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Nationale VersorgungsLeitlinie

Therapie des Typ-2-Diabetes

Evidenztabellen

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Ergänzungen und Modifikationen der Leitlinie sind über die Webseite http://www.diabetes.versorgungsleitlinien.de zugänglich.

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Systematischer Review, Metaanalyse, HTA

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Evidenzniveau (SIGN)
Network Meta-Analysis, Systematischer Review	Gross JL et al. (2011) [1]	databases: MEDLINE, EMBASE, Cochrane Library, LILACS, and ClinicalTrials.gov electronic databases + manual search + unpublished data (one) inclusion and exclusion criteria: Randomized trials at least 24 weeks in duration. Studies evaluated the effects of adding a third antihyperglycemic drug to treatment of adults aged 18 years or older with type 2 diabetes and a hemoglobin A1c (HbA1c) level greater than 7.0% who were already receiving a combination of	1)combination of metformin and a sulfonylurea + a third non-insulin antihyperglycemic drug versus placebo as third drug 2) combination of metformin and a sulfonylurea + a third non-insulin antihyperglycemic drug versus insulin as third drug (Options for third agents include insulin, -glucosidase inhibitors (acarbose), thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, and dipeptidyl peptidase-4 inhibitors)	Primary end points: change in HbA1c change in weight frequency of severe hypoglycemia. Results: Eighteen trials involving 4535 participants that lasted a mean of 31.3 weeks (24 to 52 weeks) were included. mean baseline HbA1c level of 8.8% (7.5% to 10.6%), a mean baseline BMI of 28.8 kg/m2 (24.0 kg/m2 to 34.2 kg/m2), and diabetes duration of 8.9 years (8.1 to 13.6 years). Nine studies reported adequate randomization, 0 were stopped early, and 15 did not specify whether data collectors and outcome assessors were blinded to study data. There was no evidence of publication bias when HbA1c level was used as an outcome. Results in detail for direct and indirect comparisons: see table 2+3 below	methodological weaknesses and strenght: Most of the trials were short term, and trial quality varied. With so few trials relative to antihyperglycemic agents, investigators relied on indirect comparisons, which increased the uncertainty of the findings and conclusions. The quality of trial conduct and reporting varied; only 5 of 18 studies included in the analyses were double-blind, and details of allocation were noted in only 9 of 18 studies, suggesting that other potential biases may have been introduced. Treatment regimens and patient populations varied They did a conventional meta-analysis, but because the number of randomized trials directly comparing antihyperglycemic agents was limited, they also used indirect comparisons and network meta-analysis with Bayesian software WinBUGS.	16. Lam KS et al, Diabetes Care. 1998; 17. Ko GT, Tsang CC, Ng CW, Wai HP, Kan EC. Clin Drug Investig. 2001; 18. Yale JF et al, Ann Intern Med. 2001; 19. Dailey GE et al. Am J Med. 2004; 20. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG;Ann Intern Med. 2005; 21. Kendall DM et al. Diabetes Care. 2005; 22. Ko GT, Tsang PC, Wai HP, Kan EC, Chan HC. Adv Ther. 2006; 23. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Diabetes Care. 2006; 24. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Diabetes Obes	1+

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		metformin and a sulfonylurea for at least 3 months. At least 24 weeks of follow-up, and reported changes in HbA1c level and weight and numbers of patients with severe hypoglycemic reactions as defined by the investigator or as reactions requiring third-party assistance or blood glucose levels of 1.9 mmol/L (35 mg/dL) or less. Exclusion: Studies comparing 2 formulations of insulins as a third agent in both groups were excluded. search period: From 1950 to December 2010 by using the Medical Subject Heading terms			Two independent investigators reviewed study titles and abstracts. Trials selected for detailed analysis and data extraction were analyzed by 2 investigators with an agreement value Kappa of 98%; disagreements were resolved by a third investigator. Two independent and blinded reviewers evaluated risk for bias according to the PRISMA. Cochran Q test to evaluate heterogeneity and I2 testing was used random-effects model was used because of heterogeneity They assessed the possibility of publication bias by using a funnel plot No role of funding source risk of bias except for blinding and randomization not described no clinical endpoints like mortaliity or morbidity except hypoglycemia	Metab. 2007; 25. Nauck MA et al. Diabetologia. 2007; 26. Reynolds LR, Kingsley FJ, Karounos DG, Tannock LR. Diabetes Res Clin Pract. 2007; 27. Dorkhan M, Frid A, Groop L. Diabetes Res Clin Pract. 2008; 28. Kadoglou NP, Iliadis F, Angelopoulou N, Perrea D, Liapis CD, Alevizos M. Diabet Med. 2008; 29. Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V; Curr Med Res Opin. 2009; 30. Blickle´ JF et al. Diabetes Obes Metab. 2009; 31. Hartemann-Heurtier A et al.. Diabetes Res Clin Pract. 2009; 32. Russell-Jones D et al; Diabetologia. 2009	

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		type 2 diabetes, noninsulin antihyperglycemic agents and insulins,					

Table 2. **Direct Meta-analysis Comparing Noninsulin Antihyperglycemic Agents or Insulins With Placebo and Noninsulin Antihyperglycemic Agents With Insulins: Effects on Change in HbA_{1c} Level and Weight and Severe Hypoglycemic Episodes**

Reports, *n*	Intervention	Weighted Mean Difference (95% CI) in HbA_{1c} Level, %	Weighted Mean Difference (95% CI) in Weight, *kg*	Severe Hypoglycemic Episodes (Events/Total), *n/n*	
				Intervention	Placebo or Insulin
Noninsulin antihyperglycemic agents or insulins vs. placebo					
9*	All agents	−0.96 (−1.11 to −0.81)	0.37 (−1.46 to 2.20)	8/1233	0/1016
2	Insulin	−0.71 (−0.95 to −0.47)	2.31 (0.13 to 4.48)	2/335	0/222
3†	Thiazolidinediones	−1.15 (−1.35 to −0.95)	2.40 (−1.65 to 6.45)	0/278	0/277
1	Acarbose	−0.60 (−1.16 to −0.04)	−0.96 (−1.80 to −0.12)	1/41	0/40
2	GLP-1 agonists	−1.04 (−1.24 to −0.85)	−1.40 (−2.90 to 0.08)	5/466	0/361
1	DPP-4 inhibitors	−0.89 (−1.11 to −0.67)	NA	0/113	0/116
Noninsulin antihyperglycemic agents vs. insulins					
10‡	All agents	0.29 (0.06 to 0.51)	−1.90 (−3.73 to −0.06)	6/553	15/566
6§	Thiazolidinediones	0.22 (0.07 to 0.37)	1.67 (0.98 to 2.36)	3/415	9/421
1	Acarbose	0.20 (−0.60 to 1.00)	NA	NA	NA
3	GLP-1 agonists	0.10 (−0.28 to 0.42)	−4.99 (−5.80 to −4.18)	3/138	6/145

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available.
* Six studies reported a change in body weight.
† One study reported a change in body weight, and 2 studies reported hypoglycemic episodes.
‡ Nine studies reported a change in body weight.
§ Five studies reported a change in body weight.

Table 3. **Network Meta-analysis Comparing All Noninsulin Antihyperglycemic Agents and Insulins: Mean Changes in HbA_{1c} Level and Weight**

Change in HbA_{1c} Level (95% CrI), %

Treatment	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.01 (−1.38 to −0.66)	–	–	–	–	–
Insulin	−1.08 (−1.41 to −0.77)	−0.07 (−0.41 to 0.25)	–	–	–	–
Thiazolidinediones	−0.95 (−1.27 to −0.65)	0.05 (−0.35 to 0.5)	0.12 (−0.16 to 0.41)	–	–	–
DPP-4 inhibitors	−0.94 (−1.58 to −0.36)	0.07 (−0.6 to 0.67)	0.14 (−0.51 to 0.77)	0.01 (−0.67 to 0.69)	–	–
Acarbose	−0.70 (−1.33 to −0.08)	0.31 (−0.4 to 1.03)	0.38 (−0.28 to 1.06)	0.25 (−0.39 to 0.93)	0.24 (−0.56 to 1.13)	–

Change in Weight (95% CrI), *kg*

	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.63 (−2.71 to −0.60)	–	–	–	–	–
Insulin	2.84 (1.76 to 3.90)	4.47 (3.71 to 5.26)	–	–	–	–
Thiazolidinediones	4.25 (2.76 to 5.66)	5.89 (4.54 to 7.2)	1.42 (0.29 to 2.55)	–	–	–
DPP-4 inhibitors	NA	NA	NA	NA	–	–
Acarbose	−0.96 (−2.77 to 0.73)	0.67 (−1.37 to 2.63)	−3.79 (−5.91 to −1.88)	−5.21 (−7.53 to −2.98)	NA	–

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available.

Gross JL et al. (2011) [1]

Network Meta-Analysis, Systematischer Review	McIntosh B et al. (2011) [2]	Databases, type of study, search period: MEDLINE, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were	One or more relevant drugs either (1) added to metformin because of inadequate glycemic control with metformin alone or (2) replacing metformin because of intolerance.	Outcomes: HbA1c, hypoglycemia, body weight, quality of life, long-term complications of diabetes, severe adverse events (drug related or otherwise) and mortality. #All classes of second-line agents added to metformin significantly reduced HbA1c relative to metformin alone # there were no statistically significant	methodological weaknesses and strenght: - Study selection, data extraction and quality assessment were conducted independently by 2 reviewers. Risk of bias was assessed using the SIGN-50 instrument. - Bayesian mixed-treatment	27. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Diabetes Care 2007; 28. Brazg R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Diabetes Obes Metab 2007; 30. Charbonnel B,	1(+)

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		searched for randomized controlled trials published in English from 1980 to October 2009. Additional citations were obtained from grey literature and conference proceedings inclusion and exclusion criteria: The population of interest consisted of adults and children with T2DM requiring a second-line antihyperglycemic agent because of inadequate control (hemoglobin A1c (HbA1c) > 6.5%, fasting plasma glucose (FPG) > 7 mmol/L on metformin monotherapy or because of intolerance to this therapy. Agents from the		differences between drug classes #Hypoglycemia: Thirty-four RCTs (n = 16 704). Relative to metformin monotherapy, risk was significantly elevated with insulins, sulfonylureas and meglitinides (odds ratios [ORs] were 5.2–11.0 for insulins and 8.2 for sulfonylureas). There were no significant differences between these classes. #Body weight: Treatment with sulfonylureas, meglitinides, TZDs and biphasic insulin resulted in significantly greater increases in body weight than metformin monotherapy (range 1.8–3.0 kg), with no significant differences between these classes. # Long-term complications and severe adverse events: There were insufficient data available for diabetes complications, mortality or quality of life. Most RCTs included in this review were of inadequate size or duration to detect differences in the occurrence of long-term complications of diabetes. On the basis of data available, no significant differences between treatments were found Details see below - Forty RCTs (n = 17 795) - Most trials were 6–12 months long, although 1 study was over 5 years in duration. Mean baseline HbA1c ranged from 6.6% to 10% (weighted mean ± standard deviation [SD] 8.0%	comparison (MTC) meta-analysis was conducted because of necessitating indirect comparisons (WinBUGS used) - system. literature search + - heterogeneity analysis +: All analyses conducted as random effects models; I2 or other statist. values are not shown (not in appendix 6 either) - COI + - Flowchart + - Sensitivity analysis+ - Publication bias was not assessed because of a limited number of studies for each pairwise comparison. - A majority of the RCTs in the analysis, including the largest trials, received a poor rating upon assessment for risk of bias.	Karasik A, Liu J, Wu M, Meininger G.. Diabetes Care 2006; 32. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Diabet Med 2001 33. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Diabetes Care 2005; 35. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Clin Ther 2000 38. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. JAMA 2000 41. Gómez-Perez FJ et al. Diabetes Metab Res Rev 2002 42. Goodman M, Thurston H, Penman J. Horm Metab Res 2009 43. Halimi S, Le Berre MA, Grangé V. Diabetes Res Clin Pract 2000 47. Kaku K. Curr Med Res Opin 2009; 51. Leiter LA, Harris SB,	

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		following drug classes were assessed: sulfonylureas, meglitinides, thiazolidine-diones, DPP-4 inhibitors, GLP-1 analogues, insulins and insulin analogues, alpha-glucosidase inhibitors and weight-loss agents (orlistat and sibutramine).		± 0.9%). The baseline duration of diabetes ranged from 1.8 to 10.3 years (weighted mean ± SD 6.1 ± 5.1 years). Most studies (89%) were industry funded. About two-thirds of the studies identified were of poor methodological quality; inadequate allocation concealment, failure to use an intention-to-treat analysis and lack of blinding were common limitations.		Chiasson JL, Edwards L, O'Neill MC, Van DM. Can J Diabetes 2005;. 52. Marre M, Howlett H, Lehert P, Allavoine T. Diabet Med 2002;. 53. Marre M et al. Diabetes Obes Metab 2002; 56. Moses R et al. Diabetes Care 1999;2007;9(2):194–205. 58. Nauck MA, Hompesch M, Filipczak R, Le TDT, Zdravkovic M, Gumprecht J. Exp Clin Endocrinol Diabetes 2006; 59. Nauck M et al. Diabetes Care 2009; 61. Phillips P, Karrasch J, Scott R, Wilson D, Moses R. Diabetes Care 2003; 62. Poon T et al. Diabetes Technol Ther 2005; 64. Raz I et al.Curr Med Res Opin 2008; 67. Rodger NW et al. Clin Invest Med 1995; 68. Rosenstock J et al.	

