Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

sowie

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2016-03-01-D-214 Empagliflozin

Datum: April 2016

Gemeinsamer Bundesausschuss

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Empagliflozin zur Behandlung des Diabetes mellitus Typ 2	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Sulfonylharnstoffe (SH) Metformin (MET) Gliptine Glinide Inkretinmimetika Acarbose SGLT-2-Inhibitoren Insulin
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Disease-Management-Programme (DMP) – Diabetes mellitus Typ 2 - Beschluss zur Einleitung eines Stellungnahmeverfahrens:

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Empagliflozin zur Behandlung des Diabetes mellitus Typ 2	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	o Verordnungseinschränkung/-ausschluss für Glinide zur Behandlung des Diabetes mellitus Typ 2 vom 10.03.2015 - Beschlüsse über die Nutzenbewertung nach § 35a SGB V: o Linagliptin vom 21.02.2013 sowie Linagliptin (neues AWG) vom 16.05.2013 o Saxagliptin/Metformin vom 02.05.2013 o Dapagliflozin vom 06.06.2013 sowie Dapagliflozin/Metformin vom 07.08.2014 o Lixisenatid vom 05.09.2013Saxagliptin sowie Saxagliptin/Metformin (neues AWG) vom 01.10.2013 o Sitagliptin sowie Sitagliptin/Metformin vom 01.10.2013 o Vildagliptin sowie Vildagliptin/Metformin vom 01.10.2013 o Canagliflozin vom 04.09.2014 sowie Canagliflozin/Metformin vom 05.02.2015 o Insulin degludec vom 16.10.2014 sowie Insulin degludec (neues AWG) vom 04.12.2014 und vom 20.08. 2015 o Empagliflozin vom 05.02.2015 o Albiglutid vom 19.03.2015 o Vildagliptin (erneute NB) vom 21.05.2015 o Insulin degludec/Liraglutid vom 15.10.2015 sowie Insulin degludec/Liraglutid (neues AWG) vom 4.2.2016 - Bestehende Verordnungsausschluss (AM-RL, Anlage III): Glitazone - Bestehende Verordnungseinschränkungen (AM-RL, Anlage III): schnell wirkende/lang wirkende Insulinanaloga - Therapiehinweise (AM-RL, Anlage IV): Sitagliptin vom 10.04.2008 und Vildagliptin vom 18.12.2008

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Empagliflozin zur Behandlung des Diabetes mellitus Typ 2	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	- Festbetrag SH „Antidiabetika vom Sulfonylharnstofftyp“, Gruppe 1 Stufe 2 - Festbetrag Metformin, Stufe 1 - Festbetrag Humaninsulin – „Insuline“, Gruppe 1-3 Stufe 1
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Fachinformation)
Zu bewertendes Arzneimittel	
Empagliflozin A10BX12 Jardiance®	“Jardiance® ist bei Erwachsenen mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle angezeigt als: Monotherapie Wenn Diät und Bewegung allein zur Blutzuckerkontrolle nicht ausreichen, bei Patienten, bei denen die Anwendung von Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird. Add-on-Kombinationstherapie In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn diese zusammen mit Diät und Bewegung zur Blutzuckerkontrolle nicht ausreichen (siehe Abschnitte 4.4, 4.5 und 5.1 für zurzeit vorliegende Daten zu verschiedenen Kombinationen)“.
Metformin A10BA02	Therapie des Diabetes mellitus Typ 2; insbesondere bei übergewichtigen Patienten, bei denen allein durch Diät und körperliche Betätigung keine ausreichende Einstellung des Blutzuckerspiegels erreicht wurde. Bei Erwachsenen kann Metformin in Form einer Monotherapie oder in Kombination mit anderen oralen Antidiabetika bzw. Insulin angewendet werden.
Sulfonylharnstoffe	
Glibenclamid A10BB01	Nicht-insulinabhängiger Diabetes mellitus bei Erwachsenen, wenn andere Maßnahmen wie konsequente Einhaltung der Diabetes-Diät, Gewichtsreduktion bei Übergewicht, ausreichende körperliche Betätigung nicht zu einer befriedigenden Einstellung des Blutglucosespiegels geführt haben. Glibenclamid kann als Monotherapie oder in Kombination mit Metformin verwendet werden.
Glimepirid A10BB12	Behandlung des Diabetes mellitus Typ 2, wenn eine Diät, körperliche Aktivität und Gewichtsreduktion alleine nicht ausreichen.
Gliquidon A10BB08	Nicht-insulinabhängiger Diabetes mellitus bei Erwachsenen (NIDDM, Typ II), wenn andere Maßnahmen wie konsequente Einhaltung der Diabetes-Diät, Gewichtsreduktion bei Übergewicht und ausreichende körperliche Betätigung nicht zu einer befriedigenden Einstellung des Blutglucosespiegels geführt haben. Als Monotherapie oder in Kombination mit Metformin.
Gliclazid A10BB09	Nicht insulinabhängiger Diabetes mellitus (Typ 2) bei Erwachsenen, sofern eine Diät, körperliche Aktivität u. Gewichtsreduktion alleine nicht ausreichend sind, um den Blutzuckerspiegel einzustellen.
Alpha-Glucosidase-Inhibitoren	
z.B. Acarbose A10BF01	Diabetes mellitus Typ 2 wenn durch Diät und körperliche Betätigung keine ausreichende Blutzuckereinstellung erreicht wurde, auch in Kombination mit Metformin, Sulfonylharnstoff oder Insulin.

GLP-(Glucagon-like Peptide)-1-Rezeptor-Agonisten (Inkretinmimetika)	
Albiglutid A10BX13 Eperzan®	Zur Behandlung des Typ 2 Diabetes bei Erwachsenen zur Verbesserung der Blutzuckereinstellung indiziert als: - Monotherapie, wenn Diät und Bewegung allein zur Blutzuckereinstellung nicht ausreichen bei Patienten, für die die Anwendung von Metformin aufgrund von Kontraindikationen oder Unverträglichkeit als ungeeignet angesehen wird. Kombinationstherapie in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken.
Dulaglutid Bisher kein ATC Trulicity®	Zur Behandlung des Typ 2 Diabetes bei Erwachsenen, um eine verbesserte Blutzuckerkontrolle zu erreichen als: - Monotherapie, sofern bei Patienten, für die die Einnahme von Metformin wegen Unverträglichkeit oder Kontraindikationen nicht angezeigt ist, durch Diät und Bewegung keine angemessene Blutzuckerkontrolle erreicht werden kann. Kombinationstherapie in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn durch diese zusammen mit Diät und Bewegung keine angemessene Blutzuckerkontrolle erreicht werden kann.
Exenatide A10BX04 Byetta®/Bydureon® [1]	Byetta® / Bydureon® ist angezeigt zur Behandlung des Typ 2 Diabetes mellitus in Kombination mit - Metformin - Sulfonylharnstoffen - Thiazolidindionen - Metformin und einem Sulfonylharnstoff-Präparat - Metformin und einem Thiazolidindion-Präparat bei Erwachsenen, bei denen mit der maximal verträglichen Dosis dieser oralen Therapien eine angemessene Blutzuckerkontrolle nicht erreicht werden konnte. BYETTA ist ebenfalls angezeigt als Kombinationstherapie mit Basalinsulin mit oder ohne Metformin und/oder Pioglitazon bei Erwachsenen, die mit diesen Substanzen keine angemessene Blutzuckerkontrolle erreicht haben.
Liraglutid A10BX07 Victoza®	Zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen in Kombination mit oralen Blutzucker senkenden Arzneimitteln und/oder Basalinsulin angewendet, um eine Blutzuckerkontrolle zu erreichen, wenn diese Mittel zusammen mit einer Diät und körperlicher Aktivität den Blutzuckerspiegel nicht ausreichend regulieren.
Lixisenatid [1] A10BX10 Lyxumia®	Lyxumia wird angewendet bei Erwachsenen zur Behandlung des Typ-2-Diabetes mellitus in Kombination mit oralen blutzuckersenkenden Arzneimitteln und/oder Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken
Gliptine (DPP (Dipeptidylpeptidase)-4 Hemmer)	

Linagliptin [1] A10BH05 Trajenta®	Linagliptin ist bei erwachsenen Patienten mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle indiziert: als Monotherapie • bei Patienten, wenn Diät und Bewegung allein zur Blutzuckerkontrolle nicht ausreichen und für die Metformin wegen Unverträglichkeit ungeeignet oder aufgrund einer Nierenfunktionsstörung kontraindiziert ist. als Kombinationstherapie • in Kombination mit Metformin, wenn Diät und Bewegung sowie eine Metformin-Monotherapie zur Blutzuckerkontrolle nicht ausreichen. • in Kombination mit einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung sowie eine Zweifachtherapie mit diesen beiden Arzneimitteln zur Blutzu • in Kombination mit Insulin mit oder ohne Metformin, wenn diese Behandlung alleine mit Diät und Bewegung zur Blutzuckerkontrolle nicht ausreicht.
Saxagliptin A10BH03 z.B Onglyza®	Saxagliptin ist bei erwachsenen Patienten ab 18 Jahren mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle indiziert: <u>Als Monotherapie:</u> • bei Patienten, die durch Diät und Bewegung allein nicht ausreichend kontrolliert sind und für die Metformin aufgrund von Kontraindikationen oder Unverträglichkeit ungeeignet ist. Als orale Zweifachtherapie in Kombination mit • Metformin, wenn eine Metformin-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert. • einem Sulfonylharnstoff bei Patienten, für die die Anwendung von Metformin ungeeignet erscheint, wenn eine Sulfonylharnstoff-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert. • einem Thiazolidindion bei Patienten, für die die Anwendung eines Thiazolidindions geeignet erscheint, wenn eine Thiazolidindion-Monotherapie, zusammen mit einer Diät und Bewegung, den Blut zucker nicht ausreichend kontrolliert <u>Als orale Dreifachtherapie in Kombination mit</u> • Metformin und einem Sulfonylharnstoff, wenn diese Behandlung allein, mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert. <u>Als Kombinationstherapie mit Insulin</u> (mit oder ohne Metformin), wenn diese Behandlung allein, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert
Saxagliptin/Metformin	Saxagliptin/ Metformin ist als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen

A10BD10 Komboglyze®	Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind, oder die bereits mit der Kombination von Saxagliptin und Metformin als separate Tabletten behandelt werden. Saxagliptin/ Metformin ist auch in Kombination mit Insulin (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und ewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn Insulin und Metformin allein den Blutzucker nicht ausreichend kontrollieren. Saxagliptin/ Metformin ist auch in Kombination mit einem Sulfonylharnstoff (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert.
Sitagliptin A10BH01 z.B. Januvia®	Zur Behandlung des Typ 2 Diabetes Monotherapie: - bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend senken und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist. In Kombination mit: - Metformin, wenn Ernährung und Bewegung plus Metformin allein nicht zur Blutzucker-kontrolle ausreichen. - Sulfonylharnstoff, wenn Diät und Bewegung plus eine Monotherapie mit einem Sulfonylharnstoff in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senken und wenn Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist. - Thiazolidindion, wenn die Anwendung eines Thiazolidindions angebracht ist und Diät und Bewegung plus Monotherapie mit einem Thiazolidindion den Blutzucker nicht ausreichend senken. - Sulfonylharnstoff und Metformin, wenn Diät und Bewegung plus eine Zweifachtherapie mit diesen Wirkstoffen den Blutzucker nicht ausreichend senken. - Thiazolidindion und Metformin, wenn die Anwendung eines Thiazolidindion angebracht ist und Diät und Bewegung plus eine Zweifach-therapie mit diesen Wirkstoffen den Blutzucker nicht ausreichend senken. Insulin, wenn Diät und Bewegung sowie eine stabile Insulin-dosis den Blutzucker nicht ausreichend senken.
Sitagliptin/Metformin A10BD07 Janumet®	Für erwachsene Patienten mit Typ-2-Diabetes mellitus. Sitagliptin/ Metformin ist zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle bei Patienten indiziert, bei

	denen eine Monotherapie mit Metformin in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senkt oder die bereits mit der Kombination von Sitagliptin und Metformin behandelt werden. Sitagliptin/ Metformin ist in <u>Kombination mit einem Sulfonylharnstoff</u> (z. B. als Dreifachtherapie) zusätzlich zu Diät und Bewegung bei Patienten indiziert, bei denen eine Kombination aus der jeweils höchsten vertragenen Dosis von Metformin und eines Sulfonylharnstoffs nicht ausreicht, um den Blutzucker zu senken. Janumet ist als Dreifachtherapie in Kombination mit einem Peroxisomal Proliferator- activated Receptor gamma (PPAR γ)-Agonisten (d. h. einem Thiazolidindion) zusätzlich zu Diät und Bewegung bei Patienten indiziert, bei denen die jeweils höchste vertragene Dosis von Metformin und einem PPARγ-Agonisten nicht ausreicht, um den Blutzucker zu senken. Sitagliptin/ Metformin ist auch <u>zusätzlich zu Insulin (d. h. als Dreifachtherapie)</u> indiziert als Ergänzung zu Diät und Bewegung bei Patienten, bei denen eine stabile Insulindosis und Metformin allein den Blutzucker nicht ausreichend senken.
Vildagliptin[1] A10BH02 z.B. Jalra®	Vildagliptin ist angezeigt zur Behandlung von Diabetes mellitus Typ 2 bei Erwachsenen: <u>Monotherapie</u> – bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist. In einer oralen Zweifach-Kombinationstherapie mit – Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist, – einem Sulfonylharnstoff bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen eines Sulfonylharnstoffs unzureichend eingestellt ist und bei denen Metformin wegen Kontraindikationen oder Unverträglichkeit ungeeignet ist, – einem Thiazolidindion bei Patienten mit ungenügender Blutzuckereinstellung, für die die Anwendung eines Thiazolidindions geeignet ist. <u>orale Dreifach-Kombinationstherapie mit:</u> – einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung zusätzlich zu einer Zweifachtherapie mit diesen Arzneimitteln zu keiner adäquaten glykämischen Kontrolle führen. Vildagliptin ist auch für die <u>Anwendung in Kombination mit Insulin</u> indiziert (mit oder ohne Metformin), wenn Diät und Bewegung zusätzlich zu einer stabilen Insulindosis zu keiner adäquaten glykämischen Kontrolle führen.
Vildagliptin/Metformin	Vildagliptin/ Metformin ist für die Behandlung des Typ-2-Diabetes-mellitus indiziert:

A10BD08 z.B. Eurcreas®	– Vildagliptin/ Metformin ist für die Behandlung von Erwachsenen indiziert, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine unzureichend eingestellt ist oder die bereits mit einer Kombination aus Vildagliptin und Metformin in separaten Tabletten behandelt werden. – Vildagliptin/ Metformin ist in Kombination mit einem Sulfonylharnstoff (d. h. Dreifachkombinationstherapie) zusätzlich zu Diät und Bewegung indiziert bei erwachsenen Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können. – Vildagliptin/ Metformin ist als Dreifachkombinationstherapie mit Insulin zusätzlich zu Diät und Bewegung indiziert, um die glykämische Kontrolle bei erwachsenen Patienten zu verbessern, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen.
Selektive Natrium-Glucose-Cotransport-Inhibitoren (SGLT-2-Inhibitoren)	
Dapagliflozin; Dapagliflozin/Metformin A10BX09 Forxiga®/Xigduo®	Forxiga ist bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle indiziert als: Monotherapie Wenn Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren, bei Patienten, bei denen die Anwendung von Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird. Add-on-Kombinationstherapie In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn diese den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrollieren (siehe Abschnitte 4.4, 4.5 und 5.1 bezüglich verfügbarer Daten zu verschiedenen Kombinationen).
Canagliflozin[1]; Canagliflozin/Metformin A10BX11 Invokana/Vokanamet®	Invokana wird angewendet bei Erwachsenen im Alter von 18Jahren und älter mit Typ-2-Diabetes-mellitus zur Blutzuckerkontrolle als: Monotherapie Bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen als ungeeignet erachtet wird. Kombinationstherapie Als Kombinationstherapie mit anderen Blutzucker-senkenden Arzneimitteln einschließlich Insulin, wenn diese den Blutzucker, zusammen mit Diät und Bewegung, nicht ausreichend kontrollieren (siehe Abschnitte 4.4, 4.5 und 5.1 für verfügbare Daten zu den verschiedenen Kombinationstherapien).
Glinide	

Nateglinid A10BX03 z.B. Starlix®	Kombinationstherapie mit Metformin bei Patienten mit Typ-2-Diabetes, die nicht ausreichend mit einer maximal tolerierbaren Metformin-Dosis eingestellt werden können.
Repaglinid A10BX02	Diabetes mellitus Typ 2, wenn der Blutzuckerspiegel durch Diät, Gewichtsreduktion und körperliche Aktivität alleine nicht mehr ausreichend reguliert werden kann. Repaglinid kann bei Erwachsenen mit Diabetes mellitus Typ 2 auch in Kombination mit Metformin eingenommen werden, falls die Blutzuckereinstellung mit Metformin allein nicht zufriedenstellend reguliert werden kann. Die Therapie sollte als Ergänzung zu Diät und körperlicher Bewegung begonnen werden, um die Blutzuckerwerte in Abhängigkeit von der Mahlzeit zu reduzieren.
Glitazone	*Verordnungsausschluss Anlage III - Arzneimittel-Richtlinie*
Insulin	
z.B. Humaninsulin	Zur Behandlung des Diabetes mellitus.

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

Behandlung von Typ-2-Diabetes mellitus

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „Diabetes Mellitus Typ 2“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre

eingeschränkt und die Recherche am 01.06.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP.

Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1395 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 294 Quellen eingeschlossen. Daraus konnten 112 Referenzen in die synoptische Evidenz-Übersicht aufgenommen werden.

Abkürzungen

ACP	American College of Physicians
AE	Adverse event
AM	Arzneimittel
AGI	Alpha-Glukosidaseinhibitor
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BMI	Body mass index
BIAsp	Biphasic insulin aspart
CI	Confidence Interval
CHF	Congestive heart failure
CV	cardiovascular
DAHTA	Deutsche Agentur für Health Technology Assessment
DBP	Diastolic blood pressure
DDG	Deutsche Diabetes Gesellschaft
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin
DGIM	Deutsche Gesellschaft für innere Medizin
DPP-4	Dipeptidylpeptidase IV
eGFR	Estimated glomerular filtration rate
FINS	Fasting plasma insulin
FPG	Fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GLP-1	Glucagon like peptide-1
HbA1c	Hämoglobin A1c
HDL	High density lipoprotein
HOMA-b	Homeostasis model assessment-b
HOMA-IR	Homeostasis model assessment-insulin resistance
HRQoL	Health Related Quality of Life
IAsp	Insulin Aspart
IDet	Insulin Detemir
IGlar	Insulin Glargin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITT	Intention to treat
LDL	Low density lipoprotein
MD	Mean difference

Met	Metformin
MH-OR	Mantel-Haenszel odds ratio
MI	Myocardial infarction
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NPH	neutrales Protamin Hagedorn
NVL	Nationale VersorgungsLeitlinie
OAD	Oral antidiabetic drugs
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PPG	Postprandial glucose
RCT	Randomized controlled trial
RR	Risk ratio
SAE	Severe adverse events
SBP	Systolic blood pressure
SGB	Sozialgesetzbuch
SGLT-2	Sodium dependent glucose transporter 2
SH	Sulfonylharnstoffe
SOC	Systemorganklasse
T2DM	Typ 2 Diabetes mellitus
TG	Triglyzerid
TRIP	Turn Research into Practice Database
TZD	thiazolidinediones
UTI	Urinary tract infection
WMD	Weighted mean difference
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2010 [37] Beschluss: Anlage III – Übersicht der Verordnungseinschränkungen und –ausschlüsse; Glitazone zur Behandlung des Diabetes mellitus Typ 2 Siehe auch: **IQWiG, 2008 [53]** Abschlussbericht (Auftrag A05-05A): Glitazone zur Behandlung des Diabetes mellitus Typ 2	Nutzenbewertung der Glitazone bei Patienten mit Diabetes Mellitus Typ 2 durch IQWiG im Jahr 2008. → Verordnungsausschluss der Glitazone: ,,Der Unterausschuss Arzneimittel ist nach Würdigung des Abschlussberichts des IQWiG und der Beratungen der Arbeitsgruppe „Nutzenbewertung“ zu dem Ergebnis gekommen, dass die tatbestandlichen Voraussetzungen für einen Ausschluss der Verordnungsfähigkeit von Glitazonen zur Behandlung des Diabetes mellitus Typ 2 gemäß § 92 Abs. 1 Satz 1, letzter Halbsatz SGB V erfüllt sind.‘‘
IQWiG, 2009 [54] Abschlussbericht (Auftrag A05-05C): Glinide zur Behandlung des Diabetes mellitus Typ 2	Nutzenbewertung der Glinide durch das IQWiG ergab: Keinen Beleg für einen Nutzen in der Behandlung von Patienten mit Diabetes mellitus Typ 2 für die Glinide <u>Gründe:</u> Es lagen zu vorab definierten Zielgrößen keine relevanten Studien vor und unzureichende Datenlage. Kein Beleg für einen Zusatznutzen gegenüber anderen Therapieoptionen (Vergleichsstudien gegenüber Metformin und Sulfonylharnstoffen) vorhanden.
G-BA, 2010 [19,34] Beschluss und tragende Gründe: Anlage III – Übersicht der Verordnungs-einschränkungen und –ausschlüsse Glinide zur Behandlung des Diabetes mellitus Typ 2	„Der Unterausschuss Arzneimittel ist nach Würdigung des Abschlussberichts des IQWiG und der Beratungen der Arbeitsgruppe Nutzenbewertung zu dem Ergebnis gekommen, dass die tatbestandlichen Voraussetzungen für eine Einschränkung der Verordnungsfähigkeit von Gliniden zur Behandlung des Diabetes mellitus Typ 2 gemäß § 92 Abs. 1 Satz 1, letzter Halbsatz SGB V erfüllt sind. Ausgeschlossen nach Anlage III sind Glinide zur Behandlung des Diabetes mellitus Typ 2. Hierzu zählen: - Nateglinid - Repaglinid *Ausgenommen ist die Behandlung von niereninsuffizienten Patienten mit einer Kreatinin-Clearance <25 ml / min mit Repaglinid, soweit keine anderen oralen Antidiabetika in Frage kommen und eine Insulintherapie nicht angezeigt ist.“*
G-BA, 2008 [21] Beschluss: Änderung der AM-RL in Anlage IV:	Unwirtschaftlichkeit von Exenatide: „Einsatz sollte Typ-2-Diabetikern vorbehalten bleiben, bei denen unter Ausschöpfung einer Therapie mit oralen Antidiabetika eine adäquate Blutzuckerkontrolle nicht erreicht werden konnte und die klinischen Befunde bei massivem Übergewicht (BMI > 30) vorrangig für eine

Therapiehinweis zu Exenatide	Insulinresistenz sprechen, sodass bei Zugabe von Insulin mit einer weiteren Gewichtszunahme und hohen Insulindosierungen zu rechnen ist. unwirtschaftlich.‘‘
IQWiG, 2007 [33,52] Bericht (Rapid Report): Bewertung des therapeutischen Nutzens von Exenatide	• Wirkung von Exenatide als blutzuckersenkende Therapie ist belegt, allerdings kein Beleg für eine bessere Wirkung (ähnliche Ergebnisse) von Exenatide gegenüber Insulin. Daten zu einem Vergleich mit anderen oralen Antidiabetika liegen nicht vor. • Nutzen oder Zusatznutzen von Exenatide bezüglich patientenrelevanter Endpunkte wie Folgekomplikationen des Diabetes, Mortalität, stationäre Behandlungen, hyperosmolare und ketoazidotische Komata sowie zur durch chronische Hyperglykämie bedingten Symptomatik (unzureichende Datenlage) • Als Schaden der Therapie mit Exenatide ist das Auftreten gastrointestinaler unerwünschter Ereignisse belegt. Ein Langzeitnutzen oder –schaden bzw. ein Fehlen des Langzeitnutzens oder –schaden ist nicht belegt und bleibt unklar.
G-BA, 2008 [33] Beschluss: Änderung der Arzneimittel-Richtlinie in Anlage 10: Kurzwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2	„Nach diesem Beschluss sind kurzwirksame Insulinanaloga nicht verordnungsfähig, solange sie mit Mehrkosten im Vergleich zu kurzwirksamem Humaninsulin verbunden sind. In den tragenden Gründen zu diesem Beschluss hat der G-BA ausgeführt, in welchen medizinisch begründeten Einzelfällen Insulinanaloga ausnahmsweise weiterhin verordnet werden können.“
IQWiG, 2005 [51] Abschlussbericht: Kurzwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2	• Kurze Beobachtungsdauer der Studien (5,5 -12 Monate): Ein möglicher positiver Effekt von kurzwirksamen Insulinanaloga hinsichtlich der Reduktion diabetischer Folgekomplikationen oder der Gesamtsterblichkeit kann nicht belegt ermittelt werden (Langzeitnutzen). • Keine Unterschiede bzw. unzureichende Daten hinsichtlich Lebensqualität, Gewichtszunahme, hypoglykämischen, schwerwiegender, symptomatischer noch nächtlicher Hypoglykämien bei den untersuchten Therapieoptionen. • Tendenziell mehr Therapieabbrüche aufgrund unerwünschter AM-Nebenwirkungen bzw. scherwiegende unerwartete Ereignisse unter Insulin-Glulisin und Insulin-Lispro als unter Humaninsulin.
G-BA, 2010 [38] Zusammenfassende Dokumentation über die Änderung der AM-RL: Anlage III – Übersicht der Verordnungs-einschränkungen und -ausschlüsse Langwirkende Insulinanaloga zur Behandlung des Diabetes	„Da das Ziel der Behandlung des Diabetes mellitus Typ 2 mit lang wirkenden Insulinanaloga ebenso zweckmäßig mit Humaninsulin, aber kostengünstiger, zu erreichen ist, sieht der Unterausschuss „Arzneimittel“ die zitierten tatbestandlichen Voraussetzungen für die Einschränkung der Verordnungsfähigkeit von lang wirkenden Insulinanaloga als erfüllt an.“

mellitus Typ 2	
IQWiG, 2009 [55] Bericht: Langwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 2	Kein Beleg eines Zusatznutzens der Langwirksamen Insulinanaloga gegenüber Humaninsulin (NPH Insulin) bzw. der beiden Insulinanaloga (Glargin und Detemir) untereinander. Langzeitnutzen und -schaden hinsichtlich diabetischer Folgekomplikationen von langwirksamen Insulinanaloga gegenüber Humaninsulin bzw. den Insulinanaloga gegeneinander generell nicht ausreichend untersucht.
G-BA, 2005 [18] Anforderungen an strukturierte Behandlungs-programme für Patienten mit Diabetes mellitus Typ 2 Siehe auch **G-BA, 2008 [20]** Siehe auch **IQWiG, 2011 [58]**	<u>Blutglukosesenkende Therapie:</u> „Zur Erreichung der individuellen Therapieziele sollen nach Möglichkeit zunächst nichtmedikamentöse Maßnahmen ausgeschöpft werden. Das Ziel der antihyperglykämischen Therapie, gemessen am HbA1c-Wert, ist individuell festzulegen. Wenn die Verhinderung mikrovaskulärer Komplikationen ein Therapieziel ist, ist eine normnahe Einstellung der Blutglukose anzustreben. Vorrangig sollen unter Berücksichtigung der Kontraindikationen und der Patientenpräferenzen Medikamente zur Blutglukosesenkung verwendet werden, deren positiver Effekt und deren Sicherheit im Hinblick auf die Erreichung der unter Ziffer 1.3.1 * genannten Therapieziele in prospektiven, randomisierten, kontrollierten Langzeitstudien nachgewiesen wurden. Es handelt sich in der primären Monotherapie hierbei um folgende Wirkstoffe zur blutglukosesenkenden Behandlung: - Glibenclamid (beim nicht übergewichtigen Patienten), - Metformin (beim übergewichtigen Patienten), - Human-Insulin. Sofern im Rahmen der individuellen Therapieplanung andere als die o.g. Wirkstoffe verordnet werden sollen (z. B. Insulin-Analoga, weitere orale Antidiabetika), ist die Patientin oder der Patient darüber zu informieren, dass derzeit hierfür keine ausreichenden Belege zur Sicherheit im Langzeitgebrauch sowie zur Risikoreduktion klinischer Endpunkte vorliegen. Sie oder er ist im Übrigen darüber zu informieren, ob für den jeweiligen Wirkstoff Daten zur Wirksamkeit, Steuerbarkeit und Verträglichkeit vorliegen. <u>*Therapieziele*</u>*: Die Therapie dient der Erhöhung der Lebens-erwartung sowie der Erhaltung oder der Verbesserung der von einem Diabetes mellitus beeinträchtigten Lebensqualität. Dabei sind in Abhängigkeit z. B. von Alter und Begleit-erkrankungen der Patientin oder des Patienten individuelle Therapieziele anzustreben: a) Vermeidung von Symptomen der Erkrankung (z. B. Polyurie, Polydipsie,Abgeschlagenheit) einschließlich der Vermeidung neuropathischer Symptome, Vermeidung von Nebenwirkungen der Therapie (insbesondere schwere oder rezidivierende Hypoglykämien) sowie schwerer hyperglykämischer Stoffwechsel-entgleisungen, b) Reduktion des erhöhten Risikos für kardiale, zerebrovaskuläre und sonstige makroangiopathische Morbidität und Mortalität, c) Vermeidung der mikrovaskulären Folgeschäden (insbesondere Retinopathie mit schwerer Sehbehinderung oder Erblindung, Niereninsuffizienz mit der*

	Notwendigkeit einer Nierenersatztherapie), d) Vermeidung des diabetischen Fußsyndroms mit neuro-, angio- und/oder osteoarthropathischen Läsionen und von Amputationen."
G-BA, 2008 [35] Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Sitagliptin	„Die Gabe von Sitagliptin ist auf die Fälle zu beschränken, bei denen die vorhandenen kostengünstigeren Alternativen aufgrund von Kontraindikationen nicht eingesetzt werden können, unverträglich sind oder nicht zu einer adäquaten Blutzucker-kontrolle führen. Metformin und Sulfonylharnstoffe sind bei belegtem Langzeitnutzen und günstigen Kosten orale Antidiabetika der ersten Wahl. Wenn Glitazone unter Berücksichtigung ihrer Risiken in der Second-Line-Therapie nicht in Frage kommen und die Insulintherapie noch nicht angezeigt ist, kann Sitagliptin eine Alternative sein."
G-BA, 2008 [36] Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Vildagliptin	„Vildagliptin ist nicht zur Monotherapie oder Kombination mit Insulin zugelassen. Aufgrund von Bedenken der Europäischen Zulassungsbehörde (EMEA) wurden die Anträge für diese Indikationen vom Hersteller wieder zurückgezogen. Die Zulassung der fixen Kombination mit Metformin umfasst nur die Gabe nach Versagen einer Monotherapie mit Metformin und nicht die initiale Therapie. Die Anwendung von Vildagliptin ist auf die Fälle zu beschränken, bei denen die vorhandenen kostengünstigeren Alternativen zur Behandlung des Diabetes mellitus Typ 2 wegen Kontraindikationen nicht eingesetzt werden können, unverträglich sind oder nicht zu einer adäquaten Blutzuckerkontrolle führen. Metformin und Sulfonylharnstoffe sind bei belegtem Langzeitnutzen und günstigen Kosten orale Antidiabetika der ersten Wahl. Wenn Glitazone unter Berücksichtigung ihrer Risiken in der Second-Line-Therapie nicht in Frage kommen und die Insulintherapie noch nicht angezeigt ist, kann Vildagliptin eine Alternative sein, siehe auch Therapiehinweis zu Sitagliptin. In diesen Fällen ist der wirtschaftlicheren Fixkombination Metformin/Vildagliptin Vorrang zu geben."
G-BA, 2013 [31] Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vildagliptin Siehe auch: **IQWiG, 2013 [63,72]und G-BA, 2015 [26]**	a) Monotherapie, bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist: **Zweckmäßige Vergleichstherapie:** Sulfonylharnstoff (Glibenclamid oder Glimepirid) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Ein Zusatznutzen ist nicht belegt. b) Zweifachkombination Vildagliptin mit Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist: **Zweckmäßige Vergleichstherapie:** Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens**

	gegenüber Sulfonylharnstoff (Glibenclamid oder Glimepirid) und Metformin: Ein Zusatznutzen ist nicht belegt. c) Zweifachkombination Vildagliptin mit Sulfonylharnstoff bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen eines Sulfonylharnstoffes unzureichend eingestellt ist und bei denen Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten ungeeignet ist: **Zweckmäßige Vergleichstherapie:** Humaninsulin in Kombination mit einem Sulfonylharnstoff (Glibenclamid oder Glimepirid) *(Hinweis: ggf. nur Therapie mit Humaninsulin)* ***Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Sulfonylharnstoff (Glibenclamid oder Glimepirid):*** *Ein Zusatznutzen ist nicht belegt.*
G-BA, 2013 [27] Beschluss des Gemeinsamen Bundesausschusses über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Vildagliptin/Metformin Siehe auch: **IQWiG, 2013** **[64,73]**	a) Zweifachkombination Vildagliptin/Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine unzureichend eingestellt ist: **Zweckmäßige Vergleichstherapie:** Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin und Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Ein Zusatznutzen ist nicht belegt. b) Dreifachkombination Vildagliptin/Metformin mit Sulfonylharnstoff bei Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können: **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt. c) Kombination Vildagliptin/Metformin mit Insulin, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen: **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2012 [39] Zusammenfassende	Der pU bezieht sich in den dafür vorgesehenen Abschnitten des Dossiers auf eine andere als die vom G-BA festgelegte

Dokumentation über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Linagliptin Siehe auch: **IQWiG, 2011 [56]**	zweckmäßige Vergleichstherapie. Daher gibt es insgesamt keinen Beleg für einen Zusatznutzen von Linagliptin gegenüber der zweckmäßigen Vergleichstherapie nach Festlegung des G-BA.
G-BA, 2013 [22] Beschluss des G-BA die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Linagliptin Siehe auch: **IQWiG, 2012 [59]**	(Erneute Nutzenbewertung nach § 35 a Absatz 5b SGB V) **Zweckmäßige Vergleichstherapie:** Die zweckmäßige Vergleichstherapie für Linagliptin in Kombination mit Insulin mit oder ohne Metformin, wenn diese Behandlung alleine mit Diät und Bewegung zur Blutzuckerkontrolle nicht ausreicht, bei Patienten mit Diabetes mellitus Typ 2 ist: - die Zweifachkombination von Metformin + Humaninsulin. *(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unver-träglich oder nicht ausreichend wirksam ist.)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin + Metformin:** Da die erforderlichen Nachweise nicht vollständig vorgelegt worden sind, gilt der Zusatz-nutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Abs. 1 Satz 5 SGB V).
IQWiG, 2011 [57] Rapid Report (A05-07): Nutzenbewertung einer langfristigen normnahen Blutzuckersenkung bei Patienten mit Diabetes mellitus Typ 2	Ziel der vorliegenden Untersuchung ist die Nutzenbewertung von Maßnahmen mit der Intention zu einer langfristigen, „normnahen“ Blutzuckereinstellung im Vergleich zu einer Maßnahme mit einer weniger intensiven (oder keinen) Intention zur Blutzuckereinstellung bei Patienten mit Diabetes mellitus Typ 2 hinsichtlich patientenrelevanter Therapieziele. Fazit: Bei Patienten mit Diabetes mellitus Typ 2 ist für keinen der hier untersuchten patientenrelevanten Endpunkte ein Nutzen bzw. Schaden einer „normnahen“ Blutzuckersenkung belegt, d. h. weder für die Gesamtmortalität noch für Folgekomplikationen des Diabetes mellitus (tödliche oder nicht-tödliche Myokardinfarkte, tödliche oder nicht-tödliche Schlaganfälle, terminale Niereninsuffizienz, Amputationen oder Erblindung) und auch nicht für die gesundheitsbezogene Lebensqualität. Ein belegter Nutzen bzw. Schaden hinsichtlich therapieassoziierter Faktoren (schwere Hypoglykämien oder schwerwiegende unerwünschte Ereignisse) liegt ebenfalls nicht vor. Auch ein vorteilhafter bzw. nachteiliger Effekt auf Surrogate wie Vorstufen der Erblindung oder Vorstufen der terminalen Niereninsuffizienz ist nicht nachgewiesen. *Allerdings bestehen Hinweise auf einen Schaden durch vermehrte schwere Hypoglykämien und vermehrte schwerwiegende unerwünschte Ereignisse unabhängig von Hypoglykämien. Dem steht ein Hinweis auf einen Nutzen bezüglich der Vermeidung nicht-tödlicher Herzinfarkte gegenüber.*

G-BA, 2013 [32] Beschluss des Gemeinsamen Bundesausschusses über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Saxagliptin Siehe auch **IQWiG, 2013 [67]**	a) Zweifachkombination Saxagliptin mit Metformin, wenn eine Metformin-Monotherapie den Blutzucker nicht ausreichend kontrolliert **Zweckmäßige Vergleichstherapie:** Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid oder Glimepirid) und Metformin:** Anhaltspunkt für einen geringen Zusatznutzen. b) Zweifachkombination Saxagliptin mit Sulfonylharnstoff, wenn die Anwendung von Metformin ungeeignet erscheint und wenn eine Sulfonylharnstoff-Monotherapie den Blutzucker nicht ausreichend kontrolliert **Zweckmäßige Vergleichstherapie:** Humaninsulin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) *(Hinweis: ggf. Therapie nur mit Humaninsulin)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Ein Zusatznutzen ist nicht belegt. c) Orale Dreifachkombination von Saxagliptin mit Metformin und einem Sulfonylharnstoff, wenn die Behandlung mit Metformin und einem Sulfonylharnstoff allein den Blutzucker nicht ausreichend kontrolliert **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist*) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt. d) Kombination von Saxagliptin mit Insulin (mit oder ohne Metformin), wenn die Behandlung mit Insulin (mit oder ohne Metformin) allein den Blutzucker nicht ausreichend kontrolliert. **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist)*. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt
IQWiG, 2013 [66] Saxagliptin (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V	Ziel: Bewertung des Zusatznutzens von Saxagliptin im Vergleich zur zweckmäßigen Vergleichstherapie für die Behandlung von erwachsenen Patienten ab 18 Jahren mit Typ-2-Diabetes mellitus für das im Juli 2013 neu zugelassene Anwendungsgebiet der **Monotherapie**: • Als Monotherapie bei Patienten, die durch Diät und

