 1860 (34.2%)
		  o n = 925 (clopidogrel) vs. n = 935 (ASS)
		  o balanced for baseline characteristics, excepted previous stroke (numerically higher in ASS arm)
		  o patients with comorbidities more prevalent in patients with diabetes compared with the no diabetes group
		  o patients with diabetes had higher proportion of 3-vessel disease
		
		Results patients with diabetes (clopidogrel vs. ASS) primary at 24 months (composite)
		- n = 53 (6.3%) vs. n = 84 (9.2%)
		- HR 0.69 (95% CI 0.49; 0.96), P=0.03
		- Absolute risk difference (ARD) 2.7
		- Number needed to treat (NNT) 37
		
		secondary at 24 months thrombotic composite
		- n = 36 (4.0%) vs. n = 53 (5.8%)
		- HR 0.68 (95% CI 0.45; 1.04), P=0.07
		any bleeding
		- n = 24 (2.7%) vs. n = 37 (4.1%)
		- HR 0.65 (95% CI 0.39; 1.09), P=0,11
		major cardiovascular events
		- n = 28 (3.1%) vs. n = 50 (5.4%)
		- HR 0.56 (95% CI 0.35; 0.89), p=0.01
		
		patients without diabetes (clopidogrel vs. ASS)
			n. a.
			
			Limitations (authors note):
			- open-label design
			- randomization was not stratified for diabetes status
			- lower-than-expected event rates (limited statistical power)
			- correction for multiple testing was not perfomed
			- population (performed solely in a Korean population)
				post hoc analysis of HOST-EXAM trial
				
				authors interpreted results as hypothesis generating at best

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	composite of all-cause death, nonfatal MI, stroke, readmission attributable to ACS, and major bleeding complications (defined as Bleeding Academic Research Consortium (BARC) type 3 or greater bleeding) secondary - composite end points included the thrombotic composite end point (defined as cardiac death, nonfatal MI, ischemic stroke, readmission attributable to ACS, and definite or probable stent thrombosis) and any bleeding (defined as BARC type 2 or greater bleeding) protocol was presented within the supplements; protocol of the original study was published previously	primary at 24 months - n = 94 (5.3%) vs. n = 123 (7.0%) - HR 0.76 (95% CI 0.58; 1.00), P=0.046 - ARD 1.6% - NNT 63 secondary at 24 months thrombotic composite - n = 63 (3.6%) vs. n = 93 (5.3%) - HR 0.68 (95% CI 0.49; 0.93), P=0.02 any bleeding - n = 37 (2.1%) vs. n = 50 (2.8%) - HR 0.74 (95% CI 0.48; 1.13), P=0.17 major cardiovascular events - n = 55 (3.1%) vs. n = 53 (3.0%) - HR 1.04 (95% CI 0.72; 1.52), P=0.83 predictors of the primary composite end point: - increasing age - ASS monotherapy - in patients with diabetes also HDL cholesterol level less than 40 mg/dL - in patients without diabetes male sex components of the composite see Table 2 page 540 within the publication		

Koo et al. 2021 ASS vs. Clopidogrel Monotherapie (RCT-Kohorte, nach 12 Monaten dualer Therapie, nach PCI, 2-Jahresdaten)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Koo B-K. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): An investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021;	**Objective** to compare head to head the efficacy and safety of aspirin and clopidogrel monotherapy in patients who received PCI for coronary artery disease and required chronic maintenance antiplatelet therapy	n = 5438 patients - clopidogrel group (2710 [49·8%]) - aspirin group (2728 [50·2%]) - mean age 63 years - male 75 % - hypertension 61 % - dyslipidemia 69%	**Selection bias** randomization: low concealment and unpredictability: low **Performance bias**	authors noted that standard therapy after PCI is dual antiplatelet therapy for 6–12 months followed by

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

397(10293):2487–96. https://www.ncbi.nlm.nih.gov/pub-med/34010616. [58]	**Methods**
	- investigator-initiated, prospective, randomised, open-label, multicentre trial
	- at 37 study sites in South Korea
	- registered with ClinicalTrials.gov, NCT02044250
	- HOST-EXtended Antiplatelet Monotherapy (HOST-EXAM) trial
	- trial protocol was approved by the institutional review board
	- patients aged at least 20 years
	- maintained dual antiplatelet therapy without clinical events for 6–18 months
	- after percutaneous coronary intervention with drug-eluting stents (DES)
	- patients with any ischaemic and major bleeding complications were excluded
	- patients with known hypersensitivity or contraindications for clopidogrel were excluded
	
	Intervention
	clopidogrel 75 mg once daily (monotherapy)[9]
		- previous myocardial infarction 16%
		- 50% one vessel disease
		- 18% three vessel disease
		- days from PCI to randomisation 383 vs. 380
		- 97% second generation DES (drug-eluting stent)
		- DAPT at randomization:
		  o ASS + clopidogrel ~ 82%
		  o ASS + ticagrelor ~ 10%
		  o ASS + prasugrel ~ 8%
		- completed 24-months follow-up:
		  o n = 2661 vs. n = 2677
		  o ITT and PP analyses
		  o n = 91 (1·7%) patients lost to follow-up
		
		results
		primary
		clopidogrel vs. ASS
		(completed in 5338 (98·2%) patients during 24-month)
		composite
		- 152 (5·7%) 207 (7·7%)
		- HR 0·73 (0·59–0·90) p=0·003
		- NNT 51
		thrombotic composite
		- 99 (3·7%) 146 (5·5%)
		- HR 0·68 (0·52–0·87) p=0·003
		- NNT 59
		any bleeding (BARC type ≥2)
		- 61 (2·3%) 87 (3·3%)
		- HR 0·70 (0·51–0·98) p=0·036
		- NNT 111
		all-cause death
		- 51 (1·9%) 36 (1·3%)
		- HR 1·43 (0·93–2·19) p=0·101
		cardiac death
		- 19 (0·7%) 14 (0·5%)
			blinding of participants and staff: high
			(open-label; participants and study investigators not masked to the assigned group)
			Detection bias
			blinding of evaluation: high
			(open-label; participants and study investigators not masked to the assigned group)
			Attrition bias
			lost to follow-up: low
			ITT-analysis: low
			Reporting bias
			selective result presentation: low
			
			open-label design (all endpoints had a standardised definition and were specifically adjudicated by an independent committee that was unaware of the treatment group)
			
			funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report
			
			observed event rate of the primary endpoint was lower than what was anticipated in the sample size calcu-
				indefinite duration of antiplatelet monotherapy with ASS as recommendation of choice and clopidogrel as alternative in patients who do not tolerate ASS
				
				previous identified studies (n = 2, CAPRIE, ASCET) were neither done in a dedicated percutaneous coronary intervention population nor done in the contemporary drug-eluting stent era

[9]when patients previously using potent P2Y12 inhibitors were randomly assigned to the clopidogrel group, clopidogrel 600 mg loading was recommended for ticagrelor users, while prasugrel users switched to clopidogrel 75 mg without a loading dose

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	Comperator ASS 100 mg once daily (monotherapy) for 24 months **Outcomes** superiory analyses primary - composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium (BARC) bleeding type 3 or greater secondary individual components of the primary endpoint, revascularisation, and minor gastrointestinal complications post-hoc secondary thrombotic composite (defined as cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis) and any bleeding (defined as BARC type ≥2 bleeding)	- HR 1·37 (0·69–2·73) p=0·374 non-cardiac death - 32 (1·2%) 22 (0·8%) - HR 1·47 (0·85–2·52) p=0·167 non-fatal myocardial infarction - 18 (0·7%) 28 (1·0%) - HR 0·65 (0·36–1·17) p=0·150 stroke - 18 (0·7%) 43 (1·6%) - HR 0·42 (0·24–0·73) p=0·002 ischaemic stroke - 14 (0·5%) 26 (1·0%) - HR 0·54 (0·28–1·04) p=0·064 haemorrhagic stroke - 4 (0·2%) 17 (0·6%) - HR 0·24 (0·08–0·70) p=0·010 readmission due to ACS - 66 (2·5%) 109 (4·1%) - HR 0·61 (0·45–0·82) p=0·001 major bleeding (BARC type ≥3) - 33 (1·2%) 53 (2·0%) - HR 0·63 (0·41–0·97) p=0·035 any revascularisation - 56 (2·1%) 69 (2·6%) - HR 0·82 (0·57–1·16) p=0·261 target lesion revascularisation - 24 (0·9%) 36 (1·4%) - HR 0·67 (0·40–1·12) p=0·130 target vessel revascularisation - 37 (1·4%) 48 (1·8%) - HR 0·78 (0·50–1·19) p=0·245 definite or probable stent thrombosis - 10 (0·4%) 16 (0·6%) - HR 0·63 (0·29–1·39) p=0·251 any minor gastrointestinal complications[10]	lation, suggesting a possibility of selection bias or under-reporting of events ans possible type II error (false-negative results) prespecified subgroup analyses secondary endpoints were not adjusted for multiple testing follow-up duration of 24 months might be too short to give a concrete conclusion, considering the fact that maintenance antiplatelet therapy is administered indefinitely (extended study up to 10 years) study was done in an east Asian population who are known to have lower rates of thrombotic events compared with those of White people (limit the generalisability) 50–60% of the east Asian population carry loss-offunction mutations of the CYP2C19 gene causing an attenuated antiplatelet effect of clopidogrel	

[10] such as epigastric soreness, dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, constipation, melena, or haematochezia

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- 272 (10·2%) 320 (11·9%) - HR0·85 (0·72–1·00) p=0·048 no statistically significant interaction for various subgroups		

12.5.3 Empfehlung 7-5 duale Therapie nach invasiven Verfahren (zwei Thrombozytenaggregationshemmer; in Bezug auf die Therapiedauer)

Costa et al. 2023 Dauer einer dualen Therapie (SR/MA, Thrombozytenaggregation, nach PCI, hohes Blutungsrisiko)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Costa F. Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding risk: A meta-analysis of randomized trials. Eur Heart J 2023; 44(11):954–68. https://www.ncbi.nlm.nih.gov/pubmed/36477292. [59]	**Objective**
	to estimate the impact of an abbreviated DAPT (≤3 months) compared with standard DAPT (≥6 months) after PCI in HBR patients, using the totality of available evidence from randomized clinical trials (RCTs)
	
	HBR = high bleeding risk
	
	to provide a homogenized definition for HBR patients, this was set in all studies according to a PD (PRECISE-DAPT) score ≥25, in keeping with current guideline recommendations
	
	Methods
	- PRISMA and MOOSE guidance
	- registered in PROSPERO (CRD42021284004)
	- searched PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register
		n = 11 RCT
		(RESET, OPTIMIZE, GLOBAL LEADERS, GLASSY, REDUCE, SMART CHOICE, STOPDAPT-2, TWILIGHT, TICO, ONE-MONTH DAPT, STOPDAPT-2-ACS, MASTER-DAPT)
		(n = 9006 patients with high bleeding risk, undergoing PCI with coronary stenting)
		- abbreviated DAPT, n = 4476
		  o ASS + clopidogrel, ticagrelor, or prasugrel ($P2Y_{12}$-inhibitor) followed by ASS (n = 6 studies)
		  o ASS + clopidogrel, ticagrelor, or prasugrel ($P2Y_{12}$-inhibitor) followed by $P2Y_{12}$-inhibitor (n = 5 studies)
		- standard DAPT, n = 4530
		- abbreviated DAPT 1-3 months
		- standard DAPT 6-12 months
		- mean age 70.7 – 80 years
		- women: 40%
		- ASC: 32 – 100 % (mean 58 %)
		- stable 35 – 68 %
		- hypertension 67 – 91.6 %
		- dyslipedemia 45 – 83 %
		- previous myocardial infarction 2.4 – 29 %
		- DES was used in all patients
		- multi vessel disease 26%
		- DAPT at discharge:
		  o ASS 95 – 100 %
			AMSTAR-II low
			
			(keine Liste der ausgeschlossenen Volltexte mit Ausschlussgrund vorhanden), *Hinweis*: Supplement ist leider nur als Word-Dokument verfügbar (docx), daher aktuell nicht einsehbar
			
			ad- hoc and post-hoc subgroup analyses were performed
			
			sensitivity analyses were presented
			
			authors noted that study quality was high, with blinded adjudication of events by an independent clinical event committee assuring a low probability of performance bias
			
			Limitations (authors note)
			
			abbreviated DAPT entailed different types of single antiplatelet therapy upon DAPT withdrawal (i.e. aspirin, clopidogrel, prasugrel, or ticagrelor
				„graphical abstract" vorhanden
				
				authors noted that current guidelines recommend 3 or 6 months of DAPT in high bleeding risk patients undergoing PCI for ACS or CCS or shorter treatment, based on consensus opinion
				
				authors noted that patients on OAC were excluded from the analysis despite being a recognized HBR criterion; concurrent treatment with OAC is frequent, presenting in up to 10% of patients undergoing PCI, OAC per se is different from other HBR criteria

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	of Controlled Trials (articles published between 1 January 2000 and 31 October 2021), reference lists
	- RCT
	- PCI for ACS or CCS
	- patients after PCI
	- minimum follow-up of 12 months
	- patients treated with oral anticoagulants (OAC) were excluded (for those that recruited patients with and without OAC, outcome data were selectively extracted)
	- events occurring during study phases investigating other treatment strategies than a DAPT duration comparison were censored
	
	Quality assessment
	RoB-2 tool
	
	Intervention
	- DAPT (dual antiplatelet therapy), abbreviated (≤3 months)
	
	Comperator
	- DAPT, standard (≥6 months) DAPT duration
	
	Outcomes
	co-primary safety and efficacy endpoints
		o clopidogrel 42 – 100 %
		o ticagrelor 0 – 100 %
		o prasugrel 0 – 13 %
		
		- alternative definition for HBR: in n = 7/11 RCT
		 o n = 6545 HBR patients
		  ▪ abbreviated DAPT, n = 3212
		  ▪ standard DAPT, n = 3333
		
		main results
		abbreviated DAPT vs. standard DAPT
		major or clinically relevant non-major bleeding
		- RR 0.76 (95% CI 0.61; 0.94), n = 11 studies
		major bleeding
		- RR 0.80 (95% CI 0.64; 0.99), n = 11 studies
		major advererse cardiovascular events 1
		- RR 0.97 (95% CI 0.74; 1.26), n = 11 studies
		major advererse cardiovascular events 2
		- RR 0.92 (95% CI 0.77; 1.10), n = 11 studies
		net adverse clinical events
		- RR 0.94 (95% CI 0.78; 1.14)
		all-cause death
		- RR 0.91 (95% CI 0.68; 1.23), n = 11 studies
		cardiovascular death
		- RR 0.79 (95% CI 0.65; 0.95), n = 11 studies
		myocardial infarction
		- RR 0.84 (95% CI 0.51; 1.38)
		stroke
		- RR 1.15 (95% CI 0.84; 1.60)
		definite stent thrombosis
		- RR 0.73 (95% CI 0.35; 1.50)
		definite or probable stent thrombosis
		- RR 0.84 (95% CI 0.58; 1.20)
		fatal bleeding
		- RR 0.63 (95% CI 0.24; 1.70)
			monotherapy), which in some instances were based on physician preference
			
			risk of unmeasured confounding was reported
			
			specific HBR features (e.g. history of prior intracranial bleeding, recent prior stroke, active bleeding, or bleeding within 1–2 months of study inclusion) were exclusion criteria in many of the included studies
			
			RCT tend to select a lower-risk population compared with real-world patients
				OAC drives a higher risk for bleeding due to its biological effect on systemic coagulation, but it also affects the ischaemic risk, reducing the risk of stent-related and non-stent related ischaemic events
				
				(European guidelines peri-procedural treatment with DAPT followed immediately after by P2Y12 inhibitor monotherapy is recommended for OAC patients whereas such an approach has not been tested in randomized studies in patients without indication for OAC)
				
				(PCI patients generally are treated with single antiplatelet therapy indefinitely after stenting, lifelong antiplatelet therapy is not recommended in most OAC patients due to the HBR from this combination)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- major or clinically relevant non-major bleeding (MCRB) and - major adverse cardiovascular events (MACE) - up to 12 months after PCI two different composite endpoints of MACE for all-cause death, myocardial infarction (MI) or stroke (i.e. MACE 1), and cardiovascular (CV) death, MI, or stroke (i.e. MACE 2) other safety endpoints of major bleeding (MB) as per the study definition as well as individual endpoints according to the Bleeding Academic Research Consortium (BARC) and thrombolysis in MI bleeding definitions other efficacy endpoints, including Net Adverse Clinical Events (NACE), all-cause death, CV death, MI, stroke, and stent thrombosis,	(results for sensitivity analyses see Supplementary material online, Figs S2 and S3: results were consistent when using the TIMI or BARC bleeding definitions) (funnel plots for bleeding endpoints ect. are presented in Supplementary material online, Figure S4A and B, C and D and S5) **results of subgroup analyses** clinical presentation at time of PCI (ACS or CCS) abbreviated DAPT vs. standard DAPT MCRB (p=0.62) - ACS 0.79 (0.55; 1.13) - CCS 0.87 (0.68; 1.10) MB (p= 0.17) - ACS 0.76 (0.52; 1.10) - CCS 1.08 (0.71; 1.60) MACE 1 (p=0.70) - ACS 1.01 (0.78; 1.33) - CCS 0.94 (0.68; 1.31) MACE 2 (p=0.91) - ACS 0.93 (0.76; 1.14) - CCS 0.91 (0.66; 1.22) NACE (p=0.91) - ACS 0.97 (0.75; 1.30) - CCS 0.99 (0.70; 1.40) death (p=0.76) - ACS 0.96 (0.69; 1.40) - CCS 0.90 (0.60; 1.40) CV death (p=0.97) - ACS 0.88 (0.64; 1.20) - CCS 0.87 (0.57; 1.30) (Figure 5) type of antiplatelet therapy continuation after short DAPT discontinuation (continued aspirin or a P2Y12 inhibitor after DAPT discontinuation) abbreviated DAPT vs. standard DAPT		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		MCRB (p=0.43) MB (p=0.83) MACE 1 (p=0.55) MACE 2 (p=0.59) other explored endpoints (see Supplementary material online, Figure S7) *type of DES implanted* abbreviated DAPT vs. standard DAPT MCRB (p=0.06) MB (p=0.02) MACE 1 (p=0.12) all-cause mortality (pint= 0.08) MACE 2 (p=0.23) CV mortality (p=0.85) (see Supplementary material online, Figure S8) authors noted: main findings: (i) abbreviated DAPT for 1 or 3 months was associated with lower MCRB, MB and CV mortality compared with standard DAPT in HBR patients treated with PCI; (ii) abbreviated DAPT was similarly effective compared with standard DAPT for the prevention of MACE, stent thrombosis, and other ischaemic events, irrespective of clinical presentation and type of antiplatelet agent administered after short DAPT discontinuation; (iii) these findings remained consistent irrespective of the HBR definition, either based on PD score or the ARC-HBR framework, as endorsed by guidelines (Structured Graphical Abstract)		

Gelbenegger et al. 2021 optimale Dauer und Therapie (SR/MA, Thrombozytenaggregation, nach PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Gelbenegger G. Optimal duration and combination of antiplatelet therapies following percutaneous coronary intervention: A meta-analysis. Vascul Pharmacol 2021; 138:106858. https://www.ncbi.nlm.nih.gov/pubmed/33753284. [60]	**Objective** to compare very short-term (1–3 months), short-term (6 months), standard-term (12 months) and long-term (>12 months) DAPT durations for efficacy and safety **Methods** - Systematic review, meta-analysis - PRISMA - PROSPERO registration no: CRD42020163719 - search until Dec 2019 - RCT - Comparing different DAPT durations - details available within an online appendix **Comparison** different durations of DAPT were categorized into: - very short-term (1-3 months) - short-term (6 months) - standard-term (12 months) - long-term (> 12 months) due to the large heterogeneity of compared DAPT durations in the studies, DAPT comparisons in the overall analysis were termed "any longer-term" DAPT and "any shorter-term" DAPT **Outcomes** primary	n = 26 studies (n = 103.394 patients) - all except for one study exclusively included patients who had undergone placement of a drug-eluting stent (DES) - n = 13 studies DAPT with clopidogrel - n = 10 studies DAPT with P2Y$_{12}$-inhibitor - n = 3 studies with ticagrelor - n = 5 studies with a comcept of monotherapy with P2Y$_{12}$-inhibitor - details are available within an online supplement **results** longer DAPT vs. shorter DAPT (standard DAPT vs. early drop of ASS or P2Y$_{12}$-I, followed by monotherapy of P2Y$_{12}$-I or ASS) MACE according to treatment regimen standard-term DAPT (12 months) vs. early drop of ASS (very short term DAPT, 1-3 months), followed by P2Y$_{12}$-I monotherapy - n = 657/16088 vs. n = 616/16057 - RR 1.06 (0.95; 1.18), p = 0.26, n = 5 studies any longer-term DAPT vs. early drop of P2Y$_{12}$ inhibitor (short-term DAPT, 6 months), followed by ASS monotherapy - n = 1 885/39222 vs. n = 1 599/32027 - RR 0.88 (0.81; 0.96), p = 0.002, n = 21 studies MACE according to P2Y12-inhibitor long-term DAPT (> 12 months, prasugrel or ticagrelor) vs. standard-term DAPT (12 months) - RR 0.76, 95% CI, 0.63–0.93, p = 0.007, n = 3 studies - prasugrel: RRR 48% (95% CI, 0.38–0.71) - ticagrelor: RRR 16% (95% CI, 0.77–0.92) long-term DAPT (> 12 months, clopidogrel) vs. standard-term DAPT (12 months)	AMSTAR-II critically low (u. a. keine Liste der ausgeschlossenen Volltexte mit Ausschlussgrund vorhanden, keine Risk-of-Bias Bewertung beschrieben und auch keine Berücksichtigung bei der Analyse und Diskussion der Ergebnisse, die Untersuchung eines Publication Bias wurde nicht beschrieben), *Hinweis*: Supplement ist leider nur als Word-Dokument verfügbar (docx), daher aktuell nicht einsehbar sensitivity and soubgroup analyses were performed large sample size several studies did not report on outcomes of interest three different bleeding definitions were used in the trials analysis may be underpowered for individual adverse cardiovascular events, especially in subgroup analyses on specific DAPT durations, types of antiplatelet agent and clinical presentations	authors noted that: long-term DAPT with prasugrel or ticagrelor suggested for patients with high ischemic and low bleeding risk long-term DAPT with prasugrel or ticagrelor suggested for ACS patients with high ischemic and low bleeding risk very short term DAPT followed by drop of ASS or P2Y12-inhibitors suggested for patients with high bleeding and low ischemic risk