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						Diabetes Care 1998; 70. Scott R, Loeys T, Davies MJ, Engel SS; Sitagliptin Study 801 Group. Diabetes Obes Metab 2008; 72. Van Gaal L, Maislos M, Schernthaner G, Rybka J, Segal P. Diabetes Obes Metab 2001; 77. DeFronzo RA et al. . Diabetes Care 2009;	

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Table 1: Summary of results from direct and mixed-treatment comparison (MTC) analyses

Hemoglobin A1c (change from baseline, %)

	Direct estimates		MTC estimates
Treatment vs. metformin monotherapy	Studies	WMD (95% CI)	MD (95% CrI)
Sulfonylureas	3[32,52,58]	−0.80 (−1.00, −0.59)	−0.79 (−0.95, −0.63)
Meglitinides	2[53,56]	−0.71 (−1.24, −0.18)	−0.64 (−0.93, −0.37)
TZDs	6[26,28,41,47,51,70]	−0.96 (−1.18, −0.75)	−0.82 (−1.00, −0.66)
DPP-4 inhibitors	6[27,30,42,64,70,77]	−0.78 (−0.96, −0.60)	−0.80 (−0.95, −0.65)
AG inhibitors	5[43,61,67,68,72]	−0.74 (−0.94, −0.53)	−0.74 (−0.98, −0.50)
GLP-1 analogues	4[33,58,59,62]	−0.75 (−0.96, −0.53)	−0.82 (−1.05, −0.59)
Basal insulin	—	—	−0.82 (−1.16, −0.47)
Biphasic insulin	—	—	−0.97 (−1.33, −0.61)

Overall hypoglycemia (odds ratio)

	Direct estimates		MTC estimates
Treatment vs. metformin monotherapy	Studies	WMD (95% CI)	Median OR (95% CrI)
Sulfonylureas	3[32,52,58]	4.64 (1.27, 16.97)	8.22 (4.52, 16.63)
Meglitinides	2[53,56]	6.59 (1.53, 28.29)	8.59 (3.47, 25.20)
TZDs	6[26,28,41,47,51,70]	1.56 (0.56, 4.33)	1.10 (0.54, 2.27)
DPP-4 inhibitors	7[27,28,30,42,64,70,77]	1.07 (0.59, 1.93)	1.05 (0.56, 2.21)
AG inhibitors	2[68,72]	0.49 (0.04, 5.55)	0.39 (0.01, 6.67)
GLP-1 analogues	1[33]	1.00 (0.31, 3.20)	1.12 (0.33, 3.90)
Basal insulin	—	—	5.20 (1.48, 21.46)
Biphasic insulin	—	—	11.01 (3.48, 40.43)

Body weight (change from baseline, kg)

	Direct estimates		MTC estimates
Treatment vs. metformin monotherapy	Studies	WMD (95% CI)	MD (95% CrI)
Sulfonylureas	3[32,52,58]	1.79 (1.29, 2.28)	2.01 (1.09, 2.94)
Meglitinides	2[53,56]	2.01 (−0.31, 4.32)	1.80 (0.35, 3.29)
TZDs	4[26,41,47,70]	2.30 (1.93, 2.66)	2.59 (1.66, 3.51)
DPP-4 inhibitors	3[27,42,70]	0.70 (0.20, 1.21)	0.57 (−0.45, 1.60)
AG inhibitors	3[61,68,72]	−0.90 (−1.92, 0.13)	−0.92 (−2.35, 0.51)
GLP-1 analogues	2[33,58]	−1.58 (−3.53, 0.37)	−1.79 (−3.43, −0.14)
Basal insulin	—	—	1.56 (−0.46, 3.63)
Biphasic insulin	—	—	2.96 (0.96, 5.00)

AG = alpha-glucosidase, CI = confidence interval, CrI = credible interval, DPP = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, OR = odds ratio, TZDs = thiazolidinediones, WMD = weighted mean difference

McIntosh B et al. (2011) [2]

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Evidenzniveau (SIGN)
Meta-Analysis von 5 Kohortenstudien, kein Systematischer Review	Carnethon MR et al. (2012) [3]	Pooled analysis of five longitudinal cohort studies: Atherosclerosis Risk in Communities Study, 1990–2006; Cardiovascular Health Study, 1992–2008; Coronary Artery Risk Development in Young Adults, 1987–2011; Framingham Offspring Study, 1979–2007; Multi- Ethnic Study of Atherosclerosis, 2002–2011. Participants contributed 27,125 person-years of follow-up. No systematic search of databases.	Comparison between normal weight and overweight/obese participants who had incident diabetes	Main Outcome Measures - Total, cardiovascular, and non-cardiovascular mortality: participants with normal weight diabetes experienced a significantly elevated **total mortality** (hazard ratio [HR]=2.08, 95% CI: 1.52, 2.85) and **non-cardiovascular mortality** (HR=2.32, 95% CI: 1.55, 3.48). Although the hazard for **cardiovascular mortality** was elevated, the association was not statistically significant (HR=1.52, 95% CI: 0.89, 2.58). Setting - 2,625 participants with incident diabetes.	- cohort-specific analyses to generate effect estimates that were pooled together using fixed and random effects meta-analysis. Because effect estimates were relatively homogenous across cohorts, there were no differences between fixed and random effects and so they presented fixed effects - adjustment for waist circumference, total cholesterol, high density lipoprotein cholesterol, systolic blood pressure and smoking status were done - COI not reported - Comorb. or comed. not reported - No systematic search of databases - unclear, whether research question a priori defined	9. Friedman GD et al. Journal of Clinical Epidemiology. 1988; 10. Fried LP et al. Ann Epidemiol. 1991; 11. ARIC Investigators. American Journal of Epidemiology. 1989; 12. Bild DE et al.. Am J Epidemiol. 2002; 13. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. Prev Med. 1975;	1- (kein system. Review)
Systematischer Review /Meta-Analysis	Lerch C, Richter B (2010) [4]	RCT - Suchzeitraum: wurde nicht angegeben - Datenbanken: Grundlage war	Kombinationstherapie Insulin plus OAD versus Insulinmonotherapie Kombinationspartner Metformin Insulin vs. Insulin plus	- Studienanzahl: 22 zu 25 Vergleichen, - Meta-Analysen wurden immer dann durchgeführt, wenn die Angaben für die entsprechenden Endpunkte in den jeweiligen Studien dafür ausreichend waren. - Endpunkte: HbA1c und Körpergewicht,	Methodische Schwächen/Limitationen: - Keine 2 reviewer - Keine Ausschlusskriterien angegeben - Häufig keine KI angege-	2. oudswaard AN, Cochrane Database Syst Rev 2004; 3. van Avendonk et al, Diabetes Obes Metab 2009;	1-

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		systematischer Review der Cochrane Collaboration (2) und eine weitere Literaturübersicht zur Insulintherapie des Typ 2 Diabetes mellitus (3). Eine eigene systematische Literaturrecherche in MEDLINE erfolgte zusätzlich.
		- Ein- & Ausschlusskriterien: Eingeschlossen wurden randomisierte klinische Studien bei Patienten mit Diabetes mellitus Typ 2, die zuvor noch nicht dauerhaft mit Insulin behandelt wurden. Die Studien mussten über
			Sulfonylharnstoff
			Kombinationspartner Metformin und Sulfonylharnstoff
			Kombinationspartner Acarbose
			Kombinationspartner Metformin und Rosiglitazon
			Kombinationspartner Metformin und Repaglinid
			Kombinationspartner Pioglitazon
				schwere Hypoglykämien (keine patientenrelevanten Endpunkte wie Mortalität und Morbidität)
				<u>Signifikante Ergebnisse:</u>
				- Kombinationspartner Metformin:
				  - Vier Studien mit insgesamt 466 Patienten und einer Dauer zwischen 16 und 52 Wochen untersuchten die Hinzunahme von verschiedenen Insulintherapieformen zu Metformin (8-11).
				  - In der Meta-Analyse: um 0,4 % (95 %- Konfidenzintervall [95 %-KI] von 0,02 bis 0,7) bessere HbA1c-Senkung unter der Kombinationstherapie von Insulin und Metformin gegenüber der alleinigen Insulingabe.
				  - Schwere Hypoglykämie: 10 Episoden in der Insulin-Metformin-Gruppe gegenüber 1 Episode in der Insulinmonotherapiegruppe (relatives Risiko 9,5 mit 95 %-KI 1,2 bis 72) (10).
				- Kombinationspartner Acarbose :
				  - Hier wurde nur eine Studie von 20 Wochen Dauer identifiziert (25). 163 Patienten (mittleres Alter 62 Jahre, 51 % Frauen, BMI 30 mg/m2, Diabetesdauer 7 Jahre, HbA1c 8,5 %).
				  - Es zeigte sich ein um 0,5 % (95 %-KI 0,1 bis 0,9) bessere HbA1c-Absenkung unter der Kombinati-
					ben,
					- Suche nur in Medline
					- Kein Funnelplot für Erkennen von Publikationsbias, kein Forrestplot bei Meta-Analyse
					- Kein Test auf Heterogenität
					- Keine Qualitätsbewertung oder -beschreibung der berücksichtigten Studien beschrieben, keine diesbzgl. Ausschlusskriterien beschrieben
					- Keine Angabe des Suchzeitraums für Literaturrecherche
					- Viele große RCT nicht enthalten, unklar, ob nicht gefunden (z. B. wegen kurzem Suchzeitraum oder ausgeschlossen)
					- Kein Flowchart
						8. Yki-Järvinen H et al, Ann Intern Med 1999;
						9. Civera M et al, Diab Res Clin Pract 2008;
						10. Douek IF et al.,Diabet Med 2005
						11. Kvapil M et al, Diabetes Obes Metab 2006;
						25. Schnell O et al, Diabetes Obes Metab 2007;
						26. Home PD et al, Diabetic Med 2007;
						27. Raz I et al, Clin Ther 2005;
						28. Fonseca VA et al, J Diabet Complications 2006;	

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		einen Zeitraum von mehr als drei Monaten durchgeführt worden sein.		onsgabe von Mischinsulin und Acarbose. Die Insulinmonotherapie ging mit einer mittleren Gewichtszunahme von 10 kg einher, während das Körpergewicht unter Kombinationstherapie praktisch unverändert war.
				- Kombinationspartner Metformin und Rosiglitazon: (26)
				  - Die kombinierte Therapie führte zu einer um 0,7 (95 %-KI 0,5 bis 0,7) % größeren HbA1c-Absenkung. Schwere Hypoglykämien traten nicht auf. Verglichen zur Kombinationstherapie-Gruppe lag die Gewichtszunahme in der Insulinmonotherapiegruppe um 1,1 kg (95 %-KI 0,2 bis 2,1) höher.
				- Kombinationspartner Pioglitazon :
				  - In einer Studie war die mittlere HbA1c-Absenkung unter kombinierter Insulin-Pioglitazon-Therapie um 0,6 % (95 %-KI 0,2 bis 1) ausgeprägter (27), auch in der zweiten Studie zeigte sich ein Vorteil der Kombinationstherapie (28).			

Systematischer Review	Bennett WL et al. (2011) [5] und Bennett WL et al.	Suchzeitraum: from inception through April 2010 (December 2010 for longterm outcomes) Quellen:	Interventionen head-to-head monotherapy or combination therapy comparison of oral diabetes medication:	Included Studies: 140 RCT, 26 observational studies <u>1. Longterm Outcomes</u> Included Studies: 66, 45 since 2007, the new studies were generally of short duration (less than 1 year) and had few long-term events (such as deaths and cardio-	Qualitäts-bewertung mit dem GRADE System (alle vorhandenen Studien zu einem Endpunkt werden bewertet) Sichere Aussagen sind nur bei « Strength of Evidence = High » möglich !!		1++ (Qualität des Reviews, nicht der Studien)

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Evidenzniveau (SIGN)
	(2011) [6]	MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases for original English-language Articles, unpublished data from the Food and Drug Administration and others Two reviewers: title screening, quality assessment	metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 receptor agonists Comparisons - Monotherapy as main intervention 1. Metformin versus : Thiazolidinedione, Sulfonylurea, DPP-4 inhibitor, Meglitinides, GLP-1 agonist, Combination of metformin plus thiazolidinedione, Combination of metformin plus sulfonylurea, Combination of metformin plus DPP-4 inhibitor, Combination of metformin plus meglitinides, Combination of metformin plus GLP-1 agonist 2. Thiazolidinedione versus different thiazolidinedione, • Sulfonylurea, DPP-4 inhibitor, Meglitinides, GLP-1	vascular disease), making any estimates of risk difference very imprecise 1a. All cause mortality Strength of the evidence low, Evidence insufficient : Low All-cause mortality was slightly lower with metformin than with a sulfonylurea in observational studies, but results differed between trials and observational studies. Risk for bias in the studies was moderate. Many RCTs were short (1 y) and few deaths occurred, limiting precision. Several comparisons did not address all-cause mortality; these included most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone vs. rosiglitazone, comparisons with an insulin preparation, and most combination therapy comparisons. 1b. Cardiovascular disease mortality Strength of evidence low, Evidence insufficient: Cardiovascular mortality was slightly lower with metformin than with a sulfonylurea, but results were imprecise and had moderate risk for bias. Risk for cardiovascular mortality was similar between metformin and the thiazolidinediones as monotherapy, with high imprecision of results, inconsistencies, and moderate risk for bias. Several comparisons, including most DPP-4 inhibitor and GLP-1 agonist com-			

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			agonist 3. Sulfonylurea Versus DPP-4 inhibitor, Meglitinides, GLP-1 agonist 4. DPP-4 inhibitor versus Meglitinides, GLP-1 agonist Combination therapy as main Intervention 1.Combination of metformin plus (a thiazolidinedione or a sulfonylurea or one of the meglitinides or a DPP-4 inhibitor or a GLP-1 agonist or a basal insulin or a premixed insulin) versus Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist or a basal insulin or a premixed insulin) 2. Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist or a	parisons, pioglitazone vs. rosiglitazone, and most combination therapy comparisons, did not address this outcome 1c. Cardiovascular and cerebrovascular disease morbidity Strength of Evidence low, Evidence insufficient - Results were inconclusive for comparison of metformin with a thiazolidinedione, with high imprecision and inconsistency of direction of findings. - Metformin decreased risk for fatal and nonfatal ischemic heart disease events (odds ratio, 0.43 [95% CI, 0.17 to 1.10]) compared with the combination of metformin and rosiglitazone, with a consistent direction of results but high imprecision and lack of statistical significance. - Several comparisons, including most DPP-4 inhibitor and GLP-1 agonist comparisons, pioglitazone vs. rosiglitazone, and most combination therapy comparisons, did not address this outcome. 1d. Retinopathy, Neuropathy, Nephropathy Evidence insufficient: No studies addressed the outcome of retinopathy. Strengh of Evidence: low Three comparisons were included for the			