(IQWiG-Berichte – Nr. 197)	Bewegung allein nicht ausreichend kontrolliert sind und für die Metformin aufgrund von Kontraindikationen oder Unverträglichkeit ungeeignet ist. • Der G-BA hat folgende zweckmäßige Vergleichstherapie festgelegt: Sulfonylharnstoff (Glibenclamid oder Glimepirid). **Ergebnisse** Die vom pU vorgelegten Daten sind nicht geeignet, um Aussagen zum Zusatznutzen von Saxagliptin in der Monotherapie zu treffen. Aus den vorliegenden Daten ergibt sich kein Beleg für einen Zusatznutzen von Saxagliptin gegenüber der vom G-BA festgelegten zweckmäßigen Vergleichstherapie. Folglich gibt es auch keine Patientengruppen, für die sich ein therapeutisch bedeutsamer Zusatznutzen ableiten lässt.
G-BA, 2013 [40] Beschluss des Gemeinsamen Bundesausschusses über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Saxagliptin+Metformin Siehe auch: **IQWiG, 2013 [60,68]** Und: (neues Anwendungsgebiet) **G-BA, 2013 [24]** **IQWiG, 2013 [69]**	a) Zweifachkombinationstherapie Saxagliptin/Metformin bei erwachsenen Patienten im Alter von 18 Jahren und älter, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind: **Zweckmäßige Vergleichstherapie:** Sulfonylharnstoff (Glibenclamid, Glimepirid) + Metformin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid, Glimepirid):** Anhaltspunkt für einen geringen Zusatznutzen. Addendum unter Berücksichtiung neuer Evidenz (Studie D1680L00002): kein Beleg für einen Zusatznutzen b) Dreifachkombinationstherapie Saxagliptin/Metformin + Insulin: **Zweckmäßige Vergleichstherapie:** Metformin + Humaninsulin *(ggf. Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin + Humaninsulin (ggf. nur Humaninsulin):** Ein Zusatznutzen ist nicht belegt.
	(neues Anwendungsgebiet) Dreifachkombination Saxagliptin/Metformin mit Sulfonylharnstoff, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).*

	Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin: Ein Zusatznutzen ist nicht belegt.
G-BA, 2013 [25] Beschluss des Gemeinsamen Bundesausschusses über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sitagliptin Siehe auch: **IQWiG, 2013 [70]**	a) Monotherapie bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend senken und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist: **Zweckmäßige Vergleichstherapie:** Sulfonylharnstoff (Glibenclamid oder Glimepirid) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Anhaltspunkt für einen geringen Zusatznutzen. b) Zweifachkombination Sitagliptin mit Metformin, wenn Diät und Bewegung plus eine Metformin-Monotherapie den Blutzucker nicht ausreichend senken: **Zweckmäßige Vergleichstherapie:** Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid oder Glimepirid) und Metformin:** Anhaltspunkt für einen geringen Zusatznutzen. c) Zweifachkombination Sitagliptin mit Sulfonylharnstoff, wenn Diät und Bewegung plus eine Sulfonylharnstoff-Monotherapie in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senken und wenn Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist: **Zweckmäßige Vergleichstherapie:** Humaninsulin in Kombination mit einem Sulfonylharnstoff (Glibenclamid oder Glimepirid) *(Hinweis: ggf. nur Therapie mit Humaninsulin)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Ein Zusatznutzen ist nicht belegt. d) Dreifachkombination Sitagliptin mit Sulfonylharnstoff und Metformin, wenn Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken: **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist*) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt. e) Kombination Sitagliptin mit Insulin (mit und ohne Metformin), wenn Diät und Bewegung sowie eine stabile

	Insulindosis den Blutzucker nicht ausreichend senken: **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin*(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist).* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2013 [30] Beschluss des Gemeinsamen Bundesausschusses über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sitagliptin + Metformin Siehe auch: **IQWiG, 2013 [62,71]**	a) Zweifachkombination Sitagliptin/Metformin zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle bei Patienten, bei denen eine Monotherapie mit Metformin in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senkt: **Zweckmäßige Vergleichstherapie:** Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin und Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Anhaltspunkt für einen geringen Zusatznutzen. b) Dreifachkombination Sitagliptin/Metformin mit Sulfonylharnstoff zusätzlich zu Diät und Bewegung bei Patienten, bei denen eine Kombination aus der jeweils höchsten vertragenen Dosis von Metformin und eines Sulfonylharnstoffs nicht ausreicht, um den Blutzucker zu senken: **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt. c) Dreifachkombination Sitagliptin/Metformin mit Insulin als Ergänzung zu Diät und Bewegung bei Patienten, bei denen eine stabile Insulindosis und Metformin allein den Blutzucker nicht ausreichend senken: **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin *(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin und Metformin:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2013 [29] Beschluss des Gemeinsamen Bundesausschusses über die Nutzenbewertung von	a) Monotherapie bei Patienten, bei denen Diät und Bewegung den Blutzucker nicht ausreichend kontrollieren und bei denen die Anwendung von Metformin aufgrund einer Unverträglichkeit als ungeeignet angesehen wird:

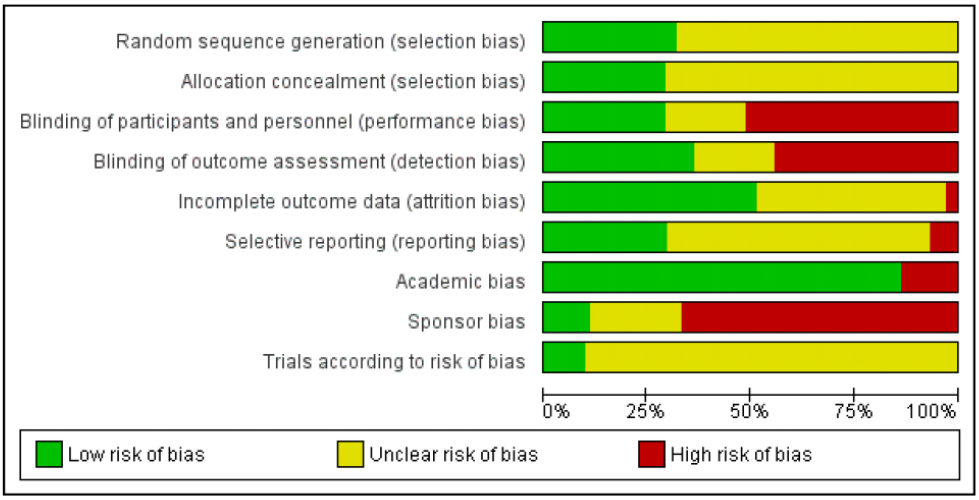
Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dapagliflozin Siehe auch: **IQWiG, 2013 [61,65]**	**Zweckmäßige Vergleichstherapie**: Sulfonylharnstoff (Glibenclamid, Glimepirid) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid, Glimepirid):** Ein Zusatznutzen ist nicht belegt. b) Add-on Kombinationstherapie mit Metformin, wenn Metformin den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert: **Zweckmäßige Vergleichstherapie:** Sulfonylharnstoff (Glibenclamid, Glimepirid) + Metformin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid, Glimepirid) + Metformin**: Ein Zusatznutzen ist nicht belegt. c) Add-on Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln (außer Metformin und Insulin), wenn diese den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrollieren: **Zweckmäßige Vergleichstherapie**: Metformin + Sulfonylharnstoff (Glibenclamid, Glimepirid) *(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin + Sulfonylharnstoff (Glibenclamid, Glimepirid**): Ein Zusatznutzen ist nicht belegt. d) Add-on Kombinationstherapie mit Insulin, wenn eine Insulintherapie den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert: **Zweckmäßige Vergleichstherapie:** Metformin + Humaninsulin *(ggf. Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin + Humaninsulin:** *Ein* Zusatznutzen ist nicht belegt.
G-BA, 2014 [23] Beschluss des Gemeinsamen Bundesausschusses über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dapagliflozin/Metformin Siehe auch: **IQWiG, 2014**	**Zugelassenes Anwendungsgebiet:** Xigduo® ist bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus indiziert, als Ergänzung zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle: - bei Patienten, bei denen der Blutzucker mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert wird - in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin bei Patienten, bei denen der Blutzucker mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert wird

[75]	- bei Patienten, die bereits mit der Kombination aus Dapagliflozin und Metformin als separate Tabletten behandelt werden. **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) Kombinationstherapie mit Metformin, wenn Metformin in der maximal verträglichen Dosis den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert: **Zweckmäßige Vergleichstherapie:**: Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin:** Ein Zusatznutzen ist nicht belegt. b) Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln außer Insulin, wenn der Blutzucker mit Metformin und diesen Arzneimitteln zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird: **Zweckmäßige Vergleichstherapie:** Humaninsulin + Metformin (Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin + Metformin**: Ein Zusatznutzen ist nicht belegt. c) Kombinationstherapie mit Insulin, wenn der Blutzucker mit Metformin und Insulin zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird: **Zweckmäßige Vergleichstherapie**: Humaninsulin + Metformin (Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin + Metformin:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2014 [42] Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Insulin degludec	**a)** Monotherapie zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen: **Zweckmäßige Vergleichstherapie:** • Humaninsulin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin:** Ein Zusatznutzen ist nicht belegt. **b)** Kombinationstherapie mit einem oder mehreren oralen Antidiabetika zur Behandlung des Diabetes mellitus Typ 2 bei

Siehe auch **IQWiG, 2014 Bewertungsmodul II [76]**	Erwachsenen: **Zweckmäßige Vergleichstherapie:** • Metformin plus Humaninsulin *(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin plus Humaninsulin:** Ein Zusatznutzen ist nicht belegt. **c)** Kombinationstherapie mit Bolusinsulin (mit oder ohne einem oder mehreren oralen Antidiabetika) zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen: **Zweckmäßige Vergleichstherapie:** • Humaninsulin plus ggf. Metformin (Hinweis: In der Kombination mit Bolusinsulin (ohne orales Antidiabetikum) im Rahmen einer ICT ist eine zusätzliche Metformin-Gabe nicht regelhaft indiziert) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Humaninsulin (plus ggf. Metformin):** Ein Zusatznutzen ist nicht belegt.
G-BA, 2014 [41] Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Insulin degludec (neues Anwendungsgebiet)	*Der vorliegende Beschluss bezieht sich ausschließlich auf das neu zugelassene Anwendungsgebiet (größere Änderung des Typs 2 nach Anhang 2 Nummer 2 Buchstabe a der Verordnung (EG) Nr. 1234/2008 der Kommission vom 24. November 2008 über die Prüfung von Änderungen der Zulassungen von Human- und Tierarzneimitteln),* ***d. h. auf die Kombination von Insulin degludec mit GLP-1-Rezeptor-Agonisten*** *zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen.* **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichs-therapie** **Zweckmäßige Vergleichstherapie:** Die zweckmäßige Vergleichstherapie für Insulin degludec zur Behandlung des Diabetes mellitus Typ 2 in der Kombination mit einem oder mehreren anderen Antidiabetika (außer Insulin) ist: Metformin plus Humaninsulin (Hinweis: Ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist oder gemäß Fachinformation nicht geeignet ist) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Metformin plus Humaninsulin:** Der Zusatznutzen gilt als nicht belegt.
G-BA, 2014 [28] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse	a) In der Monotherapie, wenn Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen als ungeeignet erachtet wird **Zweckmäßige Vergleichstherapie:** Sulfonylharnstoff (Glibenclamid oder Glimepirid)

über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Canagliflozin Siehe auch **IQWiG, 2014 [74]**	**Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Canagliflozin gegenüber einem Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Ein Zusatznutzen ist nicht belegt. b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert (Kombination mit Metformin) **Zweckmäßige Vergleichstherapie:** Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) (Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Canagliflozin in Kombination mit Metformin gegenüber Metformin und einem Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Ein Zusatznutzen ist nicht belegt. c) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert (Kombination mit einem Sulfonylharnstoff) **Zweckmäßige Vergleichstherapie:** Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) (Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Canagliflozin in Kombination mit einem Sulfonylharnstoff gegenüber Metformin und einem Sulfonylharnstoff (Glibenclamid oder Glimepirid):** Ein Zusatznutzen ist nicht belegt. d) In Kombination mit mindestens zwei anderen blutzuckersenkenden Arzneimitteln, wenn diese den Blutzucker zusätzlich zu Diät und Bewegung nicht ausreichend kontrollieren **Zweckmäßige Vergleichstherapie:** Metformin + Humaninsulin (Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich.) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Canagliflozin in Kombination mit Metformin und einem Sulfonylharnstoff gegenüber Metformin und Humaninsulin:** Ein Zusatznutzen ist nicht belegt. e) In Kombination mit Insulin (mit oder ohne orales Antidiabetikum) **Zweckmäßige Vergleichstherapie:**

	Metformin + Humaninsulin *(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich.)* **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Canagliflozin in Kombination mit Insulin (mit oder ohne orales Antidiabetikum) gegenüber Metformin und Humaninsulin:** Ein Zusatznutzen ist nicht belegt.

Hemmingsen, 2013 [49] **Sulphonylurea monotherapy for patients with type 2 diabetes mellitus**	**Fragestellung** To assess the effects of sulphonylureamonotherapy versus placebo, no intervention or other antidiabetic interventions for patients with type 2 diabetes mellitus (T2DM).
	Methodik Population: Participants with type 2 diabetes mellitus Intervention/ Komparator: • First-, second- or third-generation sulphonylureas versus placebo, diet, metformin, thiazolidinediones, insulin or any other antidiabetic comparator. • Second- or third-generation sulphonylureas versus firstgeneration sulphonylureas. Endpunkt: All-cause mortality, Cardiovascular mortality, Non-fatal macrovascular outcomes (assessed together and separately: non-fatal myocardial infarction, non-fatal stroke, amputation of lower extremity and cardial or peripheral revascularization), Microvascular outcomes, Glycaemic control (fasting plasma glucose and HbA1c), BMI, Weight, Adverse events Studiendauer: 24 Wochen bis 10,7 Jahre Suchzeitraum der syst. Recherche bis August 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 72 (n=22.589) Studienqualität/Risk of bias: Cochrane risk of bias tool
Ergebnisdarstellung No study entirely free of bias, low proportion of studies with low risk of bias **Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**  	

First-generation sulphonylureas compared with controls for DM type 2

Outcomes	Relative effect (95%CI)	Anzahl Studien (n=)	Ouality of Evidence (GRADE)	Comments
All-cause mortality				
Intervention vs placebo [30 weeks to 4.75 years]	**RR 1.46** (0.87 to 2.45)	2 (n=553)	low	Small sample size (1. 5% of the diversity-adjusted required information size)
Intervention vs insulin [4.75 to 10.0 years]	**RR 1.18** (0.88 to 1.59)	2 (n=1944)		Trial sequential analysis showed that 5.7% of the required information size to detect or reject a 10% RRR was accrued
Cardiovascular mortality				
Intervention vs placebo [30 weeks to 4.75 years]	**RR 2.63** (1.32 to 5.22)	2 (n=553)	low	Small sample size (0. 7% of the diversity-adjusted required information size)
Intervention vs insulin [4.75 to 10.0 years]	**RR 1.36** (0.88 to 1.48)	2 (n=1944)		Trial sequential analysis showed that 1.1% of the required information size to detect or reject a 10% RRR was accrued
Non-fatal macrovascular outcomes				
Composite	not estimable	See comment	See comment	No meta-analysis possible
Non-fatal myocardial infarction Intervention vs insulin [4.75 years to 10.0 years]	**RR 1.08** (0.81 to 1.45)	2 (n=1944)	low	
Cancer				
Intervention vs insulin [4.75 to 10.0 years]	**RR 0.81** (0.29 to 2.27)	2 (n=1944)	low	One study reported any cancer and the other death due to cancer
Adverse events				
All adevers events Intervention vs. alpha-glucusidase inhibitors [30 weeks]	**RR=0.63** (0.52 to 0.76)	2 (n=1,246)	low	Trial sequential analysis showed that firm evidence was not established
Drop outs due to adevers events Intervention vs. alpha-glucusidase inhibitors [30 weeks]	**RR=0.28** (0.12 to 0.67)	2 (n=1,246)	low	Trial sequential analysis showed that firm evidence was not established

Second-generation sulphonylureas compared with controls for type 2 diabetes mellitus

Outcomes	Relative effect (95%CI)	Anzahl Studien (n=)	Ouality of Evidence (GRADE)	Comments
All-cause mortality				
Intervention vs metformin [24 weeks to 4 years]	**RR 0.98** (0.61 to 1.58)	6 (n=3528)		Trial sequential analysis showed that 2.3% of the required information size to detect or reject a 10% RRR was accrued
Intervention vs thiazolidinediones [24 weeks to 4 years]	**RR 0.92** (0.60 to 1.41)	7 (n=4955)		Results of the randomeffects model. Trial sequential analysis showed that 2.5% of the required information size to detect or reject a 10% RRR was accrued
Intervention vs insulin [9 months to 10 years]	**RR 0.96** (0.79 to 1.18)	4 (n=1642)	low	c. Trial sequential analysis showed that 12.8% of the required information size to detect or reject a 10% RRR was accrued
Intervention vs incretinbased control [52 weeks to 104 weeks]	**RR 1.39** (0.52 to 3.68)	2 (n=1503)		d. Trial sequential analysis showed that 0.5% of the required information size to detect or reject a 10% RRR was accrued.
Intervention vs meglitinide [12 to 17 months]	**RR 1.44** (0.47 to 4.42)	7 (n=2038)		e. Trial sequential analysis showed that only a minor fraction of the required information size to detect or reject a 10% RRR was accrued.
Cardiovascular mortality				
Intervention vs metformin [24 weeks to 4 years]	**RR 1.47** (0.54 to 4.01)	6 (n=3528)		Trial sequential analysis showed that 2.7% of the required information size to detect or reject a 10% RRR was accrued
Intervention vs thiazolidinediones [24 weeks to 4 years]	**RR 1.30** (0.55 to 3.07)	7 (n=4955)		Trial sequential analysis showed that 0.3% of the required information size to detect or reject a 10% RRR was accrued
Intervention vs insulin [9 months to 10 years]	**RR 0.96** (0.73 to 1.28)	4 (n=1642)	low	Trial sequential analysis showed that 6.6% of the required information size to detect or reject a 10% RRR was accrued
Intervention vs meglitinide	**RR 0.97** (0.27 to	7 (n=2038)		Trial sequential analysis showed that only a minor

[12 to 17 months]	3.53)			fraction of the required information size to detect or reject a 10% RRR was accrued
Non-fatal macrovascular outcomes				
Composite				
Intervention vs metformin [6 months to 4 years]	**RR 0.67** (0.48 to 0. 93)	3 (n=3018)	low	Non-fatal macrovascular outcomes as a composite outcome were not reported in the way we predefined to assess this outcome. Trial sequential analysis showed that 5% of the required informationsize to detect or reject a 10% RRR was accrued
Intervention vs thiazolidinediones [52 weeks to 4 years]	**RR 0.91** (0.62 to 1. 33)	6 (n=4600)		
Intervention vs meglitinide [12 to 15 months]	**RR 0.50** (0.20 to 1.20)	3 (n=866)		The definition of nonfatal macrovascular outcomes was heterogenous
Non-fatal myocardial infarction				
Intervention vs metformin [24 weeks to 4 years]	**RR 1.02** (0.37 to 2.85)	4 (n=3061)	low	
Intervention vs thiazolidinediones [24 weeks to 4 years]	**RR 0.68** (0.41 to 1.14)	7 (n=4956)		
Intervention vs meglitinide [2c. 12 months to 17 months]	**RR 1.03** (0.26 to 4.08)	3 (n=726)		

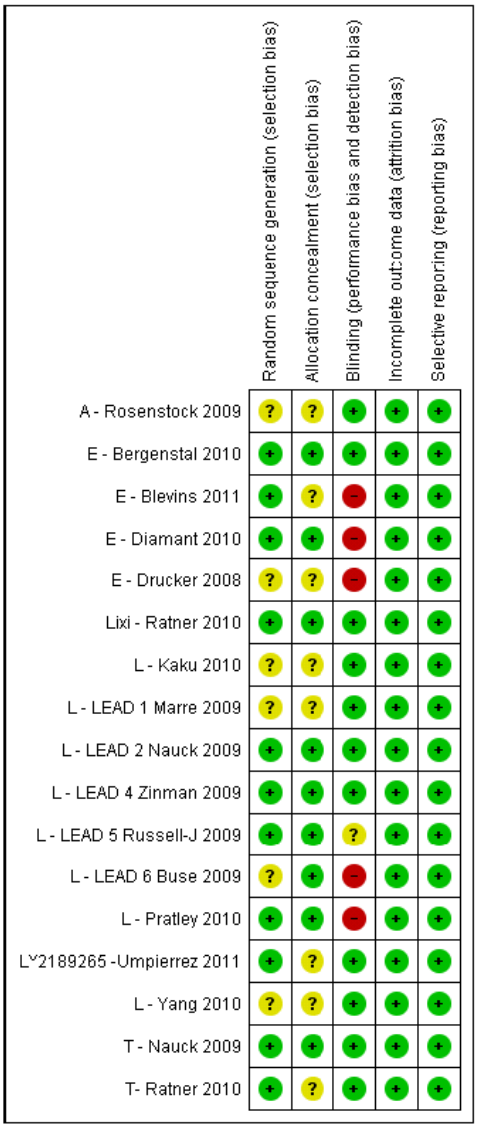
Third-generation sulphonylureas compared with controls for type 2 diabetes mellitus

Outcomes	**Relative effect (95%CI)**	**Anzahl Studien (n=)**	**Ouality of Evidence (GRADE)**	**Comments**
All-cause mortality	Not estimable	See comment	See comment	No meta-analysis possible
Cardiovascular mortality	Not estimable	See comment	See comment	No meta-analysis possible
Macrovascular outcomes	Not estimable	See comment	See comment	No meta-analysis possible
Microvascular outcomes	Not estimable	See comment	See comment	No meta-analysis possible
Adverse events				
All adverse events [6 to 12 months]	**RR 0.88** (0.78 to	3 (n=510)		Trial sequential analysis showed that firm evidence

	0.99)		low	was not established
Drop-outs due to adverse events Interventions vs thiazolidinediones [24 to 52 weeks]	**RR 0.54** (0.15 to 1.97)	2 (n=423)		

Conclusions when all sulphonylurea groups (first-, second- and third-generation) were analysed together were similar to those of second-generation sulphonylurea.

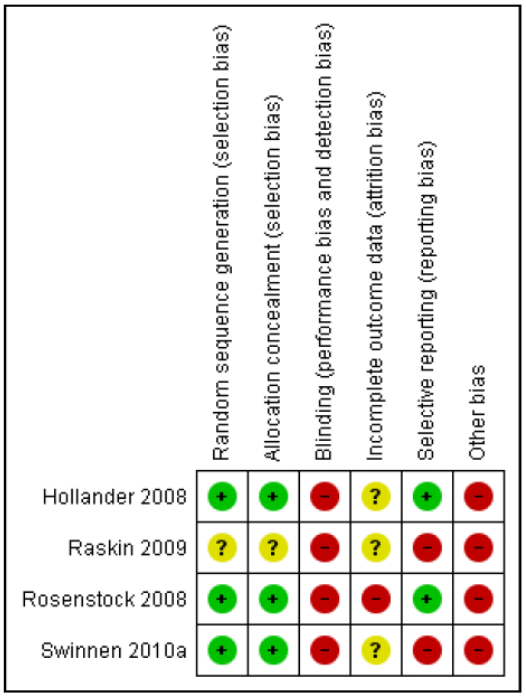
Fortsetzung **Hemmingsen, 2013**	**Anmerkungen der Autoren** • Among the 72 trials included in this analysis, we classified none of the trials as having low risk of bias according to all bias domains and we only classified seven trials as having a lower risk of bias according to a combined evaluation of sequence generation, allocation concealment and blinding. • Several of the included trials had an open-label design, which might have influenced the reporting from both the participants and the investigators. • Diagnostic criteria and definitions of outcomes differed among trials and were not always well defined. • The way sulphonylurea monotherapy or another comparator was applied to the participants varied among the trials. • In trial sequential analysis, none of the analyses of mortality outcomes, vascular outcomes or severe hypoglycaemia met the criteria for firm evidence of a RRR of 10% between interventions. **Fazit der Autoren** There is insufficient evidence from RCTs to support the decision as to whether to initiate sulphonyl urea monotherapy. Data on patient important outcomes are lacking. Therefore, large-scale and long-term randomised clinical trials with low risk of bias, focusing on patient-important outcomes are required.
Shyangdan, 2011 [98] **Glucagon-like peptide analogues for type 2 diabetes mellitus**	**Fragestellung** To assess the effects of glucagon-like peptide analogues in patients with type 2 diabetes mellitus.
	Methodik Population: Pat (>18 J) mit DM Typ 2 Intervention GLP-1 analogue (auch in Kombination mit Metformin und Sulfonylharnstoff) Komparator: placebo, insulin, an oral anti-diabetic agent, or another GLP-1

	analogue Endpunkt: HbA1C, Hypoglykämie, Gewicht, HRQoL, Adverse events Studiendauer: mind. 8 Wochen Suchzeitraum der syst. Literaturrecherche: bis März 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 (n=6899) Qualität der Studien/ Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung: **Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**  (Darstellung nur für Exanatide und Liraglutid) **Exanatide**

	Exenatide versus thiazolidinedione (pioglitazone), 1 trial: *HbA1c:* slightly greater reduction in HbA1c with once weekly exenatide than with pioglitazone 45 mg once daily (-1.5% versus -1.2%, P = 0.02). *Weight change:* Participants taking exenatide once weekly lost weight while those taking pioglitazone gained weight (-2.3 kg versus + 2.8 kg, P < 0.00001). Exenatide versus DPP-4 inhibitors (sitagliptin), 1 trail *HbA1c:* significantly greater reduction in HbA1c with once weekly exenatide than with sitagliptin 100 mg daily (-1.5%versus -0.9%, P < 0.00001). *Weight change:* once weekly exenatide led to a significantlygreater weight loss than sitagliptin 100 mg daily (-2.3 versus -0.8 kg, P = 0.0009). Exenatide versus insulin (glargine) 1 trial *HbA1c:* Once weekly exenatide led to a slightly greater reduction in HbA1c than with insulin glargine (-1.5% versus -1.3%). **Liraglutide** Liraglutide (0.9 mg) versus placebo, 1 trial *HbA1c:* The reduction in HbA1c level at end of the study was significantly greater with 0.9 mg liraglutide than with 0.6 mg liraglutide (-1.56% versus -1.46%) or placebo (-1.56% versus -0.4%). Liraglutide (1.2 mg) versus placebo, 3 trials *HbA1c:* The overall mean difference was -1.15 (95% CI -1.33 to -0.96, P < 0.00001) Liraglutide (1.8 mg) versus placebo, 4 trials *HbA1C:* difference of -1.15 (95% CI -1.31 to -0.99, P < 0.00001) Liraglutide (1.8 mg) versus insulin (glargine) 1 trial *HbA1c:* significantly more reduced with 1.8 mg liraglutide than with insulin glargine (mean difference -0.24%, 95%CI -0.39 to -0.08, P = 0.0015 according to the original analysis). Liraglutide versus sulphonylurea (glimepiride) 2 trials *HbA1c:* no significant difference between 1.2 or 1.8 mg liraglutide and glimepiride. GLP-1 agonist versus GLP-1 agonist (exenatide vs liraglutide), 1trial

	HbA1c: significantly more reduced with liraglutide(-1.22% versus -0.79%, mean difference 0.33 (95% CI 0.11 to 0.55, P < 0.0001). *Summary:* In comparison with placebo, all GLP-1 agonists reduced glycosylated haemoglobin A1c (HbA1c) levels by about 1%. Exenatide 2 mg once weekly and liraglutide 1.8 mg reduced it by 0.20% and 0.24% respectively more than insulin glargine. Exenatide 2 mg once weekly reduced HbA1c more than exenatide 10 µg twice daily, sitagliptin and pioglitazone. Liraglutide 1.8 mg reduced HbA1c by 0.33% more than exenatide 10 µg twice daily. Liraglutide led to similar improvements in HbA1c compared to sulphonylureas but reduced it more than sitagliptin and rosiglitazone. Both exenatide and liraglutide led to greater weight loss than most active comparators, including in participants not experiencing nausea. Hypoglycaemia occurred more frequently in participants taking concomitant sulphonylurea. GLP-1 agonists caused gastrointestinal adverse effects,mainly nausea. These adverse events were strongest at the beginning and then subsided. Beta-cell function was improved with GLP-1 agonists but the effect did not persist after cessation of treatment.
	Anmerkungen/Fazit der Autoren: Studies were mostly of short duration, usually 26 weeks. None of the studies was long enough to assess long-term positive or negative effects GLP-1 agonists are effective in improving glycaemic control.
Swinnen, 2011[100] **Insulin detemir versus insulin glargine for type 2 diabetes mellitus**	**Fragestellung** To assess the effects of insulin detemir and insulin glargine compared with each other in the treatment of patients with type 2 diabetes mellitus.
	Methodik Population: Pat. mit DM typ 2 Intervention: insulin detemir Komparator: insulin glargin Endpunkt: HbA1C, Hypoglykämie, Gewicht Studiendauer: >12 Wochen Suchzeitraum der syst. Literaturrecherche: Bis Jan. 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 (n=2250) Qualität der Studien/Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



<u>HbA1c (4 trials, n=2250)</u>

Not statistically significant estimated mean difference of 0.07% (95% CI -0.10 to 0.24). There was substantial statistical heterogeneity between studies (P = 0.04, I2 = 64%).

<u>Fasting glucose</u>

Insulin glargine was associated with statistical significantly lower fasting glucose at study endpoint than insulin detemir (mean difference of 0.34mmol/L [95%CI 0.01 to 0.67], but with some statistical heterogeneity [P = 0.11, I2 = 50%]

<u>Overall hypoglycaemia</u>

There was no difference between the two insulins in the relative risk of having at least one hypoglycaemic event: risk ratio of 0.98 (95% CI 0.92 to 1.05), without evidence for statistical heterogeneity (P = 0.42, I^2=0%). Similarly, there was no statistically significant difference in the event rate for overall hypoglycaemia (Analysis 1.8): rate ratio of 1.00 (95% CI 0.90 to1.11), with substantial statistical heterogeneity (P = 0.0006, I^2= 83%).

<u>Severe hypoglycaemia (4 trials n=2252)</u>

Both relative risk and rate ratio of severe hypoglycaemia were not statistically significantly lower for insulin detemir than for insulin glargine: RR 0.82 (95% CI 0.51 to 1.32)

Anmerkungen/Fazit der Autoren

	Our analyses suggest that there is no clinically relevant difference in the efficacy or the safety between insulin detemir and insulin glargine for targeting hyperglycaemia. However, to achieve the same glycaemic control insulin detemir was often injected twice daily in a higher dose but with less weight gain, while insulin glargine was only injected once-daily, with somewhat fewer injection site reactions.

Systematische Reviews

Bennett, 2011 [5] **(Agency for Healthcare Research and Quality) Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 27.**	**Fragestellung** Given the number of medications available for type 2 diabetes mellitus, clinicians and patients need information about their effectiveness and safety to make informed choices. The objective of this review was to summarize the benefits and harms of medications (metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, DPP-4-inhibitors, and glucagon-like peptide-1 [GLP-1] receptor agonists), as monotherapy and in combination, for the treatment of adults with type 2 diabetes. The EPC investigators were guided by 4 key clinical questions, which pertained to adults aged 18 years or older with a diagnosis of type 2 diabetes mellitus. The questions are paraphrased as follows: 1. Intermediate outcomes: What are the comparative effects of various treatment options on the intermediate outcomes of glycemic control as measured by A1c, body weight, and lipids, including LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides? 2. Long term outcomes: What are the comparative effects of various treatment options on long-term clinical outcomes, including all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke), retinopathy, nephropathy, and neuropathy? 3. Adverse effects: How do the various treatment options compare with regard to risks of adverse events and side effects? 4. Differences in subgroups: Do the safety and effectiveness of treatment options differ across patient subgroups, especially for adults aged 65 or older?
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: alle Wirkstoffe, die zur Behandlung des DM 2 eingesetzt werden. Endpunkt: k.A. Suchzeitraum: Systematische Literaturrecherche bis April 2010 (als Update zu dem Report aus 2007) Anzahl eingeschlossene Studien/Patienten (Gesamt): 166 (davon 71 Studien schon im Report aus 2007) Quality Assessmen/Risk of bias: RCT Jadad criteria Observations studies: development of a tool based on the recommendations in the Guide for Conducting Comparative Effectiveness Reviews 27. Guide for Conducting Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality, 2007.
	Ergebnisdarstellung

	Key Question 1. In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (see list of comparisons) for the intermediate outcomes of glycemic control (in terms of HbA1c), weight, or lipids? 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. Fifty-one of the studies had also been included in the 2007 comparative effectiveness review. HbA1c. We found that most diabetes medications (metformin, thiazolidinediones, sulfonylureas, and repaglinide) reduced HbA1c to a similar degree, by about 1 absolute percentage point when compared with baseline values, after 3 or more months of treatment. Metformin was more effective in reducing HbA1c than the DPP-4 inhibitors as monotherapy (by about 0.4 absolute percentage points). Two-drug combination therapies with metformin (such as metformin plus thiazolidinediones, metformin plus sulfonylureas, and metformin plus DPP-4 inhibitors) were generally more effective in reducing HbA1c than was metformin monotherapy (by about 1 absolute percentage point). Most combinations of metformin, sulfonylureas, and thiazolidinediones had similar efficacies in lowering HbA1c. Although we included comparisons with the GLP-1 agonists, we graded the evidence for these comparisons as insufficient or low; therefore, we were limited in our ability to draw firm conclusions about their effectiveness. Weight. Diabetes medications varied in terms of their effects on body weight. Notably, weight change was small to moderate, generally less than 2 kg between baseline and final values. Unlike thiazolidinediones or sulfonylureas, metformin was not associated with weight gain, with a mean difference of about −2.6 kg between metformin and the other drugs, in trials that lasted more than 3 months but generally less than 1 year. Although placebo-controlled trials of metformin were excluded from this review, we know from the 2007 evidence report that metformin was the GLP-1 agonists were associated with a relative weight change of about 2.5 kg. Lipids. The effects on lipid levels varied across medication type, but most were small to moderate (changes of about 0.5 mg/dL to 16 mg/dL for LDL, 0.5 mg/dL to 4 mg/dL for highdensity lipoprotein [HDL], and 0 mg/dL to 33 mg/dL for triglycerides [TG]), in studies that generally lasted between 3 and 12 months. Metformin had favorable effects on all the lipid classes: It decreased LDL more effectively than did sulfonylureas, rosiglitazone, or pioglitazone, and it decreased TG more efficiently than sulfonylureas or rosiglitazone. However, pioglitazone was more effective than metformin in decreasing TG. The addition of rosiglitazone to metformin increased LDL and HDL but also increased TG when compared to metformin monotherapy and to the combination of metformin and a sulfonylurea. The addition of pioglitazone to metformin also increased HDL but decreased TG when compared to the combination of metformin and a sulfonylurea. The addition of DPP-4 inhibitors to metformin did not have an effect on HDL in comparison with metformin monotherapy. We noted that one medication or class may have favorable effects on

	one lipid outcome and unfavorable effects on another lipid outcome. For instance, rosiglitazone was less effective than pioglitazone in decreasing LDL, and it increased HDL to a lesser extent than did pioglitazone, but both favorably decreased TG. **Key Question 2.** In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of the treatment options in terms of the following long-term clinical outcomes? (All-cause mortality, Cardiovascular mortality, Cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke), Retinopathy, Nephropathy, Neuropathy) Although we identified 41 new studies in addition to the 25 studies included in the 2007 evidence report, the new studies were generally of short duration (less than 1 year) and had few long-term events (such as deaths and cardiovascular disease), making any estimates of risk difference very imprecise. Therefore, most comparisons for this key question had a low strength of evidence. Metformin was associated with slightly lower all-cause mortality and cardiovascular disease mortality than were sulfonylureas. However, the evidence was limited by inconsistency between the trials and observational studies and the overall low precision of the results, due to the rarity of events. Data from the 2007 evidence report also showed that treatment with metformin was associated with a decreased risk of cardiovascular mortality when compared with any other oral diabetes agent or placebo, although the results for all-cause mortality and cardiovascular morbidity were not significant. We found few studies with the newer DPP-4 inhibitors and GLP-1 agonists, but overall the evidence on these newer agents was insufficient to allow us to make any meaningful conclusions. Few studies included insulin added to oral medications or compared other two-drug combination therapies. Few studies addressed microvascular outcomes of nephropathy, retinopathy, or neuropathy. We found moderate strength of evidence that pioglitazone is better than metformin at reducing short-term nephropathy, based on two short-duration RCTs. Only three comparisons were included for the outcome of neuropathy, and these studies were limited by their small sample sizes and poorly defined outcomes. We did not identify any studies for the outcome of retinopathy. **Key Question 3** In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the treatment options in terms of the following adverse events and side effects? (Hypoglycemia, Liver injury, Congestive heart failure, Severe lactic acidosis, Cancer, Severe allergic reactions, Hip and non-hip fractures, Pancreatitis, Cholecystitis, Macular edema or decreased vision, Gastrointestinal side effects) This Key Question was addressed by 107 studies.