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- MACE (the composite of myocardial infarction, stroke and cardiovascular death) - Major bleeding secondary - myocardial infarction - stroke - all-cause death - cardiovascular death - stent thrombosis (definite and probable) details on study outcome and definitins are available within an online appendix	- RR 0.91, 95% CI, 0.71–1.17, p = 0.47, n = 5 studies MACE according to ACS any longer-term DAPT (prasugrel, ticagrelor) vs. any shorter-term DAPT - RR 0.84, 95% CI, 0.77–0.92, p = 0.0001, n = 3 studies - RRR 16% any loger-term DAPT (clopidogrel) vs. any shorter-term DAPT - RR 1.04, 95% CI, 0.89–1.20, p = 0.64, n = 8 studies TIMI major bleeding any longer-term DAPT vs. any shorter DAPT - n = 433/30773 vs. n = 167/23693 - RR 1.85 (1.54; 2.22), p < 0.00001, n = 15 studies BARC 3-5 major bleeding any longer-term DAPT vs. any shorter DAPT - n = 595/28378 vs. n = 409/28219 - RR 1.54 (1.21; 1.97), p = 0.0005, n = 13 studies BARC 3-5 major bleeding according to treatment regimen drop of ass standard-term DAPT (12 months) vs. early drop of ASS (very short term DAPT, 1-3 months), followed by $P2Y_{12}$-I monotherapy - n = 279/14559 vs. 217/14530 - RR 1.61 (0.96; 2.71), p = 0.07, n = 4 studies drop of $P2Y_{12}$-I any longer-term DAPT vs. any shorter DAPT with drop of $P2Y_{12}$ inhibitor, followed by ASS monotherapy - n = 287/13092 vs. n = 168/12956 - RR 1.63 (1.22; 2.17), p = 0.001 n = 8 studies		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		myocardial infarction (overall) any longer-term DAPT vs. any shorter DAPT - RR 0.84, 95% CI, 0.73–0.95, p = 0.008 - RRR 16% - detail available within an online supplement **myocardial infarction according to treatment regimen** drop of ASS standard-term DAPT (12 months) vs. early drop of ASS (very short term DAPT, 1-3 months), followed by $P2Y_{12}$-I monotherapy - n = 384/16088 vs. n = 373/16057 - RR 1.03 (0.89; 1.18), p = 0.72, n = 5 studies *note:* text and forest plot differe (text: very short term vs. standard-term DAPT duration; forest plot: longer vs. shorter DAPT) drop of $P2Y_{12}$-I any longer-term DAPT vs. any shorter DAPT with drop of $P2Y_{12}$ inhibitor, followed by ASS monotherapy - n = 929/39222 vs. n = 864/32027 - RR 0.76 (0.66; 0.87), p = 0,0001, n = 21 studies - RRR 24% **stroke (overall)** any longer-term DAPT vs. any shorter DAPT - RR 0.93, 95% CI, 0.81–1.06, p = 0.25 - detail available within an online supplement **stroke according to treatment regimen** drop of ASS standard-term DAPT (12 months) vs. early drop of ASS (very short term DAPT, 1-3 months), followed by $P2Y_{12}$-I monotherapy - RR 0.96, 95% CI, 0.61–1.51, p = 0.85 - detail available within an online supplement drop of $P2Y_{12}$-I		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		any longer-term DAPT vs. any shorter DAPT with drop of $P2Y_{12}$ inhibitor, followed by ASS monotherapy - RR 0.90, 95% CI, 0.77–1.05, p = 0.19 - detail available within an online supplement all-cause mortality (overall) any longer-term DAPT vs. any shorter DAPT - RR 1.04, 95% CI, 0.97–1.13, p = 0.28 - detail available within an online supplement all-cause mortality according to treatment regimen drop of ASS standard-term DAPT (12 months) vs. early drop of ASS (very short term DAPT, 1-3 months), followed by $P2Y_{12}$-I monotherapy - RR 1.13, 95% CI, 0.97–1.31, p = 0.12 - detail available within an online supplement drop of $P2Y_{12}$-I any longer-term DAPT vs. any shorter DAPT with drop of $P2Y_{12}$ inhibitor, followed by ASS monotherapy - RR 1.02, 95% CI, 0.92–1.14, p = 0.64 - detail available within an online supplement cardiovascular mortality (overall) any longer-term DAPT vs. any shorter DAPT - RR 0.97, 95% CI, 0.86–1.10, p = 0.65 - detail available within an online supplement cardiovascular mortality according to treatment regimen drop of ASS standard-term DAPT (12 months) vs. early drop of ASS (very short term DAPT, 1-3 months), followed by $P2Y_{12}$-I monotherapy - RR 1.37, 95% CI, 0.96–1.95, p = 0.08 - detail available within an online supplement drop of $P2Y_{12}$-I		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		any longer-term DAPT vs. any shorter DAPT with drop of P2Y$_{12}$ inhibitor, followed by ASS monotherapy - RR 0.93, 95% CI, 0.82–1.06, p = 0.27 - detail available within an online supplement stent thrombosis (overall) any longer-term DAPT vs. any shorter DAPT - RR 0.73, 95% CI, 0.57–0.94, p = 0.02 - RRR 27% - detail available within an online supplement stent thrombosis according to treatment regimen standard-term DAPT (12 months) vs. very short term DAPT (1-3 months) with drop of ass, followed by P2Y$_{12}$-I mono-therapy - n = 90/16088 vs. n = 91/16057 - RR 1.00 (0.74; 1.34), p = 0.98, n = 5 studies any longer-term DAPT vs. any shorter DAPT with drop of P2Y$_{12}$ inhibitor, followed by ASS monotherapy - n = 142/20058 vs. n = 223/19919 - RR 0.64 (0.47; 0.88), p = 0.0006, n = 16 studies authors concluded: i) In trials with P2Y12 inhibitor drop and contin-uation of aspirin monotherapy, any longer-term DAPT duration is associated with a sig-nificant reduction of MACE, MI and ST but a higher risk of major bleeding as compared with any shorter-term DAPT duration; ii) High ischemic risk patients treated with po-tent P2Y12 inhibitors such as prasugrel and ticagrelor showed a significantly lower risk of MACE with long-term DAPT of >18 months compared with standard-term DAPT of 12 months. Likewise, in the ACS population, the extent of reduction of ischemic events with		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		longerterm DAPT duration group was significant only in patients treated with potent P2Y12 inhibitors; iii) Very short-term DAPT (1–3 months) with either aspirin or P2Y12 inhibitor drop is associated with satisfactory efficacy and safety as compared with standard-term DAPT duration of 12 months.		

CADT 2019 (HTA, verlängerte duale Therapie Thrombozytenaggregationshemmer (>12 Monate); nach PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Canadian Agency for Drugs and Technologies in Health. Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration — Recommendations. 2019 Mar. https://pub-med.ncbi.nlm.nih.gov/31246385 [61] Canadian Agency for Drugs and Technologies in Health. Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration — Project Protocol. 2018 Feb. https://pub-med.ncbi.nlm.nih.gov/30260612 [62]	**Research Question** What are the comparative clinical efficacy and safety of a shorter duration (six months to 12 months) versus a longer duration (longer than 12 months) of DAPT following PCI with BMS or DES insertion in: - all post-PCI patients - those with a prior MI - those presenting with ACS - those with diabetes - different age subgroups - those who smoke. Compared with a shorter treatment duration (six months to 12 months), what are the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor when used for a longer duration (longer than 12 months) of DAPT following PCI with BMS or DES insertion in: - all post-PCI patients - those with a prior MI	n = 7 RCT - clopidogrel most common (n = 3 trials), (OPTIDUAL, DES-LATE, PRODIGY), n = 4 trials with more than one P2Y12 inhibitor, (ITALIC, DAPT, ARCTIC-Interruption, NIPPON) - PEGASUS-TIMI 54 (ticagrelor) was excluded, did not met eligibility criteria (only identified RCT to assess the benefits and harms of long-term ticagrelor use, results were summarized and made available as supplement of the original publication) **results** Comparative Effect of Extended Versus Standard DAPT for the Whole Population (Table 2) DAPT > 12 Months vs. DAPT 6 to 12 Months Relative Risk (95% CI), No. of RCT, No. of Participants All-cause death 1.07 (0.80 to 1.42), n = 7 (n = 25,982) Cardiovascular death 0.98 (0.74 to 1.30), n = 5 (n = 21,561) Non-cardiovascular death	AMSTAR-II high limitations soubgroup analyses: small sample size *Hinweis*: supplement leider nicht verfügbar	developing stent thrombosis and de-novo recurrent ischemic events were given as reason for extending the duration of DAPT beyond 12 months discussion: "extending DAPT beyond 12 months may reduce the risk of MI and stent thrombosis, but may also increase the risk of bleeding" "no significant differences in the risk of all-cause or cardiovascular death, stroke, urgent target revascularization, MACCE, or gastrointestinal bleeding"

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- those presenting with ACS - those with diabetes - different age subgroups - those who smoke **Methods** - systematic review, meta-analysis (if possible NMA) - Medline, Embase, Cochrane Library, grey literature - PROSPERO (No. CRD42018082587) - PRISMA, Cochrane Handbook - RCT - adult patients - undergone PCI - receiving DAPT **Quality assessment** Cochrane Collaboration's risk of bias tool (RoB 2.0) **Intervention** DAPT after PCI extended duration (more than 12 months) **Comperator** DAPT for 6 to 12 months DAPT = P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) + ASS **Outcome** primary death (cardiovascular, all-cause, non-cardiovascular) secondary	2.15 (1.30 to 3.55), n = 3 (n = 14,666) Myocardial infarction 0.58 (0.48 to 0.70), n = 6 (n = 24,534) Stroke 0.94 (0.70 to 1.25), n = 6 (n = 24,534) Stent thrombosis: definite 0.49 (0.22 to 1.08), n = 5 (n = 20,825) Stent thrombosis: probable or definite 0.38 (0.21 to 0.67), n = 5 (n = 19,489) Urgent revascularization 0.60 (0.24 to 1.54), n = 2 (n = 3,136) MACCE 0.95 (0.76 to 1.19), n = 5 (n = 21,227) Gastrointestinal bleeding 0.89 (0.34 to 2.30), n = 1 (n = 3,773) TIMI major bleeding 1.42 (0.88 to 2.29), n = 4 (n = 9,579) TIMI minor bleeding 0.95 (0.53 to 1.72), n = 2 (n = 3,248) GUSTO moderate bleeding 1.68 (1.22 to 2.30), n = 2 (n = 13,046) GUSTO severe bleeding 1.41 (0.90 to 2.20), n = 2 (n = 13,046) GUSTO moderate or severe bleeding 1.57 (1.17 to 2.11), n = 2 (n = 13,046)		"one large RCT (DAPT) reported an increased risk of non-cardiovascular death (primarily cancer and trauma deaths) among participants who received extended DAPT (30 months of DAPT); this finding was not replicated in two smaller RCT" dose extendet DAPT: - clopidogrel 75 mg daily - prasugrel 10 mg daily - ticagrelor 60 mg twice daily dose first year: - clopidogrel 75 mg daily - prasugrel 10 mg daily - ticagrelor 90 mg twice daily (RCT and guideline recommendation; Canadian Cardiovascular Society)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- bleeding (major, minor, gastro-intestinal)
	- urgent target vessel revascularization
	- major adverse cardiac and cerebrovascular events
	- myocardial infarction
	- stroke
	- stent thrombosis
	
	MACCE = major adverse cardiac and cerebrovascular events
		BARC Type 3 bleeding
		1.29 (0.76 to 2.22), n = 3 (n = 16,353)
		
		BARC Type 5 bleeding
		1.72 (0.62 to 4.47), n = 3 (n = 16,353)
		
		BARC Type 2,3,5 bleeding
		0.89 (0.48 to 1.68), n = 1 (n = 1,398)
		
		authors noted current guidelines recommendations
		- tailoring the length of DAPT depending on patient characteristics
		- American College of Cardiology/American Heart Association (ACC/AHA) guidelines:
		  o DAPT for six months following PCI for patients with stable coronary artery disease and for 12 months in patients with acute coronary syndrome (ACS)
		  o with the consideration of extended DAPT beyond 12 months if potential thrombotic risk is high and bleeding risk is deemed low
		  o use of the DAPT score to identifying high-risk patients
		- European Society of Cardiology (ESC) guidelines (2017):
		  o one-year minimum duration of DAPT for patients with ACS
		- Canadian guidelines:
		  o individualized approach to selecting DAPT duration, with different recommendations for patients with ACS or non-ACS indications at the time of PCI
		
		NICE recommendations
		recommendation 1:
		- recommends that a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) be reimbursed for use beyond 12		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		months in combination with ASS in patients who recently underwent PCI with DES insertion o any decision should be made together with the patient o undergoing extended DAPT, consult at least once per year o extended DAPT treatment should not exceed three years o ticagrelor standard DAPT with 90 mg twice daily o ticagrelor extended DAPT with 60 mg twice daily - reasons: o SR of n = 7 RCT (extended DAPT beyond 12 months vs. standard DAPT (6-12 months)) ▪ myocardial infarction (MI) ▪ RR 0.58, 95% [CI], 0.48 to 0.70 ▪ NNT 174 ▪ stent thrombosis ▪ RR 0.38, 95% CI, 0.21 to 0.67 ▪ NNT 348 ▪ compared with ▪ results are mainly driven by clopidogrel because most patients enrolled in the included studies were using this P2Y12 inhibitor o SR of n = 7 RCT (extended DAPT beyond 12 months vs. standard DAPT (6-12 months)) ▪ Bleeding ▪ GUSTO moderate bleeding ▪ RR 1.68, 95% CI, 1.22 to 2.30 ▪ NNH 156 ▪ GUSTO moderate and severe bleeding ▪ RR 1.57, 95% CI, 1.17 to 2.11 ▪ results also mainly driven by clopidogrel o n = 1 large RCT (DAPT) reported a significant increase in non-cardiovascular death (RR 2.15, 95% CI, 1.30 to 3.55) among participants who received DAPT > 12 months		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		o duration of included studies extended to a maximum of 48 months, with the largest included study (i.e., the DAPT trial) following patients for up to 30 months ■ extending DAPT beyond three years after an initial 12 months treatment should be undertaken only if the patient is evaluated by a physician with expertise in cardiovascular disease recommendation 2: - recommends that selection of which P2Y12 inhibitor is used for extended DAPT be made at the discretion of the treating physician and that this be based on the individual characteristics and risk profile of each patient - reasons: o insufficient information about comparative clinical effectiveness of individual P2Y12 inhibitors (i.e., clopidogrel, prasugrel, and ticagrelor) **included studies:** 6. Collet JP et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): A randomised trial. *Lancet.* 2014;384(9954):1577. 7. Gilard M et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: The randomized, multicenter ITALIC trial. *J Am Coll Cardiol.* 2015;65(8):777. 8. Helft G et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: The OPTIDUAL randomized trial. *Eur Heart J.* 2016;37(4):365. 9. Lee CW et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: A randomized, controlled trial. *Circulation.* 2014;129(3):304.		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		10. Valgimigli M et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: A randomized multi-center trial. *Circulation.* 2012;125(16):2015. 11. Mauri L et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014;371(23):2155. 12. Nakamura M et al. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. *JACC Cardiovasc Interv.* 2017;10(12):1189.		

Yamamoto et al. 2023/21 – Watanabe et al. 2022 1 Monat DAPT + Clopidogrel Langzeittherapie (RCT, STOPDAPT-2; PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Yamamoto K. Clopidogrel Monotherapy After 1-Month DAPT in Patients With High Bleeding Risk or Complex PCI. JACC Asia 2023; 3(1):31–46. https://www.ncbi.nlm.nih.gov/pubmed/36873770. [63]	BACKGROUND: High bleeding risk (HBR) and complex percutaneous coronary intervention (PCI) are major determinants for dual antiplatelet therapy (DAPT) duration. OBJECTIVES: The aim of this study was to evaluate the effects of HBR and complex PCI on short vs standard DAPT. METHODS: Subgroup analyses were conducted on the basis of Academic Research Consortium-defined HBR and complex PCI in the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Verulam's-Eluting Cobalt-Chromium Stent-2) Total Cohort, which randomly compared clopidogrel monotherapy after 1-month DAPT with 12-month DAPT with aspirin and clopidogrel after PCI. The primary endpoint was the composite of cardi-	RESULTS: Regardless of HBR (n = 1,893 [31.6%]) and complex PCI (n = 999 [16.7%]), the risk of 1-month DAPT relative to 12-month DAPT was not significant for the primary endpoint (HBR, 5.01% vs 5.14%; non-HBR, 1.90% vs 2.02%; P (interaction) = 0.95) (complex PCI, 3.15% vs 4.07%; noncomplex PCI, 2.78% vs 2.82%; P (interaction) = 0.48) and for the cardiovascular endpoint (HBR, 4.35% vs 3.52%; and non-HBR, 1.56% vs 1.22%; P (interaction) = 0.90) (complex PCI, 2.53% vs 2.52%; noncomplex PCI, 2.38% vs 1.86%; P (interaction) = 0.53), while it was lower for the bleeding endpoint (HBR, 0.66% vs 2.27%; non-HBR, 0.43% vs 0.85%; P (interaction) = 0.36) (complex PCI, 0.63% vs 1.75%; noncomplex PCI, 0.48% vs 1.22%; P (interaction) = 0.90). The absolute difference in the bleeding between 1- and 12-month DAPT was numerically greater in patients with HBR than in those without HBR (-1.61% vs -0.42%). CONCLUSIONS: The effects of 1-month DAPT relative to 12-month DAPT were consistent regardless of HBR and complex PCI. The absolute benefit of 1-month DAPT over 12-month DAPT in reducing major bleeding was numerically greater in patients with HBR than in those without HBR. Complex PCI might not be an appropriate determinant for DAPT durations after PCI. (Short and Optimal Duration of	*Zunächst nicht bewertet und extrahiert (Abstact verfügbar)*	STOPDAPT-2

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	ovascular (cardiovascular death, myocardial infarction, definite stent thrombosis, or stroke) or bleeding (Thrombolysis In Myocardial Infarction [TIMI] major or minor) endpoints at 1 year.	Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 [STOPDAPT-2], NCT02619760; Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 for the Patients With ACS [STOPDAPT-2 ACS], NCT03462498).		
Yamamoto K. Clopidogrel Monotherapy After 1-Month Dual Antiplatelet Therapy in Patients With Diabetes Undergoing Percutaneous Coronary Intervention. JACC Cardiovasc Interv 2023; 16(1):19–31. https://www.ncbi.nlm.nih.gov/pubmed/36599584. [64]	BACKGROUND: Diabetes was reported to be associated with an impaired response to clopidogrel. OBJECTIVES: The aim of this study was to evaluate the safety and efficacy of clopidogrel monotherapy after very short dual antiplatelet therapy (DAPT) in patients with diabetes undergoing percutaneous coronary intervention (PCI). METHODS: A subgroup analysis was conducted on the basis of diabetes in the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) Total Cohort (N = 5,997) (STOPDAPT-2, n = 3,009; STOPDAPT-2 ACS [Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 for the Patients With ACS], n = 2,988), which randomly compared 1-month DAPT followed by clopidogrel monotherapy with 12-month DAPT with aspirin and clopidogrel after cobalt-chromium everolimus-eluting stent implantation. The primary endpoint was a composite of cardiovascular (cardiovascular death, myocardial infarction, definite	RESULTS: There were 2,030 patients with diabetes (33.8%) and 3967 patients without diabetes (66.2%). Regardless of diabetes, the risk of 1-month DAPT relative to 12-month DAPT was not significant for the primary endpoint (diabetes, 3.58% vs 4.12% [HR: 0.87; 95% CI: 0.56-1.37; P = 0.55]; nondiabetes, 2.46% vs 2.49% [HR: 0.99; 95% CI: 0.67-1.48; P = 0.97]; P(interaction) = 0.67) and for the cardiovascular endpoint (diabetes, 3.28% vs 3.05% [HR: 1.10; 95% CI: 0.67-1.81; P = 0.70]; nondiabetes, 1.95% vs 1.43% [HR: 1.38; 95% CI: 0.85-2.25; P = 0.20]; P(interaction) = 0.52), while it was lower for the bleeding endpoint (diabetes, 0.30% vs 1.50% [HR: 0.20; 95% CI: 0.06-0.68; P = 0.01]; nondiabetes, 0.61% vs 1.21% [HR: 0.51; 95% CI: 0.25-1.01; P = 0.054]; P(interaction) = 0.19). CONCLUSIONS: Clopidogrel monotherapy after 1-month DAPT compared with 12-month DAPT reduced major bleeding events without an increase in cardiovascular events regardless of diabetes, although the findings should be considered as hypothesis generating, especially in patients with acute coronary syndrome, because of the inconclusive result in the STOPDAPT-2 ACS trial. (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 [STOPDAPT-2], NCT02619760; Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 for the Patients With ACS [STOPDAPT-2 ACS], NCT03462498).		

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	stent thrombosis, or stroke) or bleeding (TIMI [Thrombolysis In Myocardial Infarction] major or minor) endpoints at 1 year.			
Watanabe H. Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome: The STOPDAPT-2 ACS Randomized Clinical Trial. JAMA Cardiol 2022; 7(4):407–17. https://www.ncbi.nlm.nih.gov/pubmed/35234821. [65]	OBJECTIVE: To test the hypothesis of noninferiority of 1 to 2 months of DAPT compared with 12 months of DAPT for a composite end point of cardiovascular and bleeding events in patients with ACS. DESIGN, SETTING, AND PARTICIPANTS: This multicenter, open-label, randomized clinical trial enrolled 4169 patients with ACS who underwent successful PCI using cobalt-chromium everolimus-eluting stents at 96 centers in Japan from December 2015 through June 2020. These data were analyzed from June to July 2021. INTERVENTIONS: Patients were randomized either to 1 to 2 months of DAPT followed by clopidogrel monotherapy (n = 2078) or to 12 months of DAPT with aspirin and clopidogrel (n = 2091). MAIN OUTCOMES AND MEASURES: The primary end point was a composite of cardiovascular (cardiovascular death, myocardial infarction [MI], any stroke, or definite stent thrombosis) or bleeding (Thrombolysis in MI major or minor bleeding) events at 12 months, with a noninferiority margin of 50% on the hazard ratio (HR) scale. The major	RESULTS: Among 4169 randomized patients, 33 withdrew consent. Of the 4136 included patients, the mean (SD) age was 66.8 (11.9) years, and 856 (21%) were women, 2324 (56%) had ST-segment elevation MI, and 826 (20%) had non-ST-segment elevation MI. A total of 4107 patients (99.3%) completed the 1-year follow-up in June 2021. One to 2 months of DAPT was not noninferior to 12 months of DAPT for the primary end point, which occurred in 65 of 2058 patients (3.2%) in the 1- to 2-month DAPT group and in 58 of 2057 patients (2.8%) in the 12-month DAPT group (absolute difference, 0.37% [95% CI, -0.68% to 1.42%]; HR, 1.14 [95% CI, 0.80-1.62]; P for noninferiority = .06). The major secondary cardiovascular end point occurred in 56 patients (2.8%) in the 1- to 2-month DAPT group and in 38 patients (1.9%) in the 12-month DAPT group (absolute difference, 0.90% [95% CI, -0.02% to 1.82%]; HR, 1.50 [95% CI, 0.99-2.26]). The major secondary bleeding end point occurred in 11 patients (0.5%) in the 1- to 2-month DAPT group and 24 patients (1.2%) in the 12-month DAPT group (absolute difference, -0.63% [95% CI, -1.20% to -0.06%]; HR, 0.46 [95% CI, 0.23-0.94]). CONCLUSIONS AND RELEVANCE: In patients with ACS with successful PCI, clopidogrel monotherapy after 1 to 2 months of DAPT failed to attest noninferiority to standard 12 months of DAPT for the net clinical benefit with a numerical increase in cardiovascular events despite reduction in bleeding events. The directionally different efficacy and safety outcomes indicate the need for further clinical trials. TRIAL REGISTRATION: ClinicalTrials.gov Identifiers: NCT02619760 and NCT03462498.		

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	secondary end points were cardiovascular and bleeding components of the primary end point.			
Yamamoto K. Very Short Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Patients Who Underwent Complex Percutaneous Coronary Intervention: Insight From the STOPDAPT-2 Trial. Circ Cardiovasc Interv 2021; 14(5):e010384. https://www.ncbi.nlm.nih.gov/pubmed/34003662. [66]	BACKGROUND: Safety and efficacy of clopidogrel monotherapy after very short dual antiplatelet therapy (DAPT) is uncertain in patients undergoing complex percutaneous coronary intervention (PCI). METHODS: We conducted a post hoc subgroup analysis based on the complexity of PCI in the STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy-2), which randomly compared 1-month DAPT followed by clopidogrel monotherapy with 12-month DAPT after cobalt-chromium everolimus-eluting stent implantation. Complex PCI was defined as any of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents, >60 mm total stent lengths, and target of chronic total occlusion. The primary end point was the composite of cardiovascular (cardiovascular death/myocardial infarction/definite stent thrombosis/stroke) and bleeding (TIMI [Thrombolysis in Myocardial Infarction] major/minor) end points. The major secondary end points were the cardiovascular and bleeding end points.	RESULTS: Among the 3009 study patients, there were 509 patients (16.9%) with complex PCI (1-month DAPT: N=245, and 12-month DAPT: N=264) and 2500 patients (83.1%) without complex PCI (1-month DAPT: N=1255, and 12-month DAPT: N=1245). There were no significant interactions between the complexity of PCI and the effects of 1-month DAPT versus 12-month DAPT on the primary end point (complex PCI: 1.67% versus 5.32%, hazard ratio, 0.30 [95% CI, 0.10–0.92], P=0.04, and noncomplex PCI: 2.50% versus 3.35%, hazard ratio, 0.75 [95% CI, 0.47–1.20], P=0.23; Pinteraction=0.14), and on the major secondary cardiovascular end point (complex PCI: 1.67% versus 3.04%, hazard ratio, 0.54 [95% CI, 0.16–1.79], P=0.31, and noncomplex PCI: 2.02% versus 2.39%, hazard ratio, 0.86 [95% CI, 0.50–1.47], P=0.58; Pinteraction=0.49). The cumulative 1-year incidence of the major secondary bleeding end point was significantly lower in the 1-month DAPT group than in the 12-month DAPT group regardless of the complexity of PCI (complex PCI: 0% versus 2.29%, log-rank P=0.02, and noncomplex PCI: 0.48% versus 1.38%, log-rank P=0.02). CONCLUSIONS: The effects of clopidogrel monotherapy after 1-month DAPT relative to 12-month DAPT for the primary and major secondary end points were comparable in complex PCI and noncomplex PCI without significant interactions. REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02619760.		