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			basal insulin or a premixed insulin) versus Combination of a thiazolidinedione plus (a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist) Endpunkte Intermediate outcomes : HbA1c Weight Low Densiity Lipoproteines High Density Lipoproteins Triglyceride Long-term clinical outcomes All cause mortality Cardioascular mortality Cardiovascular and cerebrovascular disease morbidity Retinopathy Neuropathy Nephropathy Harms Hypoglycemia Liver Injury Congestive Heart Fai-	outcome of neuropathy; studies had high risk for bias, small sample sizes, and poorly defined outcomes. Strenght of evidence: moderate Pioglitazone reduced the urinary albumin–creatinine ratio in 2 trials (by 15% and 19%) over metformin, suggesting less nephropathy. <u>2. Intermediate Outcomes</u> Intermediate clinical outcomes were the most frequently evaluated outcomes. We identified 121 relevant articles with data from RCTs that addressed either HbA1c, body weight, or lipids. 2a. HbA1c-Wert Strengh of Evidence: High Metformin and second-generation sulfonylureas showed similar changes in HbA1c, with a pooled between-group difference of 0.07% (95% CI -0.12% to 0.26%) for studies lasting longer than 3 months but usually less than 1 year in duration. Strength of Evidence: High Combination therapies were better than monotherapy regimens at reducing HbA1c, with an absolute difference of about 1%. In comparisons of metformin versus metformin plus thiazolidinediones, and metformin versus metformin plus sulfonylureas, the combination therapy was favored for HbA1c reduction. Strengh of Evidence: Moderate			

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			lure Lactic Acidosis Cancer Severe Allergic Reaction Hip an Non-Hip Fractures Acute Pancreatitis Cholecystitis Macular Edema Gastrointestinal Effects	When compared with DPP-4 inhibitors, metformin had a greater reduction in HbA1c, with a pooled between-group difference of -0.4% (95% CI -0.5% to -0.2%). Strength of Evidence; Moderate Comparisons of metformin versus thiazolidinediones, thiazolidinediones versus sulfonylureas, sulfonylureas versus repaglinide, and pioglitazone versus rosiglitazone showed similar reductions in HbA1c, with an absolute reduction in HbA1c of around 1% as compared with baseline values, with trials lasting 1 year or less. Strength of Evidence:; Moderate Metformin plus DPP-4 inhibitor was favored over metformin alone for HbA1c reduction. Strength of Evidence: Moderate The combination of metformin plus thiazolidinedione had a similar efficacy in reducing HbA1c as the combination of metformin plus sulfonylurea. Strength of Evidence: Low The combination of pioglitazone plus sulfonylurea was minimally favored over metformin plus pioglitazone, by an absolute difference of 0.03%. Strength of Evidence: Low The combination of metformin plus a premixed insulin analogue was minimally favored over metformin plus a basal insulin, by an absolute difference of			

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				0.30% to 0,43%. 2b. Body Weight Strength of Evidence High Metformin maintained or decreased weight to a greater extent than did thiazolidinediones (pooled between-group difference of -2.6 kg, 95% CI -4.1 kg to -1.2 kg), the combination of metformin plus a thiazolidinedione (pooled between-group difference of -2.2 kg, 95% CI -2.6 kg to -1.9 kg), or the combination of metformin plus a sulfonylurea (pooled between-group difference of -2.3 kg, 95% CI -3.3 kg to -1.2 kg). Thiazolidinediones alone or in combination were associated with weight gain. Strength of Evidence High Metformin maintained or decreased weight to a greater extent than did sulfonylureas, with a pooled between-group difference of -2.7 kg (95% CI -3.5 kg to -1.9 kg). Strength of Evidence High Sulfonylureas and the meglitinides had similar effects on body weight. Strength of Evidence Moderate GLP-1 agonists decreased weight to a greater extent than did sulfonylureas (pooled between-group difference of -2.5 kg, 95% CI -3.8 kg to -1.1 kg). Strength of Evidence Moderate Metformin plus sulfonylurea had a more			

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				favorable effect on weight than did either the combinations of a thiazolidinedione plus sulfonylurea (pooled between-group difference of -3.2 kg, 95% CI -5.2 kg to -1.1 kg) or metformin plus a thiazolidinedione (pooled between-group difference of -0.9 kg, 95% CI -1.3 kg to -0.4 kg). Strength of Evidence Moderate Metformin decreased weight to a greater extent than did DPP-4 inhibitors (pooled between-group difference of -1.4 kg, 95% CI -1.8 kg to -1.0 kg). Strength of Evidence Moderate Metformin had no significantly different effect on weight than did the combination of metformin plus DPP-4 inhibitors (pooled between-group difference of -0.2 kg, 95% CI -0.7 kg to 0.2 kg). Strength of Evidence Low Metformin plus GLP-1 agonists decreased weight to a greater extent than did several combination therapies (metformin plus sulfonylurea, metformin plus thiazolidinedione, metformin plus basal insulin, or metformin plus DPP-4 inhibitor). Strength of Evidence Low Metformin plus DPP-4 inhibitors decreased weight to a greater extent than did two standard combinations, metformin plus thiazolidinedione or metformin plus sulfonylurea. 2c. LDL Cholesterol			

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				Strength of Evidence: High Metformin decreased LDL to a greater extent than did sulfonylureas, which generally had little effect on LDL, with a pooled between-group difference of -10.1 mg/dL (95% CI -13.3 mg/dL to -7.0 mg/dL). Strength of Evidence: High The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did metformin monotherapy (pooled between-group difference of 14.5 mg/dL, 95% CI 13.3 mg/dL to 15.7 mg/dL), Strength of Evidence Moderate Metformin decreased LDL cholesterol to a greater extent than did pioglitazone, which increased LDL cholesterol, with a pooled betweengroup difference in LDL of -14.2 mg/dL (95% CI -15.3 mg/dL to -13.1 mg/dL). Strength of Evidence Moderate Metformin decreased LDL cholesterol to a greater extent than did rosiglitazone, with a pooled between-group difference in LDL of -12.8 mg/dL (95% CI -24.0 mg/dL to -1.6 mg/dL). Strength of Evidence Moderate Metformin decreased LDL to a greater extent than did DPP-4 inhibitors,with a pooled between-group difference of -5.9 mg/dL (95% CI -9.7 mg/dL to -2.0 mg/dL). Strength of Evidence Moderate			

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				The combination of metformin and rosiglitazone decreased LDL to a lesser extent than did a combination of metformin and a secondgeneration sulfonylurea, with a pooled between-group difference in LDL of 13.5 mg/dL (95% CI 9.1 mg/dL to 17.9 mg/dL). 2d HDL cholesterol Strength of Evidence High Metformin increased HDL to a lesser extent than did pioglitazone, with a pooled between group difference of -3.2 mg/dL (95% CI -4.3 mg/dL to -2.1 mg/dL). Strength of Evidence High Sulfonylureas were similar to metformin in terms of changes in HDL. Strength of Evidence High The combination of metformin and rosiglitazone increased HDL to a greater extent than did metformin monotherapy (pooled between-group difference 2.8 mg/dL, 95% CI 2.2 mg/dL to 3.5 mg/dL). Strength of Evidence Moderate Rosiglitazone increased HDL to a lesser extent than did pioglitazone (pooled between-group difference of -2.3 mg/dL, 95% CI -3.5 mg/dL to -1.2 mg/dL). Rosiglitazone alone was similar to metformin in terms of changes in HDL. Pioglitazone increased HDL to a greater extent than did sulfonylureas (pooled between-group difference of 4.3 mg/dL, 95% CI 1.9 mg/dL to 6.6 mg/dL). The combination of			

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				metformin and pioglitazone increased HDL by about 5 mg/dL relative to the combination of metformin and a sulfonylurea. The combination of metformin and rosiglitazone increased HDL to a greater extent than did the combination of metformin and a sulfonylurea (pooled between-group difference 2.7 mg/dL, 95% CI 1.4 mg/dL to 4.1 mg/dL). Strength of Evidence Moderate The combination of metformin and DPP-4 inhibitors had similar effect on HDL as did metformin monotherapy (pooled between-group difference was 0.5 mg/dL, 95% CI -1.5 mg/dL to 2.5 mg/dL). Strength of Evidence Low The combination of pioglitazone with another medication was favored for the following comparisons: pioglitazone plus metformin versus metformin monotherapy, metformin plus pioglitazone versus metformin plus sulfonylurea, and pioglitazone plus sulfonylurea versus metformin plus sulfonylurea, with a range of between-group differences from 3.1 mg/dL to10.5 mg/dL. 2e. Triglycerides Strength of Evidence High Pioglitazone decreased TG to a greater extent than did metformin (pooled between-group difference -27.2 mg/dL, 95% CI -30.0 mg/dL to -24.4 mg/dL). Strength of Evidence High			

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				Metformin monotherapy decreased TG to a greater extent than did the combination of metformin and rosiglitazone, with a pooled between-group difference in TG of -14.5 mg/dL (95% CI -15.7 mg/dL to -13.3 mg/dL). Strength of Evidence Moderate Metformin decreased TG to a greater extent than did rosiglitazone, which increased TG, with a pooled between-group difference of -26.9 mg/dL (95% CI -49.3 mg/dL to -4.5 mg/dL). Metformin decreased TG to a greater extent than did sulfonylureas (pooled between-group difference -8.6 mg/dL, 95% CI -15.6 mg/dL to -1.6 mg/dL). Strength of Evidence Moderate The combination of metformin plus rosiglitazone and the combination of metformin plus sulfonylurea had similar effects on TG. The combination of metformin and pioglitazone decreased TG to a greater extent than did the combination of metformin and a sulfonylurea, with between-group differences ranging from -10 mg/dL (p = 0.30) to -24.9 mg/dL (p = 0.045). Strength of Evidence Moderate Sulfonylureas and meglitinides had similar effects on TG (pooled between-group difference 0.2 mg/dL, 95% CI -3.8 mg/dL to 4.2 mg/dL). 3. Adverse outcomes			

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				3.1 Hypoglycemia Strength of Evidence High The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with metformin, with a pooled OR of 4.6 (95% CI 3.2 to 6.5). The range of rates for mild to moderate hypoglycemia in the metformin group was 0 to 17.7%, with a median rate of 0%. The risk of mild to moderate hypoglycemia with sulfonylureas exceeds the risk with thiazolidinediones, with a pooled OR of 3.9 (95% CI 3.0 to 4.9). The range of rates for mild to moderate hypoglycemia in the thiazolidinedione group was 0 to 92.1%, with a median rate of 4.4%. The risk of hypoglycemia with metformin plus sulfonylurea exceeds the risk of metformin plus thiazolidinediones, with a pooled OR of 5.8 (95% CI 4.3 to 7.7). The range of rates for mild to moderate hypoglycemia in the metformin plus thiazolidinediones group ranged from 0 to 9.3%, with a median rate of 1.3%. Strength of Evidence Moderate The risk of hypoglycemia with sulfonylurea exceeds the risk with DPP-4 inhibitors (20 events versus none in a single study). The risk of hypoglycemia was similar between metformin and thiazolidinediones. The risk of hypoglycemia with metformin plus sulfonylurea exceeded the risk with metformin alone, with an OR range of 0.6			

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				to 9.3. The risk of hypoglycemia was modestly higher for meglitinides than for metformin, with an OR of 3.0 (95% CI 1.8 to 5.2). The range of rates for mild to moderate hypoglycemia in the metformin group ranged from 0 to 24%, with a median rate of 3.7%. The risk of hypoglycemia was higher for metformin plus a thiazolidinedione than for metformin alone, with an OR of 1.6 (95% CI 1.0 to 2.4). The range of rates for mild to moderate hypoglycemia in the metformin group ranged from 0 to 9.1%, with a median rate of 1.4%. The combination of metformin and DPP-4 inhibitor had similar risk of hypoglycemia as that of metformin alone. The combination of metformin with a sulfonylurea had a higher risk of hypoglycemia than metformin with GLP-1 agonists Metformin combined with a basal insulin had a modestly lower risk of hypoglycemia when compared to metformin combined with a premixed insulin, with the RR ranging from 0.34 to 0.94 in 5 trials. 3b. Gastrointestinal Side Effects Strength of Evidence High Metformin was associated with twice as many GI adverse events, most commonly diarrhea, nausea, and vomiting, as were thiazolidinediones. The rates of GI ad-			

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				verse effects were similar for thiazolidinediones and sulfonylureas. Strength of Evidence Moderate Metformin was associated with more frequent GI adverse events than were DPP-4 inhibitors. Metformin was associated with twice as many GI adverse event rates as were second-generation sulfonylureas. Metformin monotherapy was associated with more frequent GI adverse events than were either the combination of metformin plus a sulfonylurea or metformin plus a thiazolidinedione, if the metformin component was of a lower dose than in the metformin monotherapy arm. Strength of Evidence Moderate The combination of metformin and sulfonylurea was associated with slightly more frequent GI adverse events than were seen with a combination of a thiazolidinedione and a sulfonylurea. 3c. Congestive heart failure Strength of Evidence Moderate The risk of CHF was higher for thiazolidinediones than for sulfonylureas (OR 1.68, 95% CI 0.99 to 2.85). Evidence insufficient No long-term trials assessed the comparative effects of the DPP-4 inhibitors and GLP-1 agonists on the risk of heart failure 3d. Cholecystitis and pancreatitis			

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				Strength of Evidence Low Two comparisons were included for the outcome of cholecystitis, and one comparison was included for the outcome of pancreatitis, with unclear conclusions. 3e. Lactate acidosis Strength of Evidence Moderate The risk of lactic acidosis was similar for metformin and sulfonylurea alone and for the two in combination. 3f. Macula Edema Evidence insufficient Only one trial reported on macular edema. The evidence was insufficient for all comparisons. 3g. Cancer Evidence insufficient Few studies addressed the outcome of cancer. 3h Liver injury Strength of Evidence High The risk of liver injury was similar for thiazolidinediones and sulfonylureas. Strength of Evidence Moderate The rates of liver injury were similar between thiazolidinediones and metformin. 3i. Fractures Strength of Evidence High The risk of fracture was higher for thiazolidinediones than for metformin. In one			