	Hypoglycemia. Hypoglycemic episodes were three to seven times as frequent in people taking sulfonylureas as in those taking metformin, thiazolidinediones, or DPP-4 inhibitors. Combination therapies that included a sulfonylurea plus metformin also had an excess hypoglycemia risk when compared to metformin plus a thiazolidinedione. Congestive heart failure. Based on a single RCT with moderate risk of bias, we found low strength of evidence that the risk of congestive heart failure (CHF) was higher with combination therapy containing rosiglitazone than with a combination of metformin and a sulfonylurea (relative risk [RR] 2.1). We also found a higher risk of CHF with thiazolidinedione monotherapy than with sulfonylurea monotherapy. We were unable to draw any useful conclusions about CHF risk from other drug comparisons of interest, either because of an absence of evidence, conflicting results, or the low quality of the studies. Gastrointestinal side effects. Metformin was associated with higher risk of gastrointestinal side effects than were all other medications, regardless of whether the metformin was used as monotherapy or as part of combination therapy. Other adverse events. We found reports of four types of adverse events that were not addressed in our previous evidence report: macular edema, cholecystitis, pancreatitis, and fractures. Except for fractures, the majority of the evidence was graded as low strength because the availability of only a few studies and events limited the assessment of consistency and precision of the results. We did find a high strength of evidence showing that thiazolidinediones, either in combination with another medication or as monotherapy, were associated with a 1.5-fold higher risk of bone fractures than was metformin alone or in combination with sulfonylurea. We also found little evidence regarding liver injury and cancer, outcomes included in the 2007 evidence report. However, in agreement with other reviews, we found a moderate strength of evidence for a lack of increased risk of lactic acidosis with metformin treatment, as compared to a sulfonylurea or a combination of metformin and sulfonylurea. **Key Question 4** Do the safety and effectiveness of these treatment options (see list of comparisons) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, cardiovascular, and cerebrovascular outcomes? Twenty-eight studies applied to Key Question 4. We found that when compared to men, women taking rosiglitazone either as monotherapy or in combination were at higher risk for bone fractures than were those taking metformin alone or in combination with sulfonylureas. However, for the majority of comparisons, the available studies did not have sufficient power to allow for subgroup analyses, and few studies

	occurred exclusively in a subpopulation. We found no conclusive information to predict which subgroups of patients might differentially respond to alternative treatments.
	Anmerkungen/Fazit der Autoren Overall, few studies contained sufficient data on event rates to make it possible to analyze major clinically important adverse events and long-term complications of diabetes. 1. We identified few published studies on long-term clinical outcomes such as cardiovascular disease, stroke, nephropathy, and neuropathy. 2. Few studies used standard measures for diabetic nephropathy and kidney function, such as estimated glomerular filtration rate, or clinical outcomes, such as time to dialysis, as outcomes in their comparisons of these medications. 3. We identified few observational studies that examined macular edema, cancer, and fractures as related to thiazolidinediones, insulin, and other medications.
Phung, 2010 [89] **Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes**	**Fragestellung** To determine the comparative efficacy, risk of weight gain, and hypoglycemia associated with noninsulin antidiabetic drugs in patients with type 2 DM not controlled by metformin alone.
	Methodik Population: Pat. DM Typ 2, bei denen keine ausreichende Blutzuckersenkung nach einer Metformin-Monotherapie erzielt wurde. Intervention: orale Antidiabetika Komparator: Placebo oder andere orale Antidiabetika in Kombination mit Metformin Endpunkt: change in HbA1c, proportion of patients achieving HbA1c goal of less than 7%, change in weight, and incidence of hypoglycemia Beobachtungsdauer: 12 bis 52 Wochen Suchzeitraum: Systematische Literaturrecherche bis Januar 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 27 (n=11.198) Quality assessment/Risk of Bias: Jaded scale
	Ergebnisdarstellung

Table 2. Results of Traditional Meta-analysis Comparing Noninsulin Antidiabetic Drugs With Placebo on Change in HbA_{1c}, HbA_{1c} Goal Achieved, Change in Body Weight, and Overall Hypoglycemia

Group vs Placebo	% Change in HbA_{1c}		HbA_{1c} Goal Achieved		Change in Body Weight, kg		Overall Hypoglycemia	
	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)
All drugs	20	−0.79 (−0.90 to −0.68)[a]	10	2.56 (1.99 to 3.28)[b]	12	0.14 (−1.37 to 1.65)[a]	19	1.43 (0.89 to 2.30)
Sulfonylureas	3	−0.79 (−1.15 to −0.43)[a]	1	3.38 (2.02 to 5.83)	2	1.99 (0.86 to 3.12)	3	2.63 (0.76 to 9.13)[a]
Glinides	2	−0.71 (−1.24 to −0.18)	1	3.20 (1.47 to 7.58)	2	0.91 (0.35 to 1.46)	2	7.92 (1.45 to 43.21)
Thiazolidinediones	3	−1.00 (−1.62 to −0.38)[b]	1	1.69 (1.24 to 2.33)	1	2.30 (1.70 to 2.90)	2	2.04 (0.50 to 8.23)
AGIs	2	−0.65 (−1.11 to −0.19)	0	NA	1	−1.80 (−2.83 to −0.77)	2	0.60 (0.08 to 4.55)
DPP-4 inhibitors	8	−0.79 (−0.94 to −0.63)[b]	6	2.44 (1.78 to 3.33)[b]	4	−0.09 (−0.47 to 0.30)[b]	8	0.67 (0.30 to 1.50)
GLP-1 analogs	2	−0.99 (−1.19 to −0.78)	1	3.96 (2.37 to 6.79)	2	−1.76 (−2.90 to −0.62)	2	0.94 (0.42 to 2.12)

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.

[a] $I^2 \geq 75\%$.

[b] $I^2 = 50\%$-75%.

Alle oralen Antidiabetika [(Sulfonylharnstoffe: 0.79; CI:0.62-0.97); Glinide: 0.65; CrI: 0.36-0.97); Thiazilidinedione (0.85; CI: 0.66-1.08); AGIs (0.64; CI: 0.26%-1.03); DPP-4 Inhibitoren (0.78; CI: 0.64-0.93); GLP-1 Agonisten (0.97; CI: 0.65-1.30)] zeigen ähnliche Reduktionen hinsichtlich des HbA1c-Wertes, wenn verglichen wird gegen Placebo.

<u>Body weight:</u>

Thiazilidinedion, Sulfonylharnstoff und Glinide waren mit einer Gewichtszunahme assoziiert (Sulfonylharnstoffe: 2.6 kg; CI: 1.15-2.96 / Glinide: 1.77 kg; CI: 0.46-3.28 / Thiazolidinedione: 2.98 Kg; CI: 0.98-3.17).

GLP-1 Agonisten, Alpha-Glukosidase Inhibitoren und DPP-4 Inhibitoren waren mit einem Gewichtsverlust oder einem neutralen Effekt assoziiert.

	Hypoglykämien: Sulfonylharnstoffe und Glinide zeigten ein höheres Risiko auf Hypoglykämien, wenn verglichen wurde mit Placebo (Sulfonylharnstoffe: RR: 4.57; CI: 2.11-11.45 / Glinide: RR: 7-50; CI: 2.12-41.52). Thiazolidinedione, GLP-1 Agonisten, Alpha-Glukosidase Inhibitoren, und DPP-4 Inhibitoren waren nicht mit einem erhöhten Risiko auf Hypoglykämien assoziiert, wenn verglichen wird mit Placebo. Sensitivity analysis: there was no significant change from results reported above when studies with a Jadad score of less than 3 were excluded from the analysis
	Fazit der Autoren: When added to maximal metformin therapy, all noninsulin antidiabetic drugs were associated with similar HbA1c reductions but differed in their associations with weight gain and risk of hypoglycemia.
Boussageon, 2012 [6] **Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials**	**Fragestellung** The aim was to review all available evidence to evaluate the risk-to-benefit balance of metformin in T2DM patients based on cardiovascular morbidity and mortality using a systematic review and meta-analysis of controlled trials.
	Methodik Population: Pat. DM Typ 2 Intervention: Metformin Komparator: Diät allein, Plazebo, Nichtbehandlung; Metformin als Add-on Therapie Endpunkt: Prim.: Gesamtmortalität, kardiovaskuläre Mortalität; Sek.: Myokardinfarkte, Schlaganfälle, periphere vaskuläre Erkrankung, Beinamputationen, mikrovaskuläre Komplikationen Suchzeitraum: systematische Literaturrecherche bis Juli 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 (n=13.110) Quality assessment/risk of bias: Jadad scale
	Ergebnisdarstellung • Es zeigten sich keine stat. signifikanten Effekte unter einer Metformintherapie hinsichtlich der Gesamtmortalität und der kardiovaskulären Mortaliät • Hinsichtlich der sekundären Endpunkte, zeigten sich keine stat. signifikanten Effekte unter Metformin.

Table 1. Characteristics of Studies or Subgroups Included in the Meta-Analysis.

Study	Trial Characteristics							Patient Characteristics				
	Jadad Score Double-Blind (Yes/N0)	Participants *n* (Metaformin /Control)	Treatments	Follow-Up (Months)	Inclusion Criteria		Primary End Point	Males (Percent)	Age (Years)	BMI (kg/m^2)	Duration of Diabetes (Years)	Initial HbA1c (Percent)
					HbA1c/FPG/Current Treatment	Overweight						
Teupe and Bergis [17]	3 N	100 (50/50)	M/diet	24	FPG 120–180 mmol/l	NS	Metabolic control	40	53.7	NA	NA	9
Hermann et al. [18]	4 Y	106 (72/34)	M+SU/Pbo+SU	6	FPG≥6.7 mmol/l	NS	Glycaemia	63	60	NA	4	6.8
DeFronzo and Goodman, Protocol 1 [24]	4 Y	289 (143/146)	M/Pbo	29	Diet alone	Y	FPG	74	53	30	6	8.3
DeFronzo and Goodman, Protocol 2 [24]	4 Y	422 (213/209)	M+SU/SU	29	FPG>7.8 mmol/l	120%–170% of ideal	FPG	85	55	29	8	8.8
UKPDS 34(a) [3]	3 N	753 (342/411)	M/diet	128	FPG 6.1–15.0 mmol/l	Y	Clinical events	47	53	31.8	<1	7.1
UKPDS 34(b) [3]	3 N	537 (268/269	M+SU/SU	78	FPG 6.1–15.0 mmol/l	Y+N	Clinical events	60	58	29.7	<1	7.5
Chiasson et al. [25]	4 Y	166 (83/83)	M/Pbo	36	HbA1c 7.2%–9.5%	NS	HbA1c	75	57	31.1	5.1	8.1
Horton et al. [19]	4 Y	350 (178/172)	M/Pbo	6	HbA1c 6.8%–11%	BMI 20–35	HbA1c	64	58.5	NA	NA	8.3
Hermann et al. [20]	4 Y	35 (16/19)	M+I/Pbo+I	12	HBA1c>reference+2%	Y	Glycaemia	54	57.5	NA	NA	8.9
Blonde et al. [23]	4 Y	486 (322/164)	Association M+SU/SU	4	HbA1c≥7.4	BMI≤40	HbA1c	57	56	30	7	9.6
Rachmani et al. [10]	Withdrawal trial, 3 N	393 (195/198)	M+UC/UC	48	NS	BMI 24–40	Clinical events	51	64	28.5	14.5	8.6
Hällsten et al. [21]	4 Y	29 (15/14)	M/Pbo	6	Newly diagnosed/ diet-treated	NS	Muscle glucose uptake	66	58	NA	NA	6.6
Garber et al. [22]	4 Y	322 (171/151)	M+SU/Pbo+SU	4	HbA1c 7%–12%	BMI 20–40	HbA1c	44	55	31	NA	8.7
Cryer et al. (COSMIC) [11]	3 N	8,732 (7,227/1,505)	M+UC/UC	12	Suboptimally controlled	NS	Clinical events	50	57.7	30	4.8	NA
Kooy et al. (HOME) [16]	4 Y	390 (196/194)	M+I/Pbo+I	51	NS	NS	Clinical events	45.6	61.5	30	13	7.9

	Hinweis: Für die Endpunkte Gesamtmortalität und kardiovaskuläre Mortalität lag eine stat. sig. Heterogenität vor, wenn die UKPDS Studien eingeschlossen wurden (I2 = 41% und 59%). Nach Ausschluss dieser Studie, zeigte sich weiterhin keine Signifikanz. **Anmerkungen/Fazit der Autoren** • Wenige Studien in der Metaanalyse • Allgemein wenige Ereignisse
Goossen, 2012 [46] **Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis**	**Fragestellung**: A systematic review of randomized, controlled trials was undertaken to comprehensively profile the safety of chronic treatment of type 2 diabetes mellitus with DPP-4 inhibitors.
	Methodik Population: Pat. mit DM Typ 2 Intervention: DPP-4 Inhibitoren Komparator: Placebo, Gliptin, anderes Antidiabetikum Endpunkt: Safety outcomes (Hypoglykämien, Nebenwirkungen) Studiendauer >18 Wochen Suchzeitraum: Systematische Literaturrecherche bis Okt. 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 67 (davon 4 Studien zu Alogliptin, 8 Studien zu Linagliptin, 8 Studien zu Saxagliptin, 20 Studien zu Sitagliptin und 27 Studien zu Vildagliptin) *(n=k.A.)* Quality assessment/risk of bias: random sequence generation, allocation concealment, efficacy analysis, dropout rate, investigator reported AEs, full AE data by SOC
	Ergebnisdarstellung • Es zeigte sich kein erhöhtes Risiko hinsichtlich der Infektionen unter einer Gliptintherapie im Vergleich zu Placebo bzw. einem anderen Antidiabetikum. • Asthenie (RR 1.57; 1.09, 2.27) und kardio- (RR 1.37; 1.00, 1.89) -bzw. vaskuläre Erkrankungen (RR 1.74; 1.05, 2.86) traten vermehrt unter DPP-4 Inhibitoren auf, im Vergleich zu Linagliptin. • Kein erhöhtes Risiko unter DPP-4 Inhibitoren hinsichtlich Hypoglykämien, wenn verglichen wird gegen Placebo bzw. stat. signifikant geringeres Risiko unter DPP-4 Inhibitoren gegenüber Sulfonylharnstoffen (RR: 0.20; 0.17-0.24). Das Risiko auf eine Hypoglykämie unter DPP-4 Inhibitoren war insgesamt niedrig, solang diese nicht mit Sulfonylharnstoffen bzw. einer Insulintherapie kombiniert wurden. Bei einer Kombination aus Sitagliptin oder Linagliptin mit Sulfonylharnstoffen oder Insulin, zeigte sich ein stat. signifikant erhöhtes Hypoglykämierisiko, wenn verglichen wird gegenüber Placebo (RR 1.86; 1.46-2.37). • Studienqualität: However, only 33 and 22% of studies, respectively, reported methods for random sequence generation and allocation concealment, so that selection bias cannot be excluded. Double-

	blinding was maintained throughout all studies, and double-dummy techniques were employed as appropriate. Primary efficacy analysis was performed by the intention-to-treat principle in 86% of studies, and 93% described discontinuations due to adverse events. Investigator-rated adverse events were reported in 52% of studies, for the remainder, the assessment method of adverse events was not disclosed. The mean discontinuation rate was 21%.
	Fazit der Autoren: A large body of data supports the long-term safety of gliptin treatment and refutes an increased risk of infections. Further research is needed to clarify a possible link to asthenia, cardiac and vascular events. For combination therapy with insulin or insulin secretagogues, a careful choice of the agent used may limit the risk of hypoglycaemia.
Hemmingsen, 2012 [47] Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses	**Fragestellung** To compare the benefits and harms of metformin and insulin versus insulin alone as reported in randomised clinical trials of patients with type 2 diabetes.
	Methodik Population: Pat. mit DM Typ 2 Intervention: Metformin und Insulin Komparator: Insulin alleine (mit oder ohne Placebo) Endpunkt: Gesamtmortalität und kardiovaskuläre Mortalität Suchzeitraum: systematische Literaturrecherche Anzahl eingeschlossene Studien/Patienten (Gesamt): 23 (n=2.117) Qualität der Studien/Risk of bias: following risk of bias domains: generation of the allocation sequence, allocation concealment, blinding of investigators and participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias
	Ergebnisdarstellung • None of the trials had low risk of bias • Keine stat. signifikanten Effekte unter Metformin und Insulin vs. Insulin alleine hinsichtlich der Gesamtmortalität oder kardiovaskulären Mortalität. • Es zeigten sich stat. signifikant mehr schwere Hypoglykämien unter einer Metformin und Insulin Therapie, wenn verglichen wird gegen Insulin alleine (RR 2,83; 95%KI 1,17-6,86). • Eine Kombination aus Metformin und Insulin führte zu einer stat. signifikanten Reduktion des HbA1c Wertes (−0,60%, 95% KI: −0,89; −0,31, p<0,001), Gewichtszunahme (−1.27, 95% KI:−2,07;−0,47, p=0,002) und einer Insulin Dosisreduktion (MD -18,65 U/Tag, 95% KI: −22,70; −14.60,P<0,001), wenn verglichen wurde gegen Insulin alleine; bei jedoch hoher Heterogenität zwischen den Studien.

	Fazit der Autoren: There was no evidence or even a trend towards improved all cause mortality or cardiovascular mortality with metformin and insulin, compared with insulin alone in type 2 diabetes. **Anmerkungen/Fazit der Autoren:** • Alle Studien hatten ein hohes Verzerrungspotential. • Hohe Heterogenität zwischen den Studien. • Wenige Daten zu den patientenrelevanten Endpunkten. • Studien teilweise von kurzer Dauer. • Metabolische Wirksamkeit meist der primäre Endpunkt in den Studien.
Karagiannis, 2012 [78] **Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis**	**Fragestellung** To assess the efficacy and safety of dipeptidyl peptidase-4 (DPP-4) inhibitors compared with metformin as monotherapy, or with other commonly used hypoglycaemic drugs combined with metformin, in adults with type 2 diabetes mellitus.
	Methodik Population: Erwachsene Pat. mit DM Typ 2 Intervention: DPP-4 Inhibitoren Komparator: Metformin Monotherapie oder einer Kombination aus Metformin mit anderen hypoglykämischen AM Endpunkt: Veränderung des HbA1c- Wertes; Anteil Patienten die einen HbA1c-Wert von <7% erreichen; Körpergewicht, Abbruchrate aufgrund jeglichen Nebenwirkungen; Auftreten von ernsten Nebenwirkungen; Gesamtmortalität, Hypoglykämien, Suchzeitraum: Systematische Literaturrecherche 1980-2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 19 (n=7136) Qualität der Studien/Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung • Majority of the studies with high and unclear risk of bias (Appendix 2) • HbA1c: Verglichen mit Metformin als Monotherapie, zeigte sich einer stat. signifikant geringere Abnahme des HbA1c-Wertes (WMD:0.20, 95% KI; 0.08- 0.32) und des Körpergewichtes (1.5, 0.9 - 2.11) unter einer DPP-4 Inhibitor Therapie. • Als Zweitlinientherapie, zeigte sich eine Unterlegenheit der DPP-4 Inhibitoren gegenüber den GLP-1 Agonisten (0.49, 0.31-0.67) und eine Vergleichbarkeit gegenüber Pioglitazon (0.09, −0.07 - 0.24) Es zeigten sich keine Vorteile der DPP-4 Inhibitoren gegenüber den Sulfonylharnstoffen hinsichtlich dem Erreichen eines HbA1c-Wertes von <7%; jedoch in Bezug auf das Körpergewicht sowohl gegenüber Sulfponylharnstoffen (WMD: −1.92, −2.34; −1.49) als auch Pioglitazon (−2.96, −4.13; −1.78), nicht aber gegenüber GLP-1 Agonisten (1.56, 0.94 - 2.18). • Allgemein traten nur wenige Hypoglykämien in den

Behandlungsgruppen auf. In den meisten Studien zeigte sich eine höhere Hyoplykämierate, wenn kombiniert wurde mit Sulfonylharnstoffen.

- Das Auftreten von ernsten Nebenwirkungen war niedriger unter einer DPP-4 Inhibitor Therapie, wenn verglichen wurde mit Pioglitazon.
- Das Auftreten von Übelkeit, Durchfällen und Erbrechen war höher unter einer Metformin oder GLP-1 Agonist Therapie, wenn verglichen wurde gegen DPP-4 Inhibitoren.
- Keine Unterschiede zwischen den Behandlungen hinsichtlich des Risikos auf Nasopharyngitis, upper respiratory tract infection, oder Harnwegsinfektionen

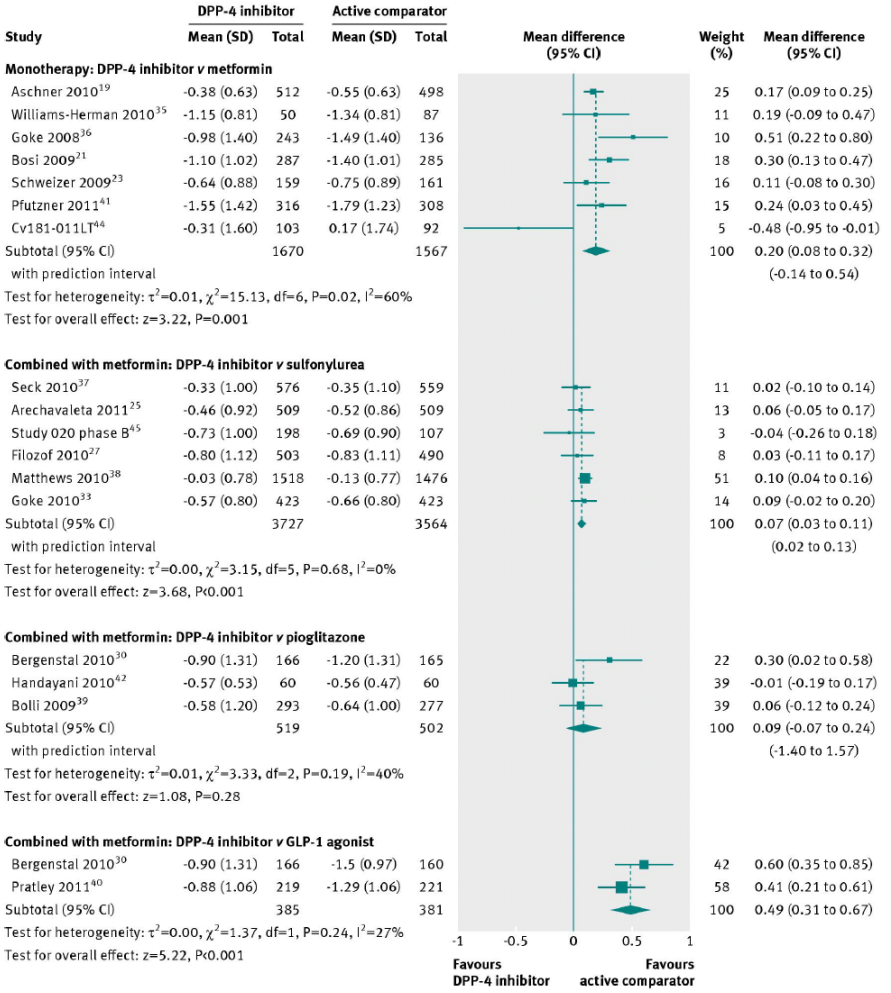


Fig 2 Weighted mean difference in change in HbA_{1c} (%) from baseline. Inverse variance random effects meta-analysis comparing DPP-4 inhibitors and other hypoglycaemic drugs

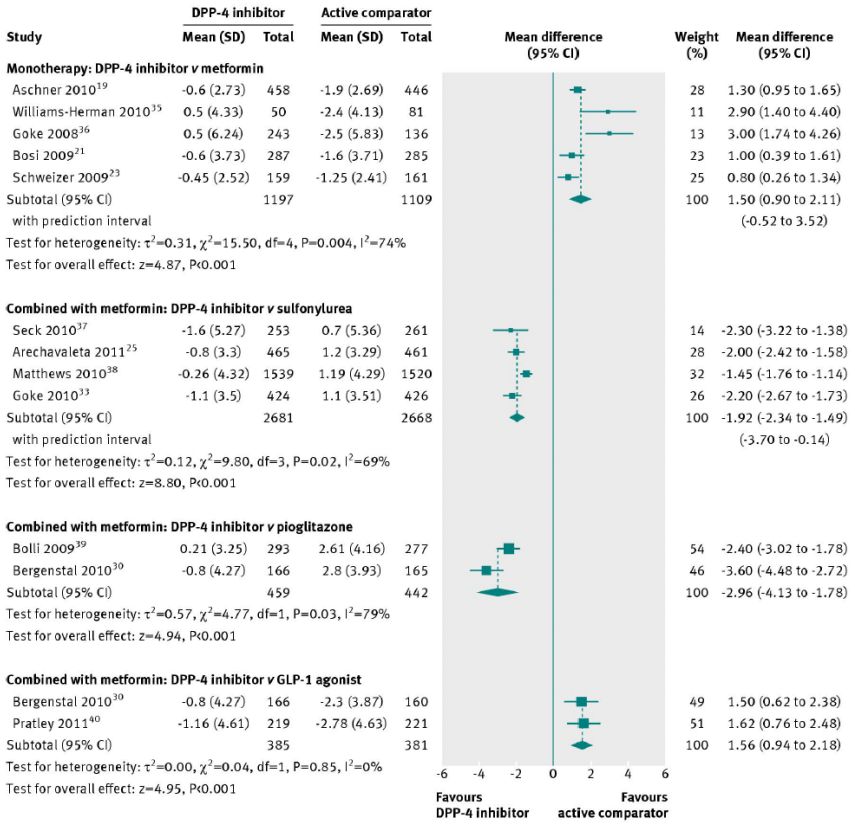


Fig 4 Weighted mean difference in change in body weight (kg) from baseline. Inverse variance random effects meta-analysis comparing DPP-4 inhibitors and other hypoglycaemic drugs

Anmerkungen/Fazit der Autoren

In patients with type 2 diabetes who do not achieve the glycaemic targets with metformin alone, DPP-4 inhibitors can lower HbA1c, in a similar way to sulfonylureas or pioglitazone, with neutral effects on body weight

Anmerkung FB-Med:

- Keine separaten Analysen zu den jeweiligen DPP-4 Inhibitoren.
- Variabilität des Verzerrungspotentials der Studien.
- Keine Sensitivitätsanalysen bzw. Metaregression um den Einfluss der Ausgangscharakteristiken zu untersuchen.

Aroda, 2012

[4]

Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review

Fragestellung

This meta-analysis was performed to support the understanding of the overall evidence by summarizing the findings from studies of the incretin-based therapies.

Methodik

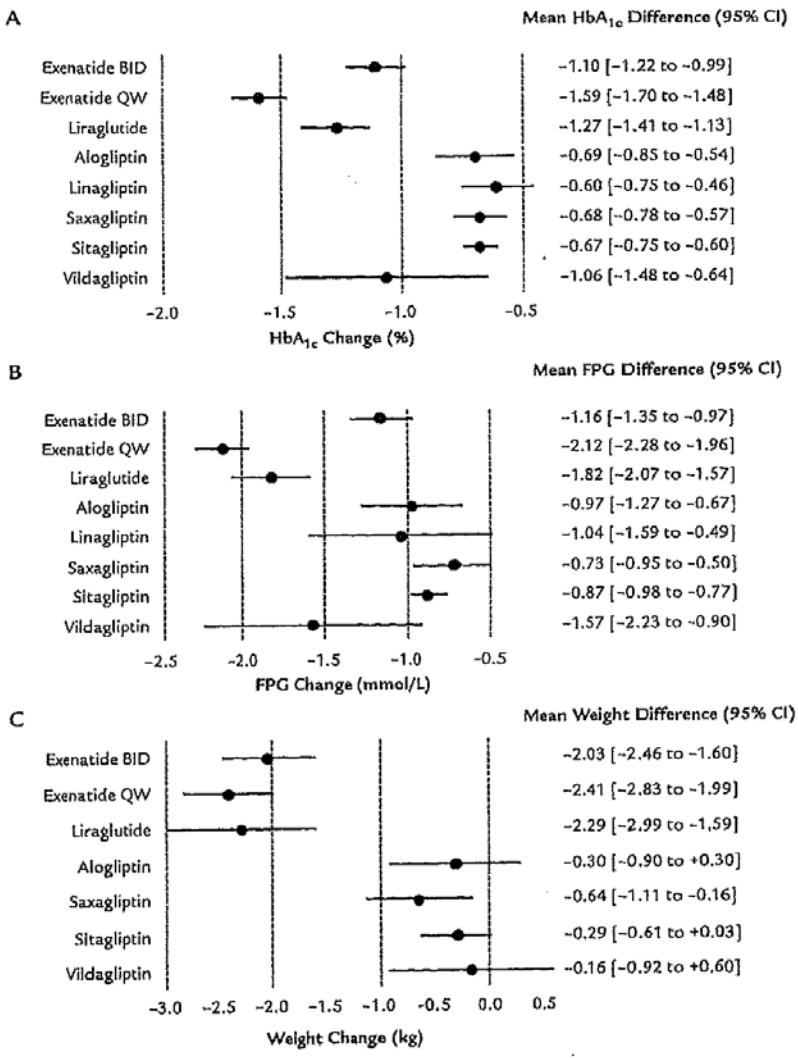
Population: Pat. mit DM Typ 2

Intervention/Komparator: GLP-1 Agonisten und DPP-4 Inhibitoren

Endpunkt: HbA1c, FPG, Gewicht

Studiendauer ≥12 Wochen

	Suchzeitraum: Systematische Literaturrecherche 1990-2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 80 (n=k.A.) Qualität der Studien/Risk of bias: judgement of study quality via discontinuation rates, medication changes prior baseline, baseline differences, blinding, analysis method
	Ergebnisdarstellung • Allgemein: Durchschnittliche Ausgangs-HbA1c-Werte variierten zwischen 7.4% - 10.3% (GLP-1 Agonisten Studien) und 7.2% - 9.3% (DPP-4 Inhibitor Studien). In den meisten Studien (76%; 61/80 Studien) wurden orale glukosesenkende AM-Therapien in Kombination mit GLP-1 Agonisten oder DPP-4 Inhibitoren gegeben. • Unter der höchsten Erhaltungstherapie-Dosierung von GLP-1 Agonisten und DPP-4 Inhibitoren zeigten sich in beiden Behandlungsgruppen vorteilhafte Veränderungen hinsichtlich des HbA1c-Wertes im Vergleich zum Ausgangswert zwischen -1.1% bis -1.6% (GLP-1 Agonisten) und -0.6% bis -1.1% (DPP-4 Inhibitoren). • Es zeigten sich durchschnittlich größere Reduktion des FPG unter Exenatid (einmal wöchentlich) oder Liraglutid (einmal täglich), als unter Exenatid (zweimal täglich) und DPP-4 Inhibitoren; mit der Ausnahme von Vildagliptin. • Die durchschnittliche Gewichtsabnahme mit GLP-1 Agonisten und DPP-4 Inhibitoren lagen bei >–2.0 (GLP-1 Agonisten) und -0.2 bis -0.6 kg (DPP-4 Inhibitoren).



Overall mean changes from baseline in (A) hemoglobin A_{1c} (HbA_{1c}), (B) fasting plasma glucose (FPG), and (C) weight with the use of glucagon-like peptide 1 receptor agonists (GLP-1RAs) or dipeptidyl-peptidase IV (DPP-4) inhibitors at the highest maintenance doses evaluated in this meta-analysis and systemic review of the efficacy of incretin-based therapies in type 2 diabetes mellitus.

Anmerkungen/Fazit der Autoren

All of the incretin-based therapies in the present meta-analysis were associated with significant reductions from baseline in HbA1, and FPG.

Anmerkung FB-Med:

- Teilweise hohe Heterogenität zwischen den Studien
- Keine Langzeitwirkungen untersucht

Zhang, 2014

[110]

Head-to-head comparison of dipeptidyl peptidase-IV

Fragestellung

In the present study, a meta-analysis of randomized clinical trials was conducted to evaluate the efficacy and safety of DPP-4 inhibitors compared with sulfonylureas as monotherapy or as add-on therapy especially to metformin, in adult patients with T2DM.

Methodik

inhibitors and sulfonylureas - a meta-analysis from randomized clinical trials.	Population: Pat. mit DM Typ 2 Intervention/Komparator: DPP-4 inhibitors, sulfonylureas Endpunkt: HbA1c, FPG, Gewicht Studiendauer ≥18 Wochen Suchzeitraum: Systematische Literaturrecherche bis Juni 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 (n=10.982) Qualität der Studien/Risk of Bias: Jadad scale
	HbA1c change, 12 trials (n=6772) the mean changes from baseline in HbA1c were significantly smaller with DPP-4 inhibitors compared with sulfonylureas with a difference of mean changes in HbA1c (sulfonylureas–DPP-4 inhibitors) of 0.105 and 95% CI 0.103 to 0.107, p<0.0001. When comparing the percentage of patients who achieved HbA1c<7% (Figure 2B), sulfonylureas showed better chances of achieving HbA1c<7% compared with DPP-4 inhibitors, MH-OR was 0.91 with 95% CI (0.84 to 0.99), p=0.03. **Body weight, 12 trials (n=9502)** Compared with sulfonylureas, the mean decreases from baseline in body weight were significantly greater with DPP-4 inhibitors: (95% CI) changes (kg): -1.652; 95% CI -1.658 to -1.646, p<0.0001. **Hypoglycaemia, 12 trials (n=9975)** MH-ORs (95% CI): 0.13 (0.11 to 0.16), p<0.0001 favouring DPP-4-Inhibitors **total adverse events, 12 trials (n=9840)** MH-ORs (95% CI): 0.79 (0.72 to 0.87), p<0.0001 favouring DPP-4-Inhibitors
	Fazit der Autoren Because most of the studies used in our meta-analysis are short in duration and the longest duration is 2 years, therefore, we could not achieve a conclusion on long-term durability and safety (≥4 years) to see which one is more desirable. Because the dosage of DPP-4 inhibitors is stable and does not need titration while the dosage of sulfonylureas is changeable and usually needs up-titration, it is difficult to say which dosage of sulfonylureas is comparative to the DPP-4 inhibitors and has less episode of hypoglycaemia than DPP-4 inhibitors.
Zhang, 2014 [109] **Combinational therapy with**	**Fragestellung** The present study systematically reviews this important aspect of T2DM management and üerforms a meta-analysis of RCTs in order to assess

metformin and sodium-glucose cotransporter inhibitors in management of type 2 diabetes: Systematic review and meta-analyse

various parameters of SGLT-2 inhibitor efficacy and safety when added to ongoing metformin therapy.

Methodik

Population: Pat. mit DM Typ 2

Intervention: SGLT-2 inhibitors in combination with metformin (hereinafter SGLT-2 inhibitor–MET)

Komparator: placebo-controlled or metformin-only (hereinafter placebo-MET)

Endpunkt: HbA1c, FPG, Gewicht

Studiendauer ≥12 Wochen

Suchzeitraum: Systematische Literaturrecherche: 2000 bis Jan 2014

Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (n=2847)

Qualität der Studien/Risk of bias: Jadad scale

Ergebnisse: SGLT-2 inhibition combined with metformin vs Placebo

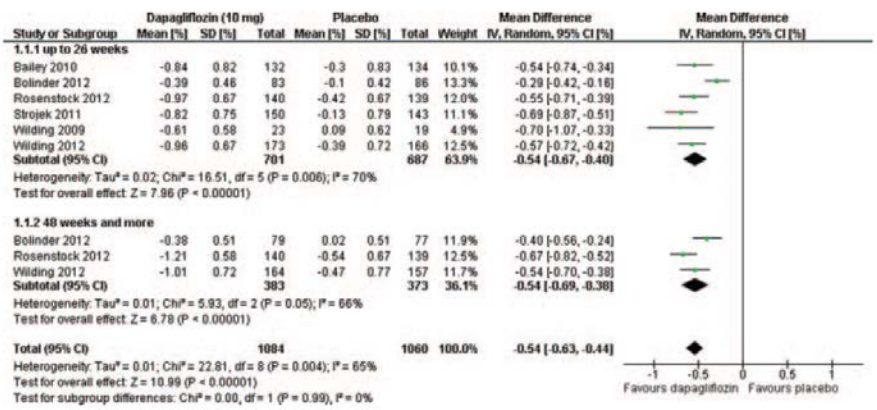
HbA1c

duration	#studies (n=)	Mean difference (95% CI)	Significance level (p)	Hetero-genity (I^2)
After 12-24 weeks	7 (n=1542)	-0.47 [-0.66, -0.27]	<0.00001	85%
After 1 year	3 (n=527)	-0.37 [-0.77, 0.03]	0.07	89%
After 2 years	2 (n=280)	-0.41 [-1.09, 0.28]	0.28	80%

Body weight

duration	#studies (n=)	Mean difference (95% CI)	Significance level (p)	Hetero-genity (I^2)
After 12-24 weeks	7 (n=1572)	-2.28 [-2.67, -1.88	<0.00001	35%
After 1 year	3 (n=659)	-2.60 [-3.17, -2.03]	<0.00001	0%
After 2 years	2 (n=465)	-3.03 [-3.90, -2.16]	<0.00001	0%

	Adverse event: The prevalence of ‘at least one study-related AE’ was 13% in the control group and 18% in the treated group
	Anmerkungen/Fazit der Autoren A few long- term trials can help in arriving conclusive evidence required to judge the potentials of this therapeutic intervention.
Clar, 2012 **[11]** **Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes**	**Fragestellung** To assess the clinical effectiveness and safety of the SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes.
	Methodik Population: Erwachsene mit DM2 (bisher unzureichend eingestellt) Intervention: Any use of SGLT2 inhibitors (dapagliflozin and canagliflozin) in dual or triple therapy, in addition to other interventions including, but not restricted to: metformin, sulphonylureas, insulin and gliptins, Komparator: placebo or another active antidiabetic medication in combination with the same antidiabetic co-medication as in the SGLT2 inhibitor group Endpunkt: HbA1C, Chnage in weight, BMI, change in QoL Suchzeitraum der syst. Recherche: bis Juli 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 (n=3849) 7 trials (n= 3398) Dapagliflozin, 6 vs Placebo and 1 vs Glipizide 1 trial Canagliflozin (n= 451) Qualitätsbewertung/Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung *HbA1C* Dapagliflozin vs Placebo (6 trials n=3398) Dapagliflozin at a dose of 10 mg/day significantly reduced HbA1c by (WMD) −0.54% (95% CI −0.67% to −0.40%, p<0.00001) after 12–26 weeks of treatment compared to placebo. There was significant heterogeneity. Dapagliflozin vs Glipizide (1trial n=451) There was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by −0.52% (95% CI −0.60% to −0.44%). Background antidiabetic therapy: metformin (≥1500 mg/day)



Meta-analysis for HbA1c change from baseline, 10 mg dapagliflozin versus placebo.

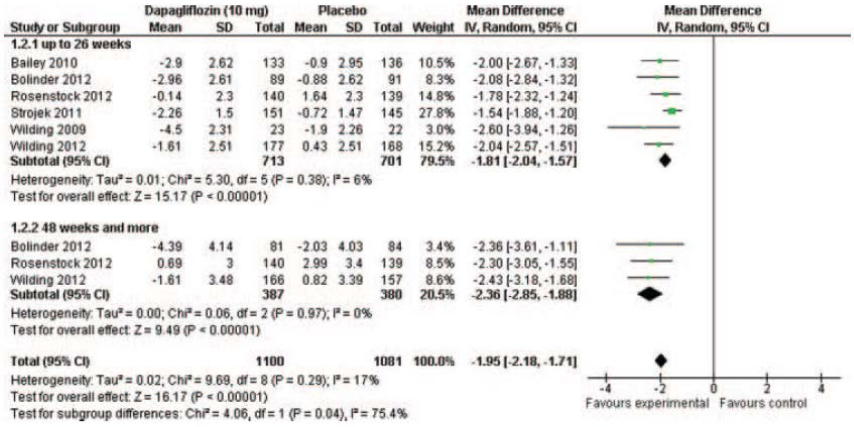
Weight

Dapagliflozin vs Placebo (6 trials n=3398)

Dapaglifozin was associated with a significant reduction in weight. Compared to placebo, weight was reduced by −1.81 kg (WMD, 95% CI −2.04 to −1.57, p<0.00001, no significant heterogeneity) after up to 26 weeks of treatment.