Lee et al. 2022 1 Monat DAPT + ASS Langzeittherapie (RCT, Post-hoc-Analyse; PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Lee Y-J. Impact of one-month DAPT followed by aspirin monotherapy in patients undergoing percutaneous coronary intervention according to clinical presentation: A post hoc analysis of the randomised One-Month DAPT trial. EuroIntervention 2022; 18(6):471–81. https://www.ncbi.nlm.nih.gov/pubmed/35470799. [67]	BACKGROUND: The impact of 1-month dual antiplatelet therapy (DAPT) followed by aspirin monotherapy according to clinical presentation has not been elucidated. AIMS: This study aimed to compare the impact of 1-month DAPT followed by aspirin monotherapy after polymer-free drug-coated stent (PF-DCS) implantation (1-month DAPT after PF-DCS) vs 6-12-month DAPT followed by aspirin monotherapy after biodegradable polymer drug-eluting stent (BP-DES) implantation (6-12-month DAPT after BP-DES) according to clinical presentation. METHODS: This is a post hoc analysis of the One-Month DAPT trial. The primary outcome was the composite of major adverse cardiac and cerebrovascular events (MACCE; a composite of cardiac death, non-fatal myocardial infarction, target vessel revascularisation, and stroke) and major bleeding.	RESULTS: Among 1,828 patients with stable coronary artery disease (CAD), 1-month DAPT after PF-DCS resulted in lower rates of the primary outcome than 6-12-month DAPT after BP-DES (3.9% vs 6.5%; hazard ratio [HR] 0.59, 95% confidence interval [CI]: 0.39-0.90; p=0.012). However, among 1,192 patients with acute coronary syndrome (ACS), the rates of the primary outcome were not significantly different between the two therapy groups (5.6% vs 3.6%; HR 1.57, 95% CI: 0.91-2.70; p=0.102) and a significant interaction was observed between therapy and clinical presentation regarding the primary outcome (P(int)=0.005). A significant interaction was observed in MACCE (P(int)=0.016), but not in major bleeding (P(int)=0.276). CONCLUSIONS: In patients undergoing drug-eluting stent implantation for non-complex lesions, the benefits of 1-month DAPT followed by aspirin monotherapy for a composite of ischaemic and bleeding outcomes were found in patients with stable CAD, but not in those with ACS. CLINICALTRIALS: gov: NCT02513810.	*Zunächst nicht bewertet und extrahiert (Abstact verfügbar)*	One-Month DAPT

Han et al. 2023 verlängerte duale Therapie (Kohortenstudie, ACS, nach PCI, ≥ 12 Monate)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Han J. Efficacy and Safety of Prolonged Dual Antiplatelet Therapy after Percutaneous Coronary Intervention in Acute Coronary Syndrome Patients. Glob Heart 2023; 18(1):11. https://www.ncbi.nlm.nih.gov/pubmed/37228657.	**Objective** to investigate the benefits and risks of applying DAPT for different durations after PCI in acute coronary syndromes (ACS) patients in China and to explored prolonged DAPT with ticagrelor in the real-world	n = 3,205 patients - mean age ~ 60 years - male ~ 75% - prior PCI ~ 37% vs. ~ 33 % - prior CABG ~ 3 % vs. ~ 1 % - prior MI ~ 8 % vs. ~ 6 % - prior stroke ~ 8 % vs. ~ 7%	n. a. adjusted by propensity score matching using logistic regression	authors noted that that prolonged DAPT is more common than the 1-year regimen in Chinese ACS patients and that effectiveness and safety of this treatment

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[68]	**Methods**
	- single-center prospective cohort study
	- real-world observation
	- PHARM-ACS Patient Registration Database (NCT04184583)
	- Department of Pharmacy, Beijing Anzhen Hospital
	- ≥18 years old
	- patients with ACS
	- diagnosed with STsegment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), unstable angina
	- after PCI
	- patients discharged between April and Dec 2018
	- follow-up at least 18 months
	- have received DAPT for at least one year
	- received clopidogrel or ticagrelor + aspirin at discharge
	- patients with major adverse cardiovascular and cerebrovascular events (MACCE), target vessel revascularization, stent thrombosis, or major bleeding event were excluded
	- treatment with three or more antiplatelet agents, with anticoagulants or alteration of antiplatelet drugs were excluded
		- hypertension ~ 61 % vs. ~ 60 %
		- hyperlipidemia ~ 37 % vs. ~ 36 %
		- ~ 98 % with statins
		- ~ 30-35 % 1 or 2 or 3 vessel disease, respectively
		- median follow-up 572 (IQR 545, 622) days
		- n = 1,004 (31.33%) patients with DAPT for 1 year
		- n = 2,201 (68.67%) patients with DAPT > 1 year
		- median DAPT time 19 (IQR 18, 20) months
		- n = 1,236 (38.56%) DAPT ticagrelor + ASS
		- n = 1,969 (61.44%) DAPT clopidogrel + ASS
		- DAPT > 1-year group with higher proportion of
		  ○ prior PCI 15.24% vs. 18.90%, P = 0.012
		  ○ prior CABG 0.50% vs. 1.59%, P = 0.010
		  ○ prior MI 5.68% vs. 8.54%, P = 0.005
		  ○ diabetes 28.19% vs. 33.35%, P = 0.004
		
		- n = 2,201 (68.67%) DAPT prolonged one year
		- n = 2,000 patients propensity score-matched
		  ○ mean age ~ 59 years
		  ○ male ~ 76%
		
		results
		- DAPT > 1-year (n = 1000) vs.
		- DAPT = 1-year patients (n = 1000)
		MACCE
		- n = 5 (0.50 %) vs. n = 13 (1.30 %)
		- adjusted HR 0.23 (0.05–1.10), p = 0.065
		All cause death
		- n = 2 (0.20 %) vs. n = 7 (0.70 %)
		- adjusted HR 0.14 (0.02–1.20), p = 0.073
		Cardiac death
		- n = 2 (0.20 %) vs. n = 2 (0.20 %)
		- adjusted HR 0.39 (0.03–4.80), p = 0.465
		MI
		- n = 1 (0.10 %) vs. n = 1 (0.10 %)
		- adjusted HR 1.00 (0.06–16.02), p = 0.999
		Stroke
		- n = 2 (0.20 %) vs. n = 5 (0.50 %)
		- adjusted HR 0.38 (0.07–2.04), p = 0.262
			panel of experts made a judgment of clinical endpoints
			
			prasugrel is not a listed medication in China → DAPT consists of clopidogrel or ticagrelor + ASS
			
			follow-up every six months (trained staff), follow-up includes telephone, WeChat, clinical visits
			
			single-center study (limited generalization)
			
			observational study
			
			choice of DAPT determinded by physician
			
			probably patients with low bleeding risk (toleration of 12 months DAPT)
				pattern require urgent verification

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	Intervention DAPT 1-year **Comperator** DAPT >1-year DAPT = clopidogrel or ticagrelor + ASS **Outcome** primary - major adverse cardiovascular and cerebrovascular events (MACCE), defined as a composite of death, myocardial infarction, and stroke occurring from 12 months after discharge - significant bleeding event (BARC ≥ 2) secondary - all-cause death, - cardiogenic death, - myocardial infarction (MI), - stroke, - target vessel revascularization, - stent thrombosis	Revascularization - n = 32 (3.20 %) vs. n = 10 (1.00 %) - HR 3.36 (1.64–6.87), p = 0.001 Stent thrombosis - n = 7 (0.69 %) vs. n = 4 (0.40 %) - HR 1.88 (0.54–6.51), p = 0.317 Bleeding BARC ≥ 2 - n = 16 (1.60 %) vs. n = 24 (2.40 %) - adjusted HR 0.63 (0.32–1.24), p = 0.179 authors interpreted survival analysis of the Kaplan-Meier curve with differences in the cumulative incidence of MACCE (log-rank P = 0.062, power = 0.71), significant bleeding events (log-rank P = 0.25), and revascularization (log-rank P < 0.001) subgroup analysis of MACCE risk data after PSM showed no significant difference in treatment effect between DAPT = 1-year and DAPT > 1-year, even in patients using different P2Y12 receptor inhibitors (P-value for interaction 0.468) (see Table 3)		

Zeymer et al. 2023 Status der antithrombotischen Therapie (Kohorte, AF, PCI, Deutschland, u. a. Therapiedauer)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Zeymer U. Current status of antithrombotic therapy and in-hospital outcomes in patients with atrial fibril-	**Objective** a prospective registry study including consecutive patients with AF undergoing PCI to determine the current	n = 1636 patients in 51 german hospitals (enrolled between 2018 and 2020) - mean age 75.5 years - age ≥ 65 years n = 1437 (87.8%)	n. a. limitations observational design (registry)	

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lation undergoing percutaneous coronary intervention in Germany. Herz 2023; 48(2):134–40. https://www.ncbi.nlm.nih.gov/pubmed/35243515. [69]	clinical practice, planned duration of combination therapies after discharge, and in-hospital events
	
	Methods
	- "Rivaroxaban in Patients with Atrial FibrillationUndergoingPCI" (RIVA-PCI) registry
	- clinicaltrials.gov NCT03315650
	- prospective, noninterventional, multicenter observational study
	- age ≥18 years
	- patients with nonvalvular AF (known or newly)
	- undergoing PCI during index hospital stay
	- follow-up until 14 months after discharge
	- treatment according to current guidelines
	- inclusion in the registry is completely independent of the medical treatment
	- patients at any RCT influencing the antithrombotic therapy were excluded
	
	Intervention
	Rivaroxaban
	
	Outcome
	- current use of antithrombotic therapies (before PCI and at discharge)
	- adherence
		- age ≥ 75 years n = 1027 (62.8%)
		- women n = 484 (29.6%)
		- prior myocardial infarction n = 395 (24.1%)
		- prior stroke n = 161 (9.8%)
		- heart failure n = 714 (43.6%)
		- hypertension n = 1492 (91.2%)
		- hyperlipidemia n = 1006 (61.5%)
		- indications for PCI:
		  ○ elective n = 860 (52.6%)
		  ○ unstable angina n = 289 (17.7%)
		  ○ non-ST-elevation myocardial infarction (NSTEMI) n = 353 (21.6%)
		  ○ ST-elevation myocardial infarction (STEMI) n = 134 cases (8.2%)
		
		- bleeding events before PCI:
		  ○ n = 37 (2.3%) cases
		- median CHA2DS2-VASc: 5 (range 1-9)
		- median HAS-BLED: 2 (range 0-6)
		
		- chronic antithrombotic treatment before PCI:
		  ○ n = 209 patients (12.8%) none
		  ○ n = 214 (13.1%) antiplatelet therapy only
		  ○ n = 279 (17.1%) VKA
		  ○ n = 934 (57.1%) NOAC
		    ▪ apixaban 372 (22.7%)
		    ▪ edoxaban 124 (7.6%)
		    ▪ rivaroxaban 386 (23.6%)
		    ▪ dabigatran 60 (3.7%)
		- intravenous anticoagulation:
		  ○ unfractionated heparin n = 1372 (83.9%)
		  ○ low-molecular-weight heparin n = 160 (9.8%)
		- drug-eluting stents n = 1615=98.7%)
		  ○ n = 1107 (67.7%) one stent
		  ○ n = 293 (17.9%) two stents
		  ○ n = 236 (14.4%) three or more stents
			possible selection bias	

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	- ischemic, embolic, and bleeding events
	
	(definitions (stroke, ischemic stroke, hemorrhagic stroke, myocardial infarction etc.) see within the publication)
		in hospital:
		- median length of stay after PCI 2 days (range 1-5)
		  o 6 months OAC and clopidogrel (most common)
		  o triple or dual therapy for 12 months more often for ACS compared to elective PCI:
		    ▪ TT 19.8% vs. 9.1% p< 0.01
		    ▪ DT 40.1% vs. 23.6% p< 0.001
		- death n = 12 (0.7%)
		- myocardial infarction n = 4 (0.2%)
		- stroke n = 4 (0.2%)
		- bleeding n = 46 (2.8%)
		- recommended duration of combination therapie
		  o 1 to 12 months
		
		at discharge:
		- n = 1079 (66.0%) dual: OAC and P2Y12 inhibitor
		- n = 5 (0.3%) dual: OAC and ASS
		- n = 425 (26.0%) triple therapy
		- n = 90 (5.5%) dual antiplatelet therapy
		- n = 37 (2.3%) monotherapy
		  o 14 antiplatelet and 23 OAC
		- n = 700 (42.8%) rivaroxaban
		- 27.5% apixaban
		- 11.5% VKA
		- 6.4% edoxaban
		- 5.5% dabigatran
		
		- doses used for the NOACs:
		- apixaban 2× 5mg (43.2%); 2× 2.5mg (48.6%); other (8.2%)
		- dabigatran 2× 150mg (22.2%); 2× 110mg (75.6%); other (5.9%)
		- edoxaban 60mg (48.2%); 30mg (49.1%); other (2.7%)
		- rivaroxaban 20mg (5.3%); 15mg (86.0%); 10mg, (2.9%); other (5.9%)
		- Clopidogrel 75mg (n= 1557, 95.2%)		

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		- ASS 100mg (n= 521, 31.8%)
		 - ticagrelor (n= 39, 2.4%)
		 - prasugrel (n= 15, 0.9%)
		
		 - oral anticoagulants in triple therapy (n= 425)
		     o rivaroxaban n = 195,
		     o apixaban n = 110,
		     o VKA n = 65,
		     o dabigatran n = 31,
		     o edoxaban n = 24
		
		 - concomitant medication with a proton pump inhibitor n = 760 (46.5%)
		
		 associations
		 ACS vs. elective PCI (n = 860 vs. n = 776)
		 - DAPT only: 7.9% vs. 3.4%, p< 0.001
		 - triple therapy: 30.4% vs. 22.0%, p< 0.001
		 - dual therapy: 59.3% vs. 72.6%, p< 0.001		

12.5.4 Zusatzinformation Hintergrundtext (E 7-5; Wirksamkeit und Sicherheit; weitere)

A21-41 (IQWIG) 2023 Clopidogrel, Prasugrel oder Ticagrelor + ASS (Rapid Report; ACS)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

A21-41 Clopidogrel, Prasugrel und Ticagrelor zur Prävention atherothrombotischer Ereignisse bei akutem Koronarsyndrom (22.02.2023) – Rapid Report, https://www.iqwig.de/download/a21-41_clopidogrel-prasugrel-und-ticagrelor-beim-akuten-koronarsyndrom_rapid-report_v1-0.pdf [70]	**Fragestellung**
	 vergleichende Nutzenbewertung von Clopidogrel, Prasugrel und Ticagrelor, jeweils in Kombination mit Acetylsalicylsäure (ASS) im Anwendungsgebiet Prasugrel-haltiger Arzneimittel, also zur Prävention atherothrombotischer Ereignisse bei erwachsenen Patientinnen und Patienten mit akutem Koronarsyndrom (ACS) mit primärer oder verzö-
		Hinweis: der Bericht bezieht sich auf eine vergleichende Nutzenbewertung; die Bewertung des Nutzens und Schadens von Clopidogrel, Prasugrel oder Ticagrelor (jeweils + ASS) wurde in anderen Berichten bereits vorgenommen:
		 - Patient*innen mit NSTE-ACS, akutes Koronarsyndrom ohne ST-Streckenhebung (Absitussberichte 2009, 2011):
		    o insgesamt ein Beleg für einen Nutzen von Clopidogrel + ASS gegenüber einer ASS-Monotherapie
		    o Behandlungszeitraum bis zu 12 Monaten
			AMSTAR-II high	eine potentielle NMA konnte nicht durchgeführt werden (Grund: fehlende Daten für die Analyse spezifischer Vergleiche)
				
				 potentielle Netzwerke vgl. S. 11 im Bericht:
				 A: STEMI + PCI
				 - Clopidogrel + ASS (Brückenkomperator)

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	gerter perkutaner Koronarintervention (PCI) hinsichtlich patientenrelevanter Endpunkte **Methodik** - Zielpopulation: Patient*innen mit ACS (d. h. instabiler Angina Pectoris, NSTEMI (Nicht-ST-Streckenhebungsmyokardinfarkt) oder STEMI (ST-Streckenhebungsmyokardinfarkt)) - mit primärer oder verzögerter PCI - gültiger Zulassungsstatus in Deutschland - getrennte Betrachtung von Patientinnen und Patienten mit STEMI + PCI und NSTEMI / IA + PCI - RCT - mind. 3 Monate Studiendauer - systeamtische Übersichtsarbeiten, HTA Berichte (letzte Suche am 18.10.2021) **Intervention** Clopidogrel, Prasugrel und Ticagrelor, jeweils in Kombination mit ASS **Kontrolle** Vergleich untereinander **Endpunkte** - Mortalität - Gesamtmortalität - Morbidität	○ basierend u. a. auf einem Vorteil bei der Myokardinfarktrate ○ demgegenüber steht ein Nachteil für Clopidogrel + ASS aufgrund erhöhter Blutungskomplikationen ○ Vergleich von Prasugrel + ASS gegenüber Clopidogrel + ASS zeigte sich für Patient*innen mit NSTE-ACS ein Hinweis auf einen Zusatznutzen u. a. bei nicht tödlichen Schlaganfällen (nur bei Patient*innen ohne Gefäßvorerkrankungen) und nicht tödlichen Myokardinfarkten ○ demgegenüber steht ein Hinweis auf einen höheren Schaden von Prasugrel + ASS aufgrund häufiger auftretender schwerwiegender Blutungen sowie ein Anhaltspunkt für einen höheren Schaden aufgrund häufiger auftretender Neoplasien ○ Vergleich von Ticagrelor mit Clopidogrel, jeweils + ASS, zeigte sich für Patient*innen mit NSTE-ACS insgesamt ein Beleg für einen beträchtlichen Zusatznutzen von Ticagrelor + ASS im Vergleich zu Clopidogrel + ASS ○ dieser basierte auf Vorteilen hinsichtlich Gesamtmortalität und kardiovaskulärer Mortalität sowie Anzahl an Myokardinfarkten ○ es zeigte sich kein höherer oder geringerer Schaden - Patient*innen mit STEMI nach primärer PCI (Abslussberichte 2009, 2011): ○ im Rahmen aller 3 Bewertungen jeweils keine Studien identifiziert, in denen die Wirkstoffkombination (Clopidogrel, Prasugrel oder Ticagrelor, jeweils +		- Prasugrel + ASS - Ticagrelor + ASS Basis: TRITON-TIMI 38 H7T-MC-TACE PLATO PHILO TICAKOREA HEALING AMI Tang 2016 Wu 2018 ISAR-REACT 5 B: NSTEMI / IA + PCI) - Clopidogrel + ASS - Prasugrel + ASS - Ticagrelor + ASS Basis: TRITON-TIMI 38 H7T-MC-TACE PLATO PHILO Yang 2020 Qui 2020 TICAKOREA ISAR-REACT 5 (zu berücksichtigen sind hier u. a. die Zulassung der drei Wirkstoffe sowie Ähnlichkeitsannahmen) Kontext zu internationalen Leitlinien: laut Bericht übereinstimmend bei Patient*innen mit ACS

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	o kardiovaskuläre Morbidität o zerebrovaskuläre Morbidität o gefäßbedingte nicht kardiovaskuläre und nicht zerebrovaskuläre Morbidität - gesundheitsbezogene Lebensqualität - Nebenwirkungen o schwerwiegende unerwünschte Ereignisse (SUEs) o Studienabbrüche wegen unerwünschter Ereignisse (UEs) o Blutungen *Hinweis*: - Clopidogrel ist laut Bericht in Kombination mit ASS für Patient*innen mit medikamentös behandeltem ACS (NSTE-ACS / STEMI) sowie NSTE-ACS nach erfolgter PCI zugelassen (Anmerkung: Information aus einer Fachinformation) Clopidogrel + ASS ist nicht für die Behandlung von Patien*tinnen mit STEMI nach primärer PCI zugelassen (Brückenkomperatorbewertung im Netzwerk) - Prasugrel ist in Kombination mit ASS nur für Patientinnen und Patienten mit ACS (NSTE-ACS / STEMI)	ASS) mit einer ASS-Monotherapie verglichen wurde o Clopidogrel + ASS ist nicht für die Behandlung von Patient*innen mit STEMI nach primärer PCI zugelassen o Beim Vergleich von Ticagrelor + ASS gegenüber Prasugrel + ASS zeigte sich im Rahmen eines indirekten Vergleichs über den Brückenkomparator Clopidogrel + ASS für Patient*innen mit STEMI nach primärer PCI kein Anhaltspunkt für einen Zusatznutzen - Insgesamt zeigt sich, dass insbesondere im Anwendungsgebiet von Prasugrel, also beim ACS nach primärer oder verzögerter PCI, keine Aussagen darüber getroffen werden können, welcher P2Y12-Inhibitor (in Kombination mit ASS) primär zur Behandlung dieser Patient*innen eingesetzt werden sollte - die vorliegende Bewertung beschäftigt sich daher mit der vergleichenden Nutzenbewertung von Clopidogrel, Prasugrel und Ticagrelor im Anwendungsgebiet von Prasugrel n = 0 SR n = 11 relevante Studien identifiziert (gesamt) (Studiencharakteristika der eingeschlossenen Studien sind in Abschnitt A3.2 dargestellt, ab S. 69 im Bericht) - Vergleiche (Wirkstoffe, Fragestellungen) - Prasugrel + ASS vs. Ticagrelor + ASS: o n = 1 Studie (ISAR-REACT 5 [21]) mit Teilpopulationen zu STEMI + PCI und NSTEMI / IA + PCI - Prasugrel + ASS vs. Clopidogrel + ASS: o n = 2 Studien (TRITON-TIMI 38 [22] und H7T-MC-TACE [23]) mit Teilpopulationen zu STEMI + PCI und NSTEMI / IA + PCI		nach PCI bis zu 12 Monate duale antithrombozytäre Therapie (DAPT aus $P2Y_{12}$-Inhibitor + ASS) Nutzen und Schaden von Clopidogrel, Prasugrel und Ticagrelor (je + ASS) bereits in mehreren Bewertungen vorgenommen Studiendauer: das Risiko für ein Rezidivereignis nach ACS ist im 1. Jahr sehr hoch (9 bis 10 %), wobei die meisten Rezidivereignisse in den ersten 3 Monaten nach ACS auftreten [DEGAM, S2e Leitlinie]. (daher Studien mit Mindestdauer von 3 Monaten eingeschlossen)

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	nach erfolgter PCI zugelassen (Anmerkung: Information aus einer Fachinformation)
	
	- wobei die Behandlung mit Prasugrel bei Patient*innen mit transitorischer ischämischer Attacke (TIA) oder Schlaganfall in der Anamnese kontraindiziert ist
	
	- Ticagrelor ist laut Bericht in Kombination mit ASS für die Behandlung von Patientinnen und Patienten mit ACS (NSTE-ACS / STEMI) zugelassen (Anmerkung: Information aus einer Fachinformation)
		- Ticagrelor + ASS vs. Clopidogrel + ASS:
		  o n = 8 Studien
		      ▪ STEMI + PCI: HEALING-AMI [24], PHILO (Teilpopulation) [25], PLATO (Teilpopulation) [26], Tang 2016 [27], TICAKOREA (Teilpopulation) [28], Wu 2018 [29]
		      ▪ NSTEMI / IA + PCI: PHILO (Teilpopulation), PLATO (Teilpopulation), Qiu 2020 [30], TICAKOREA (Teilpopulation), Yang 2020 [31]
		- kleinere Studien, in denen zusätzliche, bisher nicht berücksichtigte Endpunkte (z. B. gesundheitsbezogene Lebensqualität) berichtet werden, wurden nicht identifiziert
		
		n = 4/11 herstellergesponsort (PHILO, PLATO, TRITON-TIMI 38 und H7T-MC-TACE)
		n = 7/11 Prüfer-initiierte Studien (investor-investigated trials)
		
		n = 1 laufende Studie, n = 3 Studien mit unklarem Status, n = 2 Studien, abgeschlossen, ohne Ergebnisbericht
		
		auf Grund unvollständiger Daten wurden Anfragen zu den 4 herstellergesponsorten Studien sowie für eine prüferinitiierte Studie gestellt:
		- angeforderte Daten zu Teilpopulationen der Studien TRITON-TIMI 38 und H7T-MC-TACE wurden vom Hersteller nicht übermittelt
		daher war laut dem Bericht eine potentielle NMA (Netzwerkmetaanalyse) nicht möglich
		
		das IQWIG schlussfolgerte, dass die Datenbasis für den Vergleich Prasugrel vs. Clopidogrel, jeweils in Kombination mit ASS, sowohl für Patientinnen und Patienten mit STEMI		

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		+ PCI als auch für Patientinnen und Patienten mit NSTEMI / IA + PCI unvollständig ist die beiden Studien TRITON-TIMI 38 und H7T-MC-TACE sind die einzige identifizierte Evidenz für den Vergleich von Prasugrel vs. Clopidogrel, jeweils in Kombination mit ASS die Auswertung der verfügbaren limitierten Daten stellt damit keine valide Entscheidungsgrundlage für den G-BA dar explorative Betrachtung der verfügbaren Ergebnisse: - für keinen der Wirkstoffe Clopidogrel, Prasugrel und Ticagrelor ist ein eindeutiger Vorteil zu erkennen **eingeschlossene Studien** 21. Schupke S, Neumann FJ, Menichelli M et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. N Engl J Med 2019; 381(16): 1524-1534. https://dx.doi.org/10.1056/NEJMoa1908973. (Prasugrel + ASS vs. Ticagrelor + ASS: (ISAR-REACT 5)) 22. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357(20): 2001-2015. https://dx.doi.org/10.1056/NEJMoa0706482. (Prasugrel + ASS vs. Clopidogrel + ASS: (TRITON-TIMI 38)) 23. Eli Lilly. A Comparison of Antiplatelet Therapies in Asian Subjects With Acute Coronary Syndrome [online]. 2011 [Zugriff: 01.06.2022]. URL: https://ClinicalTrials.gov/show/NCT00830960. (Prasugrel + ASS vs. Clopidogrel + ASS: H7T-MC-TACE)) 24. Park Y, Koh JS, Lee JH et al. Effect of Ticagrelor on Left Ventricular Remodeling in Patients With ST-Segment Elevation Myocardial Infarction (HEALING-AMI). JACC Cardiovasc Interv 2020; 13(19): 2220-2234. https://dx.doi.org/10.1016/j.jcin.2020.08.007.		