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				large RCT the RR was 1.57 (95% CI 1.13 to 2.17) and women in the thiazolidinedione arm had a higher fracture risk than men. The fracture rate was 4.1% in the reference (metformin) arm. The risk of fracture was higher for combination therapy with a thiazolidinedione than for metformin plus sulfonylurea, with higher risk in women than in men. In one large RCT, the RR was 1.57 (95% CI 1.26 to 1.97) for the rosiglitazone combination therapy arm, as compared to the combination of metformin plus sulfonylurea arms. The fracture rate in the reference (metformin + sulfonylurea) arm was 1.6%.			
Systematischer Review	Esposito K et al. (2012) [7]	Suchzeitraum: Bis 4/2011 Quellen: Medline, Embase, Cochrane Central, Cinahl, Webseiten, Referenzlisten alle Sprachen Extraktion durch 2 Personen Studien: RCT Ergebnisse nach mind. 12 Wo Behandlung Mind. 30 Stu-	Zusatz von einem nicht-Insulin zur Behandlung des Typ-2-DM, bzw. Neubeginn der Behandlung: 1. Metformin, 2. Sufonylharnstoffe, 3. alpha-Glucosidase-Inhibitoren, 4. Glinide, 5. GLP-1-Analoga (Inkretinmimetika), 6. Thiazolidinedion, 7. di-Peptyl-Peptidase-4-Inhibitoren (DPP4-Inhib.), 8. Insulinanaloga Endpunkte:	Eingeschlossene Studien: 218 RCT publ. 1994-2011 mit 78.945 Patienten für primären Endpunkt 82 RCT publ. ab 2007 1 Cross-over, sonst Parallel-Design meist multinational und industriegesponsert 122 mind. doppelt blind In 83 RCT Pat. vorher ohne Medikation bzw. vorher Absetzen anderer Medikation Studiendauer: 12-134 Wochen, meist 24-26 Wochen Eingeschl. Patienten: mittl. Alter 50,2-62,7J Mittl. HbA1c-Wert 7,2-11,7% Gepoolte Ergebnisse	Alle Ergebnisse unterliegen einer Heterogenität I^2 über 85%. Die Autoren sehen das nicht als Problem. Es ist unklar, welche Qualitätsbewertung die einzelnen Studien hatten. Es wird nur über HbA1c-Wert als Endpunkt berichtet.	Als e-Referenz Nr, 1-218 (siehe bei Literatur am Ende der Evidenztabellen)	1-

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		dienteilnehmer in jedem Arm Medikation in üblicher/ empfohlener Dosierung Studienbeurteilung mit Jadad-Score, 5-stufig <3 schlechte Qualität Patienten: Nur Typ-2-DM, mind. 18J, nicht schwanger, Ohne Medikation oder mit bestehender Medikation	Primärer Endpunkt: HbA1c-Wert < 7% gepoolt, gewichtet, + Standardabweichung vom Logarithmus Weiterer Endpunkt: Mittl. Änderung des HbA1c-Werts Heterogenitätsbeurteilung mit Q-Statistik und I². – Falls Heterogenität: Random Effects Modell, sonst Fixed Effects Modell.	1.Metformin 4.827 Pat., 21 Arme, Mittl HbA1c-Wert basal 8,55% (0,78) Mittl. Änderung HbA1c-Wert : -1,21 (0,48) HbA1c-Wert<7% 42%[35,5-48,9], I² 94,2 2. Sulfonylharnstoffe 5.895 Pat. , 24 Arme Mittl HbA1c-Wert basal 7,91% (0,45) Mittl. Änderung HbA1c-Wert : -0,77 (0,29) HbA1c-Wert<7% 48,2%43-53,5], I²93,2 3. Alpha-Glucosidase-Inhibitoren 1.120 Pat, 13 Arme, Mittl. HbA1c-Wert basal 8,39% (0,57) Mittl. Änderung HbA1c-Wert 0,72 (0,41) HbA1c-Wert<7% 25.9% [18,5-34,9], I² 89,4 4. Glinide 1.050 Pat., 9 Arme, Mittl. HbA1c-Wert basal 8,15% (0,38) Mittl. Änderung HbA1c-Wert -0,64 (0,29) HbA1c-Wert<7% 39,1%[29,3-49,9], I² 90,4 5a. GLP-1-Analoga tägl. 5.783 Pat. , 33 Arme Mittl HbA1c-Wert basal 8,38% (0,35) Mittl. Änderung HbA1c-Wert -1,12 (0,23) HbA1c-Wert<7% 45,7%[42,2-49,2], I²85,4 5b. GLP-1-Analoga LAR (wöchentl.) 668 Pat. , 4 Arme Mittl. HbA1c-Wert basal 8,41 (0,13) Mittl. Änderung HbA1c-Wert -1,61 (0,16)			

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				HbA1c-Wert<7% 63,2%[54,2-71,5], I²81,7 6. Thiazolidinedion 6.655 Pat. , 41 Arme Mittl. HbA1c-Wert basal 8,62 (0,64) Mittl. Änderung HbA1c-Wert -0,96 (0,32) HbA1c-Wert<7% 33,2%[28,5-38,2], I²93,1 7. DPP4-Inhibitoren 13.847 Pat. , 60 Arme Mittl. HbA1c-Wert basal 8,11 (0,55) Mittl. Änderung HbA1c-Wert -0,74 (0,30) HbA1c-Wert<7% 39%[35,7-42,3], I²93,2 8. Insulinanaloga 8a. Basale Gabe 21.615 Pat.,57 Arme, Mittl. HbA1c-Wert basal 8,79% (0,26) Mittl. Änderung HbA1c-Wert -1,28 (0,36) HbA1c-Wert<7% 38,9%[35,7-42,2], I² 95,1 8b. Biphasische Gabe 11.921 Pat, 51 Arme Mittl. HbA1c-Wert basal 9,30% (0,60) Mittl. Änderung HbA1c-Wert -1,91 (0,64) HbA1c-Wert<7% 34,4%[31,1 37,9], I² 92,1 8c. Prandiale Gabe 2.579 Pat., 13 Arme Mittl. HbA1c-Wert basal 8,66% (0,54) Mittl. Änderung HbA1c-Wert -1,08 (0,68) HbA1c-Wert<7% 36,34%[26,3-47,7], I² 96,1 8d. Basal-Bolus Gabe			

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				2.967 Pat., 16 Arme Mittl. HbA1c-Wert basal 8,33% (0,52) Mittl. Änderung HbA1c-Wert -1,22 (0,58) HbA1c-Wert<7% 50,2%[43,0-57, 4], I² 93,0 Stratifizierte Ergebnisse We divided all arms in 7 strata from baseline HbA1c.(from < 7,5 to > 10,0). There was a progressive decrease of the proportion of patients at target for each 0,5% increment of baseline HbA1c, ranging from 57,8% of baseline </= 7 to 20,8% of baseline >/=10.(p for trend <0,0001). Similarly, there was a progressive increase in HbA1c reduction ranging from -0,53 to -2,17 (p<0,0001). We further stratified all 342 arms in insulin (137arms, 39.100 Pat) and non-insulin drugs (205, 39.845 Pat.). The relation for baseline HbA1c reached a plateau for Insulin for basal HbA1C> 9% for insulin, while the same relation for non-insulin drugs was continouos without any evidence of plateau. The relation between baseline HbA1c and reduction in HbA1c was linear for insulin but was no more evident at the highest baseline values for non-insulin drugs			
Systematischer Review mit Meta-Analyse	Hemmingsen B. et al. (2012) [8]	Suchzeitraum: until March 2011. Quellen: The Cochrane	Interventionen: Metformin + insulin versus insulin alone Endpunkte:	Included Studies: 30 publications describing 26 randomised clinical trials, randomly assigning 2.286 patients to metformin and insulin versus to insulin alone. Three trials could not	Assessment of Risk of bias with the Cochrane Instrument a random effects model and a fixed effect was used. In case of discrepancy between the		1+/- (- für long-term outcomes)

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		Library, Medline, Embase, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature and Cumulative Index to Nursing and Allied Health Literature, Abstracts presented at the American Diabetes Association and European Association for the Study of Diabetes, Congresses, Contact of relevant trial authors and pharmaceutical companies, hand searched reference lists of included trials, and searched the US Food and Drug Administration website. Studien: RCT comparing metformin and	Primary outcomes: All Cause Mortality Cardiovascular Mortaliy Secondary outcomes: macrovascular and microvascular diseases assessed as composite outcomes and in separate (non-fatal myocardial infarction, non-fatal stroke, abdominal aorta aneurism, amputation of lower extremity, cardial or peripheral revascularisation, manifestation and progression of nephropathy, end stage renal disease, manifestation and progression of retinopathy, or retinal photocoagulation) adverse events, cancer, quality of life, costs of intervention, insulin dose, glycaemic control, weight, and blood pressure	provide data for the meta-analysis because they only described the total number of patients who underwent randomisation.29 30 Accordingly, 23 trials (2117 participants) provided data for our analyses. Strength of the evidence All trials had high risk of bias. Data were sparse for outcomes relevant to patients. All Cause Mortality/Cardiovascular Mortality Metformin and insulin versus insulin alone did not significantly affect all cause mortality (relative risk 1.30, 95% confidence interval 0.57 to 2.99,p=0,77 I ²= 0) or cardiovascular mortality (1.70, 0.35 to 8.30, p=0,52, I²=0). Trial sequential analyses showed that more trials were needed before reliable conclusions could be drawn regarding these outcomes. Intermediate outcomes In a random effects model, metformin and insulin resulted in reduced HbA1c, weight gain, and insulin dose, compared with insulin alone; trial sequential analyses showed sufficient evidence for a HbA1c reduction of 0.5%, lower weight gain of 1 kg, and lower insulin dose of 5 U/day. Adverse effects In a fixed effect model, but not in a random effects model, severe hypoglycaemia was significantly more frequent with metformin and insulin than with insulin	two models, both results were reported. ´ Examination of heterogeneity with the I2 statistic (I2 ≥50% indicated substantial heterogeneity).		

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		insulin versus insulin alone (with or without placebo) and with an intervention period of at least 12 weeks all languages all outcomes inclusion irrespective of publication status and outcomes Patienten: Patients with type 2 diabetes, older than 18 years		alone (2.83, 1.17 to 6.86)			
Systematischer Review mit Meta-Analyse	Karagiannis T et al. (2012) [9]	Suchzeitraum 1980 to 2011 The last search was run on 15 March 2011. Search of abstracts 2009/2010 Quellen: No language restriction Medline, Embase, the Cochrane Library, conference proceedings, trial regis-	Interventionen: Comparison of DPP-4 with metformin as monotherapy or with a sulfonylurea, pioglitazone, a glucagon-like peptide-1 (GLP-1) agonist, or basal insulin combined with metformin Endpunkte: Primary endpoint: change of baseline HbA1c	Included studies 27 reports (15 published primary studies, eight published extensions, three unpublished extensions, and one conference abstract) with 7.136 patients randomised to a DPP-4 inhibitor and 6745 patients randomised to another hypoglycaemic drug were included in the systematic review and meta-analyses. 12 reports compared a DPP-4 inhibitor with metformin as monotherapy. A DPP-4 inhibitor combined with metformin was compared with metformin combined with a sulfonylurea, pioglitazone, and a GLP-1 agonist in nine, and three reports respectively. Study characteristics	Bias Assessment mit Cochrane Collaboration's risk of bias tool		1++ (Qualität des Reviews, nicht der zugrundeliegenden Studien)

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		ters, and drug manufacturers' websites. Studien: Randomised controlled trials that compared a DPP-4 with metformin as monotherapy or with a sulfonylurea, pioglitazone, a glucagon-like peptide-1 (GLP-1) agonist, or basal insulin combined with metformin Patienten: adults with type 2 diabetes mellitus		Almost all studies were multicentre and sponsored by pharmaceutical companies. All studies were parallel and included an active control group in a double blind design, except for the study by Pratley et al32 40 (open label design), the study by Forst et al29 (in which patients were randomised to receive double blind linagliptin (1, 5, and 10 mg) or placebo or open label glimepiride), and the study by Handayani et al42 (no blinding mentioned). Nine reports (six primary studies and three extensions) were published in 2010, while three (one primary study and two extensions) were published in 2011. of intervention was equal to or longer than one year (52 weeks). The duration in 12 studies (including their extension periods). The primary end point in all studies was the change in HbA1c from baseline. Participants' baseline characteristics were equally balanced between the study arms in each study Risk of bias assessment Random sequence generation and allocation concealment were described adequately in 16 and 10 of the 27 eligible reports, respectively. Overall risk of bias for the primary outcome was low in three, unclear in nine nd high in 14 reports (mainly because of inadequate handling of outcome data (per protocol analysis) or attrition bias resulting from high discontinuation rate). We did not assess risk of bias for the study of			

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				Handayani et al because it was available only as an abstract. There was no evidence of publication bias from the visual interpretation of the funnel plot or Egger's test (P=0.363) 1. Intermediate outcomes 1a. HbA1c/Glycemic control Seven trials (n=3237) comparing a DPP-4 inhibitor with metformin monotherapy and 10 trials (n=8912) that compared DPP-4 inhibitors with other hypoglycaemic drugs combined with metformin contributed to this analysis. Compared with metformin monotherapy, DPP-4 inhibitors were associated with a smaller decline in HbA1c (weighted mean difference 0.20, 95% confidence interval 0.08 to 0.32, 95% prediction interval −0.14 to 0.54; I2=60%) (fig 2⇓) and a lower chance of attainment of the HbA1c goal of less than 7% (risk ratio in favour of metformin 1.18, 95% confidence interval 1.07 to 1.29, I2=34%) (fig 3⇓). Exclusion of the reports at high risk of bias did not alter the effect estimate or heterogeneity As a second line treatment, DPP-4 inhibitors achieved a smaller decline in HbA1c than the other hypoglycaemic drugs (overall weighted mean difference 0.12, 0.04 to 0.2, 95% prediction interval −0.13 to 0.37; I2=70%). Exclusion of reports at high risk of bias did not alter the effect estimate or heterogeneity.			

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				Data analysis separately for each type of active comparator, DPP-4 inhibitors were less effective than sulfonylureas in reducing HbA1c (weighted mean difference 0.07, 0.03 to 0.11, 95% prediction interval 0.02 to 0.13; I2=0%) There was no significant difference, however, in the attainment of the HbA1c goal of less than 7% (risk ratio in favour of sulfonylureas 1.06, 0.98 to 1.14; I2=26%)). There was no difference in the change in HbA1c achieved between DPP-4 inhibitors and pioglitazone (weighted mean difference 0.09, −0.07 to 0.24, 95% prediction interval −1.4 to 1.57, I2=40%) . Pioglitazone, however, was associated with a higher chance of reaching the goal of less than 7% (risk ratio in favour of pioglitazone 1.33, 1.09 to 1.63, I2=0%) DPP-4 inhibitors were inferior to GLP-1 agonists both in reducing HbA1c (weighted mean difference 0.49, 0.31 to 0.67; I2=27%) and in achieving the glycaemic goal of less than 7% (risk ratio in favour of GLP-1 agonists 1.33, 1.09 to 1.63; I2=26%) 1b. Body Weight Twelve trials (n=9156) contributed data in the main analysis for the change in body weight. As monotherapy, DPP-4 inhibitors were less effective in decreasing body weight than metformin (weighted mean difference 1.50, 0.90 to 2.11;I2-74%).			