Dapagliflozin vs Glipizide (1trial n=451)

Weight decreased by −3.22 kg (95% CI −3.56 to −2.87) in the dapagliflozin arm after 52 weeks of treatment and increased by +1.44 kg (95% CI +1.09 to +1.78) in the glipizide arm (p<0.0001 between groups).



Meta-analysis for weight change from baseline, 10 mg dapagliflozin versus placebo.

	Table 2 Study quality—risk-of-bias assessment **Study** / **Sequence generation** / **Allocation concealment** / **Blinding** / **Adequate handling of incomplete outcome data** / **Total drop out from drug assignment** / **No selective reporting** / **Groups comparable at baseline** / **Adequate power** / **Funder** *Dapagliflozin* Bailey *et al*[8] / Yes / Yes / Yes (double blind) / Yes—last observation carried forward / 12% / Yes / Yes / Yes—0.5% HbA1c difference detectable / Astra-Zeneca and Bristol-Myers-Squibb Bolinder *et al*[9]/ Ljunggren *et al*[10] / Yes / Yes / Yes (double blind) / Yes—last observation carried forward / 7.1% / Yes / Yes / Unclear for primary endpoint, 2% BMD difference detectable / Astra-Zeneca and Bristol-Myers-Squibb Nauck *et al*[11] / Yes / Yes / Yes (double blind and double dummy) / Yes—last observation carried forward / 22.1% / Yes / Yes / Yes—0.35% HbA1c difference detectable / Astra-Zeneca and Bristol-Myers-Squibb Rosenstock *et al*[12] / Not reported / Not reported / Yes (double blind) / Not reported / 8% at 24 weeks, 19% at 48 weeks / Yes / Unclear / Not reported / Astra-Zeneca and Bristol-Myers-Squibb Strojek *et al*[13] / Yes / Yes / Yes (double blind and double dummy) / Yes—last observation carried forward / 8.5% / Yes / Yes / Yes—0.5% HbA1c difference detectable / Astra-Zeneca and Bristol-Myers-Squibb Wilding *et al*[14] / Not reported / Not reported / Yes (single blind during lead in, double blind during study) / Yes—last observation carried forward / 7% / Yes / Partially; matched for patient demographics, not for prior medications / Yes—0.5% HbA1c difference detectable / Astra-Zeneca and Bristol-Myers-Squibb Wilding *et al*[15] / Yes / Yes / Yes (double blind and double dummy) / Yes—last observation carried forward / 11% at 24 weeks, 15.5% at 48 weeks / Yes / Yes / Yes—0.5% HbA1c difference detectable / Astra-Zeneca and Bristol-Myers-Squibb *Canagliflozin* Rosenstock *et al*[16] / Not reported / Not reported / Yes (double blind) / Yes—last observation carried forward / 10.9% / Yes / Yes / Yes—0.55% HbA1c difference detectable / Janssen Global Services BMD, bone mineral density.
	Anmerkungen/Fazit der Autoren There are no long-term data on SGLT2 side effects, both in terms of rare complications yet to be identified, but also on the long-term effects of significant glycosuria on the urinary tract. Dapagliflozin appears effective in reducing HbA1c and weight in type 2 diabetes.
Du, 2013[13] **Comparative effects of**	**Fragestellung** The present meta-analysis aimed to compare the therapeutic efficacy of sitagliptin and metformin in the treatment of T2DM.

sitagliptin and metformin in patients with type 2 diabetes mellitus: a meta-analysis	**Methodik** Population: Pat mit DM typ 2 (regardless of gender, age, course of disease, body shape, and race) Intervention/Komparator: Sitagliptin vs Metformin Endpunkt: HbA1c, Fasting blood glucose, BMI, homeostasis model assessment-insulin resistance (HOMA-IR); and homeostasis model assessment-b (HOMA-b) Suchzeitraum der syst. Literaturrecherche: bis April 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (n=1881) Qualität der Studien/Risk of bias: following criteria used: randomization, allocation concealment, blinding, and intention to-treat (ITT) analysis
	Ergebnisdarstellung Studienqualität und risk of bias:

Table 1. Characteristics of the included studies (sitagliptin and metformin) in adults with type 2 diabetes.

Study	Participants				Methodological quality					Intervention	
	N sitagliptin/ metformin group	Age sitagliptin/ metformin group	Withdrawal sitagliptin/ metformin group	Course of treatment	Randomization	Blinding	Concealment	Baseline comparable	ITT	Sitagliptin	Metformin
Russell Jones *et al.*, 2012[15]	163/246	52 ± 11/54 ± 11	23/33	26 week	Yes	Yes	Yes	Yes	Yes	100 mg qd	2000 mg qd
Williams-Herman *et al.*, 2011[16]	55/59	51.8 ± 9.8/53.8 ± 9.6	22/13	24 week	Yes	Yes	NR	Yes	NR	100 mg qd	1000 mg bid
Aschner *et al.*, 2009[17]	528/522	NR	61/75	24 week	Yes	Yes	Yes	Yes	NR	100 mg qd	1000 mg bid
Derosa *et al.*, 2009[18]	75/76	57 ± 5/58 ± 6	6/8	12 month	Yes	Yes	Yes	Yes	NR	100 mg qd + pioglitazone 30 mg qd	850 mg bid + pioglitazone 30 mg qd
Goldstein *et al.*, 2007[19]	NR	NR	NR	24 week	Yes	Yes	NR	Yes	NR	100 mg qd	1000 mg bid
Dan *et al.*, 2012[20]	29/27	55 ± 12.5/54 ± 13.2	0/0	12 week	Yes	NR	NR	Yes	NR	100 mg qd	500 mg tid
Wan-jun *et al.*, 2012[21]	15/15	59 ± 10/57 ± 8	0/0	8 week	Yes	NR	NR	Yes	NR	100 mg qd	500 mg bid

N, number of participants; ITT, intent-to-treat population; qd, once daily; bid, twice daily; tid, three times daily; NR, not reported.

HbA1c (7 trials n=1881)

no significant difference in the influence of the two drugs on the HbA1c of the T2DM patients (P=0.148, SMD=0.13, 95% CI=-0.05, 0.30). Heterogeneity was noted among studies.

Fasting plasma glucose (7 trials n=1881)

There was a significant difference in the influence on fasting plasma glucose level between metformin and sitagliptin (P=0.000, SMD=0.23, 95% CI=0.14, 0.32).

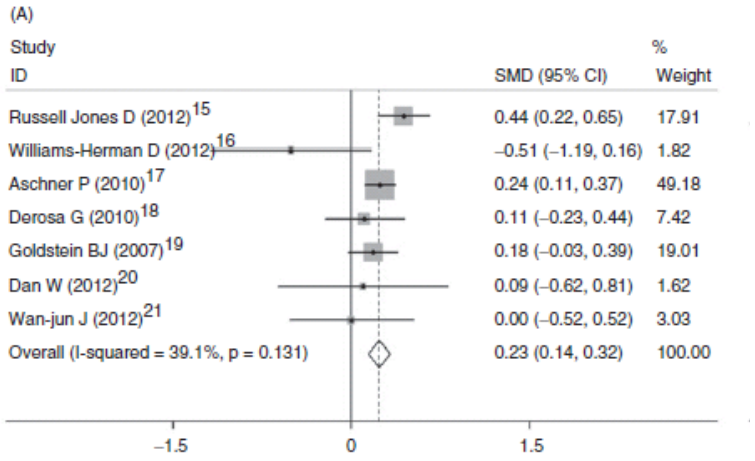
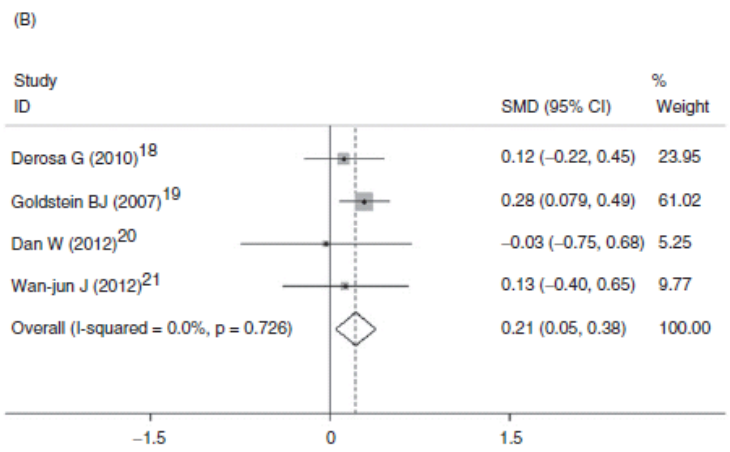


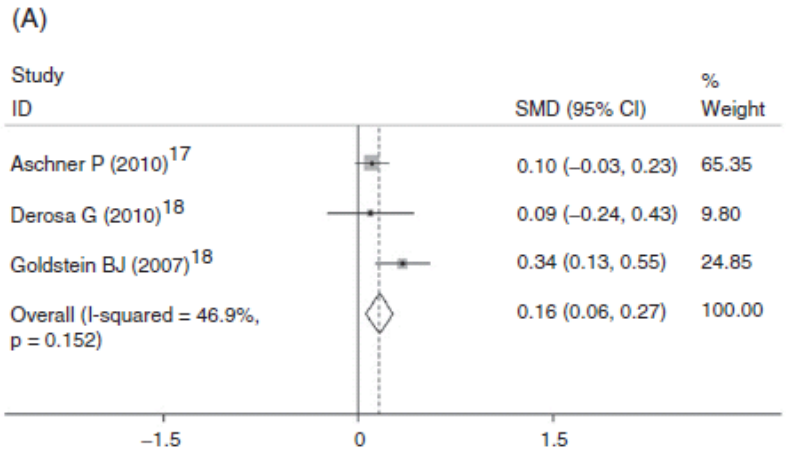
Figure 3. Effect of sitagliptin or metformin on (A) fasting plasma glucose anc

Postprandial plasma glucose level (4 trials n=575)

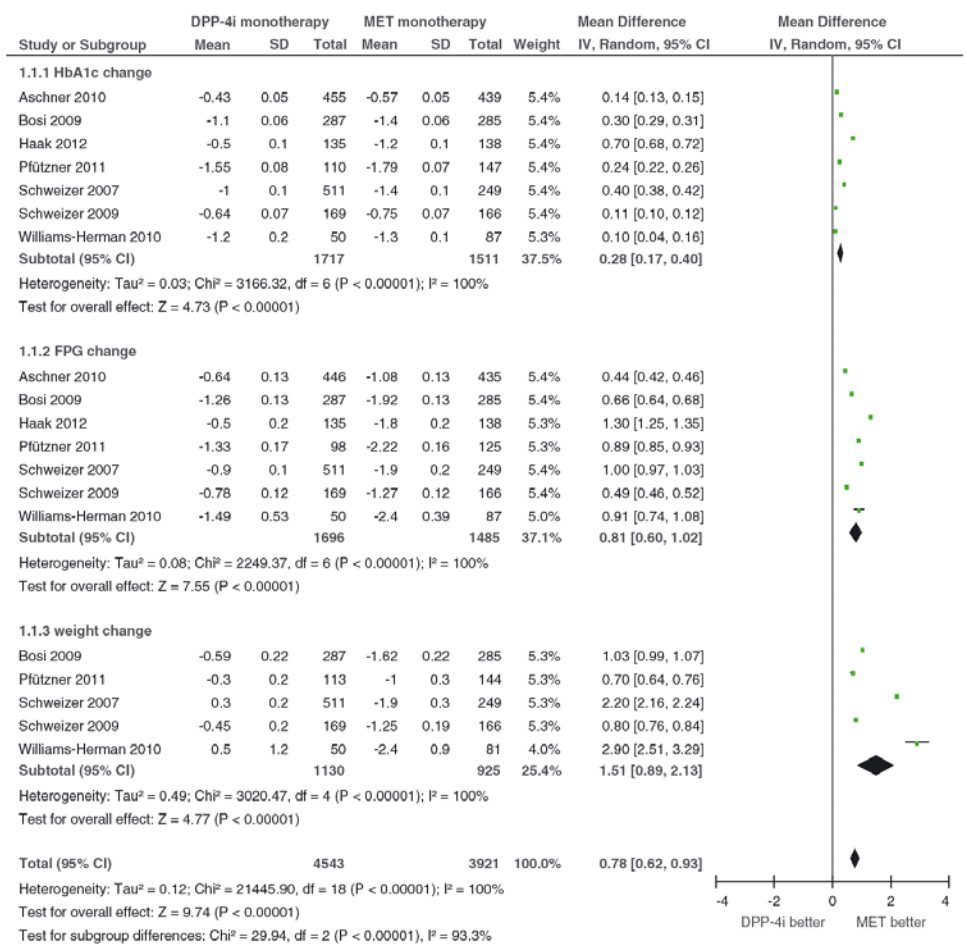
Significant difference in the influence on the postprandial blood glucose level between metformin and sitagliptin (P=0.011, SMD=0.21, 95% CI=0.05, 0.38).



nd (B) postprandial plasma glucose in T2DM patients.

	BMI (3 trials n= 243) No significant difference existed in theinfluence on BMI between metformin and sitagliptin (P=0.063, SMD=0.26, 95% CI=- 0.01, 0.54). *HOMA-IR (3 trials n=1403)* HOMA-IR (HOMA-IR = fasting blood glucose [mmol/L] x fasting blood insulin [mIU/L]/22.5) is used to evaluate insulin sensitivity. A significant difference was observed between sitagliptin and metformin in the influence on HOMA-IR (P=0.003, SMD=0.16, 95% CI=0.06, 0.27). Thus, sitagliptin is inferior to metformin in improving insulin sensitivity.  Figure 5. Effect of sitagliptin or metformin on (A) HOMA-IR and (B) HOMA-β i *HOMA-β (4 trials n=1442)* HOMA- β (HOMA- β =20 x fasting blood insulin [mIU/L]/[fasting blood glucose (mmol/L)-3.5] %) was used to evaluate the function of islet β cells. No significant difference was observed between sitagliptin and metformin in the influence on HOMA- β (P=0.285, SMD=-0.05, 95% CI=-0.15, 0.04)
	Anmerkungen/Fazit der Autoren Our findings reveal that both drugs have comparable abilities in reducing HbA1c, decreasing body weight, and improving the function of b cells, but sitagliptin is inferior to metformin in improving insulin sensitivity. **Anmerkung FB-Med:** Keine Langzeitfolgen untersucht (längstes Folluw-up 12 Monate)
Wu, 2013[105] **Efficacy and safety of**	**Fragestellung** This meta-analysis was performed to provide an update on the efficacy and safety of dipeptidyl peptidase-4 (DPP-4) inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2

dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis	diabetes mellitus.
	Methodik Population: Pat mit DM Typ 2 Intervention/ Komparator: a) DPP-4 inhibitors plus metformin as initial combination therapy b) DPP-4 inhibitor monotherapy vs metformin monotherapy Endpunkt: HbA1C, FPG Weight, adverse cardiovascular events Studiendauer: >12 Wochen Suchzeitraum der syst. Literaturrecherche bis Dez. 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 (n=7778) Qualität der Studien/Risk of bias: Jadad scale
	Ergebnisdarstellung Study | Region | Mean age (years) | Men | DPP-4 inhibitors monotherapy daily dose | DPP-4 inhibitors plus MET combination therapy daily dose | MET monotherapy daily dose | Study Duration (weeks) | Study size | Jadad Pfützner [9] | multiregional | 52 | 50% | SAXA 10 mg | SAXA 10 mg + MET 500 mg | 500 mg | 76 | 1306 | 4 Aschner [10] | multiregional | 56 | 48% | SITA 100 mg | | 2000 mg | 24 | 1050 | 5 Williams-Herman [11] | multiregional | 54 | 50% | SITA 100 mg | SITA 100 mg + MET 2000 mg | 2000 mg | 104 | 1091 | 5 Reasner [12] | multiregional | 50 | 57% | | SITA 100 mg + MET 2000 mg | 2000 mg | 18 | 1246 | 5 Bosi [13] | multiregional | 53 | 59% | VILD 100 mg | VILD 100 mg + MET 2000 mg | 2000 mg | 24 | 1179 | 2 Schweizer [14] | multiregional | 53 | 54% | VILD 100 mg | | 2000 mg | 52 | 780 | 3 Schweizer [15] | multiregional | 71 | 48% | VILD 100 mg | | 1500 mg | 24 | 335 | 4 Haak [16] | multiregional | 55 | 53% | LINA 5 mg | LINA 5 mg + MET 2000 mg | 2000 mg | 24 | 791 | 4 DPP-4, peptidyl peptidase-4; MET, metformin; SAXA, saxagliptin; SITA, stagliptin; VILD, vildagliptin; LINA, linagliptin. <u>DPP-4 inhibitor as monotherapy vs metformin</u> HbA1C: lower reduction in HbA1c level [MD=0.28, 95% CI (0.17, 0.40), p<0.00001)] FPG: lower reduction in FPG level [MD=0.81, 95% CI (0.60, 1.02), p<0.00001] Weight: lower weight loss [MD=1.51, 95% CI (0.89, 2.13), <0.00001] adverse CV events: lower risk of adverse CV events (include death from CV causes, non-fatal myocardial infarction or acute coronary syndrome, stroke, heart failure and arrhythmias) [RR=0.36, 95% CI (0.15, 0.85)] Hypoglycaemia: lower risk of hypoglycaemia [RR=0.44, 95% CI (0.27, 0.72), p=0.001] and lower risk of gastrointestinal AEs [RR=0.63, 95% CI (0.55,0.70), p<0.00001]



2. Meta-analysis of efficacy between DPP-4 inhibitors monotherapy and metformin monotherapy.

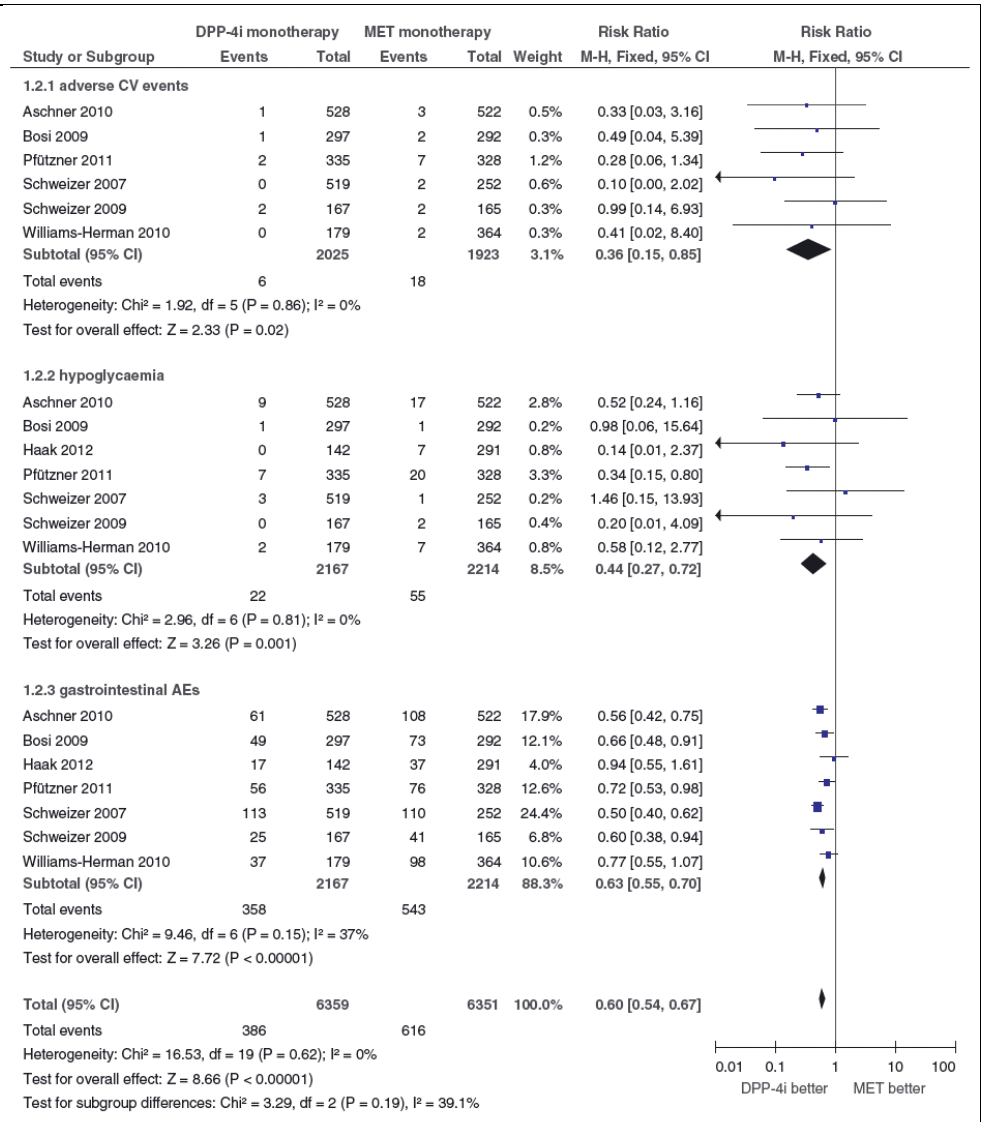


Figure 3. Meta-analysis of safety between DPP-4 inhibitors monotherapy and metformin monotherapy.

<u>DPP-4 inhibitors plus metformin vs. metformin monotherapy</u>

HbA1c: higher reduction in HbA1c level [MD=−0.49, 95% CI (−0.57, −0.40), p<0.00001]

FPG: higher reduction in FPG level [MD=−0.80, 95% CI (−0.87, −0.74), p<0.00001]

Weight: lower weight loss [MD=0.44, 95% CI (0.22, 0.67), p=0.0001]

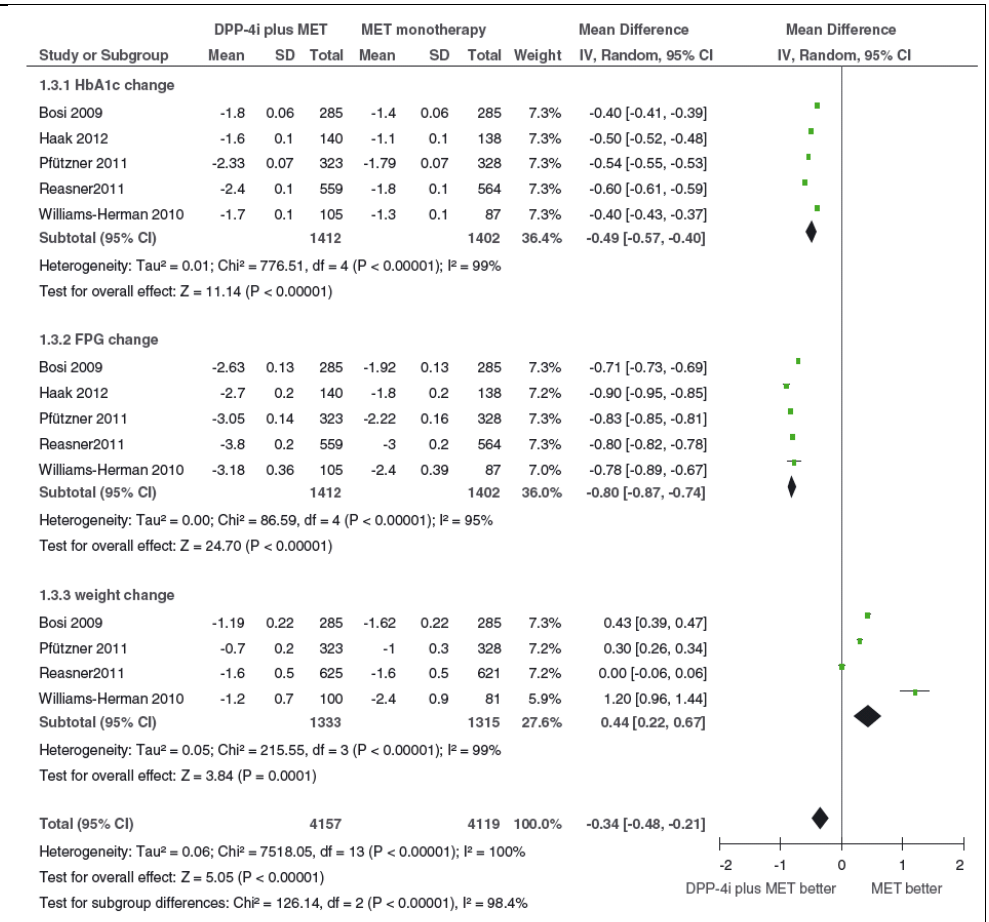


Figure 4. Meta-analysis of efficacy between DPP-4 inhibitors plus metformin as initial combination therapy and metformin monotherapy.

Anmerkungen/Fazit der Autoren

This meta-analysis compared DPP-4 inhibitors monotherapy with metformin monotherapy in T2DM, and the results showed that metformin monotherapy produced slightly, but significantly greater reduction in HbA1c, FPG and body weight than DPP-4 inhibitors monotherapy. However, DPP- 4 inhibitors monotherapy showed lower risk of adverse CV events, hypoglycaemia and gastrointestinal AEs compared with metformin monotherapy.

Anmerkung FB-Med:

Sehr unterschiedliche Follow-up Zeiten: zw. 18 und 104 Wochen, keine Langzeitfolgen

Zhuang, 2013 [112]

A meta-analysis of clinical therapeutic effect of insulin glargine

Fragestellung

This study estimated the effect and security of the two basal long-acting insulin analogs for T2DM by using meta-analysis.

Methodik

Population: Pat mit DM Typ 2

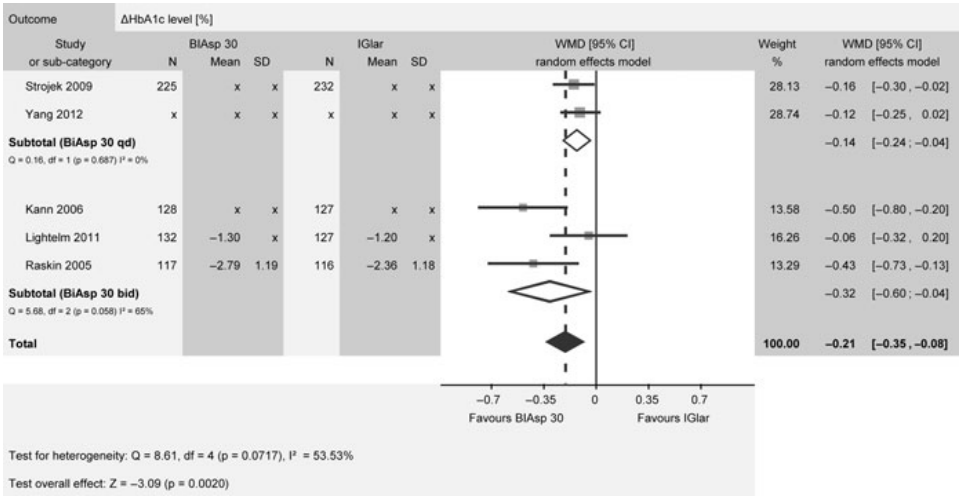
and insulin detemir for patients with type 2 diabetes mellitus	Intervention/ Komparator: insulin glargine and insulin detemir Endpunkt: HbA1C, FBG Studiendauer: >24 Wochen Suchzeitraum (Aktualität der Recherche): k.A. Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n=1.668) Qualität der Studien/Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung *Variety of HbA1c (3 trials)* OR and 95%CI of insulin glargine and insulin detemir concentration for lowing diabetic glycated hemoglobin were 0.03 [95% CI -0.08, 0.15]; not statistically significant (p = 0.57). *Variety of Fasting Plasma Glucose (FPG) (3 trials)* The results combined for meta-analysis demonstrated OR and 95% CI of insulin glargine and insulin detemir concentration for lowing diabetic fasting plasma glucose were 0.18 and [–-0.10,0.47], separately; no significantly statistical difference (p = 0.21).
	Anmerkungen/Fazit der Autoren Both insulin glargine and insulin detemir can effectively control T2DM patient's blood glucose. Their effectiveness and security are similar.
Rys, 2014 [95] **A comparison of biphasic insulin aspart and insulin glargine administered with oral antidiabetic drugs** **in type 2 diabetes mellitus – a systematic review and** **meta-analysis**	**Fragestellung:** We performed a systematic review to compare glycaemic control and selected clinical outcomes in T2DM patients inadequately controlled with OADs whose treatment was intensified by adding biphasic insulin aspart (BIAsp 30) or insulin glargine (IGlar).
	Methodik: Population: patients with type 2 diabetes Intervention/Komparator: BIAsp 30 (qd or bid) versus IGlar, both administered with OADs (all types of OADs, administered either in monotherapy or combined treatment, were considered eligible) Endpunkt: glycemic control, Suchzeitraum (Aktualität der Recherche): March 2013 Anzahl der eingeschlossenen Studien/Patienten: 5 RCTs (n=1758) Qualität der Studien/Risk of bias: Jadad criteria
	Ergebnisdarstellung:

Studies were of low to moderate quality

<u>Glycemic control</u>

HbA1c:

- a difference in favour of BIAsp 30 [WMD = -0.21% (-0.35; -0.08)];
- substantial between-study heterogeneity (p = 0.072; I^2 = 54%):main sources of heterogeneity were difference between studies in the number of daily injections of BIAsp 30 and the imbalanced OAD treatment between groups in the study by Ligthelm et al.



Fasting plasma glucose

- No difference between both BIAsp 30 and IGlar groups

Meal prandial glucose

- significantly lower mean prandial glucose increment in the BIAsp 30 group compared with the IGlar group [WMD = -14.70 mg/dl (-20.09; -9.31)] with no statistically significant heterogeneity

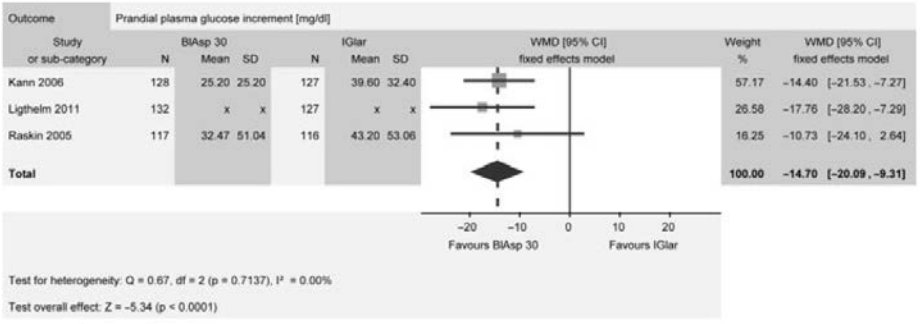


Figure 4 Weighted mean difference in mean prandial glucose increment between BIAsp 30 and IGlar

<u>Hypoglycemia</u>

- No significant difference between both treatments (2 studies), high degree of heterogeneity

<u>Weight gain</u>

	• larger weight gain after BIAsp 30 treatment [WMD = 1.78 kg (1.04; 2.52)] as compared with IGlar when admistered mit Metformin <u>Safety assessment</u> *Adverse events* • slightly greater proportion of patients experiencing at least one adverse event in the BIAsp 30 group compared with the IGlar group [60% vs. 53%; OR = 1.32 (1.02; 1.71)]. • No significant heterogeneity *Withdrawal* • No significant difference was found
	Anmerkungen/Fazit der Autoren: BIAsp 30 added to OAD therapy results in a better glycaemic control as compared with IGlar in T2DM patients. BIAsp 30 use is associated with slightly larger weight gain but no rise in risk of severe hypoglycaemic episodes. **Anmerkung FB-Med:** Stratifizierung nach Anzahl der Injektionen pro Tag und Ausschluss der Studie Ligthelm et al. zeigte ähnliche/vergleichbare (stat. sign.) Resultate zur glykämischer Kontrolle (HbA1c)
Simpson, 2015 [99] **Mortality risk among sulfonylureas: a systematic review and** **network meta-analysis**	**Fragestellung:** Since tissue selectivity and risk of hypoglycaemia diff er among sulfonylureas, we aimed to assess whether mortality and the risk of cardiovascular events also varies
	Methodik: Population: adults with type 2 diabetes Intervention/Komparator: comparison between two sulfonylurea Endpunkt: all-cause deaths, cardiovascularrelated deaths, or myocardial infarctions Suchzeitraum (Aktualität der Recherche): inception to June 11, 2014 Anzahl der eingeschlossenen Studien/Patienten:24 studies; [18 studies (n=167 327) all-cause mortality] Qualität der Studien/Risk of bias: 27-item Downs and Black49 checklist
	Ergebnisdarstellung: <u>Network-Metaanlysis</u> • 14 970 (9%) of 167 327 patients in 18 studies died: 841 (4%) of 19 334 gliclazide users, 5482 (11%) of 49 389 glimepiride users, 2106

(15%) of 14 464 glipizide users, 5296 (7%) of 77 169 glibenclamide users, 1066 (17%) of 6187 tolbutamide users, and 179 (23%) of 784 chlorpropamide users.

- Inconsistency was low for the network metaanalysis of all-cause mortality, and the relative risk of death compared with glibenclamide was:
    - 0.65 (95% credible interval 0.53–0.79) for gliclazide,
    - 0.83 (0.68–1.00) for glimepiride,
    - 0.98 (0.80–1.19) for glipizide,
    - 1.13 (0.90–1.42) for tolbutamide, and
    - 1.34 (0.98–1.86) for chlorpropamide.
- Similar associations were noted for cardiovascular-related mortality: the relative risk compared with glibenclamide was
    - 0·60 (95% credible interval 0·45–0·84) for gliclazide,
    - 0·79 (0·57–1·11) for glimepiride,
    - 1·01 (0·72–1·43) for glipizide,
    - 1·11 (0·79–1·55) for tolbutamide, and
    - 1·45 (0·88–2·44) for chlorpropamide.

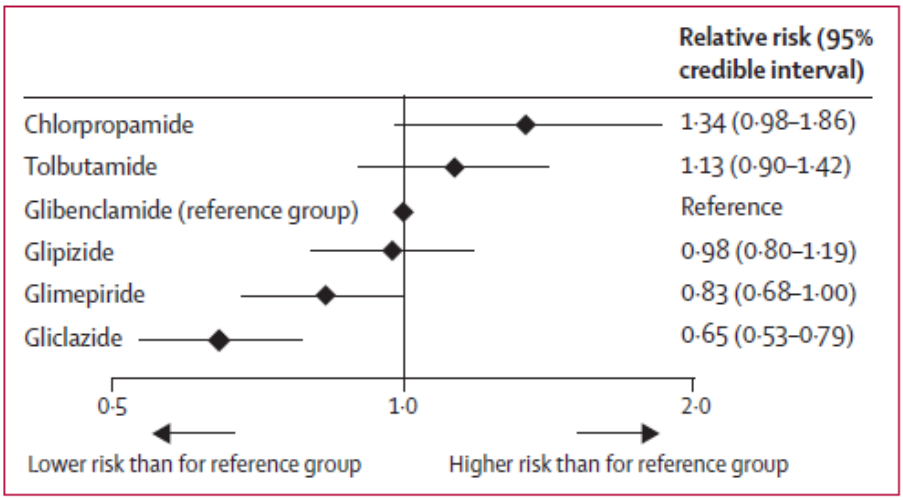
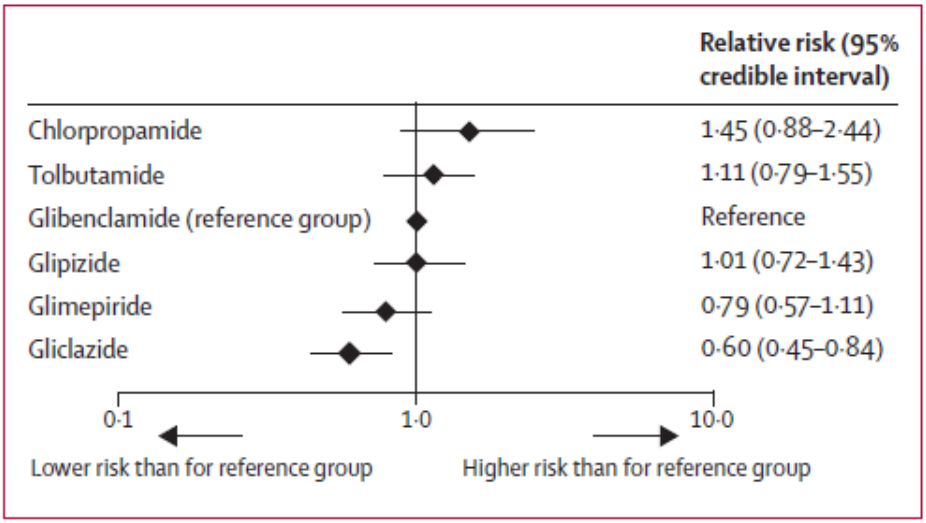


Figure 3: **Comparison of all-cause mortality between sulfonylureas using direct and indirect evidence**

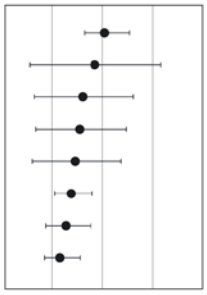
Data are pooled relative risks and 95% credible intervals calculated by network meta-analysis of direct and indirect evidence from 18 studies.[3,34–37,39,50,51,53,58,61–68]

	 ***Figure 4:*** **Comparison of cardiovascular-related mortality between sulfonylureas using direct and indirect evidence** Data are pooled relative risks and 95% credible intervals calculated by network meta-analysis of direct and indirect evidence from 13 studies.[3,34,36,37,39,52,58,61,63,64,66-68]
	Anmerkungen/Fazit der Autoren: Gliclazide and glimepiride were associated with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide. Clinicians should consider possible diff erences in risk of mortality when selecting a sulfonylurea
Monami, 2014[82] **A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes**	**Fragestellung:** To assess hypoglycaemic risk with sulphonylureas in comparison with other drugs in randomized controlled trials.
	Methodik: Population: patients with type 2 diabetes Intervention/Komparator: sulphonylureas with placebo or active drugs (oral hypoglycaemic agents, GLP- 1 receptor agonists, and/or insulin) Endpunkt: one episode of overall or severe hypoglycaemia Suchzeitraum (Aktualität der Recherche): 30 November 2013 Anzahl der eingeschlossenen Studien/Patienten: 91 trials Qualität der Studien/Risk of bias: using some of the parameters proposed by Jadad
	Ergebnisdarstellung: <u>Severe hypoglycemia:</u> • 69 trials reporting information on severe hypoglycaemia, 24 trials reported at least one event. I^2 was 20.0 (p=0.19) • The overall risk of severe hypoglycaemia was increased more than

threefold with sulphonylureas than with comparators.