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		(Ticagrelor + ASS vs. Clopidogrel + ASS: (HEAL-ING-AMI)) 25. Goto S, Huang CH, Park SJ et al. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. Circ J 2015; 79(11): 2452-2460. https://dx.doi.org/10.1253/circj.CJ-15-0112. (Ticagrelor + ASS vs. Clopidogrel + ASS: (PHILO)) 26. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361(11): 1045-1057. https://dx.doi.org/10.1056/NEJMoa0904327. (Ticagrelor + ASS vs. Clopidogrel + ASS: (PLATO)) 27. Tang X, Li R, Jing Q et al. Assessment of Ticagrelor Versus Clopidogrel Treatment in Patients With ST-elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. J Cardiovasc Pharmacol 2016; 68(2): 115-120. https://dx.doi.org/10.1097/fjc.0000000000000390. (Ticagrelor + ASS vs. Clopidogrel + ASS) 28. Park DW, Kwon O, Jang JS et al. Clinically Significant Bleeding With Ticagrelor Versus Clopidogrel in Korean Patients With Acute Coronary Syndromes Intended for Invasive Management: A Randomized Clinical Trial. Circulation 2019; 140(23): 1865-1877. https://dx.doi.org/10.1161/circula-tionaha.119.041766. (Ticagrelor + ASS vs. Clopidogrel + ASS: (TICAKOREA)) 29. Wu HB, Tian HP, Wang XC et al. Clinical efficacy of ti-cagrelor in patients undergoing emergency intervention for acute myocardial infarction and its impact on platelet aggre-gation rate. Am J Transl Res 2018; 10(7): 2175-2183. (Ticagrelor + ASS vs. Clopidogrel + ASS) 30. Qiu C, Hu J, Zhang X et al. Effects of ticagrelor and clopidogrel on serum homocysteine level and neutrophil-to-		

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		lymphocyte ratio in elderly patients with coronary heart disease. Int J Clin Exp Med 2020; 13(10): 7936-7942. (Ticagrelor + ASS vs. Clopidogrel + ASS) 31. Yang B, Zheng C, Yu H et al. Comparison of Efficacy between Clopidogrel and Ticagrelor in Patients with Acute Coronary Syndrome after Interventional Treatment and Their Effects on IL-6. Iran J Public Health 2020; 49(2): 240-248. (Ticagrelor + ASS vs. Clopidogrel + ASS)		

Sachdeva et al. 2023 P2Y12 Hemmer (Datenbankenanalyse; ACS; Clopidogrel, Prasugrel, Ticagrelor; u. a. Charakteristika der Betroffenen)

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Sachdeva A. P2Y12 Inhibitors in Acute Coronary Syndromes: A Real-World, Community-Based Comparison of Ischemic and Bleeding Outcomes. J Interv Cardiol 2023; 2023:1147352. https://www.ncbi.nlm.nih.gov/pubmed/37251366. [71]	**Objective**
	to determine the comparative effcacy and safety of the novel P2Y12 inhibitors versus clopidogrel in a large integrated healthcare delivery system, among those presenting with ACS undergoing percutaneous coronary intervention (PCI)
	
	Methods
	- Kaiser Permanente Northern California (KPNC)
	- 21 medical centers, including >250 ambulatory care facilities, pharmacies, and laboratories, providing comprehensive inpatient, emergency department and outpatient care, with nearly all care captured through its electronic health record (EHR) system
	- patients underwent PCI for ACS
	- regional cardiac catheterization laboratories of KPNC between
		n = 15,479 patients
		- mean age 66.3 years (SD ± 12.0)
		- 27.8% female
		- n = 14408 (93%) clopidogrel
		- n = 570 (3,6%) ticagrelor
		- n = 501 (3,2%) prasugrel
		- clopidogrel group (see Table 1):
		  o was older (66.5 vs. 61.3 (ticagrelor) vs. 58.1 (prasugrel) years),
		  o had a higher proportion of female patients (28.0% vs. 22.9% vs. 19.4%),
		  o was more likely to have a significant cardiovascular history such as prior CABG, cerebrovascular disease, and heart failure,
		  o had more comorbidities such as chronic kidney disease (25.2% vs. 15.1% vs. 14.8%) and hypertension (75.2% vs. 63.0% vs. 64.1%)
		  o (all p < 0.05)
		  o had lower haemoglobin and platelet values, (p < 0.001)
			n. a.
			
			propensity score (PS) matching (hypothesis of prognostic factors), minimal 1:1 match and maximal 1:5 match
			
			during the preparation of the manuscript, it was realized that hypertension was inadvertently omitted from the statistical models (both multivariate and propensity matching) for the abstract (important risk factor that should adjusted for)
			➔ model was adapted (discordance from protocol)
			
			limitations
			- observational study
			- unmeasured confounding could not be excluded
			- large sample size for clopidogrel compared with
				baseline demographic, laboratory data, procedural data, and medication use after index PCI were extracted, comorbidities (ICD-9 and 10),
				
				PRECISE DAPTscore, a validated score for predicting bleeding risk after stent implantation, was calculated for each patient (F. Costa, et al., "PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-

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	January 1st, 2012, and December 31st, 2018
	- ticagrelor was FDA-approved in 2011
	- exclusion criteria were described in detail
	- index event was assigned as the first qualified hospitalized ACS event during the study period
	
	Intervention
	- P2Y12 antagonist within 30-days post index PCI discharge
	- ticagrelor or prasugrel was compared to clopidogrel
	
	Comperator
	- clopidogrel as reference group
	
	Outcomes
	primary
	allcause mortality, hospitalized myocardial infarction, hospitalized stroke, and hospitalized bleeding events (within the first year after index ACS)
	
	note: adherence (MRA > 80%), persistence (gap between refills < 15 days), and switching (more than one P2Y$_{12}$) of P2Y$_{12}$ inhibitors were assessed
		- larger proportion of patients with prasugrel (40.7%) or ticagrelor (49.8%) had STelevation myocardial infarction (STEMI) as their PCI indication vs. clopidogrel (20%)
		 o higher proportion of these patients were classified as emergency cases and having cardiogenic shock
		- Risk score (Precise DAPT score)
		 o clopidogrel 27.7 ± 19.3
		 o ticagrelor 18.4 ± 13.6, p <0.001
		 o prasugrel 18.7 ± 16.1, p <0.001
		- Medication use post PCI
		 o ACE inhibitors
		  ▪ clopidogrel n = 8872 (61.6)
		  ▪ ticagrelor n = 406 (71.5), p <0.001
		  ▪ prasugrel n = 351 (70.1), p <0.001
		 o ARBs
		  ▪ clopidogrel n = 3680 (25.5)
		  ▪ ticagrelor n = 139 (24.5), p = 0.57
		  ▪ prasugrel n = 101 (20.2), p = 0.01
		 o Oral anticoagulation
		  ▪ clopidogrel n = 1541 (10.7)
		  ▪ ticagrelor n = 22 (3.9), p <0.001
		  ▪ prasugrel n = 30 (6.0), p <0.001
		 o Beta blockers
		  ▪ clopidogrel n = 13532 (93.9)
		  ▪ ticagrelor n = 542 (95.4), p = 0.14
		  ▪ prasugrel n = 477 (95.2), p = 0.24
		 o Statins
		  ▪ clopidogrel n = 13983 (97.1)
		  ▪ ticagrelor n = 557 (98.1), p = 0.16
		  ▪ prasugrel n = 490 (97.8), p = 0.33
		- clopidogrel use dropped over time from 94.7% of total dispensed in 2012 to 88.2% in 2018
		- ticagrelor use increased from 0% to 10.2%
		- and prasugrel use decreased from 5.3% to 1.5%
		- (p < 0.001)
		
		after propensity score matching
			- ticagrelor and prasugrel (statistical power)
			- ASS use was not available
				DAPT) score: a pooled analysis of individualpatient datasets from clinical trials," Lancet, vol. 389, pp. 25–34, 2017)
				
				authors found after propensity score matching (adjustment) in patients undergoing PCI for ACS, the use of ticagrelor vs. clopidogrel was associated with a lower risk of all-cause mortality, but similar rates for other outcomes; no difference between prasugrel and clopidogrel
				
				switch was high to clopidogrel, probably due to higher cost
				
				higher proportion of patients on clopidogrel were persistent to treatment (implications for treatment effect and prediction of stent thrombosis)

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		- n = 1 704 clopidogrel vs. n = 568 ticagrelor - n = 1 503 clopidogrel vs. n = 501 prasugrel **Outcomes** at 1 year follow-up (evaluation using log-rank test with comparison group of clopidogrel) Mortality - clopidogrel n = 622 (4.3%) - ticagrelor n = 12 (2.1%), p=0.01 - prasugrel n = 18 (3.6%), p=0.44 Myocardial infarction - clopidogrel n = 817 (5.7%) - ticagrelor n = 31 (5.5%), p=0.80 - prasugrel n = 22 (4.4), p=0.23 Stroke - clopidogrel n = 399 (2.8%) - ticagrelor n = 12 (2.1%), p=0.33 - prasugrel n = 7 (1.4%), p=0.07 Bleeding events - clopidogrel n = 519 (3.6%) - ticagrelor n = 17 (3.0%), p=0.43 - prasugrel n = 14 (2.8%), p=0.33 at 1 year follow-up (event rates in propensity score matched population) Mortality - clopidogrel n = 47 (2.8%) - ticagrelor n = 12 (2.1%), p=0.41 - clopidogrel n = 37 (2.5%) - prasugrel n = 18 (3.6%), p=0.18 MI - clopidogrel n = 75 (4.4%) - ticagrelor n = 31 (5.5%), p=0.31 - clopidogrel n = 42 (2.8%) - prasugrel n = 22 (4.4%), p=0.08		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Stroke - clopidogrel n = 22 (1.3%) - ticagrelor n = 12 (2.1%), p=0.16 - clopidogrel n = 22 (1.5%) - prasugrel n = 7 (1.4%), p=0.93 Bleeding events - clopidogrel n = 33 (1.9%) - ticagrelor n = 17 (3.0%), p=0.14 - clopidogrel n = 33 (2.2%) - prasugrel n = 14 (2.8%), p=0.44 Hazard Ratio (HR) 95% confidence interval (CI) Mortality Ticagrelor vs clopidogrel Unadjusted HR 0.49 (0.27–0.86) Multivariable adjusted HR 0.67 (0.38–1.19) Propensity adjusted HR 0.43 (0.20–0.92) Prasugrel vs clopidogrel Unadjusted HR 0.83 (0.52–1.33) Multivariable adjusted HR 1.54 (0.96–2.48) Propensity adjusted HR 1.42 (0.76–2.68) Myocardial infarction Ticagrelor vs clopidogrel Unadjusted HR 0.96 (0.67–1.37) Multivariable adjusted HR 1.26 (0.87–1.81) Propensity adjusted HR 1.07 (0.68–1.68) Prasugrel vs clopidogrel Unadjusted HR 0.77 (0.51–1.18) Multivariable adjusted HR 1.02 (0.67–1.57) Propensity adjusted HR 1.38 (0.81–2.34) Stroke		

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		Ticagrelor vs clopidogrel
		Unadjusted HR 0.75 (0.43–1.34)
		Multivariable adjusted HR 1.19 (0.67–2.12)
		Propensity adjusted HR 1.52 (0.72–3.24)
		
		Prasugrel vs clopidogrel
		Unadjusted HR 0.50 (0.24–1.06)
		Multivariable adjusted HR 0.94 (0.44–2.0)
		Propensity adjusted HR 0.94 (0.38–2.34)
		
		Bleeding events
		Ticagrelor vs clopidogrel
		Unadjusted HR 0.82 (0.51–1.34)
		Multivariable adjusted HR 1.38 (0.85–2.25)
		Propensity adjusted HR 1.77 (0.94–3.31)
		
		Prasugrel vs clopidogrel
		Unadjusted HR 0.77 (0.45–1.31)
		Multivariable adjusted HR 1.30 (0.76–2.23)
		Propensity adjusted HR 1.45 (0.75–2.80)
		
		adherence to P2Y12 inhibitor therapy
		- mean PDC
		   o clopidogrel 89.3 (SD 22.3), n = 14 408
		   o ticagrelor 89.4 (SD 21.0), n = 570, p=0.06
		   o prasugrel 88.1 (SD 22.1), n = 501, p=0.26
		- PDC > 80 %
		   o clopidogrel n = 11 914 (82,7%)
		   o ticagrelor n = 462 (81,3%), p=0.40
		   o prasugrel n = 395 (78.8%), p=0.03
		- switch
		   o clopidogrel n = 289 (2.0%)
		   o ticagrelor n = 109 (19.2%), p>0.001
		   o prasugrel n = 64 (12.8%), p>0.001
		- persistence
		   o clopidogrel n = 10671 (74.1%)		

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		o ticagrelor n = 397 (69.9%), p=0.03 o prasugrel n = 339 (67.7%), p=0.001		

Squizzato et al. 2017 Clopidogrel + ASS vs. ASS (SR)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Squizzato A. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular events. Cochrane Database Syst Rev 2017; 12(12):CD005158. https://www.ncbi.nlm.nih.gov/pubmed/29240976. [72]	**Objectives** to review the benefit and harm of adding clopidogrel to aspirin therapy for preventing cardiovascular events in people who have coronary disease, ischaemic cerebrovascular disease, peripheral arterial disease, or were at high risk of atherothrombotic disease, but did not have a coronary stent **Methods** - updated the searches of CENTRAL (2017, Issue 6), MEDLINE (Ovid, 1946 to 4 July 2017) and Embase (Ovid, 1947 to 3 July 2017) on 4 July 2017 - also searched ClinicalTrials.gov and the WHO ICTRP portal, handsearched reference lists - RCT comparing over 30 days use of ASS + clopidogrel or ASS alone - people with coronary disease, ischaemic cerebrovascular disease, peripheral arterial disease, or at high risk of atherothrombotic disease	n = 15 trials (n = 33,970 patients), reported in 30 references published between 2001 and 2017 (n = 13 studies in addition to n = 2 studies in the previous version) - daily dose of clopidogrel was 75 mg, except for one study at 100 mg - ASS daily doses varied from 70 mg to 325 mg - minimum of six weeks to a maximum of 3.4 years (mean; range 0 to 8.2 years) **Outcomes** ASS + clopidogrel vs. ASS (placebo) cardiovascular mortality - RR 0.98, 95% CI 0.88 to 1.10; participants = 31,903; studies = 7; moderate quality evidence all-cause mortality - RR 1.05, 95% CI 0.87 to 1.25; participants = 32,908; studies = 9; low quality evidence fatal and non-fatal myocardial infarction - RR 0.78, 95% CI 0.69 to 0.90; participants = 16,175; studies = 6; moderate quality evidence There was a reduction in the risk fatal and non-fatal ischaemic stroke - RR 0.73, 95% CI 0.59 to 0.91; participants = 4006; studies = 5; moderate quality evidence risk of major bleeding - RR 1.44, 95% CI 1.25 to 1.64; participants = 33,300; studies = 10; moderate quality evidence minor bleeding - RR 2.03, 95% CI 1.75 to 2.36; participants = 14,731; studies = 8; moderate quality evidence	AMSTAR-II high risk of bias was low in n = 4 trials (for all key domains, even if some of them were funded by the pharmaceutical industry other studies had high risk of bias within the domain of blinding or other bias or unclear classifications in some other domains suggestion of publication bias was reported (funnel plot) according to the GRADE system, quality of evidence was generally moderate for all outcomes except all-cause mortality (low quality) and adverse events (very low quality evidence)	authors noted that available evidence demonstrates that the use of clopidogrel plus ASS in people at high risk of cardiovascular disease and people with established cardiovascular disease without a coronary stent is associated with a reduction in the risk of myocardial infarction and ischaemic stroke, and an increased risk of major and minor bleeding compared with ASS (quality of evidence was moderate for all outcomes except all-cause mortality (low quality evidence) and adverse events (very low quality evidence)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- excluded people who had a coronary stent - studies on the optimal duration of clopidogrel plus aspirin therapy in people with coronary drug-eluting stent (DES) or non-DES (or both) were excluded **Quality assessment** Risk-of-bias, GRADE **Intervention** ASS + clopidogrel **Comperator** ASS (+ placebo) no other platelet aggregation inhibitors as co-intervention were accepted **Outcomes** primary - cardiovascular mortality, - all-cause mortality, - fatal and non-fatal myocardial infarction, - fatal and non-fatal ischaemic stroke, - adverse events secondary - major and minor bleeding post hoc - repeated revascularization - saphenous vein graF (SVG) patency - amputation	insufficient data on adverse events for meta-analyses - If reported, gastrointestinal disorders and infections were the most commonly reported (17% in the clopidogrel group and 9% in the placebo group) - minor adverse events: immune hypersensitivity, seasonal allergy, haematuria and renal failure for combination overall n = 13 myocardial infarctions and n = 23 ischaemic strokes be prevented for every 1000 patients treated with the combination in a median follow-up period of 12 months n = 9 major bleeds and n = 33 minor bleeds would be caused during a median followup period of 10.5 and 6 months repeated revascularization in the subgroup of participants undergoing coronary artery bypass grafting - RR 0.50, 95% CI 0.09 to 2.72; participants = 413; studies = 2 saphenous vein graft patency after a coronary artery bypass graft surgery - RR 1.06, 95% CI 1.01 to 1.12; participants = 662; studies = 3 amputation in the subgroup of participants undergoing a revascularization procedure for peripheral arterial disease - RR 0.68, 95% CI 0.44 to 1.05; studies = 2; participants = 931		

12.5.5 Empfehlung 7-6 duale Therapie nach invasiven Verfahren (orale Antikoagulation und Thrombozytenaggregation; in Bezug auf die Therapiedauer)

Montalto et al. 2023 Dauer einer dualen Therapie (SR/MA, nach PCI, Indikation zur Antikoagulation)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Montalto C. Dual antiplatelet therapy duration after percutaneous coronary intervention in patients with indica-tion to oral anticoagulant therapy. A systematic review and meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother 2023; 9(3):220–30. https://www.ncbi.nlm.nih.gov/pubmed/36427063. [73]	**Objective**
	 to evaluate the impact of DAPT duration after PCI irrespective of OAC type in patients with indication for such treatment
	
	 Methods
	 - SR, MA, NMA
	 - (search between Jan 2000 and Sep 2021)
	 - databases and reference lists
	 - PROSPERO CRD284001
	 - RCT
	 - lifelong oral anticoagulant therapy (VKA, DOAC), indication of OAC
	 - concomitant DAPT:
	    o PCI or ACS (with/without PCI) – DAPT (abbreviated or prolonged)
	 - comparison of abbreviated (< 3 months) vs. prolonged (≥ 3 months) strategy
	 - treatment with short DAPT and DOAC vs. longer DAPT and VKA were excluded (type of OAC influenced the incidence of bleeding): aim to compare the influence of duaration
		n = 5 RCT (n = 7 665 patients) (WOEST, ISAR-TRIPLE, AUGUSTS, SAFE-A, MASTER-DAPT)
		 - n = 3 843 abbreviated DAPT vs. n = 3 822 prolonged DAPT)
		 - undergoing PCI or suffering ACS
		 - concomitant indication of long-term OAC
		 - mean age 72 years
		 - main indication to OAC (AF): 92,2%
		 - ACS 51,1%
		 - DOAC 46,7%
		    o apixaban 81,5%
		 - DAPT
		    o clopidogrel 79,2%
		 - mean DAPT duration
		    o prolonged 6 months (range 3-12 months)
		    o abbreviated 3 months (range peri-procedural/in-hospital – 6 weeks)
		
		 results
		 abbreviated DAPT vs. prolonged DAPT
		 major bleeding
		 - 3.4% vs. 5.1%
		 - RR 0.70 (0.52; 0.95), p = 0.01, n = 5 studies
		 - NNT 58.8
		 major or clinically relevant bleeding (MCRB)
		 - 10.2% vs. 16.3%
		 - RR 0.69 (0.52; 0.91), p = 0.01, n = 5 studies
		 - NNT 16.4
		 MACE (major cardiovascular events)
		 - 7.1 vs. 7.0%
		 - RR 0.96 (0.70; 1.33), p = 0.6, n = 5 studies
			AMSTAR-II low
			
			 (keine Liste der ausgeschlossenen Volltexte mit Ausschlussgrund vorhanden)
			
			 supplemental material (Word-Dokument)
			 - geringes Risk-of-Bias für die eingeschlossenen Studien
			
			 sensitivity analyses and soubgroup analyses were performed
			
			 network meta-analyses was planned (to compare peri-procedural vs. short vs. prolonged DAPT duration)
			
			 heterogeneity in clinical endpoint definitions between studies included
				graphical abstract available
				
				 authors noted that OAC is mostly maintained long-term or lifelong whereas DAPT duration is a key modifiable factor to balance ischemic and bleeding risk
				
				 authors main findings:
				 - abbreviated DAPT (up to 6 weeks) in patients undergoing PCI or with ACS and comcomitant OAC indication is associated with reduction of major bleeding and of major or clinically relevant bleeding vs. prolonged DAPT
				 - abbreviated DAPT was