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				When added to metformin, DPP-4 inhibitors had a favourable weight profile compared with sulfonylureas (−1.92, −2.34 to −1.49; I2=69%) or pioglitazone (−2.96, −4.13 to −1.78; I2=79%) but not compared with GLP-1 agonists (1.56, 0.94 to 2.18; I2=0%). 2. Longterm outcomes 2.1 All Cause Mortality Information on mortality ... was available in almost all trials. None of the trials, however, was designed to analyse this outcome. All cause mortality did not differ between DPP-4 inhibitors and any of the comparator.There were 23 deaths in patients receiving a DPP-4 inhibitor (n=6.789) and 28 deaths in patients receiving an active comparator (n=6.505). 3. Adverse events Information on serious adverse events available in almost all trials. None of the trials, however, was designed to ana-lyse this outcome Incidence of any serious adverse event was lower with DPP-4 inhibitors than with pioglitazone (risk ratio 0.47, 0.27 to 0.82; I2=0%) and similar compared with the other active treatments 3a. Hypoglycemia As the definition of hypoglycaemia varied across trials, we did not calculate a pooled estimate for risk. Only a few hypoglycaemias were observed in any treatment arm in trials that compared a			

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				DPP-4 inhibitor with metformin as monotherapy or with pioglitazone or a GLP-1 agonist as second line treatment. On the contrary, in most trials comparing a DPP-4 inhibitor with sulfonylureas combined with metformin the risk for hypoglycaemia was higher in the group receiving a sulfonylurea. Across all studies analysed, severe hypoglycaemia (defined as an episode that required the help of another person) occurred in six patients receiving a DPP-4 inhibitor (n=6.615). In the control groups, one patient receiving metformin as monotherapy (n=1.647), 51 receiving a sulfonylurea (n=3873), one patient receiving a GLP-1 agonist (n=381), and none of the 445 patients receiving pioglitazone experienced at least one episode of severe hypoglycaemia 3b. Other adverse events Treatment with a DPP-4 inhibitor resulted in lower discontinuation rate because of any adverse event compared with metformin monotherapy (risk ratio 0.69, 0.51 to 0.94; I2=0%) or with a GLP-1 agonist combined with metformin (0.40, -0.21 to 0.76; I2=0%) Diarrhoea, vomiting, and nausea were also more common in patients receiving metformin or a GLP-1 agonist than DPP-4 inhibitors. No difference in the incidence of gastrointestinal events was evident between DPP-4 inhibitors and sulfonylureas or pioglitazone. Overall, DPP-4 inhibitors were not associated with an increased risk of			

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				nasopharyngitis (1.06, 0.95 to 1.19; I2=0%), upper respiratory tract infection (1.0, 0.83 to 1.22; I2=20%), or urinary tract infection (0.86, 0.51 to 1.45; I2=64%) compared with any of the hypoglycaemic drugs in the control groups.			
Systematischer Review und Meta-Analyse	McIntosh B. et al. (2011) [2]	Suchzeitraum: 1980 to October 2009 Quellen: Only English Language MEDLINE, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials Additional citations were obtained from grey literature and conference proceedings and through stakeholder feedback. Two reviewers independently selected studies, extracted data and assessed risk of bias.	Interventionen: all available classes of antihyperglycemic therapies in patients with type 2 diabetes inadequately controlled by metformin monotherapy. Mixedtreatment comparison and pairwise meta-analyses were conducted to pool trial results, when appropriate. The following agents were assessed: sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogues, insulins and insulin analogues, alpha-glucosidase inhibitors and weight-loss agents (orlistat and sibutramine). Endpunkte: hemoglobin A1c, body	Included studies: 49 active and non-active controlled randomized trials that compared 2 or more of the following classes of antihyperglycemic agents and weight-loss agents: sulfonylureas, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, insulins, alpha-glucosidase inhibitors, sibutramine and orlistat. Study characteristics and methodological quality Most trials were 6–12 months long, although 1 study was over 5 years in duration. Mean baseline HbA1c ranged from 6.6% to 10% (weighted mean ± standard deviation [SD] 8.0% ± 0.9%). The baseline duration of diabetes ranged from 1.8 to 10.3 years (weighted mean ± SD 6.1 ± 5.1 years). The inclusion threshold for baseline HbA1c was typically 7.0%–10%; however, some studies used thresholds as low as 6.5% or as high as 11.5%. There were also differences in the duration and dosage of metformin monotherapy at baseline, although subjects used ≥ 1500 mg for ≥ 3 months in many studies. Three scenarios for treatment history			

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		Studien: RCT Patienten: patients with type 2 diabetes inadequately controlled by metformin monotherapy hemoglobin (HbA1c > 6.5%, fasting plasma glucose (FPG) > 7 mmol/L or 2-hour postprandial glucose (PPG) > 10 mmol/L)	weight, hypoglycemia, quality of life, long-term diabetes-related complications, serious adverse drug events and mortality.	before metformin monotherapy failure were identified. Most studies (89%) were industry funded. About two-thirds of the studies identified were of poor methodological quality: inadequate allocation concealment, failure to use an intention-to-treat analysis and lack of blinding were common limitations. Publication bias was not assessed because of a limited number of studies for each pairwise comparison 1. Intermediate Outcomes 1a. HbA1c/Glycemic Control Forty RCTs (n = 17. 795) reported change from baseline in HbA1c. All classes of second-line antihyperglycemic therapies achieved clinically meaningful reductions in hemoglobin A1c (0.6% to 1.0%). No significant differences were found between classes. Effect estimates ranged from −0.65% (95% confidence interval [CI] −1.14 to −0.20) for meglitinides to −0.96% (95% CI −1.57 to −0.38) for biphasic insulins. 1b. Weight An increase in body weight was observed with the majority of second-line therapies (1.8 to 3.0 kg), the exceptions being DPP-4 inhibitors, alpha-glucosidase inhibitors and GLP-1 analogues (0.6 to −1.8 kg). 2. Longterm Outcomes There were insufficient data available for diabetes complications, mortality or quali-			

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				ty of life. 3. Adverse Events Insulins and insulin secretagogues were associated with significantly more events of overall hypoglycemia than the other agents, but severe hypoglycemia was rarely observed. 4. Quality of life There were insufficient data available for diabetes complications, mortality or quality of life			
Meta-Analysis	Monami M et al. (2010) [10]	Medline search up to November 11th, 2008 Inclusion: RCTs, either published or unpublished, performed in type 2 diabetic patients with DPP-4 inhibitors, with a duration >12 weeks Exclusion: Trials with a shorter duration; trials enrolling nondiabetic, or type 1 diabetic subjects	Intervention=oral Dipeptidyl Peptidase-4 (DPP-4) inhibitors sitagliptin and vildagliptin versus placebo or active comparators primary outcome: effect of DPP-4 inhibitors, compared with other hypoglycemic agents or a placebo, on HbA1c Secondary outcomes: BMI	41 RCTs (9 of which are unpublished) were included Results: on HbA1c: - similar efficacy in monotherapy and in combination with other agents - in placebo-controlled studies: non sign. reduction of HbA1c in unpublished trials: (-0.68; CI [-1.57; 0.21]; p=0.13) - in placebo-controlled studies: non sign. reduction of HbA1c in published trials: -0.70; CI [-0.80; -0.59]; p < 0.001 - in active-comparator studies: similar effect to that of thiazolidinediones; sulfonylureas and metformin were more effective than DPP-4 inhibitors on body weight: - non sign. effect on BMI in placebo-controlled trials (+0.2 [-0.1; 0.6] kg/m2; p=0.11; 13 trials) - significant difference in comparison	Limitations: summary data, a time-to-event analysis for categorial outcomes (including cardiovascular events) could not be performed; number of subject studies and the duration of trials performed is insufficient to draw any definitive conclusion on the long-term cardiovascular safety Study quality: (Randomization/ Dropout rate/ intention-to-treat): - Description of randomization: 4- adequate reported, 37-not adequate reported - intention-to-treat analysis: 2 –no, 2-not reported, 37 - yes - numbers of withdrawals,	Pan C, et al. Diabet Med 2008; Rosenstock J, et al. Diabetes Care 2007; Rosenstock J, et al. Diabetes Obes Metab 2007; Dejager S, et al. Horm Metab Res 2007; Scherbaum WA, et al. Diabetes Obes Metab 2008. Mari A, et al. J Clin Endocrinol Metab 2008;. Scherbaum WA, et al. Diabetes Obes Metab 2008; Pi-Sunyer FX, et al. Diabetes Res Clin Pract 2007; Ristic S, et al. Diabetes	1+

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				with thiazolidinediones (-0.2; [-0.3;-0.1] kg/m2; p=0.008) adverse events/safety: - hypoglycemia: - low risk of hypoglycemia : incidence was not significantly different from placebo ; significantly lower hypoglycemic risk than sulphonylureas, no significant differences to thiazolidinediones - others : - no association with any increase in the overall risk of adverse events in comparison with placebo (Mantel-Hensel (MH)-OR 1.03 [0.93; 1.13]; p=0.51) or thiazolidinediones (0.97 [0.81; 1.17]; p=0.75, N=5 trials) ; the incidence was significantly lower than with sulphonylureas (0.64 [0.51; 0.80]; p < 0.001, N=2 trials), metformin (0.78 [0.61; 1.00]; p=0.050, N=2 trials), and a-glucosidase inhibitors (0.51 [0.39; 0.67]; p < 0.001, N=2 trials) - risk of cardiovascular events: 0.76 [0.46-1.28]; p=0.30 (in comparison with placebo controlled groups : 0.86 [0.47-1.59], p=0.63) - risk of all-cause death compared with control groups : 0.78 [0.40-1.51], p=0.47 Authors Conclusion: DPP-4 inhibitors reduce HbA1c, although to a lesser extent than sulphonylureas, with no weight gain and no hypoglycemic	reasons for withdrawal or dropout-adequate reporting: 1-no, 7-no reported, 33- adequate reported - Description of blinding: 9-adequate reported, 32-not adequate reported - Quality assessment: Jadad score was used Heterogeneity: - Random and fixed effects model, results of random effect model were reported - Significant heterogeneity: I2 for heterogeneity on HbA1c was 94.6 (p < 0.01) Publication bias: - The Begg adjusted rank correlation test (Kendall tau:-74; p=0.13) and the Egger regression approach (intercept, -2.81 [CI, -6.91; -1.27]) suggested no major publication bias	Obes Metab 2005; Ahren B, et al. Diabetes Care 2005; Garber AJ, et al. Diabetes Obes Metab 2007; D'Alessio DA, et al. J Clin Endocrinol Metab 2008. Scott R, et al. Diabetes Obes Metab 2008; Nonaka K, et al. Diabetes Res Clin Pract 2008; Raz I, et al. Diabetologia 2006; Charbonnel B, et al. Diabetes Care 2006; Aschner P, et al. Diabetes Care 2006; Raz I, et al. Curr Med Res Opin 2008; Rosenstock J, et al. Diabetes Obes Metab 2008; Novartis website 2008, Merck website 2008, Hanefeld M, et al. Curr Med Res Opin 2007; Nauck MA, et al. Diabetes Obes Metab	

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				risk		2007; Scott R, et al. Int J Clin Pract 2007; Garber AJ, et al. Diabetes Obes Metab 2008. Fonseca V, et al. Diabetologia 2007; Bolli G, et al. Diabetes Obes Metab 2008; Bosi E, et al. Diabetes Care 2007; Goldstein BJ, et al. Diabetes Care 2007; Hermansen K, et al. Diabetes Obes Metab 2007; Pratley RE, et al. Horm Metab Res 2006; Schweizer A, et al. Diabet Med 2007;	

Meta-Analysis	Vilsbøll T et al. (2012) [11]	Electronic searches (Cochrane Library, Medline, Embase, and Web of Science) and manual searches (up to May 2011)
		Inclusion:
		RCT of adults with or without
			Intervention:
			exenatide twice daily (n=13 trials), liraglutide (n=8), and exenatide once weekly (n=4); 3 trials compared directly exenatide twice daily with liraglutide or with exenatide once weekly; dose of liraglutide in most trials was 1.2 or
				Included studies: 25 RCTs
				Results:
				- For weight loss (3395 participants with GLP-1R agonists and 3016 in control groups, 21 trials):
				  - mean reduction in body weight with the highest dose of GLP-1R agonists ranged from –7.2 to –0.2 kg.
				  - In GLP-1R agonist groups: greater weight loss than control groups
					Strenght/Limitations:
					- internal validity, but all the included trials received industry funding
					Study quality: (Randomization/ Dropout rate/ intention-to-treat):
					- random allocation: adequate in all trials
					- allocation concealment:
						Astrup A, et al. Lancet 2009;
						Elkind-Hirsch K, et al. J Clin Endocrinol Metab 2008;
						Rosenstock J, et al. Diabetes Care 2010;
						Apovian CM, et al. Am J Med 2010;
						Bergenstal R, et al. Curr
							1+