A

Comparators	MH-OR	p	# trials	patient/yr	# events	Yearly incidence
DPP-4i	10.97[4.37;27.51]	<0.001	5	4,840/4,850	55/4	1.14/0.08
SGLT-2i	7.03[0.36-136.64]	0.20	1	401/400	3/0	0.75/0.00
Glinides	4.02[0.44-36.67]	0.22	2	497/515	3/0	0.60/0.00
Metformin	3.51[0.47-26.34]	0.22	2	7,266/7,330	9/2	0.12/0.03
GLP-1RA	2.86[0.40-20.70]	0.30	3	2,067/2,080	6/1	0.29/0.05
Glitazones	2.38[1.13-5.03]	0.02	9	9,147/9,548	27/9	0.29/0.09
Placebo	1.89[0.76-4.71]	0.17	2	13,734/9981	16/6	1.17/0.60
Insulin	1.43[0.72-2.88]	0.31	2	13,802/10,206	16/16	0.12/0.16



B

Comparators	MH-OR	p	# trials	patient/yr	# events	Yearly incidence
SGLT-2i	18.69[10.58;33.02]	<0.001	1	401/400	162/14	40.4/3.5
DPP-4i	6.76[4.27;10.69]	<0.001	7	6,445/6,436	998/171	15.5/2.7
alfa-GI	5.82[2.66;12.70]	<0.001	6	225/362	77/33	34.2/9.2
GLP-1RA	4.05[2.43-6.75]	<0.001	5	2,376/2,702	532/327	22.4/12.1
Glitazones	4.34[3.40-5.55]	<0.001	29	21,284/21,670	1,913/551	9.0/2.6
Placebo	3.34[1.70-6.57]	<0.001	4	13,866/10,113	353/141	2.5/1.4
Metformin	2.74[1.57-4.79]	<0.001	8	8,305/8,409	604/195	7.3/2.3
Insulin	1.37[0.63-2.97]	0.42	4	13,898/10,388	371/403	2.7/3.9
Glinides	1.35[1.01-1.75]	0.041	6	1,036/1,482	130/156	12.5/10.5

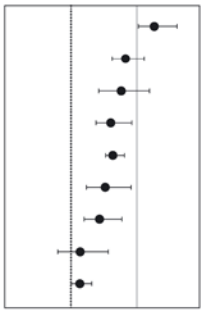


Figure 3. Mantel–Haenszel odds ratio (MH-OR) with 95% Confidence Interval (LL, Lower Limit, UL, Upper Limit) for severe (Panel A) and any (Panel B) hypoglycaemia in comparison with other classes of hypoglycaemic agents or placebo.

<u>Any hypoglycemia</u>

- 70 trials, 5 of which reported 0 events: I^2=0.0 (p=0.98)
- The overall risk (MH-OR) of hypoglycaemia with sulphonylureas versus comparators was 3.69 [3.47–3.93] (p<0.001).
- The increase in risk was statistically significant in comparisons with placebo/no therapy and any active drug, including glinides, with the only exception of insulin.

Anmerkungen/Fazit der Autoren:

In conclusion, hypoglycaemia, including severe hypoglycaemia, is frequent in patients treated with sulphonylureas, particularly when baseline HbA1c levels are lower and BMI levels higher. Further studies are needed to characterize predictors for the identification of patients at higher risk

Anmerkung FB-Med:

The definition of hypoglycaemia differed across trials.

Monami, 2013 [83]	**Fragestellung:**

Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials	To collect all available data on cardiovascular safety of sulfonylurea
	Methodik: Population: patients with type 2 diabetes Intervention/Komparator: sulfonylureas with placebo or active drugs (oral gypoglycaemic agents, GLP-1 receptor agonists and/or insulin) Endpunkt: Major cardiovascular events (MACE) and mortality Suchzeitraum (Aktualität der Recherche): 31 October 2012 Anzahl der eingeschlossenen Studien/Patienten: 116 trials Qualität der Studien/Risk of bias: some of the parameters proposed by Jadad
	Ergebnisdarstellung: • limitations in trial quality and under-reporting of information on cardiovascular events and mortality <u>MACE (Major cardiovascular events)</u> • 62 trials, 32 detected no events, analysis based on 30 trials: The use of sulfonylureas was not associated with any significant difference in the incidence of MACE with respect to comparators I^2 was 49.3 (p=0.002). <u>MI (Myocardial infarction)</u> • 57 trials of whicht 34 detected no events; based on 23 trials: use of sulfonylureas was not associated with any significant difference in the incidence of MI with respect to comparators <u>Stroke:</u> • 16 trials reporting at least one stroke: a significantly higher risk was observed in association with sulfonylureas (MH-OR: 1.28 [1.03–1.60], p=0.026) • increase in risk reached statistical significance in direct comparisons with DPP4 inhibitors (MH-OR: 4.51 [1.60–12.66], p=0.004) and in trials with glimepiride (MH-OR: 4.22 [1.65–10.79], p=0.003) <u>All-cause and cardiovascular mortality:</u> • 88 trials, 37 of which reported at least one death: significant increase in mortality was observed with sulfonylureas (MHOR: 1.22 [1.01–1.49], p=0.047 versus placebo • No significant association with all-cause or cardiovascular mortality was observed for trials with different comparators, or for individual sulfonylureas <u>Severe Hypoglycaemia</u> • In trials reporting at least one event, sulfonylureas were associated with a significantly increased risk of severe hypoglycaemia in comparison with metformins (N=2 trials; MH-OR: 14.72 [2.81–77.30], p=0.001)

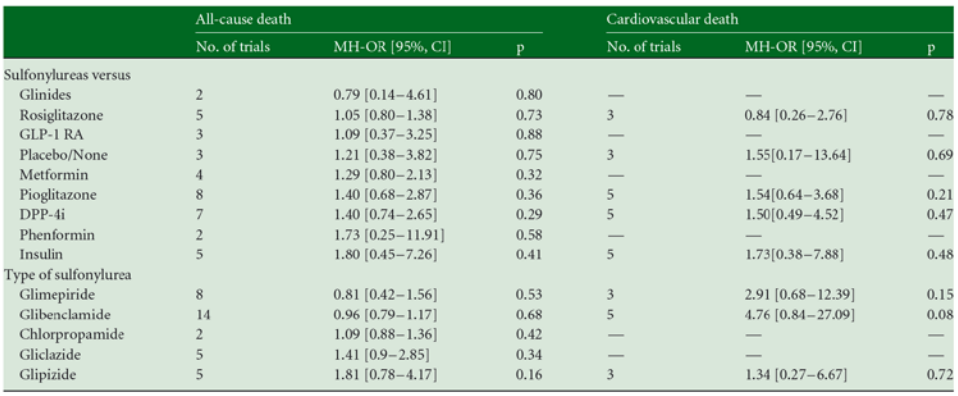
	 All-cause death / Cardiovascular death No. of trials / MH-OR [95%, CI] / p / No. of trials / MH-OR [95%, CI] / p Sulfonylureas versus Glinides 2 0.79 [0.14–4.61] 0.80 — — — Rosiglitazone 5 1.05 [0.80–1.38] 0.73 3 0.84 [0.26–2.76] 0.78 GLP-1 RA 3 1.09 [0.37–3.25] 0.88 — — — Placebo/None 3 1.21 [0.38–3.82] 0.75 3 1.55[0.17–13.64] 0.69 Metformin 4 1.29 [0.80–2.13] 0.32 — — — Pioglitazone 8 1.40 [0.68–2.87] 0.36 5 1.54[0.64–3.68] 0.21 DPP-4i 7 1.40 [0.74–2.65] 0.29 5 1.50[0.49–4.52] 0.47 Phenformin 2 1.73 [0.25–11.91] 0.58 — — — Insulin 5 1.80 [0.45–7.26] 0.41 5 1.73[0.38–7.88] 0.48 Type of sulfonylurea Glimepiride 8 0.81 [0.42–1.56] 0.53 3 2.91 [0.68–12.39] 0.15 Glibenclamide 14 0.96 [0.79–1.17] 0.68 5 4.76 [0.84–27.09] 0.08 Chlorpropamide 2 1.09 [0.88–1.36] 0.42 — — — Gliclazide 5 1.41 [0.9–2.85] 0.34 — — — Glipizide 5 1.81 [0.78–4.17] 0.16 3 1.34 [0.27–6.67] 0.72 MH-OR, Mantel-Haenszel odds ratio with 95% confidence intervals; "—", less than two trials reporting events (or no events) allowing no formal meta-analysis; GLP-1 RA, glucagon-like peptide-1 receptor agonists; DPP-4i, dipeptidyl peptidase-4 inhibitors. **Anmerkungen/Fazit der Autoren:** In type 2 diabetes, the use of sulfonylureas is associated with increased mortality and a higher risk of stroke, whereas the overall incidence of MACE appears to be unaffected. Significant differences in cardiovascular risk could be present in direct comparisons with specific classes of glucose-lowering agents, such as DPP4 inhibitors, but this hypothesis needs to be confirmed in long-term cardiovascular outcomes trials.
Monami, 2013 **[84]** **Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials**	**Fragestellung:** The aim of the present meta-analysis is the assessment of the overall efficacy and safety profile of sodium glucose co-transport-2 (SGLT-2) inhibitors
	Methodik: Population: patients with type 2 diabetes Intervention/Komparator: comparing a SGLT-2 inhibitor with a non-SGLT-2 inhibitor agent Endpunkt: • HbA1c at 12, 24 and 52 weeks • Hypoglycaemia • genital and urinary infections Suchzeitraum (Aktualität der Recherche): until 21 May 2013 Anzahl der eingeschlossenen Studien/Patienten: 25 RCTs (n=11,152) Qualität der Studien/Risk of bias: some of the parameters proposed by Jadad
	Ergebnisdarstellung: <u>HbA1c</u>

Table 4. Differences in means in HbA1c between sodium glucose co-transport-2 inhibitors and active comparators at 12 and 24 weeks in trials included in the meta-analysis.

	Sodium glucose co-transport-2 inhibitorsversus		
HbA1c (%)	Glipizide	Metformin	Sitagliptin
N arms	(1)	(5)	(2)
12 weeks	0.3 [0.2; 0.4]*	0.0 [−0.1; −0.1]	0.0 [−0.3; 0.3]
N arms	(1)	(5)	(1)
24 weeks	0.3 [0.2; 0.5]*	0.1 [−0.1; 0.2]	−0.2 [−0.4; −0.1]*

*p < 0.05; **p < 0.001.

Weight change/BMI

- head-to-head comparison with sitagliptin, canagliflozin was associated with a significantly lower BMI at 12 weeks (−1.0 [−2.0; 0.0] kg/m2, p=0.049), 24weeks (−1.2 [−2.2; −0.2] kg/m2, p=0.02) and 52weeks (−1.0 [−2.0; 0.0] kg/m2, p=0.42).

Metabolic paramters:

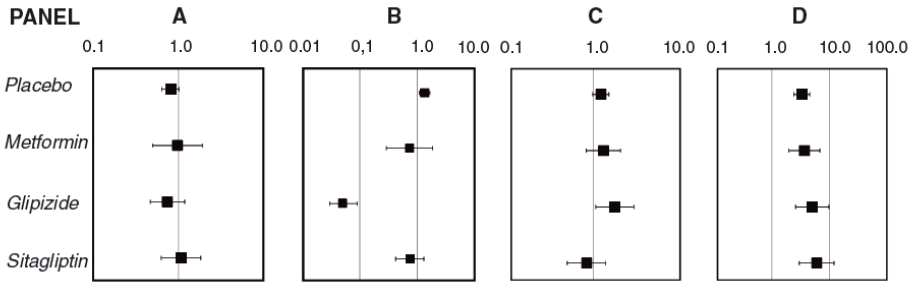
- SGLT-2 inhibitors reduced FPG not only in placebo-controlled trials, but also in direct comparisons with metformin and sitagliptin (−0.5 [−0.9; −0.1] and−0.8 [−1.3;−0.2] mmol/l, respectively)
- SGLT-2 inhibitors determined a modest but statistically significant increase in HDL cholesterol

Table 5. Differences in means in fasting plasma glucose, lipid profile, creatinine, hematocrit and blood pressure at the endpoint, between sodium glucose co-transport-2 and active comparators/placebo in trials included in the meta-analysis.

	Sodium glucose co-transport-2 inhibitors versus	
Differences in means	All comparators	Only placebo
Fasting plasma glucose (mmol/l)	−1.0 [−0.9; −1.2]**	−1.2 [−1.0; −1.4]**
Total cholesterol (mmol/l)	0.1 [−0.1; 0.2]	0.0 [−0.1; 0.1]
HDL cholesterol (mmol/l)	0.1 [0.0;0.1]*	0.0 [−0.1; 0.1]
LDL cholesterol (mmol/l)	0.1 [−0.1; 0.2]	0.0 [−0.1; 0.1]
Triglycerides (mmol/l)	−0.1 [−0.3; 0.0]	−0.1 [−0.3; 0.1]
Creatinine (µmol/l)	—	−0.7 [−1.7; 0.3]
Hematocrit (%)	—	1.4 [0.2; 2.7]*
Systolic blood pressure (mmHg)	—	−1.2 [−1.4; −1.0]**
Diastolic blood pressure (mmHg)	—	−1.9 [−2.6; −1.1]**

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*p < 0.05; **p < 0.001.

Adverse events:

	• significantly lower risk was found in comparison of SGLT-2 inhibitors with sulphonylurea (1 RCT) • incidence genital infections was significantly increased with SGLT-2 inhibitors (s3.90 [3.00–5.07], p<0.001).  **Serious adverse events** **Total hypoglycaemia** **Urinary infections** **Genital infections** **Trials MH-OR, 95% CI p N trials MH-OR, 95% CI p N trials MH-OR, 95% CI p N trials MH-OR, 95% CI p** *Placebo* 22 0,81[0.64;1.01] 0.057 20 1,34[1.09;1.65] <0.001 21 1.23[0.99;1.52] 0.05 21 3.32[2.40;4.59] <0.001 *Metformin* 5 0,97[0.50;1.89] 0.93 3 0,73[0.29;1.84] 0.50 5 1.31[0.83;2.07] 0.25 5 3.68[1.98;6.82] <0.001 *Glipizide* 1 0.74[0.47;1.18] 0.20 1 0.05[0.03;0.09] <0.001 1 1.78[1.07;2.96] 0.02 1 5.07[2.60;9.88] <0.001 *Sitagliptin* 3 1.07[0.63;1.81] 0.81 2 0.74[0.42;1.30] 0.29 3 0.84[0.50;1.39] 0.29 3 6.04[3.01;12.11] <0.001
	Anmerkungen/Fazit der Autoren: SGLT-2 inhibitors are effective in the treatment of type 2 diabetes, providing additional benefits, such as weight loss, reduction of blood pressure and increase in high-density lipoprotein (HDL)-cholesterol. Apart from genital and urinary infections, rather frequent but usually mild, SGLT-2 inhibitors appear to be well tolerated
Liakos, 2014 [80] **Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis**	**Fragestellung:** To assess the efficacy and safety of the novel sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin compared with placebo or other antidiabetic agents in patients with type 2 diabetes

	Methodik:
	
	Population: adults with type 2 diabetes
	
	Intervention/Komparator: empagliflozin versus placebo or any other antidiabetic medication
	
	Endpunkte:
	
	• primary outcome: absolute change in HbA1c (%) (glycemic efficacy)
	• Secondary efficacy outcomes:
	  o change in body weight (kg),
	  o change in systolic and diastolic blood pressure (mm Hg) and
	  o patients achieving the HbA1c target of <7%.
	• Safety outcomes included:
	  o patients experiencing at least one episode of hypoglycaemia or a major hypoglycaemic event
	  o change in estimated glomerular filtration rate (eGFR, ml/min/1.73m2),
	  o incidence of urinary and genital tract infections, and
	  o incidence of adverse events related to volume depletion, based on definition utilized in individual studies.

	• Additional outcomes:
	  o all-cause mortality
	  o Scardiovascular outcomes
	
	Suchzeitraum (Aktualität der Recherche): from inception to December 19, 2013
	
	Anzahl der eingeschlossenen Studien/Patienten: 10 studies (n=6203)
	
	Qualität der Studien/Risk of bias: Cochrane risk of bias tool

	Ergebnisdarstellung: • 8 studies high risk of bias due to imputation method for HbA1c (potential bias favouring the study drug), two trials low risk of bias. <u>HbA1c</u> • Empagliflozin had glycaemic efficacy similar to other antidiabetic agents (metformin and sitagliptin), both at the 10-mg and the 25-mg dosing regimens (WMD 0.04%; 95% CI –0.07 to 0.16%; I2 =0% and –0.11%; 95% CI –0.25 to 0.03%; I2 =25% respectively) <u>Body weight change</u> • Empagliflozin (3 studies) associated with significant weight loss when compared with other antidiabetic medications (WMD –2.15 kg; 95% CI –3.03 to –1.27 kg; I2 =56% for the 10-mg dose, and –2.56 kg; 95% CI –3.57 to –1.55 kg; I2 =66% for the 25-mg dose) <u>Blood pressure</u> • Empagliflozin associated with significant diastolic and systolic blood pressure reduction when compared with other antidiabetic medications <u>Urinary tract infection (UTI)</u> • Empagliflozin associated with significant higher risk of UTI when compared with other antidiabetic medications

Outcome	Comparator	Empagliflozin 10 mg		Empagliflozin 25 mg	
		Number of studies	Effect estimate (95% CI); I^2 *	Number of studies	Effect estimate (95% CI); I^2 *
Systolic blood pressure (mm Hg)	Placebo	9	−3.49 (−4.32 to −2.67); 0%	9	−4.19 (−5.17 to −3.20); 32%
	Active agent	3	−3.53 (−5.37 to −1.69); 0%	3	−4.24 (−6.08 to −2.41); 0%
Diastolic blood pressure (mm Hg)	Placebo	6	−1.28 (−2.04 to −0.51); 41%	6	−1.88 (−2.71 to −1.04); 56%
	Active agent	3	−1.66 (−2.75 to −0.57); 0%	3	−2.54 (−3.63 to −1.45); 0%
Estimated glomerular filtration rate (ml/min/1.73 m^2)	Placebo	5	−0.09 (−1.14 to 0.96); 0%	5	−0.84 (−2.29 to 0.62); 59%
Patients achieving haemoglobin A1c <7%	Placebo	7	3.83 (2.98 to 4.90); 0%	7	4.40 (3.17 to 6.12); 47%
	Active agent	3	0.86 (0.63 to 1.18); 0%	3	1.26 (0.93 to 1.71); 0%
Incidence of urinary tract infections	Placebo	10	1.20 (0.92 to 1.57); 0%	10	1.03 (0.81 to 1.32); 0%
	Active agent	3	1.04 (0.58 to 1.86); 0%	3	1.14 (0.64 to 2.03); 0%
Incidence of genital tract infections	Placebo	9	4.39 (2.10 to 9.19); 20%	10	3.31 (1.55 to 7.09); 37%
	Active agent	3	3.34 (1.03 to 10.76); 0%	3	4.17 (1.32 to 13.15); 0%
Incidence of volume depletion	Placebo	3	0.98 (0.20 to 4.91); 0%	3	1.01 (0.42 to 2.43); 0%

CI, confidence interval.
*For systolic and diastolic blood pressure and estimated glomerular filtration rate the effect estimate is weighted mean difference from inverse-variance random-effects meta-analysis. For the remaining outcomes the effect estimate is odds ratio from Mantel–Haenszel random-effects meta-analysis.

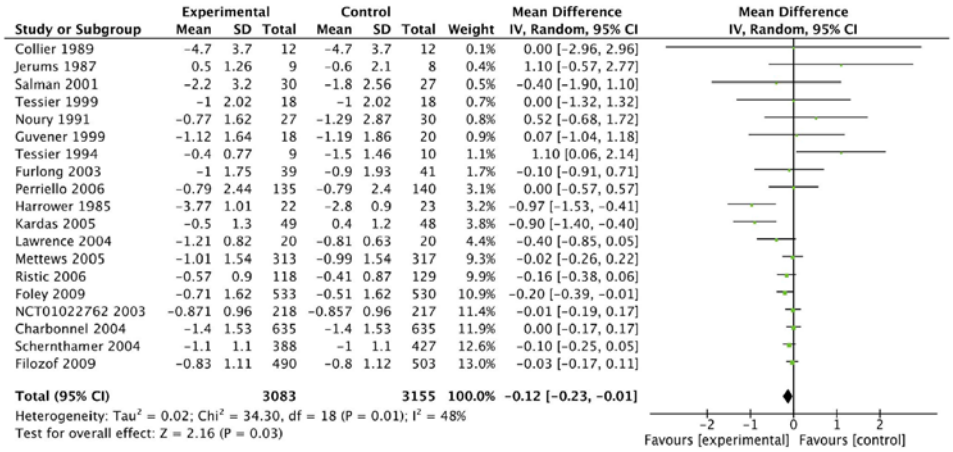
- No data available on mortality and cardiovascular outcomes

Anmerkungen/Fazit der Autoren:

Empagliflozin effectively lowers blood glucose and provides additional clinical benefits including body weight and blood pressure reduction.

Anmerkung FB-Med:

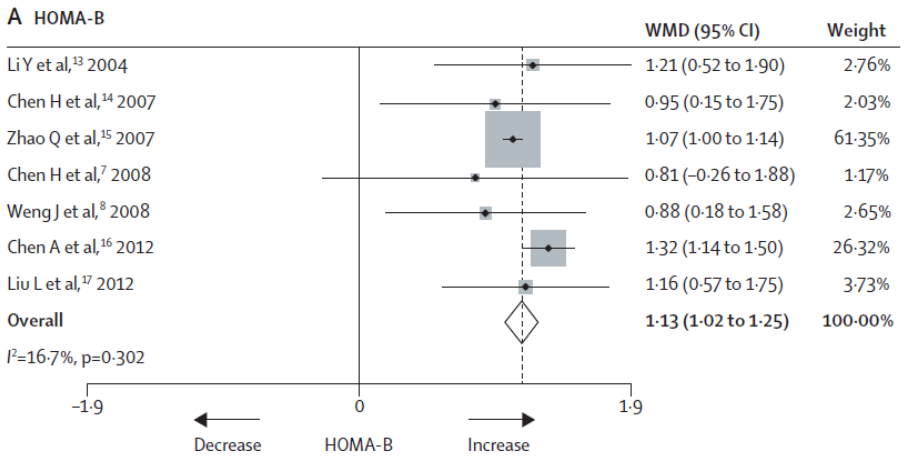
Keine Sensititvitätsanalyse mit Studien guter Qualität. Überschätzung der Wirksamkeit durch Verzerrung durch Imputation von HbA1c-werten in 8 von 10 Studien.

Landmann, 2014 [79] **Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Trials**	**Fragestellung:** to assess in a systematic review and meta-analysis of randomized controlled trials the safety and efficacy of gliclazide compared to other oral glucose-lowering agents
	Methodik: Population: patients with type 2 diabetes Intervention/Komparator: gliclazide with other oral blood glucose lowering drugs Endpunkt: HbA1c change, incidence of severe hypoglycemia, weight change, cardiovascular events, mortality Suchzeitraum (Aktualität der Recherche): 31 October 2009 Anzahl der eingeschlossenen Studien/Patienten: 19 RCTs (n=3,083) Qualität der Studien/Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung: • There was a considerable amount of heterogeneity between and bias in studies <u>HbA1c:</u> • Compared to other glucose lowering agents except metformin, gliclazide was slightly more effective (20.13% (95%CI: 20.25, 20.02, I2=55%)).  **Figure 2. Forest plot of the main effect outcome.** The main effect outcome HbA1c; gliclazide versus other glucose lowering agents. Metf = metformin, SU is sulphonylurea, Pio is pioglitazone. doi:10.1371/journal.pone.0082880.g002 <u>Hypoglycemic events:</u> • One out of 2,387 gliclazide users experienced a severe hypoglycemic event, whilst also using insulin. There were 25 confirmed non-severe hypoglycemic events (2.2%) in 1,152 gliclazide users and 22 events (1.8%) in 1,163 patients in the comparator group (risk ratio 1.09 (95% CI: 0.20, 5.78, I2 77%)).

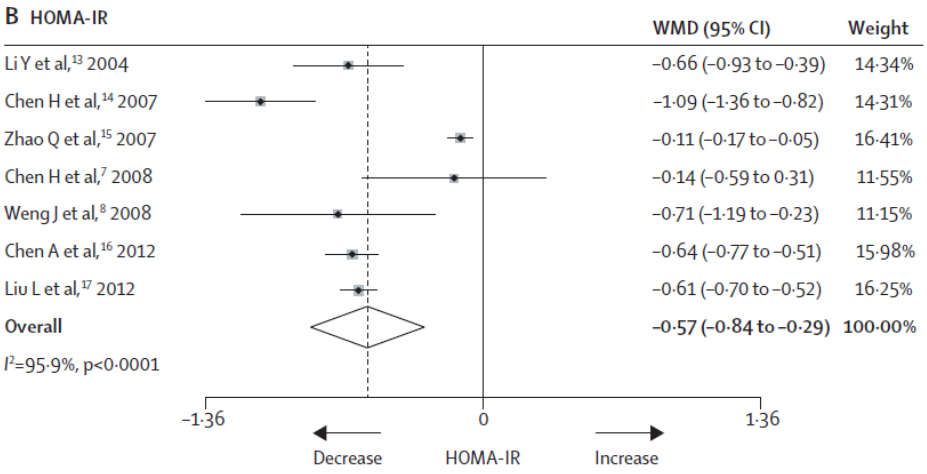
	Anmerkungen/Fazit der Autoren: The methodological quality of randomized trials comparing gliclazide to other oral glucose lowering agents was poor and effect estimates on weight were limited by publication bias. The number of severe hypoglycemic episodes was extremely low, and gliclazide appears at least equally effective compared to other glucose lowering agents. None of the trials were designed for evaluating cardiovascular outcomes, which warrants attention in future randomized trials
Kaercher, 2013 **[77]** **Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis**	**Fragestellung:** to assess the effect of short-term intensive insulin therapy on the pathophysiological defects underlying type 2 diabetes mellitus
	Methodik: Population: adults aged 18 years or older with newly diagnosed type 2 diabetes mellitus Intervention/Komparator: shortterm intensive insulin therapy (before and after treatment) Endpunkt: β-cell function (assessed by Homeostasis Model Assessment of β-cell function [HOMA-B]) or insulin resistance (assessed by Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]) Suchzeitraum (Aktualität der Recherche): 1950 and Nov 19, 2012 Anzahl der eingeschlossenen Studien/Patienten: 7 studies (n=839) Qualität der Studien/Risk of bias: selection bias, description of losses or exclusions, and assessment of efficacy
	Ergebnisdarstellung: Table 2: Assessment of studies for risk of bias • post-intensive insulin therapy increase in Homeostasis Model Assessment of β-cell function as compared with baseline (1. 13, 95% CI 1. 02 to 1. 25)

	Selection bias	Insulin therapy efficacy assessed	Stopped early	Dropout rate (%)	Outcome assessment accurate
Li Y et al[13]	No	Yes	No	10·3%	Yes
Chen H et al[14]	No	Yes	No	NR	Yes
Zhao Q et al[15]	No	Yes	No	NR	Yes
Chen H et al[7]	No	Yes	No	12·0%	Yes
Weng J et al[8]	No	Yes	No	5·3%	Yes
Chen A et al[16]	No	Yes	No	21·3%	Yes
Liu L et al[17]	No	Yes	No	NR	Yes

NR=not reported.



- a decrease in Homeostasis Model Assessment of Insulin Resistance (–0.57, –0. 84 to –0. 29). In the four studies that assessed glycaemic remission (n=559 participants)



- the proportion of participants in drug-free remission was about 66. 2% (292 of 441 patients) after 3 months of follow-up, about 58. 9% (222 of 377 patients) after 6 months, about 46. 3% (229 of 495 patients) after 12 months, and about 42. 1% (53 of 126 patients) after 24 months. Patients who achieved remission had higher body-mass index than those who did not achieve remission (1. 06 kg/m2, 95% CI 0. 55 to 1. 58) and lower fasting plasma glucose (–0. 59 mmol/L, 95% CI –1. 11 to –0・07) at baseline.

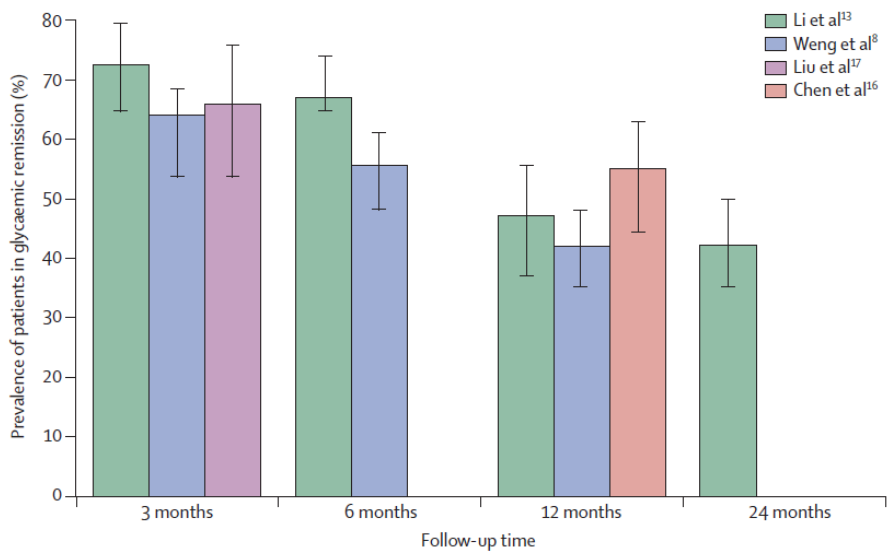
	
	Anmerkungen/Fazit der Autoren: Short-term intensive insulin therapy can improve the underlying pathophysiology in early type 2 diabetes mellitus, and thus might provide a treatment strategy for modifying the natural history of diabetes.
Hou, 2015 [50] **Efficacy and safety of sitagliptin compared with sulfonylurea therapy in patients with type 2 diabetes showing inadequately controlled glycosylated hemoglobin with metformin monotherapy: A meta-analysis**	**Fragestellung:** a meta-analysis was conducted of the outcomes of all published RCTs comparing sitagliptin with sulfonylureas in the treatment of type 2 diabetes mellitus
	Methodik: Population: inclusion of patients with type 2 diabetes who had not been achieving their glycemic targets with metformin monotherapy; Intervention/Komparator: combined metformin and sitagliptin therapy with combined metformin and sulfonylurea therapy in the treatment groups Endpunkt: HbA1c Suchzeitraum (Aktualität der Recherche): January 2000 and December 2012 Anzahl der eingeschlossenen Studien/Patienten: 6 RCTs (n=3,585) Qualität der Studien/Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung: • Moderate to high quality studies included in meta-analysis

Table II. Results of quality assessment of six randomized controlled trials.

First author, year (ref)	Allocation concealment	Blinding	Randomization	Percentage that completed the trial	Intention-to-treat analysis	Free of selective reporting	Groups comparable at baseline
Nauck, 2007 (16)	Yes	Yes, double blind	Computer-generated allocation schedule	68	Yes	Yes	Yes
Arechavaleta, 2011 (14)	Yes	Yes, double blind	Computer-generated allocation schedule	90	Yes	Yes	Yes
Srivastava, 2012 (18)	Unclear	Unclear	Computer-generated random number	100	No	Yes	Yes
Seck, 2010 (17)	Yes	Yes, double blind	Computer-generated allocation schedule	43	Yes	Yes	Yes
Li, 2012 (20)	Unclear	Unclear	Random number table	100	No	Yes	Yes
Koren, 2012 (19)	No	Open-label crossover trial	Recruitment order	85	Yes	Yes	Yes

HbA1c

- No significant difference between the metformin plus sitagliptin and the metformin plus sulfonylurea groups

Body weight:

- metformin plus sitagliptin group was found to experience a significantly greater loss in body weight compared with the metformin plus sulfonylurea group (WMD=-1.82; 95% CI, -1.91 to -1.73; P<0.00001).

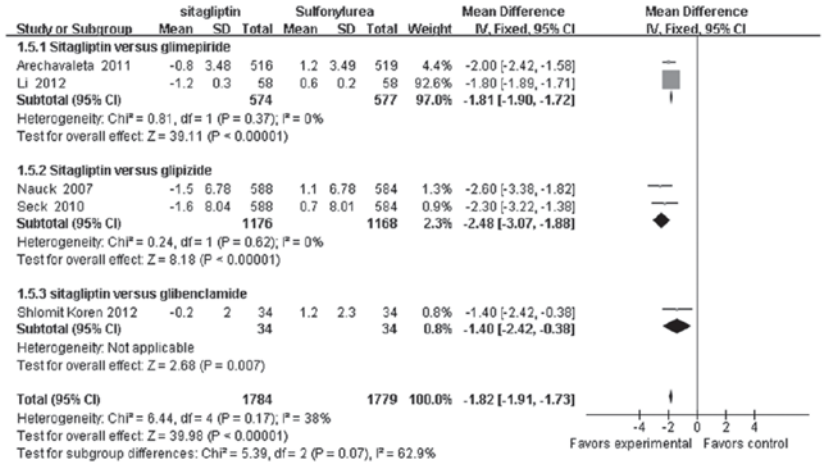
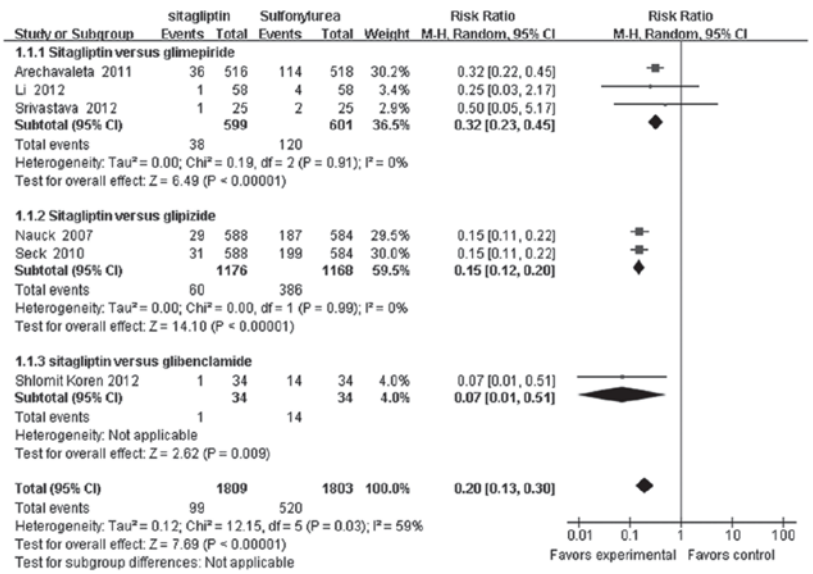


Figure 4. Comparison of changes in body weight between the metformin plus sitagliptin and the metformin plus sulfonylurea groups. SD, standard deviation; CI, confidence interval.

Hypoglycemic events

- metformin plus sitagliptin group was found to experience significantly fewer hypoglycemic events compared with the metformin plus sulfonylurea group (RR=0.20; 95% CI, 0.13-0.30; P<0.00001)

	 Figure 5. Comparison of occurrence of hypoglycemic events between the metformin plus sitagliptin and the metformin plus sulfonylurea groups. M-H, Mantel-Haenszel; CI, confidence interval.
	Anmerkungen/Fazit der Autoren: Metformin plus sitagliptin therapy may decrease HbA1c values in patients with type 2 diabetes mellitus who are not achieving their glycemic targets with metformin monotherapy in a manner similar to metformin plus sulfonylurea therapy, whilst posing a lower risk of hypoglycemia, and yielding a more beneficial effect on body weight.
Hemmingsen, 2014 [48] **Sulfonylurea versus metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized clinical trials and trial sequential analysis**	**Fragestellung:** to assess whether the use of second- and third-generation sulfonylurea agents is associated with benefits and harms in terms of patient-important outcomes compared with metformin
	Methodik: Population: patients 18 years or older with type 2 diabetes Intervention/Komparator: second- and third-generation sulfonylurea versus metformin monotherapy Endpunkte: all-cause mortality, cardiovascular mortality, nonfatal macrovascular outcomes as a composite outcome, nonfatal myocardial infarction, nonfatal stroke, amputation of lower extremity, cardiac or peripheral revascularization, microvascular outcomes as a composite outcome, nephropathy, retinal photocoagulation, adverse events, serious adverse events, drop-outs due to adverse events, mild hypoglycemia, severe hypoglycemia, cancer, intervention failure, change in fasting blood glucose level from baseline, change in HbA1c concentration from baseline, change in body mass index (BMI) from baseline, change in weight from baseline, quality of life Suchzeitraum (Aktualität der Recherche): August 2011 Anzahl der eingeschlossenen Studien/Patienten: 14 trials (n=4560) Qualität der Studien/Risk of bias: risk-of-bias domains: sequence

generation, concealment of allocation, blinding of participants and investigators, blinding of outcome assessors, completeness of outcome data, selective outcome reporting academic bias and sponsor bias

Ergebnisdarstellung:

Risk of bias

Table 4: Risk-of-bias assessment of the trials included in the meta-analysis*

Trial	Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors (detection bias)	Completeness of outcome data (attrition bias)	Selective reporting (reporting bias)	Academic bias	Sponsor bias
ADOPT, 2006[20–26]	Low	Low	Low	Low	Low	Low	Low	High
Campbell et al., 1994[27]	Unclear	Unclear	High	High	Low	Unclear	Low	Unclear
Collier et al., 1989[28]	Unclear	Unclear	High	High	Unclear	Unclear	Low	High
DeFronzo et al., 1995[29]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Derosa et al., 2004[42]	Unclear	Unclear	High	High	Low	Unclear	Low	Unclear
Hermann et al., 1991a[30]	Low	Unclear	High	High	Unclear	Unclear	Low	High
Hermann et al., 1991b[31–34]	Low	Low	Low	Low	Low	Low	High	High
Kamel et al., 1997[35]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Lawrence et al., 2004[36]	Unclear	Unclear	High	Low	Low	Unclear	Low	High
Tang et al., 2004[41]	Unclear	Unclear	High	High	Unclear	Unclear	Low	Low
Tessier et al., 1999[37]	Unclear	Unclear	High	High	Low	Unclear	Low	High
Tosi et al., 2003[38]	Low	Low	Low	Low	Unclear	Low	Low	High
UKPDS 34, 1998[2,39,40]	Low	Low	High	Low	Unclear	High	Low	High
Yamanouchi et al., 2005[43]	Low	Low	High	High	Low	Unclear	Low	Unclear

Note: ADOPT = A Diabetes Outcome Progression Trial, UKPDS = United Kingdom Prospective Diabetes Study.
*The Cochrane risk-of-bias tool was used to assess the risk of bias for each study. Low risk = bias, if present, is unlikely to alter the results seriously, unclear risk = bias raises some doubt about the results, high risk = bias may alter the results seriously.[10]

<u>All-cause mortality and cardiovascular mortality</u>

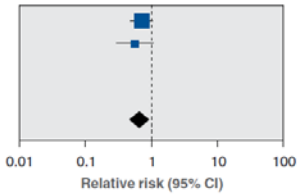
- No significant effect

<u>Non-fatal macrovascular outcomes</u>

- Sulfonylurea significantly decreased the risk compared with metformin: RR 0.67, 95% CI 0.48 to 0.93
- However, the definition of this outcome varied among trials, and trial sequential analysis showed that more trials are needed before reliable conclusions can be drawn.