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- studies with DT with DOAC vs. TT with VKA were excluded **Intervention/Comparator** - DAPT on top of OAC - two-arm analysis (short vs. standard DAPT) o abbreviated (≤ 6 weeks) o prolonged (≥ 3 months) - three-arm analysis (periprocedural vs. short vs. longer DAPT) o periprocedural o short (4-6 weeks) o longer (≥ 3 months) (NMA: impact of peri-procedural DAPT vs. longer treatment) **Quality assessment** Risk-of-Bias (RoB-2), GRADE **Outcomes** primary - occurrence of major bleedings - composite of major or clinically relevant non-major bleedings (MCRB) safety - composite of major adverse cardiovascular events (MACE) secondary - MACE (all-cause deaths)	MACE (major cardiovascular events with cardiovascular mortality instead of all-cause mortality) - RR 0.95 (0.75–1.2); P = 0.7 (supplement) all-cause death - RR 0.89 (0.61; 1.31), n = 5 studies cardiovascular death - RR 0.91 (0.68; 1.2), n = 5 studies myocardial infarction - 3.1 vs. 2.5% - RR 1.15 (0.81–1.60), p = 0.4, n = 5 studies ischaemic stroke - 0.7 vs. 1.2% - RR: 0.64 (0.32–1.26); p = 0.1, n = 5 studies stent thrombosis - 0.7 vs. 0.5% - RR: 1.24 (0.5–3.0); p = 0.6, n = 5 studies results were consistent in the sensitivity and subgroup analysis authors noted for network meta-analysis - peri-procedural DAPT had the highest probability to prevent o major or clinically relevant bleeding (97.1%) vs. 2.54% vs. 0.39% o major bleeding (92.0%) vs. 6.87% vs. 1.12% o MACE (58.4%) vs. 18.4% vs. 23.2% - when compared with both short (4–6 weeks) and longer (≥3 months) DAPT regimens MCRB, periprocedural DAPT vs. prolonged DAPT - OR 0.46 (0.25–0.77); high confidence periprocedural DAPT vs. short DAPT - OR 0.53 (0.22–1.02); moderate confidence		not associated with an excess cardiac ischemic events - DAPT limited to peri-procedural/in-hospital period ranked highest to be the best treatment strategy to reduce bleeding events vs. short and prolonged DAPT

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- MACE (cardiovascular mortality) o individual definitions	major bleedings periprocedural DAPT vs. prolonged DAPT - RR 0.55 (0.29–0.97); high confidence periprocedural DAPT vs. short DAPT - RR 0.58 (0.23–1.26); moderate confidence		

Smits et al. 2022/2021 (RCT, ACS, nach PCI, hohes Blutungsrisiko, MASTER DAPT)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Smits PC. Abbreviated Antiplatelet Therapy After Coronary Stenting in Patients With Myocardial Infarction at High Bleeding Risk. J Am Coll Cardiol 2022; 80(13):1220–37. https://www.ncbi.nlm.nih.gov/pubmed/36137672. [74]	OBJECTIVES: The objective of this study was to investigate the safety and efficacy of an abbreviated APT regimen after coronary stenting in an HBR population presenting with acute or recent myocardial infarction. METHODS: In the MASTER DAPT trial, 4,579 patients at HBR were randomized after 1 month of dual APT (DAPT) to abbreviated (DAPT stopped and 11 months single APT or 5 months in patients with oral anticoagulants) or nonabbreviated APT (DAPT for minimum 3 months) strategies. Randomization was stratified by acute or recent myocardial infarction at index procedure. Coprimary outcomes at 335 days after randomization were net adverse clinical outcomes events (NACE); major adverse cardiac and cerebral events (MACCE); and type 2, 3, or 5 Bleeding Academic Research Consortium bleeding.	RESULTS: NACE and MACCE did not differ with abbreviated vs nonabbreviated APT regimens in patients with an acute or recent myocardial infarction (n = 1,780; HR: 0.83; 95% CI: 0.61-1.12 and HR: 0.86; 95% CI: 0.62-1.19, respectively) or without an acute or recent myocardial infarction (n = 2,799; HR: 1.03; 95% CI: 0.77-1.38 and HR: 1.13; 95% CI: 0.80-1.59; P(interaction) = 0.31 and 0.25, respectively). Bleeding Academic Research Consortium 2, 3, or 5 bleeding was significantly reduced in patients with or without an acute or recent myocardial infarction (HR: 0.65; 95% CI: 0.46-0.91 and HR: 0.71; 95% CI: 0.54-0.92; P(interaction) = 0.72) with abbreviated APT. CONCLUSIONS: A 1-month DAPT strategy in patients with HBR presenting with an acute or recent myocardial infarction results in similar NACE and MACCE rates and reduces bleedings compared with a nonabbreviated DAPT strategy. (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen [MASTER DAPT]; NCT03023020).	*Zunächst nicht bewertet und extrahiert (Abstact verfügbar)*	MASTER-DAPT
Smits PC. Abbreviated Antiplatelet Therapy in Patients at High Bleeding	BACKGROUND: The optimal duration of antiplatelet therapy (APT) in patients at high bleeding risk with or	RESULTS: Net adverse clinical outcomes or major adverse cardiac and cerebral events did not differ with abbreviated versus nonabbreviated APT regimens in patients with OAC		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Risk With or Without Oral Anticoagulant Therapy After Coronary Stenting: An Open-Label, Randomized, Controlled Trial. Circulation 2021; 144(15):1196–211. https://www.ncbi.nlm.nih.gov/pubmed/34455849. [75]	without oral anticoagulation (OAC) after coronary stenting remains unclear. METHODS: In the investigator-initiated, randomize, open-label MASTER DAPT trial (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen), 4579 patients at high bleeding risk were randomized after 1-month dual APT to abbreviated or nonabbreviated APT strategies. Randomization was stratified by concomitant OAC indication. In this subgroup analysis, we report outcomes of populations with or without an OAC indication. In the population with an OAC indication, patients changed immediately to single APT for 5 months (abbreviated regimen) or continued ≥2 months of dual APT and single APT thereafter (nonabbreviated regimen). Patients without an OAC indication changed to single APT for 11 months (abbreviated regimen) or continued ≥5 months of dual APT and single APT thereafter (nonabbreviated regimen). Coprimary outcomes at 335 days after randomization were net adverse clinical outcomes (composite of all-cause death, myocardial infarction, stroke, and Bleeding Academic Research Consortium 3 or 5 bleeding events); major adverse cardiac and cerebral events (all-cause death, myocardial infarction, and stroke); and	indication (n=1666; hazard ratio [HR], 0.83 [95% CI, 0.60-1.15]; and HR, 0.88 [95% CI, 0.60-1.30], respectively) or without OAC indication (n=2913; HR, 1.01 [95% CI, 0.77-1.33]; or HR, 1.06 [95% CI, 0.79-1.44]; P(interaction)=0.35 and 0.45, respectively). Bleeding Academic Research Consortium 2, 3, or 5 bleeding did not significantly differ in patients with OAC indication (HR, 0.83 [95% CI, 0.62-1.12]) but was lower with abbreviated APT in patients without OAC indication (HR, 0.55 [95% CI, 0.41-0.74]; P(interaction)=0.057). The difference in bleeding in patients without OAC indication was driven mainly by a reduction in Bleeding Academic Research Consortium 2 bleedings (HR, 0.48 [95% CI, 0.33-0.69]; P(interaction)=0.021). CONCLUSIONS: Rates of net adverse clinical outcomes and major adverse cardiac and cerebral events did not differ with abbreviated APT in patients with high bleeding risk with or without an OAC indication and resulted in lower bleeding rates in patients without an OAC indication. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03023020.		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	type 2, 3, or 5 Bleeding Academic Research Consortium bleeding.			
Frigoli E. Design and rationale of the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER DAPT) Study. Am Heart J 2019; 209:97–105. https://www.ncbi.nlm.nih.gov/pubmed/30703644. [76]	BACKGROUND: The optimal duration of antiplatelet therapy in high-bleeding risk (HBR) patients with coronary artery disease treated with newer-generation drug-eluting bioresorbable polymer-coated stents remains unclear. DESIGN: MASTER DAPT (clinicaltrial.gov-NCT03023020) is an investigator-initiated, open-label, multicenter, randomized controlled trial comparing an abbreviated versus a standard duration of antiplatelet therapy after bioresorbable polymer-coated Ultimaster (TANSEI) sirolimus-eluting stent implantation in approximately 4,300 HBR patients recruited from ≥100 interventional cardiology centers globally. After a mandatory 30-day dual-antiplatelet therapy (DAPT) run-in phase, patients are randomized to (a) a single antiplatelet regimen until study completion or up to 5 months in patients with clinically indicated oral anticoagulation (experimental 1-month DAPT group) or (b) continue DAPT for at least 5 months in patients without or 2 in patients with concomitant indication to oral anticoagulation, followed by a single antiplatelet regimen (standard antiplatelet regimen). With a final sample size of 4,300 patients, this study is powered to assess the noninferiority of the abbreviated antiplatelet regimen with respect to the net adverse clinical and major adverse cardiac and cerebral events composite end	CONCLUSIONS: The MASTER DAPT study is the first randomized controlled trial aiming at ascertaining the optimal duration of antiplatelet therapy in HBR patients treated with sirolimus-eluting bioresorbable polymer-coated stent implantation.		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	points and if satisfied for the superiority of abbreviated as compared to standard antiplatelet therapy duration in terms of major or clinically relevant nonmajor bleeding. Study end points will be adjudicated by a blinded Clinical Events Committee.			

12.5.6 Zusatzinformation Hintergrundtext (E 7-6; Wirksamkeit und Sicherheit)

Bainey et al. 2020/2018 Rivaroxaban + ASS vs. ASS (RCT, PCI, COMPASS-PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Bainey KR. Rivaroxaban Plus Aspirin Versus Aspirin Alone in Patients With Prior Percutaneous Coronary Intervention (COMPASS-PCI). Circulation 2020; 141(14):1141–51. https://www.ncbi.nlm.nih.gov/pubmed/32178526. [77]	BACKGROUND The COMPASS trial (Cardiovascular Outcomes for People using Anticoagulation Strategies) demonstrated that dual pathway inhibition (DPI) with rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily versus aspirin 100 mg once daily reduced the primary major adverse cardiovascular event (MACE) outcome of cardiovascular death, myocardial infarction, or stroke, as well as, mortality, in patients with chronic coronary syndromes or peripheral arterial disease. Whether this remains true in patients with a history of percutaneous coronary intervention (PCI) is unknown. METHODS In a prespecified subgroup analysis from COMPASS, we examined the outcomes of patients with chronic coronary syndrome with or without a previous PCI treated with DPI versus	RESULTS Of the 27 395 patients in COMPASS, 16 560 patients with a chronic coronary syndrome were randomly assigned to DPI or aspirin, and, of these, 9862 (59.6%) had previous PCI (mean age 68.2±7.8, female 19.4%, diabetes mellitus 35.7%, previous myocardial infarction 74.8%, multivessel PCI 38.0%). Average time from PCI to randomization was 5.4 years (SD, 4.4) and follow-up was 1.98 (SD, 0.72) years. Regardless of previous PCI, DPI versus aspirin produced consistent reductions in MACE (PCI: 4.0% versus 5.5%; hazard ratio [HR], 0.74 [95% CI, 0.61-0.88]; no PCI: 4.4% versus 5.7%; HR, 0.76 [95% CI, 0.61-0.94], P-interaction=0.85) and mortality (PCI: 2.5% versus 3.5%; HR, 0.73 [95% CI, 0.58-0.92]; no PCI: 4.1% versus 5.0%; HR, 0.80 [95% CI, 0.64-1.00], P-interaction=0.59), but increased major bleeding (PCI: 3.3% versus 2.0%; HR, 1.72 [95% CI, 1.34-2.21]; no PCI: 2.9% versus 1.8%; HR, 1.58 [95% CI, 1.15-2.17], P-interaction=0.68). In those with previous PCI, DPI compared with aspirin produced consistent (robust) reductions in MACE irrespective of time since previous PCI (as early as 1 year and as far as 10 years; P-interaction=0.65), irrespective of having a previous myocardial infarction (P-interaction=0.64). CONCLUSIONS	*Zunächst nicht bewertet und extrahiert (Abstact verfügbar)*	COMPASS-PCI

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	aspirin alone. Among patients with a previous PCI, we studied the effects of treatment according to the timing of the previous PCI.	DPI compared with aspirin produced consistent reductions in MACE and mortality but with increased major bleeding with or without previous PCI. Among those with previous PCI 1 year and beyond, the effects on MACE and mortality were consistent irrespective of time since last PCI. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01776424.		
Anand SS. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: An international, randomised, double-blind, placebo-controlled trial. Lancet 2018; 391(10117):219–29. https://www.ncbi.nlm.nih.gov/pubmed/29132880. [78]	BACKGROUND Patients with peripheral artery disease have an increased risk of cardiovascular morbidity and mortality. Antiplatelet agents are widely used to reduce these complications. METHODS This was a multicentre, double-blind, randomised placebo-controlled trial for which patients were recruited at 602 hospitals, clinics, or community practices from 33 countries across six continents. Eligible patients had a history of peripheral artery disease of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease), of the carotid arteries (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or coronary artery disease with an ankle-brachial index of less than 0·90. After a 30-day run-in period, patients were randomly assigned (1:1:1) to receive oral rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or to aspirin once	FINDINGS Between March 12, 2013, and May 10, 2016, we enrolled 7470 patients with peripheral artery disease from 558 centres. The combination of rivaroxaban plus aspirin compared with aspirin alone reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke (126 [5%] of 2492 vs 174 [7%] of 2504; hazard ratio [HR] 0·72, 95% CI 0·57-0·90, p=0·0047), and major adverse limb events including major amputation (32 [1%] vs 60 [2%]; HR 0·54 95% CI 0·35-0·82, p=0·0037). Rivaroxaban 5 mg twice a day compared with aspirin alone did not significantly reduce the composite endpoint (149 [6%] of 2474 vs 174 [7%] of 2504; HR 0·86, 95% CI 0·69-1·08, p=0·19), but reduced major adverse limb events including major amputation (40 [2%] vs 60 [2%]; HR 0·67, 95% CI 0·45-1·00, p=0·05). The median duration of treatment was 21 months. The use of the rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin alone group (77 [3%] of 2492 vs 48 [2%] of 2504; HR 1·61, 95% CI 1·12-2·31, p=0·0089), which was mainly gastrointestinal. Similarly, major bleeding occurred in 79 (3%) of 2474 patients with rivaroxaban 5 mg, and in 48 (2%) of 2504 in the aspirin alone group (HR 1·68, 95% CI 1·17-2·40; p=0·0043). INTERPRETATION Low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events when compared with aspirin alone. Although major bleeding was increased, fatal or critical organ bleeding was not. This combination therapy represents an important advance in the management of patients with peripheral artery disease.		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	a day (100 mg and rivaroxaban placebo twice a day). Randomisation was computer generated. Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation. The primary outcome was cardiovascular death, myocardial infarction or stroke; the primary peripheral artery disease outcome was major adverse limb events including major amputation. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.	Rivaroxaban alone did not significantly reduce major adverse cardiovascular events compared with asprin alone, but reduced major adverse limb events and increased major bleeding.

FUNDING
Bayer AG. | | |
| Connolly SJ. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: An international, randomised, double-blind, placebo-controlled trial. Lancet 2018; 391(10117):205–18. https://www.ncbi.nlm.nih.gov/pubmed/29132879. [79] | BACKGROUND
Coronary artery disease is a major cause of morbidity and mortality worldwide, and is a consequence of acute thrombotic events involving activation of platelets and coagulation proteins. Factor Xa inhibitors and aspirin each reduce thrombotic events but have not yet been tested in combination or against each other in patients with stable coronary artery disease.

METHODS
In this multicentre, double-blind, randomised, placebo-controlled, outpatient trial, patients with stable coronary artery disease or peripheral artery disease were recruited at 602 hospitals, clinics, or community centres in 33 countries. This paper reports on patients with coronary artery disease. Eligible patients with coronary artery disease had to have had | FINDINGS
Between March 12, 2013, and May 10, 2016, 27 395 patients were enrolled to the COMPASS trial, of whom 24 824 patients had stable coronary artery disease from 558 centres. The combination of rivaroxaban plus aspirin reduced the primary outcome more than aspirin alone (347 [4%] of 8313 vs 460 [6%] of 8261; hazard ratio [HR] 0·74, 95% CI 0·65-0·86, p<0·0001). By comparison, treatment with rivaroxaban alone did not significantly improve the primary outcome when compared with treatment with aspirin alone (411 [5%] of 8250 vs 460 [6%] of 8261; HR 0·89, 95% CI 0·78-1·02, p=0·094). Combined rivaroxaban plus aspirin treatment resulted in more major bleeds than treatment with aspirin alone (263 [3%] of 8313 vs 158 [2%] of 8261; HR 1·66, 95% CI 1·37-2·03, p<0·0001), and similarly, more bleeds were seen in the rivaroxaban alone group than in the aspirin alone group (236 [3%] of 8250 vs 158 [2%] of 8261; HR 1·51, 95% CI 1·23-1·84, p<0·0001). The most common site of major bleeding was gastrointestinal, occurring in 130 [2%] patients who received combined rivaroxaban plus aspirin, in 84 [1%] patients who received rivaroxaban alone, and in 61 [1%] patients who received aspirin alone. Rivaroxaban plus aspirin reduced mortality when compared with aspirin alone (262 [3%] of 8313 vs 339 [4%] of 8261; HR 0·77, 95% CI 0·65-0·90, p=0·0012). | | |

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	a myocardial infarction in the past 20 years, multi-vessel coronary artery disease, history of stable or unstable angina, previous multi-vessel percutaneous coronary intervention, or previous multi-vessel coronary artery bypass graft surgery. After a 30-day run in period, patients were randomly assigned (1:1:1) to receive rivaroxaban (2·5 mg orally twice a day) plus aspirin (100 mg once a day), rivaroxaban alone (5 mg orally twice a day), or aspirin alone (100 mg orally once a day). Randomisation was computer generated. Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. The primary outcome of the COMPASS trial was the occurrence of myocardial infarction, stroke, or cardiovascular death. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.	INTERPRETATION In patients with stable coronary artery disease, addition of rivaroxaban to aspirin lowered major vascular events, but increased major bleeding. There was no significant increase in intracranial bleeding or other critical organ bleeding. There was also a significant net benefit in favour of rivaroxaban plus aspirin and deaths were reduced by 23%. Thus, addition of rivaroxaban to aspirin has the potential to substantially reduce morbidity and mortality from coronary artery disease worldwide. FUNDING Bayer AG.		

Greenberg et al. 2019 Rivaroxaban + ASS vs. ASS (RCT, Post hoc Analyse, thromboembolische Ereignisse, HF, CAD, AF, COMMANDER HF)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Greenberg B. Association of Rivaroxaban With Thromboembolic Events in Patients With Heart Failure, Coronary Disease, and Sinus Rhythm: A Post Hoc Analysis of the COMMANDER HF Trial. JAMA Cardiol 2019; 4(6):515–23. https://www.ncbi.nlm.nih.gov/pubmed/31017637. [80]	OBJECTIVE To examine whether low-dose rivaroxaban was associated with reduced thromboembolic events in patients enrolled in the COMMANDER HF trial. DESIGN, SETTING, AND PARTICIPANTS	RESULTS Of 5022 patients, 3872 (77.1%) were men, and the overall mean (SD) age was 66.4 (10.2) years. Over a median (interquartile range) follow-up of 19.6 (11.7-30.8) months, fewer patients assigned to rivaroxaban compared with placebo had a thromboembolic event including sudden/unwitnessed deaths: 328 (13.1%) vs 390 (15.5%) (hazard ratio, 0.83; 95% CI, 0.72-0.96; P = .01). When sudden/unwitnessed deaths were excluded, the results analyzing thromboembolic	*Zunächst nicht bewertet und extrahiert (Abstact verfügbar)*	COMMANDER-HF

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	Post hoc analysis of the COMMANDER HF multicenter, randomized, double-blind, placebo-controlled trial in patients with CAD and worsening HF. The trial randomized 5022 patients postdischarge from a hospital or outpatient clinic after treatment for worsening HF between September 2013 and October 2017. Patients were required to be receiving standard care for HF and CAD and were excluded for a medical condition requiring anticoagulation or a bleeding history. Patients were randomized in a 1:1 ratio. Analysis was conducted from June 2018 and January 2019. INTERVENTION Patients were randomly assigned to receive 2.5 mg of rivaroxaban given orally twice daily or placebo in addition to their standard therapy. MAIN OUTCOMES AND MEASURES For this post hoc analysis, a thromboembolic composite was defined as either (1) myocardial infarction, ischemic stroke, sudden/unwitnessed death, symptomatic pulmonary embolism, or symptomatic deep venous thrombosis or (2) all of the previous components except sudden/unwitnessed deaths because not all of these are caused by thromboembolic events.	events were similar: 153 (6.1%) vs 190 patients (7.6%) with an event (hazard ratio, 0.80; 95% CI, 0.64-0.98; P = .04). CONCLUSIONS AND RELEVANCE In this study, thromboembolic events occurred frequently in patients with HF, CAD, and sinus rhythm. Rivaroxaban may reduce the risk of thromboembolic events in this population, but these events are not the major cause of morbidity and mortality in patients with recent worsening of HF for which rivaroxaban had no effect. While consistent with other studies, these results require confirmation in prospective randomized clinical trials. TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT01877915.		

NICE 2019 Rivaroxaban + ASS vs. ASS (HTA, koronare Herzkrankheit oder periphere arterielle Verschlusskrankheit)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

NICE -ER: Single Technology Appraisal Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [ID1397] Committee Papers. 17. Oktober 2019 https://www.nice.org.uk/guidance/ta607/evidence/committee-papers-pdf-6955673437 [81]	**Objective** main aim was to test the hypothesis that rivaroxaban 2.5mg bd plus aspirin (or rivaroxaban 5mg bd alone) was superior to aspirin in the above population
	
	 Methods
	 - SR of RCT
	 - adults with coronary or peripheral artery disease, excluding people with atrial fibrillation, at high risk of ischaemic events
	
	 Intervention rivaroxaban + ASS
	
	 Comperator in stable CAD
	 - ASS
	 - ASS in combination with ticagrelor 60 mg twice daily
	
	 in PAD
	 - ASS
	 - Clopidogrel
	
	 Outcomes
	 - non-fatal myocardial infarction (STEMI and NSTEMI)
	 - non-fatal stroke
	 - urgent coronary, cerebrovascular or peripheral revascularisation
	 - bleeding events
		rivaroxaban 2 x 2,5 mg / day + ASS vs. ASS n = 1 RCT (COMPASS trial)
		 - n = 9152 vs. n = 9126 patients
		 - CAD and peripheral artery disease subgroup
		    o n = 1656 vs. n = 1641
		 - CAD and heart failure subgroup
		    o n = 1909 vs. 1912
		 - CAD and poor renal function subgroup
		    o n = 1824 vs. n = 1873
		
		 ticagrelor 2 x 60 mg / day + ASS vs. ASS n = 1 RCT (PEGASUS trial) – stable CAD (TA420)
		 - indirect treatment comparison (using the Bucher method) of rivaroxaban + ASS vs. ticagrelor + ASS
		
		 results primary composite of CV death, stroke, or myocardial infarction (COMPASS study) rivaroxaban 2 x 2,5 mg / Tag + ASS vs. ASS
		 - incidence: n = 376 (4.1%) vs. n = 496 (5.4%)
		 - incidence rate (per 100 patient-years (95% confidence interval (CI)):
		    o 2.18 per 100 PY (1.97-2.41) vs.
		    o 2.88 per 100 PY (2.64-3.15)
		 - HR 0.76 (95% CI 0.66; 0.86), p < 0.001
		
		 soubgroups CAD and Peripheral artery disease subgroup
		 - incidence: n = 94 (5.7%) vs. n = 138 (8.4%)
		 - incidence rate:
		    o 3.06 per 100 PY (2.47-3.75) vs.
		    o 4.55 per 100 PY (3.83-5.38)
		 - HR 0.67 (0.52-0.87), p = 0.00262
		
		 CAD and heart failure subgroup
			AMSTAR-II high
			
			 ERG (review group) agrees with the company's assessment of the COMPASS RCT finding it to be a well-conducted study which is likely to be at a low risk of bias
			
			 limitations some data were missing for ticagrelor 2 x 60 mg / day + ASS;
			
			 there are a couple of clinical issues for the comparison of rivaroxaban 2.5mg bd + ASS and ticagrelor 60mg bd + ASS: heterogeneity regarding inclusion criteria (e. g. PEGASUS recruited patients with prior MI, while in the COMPASS trial the proportion of subjects with a history of MI was 62%); definition for major bleeding differs
			
			 the are no key clinical issues in the comparison of rivaroxaban + ASS versus ASS
				authors noted that coronary artery disease (CAD) or coronary heart disease (CHD) are the most common CVD
				
				 few advances in antithrombotic therapy for secondary prevention of CV events; thrombogenic risk is high (not the same for all patients with CAD)
				
				 ischemic risk determined by patients history and extent of narrowing of coronary arteries
				
				 patients with CAD have other risk factors such as PAD, heart failure or poor renal function
				
				 The investigated mechanism of action of rivaroxaban has shown synergistic effects with aspirin in secondary prevention for patients with established cardiovascular disease.
				