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		type 2 diabetes and who had BMI of 25 or more;
		Intervention: GLP-1R agonist (exenatide given twice daily, exenatide given once weekly (as a long acting release), and liraglutide given once daily) in clinically relevant doses (at least 10 µg/day for exenatide (5 µg twice daily), 2 mg/week for exenatide once weekly, and 1.2 mg/day for liraglutide once daily) versus control group: placebo, no intervention, or antidiabetic drugs
		If trials included more than one control group, data from the most weight neutral intervention (for example, placebo instead of
			1.8 mg/day; in one trial - of 2.4 and 3 mg/day; doses of exenatide were 10 to 20 µg/day or 2 mg/week.
			control groups received placebo, third generation sulphonylurea compounds, insulin, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, or metformin. In trials of patients with type 2 diabetes, cointerventions given to the intervention and control group included metformin, sulphonylurea compounds, or thiazolidinediones.
			Main outcome:
			weight loss
				(weighted mean difference −2.9 kg, 95% CI –3.6 to –2.2; 21 trials, 6411 participants)
				- Subgroup analyses:
				  - weight loss in the GLP-1R agonist groups for patients without diabetes (–3.2 kg, CI –4.3 to–2.1; three trials)
				  - weight loss in the GLP-1R agonist groups for patients with diabetes (–2.8 kg, CI –3.4 to –2.3; 18 trials).
				- no difference in body weight changes for liraglutide versus exenatide twice daily (−0.4 kg, 95% CI –1.3 to 0.6), or for exenatide as a long acting release versus exenatide twice daily (–0.6 kg, –1.5 to 0.3).
				- weight reduction in trials assessing exenatide twice daily (–2.8 kg, –2.9 to –2.7), exenatide once weekly (–2.8 kg, –5.2 to –0.3), and liraglutide (–2.2 kg, –3.5 to –0.9).
				- weight reduction for trials with placebo (–1.9 kg, –2.9 to –0.9; 10 trials), insulin (–4.8 kg, –5.1 to –4.5; six trials), oral antidiabetic drugs including metformin or sulphonylurea compounds (–3.0 kg, –4.9 to –1.2; three trials), and dipeptidyl peptidase 4 inhibitors (–2.0 kg, –2.9 to –1.1; two trials).
				- For secondary outcomes:
				  - beneficial effects of GLP-1R agonists on systolic and diastolic
					adequate in all trials
					- intention-to-treat analysis in all trials
					- numbers of withdrawals, reasons for withdrawal or dropout
					- patient characteristics at baseline and the diagnostic criteria for type 2 diabetes were very similar across trials; baseline treatment and control groups were balanced
					- Blinding: 13 trials were double blind, none of included trials reported the success of blinding
					- All trials reported clinically relevant outcome measures, provided a clear description of losses to follow-up, accounted for patients with missing data in the analyses, and undertook sample size calculations.
					- None of the trials were terminated prematurely.
					- no evidence of reporting bias when comparing published trial protocols with subsequent trial reports was founded
						Med Res Opin 2009;
						Bergenstal RM, et al. Lancet 2010;
						Blevins T, et al. J Clin Endocrinol Metab 2011;
						Bunck MC, et al. Diabetes Care 2009;
						Buse JB, et al. Diabetes Care 2004;
						Buse JB, et al. Lancet 2009;
						Davis SN, et al. Diabetes Care 2007;
						DeFronzo RA, et al. Diabetes Care 2010;
						Derosa G, et al. Diabetes Technol Ther 2010;
						Diamant M, et al. Lancet 2010;
						Drucker DJ, et al. Lancet 2008;
						Garber A, et al. Lancet 2009;
						Heine RJ, et al. Ann Intern Med 2005;
						Kendall DM, et al. Diabetes Care 2005;
						Marre M, et al. Diabet Med 2009;
						Moretto TJ, et al. Clin	

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		insulin) were included. Randomised comparisons between exenatide and liraglutide were included. Duration of at least 20 weeks that assessed clinically relevant doses (see "intervention").		blood pressure, plasma concentrations of cholesterol, and glycaemic control; not significant effect on plasma concentrations of liver enzymes. GLP-1R agonists were associated with nausea, diarrhoea, and vomiting, but not with hypoglycaemia. Descriptive statistics: - All trials were multicentred (mean number of clinical sites 68) and multinational. - Most trials were done in the US and Europe. - duration of individual trials ranged from 20 to 52 weeks. - 3 trials included patients without diabetes, remaining trials - with type 2 diabetes - Mean BMI ranged from 29 to 41, and mean weight from 82 to 111 kg - For patients with type 2 diabetes: mean concentration of fasting plasma glucose at baseline ranged from 8.0 to 11.7 mmol/L for GLP-1R agonist groups, and from 8.2 to 11.2 mmol/L for control groups; mean values of HbA1c at baseline ranged from 7.6% to 10.4% for GLP-1R agonists and 7.4% to 10.3% for controls. Author conclusions: evidence that treatment with GLP-1R agonists leads to weight loss in	Heterogeneity: - Both random and fixed effects model were used - I2 tests - Heterogeneity: evidence of intertrial heterogeneity (tau2=2.4, P<0.01), but no evidence of bias or small study effects in regression analyses. - Random effects meta-regression of the primary meta-analysis found that BMI at baseline and trial duration did not predict the size of the estimated intervention or explain intertrial heterogeneity (P=0.293 and P=0.284). Publication bias: - See "Study quality"	Ther 2008; Nauck M, et al. Diabetes Care 2009; Nauck MA, et al. Diabetologia 2007; Pratley RE, et al. Lancet 2010; Russell-Jones D, et al. Diabetologia 2009; Zinman B, et al. Diabetes Care 2009;	

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Evidenzniveau (SIGN)
				overweight or obese patients with or without type 2 diabetes mellitus			
Meta-Analysis	Hirst JA et al. (2012) [12]	MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from 1950 to June 2010 Inclusion criteria: 1) RCT 2) participants with diabetes; 3) follow-up of at least 12 weeks; 4) treatment group of metformin monotherapy, or metformin as an add-on therapy; 5) placebo or background treatment comparator group; 6) randomize patients to a fixed dose of metformin; 7) blind patients to oral medications; 8) use the same	Outcome measures: change in HbA1c levels from baseline to the end of the trial, total adverse events, and gastric adverse events (diarrhea and abdominal cramps).	Included trials: 35 RCTs (7 – for comparison analysis) = 7,960 participants Results: - Metformin monotherapy versus placebo lowered HbA1c by 1.12% (95% CI 0.92–1.32, P<0.00001)= reduction of 12 mmol/mol more with metformin than placebo; in 10 trials with > or = 24 weeks HbA1c was 1.19% lower (CI 0.98–1.41) in metformin groups - metformin+ oral therapy versus placebo+oral therapy lowered HbA1c by 0.95% (CI 0.77–1.13, P<0.00001) = reduction of 11mmol/mol more with metformin than in the comparator group; in 11 trials with > or = 24 weeks HbA1c was 0.94% lower (0.76–1.13; I2 = 78.6%) in the metformin groups - metformin+ insulin therapy versus insulin only lowered HbA1c by 0.60% (95% CI 0.30–0.91; P = 0.0001) = reduction of 6 mmol/mol more in the metformin groups - significantly greater reduction in HbA1c using higher doses of metformin (reduction in HbA1c of 0.26% (95% CI 0.14–0.38; P , 0.0001) compared with lower doses of metformin with no significant increase in side effects - number of adverse events: most commonly =gastrointestinal events, but al-	Study quality: (Randomization/ Dropout rate/ intention-to-treat): - only 8 stated the method of randomization - intention-to-treat analysis n. a. - numbers of withdrawals, reasons for withdrawal or dropout n.a. - Blinding: All of the included trials were double blinded, with the exception of one trial = partially blinded Heterogeneity: - random/fixed effects model - I2 tests (HbA1c): for Metformin monotherapy I2 = 80,2 %, for metformin added to oral therapy I2 = 77.1 %, for metformin+ insulin therapy I2 = 79.8%; for adverse events see results - Sign. heterogeneity (p=0.000) - no single factor could explain the heterogeneity was founded Publication bias:	(reported in supplementary data) Avilés-Santa L, et al. Ann Intern Med.1999 Aug 3;131(3):182-8. Bosi E, et al. Diabetes Obes Metab. 2009 May;11(5):506-15. Chiasson JL, et sl. Diabetes Care. 2001 Jun;24(6):989-94. Damsbo P, et al. Diabetes Care. 1998 Sep;21(9):1489-94. DeFronzo RA, et al. N Engl J Med. 1995 Aug 31;333(9):541-9. Derosa G, et al. Metabolism. 2009 Aug;58(8):1059-66. Douek IF, et al .Diabet Med. 2005 May;22(5):634-40. Fujioka K, et al. Diabetes Obes Metab. 2005 Jan;7(1):28-39. Garber AJ, et al. Am J Med. 1997 Dec;103(6):491-7.	1-

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Evidenzniveau (SIGN)
		metformin dose for each patient in the trial; and 9) use the same fixed dose of any other oral glucose-lowering medication used in combination with metformin in both the metformin and comparator arms.		so hypoglycemia, dizziness, headache, urinary tract infection, hypertension, coughing, and palpitations; - increased in metformin-treated groups in the monotherapy trials (RR 1.13 [95% CI 1.06–1.21]; I2 = 3%, P =0.0003), and in oral combination trials (RR 1.03 [0.95–1.12]; I2 = 82%, P = 0.45) - in insulin trials=not significantly different between the metformin group and the comparator group (2.37 [0.65–8.67]; I2 = 73%, P =0.19) Descriptive statistics: - 15 trials with metformin monotherapy compared with placebo, no treatment, or diet (2,424 participants); 12 metformin treatment in combination with another oral antihyperglycemic medication compared with the other medication (4,511 participants); and 13 - metformin in combination with insulin treatment compared with patients on insulin treatment only (1,025 participants) - Five trials with multiple arms Authors conclusion: Evidence supports the effectiveness of metformin therapy in a clinically important lowering of HbA1c used as monotherapy and in combination with other therapeutic agents. There is potential for using higher doses of metformin to maximize glycemic control in diabetic patients without increa-	- N.a.	Giugliano D, et al. Eur J Clin Pharmacol. 1993;44(2):107-12. Goldstein BJ, et al. Diabetes Care. 2007 Aug;30(8):1979-87. Grant PJ. Diabetes Care. 1996 Jan;19(1):64-6. Hällsten K, et al. Diabetes. 2002 Dec;51(12):3479-85. Hermann LS, et al. Diabetes Obes Metab. 2001 Dec;3(6):428-34. Hoffmann J, et al. Am J Med. 1997 Dec;103(6):483-90. Horton ES, et al .Diabetes Care. 2000 Nov;23(11):1660-5. Iozzo P, et al Diabetes Care. 2003 Jul;26(7):2069-74. Jacobsen IB, et al .Basic Clin Pharmacol Toxicol. 2009 Sep;105(3):145-9. Jadzinsky M, et al .Diabetes Obes Metab. 2009 Jun;11(6):611-22. Khan AS, et al. Diabet Med. 2006	

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Inter-ventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Eviden-zniveau (SIGN)
				sing gastrointestinal effects.		Oct;23(10):1079-84. Lewin A, et al Clin Ther. 2007 May;29(5):844-55. List JF, et al Diabetes Care. 2009 Apr;32(4):650-7. Lund SS, et sl .PLoS One. 2008;3(10):e3363. Meyer L, et al. Diabetes Care. 2002 Dec;25(12):2153-8. Moses R, et al. Diabetes Care. 1999 Jan;22(1):119-24. Natali A, et al. Diabetes Care. 2004 Jun;27(6):1349-57. Perez A, et al. Curr Med Res Opin. 2009 Dec;25(12):2915-23. Ponssen HH, et al. Clin Ther. 2000 Jun;22(6):709-18. Robinson AC, et al . Diabetes Care. 1998 May;21(5):701-5. Ryysy L, et al. Diabetes Care. 2001 Mar;24(3):549-54. Viljanen AP, et al .J Clin Endocrinol Metab. 2005 Dec;90(12):6523-8.	

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Evidenzniveau (SIGN)
						Williams-Herman D, et al. Curr Med Res Opin. 2009 Mar;25(3):569-83. Wolever TMS, et al. Nutr Res. 2000;20(10):1447-56 Wulffelé MG, et al .Diabetes Care. 2002 Dec; 25 (12):2133-40. Yki-Järvinen H, et al .Ann Intern Med. 1999 Mar 2;130(5):389-96.	
Meta-Analysis	Lamanna C. et al. (2011) [13]	MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched up to 31 October 2009 Inclusion criteria: RCT comparing metformin, it placebo, active glucose-lowering therapies or no therapy, duration >/= 52 week, concurrent therapies were not different in metformin and comparator arms,	Main outcomes: cardiovascular morbidity and mortality in patients treated with metformin	Included studies: 35 RCTs Results: - On cardiovascular events (12 RCTs, 5455 patients with metformin and 8996 – in comparator group, non-diabetic and diabetic patients): - Overall - no sign. effects on cardiovascular events - Sign. reduction of cardiovascular events in comparison with placebo or -no therapy - in comparison with rosiglitazone (2 RCTs): OR for major cardiovascular events in patients with metformin: 1.06 (95 % CI 0.87-1.28, p=0.57) - No significant effect of metformin on the incidence of myocardial infarction, stroke or heart failure (MH-OR 0.90 [0.71 1.14], 0.92 [0.65-1.29], 1.12 [0.25-9.04]), all	Study quality: (Randomization/ Dropout rate/ intention-to-treat): - random allocation: in 21 RCTs not adequate - allocation concealment: : in 21 RCTs not adequate - intention-to-treat analysis: only in 17 RCTs - yes - numbers of withdrawals, reasons for withdrawal or dropout: n.a. - baseline treatment and control groups were balanced: n.a. - Blinding: in 22 RCTs not adequate - PRISMA Checklist and Jadad score for quality assestment were used	UK Prospective Diabetes Study (UKPD5Lancet 1998; 352: 854~865. Selvin Eet al. Arch Intern Med 2008 References im Appendix: Hermann LS, et al .Diabetes Obes Metab. 2001; 3(6):428-34. Yki-Järvinen H et al 1999 Mar 2;130(5):389-96 Campbell IW, et al Diabete Metab. 1994 Jul-Aug;20(4):394-400. Klein W. Diabete Metab. 1991 May;17(1 Pt 2):235-40.	1-

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Evidenzniveau (SIGN)
		trials in which cardiovascular events were a pre-defined end-point together with trials de-signed for other (mainly metabolic) endpoints; Studies with no events were excluded		p<0.35 - On all cause and cardiovascular mortality: - 5 RCTs with at least one event: - no effect on all cause mortality - signitkant increase of mortality - in the 2 trial with metfor-min+sulphonylureas - Similar results for cardiovascular mortality: MH-OR in 5 trials was 0.923 [0.361-2.320], (p = 0.86); - signiticant reduction of mortality in 4 RCTs with metformin monother-apy (MH-OR 0.554 [0.356-0.890], p=0.014) - meta-regression: more beneficial effect on all-cause mortality in tri-als of longer duration (Intercept: 0.612[0.138-1.087]: Slope: -0.002[-0.003 to -0.00004[, p = 0.008), and with higher proportion of women (Intercept: 2.237[0.184-4.290]; Slope: -0.039[-0.076 to -0.003[, p = 0.034) Descriptive statistics: - in total, 7171 participants with metfor-min and 11301 participants with com-parator were included - 451 cardiovascular events in metformin group and 775 – in comparator group - Median duration was 112 weeks (range 52-343 weeks) - 8 trials did non describe cardiovascu-	- Power analysis – 90% Heterogeneity: - Both random and fixed effects model, results of random effects model were reported - I2 tests - Heterogeneity: not signifi-cant (p=0.46, Q=10.08) Publication bias: - Was assessed (Funnel plot, Eggers test) - No evidence for publication bias (p=0.46)	Vähätalo M, et al Scand J Prim Health Care. 2007 Sep;25(3):147-53 Yamanouchi T et al Diabet Med. 2005 Aug;22(8):980-5. Douek IF, et al Diabet Med. 2005 May;22(5):634-40 Schweizer A, et al Diabet Med. 2007 Sep;24(9):955-61. Epub 2007 Schernthaner G, et al Clin Endocrinol Metab. 2004 Dec;89(12):6068-76 Derosa G, et al Metabo-lism. 2009 Aug;58(8):1059-66. Epub 2009 Gregorio F, et al Diabet Med. 1999 Dec;16(12):1016-24. Teupe B, et al Diabete Metab. 1991 May;17(1 Pt 2):213-7 Charbonnel B, et al Diabetologia. 2005 Jun;48(6):1093-104. Epub 2005 Barnett AH et al Int J Clin Pract. 2007 Oct;61(10):1614-25. Erratum in: Int J Clin Pract. 2008	