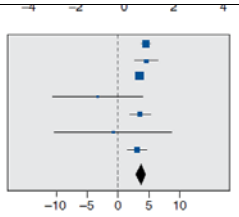
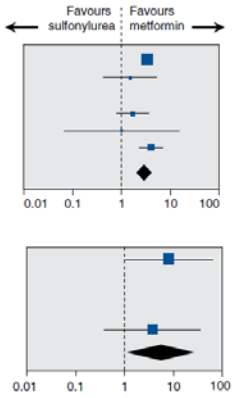
C: Nonfatal macrovascular outcomes

ADOPT 2006[20–26]	41/1447	58/1455	0.71 (0.48–1.05)
Hermann et al., 1991b[31–34]	9/34	18/38	0.56 (0.29–1.07)
Tosi et al., 2003[38]	0/22	0/22	Not estimable
Yamanouchi et al., 2005[43]	0/37	0/39	Not estimable
Overall	50/1540	76/1554	0.67 (0.48–0.93)
Heterogeneity: I^2 = 0%			



<u>Body weight gain</u>

- Sulfonylurea resulted in greater weight gain compared with metformin

	C: Weight  ADOPT 2006[20–26] 1.6 ± 11.6 1441 −2.9 ± 10.7 1454 4.50 (3.69 to 5.31) Campbell et al., 1994[27] 2.6 ± 3.9 24 −2 ± 2.9 24 4.60 (2.66 to 6.54) DeFronzo et al., 1995[29] −0.3 ± 2.9 209 −3.8 ± 2.9 210 3.50 (2.94 to 4.06) Hermann et al., 1991a[30] 73.2 ± 9.8 10 76.5 ± 7.3 12 −3.30 (−10.65 to 4.05) Hermann et al., 1991b[31–34] 2.8 ± 3.1 19 −0.8 ± 2.2 19 3.60 (1.89 to 5.31) Tessier et al., 1999[37] 81.5 ± 17.2 18 82.3 ± 11.6 18 −0.80 (−10.38 to 8.78) Tosi et al., 2003[38] 0.8 ± 2.7 20 −2.3 ± 2.4 19 3.10 (1.50 to 4.70) Overall 1741 1756 3.77 (3.06 to 4.47) Heterogeneity: I^2 = 39% <u>Fasting blood glucose level, HbA1c</u> • No significant effect <u>Hypoglycemia:</u> • significantly more patients in the sulfonylurea arm than in the metformin arm had mild hypoglycemia (RR 2.95, 95% CI 2.13 to 4.07) and severe hypoglycemia (RR 5.64, 95% CI 1.22 to 26.00). **A: Mild hypoglycemia** Events, *n/N* Study | Sulfonylurea | Metformin | Relative risk (95% CI) ADOPT 2006[20–26] 549/1447 167/1455 3.31 (2.82–3.87) DeFronzo et al., 1995[29] 6/209 4/210 1.51 (0.43–5.26) Derosa et al., 2004[42] 0/81 0/83 Not estimable Hermann et al., 1991b[31–34] 12/34 8/38 1.68 (0.78–3.61) Tosi et al., 2003[38] 1/22 1/22 1.00 (0.07–15.00) UKPDS 34 1998[2,39,40•] 49/277 15/342 4.03 (2.31–7.03) Overall 617/2070 195/2150 2.95 (2.13–4.07) Heterogeneity: I^2 = 29% **B: Severe hypoglycemia** ADOPT et al., 2006[20–26] 8/1447 1/1455 8.04 (1.01–64.23) Derosa et al., 2004[42] 0/81 0/83 Not estimable Hermann et al., 1991b[31–34] 0/34 0/38 Not estimable Tosi et al., 2003[38] 0/22 0/22 Not estimable UKPDS 34 1998[2,39,40•] 3/277 1/342 3.70 (0.39–35.41) Overall 11/1861 2/1940 5.64 (1.22–26.00) Heterogeneity: I^2 = 0%  **Anmerkungen/Fazit der Autoren:** Some evidence suggests that, compared with metformin, second- and third-generation sulfonylureas may not affect all-cause or cardiovascular mortality but may decrease the risk of nonfatal macrovascular outcomes among patients with type 2 diabetes. They may also increase the risk of hypoglycemia. In general, the available data were too few and inconsistent to provide firm evidence concerning patient-important outcomes in relation to the benefits and harms of sulfonylurea versus metformin monotherapy.
Giugliano, 2011 [45] **Multiple HbA1c targets and insulin analogues in type 2 diabetes: a systematic review**	**Fragestellung:** to assess the role of insulin analogues to reach different hemoglobin A1c (HbA1c) targets (from 6.5% to 8%) in type 2 diabetic patients
	Methodik: Population: type 2 diabetic patients Intervention/Komparator: insulin regimens (basal, prandial, biphasic, and basal-bolus) with insulin analogues Endpunkt: different hemoglobin targets: HbA1c <6.5%, <7.0%, <7.5%, and <8.0%

Suchzeitraum (Aktualität der Recherche): August 2010

Anzahl der eingeschlossenen Studien/Patienten: 53 RCTs (n=32,689)

Qualität der Studien/Risk of bias: Jadad scale

Ergebnisdarstellung:

- Large proportion of studies of low quality (Jadad <3 points) due to lack of blinding (not possible for insulin regimens)
- The proportion of patients at target was highest with the basal-bolus regimen ranging from 27.8% (95% CI, 22.2–34%) for the HbA1c target <6.5% to 88% (CI 83–92%) for the HbA1c target <8%.
- Biphasic insulin regimen ranked second at any HbA1c target, while prandial and basal regimens alternated across different HbA1c targets.

Table 2
Proportions of patients at target with different insulin regimens

HbA1c target	Basal 43 arms n=18,976	Biphasic 28 arms n=9950	Prandial 9 arms n=1605	Basal-bolus 12 arms n=2158
<6.5%	20.8% (18–23.7) I^2=99.2	23.9% (21.4–26.5) I^2=98.5	19.1% (7.5–34.5) I^2=99.7	27.8% (22.2–33.8) I^2=98.6
<7.0%	39.0% (34.1–44.2) I^2=97.8	42.1% (38.9–45.2) I^2=99.6	35.5% (18.1–53.1) I^2=98.5	52.3% (46.4–58.5) I^2=79.9
<7.5%	55.9% (50.8–60.9) I^2=99.6	62.9% 58.5–67.2 I^2=99.8	54.7% (41.2–67.9) I^2=105.4	75.0% (67.7–81.7) I^2=123.4
<8.0%	73.1% (68–77.8) I^2=134.5	78.4% 74.2–82.4 I^2=143.4	75.1% (67.4–82.1) I^2=134.4	87.9% (82.6–92.3) I^2=98.5

Data are as pooled estimates and 95% CI.

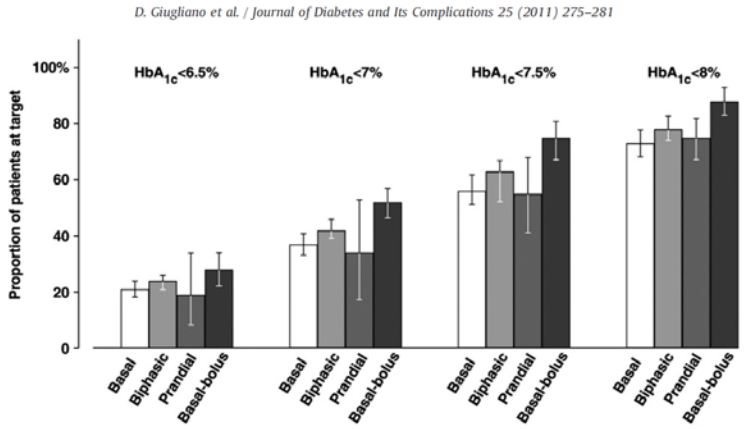
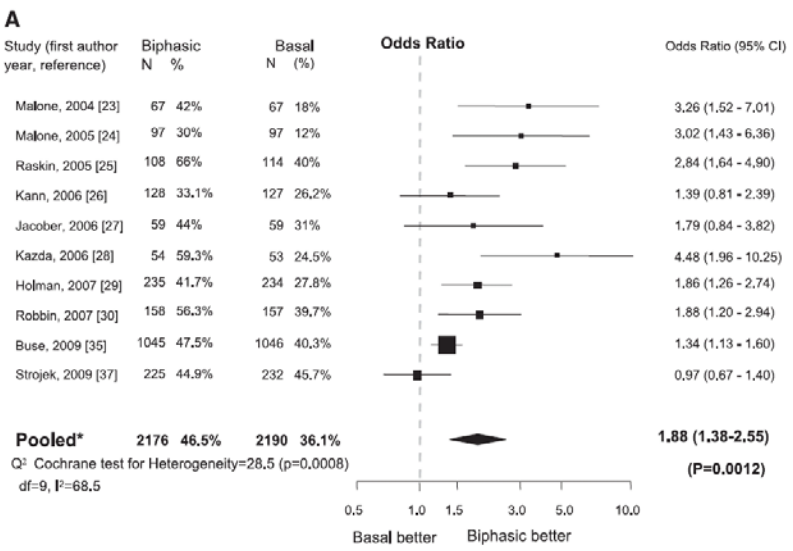
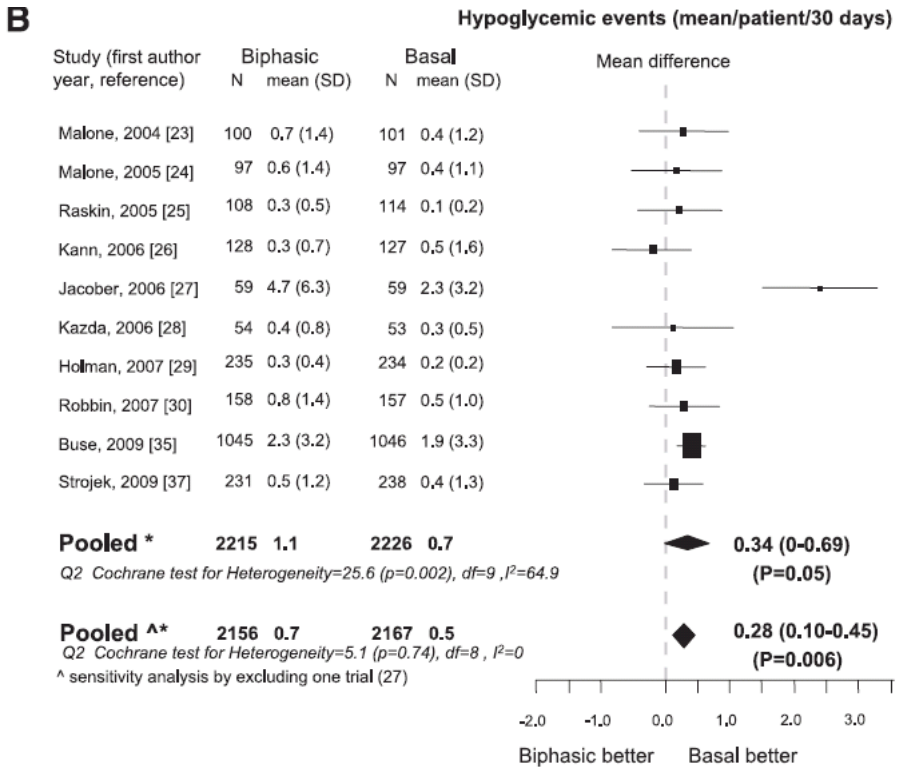


Fig. 2. Proportions of type 2 diabetic patients reaching different HbA1c targets with different insulin regimens. Data are as pooled estimates and 95% CI.

	Anmerkungen/Fazit der Autoren: At any HbA1c target, basal-bolus insulin regimens with insulin analogues obtained the best results, which may be useful for detailing the best treatment effect in individual patients **Anmerkung FB-Med:** Substantial heterogeneity among the studies (although results were qualitatively similar) → source is unclear
Giugliano, 2011 [44] **Efficacy of Insulin Analogs in Achieving the Hemoglobin A1c Target of <7% in Type 2 Diabetes**	**Fragestellung:** Insulin analogs are increasingly used in patients with type 2 diabetes. We compared the effect of basal, biphasic, prandial, and basal-bolus insulin regimens with insulin analogs to reach the hemoglobin A1c (HbA1c) target of <7% in people with type 2 diabetes.
	Methodik: Population: patients with type 2 diabetes Intervention/Komparator: insulin regimens (basal, biphasic, prandial or basal-bolus) using insulin analogs were evaluated • the biphasic regimen consisted of the biphasic (premixed) insulin analogs lispro 25/75, lispro 50/50, aspart 30/70, aspart 50/50, and aspart 70/30, with the numbers denoting the percentage of the rapid-acting/the long-acting component; • the basal regimen consisted of basal insulin analogs comprising the longacting insulins glargine, detemir, and lispro/neutral protamine lispro; • the prandial regimen consisted of prandial insulin analogs, comprising short-acting insulins lispro, aspart, and glulisine; and • the basal-bolus regimen consisted of any combination of prandial and basal insulin analogs. Endpunkt: HbA1c goal of <7% Suchzeitraum (Aktualität der Recherche): 1980 to January 2010 Anzahl der eingeschlossenen Studien/Patienten: 16 RCTs (n=7,759) Qualität der Studien/Risk of bias: Jadad scale
	Ergebnisdarstellung: <u>Proportion of patients with HbA1c <7%</u> A greater proportion of patients achieved the HbA1c goal of <7% with both biphasic (odds ratio 1.88 [95% CI 1.38– 2.55] and prandial (2.07 [1.16–3.69]) insulin compared with basal insulin; this was associated for biphasic insulin with greater hypoglycemia (event/patient/30 days, mean difference, 0.34 [range 0–0.69]) and weight gain in kg (1.0 kg [0.28–1.73]). See Figure: A) HbA1c <7%; B) hypoglycaemic events





Compared with biphasic insulin, the basal-bolus regimen was associated with a greater chance to reach the HbA1c goal (odds ratio 1.75 [95% CI 1.11–2.77]), with no greater hypoglycemia or weight gain.

Anmerkungen/Fazit der Autoren:

The effect of insulin analogs on long-term diabetes complications is still lacking.

A greater proportion of type 2 diabetic patients can achieve the HbA1c goal <7% with biphasic or prandial insulin compared with basal insulin; in absolute terms, the basal bolus regimen was best for the attainment of

	the HbA1c goal.
Esposito, 2011 **[16]** **Insulin analogs and glycosylated hemoglobin target of less than 7% in type 2 diabetes: a systematic review of randomized trials**	**Fragestellung:** Evaluation of effectiveness of insulin regimens with insulin analogs to reach the glycosylated hemoglobin (HbA1c) target of <7% in patients with type 2 diabetes.
	Methodik: Population: Patients with type 2 diabetes Intervention/Komparator: insulin analogs Endpunkt: taget of <7% HbA1c Suchzeitraum (Aktualität der Recherche): September 2010 Anzahl der eingeschlossenen Studien/Patienten: 55 RCTs (n=33,244) Qualität der Studien/Risk of bias: Jadad scale
	Ergebnisdarstellung: TABLE 2. ANALYSIS FOR THE 87 TRIALS WITH 135 ARMS *Insulin regimen* | *Arms* | *N* | *Final HbA1c Median (interquartile)* | *Target: HbA1c <7% pooled (95% CI)* | I^2 | *P value* Basal: 45 | 19447 | 7.25 (7.06–7.44) | 42.5% (36.6%–48.3%) | 95.7% | 0.01 Reported target: 12 | 2168 | 7.83 (7.5–8.10) | 29.8% (18.5%–41.2%) | 94.6% Calculated target: 57 | 21615 | 7.34 (7.1–7.7) | 37.2% (31.5%–43.1%) | 96.1% Pooled Biphasic: 29 | 9792 | 7.3 (7.0–7.53) | 44.9% (39.2%–50.7%) | 89.3% | <0.001 Reported target: 20 | 1832 | 8.1 (7.7–8.3) | 21.2% (14.4%–28.9%) | 89.6% Calculated target: 49 | 11624 | 7.49 (7.1–8.0) | 35.3% (28.9%–42.1%) | 85.7% Pooled Prandial: 9 | 1605 | 7.31 (7.05–7.7) | 39.6% (28.6%–51.3%) | 94.6% | 0.5 Reported target: 4 | 992 | 7.6 (7.05–8.1) | 33.3% (8.4%–65.0%) | 96.8% Calculated target: 13 | 2597 | 7.3 (7.05–7.76) | 37.5% (27.7%–47.9%) | 96.6% Pooled Basal-bolus: 13 | 2400 | 7.0 (6.8–7.1) | 52.2% (42.2%–62.7%) | 92.1% | 0.2 Reported target: 3 | 567 | 7.46 (6.8–7.56) | 45.7% (8.4%–86.3%) | 89.7% Calculated target: 16 | 2967 | 7.02 (6.8–7.25) | 51.2% (41.4%–61.1%) | 93.7% Pooled The I^2 parameter represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance. P value refers to the difference of post-treatment (final) HbA1c values between published and estimated target. HbA1c, glycosylated hemoglobin; CI, confidence interval. The proportion of patients at target (HbA1c <7%) was 37.2% [95% confidence interval (CI), 31.5-43.1%] with basal insulin, 35.3% (28.9-42.1%) with biphasic insulin, 37.5% (27.7-47.9%) with prandial insulin, and 51.2% (41.4-61.1%) for basal-bolus insulin, with high heterogeneity (I(2) >80% for all).
	Anmerkungen/Fazit der Autoren: The HbA1c target <7% can be achieved in a proportion of patients ranging from 35% to 51%, depending on the particular insulin regimen. At least one half of patients with type 2 diabetes receiving insulin analogs do not reach the HbA1c target.
Gerrald, 2012 [43] **Saxagliptin and sitagliptin in adult patients with type 2 diabetes: a**	**Fragestellung:** To compare efficacy and safety of sitagliptin and saxagliptin with placebo and other hypoglycaemic medications in adults with type 2 diabetes
	Methodik:

systematic review and meta-analysis	Population: patients with type 2 diabetes Intervention/Komparator: sitagliptin or saxagliptin in FDA approved doses vs. other diabetes mediations or placebo Endpunkt: HbA1c, weight change, lipid concentrations Suchzeitraum (Aktualität der Recherche): from inception to 3 Feb 2011 Anzahl der eingeschlossenen Studien/Patienten: 32 articles (n=12,944) Qualität der Studien/Risk of bias: criteria based on the US Preventive Serivice Task Force and National Health Service Centre for Reviews and Dissemination
	Ergebnisdarstellung: 2 studies of good, remaining of fair quality **Mean change of HbA1c** *Sitagliptin vs. placebo, monotherapy* Mean difference: -0.824 (-0.948 to -0.700) *Sitagliptin vs. placebo, add on* Mean difference: -0.560 (-0.767 to -0.352) *Saxagliptin vs. placebo, monotherapy* Mean difference: -0.562 (-0.699 to -0.424) *Saxagliptin vs. placebo, add on* Mean difference: -0.710 (-0.805 to -0.614) **Mean body weight change** *Sitagliptin vs. placebo, monotherapy* Mean difference: 0.645 (0.442 to 0.847)
	Anmerkungen/Fazit der Autoren: Sitagliptin and saxagliptin result in a similar modest HbA1c reductions and do not increase the risk of hypoglyceamia unless combined with other therapies.
Gamble, 2015 [17] **Incretin-based medications for type 2 diabetes: an overview**	**Fragestellung:** To summarize evidence from and assess the quality of published systematic reviews evaluating the safety, efficacy and effectiveness of incretin-based medications used in the treatment of type 2 diabetes
	Methodik:

of reviews	Population: patients with type 2 diabetes Intervention/Komparator: glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide,liraglutide or lixisenatide) or dipeptidyl-peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin or alogliptin) Endpunkt: glycaemic control (HbA1c), fasting plasma glucose and proportion achieving a target value], macrovascular complications (i.e. cardiovascularmortality, non-fatal and fatalmyocardial infarction, fatal and non-fatal stroke), microvascular complications (i.e. renal disease, neuropathy and retinopathy) and hypoglycaemia. Secondary outcomes included all-cause mortality, quality of life, weight change, cancer, pancreatitis, infections, hypersensitivity reactions, gastrointestinal adverse effects, blood pressure control and lipid control Suchzeitraum (Aktualität der Recherche): until 31 October 2013 Anzahl der eingeschlossenen Studien/Patienten: 84 systematic reviews; 51 reviews that evaluated GLP-1 receptor agonists and 64 reviews that evaluated DPP-4 inhibitors Qualität der Studien/Risk of bias: AMSTAR
	Ergebnisdarstellung: • majority of reviews being of low or moderate quality *Glycemic control:* • no clinically significant reductions in HbA1c were observed in high-quality systematic reviews • GLP-1 receptor agonists reduced HbA1c compared with placebo (11 WMD estimates, minimum WMD −0.72, maximum WMD −1.26) and metformin (WMD −0.75, −0.96 to −0.54), but did not reduce HbA1c compared with insulin. • Pooled estimates from six systematic reviews found that GLP-1 receptor agonists significantly reduced HbA1c compared with DPP-4 inhibitors (n=8 pooled estimated, minimum WMD −0.4, maximum WMD −0.6, all p values <0.05).

Intervention: DPP-4 Inhibitors and GLP-1 Receptor Agonists
Outcome: Change in HbA1c

Systematic Review Author, Year	Comparator	Number of Studies Meta-Analyzed	Weighted Mean Difference (95% CI)	AMSTAR Score
DPP-4 Inhibitor				
CADTH, 2010	Metformin	6	-0.78 (-0.96, -0.60)	11
CADTH, 2010	Sulfonylureas	2	0.05 (-0.04, 0.14)	11
CADTH, 2010	Thiazolidinediones	2	-0.10 (-0.16, -0.04)	11
Sitagliptin, 100 mg				
Jonas, 2011	Placebo	7	-0.79 (-0.92, -0.66)	9
Norris, 2008	Placebo	5	-0.81 (-0.94, -0.68)	9
GLP-1 Receptor Agonist				
Gross, 2011	Placebo	2	-1.04 (-1.23, -0.85)	9
CADTH, 2010	Insulin	2	-0.01 (-0.27, 0.25)	11
Gross, 2011	Insulin	3	0.10 (-0.25, 0.45)	9
CADTH, 2010	Metformin	4	-0.75 (-0.96, -0.54)	11
Exenatide, 5 mcg				
Jonas, 2011	Placebo	5	-0.72 (-0.99, -0.45)	9
Norris, 2008	Placebo	3	-0.59 (-0.78, -0.40)	9
Exenatide, 10 mcg				
Jonas, 2011	Placebo	8	-0.90 (-1.07, -0.73)	9
Norris, 2008	Placebo	4	-0.97 (-1.15, -0.79)	9
Shyangdan, 2011	Exenatide 2 mg	2	0.55 (0.26, 0.84)	10
Liraglutide, 0.6 mg				
Jonas, 2011	Placebo	4	-1.10 (-1.45, -0.75)	9
Liraglutide, 1.2 mg				
Shyangdan, 2011	Placebo	3	-1.15 (-1.33, -0.97)	10
Jonas, 2011	Placebo	4	-1.28 (-1.56, -1.00)	9
Shyangdan, 2011	Liraglutide 1.8 mg	4	0.10 (-0.03, 0.23)	10
Liraglutide, 1.8 mg				
Shyangdan, 2011	Placebo	4	-1.15 (-1.31, -0.99)	10
Jonas, 2011	Placebo	5	-1.26 (-1.49, -1.03)	9
Taspoglutide, 20 mg				
Shyangdan, 2011	Placebo	2	-0.87 (-1.16, -0.58)	10

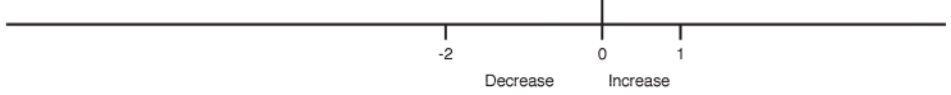


Figure 2. Results from high-quality quantitative systematic reviews for weighted mean differences in glycated haemoglobin (HbA1c) between dipeptidyl-peptidase-4 (DPP-4) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists and comparators. AMSTAR, Assessment of Multiple Systematic Reviews; CADTH, Canadian Agency for Drugs and Technologies in Health.

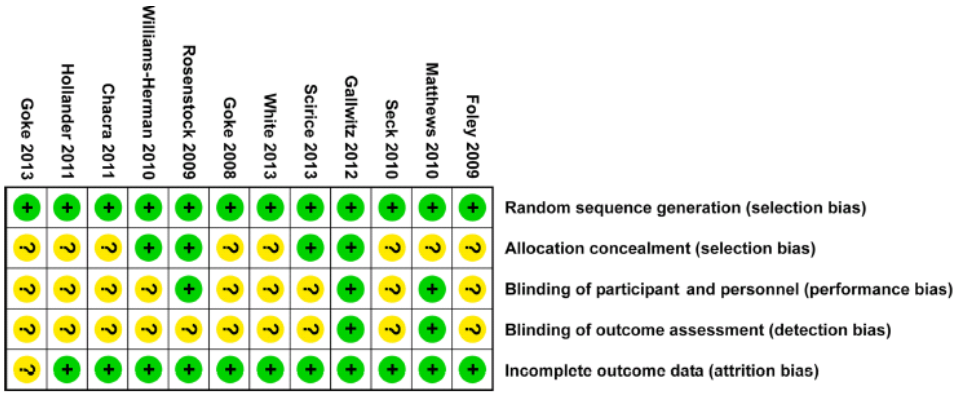
- incretin-based medications were not associated with a clinically significant risk of hypoglycaemia compared with placebo or active comparators
    - In fact, compared with sulphonylureas and insulin, two agents known to increase the risk of hypoglycaemia, incretin-based medications were associated with a reduced risk of hypoglycaemia.
- Third, our findings also confirm the well-known gastrointestinal adverse effects of incretin-based medications, notably GLP-1 receptor agonists which have a two-to-threefold increased risk of nausea and diarrhoea, and a three-to-fourfold increased risk of vomiting compared with placebo

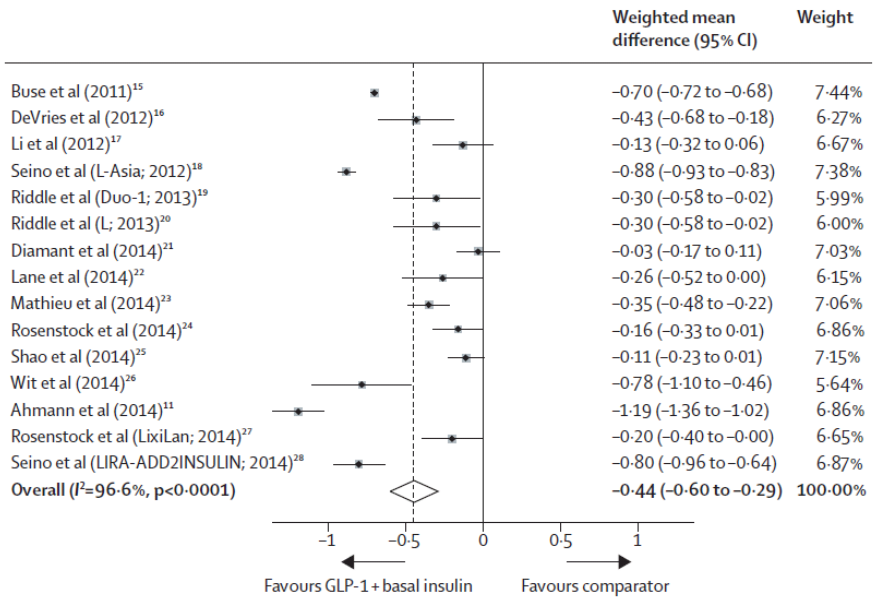
Anmerkungen/Fazit der Autoren:

The evidence to date does not suggest any definitive benefits of incretin-based medications, beyond glucose-lowering, for patients with type 2 diabetes.

Esposito, 2014

Fragestellung:

[15] **Glycaemic durability with dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials**	To evaluate glycaemic durability with dipeptidyl peptidase-4 (DPP-4) inhibitors in type 2 diabetes.
	Methodik: Population: adults with type 2 diabetes Intervention/Komparator: Any DPP-4 inhibitor (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) vs. Endpunkt: difference in HbA1c between final and intermediate points Suchzeitraum (Aktualität der Recherche): December 2013 Anzahl der eingeschlossenen Studien/Patienten: 12 studies (n= 14,829) Qualität der Studien/Risk of bias: Cochrane Collaboration's tool to assess risk of bias
	Ergebnisdarstellung:  The difference in HbA1c changes between final and intermediate points averaged 0.22% (95% CI 0.15% to 0.29%), with high heterogeneity (I2=91%, p<0.0001). Estimates of differences were not affected by the analysis of six extension trials (0.24%, 0.02 to 0.46), or five trials in which a DPP-4 inhibitor was added to metformin (0.24%, 0.16 to 0.32).
	Anmerkungen/Fazit der Autoren: There is evidence that the effect of DPP-4 inhibitors on HbA1c in type 2 diabetes significantly declines during the second year of treatment. **Anmerkung FB-Med:** Hohe Heterogenität, die nicht erklärbar ist und auch in Sensitivitätsanalysen sichtbar war.
Eng, 2014 **[14]** **Glucagon-like**	**Fragestellung:** to assess the effect of Combination treatment with a glucagon-like peptide-1 (GLP-1) agonist and basal insulin on glycaemic control, hypoglycaemia, and weight gain in patients with type 2 diabetes

peptide-1 receptor agonist and basal insulin combination tre atment for the management of type 2 diabetes: a systematic review and meta-analysis	**Methodik:** Population: adults with type 2 diabetes Intervention/Komparator: GLP-1 agonist and basal insulin combination treatment versus another treatment strategy Endpunkt: changes in glycated haemoglobin (HbA1c); proportion of participants with an HbA1c of 7.0% or lower at the end of the intervention period; number of participants with any hypoglycaemic episode Suchzeitraum (Aktualität der Recherche): Jan 1, 1950, and July 29, 2014 Anzahl der eingeschlossenen Studien/Patienten: 15 studies (N=4348) Qualität der Studien/Risk of bias: by two reviewer according to PRISMA
	Ergebnisdarstellung: All 15 randomised controlled trials reported adequate randomisation, none was stopped early, and 12 were multicentre. However, eight studies did not specify whether data collectors and outcome assessors were masked to treatment allocation and only two were not funded by industry.(more specific information in Appendix) *<u>Comparison between other anti-diabetic treatments and GLP-1 agonist and basal insulin combination:</u>* **HbA1c:** A  Compared with other anti-diabetic treatments, GLP-1 agonist and basal insulin combination treatment yielded an improved mean reduction in glycated haemoglobin (HbA1c) of –0.44% (95% CI –0.60 to –0.29), an improved likelihood of achieving the target HbA1c of 7.0% or lower

(relative risk [RR] 1.92; 95% CI 1.43 to 2.56),

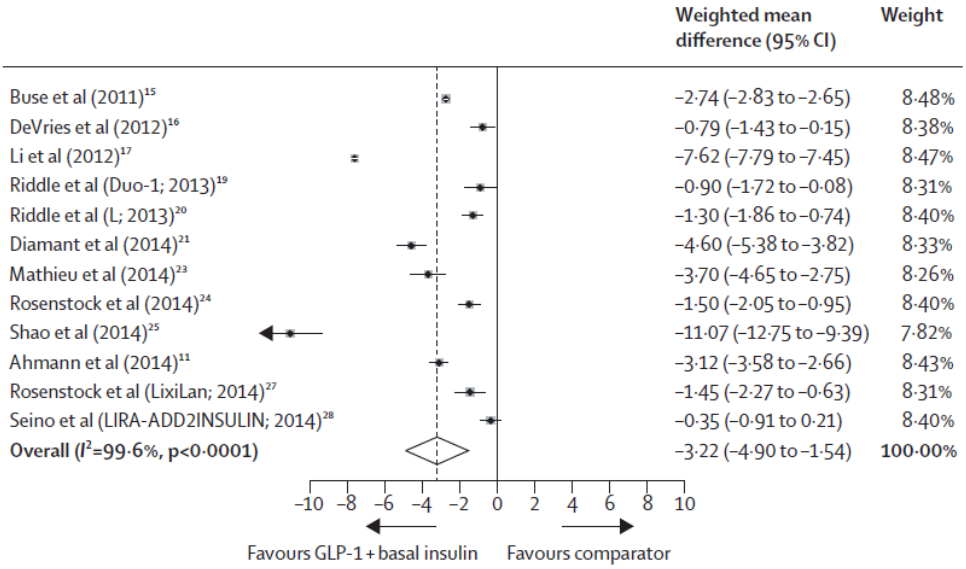
Hypoglycemia

Compared with other anti-diabetic treatments, GLP-1 agonist and basal insulin combination treatment yielded no increased relative risk of hypoglycaemia (0.99; 0.76 to 1.29)

Body weight

mean reduction in weight of –3.22 kg (–4.90 to –1.54) in favour for GLP-1 agonist and basal insulin combination

C

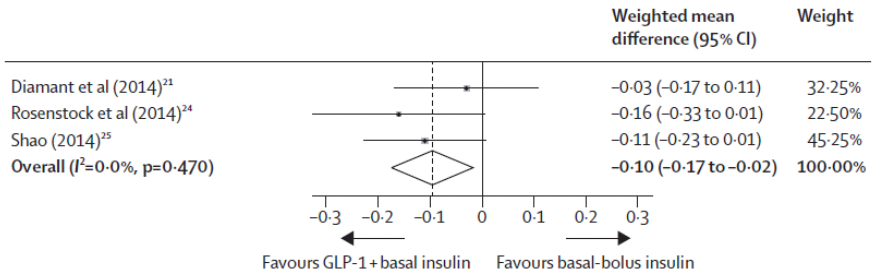


Comparison between other basal insulin regimens and GLP-1 agonist and basal insulin combination

HbA1c

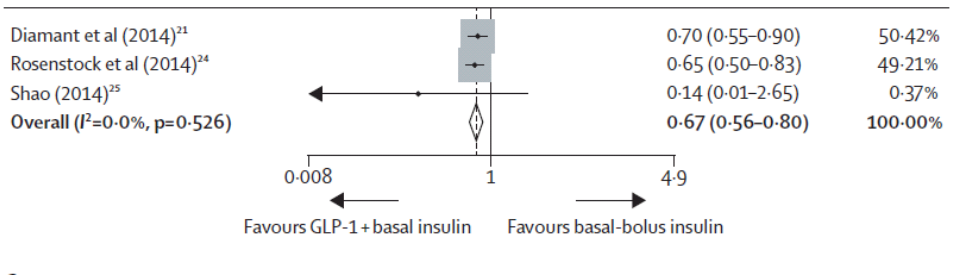
Significant reduction ob HbA1c of –0.1% (–0.17 to –0.02) in favour for GLP-1 agonist and basal insulin,

B



Hypoglycemia:

lower relative risk of hypoglycaemia (0.67, 0.56 to 0.80) in favour for GLP-1 agonist and basal insulin

	B  **Body weight:** reduction in mean weight (–5.66 kg; –9.8 to –1.51) in favour for GLP-1 agonist
	Anmerkungen/Fazit der Autoren: GLP-1 agonist and basal insulin combination treatment can enable achievement of the ideal trifecta in diabetic treatment: robust glycaemic control with no increased hypoglycaemia or weight gain. This combination is thus a potential therapeutic strategy that could improve the management of patients with type 2 diabetes
Craddy, 2014 **[12]** **Comparative Effectiveness of Dipeptidylpeptidase-4 Inhibitors in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison**	**Fragestellung:** To compare the safety and efficacy of the dipeptidylpeptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes and inadequate glycemic control.
	Methodik: Population: patients of any age or sex with type 2 diabetes and insufficient glycemic control (including first-, second-, and thirdline treatment regimens) Intervention: any DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin), GLP-1 or sodium-glucose cotransporter 2 inhibitors, or pioglitazone used in the treatment of type 2 diabetes (as monotherapy, dual or triple therapy) Komparator: any pharmacologic antidiabetic treatment, placebo, or standard of care for diabetes. Endpunkt: HbA1c (mean change from baseline and proportion of patients achieving HbA1c target), fasting plasma glucose (FPG), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body weight, and hypoglycemia and serious adverse events Suchzeitraum (Aktualität der Recherche): November 30, 2012 Anzahl der eingeschlossenen Studien/Patienten: 85 publications from 83 RCTs (n=not reported) Qualität der Studien/Risk of bias: according to the methods and assessment instruments recommended by the HTA authorities in France, Germany, Italy, Spain, UK, USA, and Canada

	Ergebnisdarstellung: • Majority of included studies with moderate to low quality: risk of bias! • MTCs (mixed treatment comparison) demonstrated no differences between DPP-4 inhibitors in mean change from baseline in glycosylated hemoglobin (HbA1c) or body weight, or the proportions of patients achieving HbA1c <7% or experiencing a hypoglycemic event • patients on alogliptin plus metformin, who achieved HbA1c <7% more frequently than those treated with saxagliptin plus metformin [OR 6.41 (95% CI 3.15–11.98) versus 2.17 (95% CI 1.56–2.95)].
	Anmerkungen/Fazit der Autoren: This systematic review and MTC showed similar efficacy and safety for DPP-4 inhibitors as treatment for type 2 diabetes, either as monotherapy or combination therapy.
Amate et al. 2015 [1] **Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: systematic review and meta-analysis**	**Fragestellung:** Our review analyses the studies that have specifically compared the association iDPP4/metformin with glimepiride/metformin, both in second line pharmacotherapy of type 2 diabetes mellitus (DM2).
	Methodik: Population: patients with type 2 diabetes Intervention/Komparator: glimepiride versus any iDPP4 both used together with metfpomin Endpunkte: %HbA1c variation, fasting plasma glucose variation, patients achieving the therapeutic objective of HbA1c <7%, treatment dropouts due to lack of effectiveness and rescue treatments needed; safety endpoints: variables included were as follows: weight variation at the end of treatment; presentation of any type of adverse event; presentation of serious adverse events; patients who experienced any type of hypoglycaemia; patients who experienced severe hypoglycaemia; treatments suspended due to adverse effects; and deaths for any reason Suchzeitraum (Aktualität der Recherche): Cochrane libarary database, Medline via Pubmed until 31 December 2013 Anzahl der eingeschlossenen Studien/Patienten: 6 articles (n=5,637 patients) Qualität der Studien/Risk of bias: Cochrane risk of bias tool
	Ergebnisdarstellung:

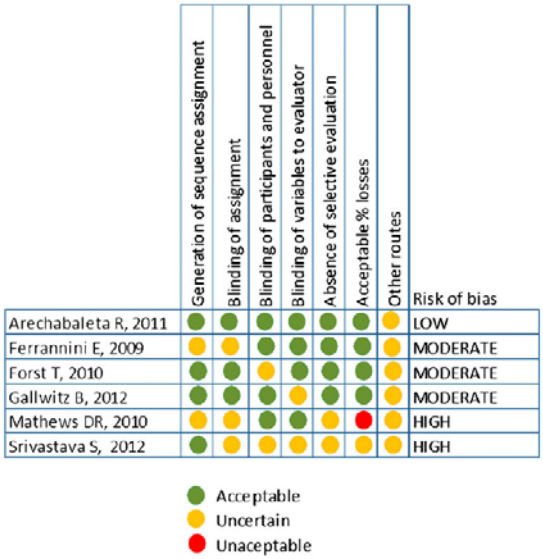


Figure 2 Assessment of the methodological quality of studies

Effectiveness

Reduction in HbA1c levels: (4 trials)

- Patients treated with glimepiride have a 12% greater reduction compared with those treated with iDPP4, WMD –0.12 (CI: -0.16, -0.07)

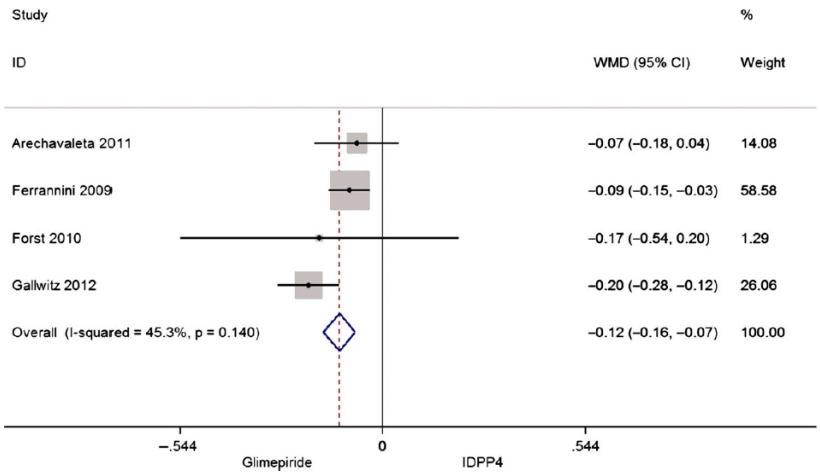


Figure 3 Meta-analysis of HbA1c (%) reduction after treatment

Proportion of patients achieving the objective of HbA1c < 7%: (3 trials)

- meta-analysis shows a favourable result for glimepiride versus IDDP4, OR: 1.14 (CI: 1.01, 1.28; I2 = 13.5%).