				 Rivaroxaban + aspirin in patients with estab-

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- limb ischemia (including limb amputation)
	- mortality
	- adverse effects of treatment
	- health-related quality of life
	
	major bleeding was defined as a composite of:
	- fatal bleeding, and/or
	- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or
	- bleeding into the surgical site requiring re-operation, and/or
	- bleeding leading to hospitalisation (with or without an overnight stay)
	
	(subgroups:
	- People with coronary artery disease who also have poor renal function
	- People with coronary artery disease who also have peripheral arterial disease
	- People who have had a previous myocardial infarction
	- People who have had multiple myocardial infarctions)
	
	authors conducted an economic modelling (ASS vs. ticagrelor 60 mg
		- incidence: n = 105 (5.5%) vs. n = 151 (7.9%)
		- incidence rate:
		   o 3.12 per 100 PY (2.55-3.78) vs.
		   o 4.60 per 100 PY (3.89-5.39)
		- HR 0.68 (0.53-0.87), p = 0.002
		
		CAD and poor renal function subgroup
		- incidence: n = 119 (6.5%) vs. n = 165 (8.8%)
		- incidence rate:
		   o 3.42 per 100 PY (2.84-4.10) vs.
		   o 4.71 per 100 PY (4.02-5.48)
		- HR 0.73 (0.57-0.92), p = 0.007
		
		intervention was superior to control and was stopped early after a mean follow-up of 23 months
		
		major bleeding (ISTH criteria, composite)
		(COMPASS study)
		rivaroxaban 2 x 2,5 mg / Tag + ASS vs. ASS
		- incidence: n = 288 (3.1%) vs. n = 170 (1.9%)
		- incidence rate:
		   o 1.67 per 100 PY (1.48-1.87) vs.
		   o 0.98 per 100 PY (0.84-1.14)
		- HR 1.70 (1.40-2.05), p < 0.001
		
		soubgroups
		CAD and Peripheral artery disease subgroup
		- incidence: n = 52 (3.1%) vs. n = 36 (2.2%)
		- incidence rate:
		   o 1.70 per 100 PY (1.27-2.23) vs.
		   o 1.17 per 100 PY (0.82-1.62)
		- HR 1.43 (0.93-2.19), p = 0.09819
		
		CAD and heart failure subgroup
		- incidence: n = 49 (2.6%) vs. n = 36 (1.9%)
		- incidence rate:
		   o 1.46 per 100 PY (1.08-1.92) vs.
		   o 1.08 per 100 PY (0.76-1.50)
				lished CAD or symptomatic PAD has been assessed by the EMA via the EU centralised procedure. Marketing authorisation was received on the 23 August 2018.

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	bd + ASS) (SR with single trial PEG-ASUS; NICE TA420) and rivaroxaban 2.5 mg bd + ASS vs. ASS (single trial, COMPASS); no head to head comparison
	➔ indirect treatment comparison (using the Bucher method)
		- HR 1.35 (0.87-2.07), p = 0.17489
		
		CAD and poor renal function subgroup
		- incidence: n = 75 (4.1%) vs. n = 55 (2.9%)
		- incidence rate:
		  o 2.17 per 100 PY (1.71-2.72) vs.
		  o 1.55 per 100 PY (1.16-2.01)
		- HR 1.41 (1.00-2.00), p = 0.05058
		
		myocardial infarction
		(COMPASS study)
		rivaroxaban 2 x 2,5 mg / Tag + ASS vs. ASS
		- incidence: n = 178 (1.9%) vs. n = 205 (2.2%)
		- incidence rate:
		  o 1.02 per 100 PY (0.87-1.18) vs.
		  o 1.18 per 100 PY (1.03-1.36)
		- HR 0.86 (0.70-1.05), p = 0.14
		
		stroke
		(COMPASS study)
		rivaroxaban 2 x 2,5 mg / Tag + ASS vs. ASS
		- incidence: n = 83 (0.9%) vs. n = 142 (1.6%)
		- incidence rate:
		  o 0.47 per 100 PY (0.38-0.59) vs.
		  o 0.82 per 100 PY (0.69-0.96)
		- HR 0.58 (0.44-0.76), p <0.001
		
		CV death
		(COMPASS study)
		rivaroxaban 2 x 2,5 mg / Tag + ASS vs. ASS
		- incidence: n = 160 (1.7%) vs. n = 203 (2.2%)
		- incidence rate:
		  o 0.91 (0.77-1.06) vs.
		  o 1.16 (1.00-1.33)
		- HR 0.78 (0.64-0.96), p = 0.02
		
		indirect comparison of rivaroxaban + ASS and ticagrelor + ASS in the COMPASS population		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		rivaroxaban + ASS vs. ASS / ticagrelor + ASS vs. ASS HR [95%CI] for comparison rivaroxaban + ASS vs ticagrelor + ASS Stroke/MI/CV death - HR 0.90 [0.75, 1.09] All-cause death - HR 0.92 [0.74, 1.15] CV death - HR 0.94 [0.71, 1.25] Stroke - HR 0.77 [0.53, 1.14] Ischaemic stroke - HR 0.67 [0.44, 1.02] Myocardial Infarction - HR 1.02 [0.79, 1.32] Major adverse limb event (MALE) - HR 0.65 [0.36, 1.18] Amputations - ITC not feasible Acute limb ischaemia (ALI) - HR 0.82 [0.26, 2.60] Venous thromboembolism (VTE) - HR 1.85 [0.06, 54.97] Major bleeding - HR 0.73 [0.50, 1.07] Intracranial bleeding - HR 0.87 [0.40, 1.89] Haemorrhagic stroke (HS) - HR 1.54 [0.44, 5.34] Gastrointestinal bleeding - ITC not feasible Fatal bleeding - HR 1.49 [0.47, 4.69] **clinical treatment pathway (NICE recommendation)** - recommendations differ during the acute period and long-term management		

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		- acute: dual therapy, followed by low-dose ASS monotherapy
		  o ticagrelor 60 mg twice daily + ASS in patients experienced myocardial infarction 1-2 years earlier
		(Table 1, page 7)
		pathways for CAD
		myocardial infarction (cardiac rehabilitation or further MI), CG172
		- DAPT for up to 12 months (ASS + 2nd antiplatelet), followed by ASS monotherapy (clopidogrel if ASS is contraindicated or if hypersensitive to ASS)
		stable angina (management), CG126
		- ASS monotherapy
		acute and long term management
		unstable angina and NSTEMI (early management), CG94
		- ASS monotherapy (clopidogrel if hypersensitive)
		ticagrelor 90 mg + ASS (TA236)
		prasugrel + ASS (TA182)
		rivaroxaban 2,5 mg twice daily + ASS (TA335)
		- followed by
		  o ticagrelor 60 mg twice daily + ASS
		  o rivaroxaban 2,5 mg twice daily + ASS
		
		note:
		Rivaroxaban, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. (restriction see within the publication page 8f)
		
		rivaroxaban 2.5 mg twice daily in combination with a daily dose of aspirin 75-100mg
		
		duration of treatment determined for each individual patient and should consider the risk for thrombotic events versus the bleeding risks		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Note: Other doses, tablet strengths used in other indications **included studies** Eikelboom JW et al N Engl J Med. 2017 Oct 5;377(14):1319-1330 Anand SS et al Lancet. 2018 Jan 20;391(10117):219-229		

Zhao et al. 2018 Ticagrelor + ASS vs. Ticagrelor vs. ASS (RCT, 1 Jahr nach CABG)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Zhao Q. Effect of Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone on Saphenous Vein Graft Patency 1 Year After Coronary Artery Bypass Grafting: A Randomized Clinical Trial. JAMA 2018; 319(16):1677–86. https://www.ncbi.nlm.nih.gov/pubmed/29710164. [82]	OBJECTIVE To compare the effect of ticagrelor + aspirin or ticagrelor alone vs aspirin alone on saphenous vein graft patency 1 year after CABG. DESIGN, SETTING, AND PARTICIPANTS Randomized, multicenter, open-label, clinical trial among 6 tertiary hospitals in China. Eligible patients were aged 18 to 80 years with indications for elective CABG. Patients requiring urgent revascularization, concomitant cardiac surgery, dual antiplatelet or vitamin K antagonist therapy post-CABG, and who were at risk of serious bleeding were excluded. From July 2014 until November 2015, 1256 patients were identified and 500 were enrolled. Follow-up was completed in January 2017. INTERVENTIONS Patients were randomized (1:1:1) to start ticagrelor (90 mg twice daily) + aspirin (100 mg once daily) (n = 168), ticagrelor (90 mg twice	RESULTS Among 500 randomized patients (mean age, 63.6 years; women, 91 [18.2%]), 461 (92.2%) completed the trial. Saphenous vein graft patency rates 1 year post-CABG were 88.7% (432 of 487 vein grafts) with ticagrelor + aspirin; 82.8% (404 of 488 vein grafts) with ticagrelor alone; and 76.5% (371 of 485 vein grafts) with aspirin alone. The difference between ticagrelor + aspirin vs aspirin alone was statistically significant (12.2% [95% CI, 5.2% to 19.2%]; P < .001), whereas the difference between ticagrelor alone vs aspirin alone was not statistically significant (6.3% [95% CI, -1.1% to 13.7%]; P = .10). Five major bleeding episodes occurred during 1 year of follow-up (3 with ticagrelor + aspirin; 2 with ticagrelor alone). CONCLUSIONS AND RELEVANCE Among patients undergoing elective CABG with saphenous vein grafting, ticagrelor + aspirin significantly increased graft patency after 1 year vs aspirin alone; there was no significant difference between ticagrelor alone and aspirin alone. Further research with more patients is needed to assess comparative bleeding risks. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02201771.	*Zunächst nicht bewertet und extrahiert (Abstact verfügbar)*	(DACAB Studie)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	daily) (n = 166), or aspirin (100 mg once daily) (n = 166) within 24 hours post-CABG. Neither patients nor treating physicians were blinded to allocation. MAIN OUTCOMES AND MEASURES Primary outcome was saphenous vein graft patency 1 year after CABG (FitzGibbon grade A) adjudicated independently by a committee blinded to allocation. Saphenous vein graft patency was assessed by multislice computed tomographic angiography or coronary angiography.			

12.5.7 Empfehlung 7-7 Tripeltherapie (orale Antikoagulation + 2 Thrombozytenaggregationshemmer; in Bezug auf die Dosierung sowie Therapiedauer)

Shah et al. 2019 kurz- vs. langzeitige Tripeltherapie (SR, Stent, Indikation zur Antikoagulation)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Shah R. Short-term versus long-term triple antithrombotic therapy for patients with coronary stents and requiring oral anticoagulation: A meta-analysis of randomized clinical trials. Coron Artery Dis 2019; 30(2):116–23. https://www.ncbi.nlm.nih.gov/pubmed/30589646. [83]	**Objective** to conduct a meta-analysis of selected RCT to assess the efficacy and safety of shorter duration (≤ 6 weeks) triple therapy (TT with OAC) vs. longer duration (6-12 months) TT **Methods** - SR of RCT - PRISMA, meta-analyses guidelines - PubMed, ClinicalTrials, Cochrane databases - Cross-referencing	n = 3 RCT (n = 1 883 patients) - mean age 70.3 to 73.9 years - duration of TAT (short 4-6weeks, long 6-12 months) - OAC indication AF (69.4-100%) - index event ACS (27.5-50.1%) - index event stable CAD (49.1-72.5%) - clopidogrel (96.5-100%) - prasugrel (0.6-0.9%) - ticagrelor (2.5-2.6%) **Results** short-term TT vs. long-term TT primary	AMSTAR-II moderate high quality trials based on Cochrane guidelines (low risk of bias) significant heterogeneity was reported, sensitivity analyses did not reveal an impact on summary results type of coronary stent and P2Y12-inhibitor varied across the studies open-label RCT	authors noted that oral anticoagulation (OAC) is indicated additional to DAPT in 5-10% of patients with coronary stents authors concluded that short-term TT after stenting was associated with similar rates of MI, stroke, stent thrombosis, and TIMI major bleeding, but

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- patients undergoing coronary stenting (PCI) - including patients with additional indication of OAC (long-term use) **Intervention** short-term triple therapy (TT), no more than 6 weeks **Comperator** long-term TT, 6-12 months **Quality assessment** Cochrane Risk-of-Bias tool **Outcomes** primary - major adverse cardiovascular events (MACE), defined as composite of cardiac death, myocardial infarction, stent thrombosis, or stroke secondary - cardiac mortality - all-cause mortality - myocardial infarction - stroke - stent thrombosis safety - thromboslysis in myocardial infarction (TIMI) major bleeding - any bleeding events	MACE - RRR 31% - RR 0.69 (95% CI 0.50; 0.96), p=0.031 (soubgroup analyses: short-term vs. 12 months: decreased risk (RR 0.60 (95% CI 0.41; 0.89), p = 0.011), short-term vs. 6 months: no difference (RR 1.01 (95% CI 0.54; 1.88), p = 0.97) secondary cardiac mortality - RR 0.62 (95% CI 0.43; 0.91), P = 0.014 (soubgroup analyses: short-term vs. 12 months: decreased risk (RR 0.62 (95% CI 0.41; 0.92), p = 0.02), short-term vs. 6 months: no difference (RR 0.67 (95% CI 0.27; 1.67), p = 0.39) all-cause mortality - RR 0.55 (95% CI 0.32; 0.97), p = 0.040 (supplement: sensitivity analysis was nonsignificant, but with strong trend favouring short-term TT) myocardial infarction - RR 0.64 (95% CI 0.32; 1.30), p = 0.222 (soubgroup analyses showed similar results for 6 and 12 months (RR 1.26 (95% CI 0.23; 6.90), p = 0.78; RR 0.56 (95% CI 0.26; 1.21), p = 0.14) stroke - RR 0.913 (95% CI 0.43; 1.93), p = 0.811 (soubgroup analyses showed similar results for 6 and 12 months (RR 1.07 (95% CI 0.33; 3.41), p = 0.90; RR 0.81 (95% CI 0.30; 2.16), p = 0.67) stent thrombosis - RR 0.64 (95% CI 0.24; 1.72), p = 0.383	all patients received warfarin, thus findings not be generalized to patients receiving novel OAC (NOAC), but warfarin commonly used worldwide (cost, only anticoagulant effective for patients with mechanical valves)	with decreased rates of MACE, cardiac mortality, all-cause mortality, and any bleeding events soubgroup analyses suggested that 6 months TT provided no benefit over short-term TT (≤ 6 weeks) and that prolonged TT beyond 6 months is harmful findings support the current guidelines discussion: combination of oral antiplatelet therapy and OAC significant increase the risk of bleeding (Gibson et al. N Engl J Med 2016)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		(soubgroup analysis showed similar results for 6 and 12 months) safety major bleeding - RR 1.10 (95% CI 0.70; 1.72), p = 0.664 - (soubgroup: short-term vs. 12 months: RR 0.91 (95% CI 0.47; 1.77), p = 0.80, 6 months: RR 1.28 (95% CI 0.70; 2.35), p = 0.412) any bleeding events - RR 0.77 (95% CI 0.67; 0.89), p < 0.001 - (soubgroup: short-term vs. 12 months: decreased risk (RR 0.60 (95% CI 0.48; 0.75), p < 0.001), 6 months: no difference RR 0.91 (95% CI 0.76; 1.09), p = 0.34)) **Included studies** Dewilde et al. Lancet 2013 Use of clopidogrel with or without ASS in patients taking oral anticoagulant therapy and undergoing PCI: an open-label RCT (WOEST) Fiedler et al. J Am Coll Cardiol 2015 Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-Triple trial (ISAR-TRIPLE) Gibson et al. N Engl J Med 2016 Prevention of bleeding in patients with atrial fibrillation undergoing PCI. (PIONEER-AF-PCI) Gibson et al. Circulation 2017 Recurrent hospitalization among patients with atrial fibrillation undergoing intracoronary stenting treated with 2 tretament strategies of rivaroxaban or a dose-adjusted oral vitamin-K antagonist treatment stategy. PIONEER-AF-PCI)		

Peterson et al. 2021 duale (Dabigatran + P2Y$_{12}$) vs. Tripletherapie (Warfarin + P2Y$_{12}$ + ASS) (RCT, „Landmark"-Analyse, AF, PCI, RE-DUAL PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Peterson BE. Evaluation of Dual Versus Triple Therapy by Landmark Analysis in the RE-DUAL PCI Trial. JACC Cardiovasc Interv 2021; 14(7):768–80. https://www.ncbi.nlm.nih.gov/pubmed/33826497. [84]	**Objective** to explore the early vs. late benefits and risks of dabigatran dual therapy vs. warfarin triple therapy in the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial
	
	Methods
	- Landmark analysis of RE-DUAL PCI trial
	- open-label RCT
	- patients with nonvalvular atrial fibrillation
	- undergo PCI
	- USA (< 80 years), Japan (< 70 years), 3 arms
	- older patients (≥ 80 or 70 years) received 2 x 110 mg dabigatran, 2 arms
	- increased risk for bleeding and thrombotic events
	- 3 arms (1:1:1)
	
	Intervention dabigatran 2 x 110 mg / day or dabigatran 2 x 150 mg / day + P2Y$_{12}$-inhibitor (no ASS)
	
	Comperator warfarin + P2Y$_{12}$-inhibitor + ASS (ASS discontinued after 90 days in patients with DES – drug-eluting
		n = 2,725 patients
		- all included in the main 30-days landmark analysis
		- n = 2,251 (82.6%) undergone stenting with DES
		   o included in the secondary 90-days analysis
		   o n = 1,425 with dabigatran DT
		   o n = 826 with warfarin TT
		   o mean time from PCI to randomization 1.5 ± 1.17 days (median 1 day)
		   o median follow-up 12.9 months (IQR 9-18 months)
		
		results
		before 30 days
		ISTH MBE (International Society on Thrombosis and Hemostasis; major bleeding event(s)/ CRNMBE (clinically relevant nonmajor bleeding event)
		dabigatran 2 x 110 mg DAT vs. warfarin TT
		- total: n = 981 vs. n = 981 patients
		- n = 40 (4.1%) vs. n = 86 (8.8%)
		- HR 0.45 (0.31–0.66) p<0.0001
		- ARD -4.7
		(ARD = absolute risk difference)
		
		dabigatran 2 x 150 mg DAT vs. warfarin TT
		- total n = 763 vs. n = 764
		- n = 29 (3.8%) vs. n = 61 (8.0%)
		- HR 0.46 (0.30–0.72) p=0.0006
		- ARD -4.2
		
		DTE (death or thromboembolic event) or unplannes revascularisation
		dabigatran 2 x 110 mg DAT vs. warfarin TT
		- total: n = 981 vs. n = 981 patients
		- n = 28 (2.9%) vs. n = 20 (2.0%)
		- HR 1.39 (0.79–2.47) p=0.26
		- ARD 0.9
			Selection bias randomization: low concealment and unpredictability: low
			Performance bias blinding of participants and staff: high (open-label)
			Detection bias blinding of evaluation: unclear (open-label; clinical endpoints were centrally adjudicated by independent committee members who were blinded to treatment assignment)
			Attrition bias lost to follow-up: low ITT-analysis: low (post hoc analyses, subgroup analyses; all patients enrolled were included in the main 30-day analysis)
			Reporting bias selective result presentation: low
			
			limitations open-label design
			
			multiple comparisons that exist with any secondary analysis of a clinical trial; study was not powered for this landmark analysis, nor was this a pre-specified analysis
				Landmark analysis to understand whether dabigatran, ASS cessation, or both contribute to lower bleeding rates in DT vs. TT (early time period when ASS was withdrawn from both dabigatran arms)
				
				in 2016 RE-DUAL PCI results were first published (DT dabigatran 110 mg and 150 mg + clopidogrel vs. triple therapy with warfarin); significant reduced bleeding risk in DT vs. TT, DT noninferior to TT related to death or thromboembolic events or unplanned revascularisation
				
				authors concluded that the first 30 days post-PCI are the most critical, especially for bleeding risk
				
				authors concluded that in the early phase of treatment both doses of dabigatran plus a P2Y12 inhibitor resulted in a substantial

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	stents and after 30 days in patients with BMS – bare-metal stents) after discontinuing ASS: DT with P2Y$_{12}$-inhibitor + warfarin or respective dose of dabigatran for 12 months P2Y$_{12}$-inhibitor = clopidogrel or ticagrelor **Outcomes** primary - time to the first major or clinically relevant nonmajor (CRNM) bleeding event (definition: ISTH) - composite of time to DTE (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization secondary - time to DTE, stent thrombosis, or myocardial infarction Landmark analysis was performed at 30 and 90 days (patients with BMS were not included in the primary 90 days analyses, but in the supplement analyses and the primary 30 days analyses) protocol Cannon CP, Gropper S, Bhatt DL, et al. Design and rationale of the RE-DUAL PCI Trial: a prospective, randomized, phase 3b study comparing the safety and efficacy of dual antithrombotic therapy with	dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 763 vs. n = 764 - n = 12 (1.6%) vs. n = 17 (2.2%) - HR 0.70 (0.33–1.46) p=0.34 - ARD -0.6 net clinical benefit dabigatran 2 x 110 mg DAT vs. warfarin TT - total: n = 981 vs. n = 981 patients - n = 66 (6.7%) vs. n = 100 (10.2%) - HR 0.65 (0.47–0.88) p=0.0062 - ARD -3.5 dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 763 vs. n = 764 - n = 41 (5.4%) vs. n = 74 (9.7%) - HR 0.54 (0.37–0.79) p=0.0015 - ARD -4.3 after 30 days (14 months average) ISTH MBE (International Society on Thrombosis and Hemostasis; major bleeding event(s)/ CRNMBE (clinically relevant nonmajor bleeding event) dabigatran 2 x 110 mg DAT vs. warfarin TT - total: n = 912 vs. n = 867 patients - n = 111 (11.9%) vs. n = 178 (20.3%) - HR 0.55 (0.43–0.69) p<0.0001 - ARD -8.4 (ARD = absolute risk difference) dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 721 vs. n = 679 - n = 125 (17.1%) vs. n = 135 (19.6%) - HR 0.82 (0.65–1.05) p=0.12 - ARD -2.5		reduction in bleeding risk compared with warfarin TT (early net clinical benefit in both doses dabigatran), without increased numerical thrombotic events in dabigatran 2 x 150 mg during first 30 days: - for dabigatran 110 mg (55% reduction in bleeding) - for dabigatran 150 mg (54% rediction in bleeding) - DT group with 2 x 110 mg dabigatran had numerical higher rates of DTE or unplanned revascularization