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Inter-ventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Eviden-zniveau (SIGN)
				kar events Authors conclusion: Available evidence seems to exclude any overall harmful effect of metformin on cardiovascular risk, suggesting a possible benefit versus placebo/no treatment.		Jan;62(1):171 Maji D, et al. J Indian Med Assoc. 2005 Nov;103(11):609-11. Kahn SE, et al. N Engl J Med. 2006 Dec 7;355(23):2427-43. Epub 2006 Dec 4. Erratum in: N Engl J Med. 2007 Mar 29;356(13):1387-8. Kooy A, et al. Arch Intern Med. 2009 Mar 23;169(6):616-25 Palomba S, et al. J Clin Endocrinol Metab. 2007 Aug;92(8):3128-35. Epub 2007 May 22. Ibanez L, et al. J Pediatr 2004;144:23-29. Harborne L, et al. J Clin Endocrinol Metab. 2003 Sep;88(9):4116-23. Tomazic J, et al. Acta Dermatovenerol Alp Panonica Adriat. 2005;14:99-105. Li CL, et al. Diabet Med. 1999 Jun;16(6):477-81. Martínez E, et al. Antivir Ther. 2003 Oct;8(5):403-10. Gambineri A, et al. J	

Studien-typ	Quelle	Untersuchte Studien	(verglichene) Inter-ventionen/ (ggf. Dosierung)	Ergebnisse	Bemerkungen	Literaturbelege	Eviden-zniveau (SIGN)
						Clin Endocrinol Metab. 2006 Oct;91(10):3970-80. Epub 2006 Jul 25. Lund SS, et al. PLoS One. 2008;3(10):e3363. Epub 2008 Oct 9. Charles MA, et al. Diabetes Care. 1998 Nov;21(11):1967-72 Zhang JL, et al. Am J Hypertens. 2009 Aug;22(8):884-90. Epub 2009 Stakos DA, et al. Heart. 2005 May;91(5):589-94. Schuster D, et al. Diabetes Care. 2004 Nov;27(11):2768-9.Abstract n.a. Ramachandran A, et al. Diabetologia. 2006 Feb;49(2):289-97. Epub 2006 Ibáñez L, et al. J Clin Endocrinol Metab. 2008 May;93(5):1841-5. Epub 2008 Mar 4.	

Einzelstudien

Quelle/ Studientyp	Population	(verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up	Outcomes	Ergebnisse	Bemerkungen	Evidenzniveau (SIGN/ CEBM Oxford)
ORIGIN Trial Investigators (2012) [14] RCT	Total of population (n = 12537) Pat. characteristics: Mean age 63.5 years with cardiovascular risk factors and Type II diabetes or impaired glucose tolerance Inclusion criteria: Participants > 50 years with a prior CV event (myocardial infarction, stroke, or revascularization); angina with documented ischaemia; albuminuria; left ventricular hypertrophy; angiographic evidence of > 50% stenosis of a coronary, carotid, or lower extremity artery; or an ankle/brachial index < 0.9 were recruited if they also had a history of type 2 diabetes that was stable on 0 or 1 oral glucose lowering agents; or IFG, IGT or	Glargine versus standard care: insulin glargine added an evening injection to their glycemic-control regimen (glimepiride, metformin, rapid-acting insulin were permitted) versus standard care on the basis of the investigator's best judgment and local guidelines (it was permitted to use any glucose lowering agent apart from insulin glargine. Pat. were also advised to avoid insulin until maximal doses of 2 different oral glucose lowering agents were required). Median follow-up was 6.2 years. (2-by-2 factorial design with n-3-fatty acid vs. placebo, not reported here)	Two coprimary composite outcomes: # death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, # composite of any of these events plus revascularization procedure (cardiac, carotid, or peripheral), or hospitalization for heart failure. Secondary outcomes: Other adjudicated outcomes were a composite microvascular outcome, incident cases of diabetes in participants without baseline diabetes, all-cause mortality and new or recurrent cancers. Hypoglycemic episodes and weight were also recorded.	primary outcomes: - 1. hazard ratios of 1.02 (95% confidence interval [CI], 0.94 to 1.11; P = 0.63) - 2. HR 1.04 (95% CI, 0.97 to 1.11; P = 0.27) Secondary outcomes: - no significant difference in mortality (hazard ratio, 0.98; 95% CI, 0.90 to 1.08; P = 0.70) or microvascular events (hazard ratio, 0.97; 95% CI, 0.90 to 1.05; P = 0.43). - no significant difference in each component of the two coprimary outcomes or in the incidence of any cancer (hazard ratio, 1.00; 95% CI, 0.88 to 1.13; P = 0.97), death from cancer (hazard ratio, 0.94; 95% CI, 0.77 to 1.15; P = 0.52) - Severe Hypoglycemia 1% vs. 0.31 %, p<0.001 - Weight: +1.6 kg vs. -0.5 kg - HbA1c: 6.2 % vs. 6.5% (Median in yr 7 after baseline)	Flowchart: yes suppl. appendix ITT: yes Randomization not described in detail Blinding: No Groups comparable/ similar: yes COI: yes suppl. Power calculation: yes, but adjusted by extension of the trial for 2 years The overall type I error rate of 5% for the two coprimary outcomes was partitioned such that the first coprimary outcome was tested at a P value of 0.044 and the second coprimary outcome was tested at a P value of 0.01 supplementary table S 1: 1212 pat. had stopped glarigin, reason stopped glargin adherence were 90.3% «Refusal » without details mentioned. At this time, 80% were using any insulin, 35% were not using any oral glucose-lowering agents, and 47% were using metformin. Few participants in the standard-care group used insulin during the trial - by the end of the study, 11%	1(+)

Quelle/ Studientyp	Population	(verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up	Outcomes	Ergebnisse	Bemerkungen	Evidenzniveau (SIGN/ CEBM Oxford)
	newly detected diabetes based on either a FPG ≥ 6.1 mmol/L [110 mg/dL] or a 2 hour plasma glucose ≥ 7.8 mmol/L [140 mg/dL] after a 75 g oral glucose load. Exclsuion criteria: unwillingess or an inability to inject insulin or do capillary glucose self-testing, a clear indication for, or intolerance to insulin or omega 3 fatty acids, unwillingness to stop thiazolidinediones if allocated to glargine, heart failure, coronary artery bypass surgery within the prior 4 years with no intervening CV event, or cancer affecting survival.				AEs: described CI: described Funding, regulatory support, site monitoring, drug distribution, and insulin glargine (Lantus) were provided by Sanofi	
Gallwitz et al. (2012) [15] RCT – non-inferiority-	Total of population (n = 1029, 515/514 each group) multicentered at 128 centres in 14 countries recruited between Sept 5, 2006, and March 29, 2011.	Exenatide twice daily versus glimepiride once daily as add-on to metformin (Exenatide injected subcutaneously within 60 min before breakfast and evening meals, starting at 5 µg	primary outcome: time to inadequate glycaemic control and need for alternative treatment, defined as an HbA1c concentration of more than 9% after the first 3 months of treatment, or more than	primary outcome: Median time to inadequate HbA1c control was 180 weeks with exenatide versus 142·1 weeks (52·3) with glimepiride (p=0·032). 203 (41%) of 490 patients in the	ITT was stated, but per-protocol-analysis was done → They randomly assigned 515 patients to the exenatide group and 514 to the glimepiride group, but only 490, resp. 487 Pat. were analysed. In the exenatide group 174 disconti-	1-

Quelle/ Studientyp	Population	(verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up	Outcomes	Ergebnisse	Bemerkungen	Evidenzniveau (SIGN/ CEBM Oxford)
study	Pat. characteristics: Patients aged 18–85 years with type 2 diabetes inadequately treated by metformin. Inclusion and exclusion criteria: Eligible participants had type 2 diabetes; were overweight to obese (body-mass index [BMI] ≥25 kg/m² to <40 kg/m²); aged 18–85 years; had been on stable, maximum tolerated doses of metformin; and had developed suboptimum glycaemic control, defi ned by a glycated haemoglobin (HbA1c) concentration of 6·5% and more or 9·0% and less. Exclusion criteria were contraindications for metformin or limepiride, according to the product-specifi c label; active or untreated malignancy or remission for less than 5	twice daily for 4 weeks, followed by 10 µg twice daily for the remaining study period. Starting dose for patients in the glimepiride group was 1 mg per day, adjusted every 4 weeks, according to tolerability, up to the maximum tolerated dose. Concomitant metformin was continued throughout the study for all patients, in the same form and at the same dose as used at study entry.	7% at two consecutive visits after the first 6 months. Secondary outcomes were markers of β-cell function, bodyweight, hypoglycaemia, and surrogate markers of cardiovascular risk (blood pressure and heart rate).	exenatide group had treatment failure compared with 262 (54%) of 487 in the glimepiride group (risk diff erence 12·4%, 95% CI 6·2–18·6). hazard ratio 0.748 [0·623–0·899]; p=0·002. The upper onesided CI of the Cox propor tional hazard analysis was 0·899, which was less than the predefi ned non-inferiority value of 1.25. According to the two-sided 95% CI, exenatide was more eff ective than glimepiride as add-on treatment for patients with metformin failure (95% CI 0·623–0·899; p=0·002)	nued : inter alia 49 had an adverse event*, 4 patients died. In the glimepirid group 128 discontinued inter alia 17 adverse event*, 2 patients died. *p=0·001 No Blinding They declared non-inferiority of exenatide to glimepiride if the 97·5% CI for the hazard ratio (HR) ; if non-inferiority was shown, they tested superiority with 95% CI. Power calculation: yes, but they calculated sample size only on the basis of the non-inferiority test of exenatide versus glimepiride, not for superiority Randomization : yes, described in detail Groups similar AEs described : yes CI described : yes Flowchart : yes Funding Eli Lilly and Company; Amylin Pharmaceuticals. The sponsor took part in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to the data and responsibility for the content of the report. COI : reported. First and last author	

Quelle/ Studientyp	Population	(verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up	Outcomes	Ergebnisse	Bemerkungen	Evidenzniveau (SIGN/ CEBM Oxford)
	years; evidence of renal or liver disease or dysfunction; haemoglobinopathy or clinically signifi cant chronic anaemia; active proliferative retinopathy or macular oedema; or severe gastrointestinal disease. Excluded drugs were those aff ecting gastrointestinal motility, chronic systemic gluco corticoids, prescription drugs to promote weight loss in the past 3 months, and treatment for more than 2 weeks in the past 3 months with insulin, thiazo lidinediones, α-glucosidase inhibitors, sulphonylureas, or meglitinides.				consultants for Eli Lilly. Most of the Coauthors employees of Eli Lilly and Comp. glimepiride dose used was fairly low : mean glimepiride dose was 2•01 (SD 1•02) mg per day and Mean exenatide dose was 17•35 (SD 4•07) µg per day	

2 Evidenztabelle HbA1c-Senkung (und weitere Endpunkte)

Zusammenstellung der Studienevidenz zum Kapitel Pharmakotherapie

Evidenztabelle HbA1c-Senkung bei endpunktbezogenen Studien – Zusammenstellung Egidi/Abholz für DEGAM – Fassung 06/2012, Ergänzung ÄZQ Feb. 2013

"Titel" (Jahr), Autor, Journal, Studientyp	UKPDS 33 (1998), *UKPDS Group, Lancet, RCT [16]*	UKPDS 34 (1998), *UKPDS Group, Lancet, RCT [17]*	Kumamoto (1995), *Ohkubo et al, Diab. Res. and Clin. Prac., RCT [18]*	STENO-2 (2003), *Gaede et al, NEJM, RCT [19]*	PRO-ACTIVE *(2005), Dormandy et al, Lancet, RCT [20]*	ACCORD (2008), *Diabetes Study group, NEJM, RCT [21]*	ADVANCE (2008), *ADVANCE Collaborative Group, NEJM, RCT [22]*	VADT (2008), *Duckworth, NEJM, RCT [23]*
Patientencharakteristika	Neu diagnostizierter Diabetes, 48-60 Jahre alt, Median 54.	Wie UKPDS 33, jedoch nur die übergewichtigen und adipösen Patienten (BMI>25), mit zusätzlicher Gabe von Metformin	Insulin-behandelt, durchschnittlich 48 Jahre alt, duchschnittlicher BMI 21,5.	Mikroalbuminurie. Durchschnittliches Alter 55 Jahre, durchschnittlicher BMI 30 kg/m2, durchschnittlicher Blutdruck 148/86 mmHg	Durchschnittlich 62 Jahre alte Patienten, 47 % nach Infarkt, 19 % nach Insult, 20 % mit pAVK, BMI 31, RR 144/83 mmHg	Durchschnittliches Alter 62,2 Jahre, durchschnittlicher BMI 32,2 kg/m2, durchschnittlicher Blutdruck 136/75 mmHg, 35 % mit kardiovaskulären Vorerkrankungen, 65 % Weiße, 14 % Raucher	Über 55-jährige Diabetiker mit makro- oder mikrovaskulären Erkrankungen oder mind. 1 zusätzlichen Risikofaktor – meist aus dem pazifischen Raum	Im Schnitt 60,5-jährige männliche Veteranen mit HbA1c >7,5 bzw-8,3 %.BMI 31,2, RR 132,76 mmHg, 40 % makrovask. 62 % mikrovask.-Vorerkrankungem
Ausschlusskriterien	Nüchtern-Plasmaglukose <60 oder >150mg % nach 3-monatiger Diät Ketonurie, Niereninsuffizienz Krea>1,75, makrovaskuläre Erkrankungen, Herzinsuffizienz, Retina-Laserung, maligne Hypertonie, beru-	Wie UKPDS 33, aber BMI <25	Kreatinin >1,5 mg/dl, Alter über 70, normale Werte für Blutdruck und Cholesterin, Ketonurie, schwere Diabetes-Komplikationen oder -Endpunkte	Alter über 65 und unter 40 Jahre, sekundärer und Typ-1-Diabetes, Alkohol-Missbrauch, nichtdiabetische Nephropathie, schwere Allgemeinerkrankung	Herzinsuffizienz, Alter < 35, >75, alleinige Insulintherapie zuvor; kardiovaskuläre Vorerkrankungen, Bein-Ulcera, Leberfunktions-Störung	Häufige Hypoglykämien, Ablehnung von Plasmaglukose-Kontrollen und Insulin-Injektionen, BMI >45 kg/m2 oder Kreatinin >1,5 mg%.	Kontraindikation gegen oder zwingende Indikation für eines der Studienmedikamente.	symptomatische Stenokardien, Herzinsuffizienz, Kreatinin über 1,6 mg/dl, erwartete Lebenserwartung unter 7 Jahre, BMI über 40 kg