FPG (fasting plasma glucose) variation

- glimepiride/metformin produces a reduction 0.21 mmol/l greater than with iDPP4/metformin (I^2 = 17.4%).

Dropouts because of lack of effectiveness

- there are significantly fewer dropouts, 50%, in the glimepiride group compared with the iDPP4 group

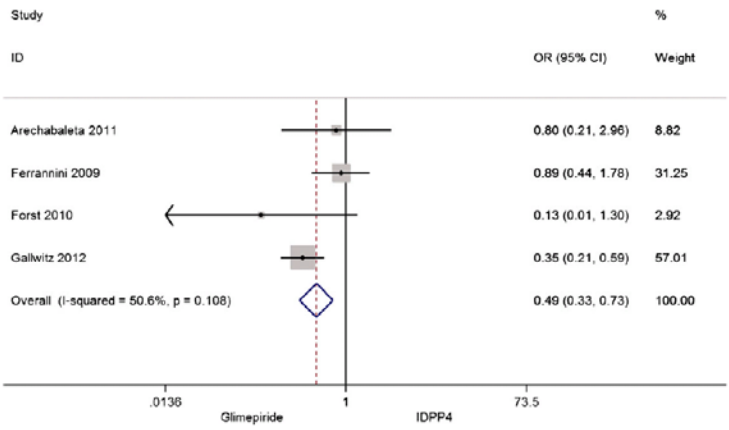


Figure 4 Risk of dropout because of the lack of effectiveness

Need for rescue treatments (2 trials)

- in the group treated with glimepiride/metformin, the risk of needing rescue treatments is 20% less than in the iDPP4/metformin group (OR: 0.80, 95% CI: 0.65, 0.99; I2 = 0.0%).

<u>Safety</u>

Weight variation

- The greatest weight reduction, that corresponds to a difference of 1.63% from the basal level, is seen with the treatment of linagliptine after 104 weeks, while the greatest increase, which is 1.76% compared with the basal weight, is observed after 52 weeks of treatment with glimepiride.
- The overall difference between the increase in weight experienced in the groups treated with glimepiride and the decrease in weight observed in those treated with iDPP4 is 2.1 kg (95% CI: 1.78, 2.24; I2 = 74.3%).

Hypoglycaemia (4 trials):

- patients treated with glimepiride: there are more cases of patients suffering from hypoglycaemia than in those treated with IDPP4: OR: 5.07 (95% CI: 4.33, 5.93; I2 = 59.2%)

Discontinuation caused by adverse events (4 trials):

- greater proportion in the group treated with glimepiride, OR: 1.45 (95% CI: 1.17, 1.81; I2 = 69.2%).

Deaths for any reason

- The combined analysis does not show any difference

Anmerkungen/Fazit der Autoren:

	A greater effectiveness is seen in the glimepiride/metformin association, which should not be diminished by slight differences in adverse effects, with absence of severe hypoglycaemia in over 98% of patients under treatment.
Mearns, 2015 **[81]** **Comparative Efficacy and Safety of Antidiabetic Drug Regimens Added to Metformin Monotherapy in Patients with Type 2 Diabetes: A Network Meta-Analysis**	**Fragestellung** We performed a NMA (Network meta-analysis) to assess the comparative efficacy and safety of adjunctive antidiabetic medication therapies in patients with Type 2 DM not adequately controlled on stable and optimized metformin monotherapy.
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: non-insulin and long-acting, once-daily basal insulin agents (as a single or combination adjunctive therapy) to another antidiabetic therapy or placebo (in addition to metformin) Endpunkt: Change in HbA1c; Body Weight; Urinary and Genital Tract Infection; Systolic Blood Pressure; Confirmed Hypoglycemia Suchzeitraum: Systematische Literaturrecherche bis Mai 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 62 RCTs (n = 32,185 participants) Quality Assessment/Risk of bias: Cochrane Risk of Bias Tool → The overall quality of RCTs was rated as good to unclear with the majority of studies having few domains with a high risk of bias

Figure S2. Risk of Bias Assessment of Randomized Controlled Trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting	Other bias
Defronzo 2014	?	?	?	?	+	+	-
Bolli 2014	?	?	+	?	?	+	+
Derosa 2014	+	+	+	?	-	-	?
Haring 2014	+	+	?	?	+	+	+
Nauck 2014	?	?	+	?	+	-	-
Ridderstrale 2014	+	+	+	?	-	+	+
White 2014	+	+	+	?	+	+	-
Charbonnel 2013	+	+	-	?	?	+	+
Chawla 2013	+	?	?	?	-	-	-
Cefalu 2013	+	+	+	+	+	+	-
Derosa 2013	+	+	+	?	?	+	+
Lavalle-Gonzalez 2013	+	+	+	+	+	+	-
Rosenstock 2013	+	+	+	?	+	+	-
Rosenstock 2013b	?	+	-	?	+	+	+
Aschner 2012	+	+	-	?	?	+	-
Bergenstal 2012	+	+	?	+	-	-	+
DeFronzo 2012	?	?	+	?	-	-	-
Derosa 2012	?	+	+	?	+	+	+
Derosa 2012b	?	+	+	?	+	-	+
Gallwitz 2012	+	+	-	?	-	+	?
Gallwitz 2012b	+	+	+	+	-	+	-
Ljunggren 2012	+	+	+	+	+	+	+
Pan 2012	?	?	?	?	+	+	-
Rizzo 2012	?	?	-	+	+	-	-
Rosenstock 2012	?	?	?	?	+	+	+
Ross 2012	+	+	+	+	+	+	+
Arechavaleta 2011	+	+	+	?	+	+	+
Nauck 2011	+	+	+	?	-	+	-
Pfützner 2011	?	?	?	?	+	+	+
Taskinen 2011	?	?	?	?	+	+	+
Wang 2011	+	-	-	?	?	-	-
Yang 2011	+	?	+	?	+	+	-
Bailey 2010	+	+	+	+	+	+	-
Filozof 2010	?	?	+	?	+	-	-
Goke 2010	+	+	+	?	-	+	-
Pratley 2010	+	+	-	+	-	+	+
Rigby 2010	?	?	-	?	-	-	-
Scheen 2010	?	?	+	?	+	+	-
DeFronzo 2009	+	+	+	?	-	+	-
Ferrannini 2009	?	?	+	?	-	+	-
Goodman 2009	?	?	?	?	+	+	+
Nauck 2009	+	+	?	?	-	+	+
Nauck 2009b	+	+	+	?	-	+	+
Hamann 2008	+	+	+	?	-	+	+
Khanolkar 2008	?	?	-	?	+	-	-
Raz 2008	+	?	?	?	+	+	-
Scott 2008	?	?	?	?	+	+	-
Bosi 2007	?	?	?	?	+	+	-
Nauck 2007	?	?	?	?	+	+	-
Ristic 2006	+	+	+	?	+	+	-
DeFronzo 2005	?	?	+	?	+	+	+
Feinglos 2005	?	?	?	?	+	+	+
Matthews 2005	?	?	+	?	+	+	+
Ahren 2004	?	?	?	?	+	+	+
Gomez-Perez 2002	?	?	?	?	-	+	-
Marre 2002	+	+	+	?	+	+	-
Charpentier 2001	+	+	+	?	+	+	-
Van 2001	+	?	+	?	-	+	+
Halimi 2000	?	?	?	?	+	-	-
Fonseca 2000	+	?	+	+	+	+	-
Moses 1999	?	?	?	?	+	+	+
Rosenstock 1998	?	?	?	?	-	+	+

Ergebnisdarstellung

Change in HbA1c

<u>SGLT2 Inhibitors</u>

- Similar effects on reducing HbA1c when compared to placebo (ranging from 0.48% for dapagliflozin to 0.72% for canagliflozin).
- Compared to the other active single agents, canagliflozin was associated with statistically significant reductions in HbA1c compared with dapagliflozin, nateglinide and saxagliptin; and empagliflozin was

	significantly more efficacious compared to dapagliflozin and saxagliptin. • Dapagliflozin was inferior in reducing HbA1c when compared to 11 (50%) of the other active single agents • all SGLT-2 inhibitors were found to be clinically sig. superior to placebo (lower bound of the 95%CI depicted an HbA1c reduction greater than 0.3%) • none of the SGLT2 inhibitors were clinically superior in reducing HbA1c to any other active agents analyzed. <u>Combination Agents.</u> • Combination agents were associated with significant reductions in HbA1c when compared to placebo (alogliptin/pioglitazone: 1.24, 95% CI: 1.02–1.45%; empagliflozin/linagliptin: 1.13%, 95% CI: 0.92–1.34%). • Alogliptin/pioglitazone significantly reduced HbA1c when compared to all other therapies except for insulin glargine, glibenclamide and repaglinide; • Empagliflozin/linagliptin was more efficacious when compared to all other active single agents except for insulin glargine, glibenclamide, repaglinide and acarbose. • In terms of clinical superiority (lower bound of the 95%CI depicted an HbA1c reduction greater than 0.3%) alogliptin/pioglitazone and empagliflozin/linagliptin were clinically superior to 52% and 24% of the other antidiabetic medications analyzed, respectively. Alogliptin/pioglitazone was clinically superior to all DPP-4 inhibitors, colesevelam, dapagliflozin, glipizide, lixisenatide, miglitol, nataglinide, empagliflozin and pioglitazone. • Empagliflozin/linagliptin was clinically superior to canagliflozin, dapagliflozin, glipizide, miglitol, nateglinide and saxagliptin. <u>All Other Agents</u> • All antidiabetic agents were associated with statistically significant reductions in HbA1c relative to placebo, ranging from 0.43% for miglitol to 1.29% for glibenclamide • Exenatide showed significant reductions in HbA1c when compared to the DPP-4 inhibitors, lixisenatide, miglitol, nateglinide, glipizide and dapagliflozin. **Body Weight** <u>SGLT2 Inhibitors</u> • All SGLT2 inhibitors were associated with significant weight loss when compared to placebo (range: 2.08–2.17 kg)

	• SGLT2 inhibitors were associated with statistically greater weight loss compared to allother agents analyzed except GLP-1 analogs, empagliflozin/ linagliptin and miglitol. <u>Combination Agents</u> • empagliflozin/linagliptin was associated with significant weight loss compared to all other agents except SGLT-2 inhibitors, and GLP-1 analogs. • In terms of clinically superior weight gain, (lower bound of the 95%CI depicted a decrease in weight less than 2.3 kg), alogliptin/pioglitazone was associated with clinically superior weight gain compared to SGLT2 inhibitors, empagliflozin/linagliptin, GLP-1 analogs, and miglitol (range: 3.54–4.65 kg). <u>All Other Agents</u> • GLP-1 analogs and miglitol were associated with significant weight loss (range: 1.15–2.26 kg) but there was no weight change with acarbose, any DPP-4 inhibitor, colesevelam and nateglinide when compared to placebo. • When comparing active agents, GLP-1 analogs were associated with statistically greater weight loss when compared to all other agents except SGLT2 inhibitors and miglitol. While several agents exhibited statistically significant weight loss, no agent demonstrated clinically superior weight loss compared to placebo (lower bound of the 95%CI depicted a decrease in weight less than 2.3 kg). • When comparing the clinical superiority of single active agents, TZDs were associated with clinically superior weight gain when compared to GLP-1 analogs (range: 3.22–4.41 kg). **Systolic Blood Pressure** <u>SGLT2 Inhibitors</u> • All SGLT2 inhibitors were associated with a decrease in SBP compared with placebo in the NMA (range: 4.14–5.14 mmHg. When comparing active agents, SGLT2 inhibitors significantly reduced SBP when compared to the SUs (glimepiride, glipizide) (range: 4.4–5.64 mmHg), and saxagliptin and sitagliptin (range: 2.26–5.79 mmHg) • No SGLT2 inhibitor showed clinical superiority (lower bound of the 95%CIs depicted a decrease in SBP less than 5 mmHg) compared to placebo or another active agent. <u>Combination Agents</u> • Empagliflozin/linagliptin was associated with a decrease in SBP when compared with placebo in the NMA (5.43 mmHg, 95% CI: 2.47–8.39 mmHg). In head to head comparisons, empagliflozin/linagliptin significantly reduced SBP when compared to SUs, linagliptin, saxagliptin and sitagliptin; however it did not show clinical superiority

	compared to any other active agents. There were no data to evaluate alogliptin/pioglitazone for this endpoint. All Other Agents. • Liraglutide (3.04 mmHg, 95% CI: 1.03–5.05 mmHg) and sitagliptin (1.88 mmHg, 95% CI: 0.38–3.38 mmHg) were associated with a decrease in SBP compared with placebo. No medication showed clinical superiority (lower bound of the 95%CIs depicted a decrease in SBP less than 5 mmHg) compared to placebo or another active agent; however, there were no data to evaluate 12 (48%) of the agents for this endpoint. **Confirmed Hypoglycemia** SGLT2 Inhibitors • Upon NMA, the SGLT2 inhibitors were not associated with an increased risk of confirmed hypoglycemia compared with placebo. In the active drug comparisons, insulin glargine, nateglinide and all SUs were associated with significantly higher rates of confirmed hypoglycemia compared to any SGLT2 inhibitor (RR range, 4.14–22.93). Combination Agents • Empagliflozin/linagliptin was not associated with increased risk of hypoglycemia compared with placebo in the NMA (0.38, 95% CI: 0.06–2.34). In the active drug comparisons, insulin glargine, nateglinide, both meglitinides and all SUs were associated with significantly higher rates of confirmed hypoglycemia compared to empagliflozin/linagliptin (RR range, 10.54–49.88). There were no data to evaluate alogliptin/pioglitazone for this endpoint. All Other Agents • All GLP-1 analogs, DPP-4 inhibitors, TZDs, repaglinide and acarbose were not associated with an increased risk of confirmed hypoglycemia compared with placebo. • In the active drug comparisons, insulin glargine and all SUs were associated with significantly higher rates of confirmed hypoglycemia compared to any SGLT2 or DPP-4 inhibitor (RR range, 4.32–71.29). There were no data to evaluate glibenclamide, colesevelam and miglitol for this endpoint. **Urinary and Genital Tract Infection** • NMA suggested canagliflozin and empagliflozin were associated with an increased risk of GTI when compared with placebo; with dapagliflozin (RR 2.16, 95% CI 0.97–4.82) trending towards an increased risk versus placebo. However, only 10 identified RCTs evaluating 8 of 25 agents reported GTI data

	Anmerkungen/Fazit der Autoren • Our HbA1c results showed both statistical differences and clinical superiority between antidiabetic therapies. • All therapies significantly reduced HbA1c, but to differing degrees when compared to placebo. Combination therapies (empagliflozin/linagliptin and alogliptin/pioglitazone) and insulin glargine were statistically and clinically superior in reducing HbA1c compared to a majority of other antidiabetic agents. • As a class, the SGLT2 inhibitors were similar in efficacy to other non-insulin monotherapies recommended by the ADA as add-ons to metformin, which warrants an update to clinical practice guidelines to include them as a treatment option. • The newest class of antidiabetic agents, the SGLT2 inhibitors, was found to provide similar HbA1c efficacy to other non-insulin monotherapies (albeit not oral combination therapies) with the added benefits of weight loss, reduced SBP and a low risk of hypoglycemia; but at a cost of an increased risk of GTI. • Combination therapies resulted in some of the largest reductions in HbA1c and may be appropriate for patients requiring profound (>1%) HbA1c reductions after failing optimized metformin.
Patil,2012 **[88]** **Meta-Analysis of Effect of Dipeptidyl Peptidase-4 Inhibitors on Cardiovascular Risk in Type 2 Diabetes Mellitus**	**Fragestellung** The aim of this meta-analysis was to determine the effects of DPP4 inhibitors on CV events by analyzing all relevant randomized controlled trials (RCTs) of patients with type 2 DM treated with DPP4 inhibitor monotherapy versus other oral hypoglycemic agents or placebo.
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: DPP4 inhibitor monotherapy versus other oral hypoglycemic agents or placebo Endpunkt: adverse CV side effects (death from CV causes, nonfatal myocardial infarction or acute coronary syndrome, stroke, heart failure, and arrhythmias Suchzeitraum: Systematische Literaturrecherche 1980 to September 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 18 RCTs (8,544 patients → (4,998 randomized to a DPP4 inhibitor and 3,546 to placebo) Quality Assessment/Risk of bias: Jadad criteria (Overall, included studies were of adequate methodologic quality (mean Jadad score 3.5 for included studies, 14 of 20 studies had a score ≥ 3).

Studies included for meta-analysis with basic characteristics of enrolled patients and details about drug therapy in dipeptidyl peptidase-4 inhibitor and comparator arms

Study	Region	Mean Age (years)	Men	DPP4 Inhibitor	Dose (mg)	Comparator	Duration (weeks)	Study Size	Follow-Up (person-years)	Jada Scor
Bosi et al[14]	multiregional	53	59%	vildagliptin	50	metformin	24	1,179	28,296	2
DeFronzo et al[12]	multiregional	53	53%	alogliptin	12.5, 25	placebo	26	329	8,554	5
Pfützner et al[10]	multiregional	52	50%	saxagliptin	10	metformin	76	1,306	99,256	4
Williams-Herman et al[4]	multiregional	54	50%	sitagliptin	100	metformin	104	1,091	113,464	5
Aschner et al[13]	multiregional	56	48%	sitagliptin	100	metformin	24	1,050	25,200	5
Foley and Sreenan[11]	multiregional	55	59%	vildagliptin	50	sulfonylureas	104	1,092	113,568	4
Rosenstock et al[8]	multiregional	53	51%	saxagliptin	2.5, 5, 10	placebo	24	401	9,624	5
Schweizer et al[6]	multiregional	71	48%	vildagliptin	100	metformin	24	335	8,040	4
Chan et al[15]	multiregional	69	48%	sitagliptin	25, 50, 100	sulfonylureas	54	91	4,914	4
Schweizer et al[5]	multiregional	53	54%	vildagliptin	100	metformin	52	780	40,560	3
Pi-Sunyer et al[9]	multiregional	51	56%	vildagliptin	50, 100	placebo	24	354	8,496	3
Rosenstock et al[7]	multiregional	54	55%	vildagliptin	50	TZD	104	598	62,192	5
Foley et al[17]	North America	57	58%	vildagliptin	100	placebo	52	59	3,068	3
Unpublished[18]	Asia	61	72%	alogliptin	6.25, 12.5, 25, 50	voglibose, placebo	52	474	24,648	2
Unpublished[3]	multiregional	55	44%	saxagliptin	2.5, 5	placebo	24	365	8,760	2
Unpublished[16]	North America	55	39%	saxagliptin	5	metformin, placebo	116	36	4,176	2
Unpublished[20]	Asia	51	55%	saxagliptin	5	placebo	24	568	13,632	2
Unpublished[19]	Asia	48	56%	saxagliptin	5	placebo	24	213	5,112	2

TZD = thiazolidinediones

Ergebnisdarstellung

- 2,228 patients (44.6%) were treated with vildagliptin, 1,343 (26.9%) with saxagliptin, 772 with sitagliptin (15.4%), and 655 (13.1%) with alogliptin
- Overall, use of DPP4 inhibitors was associated with a lower risk of adverse CV effects (RR 0.48, 95% CI 0.31 to 0.75, p=0.001 and a lower risk of nonfatal myocardial infarction or acute coronary syndrome (RR 0.40, 95% CI 0.18 to 0.88, p=0.02)
- Subgroup analysis by the studied DPP4 inhibitors showed a significantly lower risk of adverse CV events with sitagliptin (RR 0.37, 95% CI 0.21 to 0.68, p=0.001) but not with saxagliptin (RR 0.64, 95% CI 0.23 to 1.76, p= 0.39), alogliptin (RR 1.73, 95% CI 0.21 to 13.93, p=0.61), or vildagliptin (RR 0.50, 95% CI 0.13 to 1.92, p=0.31; Figure 4).
- Risk of adverse CV events with DPP4 inhibitor therapy was not significantly different compared to placebo (RR 1.05, 95% CI 0.39 to 2.82, p= 0.92) but was significantly lower compared to metformin (RR 0.42, 95% CI 0.20 to 0.87, p=0. 02) and other oral hypoglycemic agents including sulfonylureas and thiazolidinediones (RR 0.33, 95% CI 0.16 to 0.67, p=0.002).
- In addition, studies with a duration of 52 weeks demonstrated a lower risk of adverse CV events with DPP4 inhibitor treatment compared to control (RR 0.37, 95% CI 0.21 to 0.63, p=0.0003), which was not seen in the subset of studies with 52 weeks of DPP4 inhibitor therapy (RR 0.78, 95% CI 0.38 to 1.60, p=0.50)
- Analysis without including studies that had no events in the 2 arms showed no change in effect size; the RR of major adverse CV side effects was 0.48 (95% CI 0.31 to 0.75, p=0.001). In analysis without including sitagliptin studies, the RR for major adverse CV side effects with other DPP4 inhibitors was 0.65 (95% CI 0.35 to 1.23, p= 0.19)

	compared to placebo or other oral hypoglycemic agents. • There was no significant heterogeneity within the group of pooled studies (I2 0%, p=0.68). The funnel plot did not show evidence for publication bias.
	Anmerkungen/Fazit der Autoren ⇒ The present meta-analysis demonstrated a significant decrease in events when DPP4 inhibitors were compared to other type 2 DM glucose-lowering therapies, DPP4 inhibitors did not decrease events compared to placebo ⇒ Nevertheless, we cannot determine whether the difference between CV outcomes in our meta-analysis was due to decreased risks with DPP4 inhibitors or increased risks with active type 2 DM comparators (sulfonylureas, thiazolidinediones, metformin, etc.).
Orme, 2014 **[87]** **A systematic review and mixed-treatment comparison of dapagliflozin with existing anti-diabetes treatments for those with type 2 diabetes mellitus inadequately controlled by sulfonylurea monotherapy**	**Fragestellung** The primary objective of this study was to estimate the relative effect of the novel agent dapagliflozin versus existing classes of anti-diabetes therapy on key outcomes of interest, including HbA1c, weight, systolic blood pressure, and hypoglycaemia, when used as add-on treatments to SUs for patients with T2DM inadequately controlled by SU monotherapy with diet and exercise.
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: Pharmacological therapies that would be added to a SU in clinical practice when SU monotherapy does not provide adequate glycaemic control/ Active arms: Dual therapies of interest namely drugs/doses licensed in the EU, as a dual therapy in combination with a SU and as used in clinical practice Endpunkt: HbA1c, weight, systolic blood pressure, proportion (number) of patients experiencing at least 1 hypoglycaemia episode Suchzeitraum: Syst. Literaturrecherche (bis April 2013) Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs (k.A.) Quality Assessment/Risk of bias: Cochrane Collaboration's tool for assessing risk of bias → The quality assessment of the included studies indicated a low risk of bias overall
	Ergebnisdarstellung ⇒ **5 Studien:** DPP-4 inhibitors (3 studies), GLP-1 analogues (1 study) and SGLT2 inhibitors (1 study)

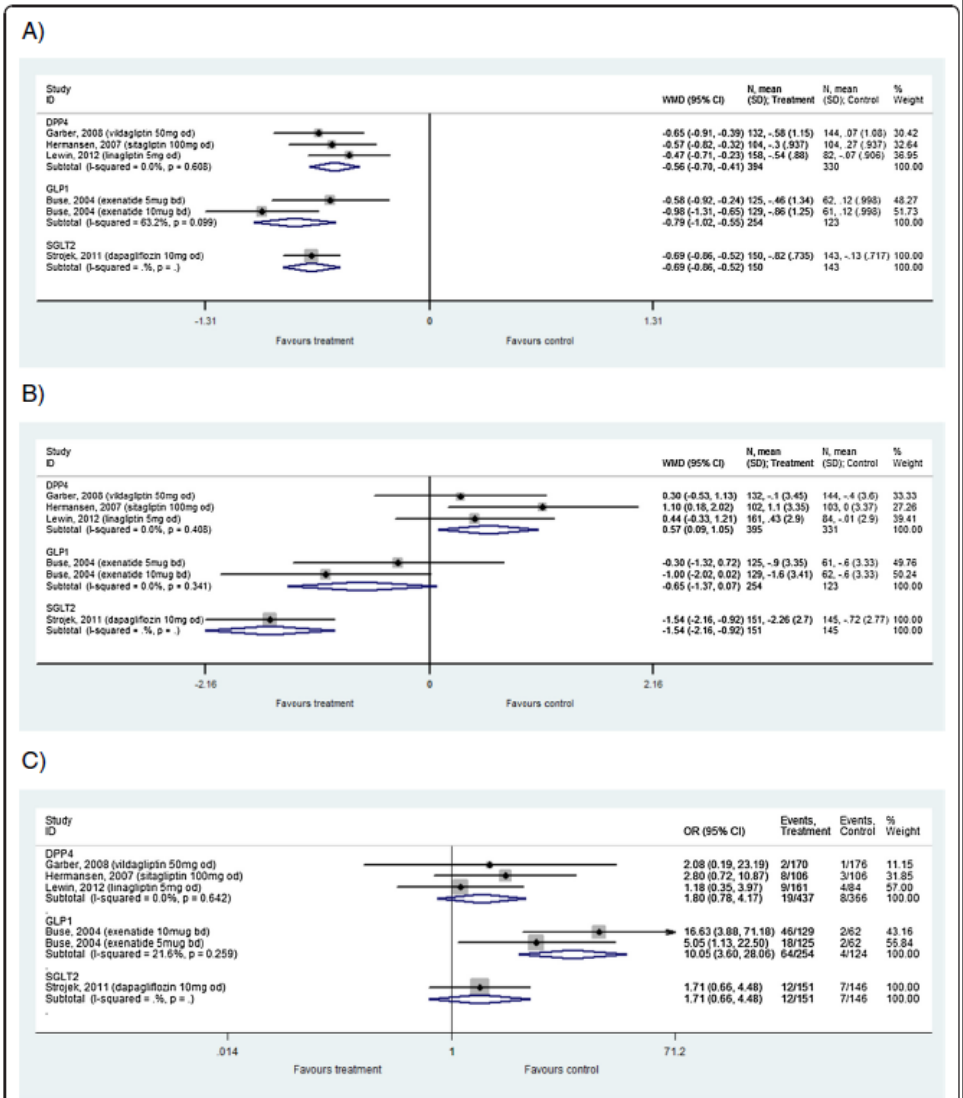
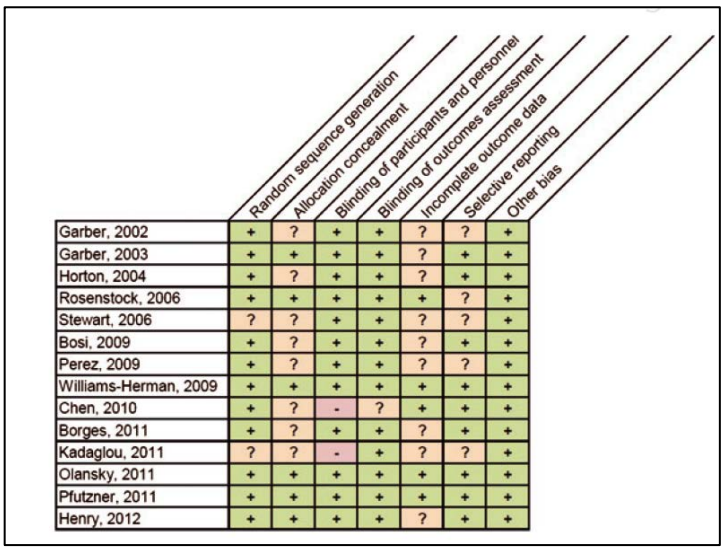


Figure 3 Direct meta-analysis forest plots versus placebo-control. A) HbA1c weighted mean difference, **B)** weight (kg) weighted mean difference, **C)** hypoglycaemia odds ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1 analogues; N, number of patients; OR, odds ratio; SD, standard deviation; SGLT2, sodium glucose co-transporter 2 inhibitors; WMD, weighted mean difference.

Anmerkungen/Fazit der Autoren

- Dapagliflozin, the first-in-class SGLT2 inhibitor was compared with 2 classes of anti-diabetes treatments licensed in the EU for use as add-on therapy to SUs for patients with T2DM in the current NMAs.
- All 3 classes of treatment provided better short-term glycaemic control when used in combination with an SU compared to SU monotherapy, with no significant differences between classes. However, NMA revealed that there were differences between dapagliflozin and the other classes of treatment in terms of impact on weight (dapagliflozin compared to
- DPP-4 inhibitors) and incidence of hypoglycaemia (dapagliflozin compared to GLP-1 analogues).
- Careful consideration and comparison of drug class risk-benefits

	should be made when selecting appropriate add-on drug combinations for the treatment of T2DM.
	Hinweis FbMed • This study was funded by Bristol-Myers Squibb Rueil-Malmaison, France and AstraZeneca, Brussels, Belgium. MO is a paid consultant of Bristol-Myers Squibb. PF, IDL, GW and MR are employees of Bristol-Myers Squibb. IDL and GW are also shareholders of Bristol-Myers Squibb. RT was an employee of AstraZeneca throughout the duration of the study.
Phung, 2013 **[90]** **Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis**	**Fragestellung** we conducted a systematic review andmeta-analysis to evaluate the effect of early combination pharmacotherapy in patients with diagnosed type 2 diabetes, compared to metformin monotherapy.
	Methodik Population: Pat. mit DM Typ II (newly diagnosed within 3months) Intervention/ Komparator: combination regimen that includes metformin to metformin monotherapy Endpunkt: A1c, FPG, hypoglycaemia, measures of insulin sensitivity or measures of pancreatic β-cell function Suchzeitraum: Syst. Literaturrecherche (bis Juli 2012) Anzahl eingeschlossene Studien/Patienten (Gesamt): 15 RCTs Quality Assessment/Risk of bias: Cochrane Risk of Bias tool 
	Ergebnisdarstellung

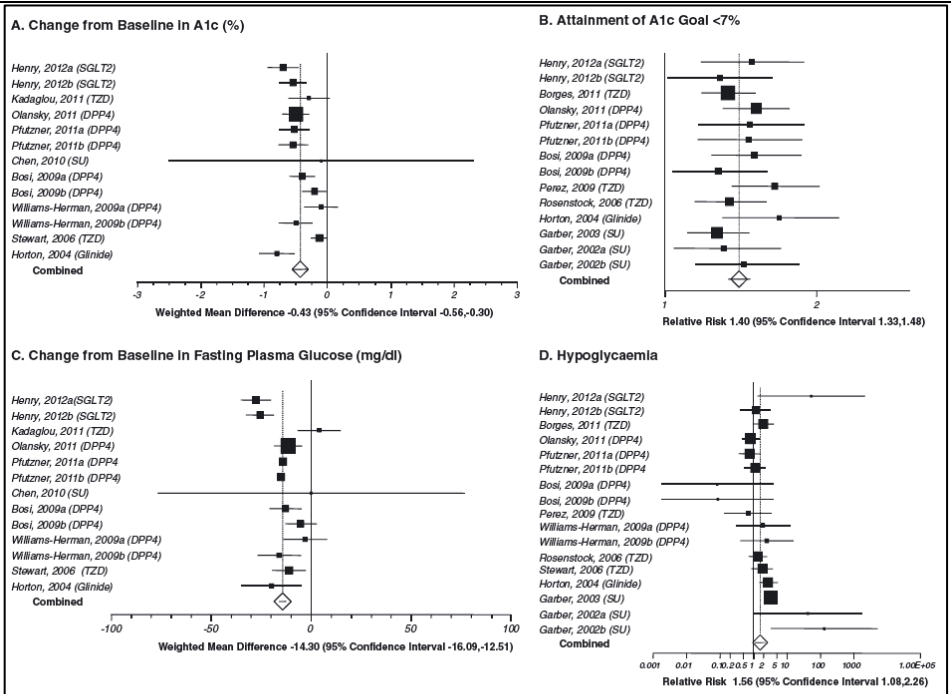


Figure 3. Results of meta-analysis of studies comparing early combination therapy with metformin to metformin monotherapy on change from baseline in glycosylated haemoglobin (A1c) (A), attainment of A1c goal <7% (B), change from baseline in fasting plasma glucose (C) and hypoglycaemia (D). Notes: Henry, 2012a and b [25] were two separate trials published within the same article. Other notations of a and b refer to different dosing arms of the combination therapy. Abbreviations: DPP-4, dipeptidyl peptidase-4 inhibitor; SGLT-2, sodium glucose transporterase-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

- Combination therapy significantly reduced A1c compared to metforminmonotherapy [WMD−0.43% (−0.56 to−0.30)]
- Combination therapy significantly increased the attainment of goal A1c compared to metformin monotherapy [RR 1.40 (1.33–1.48)] → Neither heterogeneity (I^2 =0%) nor publication bias (Egger's p-value=0.23) was detected.
- Combination therapy significantly reduced FPG compared to metformin monotherapy [WMD −14.30 mg/dl (−16.09 to −12.51)]
- A significant increase in the risk of hypoglycaemia was found with combination therapy in comparison to metformin monotherapy [RR 1.56 (1.08–2.26)] A moderate level of heterogeneity was found (I^2 =52.7%) although publication bias was not detected (Egger's p-value=0.55). In a sensitivity analysis whereby SUs and glinides were excluded (13 comparisons analysed), the risk of hypoglycaemia was no longer significantly increased in the combination group compared tometformin monotherapy [RR 1.20 (0.91–1.56)].