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	dabigatran etexilate versus warfarin triple therapy in patients with nonvalvular atrial fibrillation who have undergone percutaneous coronary intervention with stenting. Clin Cardiol 2016;39:555–64. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377: 1513–24.	DTE (death or thromboembolic event) or unplannes revascularisation dabigatran 2 x 110 mg DAT vs. warfarin TT - total: n = 912 vs. n = 867 patients - n = 121 (12.7%) vs. n = 111 (11.7%) - HR 1.09 (0.84–1.40) p=0.53 - ARD 1 dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 721 vs. n = 679 - n = 78 (10.4%) vs. n = 81 (11.0%) - HR 0.94 (0.69–1.28) p=0.67 - ARD -0.6 net clinical benefit dabigatran 2 x 110 mg DAT vs. warfarin TT - total: n = 912 vs. n = 867 patients - n = 196 (21.5%) vs. n = 249 (28.7%) - HR 0.70 (0.58–0.85) p=0.0002 - ARD -7.2 dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 721 vs. n = 679 - n = 181 (25.1%) vs. n = 185 (27.2%) - HR 0.88 (0.72–1.08) p=0.22 - ARD -2.1 secondary endpoints show not statistically significant differences at 90 days among patients with DES ISTH MBE (International Society on Thrombosis and Hemostasis; major bleeding event(s)/ CRNMBE (clinically relevant nonmajor bleeding event) dabigatran 2 x 110 mg DAT vs. warfarin TT - total n = 804 vs. n = 826 - n = 55 (6.8%) vs. n = 135 (16.3%) - HR: 0.40; 95% CI: 0.29 to 0.54; p < 0.0001		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 621 vs. n = 638 - n = 56 (9.0%) vs. n = 100 (15.7%) - HR: 0.54; 95% CI: 0.39 to 0.75; p = 0.0003 DTE (death or thromboembolic event) or unplannes revascularisation dabigatran 2 x 110 mg DAT vs. warfarin TT - total n = 804 vs. n = 826 - n = 37 (4.6%) vs. n = 30 (3.6%) - HR: 1.26; 95% CI: 0.78 to 2.04; p = 0.34 dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 621 vs. n = 638 - n = 24 (3.9%) vs. n = 25 (3.9%) - HR: 0.97; 95% CI: 0.55 to 1.70; p = 0.92 net clinical benefit dabigatran 2 x 110 mg DAT vs. warfarin TT - total n = 804 vs. n = 826 - 10.7% vs. 18.5% - HR: 0.55; 95% CI: 0.42 to 0.72; p < 0.0001 dabigatran 2 x 150 mg DAT vs. warfarin TT - total n = 621 vs. n = 638 - 12.2% vs. 18.2%; - HR: 0.64; 95% CI: 0.48 to 0.86; p = 0.0025		

Kerneis et al. 2019 NOAC duale vs. Tripletherapie vs. Warfarin Tripletherapie (RCT, AF, PIONEER AF-PCI)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Kerneis M. Novel Oral Anticoagulant Based Versus Vitamin K Antagonist Based Double Therapy Among Stented Patients With Atrial Fibrillation: Insights From the PIONEER	**Objective** to compare the rate of cardiovascular or bleeding related hospitalizations between rivaroxaban based with VKA based double therapy among	n = 2124 - group 1: n = 709 patients - group 2: n = 709 patients - group 3: n = 706 patients	**Selection bias** randomization: low concealment and unpredictability:	authors noted that PIONEER AF-PCI demonstrated that rivaroxaban + P2Y$_{12}$-inhibitor

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AF-PCI Trial. Circ Cardiovasc Interv 2019; 12(11):e008160. https://www.ncbi.nlm.nih.gov/pubmed/31707805. [85]	subjects undergoing PCI enrolled in PIONEER AF-PCI trial
	
	Methods
	- PIONEER AF-PCI
	- patients with paroxysmal, persistent, or permanent nonvalvular AF
	- underwent PCI
	- n = 2124 patients were randomized to 3 groups:
	    o rivaroxaban 15 mg / day + $P2Y_{12}$-I for 12 months (1)
	    o rivaroxaban 2 x 2,5 mg / day + DAPT for 1, 6 or 12 months(2)
	    o standard: VKA + DAPT for 1, 6 or 12 months (3)
	- stratification according to prespecified duration of DAPT (1, 6, or 12 months)
	- after prespecified DAPT duration subjects of (2) were switched to rivaroxaban 15 mg + low dose ASS; subjects of (3) were switched to VKA + low dose ASS
	- exclusion criteria e. g.: history of stroke or TIA, significant gastrointestinal bleeding within 12 months of randomization, creatinine clearance less than 30 mL per minute
		study period after the prespecified duration of DAPT (determined by study investigator)
		n = 906 were prespecified to a 1 or 6 months DAPT duration
		- n = 716 with rivaroxaban and n = 361 with warfarin were included in the analyses (DT)
		    o group 1: n = 359 (50.6%) riva + $P2Y_{12}$
		    o group 2: n = 357 (50.4%) riva + ASS
		    o group 3: n = 361 (51.1%) VKA + ASS
		- mean age ~ 71 years
		- female ~ 25 %
		- $P2Y_{12}$: clopidogrel: 95.4 vs. 97 %
		- patients on rivaroxaban were more likely to have an elective revascularisation an take more often a beta blocker, ACE-inhibitor or ARB, and statins
		- median follow-up
		    o 1 month DAPT: 332.0 days
		    o 6 months DAPT: 183.0 days
		
		results
		hospitalizations (at least one event) (patients)
		- n = 93 (15.2%) patients assigned to NOAC + one antiplatelet agent (SAPT)
		- n = 65 (22.1%) patients assigned to VKA + SAPT
		
		multiple hospitalizations (patients)
		- n = 20 (3.3%) patients assigned to NOAC + one antiplatelet agent (SAPT)
		- n = 15 (5.1%) patients assigned to VKA + SAPT
		
		primary endpoint (rehospitalizations)
		- NOAC + SAPT vs. VKA + SAPT
		- n = 124 (20.3%) vs. n = 87 (29.6%)
		- 34.1 events per 100 patient years vs. 50.8 events per 100 patient years
		- HR 0.65 (95% CI 0.45; 0.93), p = 0.008
		
		- no modification of treatment effect by HAS-BLED or CHA_2DS_2VASc scores
			low
			Performance bias
			blinding of participants and staff: high
			(open-label)
			Detection bias
			blinding of evaluation: unclear
			(open-label)
			Attrition bias
			lost to follow-up: low
			ITT-analysis: low
			(subgroup analyses)
			Reporting bias
			selective result presentation: low
			
			limitations
			open-label design
			
			sensitivity analyses were performed
			
			soubgroup analyses; total number of subjects was low (underpowered)
			
			assumption that subjects adhere to their treatment regimen (ITT)
			
			early period after PCI (high risk period) was not included - analysis does not reflect the acute phase of first weeks after PCI
				reduced the risk of rehospitalization vs. VKA + DAPT in patients with AF undergoing PCI
				
				soupgroup analysis adds that after discontinuation of one of the 2 antiplatelet agents, rivaroxaban based DT still reduced the rate of bleeding or cardiovascular related rehospitalization vs. VKA based regimen

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	- all subjects with prespeci-fied duration of 12 months DAPT were excluded
	
	Intervention
	- DT with rivaroxaban 15 mg + P2Y12-I (1)
	- DT with rivaroxaban 15 mg + low dose ASS*
	Comperator
	- DT with VKA + low dose ASS*
	(*after prespecified DAPT duration)
	
	Outcomes
	primary
	- bleeding and cardiovascular rehospitalizations among subjects on NOAC DT vs. VKA DT
	analysed was the time after discontinuing/switch
	
	design and results published previously:
	Gibson et al. NEJM 2016
	Gibson et al. AM Heart J 2015
	(enthalten in Shah et al. 2019 [83])
		- 1 months DAPT group
		  o 69 events vs. 49 events
		  o 39.8 events per 100 patients years vs. 60.6 events per 100 patient years
		  o HR 0.62 (0.37; 1.02), p = 0.010
		
		- 6 months DAPT group
		  o 55 events vs. 38 events
		  o 29.0 events per 100 patient years vs. 42.0 events per 100 patients years
		  o HR 0.74 (0.46; 1.17), p = 0.21
		
		- rivaroxaban + $P2Y_{12}$-inhibitor vs. VKA + ASS
		  o HR 0.62 (0.41; 0.93), p < 0.001
		  o DAPT 1 month: HR 0.44 (0.24; 0.83), p < 0.001
		  o DAPT 6 months: 34 vs. 38 (numerical)
		  o details on supplement
		
		- rivaroxaban + ASS vs. VKA + ASS
		  o HR 0.68 (0.44; 1.05), p = 0.026
		  o DAPT 1 month: 43 vs. 49 (numerical)
		  o DAPT 6 months: 21 vs. 38 (numerical)
		  o details on supplement		

12.5.8 Zusatzinformation Hintergrundtext (E 7-7)

Marquis-Gravel et al. 2020 (Vergleich internationaler Leitlinienempfehlungen, CAD)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Marquis-Gravel G. A Critical Comparison of Canadian and International Guidelines Recommendations	**Objective**	**DAPT duration** - multiple studies from the early 2010s demonstrated noninferiority of reduced DAPT duration	n. a.	authors noted that antiplatet therapy for patients with CAD

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for Antiplatelet Therapy in Coronary Artery Disease. Can J Cardiol 2020; 36(8):1298–307. https://www.ncbi.nlm.nih.gov/pubmed/32553812. [86]	to put Canadian guidelines into perspective via-a-vis international recommendations, major topics:
	- DAPT duration following drug-eluting stent (DES) implantation
	- DAPT following percutaneous coronary intervention (PCI) in patients with atrial fibrillation (AF) and ndication for OAC
	- DAPT management for noncardiac surgery following PCI with DES
	
	Methods
	- Scientific societies from Canada, United States and Europe published updated recommendations for CAD
	- 2018 Canadian Association of Interventional Cardiology (CCS) published 39 updated recommendations on antiplatelet therapy (management in AF, PCI)
	- 2016 the American College of Cardiology (ACC/AHA) published a focused update of DAPT duration
	- 2016 AHA/ACC/Herat Thythm Society (HRS) published recommendations for AF, ACS
	- Since 2017 European societies published sequentially 5 different sets of guidelines or consensus documents (DAPT duration, DAPT in patients requiring OAC)
	- CCS categorized recommendations according to strength an level of evidence
		(< 12 months), following PCI (grounded by thrombotic and bleeding events)
		- later studies for superiority showed that continuation of DAPT > 12 months was superior to interrupted DAPT within 12 months, following PCI with DES and in patients with myocardial infarction
		- multiple metananlyses for bleeding risk in longer duration of DAPT
		   o benefit for patients with MI and technically complex PCI
		- CCS, ACC/AHA, ESC provide 5, 14 and 24 recommendations on duration of DAPT (with 1-3 to 36 months), Table 1 within the publication
		
		- all guidelines agree that the individual approach should balance the likelihood of bleeding and expected thrombotic risk reduction
		   o risk factors to weighing (supplement)
		   o prediction models
		   o risk score (validated) – lack of validation contributes to heterogeneous ways of implementation
		
		- ACC/AHA and ESC recommend a 6-month duration of DAPT (based on noninferiority trials)
		- CCS also recommends 6 months DAPT for most patients, but provides the option of continuing up to one year (thrombotic risk)
		- high-quality of evidence
		- in patients with high bleeding risk DAPT can be shortened to 3 months (all guidelines)
		- ESC provides an additional recommendation to 1 months if safety concerns with DAPT (2 large RCT, comparing novel stents with bare-metal in patients with high bleeding risk (no control with other length) (low grade recommendation)
		- CCS and ESC incorporate PCI complexity features as criteria to consider duration of DAPT beyond 6 months (MA of 6 RCT) – effect modifier
				evolved dramatically over the last decades
				
				that dual antiplatelet therapy (DAPT) duration can be tailored to individual ischemic and bleeding risks
				
				that strategies to personalize antiplatelet therapiy have benn developed when concomitant oral anticoagulation (OAK) is indicated
				
				the review finds broad agreement across international expert consensus documents on the majority of recommendations (DAPT, TT, perioperative management),
				
				unanswered questions: place of ASS in secondary prevention of CAD, ASS-free strategies early after PCI, safe minimal duration of DAPT with newer-generation stents
				
				international committee with relevant expertise and representation could be a solution to update more frequently

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	Quality assessment GRADE	- all guidelines recommend 12 months DAPT strongly for patients with ACS treated with PCI - can be shortened to 6 months in patients at higher bleeding risk (exploration from trials with mixed population, stable angina and ACS) - all guidelines recommend prolonged DAPT >12 months in selected patients with lower bleeding than thrombotic risk (CCS 3 years, ACC/AHA and ESC > 12 months) - after 12 months CCS favours ticagrelor 60 mg twice daily or clopidogrel 75 mg over prasugrel (PEGASUS-TIMI and DAPT trial) - in patients with previous MI, the ESC suggests ticagrelor 60 mg 2x daily over ticagrelor 90 mg 2x daily or prasugrel (PEGASUS-TIMI, and MA) - ESC/EACTS on myocardial revascularization recommends the addition of rivaroxaban 2,5 mg twice daily to ASS and Clopidogrel in patients with ACS, no history of TIA or stroke, at high ischemic risk, and low bleeding risk (low-grade recommendation, based on TIMI trial) - 2019 ESC for CCS: addition of P2Y12-inhibitor or rivaroxaban 2,5 mg twiche daily + ASS can be considered in patients at high and moderate ischemic risk and not at high risk of bleeding (long-term secondary prevention) (COMPASS trial) - absence of properly powered hed-to-head RCT; expert opinion - **future evidence:** SMART-DATE (6 month duration), SMART-CHOICE (mono vs- duale therapy), STOPDAPT-2 (short and optimal duration), ISAR-REACT 5 (prasugrel vs. ticagrelor), TROPICAL-ACS (P2Y12-inhibitor de-escalation after discharge), TOPIC (timing)		and avoiding duplication of resources future directions: AUGUST trial (P2Y12-I + OAC after ACS, PCI), OAC apixaban or VKA + ASS or placebo ENTRUST-AF PCI (DT Edoxaban + P2Y12-I vs. TT with VKA), non-inferiority SAFE A (safety of apixaban + ASS + P2Y12-I) MASTER-DAPT (long term OAC) authors added some information for DAPT management after non-cardiac surgery (see within the publication)

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		Antithrombotic therapy in patients with AF undergoing PCI
		
		- evidence on long-term safety and efficacy of combination of different antiplatelet and OAC regimen
		- Gibson et al. NEJM 2016 (Rivaroxaban, PIO-NEER-AF-PCI), Cannon et al. NEJM 2017 (Dabigatran, Re-DUAL-PCI), Dewilde et al. Lancet 2013 (Clopidogrel, WOEST), Fiedler et al. J Am Coll Cardiol 2015 (Clopidogrel, ISAR-TRIPLE), Lopes et al. NEJM 2019 (Apixaban, AUGUST), Vranckx et al. Lancet 2019 (Edoxaban, EN-TRUST-AF PCI)
		- Limitations:
		   o lack of statistical power (thrombotic events);
		   o exclusion of patients in higher spectrum of bleeding risks (substantial proportion of the PCI population in clinical practice)
		   o heterogenous guideline recommendations because some guidelines published before study results were published
		- CCS antiplatelet and AF guidelines provide 6 and 2 recommenadations (AF, undergoing PCI)
		- 2019 AHA/ACC/HRS update provides 5 recommendations (AF and ACS)
		- ESC guidelines provide 9 recommendations (DAPT following PCI, indication for OAC)
		- also within the 2018 guideline omyocardial revascularization
		
		- guidelines recommend (indication for OAC, undergoing PCI) a strategy involving a progressive decrease of antithrombotic intensity across 3 sequential time periods
		   o initial period of TT
		   o followed by period of dual pathway (OAC + single antiplatelet agent)
		   o followed by OAC alone (± 1 antiplatelet agent)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

		- variations involved mainly the duration of each treatment phase
		
		initial phase:
		- CCS and ESC guidelines: peri-PCI period: TT duration may be extended up to 6 months (trade-off between bleeding and thrombotic risk)
		- in patients with ACS or undergoing elective PCI with high-risk thrombotic features guidelines allow discontinuation of ASS following the peri-PCI period or continuation of ASS up to 6 months (strong recommendation, moderate quality of evidence)
		- suggest a dual pathway with clopidogrel + AOC for at least 3 months after DES in absence of high-risk features (weak recommendation, moderate-quality evidence)
		- in ESC DT (clopidogrel + OAC) can replace the initial TT in patients at higher risk of bleeding than thrombotic risk (based on WOEST, PIONEER-AF-PCI), *note*: lack of statistical power
		- AHA/ACC/HRS favour dual pathway (OAC + P2Y12-inhibitor) after discharge following PCI (based on WOEST, RE-DUAL, PIONEER-AF-PCI) (no signals of harm with DT)
		- For those treated with TT, transistion to DT at no longer than 4-6 weeks is considered
		- all guideline recommend clopidogrel as P2Y12-I
		- Standard dose ASS is preferred ofer high dose (81-100 mg/d)
		- OAC for TT:
		    o rivaroxaban 2,4 mg twice daily (PIONEER-AF-PCI), or
		    o warfarin (INR target 2.0-2.5) (CCS guidelines)
		    o NOAC over warfarin, when combination is required (ESC 2019, ESC/EACTS, AHA/ACC/HRS)
		
		treatment following the initial phase of TT
		- all guidelines recommend dual pathway (OAC + antiplatelet agent)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- usually clopidogrel is antiplatelet agent of choice for DT in AF after PCI, ESC allow ASS (ISAR-TRI-PLE) - CCS do not recommend specific OAC agent (PIO-NEER-AF-PCI, RE-DUAL PCI, WOEST), rivaroxaban 15 mg / daily (10 mg in patients with renal dysfunction), dabigatran 110 or 150 mg twice daily, or warfarin - Dabogatran 110 mg twice daily not approved in USA (AHA/ACC/HRS DT with warfarin + clopidogrel or ticagrelor OR DT with dabigatran 2 x 150 mg daily or rivaroxaban 15 mg daily + clopidogrel) - ESC do not favour specific OAC for DT (if rivaroxaban is used: 15 mg daily (PIONEER-AF)) - 2019 ESC (CCS) also recommend dabigatran dose of 110 mg twice daily (over 150 mg twice daily) if bleeding concerns prevail over thrombotic concerns) **_long-term phase_** - beyond 12 months follow-up after PCI all guidelines recommend OAC alone (generally) - CCS: there is a provision to add a single antiplatelet agent to OAC, according to ischemic and bleeding risk (low-level evidence)		

Mishra et al. 2019 antithrombotische Therapie (SR, AF, PCI, u. a. Übersicht Dauer duale und Tripeltherapie)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Mishra A. Antithrombotic Therapy in Patients With Atrial Fibrillation and Coronary Artery Disease Undergoing Percutaneous Coronary Intervention. J Cardiovasc Pharmacol 2019; 74(2):82–90. https://www.ncbi.nlm.nih.gov/pubmed/31306367. [87]	**Objective** to summerize data regarding the safety and efficacy of various antithrombotic regimens in patients with nonvalvular AF in the setting of PCI with DES, BMS and others **Methods**	n = 76 studies - n = 8 guidelines - n = 35 RCT - n = 17 meta-analyses - n = 16 observational studies **Results** antithrombotic regimen in patients with nonvalvular AF, PCI introduction:	AMSTAR-II critically low (no meta-analysis), no protocol, no list of excluded studies, no Risk-of-Bias assessment and no discussion of the Risk-of-Bias	authors comcluded that in most patients with nonvalvular AF who requiring anticoagulation after PCI: 30 days of TT followed by DT or DT alone for

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	- SR: PubMed, Web of Science, Cochrane Library, ClinicalTrials, Google Scholar
	- RCT, MA, cohort studies, guidelines
	- ACS, CAD, AF
	- PCI
		- ~15 % of patients with AF have a history of MI
		- ~5-15% will require stenting
		- ~18-47% have CAD
		- potential need for future PCI while receiving long-term OAC (oral anticoagulation) therapy
		- international guidelines agree the duration of TT should be minimized
		- TT duration depends on ischemic and bleeding risk
		- after 12 months of PCI, monotherapy with OAC is recommended in low ischemic risk
		
		trials comparing DT with TT
		- guidelines recommend the use of TT even for a short period
		- new RCT suggested that DT ist superior to TT (WOEST, ISAR-TRIPLE, Pioneer-AF, Re-DUAL):
		   o WOEST: TT (ASS+clopidogrel+VKA) had higher rates of TIMI bleeding and all-cause mortality vs. DT (clopidogrel + VKA)
		
		   o ISAR-TRIPLE: no difference in primary endpoint (composite) or TIMI major bleeding
		
		   o Pioneer-AF: rivaroxaban group experienced less bleeding than VKA group, no differene in MACE or ST
		
		   o Re-Dual: dabigatran groups had lower rates of bleeding than VKA group, MACE and ST did not differ
		- cohort studies suggest that the bleeding risk with TT is high, compared with DT, regardless of the regimen
		- meta-analyses found that the DT group had significant lower rates of thrombolysis in MI, major bleeding, minor bleeding compared to TT, with
				up to 12 months seems appropriate
				
				TT can be extended for 3-6 months in ACS patients with intermediate to low bleeding propensity
				
				preferred agend should be clopidogrel (limited data for other P2Y12-I for DT and TT)
				
				NOAC have emerged as the preferred drug over VKA (in DT and TT combination)
				
				limited data suggest that reduced NOAC dose may be efficacious and safe
				
				bleeding risk should be considered, possible PPI use
				
				for most patients with AF 12 months after PCI, requiring OAC, antiplatelet therapy can be safely discontinued

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		similar rates of all-cause mortality, cardiovascular mortality, MI, ST, stroke NOAC and newer P2Y12-inhibitors (DT and TT), in AF NOAC vs. VKA: - full-dose VKA was the OAC of choice in patients with AF - new evidence suggested that NOAC be noninferior or superior to VKA regimen in preventing thromboembolism with similar or better rates of bleeding - (ROKET-AF, Danish health registry (Lee et al.), McWilliams et al.)) newer P2Y12-inhibitors (DT and TT) - TRANSLATE-ACS, TRITON-TIMI, n = 2 cohort studies - no high-quality study exists comparing various regimen for TT with newer P2Y12-inhibitors - current guideline do not recommend the use of prasugrel or ticagrelor as part of TT regimen - a DT with prasugrel or ticagrelor may be appropriate for patients with high ischemic/thrombotic risk and low bleeding risk shorter vs. longer DAPT duration, undergoing PCI - tradeoff between bleeding and ischemic/ST risk - evidence on optimal standard duration is still lacking - EXCELLENT, OPTIMIZE, ITALIC, SECURITY, ISAR-SAFE, ARTIC, PRODIGY, DES-LATE - SMART-DATE - Benefit of extended DAPT may be stent specific - RESET, PRODIGY, DAPT trial, DAPT-STEMI trial antithrombotic regimen in non-ACS AF patients undergoing PCI - antiplatelet therapy after PCI was found to be safer and more effective than OAC		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- decision to give ≥ 12 months DAPT after PCI with first generation DES was based on expert opinion - no RCT for duration of DAPT in non-ACS undergoing PCI - Canadian guidelines recommend 1 (BMS) to 3 (DES) months of DT (VKA or rivaroxaban + clopidogrel) for low risk elective PCI and 1-6 months TT (VKA or rivaroxaban, clopidogrel + ASS), followed by DT through 12 months in high risk elective PCI - European guidelines do not differentiate antithrombotic regimen or duration based on stent type: TT (ASS, clopidogrel, VKA or NOAC) for 1 months followed by DT (clopidogrel or ASS + VKA or NOAC) up to 12 months for low ischemic risk patients - clopidogrel is the recommended P2Y12-inhibitor - CHEST guideline does not differentiate between SIHD and ACS in AF, PCI: 1-6 months of TT (ASS, clopidogrel, VKA or NOAC) in high thrombotic/low bleeding risk, followed by DT (clopidogrel and VKA or NOAC) until 12 months; 12 months DT in high bleeding/low thrombotic risk patients, 1-3 months TT in patients with balanced thrombotic/bleeding risk, followed by up to 12 months DT (similar recommendations for Noth American Expert Document) antithrombotic regimen in elderly ≥ 65 years, need of anticoagulation - high risk of MACE and bleeding - most patients are not eligible for higher doses, need reduced doses - TT only for single cases - DAPT may not be an optimal treatment for prevetion of thromboembolism in AF - ongoing trials strategies to improve bleeding complications - gastrointestinal: proton-pump inhibitor (PPI)		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- interactions should be observed - NOAC preferred over VKA - Clopidogrel preferred to newer P2Y12-inhibitors - Low-dose ASS - Targeting a lower INR		