"Titel" (Jahr), Autor, Journal, Studientyp	UKPDS 33 (1998), *UKPDS Group, Lancet, RCT [16]*	UKPDS 34 (1998), *UKPDS Group, Lancet, RCT [17]*	Kumamoto (1995), *Ohkubo et al, Diab. Res. and Clin. Prac., RCT [18]*	STENO-2 (2003), *Gaede et al, NEJM, RCT [19]*	PRO-ACTIVE *(2005), Dormandy et al, Lancet, RCT [20]*	ACCORD (2008), *Diabetes Study group, NEJM, RCT [21]*	ADVANCE (2008), *ADVANCE Collaborative Group, NEJM, RCT [22]*	VADT (2008), *Duckworth, NEJM, RCT [23]*
	fliche Gründe gegen Insulinbehandlung.Schwere Krankheit. Kognitive Störungen. Unkorrigierte endokrinologische Störungen							
Patientenzahl	3.867	753 (davon 342 mit Metformin)	110	160	5.238	10.251	11.140	1.791
Studienlaufzeit	10 Jahre	10,7 Jahre	6 Jahre	7,8 Jahre	2,9 Jahre	Nach 3,5 Jahren abgebrochen (Blutzuckerarm)	4,3 Jahre	5,6 Jahre
Verblindung	Keine	Keine	Keine	Keine	Keine	Keine	Keine	Keine
Faktorielles Design	Ja – zugleich Untersuchung RR-Senkung	Wie UKPDS 33	Nein, aber zusätzliche Randomisierung in Primär- und SekundärpräventionsKohorte	Nein	Nein	3-fach-faktorielles Design (Plasmaglukose-/RR- und Lipid-Senkung)	2-fach-faktorielles Design	Nein
Eingesetzte Substanz(en)	*Intensive Behandlung mit* Chlorpropamid, Glibenclamid, Glipizid, Insulin *versus konventionelle Behandlung mit Diät (bis max. Nüchtern-BZ 15 mmol/l.)*	Metformin vs-„konventionelle Behandlung"	Insulin intensiviert vs konventionell (Mischinsulin)	intensive Ernährungsberatung, ½ Stunde Bewegungs-training 3-5 Tage pro Woche, Raucher-Entwöhnung, 2x50 mg Captopril unabhängig vom Blutdruck, Vitamin C und E, ASS 150	Pioglitazon vs Placebo als Zusatz zu laufender Therapie mit Glibenclacla-mid/Metformin/Insulin	Rosiglitazon 91 vs. 58 %, Metformin 95 vs 87 %, Glimepirid 78 vs 68 %, Repaglinid 50 vs 18 %, Alpha-Glukosidase-hemmer 23 vs 5 %, Inkretin-Mimetika 18 vs 5 %, Insulin 77 vs 5 %. 10 vs 1 % mit 4 und	Intervention: Gliclazid, andere SH-Stoffe gestoppt. Zusätzlich Metformin, Glitazon. Insulin, Acarbose zur Erreichung des HbA1c-Ziels *(Intensive (Ziel HbA1c 6,5 %) versus Standard-*	Bei BMI >27 Metformin und Rosiglitazon, bei BMI <27 Glimepirid und Rosiglitazon. Insulin dazu bei HbA1c >6 % in der Interventions- und >9 % in der Kontrollgruppe *(Intensiv versus*

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				bei KHK, Metformin bei Übergewich-tigen, Gliclazid bei Schlanken, Therapieintensivierung bei HbA1c 7,0; Blutdruck-Senkung unter 140/85 mmHg(ab dem Jahr 2000 unter 130/80, Statine bei Cholesterin > 5 mmol/l, zusätzlich Fibrat bei Triglyceriden >4 mmol/l *(Intensive versus konventionelle Behandlung mit unterschiedlichen Behandlungszielwerten)*		mehr antiglykämischen Wirkstoffen *(Intensive (Ziel HbA1c 6%) versus Standard-Behandlung (Ziel HbA1c 7-7.9%))*	*Behandlung (Ziel „defined on the basis of local guidelines")*	*Standard-Behandlung. Nach BZ-Kontrolle: Maximaldosis versus halbe Dosis)*
Primärer Endpunkt	Sammelendpunkt aus allen denkbaren Diabetes-assoziierten Endpunkten. Nach 10 Jahren Studienlaufzeit Protokollwidrige Hinzufügung des Endpunktes Retina-Koagulation	Wie UKPDS 33	Auftreten bzw. Progression von Retinopathie, Nephropathie und Neuropathie	Sammelendpunkt: Kardiovaskulärer Tod,Infarkt, Bypass, PTCA, Insult, Amputation, Revakularisation einer Beinarterie *nach 8 Jahren* Auftreten einer Nephropathie *nach*	Erstes Auftreten jeweils eines der genannten Ereignisse *(kombinierter Endpunkt aus Gesamtmortalität, Herzinfarkt, Schlaganfall, ACS, Bypass-OP (kardial/ peripher),*	Herzinfarkt, Schlaganfall oder kardiovaskulärer Tod	Herzinfarkt, Schlaganfall, Nephropathie, Retinopathie , Kardiovaskulärer Tod *(kombinierter Endp. mikro- und makrovask. Ereignisse,* getrennt makrovas. und	Zeit bis zum ersten kardiovaskulären Ereignis *(komb. Endp. aus Herzinfarkt, Schlaganfall, kardiovask. Tod, Herzinsuff., Bypass-OP (kardial/ peripher, zerebral), Amputation)*

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				4 Jahren	*Amputation)*		mikorvask. Ereignisse)	
Sekundäre Endpunkte	21 klinische Endpunkte einzeln wie z. B. Herzinfarkt; *7 aggregierte Endpunkte*	21 klinische Endpunkte einzeln wie z. B. Herzinfarkt *7 aggregierte Endpunkte*		Inzidenz von Retinopathie und Neuropathie	Nicht prädefiniert!	Mortalität, Hypoglykämien, Lebensqualität	Gesamt-Sterblichkeit, Herzinsuffizienz, Demenz, Sehverschlechterung, Krankenhauseinweisung	Stenokardien, Claudicatio, Tod, TIA, mikrovask. Komplikstionen, Hypoglykämien
Ausgewogene Begleitbehandlung	??	??	??	Es handelte sich bereits um eine komplexe Intervention	Ja	Ja	Nein – fast 3x so viele Studien-Visiten in der Interventions-Gruppe, stärkere RR-Senkung (136/74 vs 138/74), ASS 64,1 vs. 61,1 %	Ja
HbA1c-Senkung	Senkung von 7,9 auf 7,0 %,	Senkung von 8,0 auf 7,4 %	Senkung von 9,1 auf 7,1 %	Interventions-Gruppe 8,4=>7,6 %, Kontrollgruppe 8,8=>9,0 %	Senkung von 7,9 auf 7,1 %	Senkung von 8,1 auf 6,4 % (Kontrollgruppe 7,5 %)	von 7,5 auf 6,5 % Int-Gruppe (Kontrollgruppe auf 7,0 %)	von 9,4 auf 6,4 % resp. auf 8,4 %
ARR primärer Endpunkt	3,2 %	13,5 %, *p=0.002*	Primärpräv.-Kohorte Retinopathie 11,5 %, Nephropathie 2,8 % Sek-Präv-Kohorte Retinopathie 12 %, Nephropathie 4 %	20 % für kardiovask. Ereignisse *(p=0.007)* Nephropathie 18,75 %, Retinopathie 16,25 %, Neuropathie	Nicht errechenbar – keine signifikante Endpunkt-Senkung *(HR 0.90; 95% CI 0.80-1.02, p= 0,095)*	*ARR 0.3 % (HR 0.90; 95% CI 0.78-1.04, p=0.16)*	1,1 % Nephropathie, *HR 0.79: 95% CI 0.66-0.93, p= 0.006* *prim. Endp.:* *kombin.: ARR 1.9%, HR 0.90; 95% CI 0.82-0.98,*	Keine

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				23,75 %, Erblindung 7,5 %			*p=0.01)* *makrovask.:* *n.s., ARR 0.6%, HR 0.94; 95% CI 0.84-1.06, p=0.32)* *mikrovask.:* *ARR 1.5%, HR 0.86; CI 95% 0.77-0.97, P=0.01)*	
NNT/Jahr primärer End-punkt	310	79	Primärprävention Retinopathie 52 Nephropathie 214 Sek-Prävention Retinopathie 50 Nephropathie 2	Nephropathie 57 Retinopathie 110 Erblindung 100 Neuropathie 110 Kardiovask. Ereignisse 39	Nicht errechenbar – keine signifikante Endpunkt-Senkung	n.s.	361	Nicht errechbar – keine signifikante Endpunkt-Senkung
ARR makro-vaskuläre Ereignisse	Nicht signifikant	Diabetes-Mortalität 5,3 %, *p=0.001;* Gesamt-Mortalität 7,1 % *p=0.01*; Herzinfarkt 7,0 % *p=0.01*	Nicht untersucht	Nicht unterschieden	Nicht errechenbar – keine signifikante Endpunkt-Senkung	*Nicht zusammengefasst untersucht*	Kein Unterschied	Nicht errechbar – keine signifikante Endpunkt-Senkung
Gesamtmortalität	*RR 0.94 (p=0.44; CI 0.80-1.10); ARR 1%*	ARR Mortalität 7,1 % *p=0.01*	n.u.	n.u.	*Kein Unterschied , HR 0.96 (95% CI 0,76-1.18), n.s.*	*HR 1.22 (95% CI 1.01-1.46, p= 0.04) sek. Endp.) -> daher Studienabbruch nach 3,5 Jahren in diesem Studienarm*	*Kein Unterschied, HR 0.93; 95% KI 0.83-1.06; p=0.28, n.s.)*	*Kein Unterschied, HR 1.07, 95% KI 0.81-1.42; p=0.62, n.s.)*

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Häufigkeit UAW	Schwere Hypoglykämien (Hilfe Dritter erforderlich) pro Jahr 0,5 % unter Glibenclamid, 2,2 % unter Insulin. Gewichtszunahme Glibenclamid 1,7 kg, Insulin 4 kg stärker als in Vergleichsgruppe	6 %	6 Patienten in der Interventions- und 4 in der Kontrollgruppe mit milder Hypoglykämie – bei keinem Hilfe Dritter erforderlich	Nicht unterschieden	Absolut 2 % mehr Krankenhaus-Einweisungen wegen kardialer Dekompensationen	>10 kg Gewichtszunahme bei 28 vs 14 %, schwere Hypoglykämien (Hilfe Dritter erforderlich) bei 10,5 vs 3,5 % Studie vorzeitig abgebrochen wg. Übersterblichkeit (nach 3.5 Jahren 257 (5,01 %) vs. 203 Tote (3,96 %) Abs. Risikoanstieg 1,05 %, NNH= 95	Schwere Hypoglykämien 2,7 vs 1,5 %	24,1 vs 17,6 %. Hypoglykämien waren stärkster Prädiktor für Sterblichkeit. 1.333 vs. 899 symptomatische Hypoglykämien
NNH/Jahr UAW	NNH schwere Hypoglykämie 71 bei Glibenclamid, 56 bei Insulin	Schwere Hypoglykämie 167	Nicht berechenbar	Nicht berechenbar	144 für stat. Einweisung mit Lungenödem	95 für Tod 50 für schwere Hypoglykämien, 25 für Gewichtszunahme um >10 kg	358 für schwere Hypoglykämien	75
Randomisierung	+	+	*(+), aber keine Details beschrieben*	+	+	*(+), keine Details beschrieben*	+	+
ITT	+	+	+	-	+	+	+	+
Poweranalyse	*(+)*	+	-	+	+	+	*(+), Anpassung im Verlauf durch Studienverlängerung und Endpunktzusammenlegung*	+
Vergleichbarkeit	+	+	+	+	+	+	+	+

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der Gruppen				*(supplementary material)*				
adäquate Kontrollintervention	+	+	+	+	+	*(+)*	-	+
KI Angabe	+	+	-	+	+	+	+	+
COI	*n.a.*	*n.a.*	-	+	+	+	+	+
Sonstige Bemerkungen	*Wenig Angaben zur genauen statist. Auswertung in dieser Publikation zu finden; auch in der verwiesenenen Publ. zum Studiendesign von 1991 wenig konkrete Angaben dazu. Daher Powerberechung und adäquate Adjustierung der Signifikanzniveaus nur eingeschränkt beurteilbar. 7 verschiedene prim. Endpunkte und 21 sek. Endp, die fraglich alle a priori festgelegt wurden. Zur Begleittherapie im Verlauf kaum Angaben, nur*	*Siehe UKPDS 34*	*Kleine Fallzahlen, Subgruppen der einzelnen Kohorten jeweils ca. 25 Pat.*		*Funded by Takeda and Lilliy*		*Major financial sponsor Servier, viele der Autoren COI durch Verbindung zu Servier und vielen weiteren PU*	*97% der Studienpopulation Männer*

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	Baselineangaben.							
Evidenzniveau nach SIGN	*1(+)*	*Siehe UKPDS 34*	*1(+)*	*1+*	*1+*	*1+*	*1(+)*	*1+*

3 Abkürzungsverzeichnis

Abkürzung	Erläuterung (ggf. deutsche Übersetzung)
AE	Adverse events
CI oder KI	confidence interval oder Konfidenzintervall
CoI	conflicts of interest
FEM	fixed-effect model
HR	hazard ratio
ITT	intention to treat
MA	metaanalysis
n.r.	not reported
NNT	number needed to treat
ns	not significant
OR	odds ratio
P	Patients
REM	random-effect model
RR	risk ratio
SR	Systematic review

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