Kwon et al. 2021 Trends im antithrombotischen und antikoagulativen Therapieregime (Kohortenstudie, AF, PCI, Korea)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Kwon S. Impact of Non-Vitamin K Antagonist Oral Anticoagulants on the Change of Antithrombotic Regimens in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention. Korean Circ J 2021; 51(5):409–22. https://www.ncbi.nlm.nih.gov/pubmed/33764010. [88]	**Objective**
	to investigate how periprocedural antithrombotic regimens have been changed since the introduction of NOAC (non-vitamin K antagonist oral anticoagulants) among Korean patients with AF undergoing PCI
	
	Methods
	- retrospective cross-sectional study
	- claims database of the Health Insurance Review and Assessment during 2013–2018
	- n = 27,594 patients with AF (diagnostic codes of I48.0-48.4 or I48.9) undergoing PCI (procedural codes of M6551, M6552, M6561-6564, M6571, and M6572)
	- patients with mitral stenosis (I50, I52, and I59) or prosthetic heart valves (Z952-Z954) were excluded
	
	Intervention
		n = 27,594 patients with AF undergoing PCI (2013-2018)
		- number of patients with AF undergoing PCI:
		  o n = 3,913 in 2013
		  o n = 5,075 in 2018
		- number of patients who had coronary stent implantation
		  o n = 3,380 (86.4%) in 2013
		  o n = 4,432 (87.3%) in 2018
		- mean age
		  o 69.4 years in 2013
		  o 71.3 years in 2018, (p for trend <0.001)
		- proportion of females
		  o 35.2% in 2013
		  o 30.7% in 2018, (p for trend <0.001)
		- prevalence of dyslipidemia, congestive heart failure, and renal and liver diseases
		  o increased over the years
		- prevalence of MI, intracranial hemorrhage, and gastrointestinal bleeding
		  o decreased over the years
		  o (p for trend <0.001 in all cases except intracranial hemorrhage [p for trend =0.009] and gastrointestinal bleeding [p for trend =0.004])
		- CHA2DS2-VASc and HAS-BLED scores
		  o 3.7±1.8 and 3.3±1.1 in 2013
		  o 4.0±1.9 and 3.5±1.0 in 2018
		  o (p for trend <0.001 for both scores)
		- CHA2DS2-VASc scores ≥2
			n. a.
			
			limitations
			may be discrepancy between prescriptions and medications actually consumed
			
			lack of detailed clinical information or medical records
			
			study focused on the periprocedural period; long-term therapy was not assessed
				authors concluded that since introduction of NOAC, the patterns of periprocedural antithrombotic regimens changed rapidly towards mor TAT (triple therapy), specially with NOAC
				
				to evaluate the risks of ischemic stroke and bleeding, the CHA2DS2-VASc and HAS-BLED scores were used; high risk: CHA2DS2-VASc score ≥2 or HAS-BLED score ≥3

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	antithrombotic agents:
	- aspirin, clopidogrel, prasugrel, ticagrelor, warfarin, and NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban)
	- (in Korea, NOAC was fully reimbursed after July 2015)
	
	Outcomes
	- annual prevalence of PCI and prescriptions of each antithrombotic agent, including antiplatelet agents and oral anticoagulants, within 30 days after PCI
		o 89.1% in 2013
		  o 91.5% in 2018
		- HAS-BLED scores ≥3
		  o 80.0% in 2013
		  o 84.9% in 2018
		
		Temporal trends of antithrombotic regimens among patients with AF undergoing PCI
		2013 vs. 2018
		- Patients with AF undergoing PCI
		  o n = 3,913 vs. n = 5,075
		- Triple therapy (NOAC)
		  o n = 39 (1.0%) vs. n = 2,027 (39.9%), p <0.001
		- Triple therapy (warfarin)
		  o n = 956 (24.4%) vs. n = 308 (6.1%), p <0.001
		- Double therapy (NOAC)
		  o n = 1 (0.0%) vs. n = 115 (2.3%), p <0.001
		- Double therapy (warfarin)
		  o n = 25 (0.6%) vs. n = 10 (0.2%), p<0.001
		- DAPT
		  o n = 2,815 (71.9%) vs. n = 2,525 (49.8%), p<0.001
		- SAPT (single antiplatelet therapy)
		  o n = 50 (1.3%) vs. n = 58 (1.1%), p= 0.284
		- Patients with NOAC-based regimens
		  o n = 40 vs. n = 2,142
		- Patients with regular-dose NOAC
		  o n = 17 (42.5%) vs. n = 398 (18.6%), p<0.001
		- Patients with reduced-dose NOAC
		  o n = 23 (57.5%) vs. n = 1,744 (81.4%), p<0.001
		
		soubgroup analyses
		patients with with high risk of systemic thromboembolism*		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- n = 3,486 vs. n = 4,641 - Triple therapy (NOAC) ○ n = 38 (1.1%) vs. n = 1,904 (41.0%), p<0.001 - Triple therapy (warfarin) ○ n = 870 (25.0%) vs. n = 284 (6,1%), p<0,001 - DAPT ○ n = 2,489 (71.4%) vs. n = 2,254 (48.6%), p<0.001 patients with high risk of bleeding - n = 3,132 vs. 4,310 - Triple therapy (NOAC) ○ n = 36 (1.1%) vs. n =1,778 (41.3%), p>0.001 - Triple therapy (warfarin) ○ n = 802 (25,6%) vs. n = 256 (5,9%), p<0,001 - DAPT ○ n = 2,207 (70.5%) vs. n = 2,091 (48.5%), p<0.001 NOAC type 2013 to 2018 - rivaroxaban and apixaban are the two most preferred NOACs - dabigatran uses 75.6% to 7.9% - apixaban use to 34.3% - edoxaban use to 24.2% for P2Y12 inhibitors, clopidogrel was the most preferred choice (ticagrelor use has been substantially increased) Predictors of favoring triple antithrombotic therapy over dual antiplatelet therapy - age ≥75 OR 1.890; 95% CI, 1.576–2.267 (most significant predictor of TAT) - age of 65–74 years, - congestive heart failure, - CHA2DS2-VASc scores ≥2,		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		- hypertension, - systemic thromboembolic events favoring DAPT over TAT - female sex, - peripheral arterial disease, - MI, - dyslipidemia, - renal disease, - intracranial haemorrhage OR, 0.375; 95% CI, 0.170–0.827 (most potent predictor of DAPT)		

12.6 Versorgungskoordination

12.6.1 Daten aus dem deutschen Versorgungskontext

Qualitätsbericht 2021 Disease-Management-Programme Nordrhein

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Qualitätsbericht 2021 Disease-Management-Programme Nordrhein www.zi-dmp.de [89]	Die Autor*innen geben an, dass seit 1.5.2003 in Deutschland Verträge zum DMP KHK abgeschlossen warden können; in Nordrhein besteht der Vertrag seit 2004 (drittältestes strukturiertes Versorgungsprogramm) insbesondere die Symptomatik sowie die Lebensqualität der Betroffenen sollen günstig beeinflusst warden; weitere Ziele sind die Reduktion der Sterblichkeit sowie der kardiovaskulären Morbidität	In 2021 255 697 Betroffene im DMP KHK insgesamt (Abnahme um -6 317 im Vergleich zum Vorjahr) Hausärztlich betreut: 98,2% Anzahl der aktiven ärztlichen Teilnehmenden: 5 066 Betroffene mit aktueller Folgedokumentation: 248 368 (97,1%) (Abnahme um -5 851 im Vergleich zum Vorjahr) - Hinweis: alle nachfolgenden Darstellungen beziehen sich auf diese Teilgruppe Anteil Frauen: 35,1% Anzahl teinehmender stationärer Einrichtungen: 61 Anteil der DMP-Betreuten von den Erkrankten: ca. 70% Mittleres Alter: 72,8 Jahre (SD 11,2) Alter ≥ 76 Jahre; 45,3% Mittlere DMP-Teilnahmedauer: 7,8 Jahre (SD 5,2 Jahre) DMP-Teilnahmedauer ≥ 10 Jahre: 35,4%	n. a.	Ausführliche Darstellung der Ziele unter www.zi-dmp.de/dmp-atlas_nrw als Herausforderung beschrieben wird das große Ausmaß an Multimorbidität bei Betroffenen im DMP KHK (Alter und Multimorbidität werdeb als von großer Bedeutung für die Weiterentwicklung des Programms beschrieben)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		98,3% der Betreuten weisen mind. eine Begleit- und Folge-erkrankung auf: - arterielle Hypertonie (88,5 Prozent) - Fettstoffwechselstörung (78,8 Prozent) - Diabetes mellitus (48,3 Prozent) - bei > einem Viertel: kardiovaskuläre Begleiter-krankung – also ein nicht tödlicher Herzinfarkt oder ein akutes Koronarsyndrom (ACS), eine chronische Herzinsuffizienz, eine arterielle Ver-schlusskrankheit oder ein nicht tödlicher Schlaganfall Komorbidität - keine/andere 24,5% - Diabetes mellitus 20,2% - kardiovaskulär 27,1% - Diabetes + kardiovaskulär 28,2% Komorbidität im Detail (häufig dokumentierte Begleiterkran-kung) - Arterielle Hypertonie 88,5% - Asthma bronchiale 6,2% - Chronische Herzinsuffizienz 17,5% - COPD 17,2% - Diabetes mellitus 48,3% - Fettstoffwechselstörung 78,8% - Herzinfarkt oder akutes Koronarsyndrom 40,3% - Periphere arterielle Verschlusskrankheit (pAVK) 11,0% - Schlaganfall 5,1% - Multimorbidität (≥ 3 Begleiterkrankungen) 67,5% Blutdruck (mmHg) - < 130/85: 33,8% - 130/85 - <140/90: 30,8% - 140/90 - < 160/100: 28,0% - ≥ 160/100: 7,3% LDL-Cholesterin - < 70 mg/dl: 22,4% - ≥ 70 und < 100 mg/dl: 39,2% - ≥ 100 und ≤ 135 mg/dl: 25,1% - > 135 mg/dl: 13,3%		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Medikamentöse Therapie - Thrombozytenaggregations-Hemmer (TAH): 82,8% - Antikoagulanzien: 11,1% - Betablocker: 77,1% - ACE-Hemmer: 66,4% - Sartane: 9,0% - Diuretika: 30,0% - Statine: 82,2% Einflussfaktoren auf die Verordnungsquoten: Alter und Geschlecht sowie Begleiterkrankungen, z. B. - bei Betroffenen mit anamnetisch dokumentiertem Herzinfarkt oder Schlaganfall erhöhte Verordnungshäufigkeit von TAH: 90,7% bzw. 87,2%, Betablockern (84,6% bzw. 79,8%) sowie Statinen (88,0% bzw. 83,8%) - bei Betroffenen mit chronischer Herzinsuffizienz höher Verordnungsquoten von Betablockern (84,2%) sowie ACE-Hemmern (70,3%) **Versorgungsqualität der Betroffenen im DMP KHK** (zum April 2021: anhand verschiedener Qualitätsziele) - die beiden Ziele zum Anteil an geschulten Patientinnen und Patienten sind derzeit noch nicht sinnvoll auswertbar - im aktuellen Berichtsjahr erstmalig Diabetes- und Hypertonieschulungen zusammengefasst - Aussagen zu den Schulungen beziehen sich nun auf einen Zeitraum von zwei Jahren - Betablocker-Verordnung bezieht sich nur noch auf Betroffene mit einem neu aufgetretenen Herzinfarkt - Veränderung hinsichtlich der Statin-Dokumentation (Erfassung, ob aktuell eine niedrige, mittlere oder hohe Statindosis verordnet wird + neues Qualitätsziel hinsichtlich der Frage, ob die Statin-Verordnung leitliniengerecht erfolgt) - weiteres neues Ziel: Anteil an KHK-Patientinnen und -Patienten, die regelmäßig sportliches Training betreiben		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		Von den derzeit auswertbaren Qualitätszielen mit quantitativer Vorgabe werden die Ziele hinsichtlich der Medikation erreicht und die Quote der Patientinnen und Patienten, denen das Vermeiden von Angina pectoris-Beschwerden gelingt, liegt deutlich über der Zielvorgabe (Abb. 2): Betroffene mit u. a.: Blutdruck < 140/90 mm Hg: 63,9% (140 384 von 219 785) Nicht-rauchen: 84,7% (210 450 von 248 358) TAH verordnet: 82,8% (181 738 von 219 505) Betablocker verordnet nach Herzinfarkt: 85,7% (1 423 von 1 661) Statine verordnet: 82,2% (192 586 von 234 248) Statine leitliniengerecht verordnet: 84,5% (162 735 von 192 586) keine Angina pectoris Beschwerden mehr: 93,9% (233 283 von 248 362) Sportliches Training betreiben: 31,3% (60 368 von 192 879), Limitation: betagtes Patient*innenkollektiv Im Bericht angegeben: langfristige zeitliche Veränderungen der erreichten Zielquoten in den meisten Zielvorgaben stabil z. B. kontinuierlich etwa zwei Drittel der Betroffenen mit arterieller Hypertonie erreichte einen Blutdruck unter 140/90 mmHg; etwas mehr als acht von 10 Betroffene erhielten Thrombozytenaggregationshemmer (TAH); leichter Anstieg bei Statinverordnungen (u. a. durch ausführlichere Dokumentationsvorgaben) sowie bei Betroffenen ohne Angina Pectoris Beschwerden ergänzend angegeben, dass seit 2021 in der KHK-Dokumentation nicht mehr unterschieden wird zwischen der Diabetes- und Hypertonie-Schulung zudem kann seit 2021 erstmals eine KHK-spezifische Schulung veranlasst warden, unabhängig von der Begleiterkrankung (die Zahl der empfohlenen Schulungen hat seitdem zugenommen)		

Kirsch et al. 2020 Disease Management Program (guideline-adherence, patients with coronary artery disease after acute myocardial infarction)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

Kirsch et al. Patients with coronary artery disease after acute myocardial infarction: effects of continuous enrollment in a structured Disease Management Program on adherence to guideline-recommended medication, health care expenditures, and survival. Eur J Health Econ. 2020 Jun;21(4):607-619. doi: 10.1007/s10198-020-01158-z. Epub 2020 Feb 1. https://pubmed.ncbi.nlm.nih.gov/32006188/
 	
 [90]
	Objective
	 to compare guideline-recommended medication, health care expenditures, and survival of patients previously and continuously enrolled and not enrolled in the German DMP for coronary artery disease (CAD) after an AMI, from the perspective of a third-party payer over a follow-up period of 3 years
	
	 Methods
	 - pseudonymized claims data provided by the Allgemeine Ortskrankenkasse Bayern (AOK Bayern), a large regional statutory health insurance fund in the German federal state of Bavaria, covering the years 2008–2014
	 - patients continuously insured within AOK Bayern
	 - individuals with a hospitalization (main discharge diagnosis of AMI (ICD-10 I21)) between Jan 2009 and Dez 2011
	 - AMI before 2009 were excluded
	 - AMI after 2011 were excluded to guarantee a 3-year follow-up period
	 - patients were excluded if they died within 30 days after AMI, to avoid a nega-
		study population: 15,360 patients
		 - 4 100 enrolled and 11 260 not enrolled in the DMP
		 - propensity score matching: 3 870 pairs of patients enrolled and not enrolled in the DMP CAD after AMI
		 - median age 74 years
		 - female: ~34%
		 - smokers: 5-7%
		 - dyslipidemia: 18-19%
		 - atrial hypertonia: 30-32%
		
		 - after matching, only the standardized mean difference of HMG compensations (0.161) were above the threshold of 0.10
		
		 Results
		 primary
		 (DMP vs. not DMP)
		
		 PDC
		
		 - PDC rates over the three year follow up after AMI:
		     o anti-platelet agents: 76.43% vs. 70.66%
		     o statins: 54.18% vs. 52.13%
		     o ACE-inhibitors: 60.95% vs. 58.92%
		 - PDC rates over the first year after AMI:
		     o ß-blockers: 61.95% vs. 52.64%
		     o only the difference for ß-blockers were rated as statistically significant (*supplement Table 2; **DOCX**-document*)
		
		 Costs
		 (DMP vs. not DMP)
		 - adjusted mean health care expenditures per day per person for all three observation years:
		     o €58.24 [€53.36;€63.81] vs.
		     o €72.72 [€67.56;€78.38]
		     o p < 0.001
		 - adjusted mean health care expenditures per day per person for the first observation year:
			n. a.
			
			 note: supplement only available as Word-document
			
			 Limitations:
			
			 only data from a large regional statutory health insurance fund in the German federal state of Bavaria (eingeschränkte Übertragbarkeit)
			
			 "caliper" matching tends to result in estimates of treatment effect with less bias compared to other methods (konservativer Ansatz)
			
			 long period, 1 year before AMI and a 3-year follow-up period were available
			 (Vorteil gegenüber RCT; versorgungsnahe Analyse)
			
			 socioeconomic status, which may differ from their individual status (depriviation index as a proxy); e. g. a significant positive impact of height of old-age pensions on enrollment in the DMP (well balanced after matching)
			
			 treatment choices may be based on selection bias (no RCT); unmeasured confounding
			
			 (pharmacy-dispensing data were used (PDC), which does not allow definite judgment as to whether
				hypothesis: adherence to guideline recommended medication has a protective effect on death in patients after AMI:
				 - an extended model was estimated that included the additional covariates of PDC rates for antiplatelet agents, statins, β-blockers, and ACE-inhibitors
				
				 authors noted that being enrolled in the DMP CAD after AMI is a promising strategy as it is associated with enhanced guideline-recommended medication, lower total health care expenditures and reduced risk of death
				
				 authors discussed a protective effect of being female on survival and assumed that women after hospital discharge might have a better prognosis;

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	tive overestimation of proportion of days covered (PDC) rates - patients were excluded as control if they were enrolled in the DMP CAD during the year before AMI or during the 3-year follow-up period propensity score (1:1) matching with caliper method was conducted generalized linear and Cox proportional hazard models were used hierarchical morbidity group (HMG) compensation (control variable) - related to 80 costly chronisc diseases and serious illnesses (1-year follow-up costs of the HMG group from a regression analysis) - differentiated comorbidity index - HMG groups in the year before index date - compensations reflect the predicted costs in the first year after the index date confirmed by the ethics committee of the State Chamber of Physicians of Bavaria, no ethical approval was required for this study **Intervention** patients enrolled enrolled in the Disease Management Program (DMP)	○ €71.18 [€66.55;€76.26] vs. ○ €85.45 [€80.28;€90.84] ○ p < 0.001 Details: - Health care expenditures year 2 ○ N=3337 €24.05 [€21.79;€26.45€] vs. ○ N=3106 €22.98 [€20.69;€25.34] - Health care expenditures year 3 ○ N=3008 €22.04 [€19.98;€24.53€] vs. ○ N=2684 €19.45 [€17.42;€21.73] - Outpatient care all 3 years ○ N=3870 €3.06 [€2.38;€3.90€] vs. ○ N=3870 €2.75 [€2.20;€3.48€] - Outpatient care year 1 ○ N=3870 €2.95 [€2.20;€3.90] vs. ○ N=3870 €2.75 [€2.14;€3.57] - Outpatient care year 2 ○ N=3337 €2.65 [€1.94;€3.83] vs. ○ N=3106 €2.37 [€1.75;€3.34] - Outpatient care year 3 ○ N=3008 €3.16 [€2.17;€4.89] vs. ○ N=2684 €2.14 [€1.50;€3.19] ○ p < 0.05 - Medication all 3 years ○ N=3870 €3.95 [€3.68;€4.23] vs. ○ N=3870 €4.17 [€3.92;€4.45] - Medication year 1 ○ N=3870 €4.63 [€4.33;€4.92] vs. ○ N=3870 €4.80 [€4.49;€5.15] - Medication year 2 ○ N=3337 €3.21 [€2.90;€3.56] vs. ○ N=3106 €3.18 [€2.93;€3.47] - Medication year 3 ○ N=3008 €2.66 [€2.42;€3.01] vs. ○ N= 2684 €2.71 [€2.44;€3.03] - Hospitalization all 3 years*** ○ N=3870 €48.60 [€44.00;€54.07] vs. ○ N=3870 €61.85 [€56.73;€67.43] ○ p < 0.001 - Hospitalization year 1	patients had actually taken the medication collected at the pharmacy); Vorteil gegenüber Fragebögen: Vollständigkeit der Daten (Rücklaufquote) for all covariates, correlation of Schoenfeld residuals with survived days was examined, and the Kolmogorov–Smirnov supreme test was conducted; additionally sensitivity analyses were performed (Korrekturen für multiples Testen wurden nicht beschrieben)	as well as for angina pectoris, where several other studies available which found a relationship estimating a prognostic value of preinfarction angina pectoris by indicating less extensive infarct size resulting in better short- and long-term survival

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	for coronary artery disease (CAD) after an AMI
	
	Comperator
	patients not enrolled enrolled in the DMP after an AMI
	
	Outcomes
	primary
	- adherence rates (based on proportions of days covered (PDC))
	- average overall costs in euro (€) per person per day insured
	- survival days
	
	adherence based on ATC: anatomical therapeutic chemical classification system for: anti-platelet agents (B01A), statins (C10), β-blockers (C07), and angiotensin converting enzyme (ACE) inhibitors (C09A and C09B)
	
	PDC (observation period): the total number of days supplied for filled prescriptions, given the number of defined daily doses (DDDs) per prescription
	
	DDDs supplied by the scientific institute of the AOK ('WIdO') based on a German adaption of the WHO database (if discrepancies were seen, the dosage from the national guidelines was used)
		o N=3870 €59.92 [€55.32;€64.77] vs.
		o N=3870 €72.86 [€67.87;€77.97]
		- Hospitalization year 2
		  o N=3337 €16.46 [€14.65;€18.44] vs.
		  o N=3106 €16.03 [€14.27;€17.85]
		- Hospitalization year 3
		  o N=3008 €14.99 [€13.37;€16.83] vs.
		  o N =2684 €13.55 [€11.85;€15.28]
		- Rehabilitation all 3 years
		  o N=3870 €1.91 [€1.72;€2.11] vs.
		  o N=3870 €2.39 [€2.16;€2.65]
		  o p < 0.001
		- Rehabilitation year 1
		  o N=3870 €3.14 [€2.93;€3.37] vs.
		  o N=3870 €3.52 [€3.27;€3.77]
		  o p < 0.05
		- Rehabilitation year 2
		  o N=3337 €0.45 [€0.36;€0.56] vs.
		  o N=3106 €0.35 [€0.28;€0.43]
		- Rehabilitation year 3
		  o N=3008 €0.35 [€0.27;€0.43] vs.
		  o N=2684 €0.30 [€0.24;€0.37]
		- Remedies all 3 years
		  o N=3870 €1.11 [€1.01;€1.22] vs.
		  o N=3870 €1.46 [€1.34;€1.61]
		  o p < 0.001
		- Remedies year 1
		  o N=3870 €1.11 [€1.01;€1.22] vs.
		  o N=3870 €1.49 [€1.35;€1.64]
		  o p < 0.001
		- Remedies year 2
		  o N=3337 €0.70 [€0.62;€0.78] vs.
		  o N=3106 €0.90 [€0.80;€1.02]
		  o p < 0.001
		- Remedies year 3
		  o N=3008 €0.81 [€0.70;€0.95] vs.
		  o N=2684 €0.80 [€0.70;€0.96]		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar

	in case of hospitalizations, it was assumed that drugs were supplied by the hospital and thus the number of days that needed to be covered was reduced by the length of hospital stays
	
	costs were calculated by summing up every patient's costs by category and year and dividing them by the number of days the patient was insured in that period
		- authors noted that hospitalization costs far exceeded costs of medication, outpatient care, rehabilitation, and remedies for each observation year
		- differences mainly driven by higher inpatient expenditures in the first year after AMI
		- compared to the first year after AMI, in which significantly higher health care expenditures arise in the non-DMP group with regard to hospitalization ($p < 0.001$), rehabilitation ($p < 0.05$) and remedies ($p < 0.001$), in year two only costs for remedies ($p < 0.001$) and in year three only costs for ambulatory care ($p < 0.05$) were significantly different
		Survival days
		(DMP vs. not DMP)
		- base case survival analysis (Table 3 and Fig. 2)
		    o hazard ratio (HR) 0.757 (95% CI 0.700–0.819)
		    o $p < 0.001$
		- authors noted significant confounder: e. g. additional enrollment in DMP COPD and DMP type 2 diabetes; as well as age and congestive heart failure, atrial hypertonia (increased risk of death)		

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