Anmerkungen/Fazit der Autoren

- The results of this meta-analysis suggest that the use of combination therapy versus metformin monotherapy upon initiation of pharmacologic therapy in type 2 diabetes is beneficial in improving glycaemic outcomes.
- The studies that were included in the analysis had an inconsistent definition of treatment-naive, with some studies allowing patients to

<table>
<tr><td></td><td>be included even if they had use of antidiabetic drugs in the distant past.</td></tr>
<tr><td></td><td>Anmerkung FB-Med:
O. J. P. and D. M. S. (who designed the study) have received grant funding fromMerck & Co, Inc. S. S. E. and S. N. R. are employees of Merck & Co, Inc.</td></tr>
<tr><td rowspan="3">Poolsup,2012
[91]
Efficacy of Various Antidiabetic Agents as Add-On Treatments to Metformin in Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis</td><td>Fragestellung
Our paper was aimed at determining the efficacy of combination therapy of metformin with any antidiabetic agents in type 2 diabetes inadequately controlled with metformin alone</td></tr>
<tr><td>Methodik
Population: Pat. mit DM Typ II
Intervention/ Komparator: metformin alone compared with two different antidiabetic drugs in combination with metformin
Endpunkt: HbA1c
Suchzeitraum: Syst. Literaturrecherche (k.A. zum Suchzeitraum)
Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs (k.A.)
Quality Assessment/Risk of bias: Jadad’s scale
<table>
<tr><th colspan="2">Studie</th><th>Quality Score</th></tr>
<tr><td>1</td><td>Scott et al.</td><td>3</td></tr>
<tr><td>2</td><td>Bolli et al.</td><td>3</td></tr>
<tr><td>3</td><td>Charbonnel</td><td>5</td></tr>
<tr><td>4</td><td>Garber et</td><td>4</td></tr>
<tr><td>5</td><td>Umpierrez</td><td>2</td></tr>
<tr><td>6</td><td>Hamann et</td><td>4</td></tr>
<tr><td>7</td><td>Derosa et</td><td>5</td></tr>
<tr><td>8</td><td>Kvapil et al.</td><td>3</td></tr>
</table></td></tr>
<tr><td>Ergebnisdarstellung
<u>Medikamentenvergleiche</u>
1. thiazolidinediones (TZDs) vs. dipeptidyl peptidase IV inhibitors (DPP IV inhs) (n=2 Studien)
2. TZDs vs. sulphonylureas (SUs) (n=4 Studien)
3. pioglitazone versus rosiglitazone (n=1 Studie)</td></tr>
</table>

4. biphasic insulin aspart 30 versus glibenclamide (n=1 Studie)

HbA1c

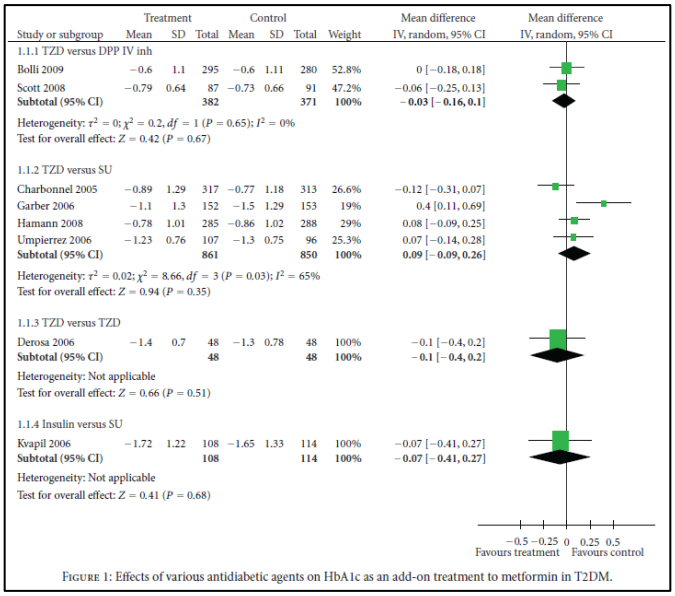


FIGURE 1: Effects of various antidiabetic agents on HbA1c as an add-on treatment to metformin in T2DM.

FPG

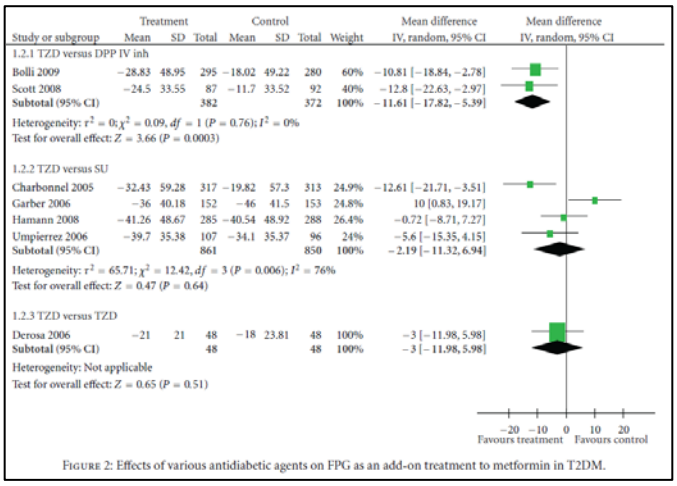


FIGURE 2: Effects of various antidiabetic agents on FPG as an add-on treatment to metformin in T2DM.

FPI

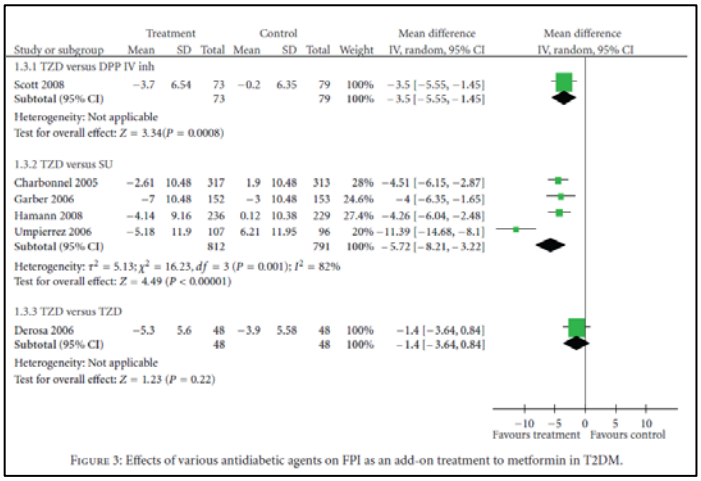


FIGURE 3: Effects of various antidiabetic agents on FPI as an add-on treatment to metformin in T2DM.

<table>
<tr><td></td><td>Anmerkungen/Fazit der Autoren
The results of this analysis suggest that TZDs were as effective as DPP IV inhs in reducing HbA1c value in type 2 diabetes patients who had been treated with metformin alone.
However, FPG better improved with TZDs than with DPP IV inhs. From its mechanism of actions, TZDs may reduce FPI more than does DPP IV inhs.
Given the limitations of the published data, large sample size, high quality, randomized controlled trials of combination treatment withmetformin, and other agents are warranted.</td></tr>
<tr><td rowspan="2">Price, 2015 [92]
Comparative cardiovascular morbidity and mortality in patients taking different insulin regimens for type 2 diabetes: a systematic review</td><td>Fragestellung
evaluated the incidence of CV morbidity and mortality in adults with type 2 diabetes taking different insulin regimens</td></tr>
<tr><td>Methodik
Population: Pat. mit DM Typ II
Intervention/ Komparator: k.A.
Endpunkt: Primär: incidence of CV (fatal and/or non-fatal myocardial infarction (MI), fatal and/or non-fatal stroke, CV death, and major acute coronary event (MACE) as defined by the studies reviewed. Sekundär: all-cause mortality
Suchzeitraum: Syst. Literaturrecherche (bis Februar 2014)
Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 Studien (2 RCTs & 6 Kohortenstudien)
Quality Assessment/Risk of bias: Cochrane Risk of Bias tool (RCTs) und Newcastle-Ottawa Scale (Kohortenstudien)
<table>
<tr><th colspan="8">Appendix C. Assessment of RCTs for risk of bias using the Cochrane risk of bias tool</th></tr>
<tr><th>Study</th><th>Random sequence generation?</th><th>Allocation concealment?</th><th>Blinding of participants and personnel?</th><th>Blinding of outcome assessment?</th><th>Incomplete outcome data addressed?</th><th>Free of selective reporting?</th><th>Free of other bias?</th><th>Overall risk of bias</th></tr>
<tr><td>Raz et al., 2009</td><td>Unclear</td><td>Unclear</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td><td>High</td></tr>
<tr><td>UGDP, 1982</td><td>Yes</td><td>Unclear</td><td>Yes</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>High</td></tr>
</table></td></tr>
</table>

Appendix D. Assessment of cohort studies for risk of bias using the Newcastle-Ottawa Scale

	Selection				Comparability		Outcome		Score
Study	Represent-ativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of design or analysis (* if adjusted for HbA1c, * if multiple factors)	Assessment of outcome	Was follow-up long enough for outcome to occur? (>2 years)	Adequacy of follow-up of cohorts	Overall risk of bias
Gamble et al., 2010	Truly representative*	Same community*	Secure record: insulin prescription records from community pharmacies (total cumulative insulin exposure)*	Yes*	Age, sex, chronic disease score, severity of diabetes, oral diabetes medications, selected medications, hospital admission 1 year prior to insulin exposure*	Record linkage: vital statistics and ICD-9 codes*	Yes*	Complete follow-up*	8
Hall et al., 2012	Truly representative*	Same community*	Secure record: insulin prescription records from general practitioner (>1 insulin prescriptions required)*	Yes*	Age, sex, diabetes duration, escalation 2004-2007, cholesterol, BMI, smoking status, eGFR, history of vascular disease and its risk factors (hyperlipidaemia, body mass index, smoking status, estimated GFR, microalbuminuria), oral diabetes medications and cardiovascular therapies, year of starting insulin, most recent HbA1c**	Record linkage: Read codes from general practitioner records*	Yes*	Complete follow-up*	9
Juhaeri et al., 2009	Truly representative*	Same community*	Secure record: insulin prescription records from community pharmacies (number of insulin prescriptions required not stated)*	No	Age, sex, history of hypertension, history of dislipidaemia, days supply, duration of diabetes *	Record linkage: ICD-9CM codes*	No	Complete follow-up*	6
Kress et al., 2012	Truly representative*	Same community*	Secure record: insulin prescription records from general practitioner (1 or more insulin prescriptions required)*	No	Age, sex, region, urban residency, diabetologist care, private health insurance, Charlson comorbidity score, hypertension, hyperlipidaemia, depression, co-medication with insulin, previous treatment with regular insulin, co-medication with oral diabetes medications, co-medication with antihypertensives, lipid-lowering drugs, antithrombotic agents, baseline microvascular complications*; HbA1c adjustment in sensitivity analysis*	Record linkage: ICD-10 codes*	Yes*	Complete follow-up*	8
Rathmann et al., 2013	Truly representative*	Same community*	Secure record: insulin prescription records from general practitioner (1 or more insulin prescriptions required)*	No	Age, sex, region, urban residency, diabetologist care, private health insurance, Charlson comorbidity score, hyptertension, hyperlipidaemia, co-medication with insulin, previous treatment with regular insulin, co-medication with oral diabetes medications, co-medication with antihypertensives, lipid-lowering drugs, antithrombotic agents, baseline micro & macro - vascular complications, hypoglycaemias at baseline and during study period*	Record linkage: ICD-10 codes*	Yes*	Complete follow-up*	7
Rhoads et al., 2009	Truly representative*	Same community*	Secure record: insulin prescription records from community pharmacy claims (1 or more insulin prescriptions required) *	No	Age, comorbidities, Charlson comorbidity score, medications, healthcare resource use, access to endocrinologist, in-patient vs out-patient insulin initiation, insurance type, insulin co-payment level, geographic region, medication possession ratio, concomitant glucose-lowering and lipid-lowering medication, hypoglycaemia, year of insulin initiations, HbA1c **	Record linkage: ICD-10 codes*	Yes*	Complete follow-up*	8

* item met inclusion criteria

Ergebnisdarstellung

Study/trial or database	Study population	Insulin exposures	Patients (n)	Study period (mean follow-up (months))
Randomised clinical trials				
Raz *et al*[14] (HEART2D)	Patients with T2DM +recent MI	Insulin lispro NPH insulin or insulin glargine	557 558	2002–2005 (32)
UGDP[15]	Incident T2DM	Fixed: U-80 Lente Iletin insulin (10, 12, 14 or 16 U/day) Variable: U-80 Lente Iletin insulin or other insulins, as much as required to maintain 'normal' glucose control (minimum 5 U/day)	210 204	1961–1975 (150)
Cohort studies				
Gamble *et al*[16] (Saskatchewan Health)	New users of insulin	Low exposure: <3 rx's/year Moderate exposure: 3<12 rx's/year (<1 vial/month) High exposure: ≥12 rx's/year (<1 vial/month)	1443	1991–1996 (61)
Hall *et al*[17] (The Health Information Network)	New users of insulin	Premixed insulin (after 2 or 3 baseline OADs) NPH insulin (after 2 or 3 baseline OADs) Basal insulin (after 2 or 3 baseline OADs)	1399 601 1427	2000–2008 (43)
Juhaeri *et al*[18] (PharMetrics)	T2DM and new users of insulin	Insulin glargine monotherapy Insulin glargine+other insulins Other insulin regimen (lispro, aspart, regular, premixed or mixed) Long-acting/intermediate-acting insulin (ultralente, NPH, lente)	11 534 16 540 30 979 6566	2001–2007 (NR)
Kress *et al*[19] (IMS Disease Analyzer)	T2DM and new users of insulin glulisine and regular insulin	Insulin glulisine Regular human insulin	952 11 157	2004–2010 (42)
Rathmann and Kostev[20] (IMS Disease Analyzer)	New users of insulin aspart and regular insulin	Insulin aspart (rapid-acting) Regular human insulin (short-acting)	3154 3154	2000–2011 (42)
Rhoads *et al*[21] (IMS Disease Analyzer)	T2DM and new users of insulin glargine and NPH insulin	Insulin glargine NPH insulin	14 730 5461	2001–2005 (24)

2 RCTs (HEART2D trial & UGDP study)

- no statistically significant differences in CV outcomes reported in the HEART2D trial or the UGDP study
- no statistically significant differences in all-cause mortality reported in the HEART2D trial (RR=1.00, 95% CI 0.69 to 1.45) or the UGDP study (RR=1.03, 95% CI 0.74 to 1.44

<u>HEART2D:</u>

- no differences in the risk of non-fatal MI (RR=1.06, 95% CI 0.73 to 1.53), fatal MI (RR=1.00, 95% CI 0.45 to 2.21), and non-fatal or fatal MI (RR=1.00, 95% CI 0.72 to 1.39).
- number of patients who experienced a stroke (n=37) → no between-group differences in the risk of a nonfatal stroke (RR=1.19, 95% CI 0.62 to 2.29), fatal stroke (RR=1.50, 95% CI 0.25 to 8.96), and non-fatal or fatal stroke (RR=1.18, 95% CI 0.62 to 2.23).
- The RR of CV death in the HEART2D trial was 1.05 (95% CI 0.70 to 1.58) and 1.00 (95% CI 0.63 to 1.57) in the UGDP trial

<u>UGDP study:</u>

	o similar results for the risk of a fatal or non-fatal MI (RR=1.03, 95% CI 0.70 to 1.51), non-fatal MI (RR=1.00, 95% CI 0.62 to 1.60) and fatal MI alone (RR=1.12, 95% CI 0.52 to 2.39) o The RR of CV death in the UGDP trial was 1.00 (95% CI 0.63 to 1.57) <u>6 Kohortenstudien</u> ⇒ (n= 4 Kohortenstudien): a statistically significant difference in the risk of a non-fatal or fatal MI: insulin aspart versus regular insulin (HR=0.69, 95% CI 0.54 to 0.88) and NPH insulin versus other basal insulin regimens (HR=1.39, 95% CI 1.14 to 1.69). ⇒ (n=3 Kohortenstudien:) Fatal+non-fatal stroke was evaluated for five different insulin-exposure contrasts of which two exposure contrasts indicated risk differences in fatal+non-fatal stroke: other insulin regimen versus long-acting/ intermediate-acting insulin (HR=1.20, 95% CI 1.04 to 1.40) and insulin aspart versus regular human insulin (HR=0.58, 95% CI 0.45 to 0.74). ⇒ (n= 1 Kohortenstudie): no statistically significant difference in the risk of MACE among users of different insulin regimens ⇒ (n= 1 Kohortenstudie): Only one cohort study, Gamble and colleagues, included all-cause mortality as an outcome of interest. They found a dose– response relationship whereby more insulin exposure was associated with a higher risk of mortality
	Anmerkungen/Fazit der Autoren • This systematic review documents a lack of high-quality evidence examining CV outcomes of different insulin regimens used to treat patients with type 2 diabetes. • none of the included studies examined CV risk across identical exposure categories • We found no clear pattern of harm or benefit for any particular insulin regimen. • Results from the included RCTs must be interpreted **with caution** given their susceptibility to bias and lack of generalisability to today's type 2 diabetes population. For example, treatment algorithms for type 2 diabetes and insulin formulations have changed substantially since the UGDP was completed over 30 years ago. Furthermore, the HEART2D trial was conducted in a specific high-risk post-MI population.
Rys, 2015 [94] **Systematic review and meta-analysis of randomized**	**Fragestellung** We performed a systematic review combining all data from randomized clinical trials (RCTs) in T2DM to compare efficacy and safety outcomes of IGlar with several other insulin regimens in order to make synthetic and

clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus	reliable conclusions.
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: comparing IGlar, added to OAD or/and in combination with bolus insulin, with human insulin (NPH) or insulin detemir (IDet) in the same regimens, as well as with premixed insulin (MIX) Endpunkt: **Primär:** HbA1c level; overall, severe or nocturnal hypoglycemic events, **Sekundär:** glycemic control, Treatment satisfaction, quality of life, weight, AE, SAE Suchzeitraum: Syst. Literaturrecherche (bis Dezember 2012) Anzahl eingeschlossene Studien/Patienten (Gesamt): 28 Studien (k.A.) Quality Assessment/Risk of bias: Jadad scale → The credibility of included RCTs, assessed according to the Jadad scale, oscillated between 1 and 3 points on the 5-point scale and was mainly downgraded due to the lack of double blinding
	Ergebnisdarstellung **IGlar versus NPH** Glycemic control: ⇒ basal + OAD regimen demonstrated a favorable effect of IGlar over NPH with respect to target HbA1c without nocturnal hypoglycemia (2 RCTs; RR = 1.32 [1.09, 1.59]), while the mean reduction in HbA1c level was comparable in both arms (9 RCTs; WMD = -0.03 % [-0.10, 0.04] (-0.3 mmol/mol [-1.1; 0.4])) ⇒ No difference between IGlar and NPH, both in combination with prandial insulin, was observed with respect to the mean reduction of HbA1c (2 RCTs; WMD = 0.02 % [-0.30, 0.35] (0.2 mmol/mol [-3.3; 3.8])) as well as the number of T2DM patients achieving target HbA1c (1 RCT; RB = 1.14 [0.91; 1.44]) Hypoglycemia: ⇒ Meta-analysis of five studies assessing IGlar in comparison with NPH, both added to OAD, revealed a borderline difference toward lower risk of overall hypoglycemia in patients treated with IGlar (RR = 0.92 [0.84, 1.001]). ⇒ Moreover, IGlar + OAD significantly reduced number of patients experiencing symptomatic (6 RCTs; RR = 0.89 [0.83, 0.96]) and nocturnal events (6 RCTs; RR = 0.63 [0.51; 0.77]). The risk of severe hypoglycemia was comparable between interventions (5 RCTs; RR = 0.76 [0.47, 1.23]) ⇒ Meta-analysis of the 2 RCTs assessing basal + bolus scheme

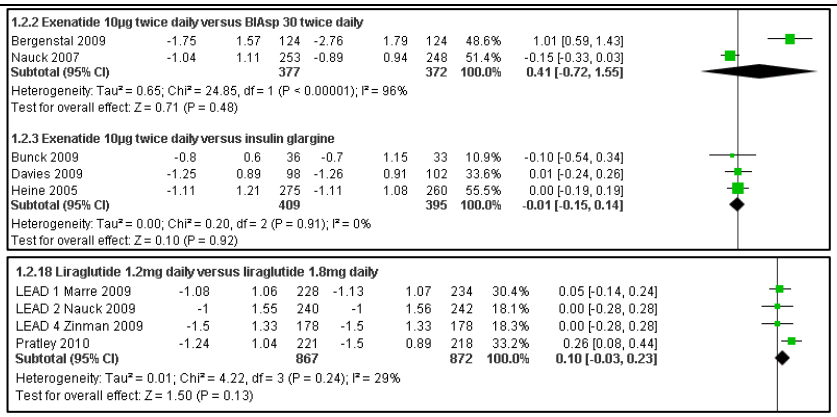
	demonstrated less frequent nocturnal hypoglycemic events in patients treated with IGlar as compared to protamine insulin (RR = 0.77 [0.63, 0.94]). Additionally, a tendency toward lower risk of severe hypoglycemic events was shown in patients treated with IGlar (RR = 0.22 [0.05, 1.02]) Weight gain: ⇒ IGlar and NPH did *not differ significantly* with respect to weight gain when administered within basal + OAD or basal + bolus ± OAD regimens Treatment satisfaction and quality of life: ⇒ superior treatment satisfaction of IGlar over NPH, both added to OAD (1 RCT; WMD = 0.60 [0.07; 1.13]) Safety: ⇒ *No difference* with regard to the risk of adverse events related to study drug and the risk of study discontinuations due to adverse events. ⇒ Only single cases of mortality were reported in two RCTs comparing IGlar + OAD with NPH + OAD (2 RCTs) ⇒ both basal insulins in basal + OAD scheme with no differences between treatment arms (1 RCT) **IGlar versus premixed insulins (MIX)** Glycemic control: ⇒ significantly more patients treated with IGlar + OAD achieved target HbA1c without nocturnal hypoglycemia when compared to MIX monotherapy (1 RCTS; RR = 1.61 [1.22, 2.13]) ⇒ IGlar combined with OADs exerted a greater reduction in mean level of HbA1c (3 RCTs; WMD = -0.36 % [-0.54, -0.18] (-3.9 mmol/mol [-5.9; -2.0])) and was associated with a higher chance of reaching target HbA1c (2 RCTs; RR = 1.49 [1.03, 2.16]). ⇒ MIX + OAD provided larger reduction of HbA1c (5 RCTs; WMD = 0.26 % [0.12, 0.40] (2.8 mmol/mol [1.3, 4.4])) and allowed to achieve target HbA1c in a higher number of patients (5 RCTs; RR = 0.79 [0.66, 0.94]). ⇒ Meta-analysis of five studies demonstrated that IGlar added to prandial insulin compared with MIX ± OAD showed a trend toward lower mean HbA1c (WMD -0.19 % [-0.43,0.06] (-2.1 mmol/mol [-4.7, 0.7])) and was associated with a higher percentage of patients who reached target HbA1c (RR = 1.26 [1.12, 1.42]). Hypoglycemia: ⇒ A meta-analysis of two studies comparing IGlar + OAD versus MIX monotherapy demonstrated *no difference* between groups with

	respect to the risk of overall hypoglycemia (RR = 0.90 [0.78; 1.04]) ⇒ significantly lower number of symptomatic (2.62 vs. 5.73 events/patient-year; p\0.001) as well as nocturnal (0.051 vs. 1.04 events/ patient-year; p\0.05) hypoglycemic events in IGlar group (1 RCT) ⇒ IGlar as compared to MIX, both administered together with OAD, demonstrated lower risk of overall (3 RCTs; RR = 0.88 [0.82, 0.95]) and symptomatic hypoglycemia (3 RCTs; RR = 0.75 [0.68, 0.83]) → *no differences* were found with respect to the risk of nocturnal (2 RCTs; RR = 1.01 [0.90, 1.14]) and severe events (5 RCTs; RR = 0.86 [0.30, 4.43]) ⇒ IGlar added to prandial insulin when compared to MIX ± OAD therapy demonstrated similar impact with respect to all assessed hypoglycemic endpoints including overall (2 RCTs; RR = 1.01 [0.93; 1.10]), symptomatic (2 RCTs; RR = 1.02 [0.95; 1.10]), severe (5 RCTs; RR = 0.74 [0.46, 1.20]), and nocturnal events (3 RCTs; RR = 0.98 [0.87; 1.10]) <u>Weight gain:</u> ⇒ Meta-analysis of three RCTs comparing IGlar added to OAD with MIX monotherapy demonstrated comparable weight gain in both groups (WMD = -2.02 kg [-5.11; 1.07]), although this result has limited credibility due to a significant between-study heterogeneity (p = 0.03) ⇒ lower mean body weight gain in patients receiving IGlar + OAD than in those who were on MIX ? OAD therapy (3 RCTs; WMD = -1.27 kg [-1.56, -0.97]) ⇒ IGlar combined with prandial insulin provided comparable effect on weight gain as MIX ± OAD (5 RCTs; WMD = 0.37 kg [-0.20; 0,94]) <u>Treatment satisfaction and quality of life:</u> ⇒ *no evidence* was found for the difference in overall treatment satisfaction or quality of life between IGlar and MIX <u>Safety:</u> ⇒ No evidence for the difference between IGlar and MIX with respect to both overall adverse events and treatment associated adverse events was found regardless of treatment schemes that were directly compared. ⇒ The proportion of premature withdrawals due to adverse events was lower in IGlar + OAD group when compared to MIX + OAD (5 RCTs; RR = 0.41 [0.22, 0.76]), but not to MIX monotherapy (2 RCTs; RR = 0.52 [0.13, 1.99]) ⇒ Comparable number of withdrawals due to adverse events was observed for the comparison between IGlar + bolus ± OAD vs. MIX ±

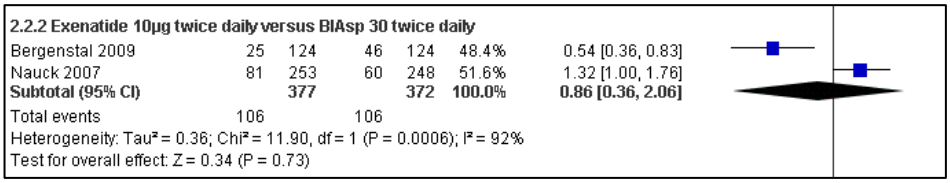
	OAD (4 RCTs; RR = 1.44 [0.63, 3.28]). ⇒ IGlar decreased the number of severe adverse events when used with OAD (3 RCTs; RR = 0.71 [0.52, 0.98]), but not as adjunctive to prandial insulin (5 RCTs; RR = 1.05 [0.78, 1.42]) **IGlar versus IDet** Glycemic control: ⇒ no difference between IGlar and IDet, both added to OAD, with respect to proportion of patients reaching target HbA1c level with either no overall (RR = 1.05 [0.83, 1.35]) or symptomatic hypoglycemic events (RR = 1.07 [0.87, 1.33]) → Meta-analysis of both RCTs demonstrated comparable reduction in mean HbA1c in both groups (WMD = 0.05 % [-0.07, 0.16] (0.5 mmol/mol [-0.8, 1.7])) ⇒ *no evidence* for overall hypoglycemia (1 RCT; RR = 1.41 [1.12, 1.78]) and no difference between interventions with respect to the number of patients achieving target HbA1c without symptomatic hypoglycemia (1 RCT; RR = 1.21 [0.75, 1.95]) ⇒ IGlar was associated with a larger reduction in mean HbA1c level (2 RCTs; WMD = -0.25 % [-0.40, -0.09] (-2.7 mmol/mol [-4.4; 1.0])) and allowed to reach a target HbA1c level (\7 % (53 mmol/mol)) by significantly more patients when compared to IDet (2 RCTs; RR = 1.23 [1.03, 1.47]) Hypoglycemia: ⇒ The risk of hypoglycemia in patients treated with both LAA added to OAD was comparable with respect to overall (1 RCT, RR = 1.05 [0.93, 1.19]), symptomatic (2 RCTs; RR = 0.99 [0.90, 1.08]), severe (2 RCTs; RR = 1.31 [0.70, 2.45]) and nocturnal hypoglycemic events (1 RCT; RR = 0.98 [0.77, 1.24]). ⇒ Both LAA administered according to basal + bolus ± OAD regimen were associated with comparable risk of overall, symptomatic, severe and nocturnal hypoglycemic episodes. Weight gain: ⇒ Meta-analysis of two RCTs comparing IGlar versus IDet, both added to OAD therapy, demonstrated higher body weight gain in IGlar group (WMD = 0.77 kg [0.44, 1.11]) ⇒ IGlar was also associated with a higher body weight increase as compared to IDet, when both analogs were administered together with prandial insulins (2 RCTs; WMD = 1.24 kg [0.59, 1.89]) Treatment satisfaction and quality of life: ⇒ One study comparing both LAA in basal + OAD regimen reported that IGlar was associated with a higher treatment satisfaction when compared to IDet as measured with DTSQ questionnaire (for overall

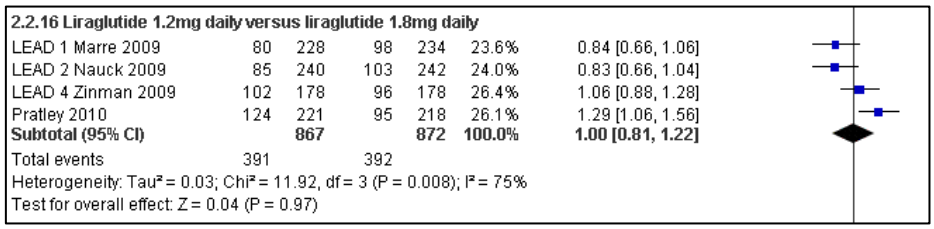
	result p\0.001), but no difference was shown when measured with DSC-R, WHO- 5 Well Being and HFS questionnaires Safety: ⇒ significantly lower in IGlar group as compared to IDet, when both interventions were administered in addition to OAD therapy (RR = 0.40 [0.24, 0.69]), but not as adjuncts to bolus insulin (RR = 0.54 [0.22; 1,32]) ⇒ risk of serious adverse events did *not differ* between both LAA administered either together with OAD (1 RCT; RR = 1.26 [0.87, 1.83]) or in combination with prandial insulin (2 RCTs; RR = 0.71 [0.43, 1.16]). ⇒ comparable risk between IGlar and IDet in basal + bolus regimens with respect to overall adverse events (2 RCTs; RR = 1.02 [0.94, 1.21]) ⇒ lower risk of application site reactions in IGlar group as compared to IDet (2 RCTs; RR = 0.22 [0.07; 0.55])
	Anmerkungen/Fazit der Autoren • Although available evidence did not allow us to compare IGlar + bolus with NPH + bolus, the analysis of individual endpoints demonstrated comparable reduction of HbA1c in each arm, but with concomitantly lower rate of symptomatic and nocturnal hypoglycemia in IGlar group • In conclusion, for the majority of examined efficacy and safety outcomes, IGlar use in T2DM patients was superior or at least non-inferior to the alternative insulin treatment options
	Hinweis FbMed ⇒ P.R, P.W, A.R-S. and G.N. are employees of HTA Consulting, the company that received grant from Sanofi Poland for this project. HTA Consulting received also grants from Novo Nordisk Pharma Poland for other scientific projects. J.L and A.S. are employees of Sanofi Poland. MTM received remuneration for lectures and Advisory Board membership.
Shyangdan, 2010 [97] **Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis**	**Fragestellung** This review aims to investigate the effectiveness of GLP-1 analogues in patients with type 2 diabetes mellitus who are not achieving satisfactory glycaemic control with one or more oral glucose lowering drugs.
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: compared a GLP-1 analogue with a placebo, insulin, an oral glucose lowering agent, or another GLP- 1 analogue, in

	dual or triple therapy Endpunkt: **Primär:** HbA1c, weight change and adverse effects, including hypoglycaemia; **Sekundär:** BP (blood pressure), FPG (fasting blood glucose) and PPG (post-prandial glucose), plasma lipids, beta cell function, and health related quality of life Suchzeitraum: Syst. Literaturrecherche (bis Juli 2010) Anzahl eingeschlossene Studien/Patienten (Gesamt): 28 RCTs Quality Assessment/Risk of bias: Cochrane Collaboration's tool for assessing risk of bias → Studies were mainly of *moderate to high quality*, with most studies fulfilling five to seven of the seven quality criteria → Four studies only fulfilled four of the criteria, while ten fulfilled five criteria, seven fulfilled six criteria, and seven fulfilled seven criteria. Many studies had one or more arms with losses to follow-up of 20% or more.
	Ergebnisdarstellung Vergleiche: 1. albiglutide and taspoglutide against placebo 2. exenatide against placebo, insulin, glibenclamide, rosiglitazone; 3. exenatide twice daily against exenatide once weekly 4. exenatide once weekly against sitagliptin and pioglitazone 5. liraglutide against placebo, exenatide, glimepiride, rosiglitazone, sitagliptin and insulin glargine The results showed that GLP-1 agonists are effective in improving glycaemic control and promoting weight loss, with a low risk of hypoglycaemia, and can be an alternative to immediate insulin in patients failing on combined oral glucose lowering agents. 1. <u>Change in HbA1c (%): GLP-1 agonists versus active comparators (anderen Studien nicht mit aufgeführt, da Evidenz ausschließlich auf einer RCT basiert)</u> ⇒ Results varied against active comparators. Liraglutide 1.8 mg daily was superior to glargine, rosiglitazone 4 mg daily, sitagliptin 100 mg daily and exenatide 10 µg twice daily. Exenatide 10 µg twice daily was equivalent to both insulin and rosiglitazone 4 mg twice daily, taking differences in HbA1c of less than 0.5% as being not clinically significant. Long acting exenatide (2 mg weekly) was superior to exenatide 10 µg twice daily, glargine, sitagliptinand pioglitazone 45 mg daily.



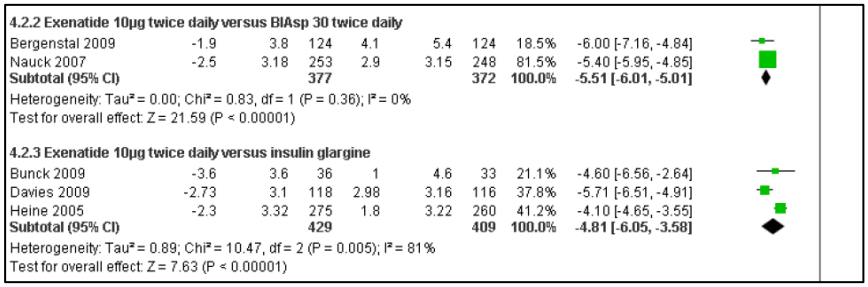
2. <u>Percentage of patients achieving HbA1c ≤7% GLP-1 agonists versus active comparators (anderen Studien nicht mit aufgeführt, da Evidenz ausschließlich auf einer RCT basiert</u>

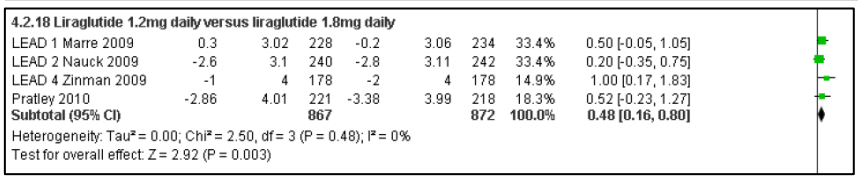




3. <u>Weight changes (kg): GLP-1 agonists versus active comparators (anderen Studien nicht mit aufgeführt, da Evidenz ausschließlich auf einer RCT basiert</u>

⇒ Exenatide and liraglutide caused greater weight loss than all active comparators, most of which led to weight gain. Weight loss was independent of nausea. A study that followed trial patients for longer has shown that temporal patterns of weight loss can vary amongst patients.





4. <u>Hypoglycaemia and adverse events</u>

⇒ no significant differences in the incidence of hypoglycaemia in trials

	comparing albiglutide or taspoglutide and placebo. ⇒ The incidence of major hypoglycaemia was very low (in absolute terms) in patients taking GLP-1 agonists, and the incidence of minor hypoglycaemia was low (under 10%) compared to most other glucose lowering agents except metformin. ⇒ Hypoglycaemia was seen most often when GLP-1 analogues were used in combination with sulphonylureas, in which cases it was probably due to those rather than the GLP1 agonist. The most commonly reported adverse events with GLP-1 agonists were gastrointestinal, and included nausea, vomiting and diarrhoea. These adverse events were worst at the beginning and reduced over the course of therapy. Most patients did not get nausea while taking a GLP-1 agonist.
	Anmerkungen/Fazit der Autoren ⇒ GLP-1 agonists are effective in improving glycaemic control when added to dual therapy, and at least in the short term, can be an alternative to starting insulin. ⇒ Our meta-analysis showed that there was little advantage of the 1.8 mg dose over the 1.2 mg dose of liraglutide, with no difference in HbA1c, but slightly greater weight loss. ⇒ The incidence of hypoglycaemia is low, because of their glucose dependent action. They also cause weight reduction, in contrast to the weight gain seen with sulphonylureas, the glitazones and insulin, and the weight neutral effects of the gliptins. ⇒ How long they would work for in a progressive disease is not yet known. They are a useful addition to the therapeutic armamentarium in type 2 diabetes.
Zhu, 2013 **[111]** **Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials**	**Fragestellung** This study aimed to compare the efficacy between metformin and glimepiride in monotherapy of T2DM through a meta-analysis and supply the evidence that was missing from previous reviews and clinical guidelines
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: comparing glimepiride with metformin as monotherapy of T2DM Endpunkt: BMI (body mass index), SBP (systolic blood pressure), DBP (diastolic blood pressure), FPG (fasting plasma glucose), HbA1c (glycosylated hemoglobin level), PPBS (postprandial blood sugar), TC (total cholesterol), HDL (high-density lipoprotein), LDL (low-density

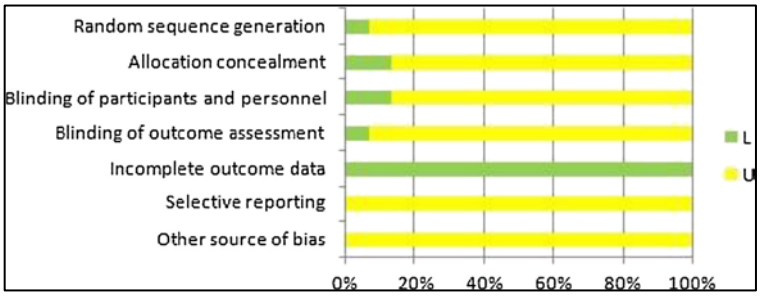
	lipoprotein), TG (triglycerides) and FINS (fasting plasma insulin) Suchzeitraum: Syst. Literaturrecherche (bis März 2013) Anzahl eingeschlossene Studien/Patienten (Gesamt): 15 RCTs (n= 1681 participants) Quality Assessment/Risk of bias: Cochrane's risk of bias tool  ⇒ The attrition bias of all included studies was low (few missing data) ⇒ Other key aspects among studies were mostly unclear in risk of bias except two studies
	Ergebnisdarstellung ⇒ The SMDs between metformin and glimepiride were only statistically significant on TC (0.33 [0.03, 0.63], P = 0.03), LDL (0.35 [0.16, 0.53], P = 0.00002), and TG (0.26 [0.05, 0.46], P = 0.01), indicating that efficacy of metformin was statistically significant over glimepiride in lipid metabolism indices ⇒ The differences in glycemic control (e.g. HbA1c and PPBS) and cardiovascular indices (e.g. blood pressure) were not statistically significant. ⇒ there were significant heterogeneities among studies in SBP (I2 = 86%, P < 0.0001), DBP (I2 = 87%, P < 0.00001), PPBS (I2 = 81%, P < 0.00001), TC (I2 = 79%, P < 0.0001), HDL (I2 = 86%, P < 0.00001) and FINS (I2 = 91%, P < 0.00001). ⇒ Sensitivity analysis checked whether the overall effects would be different if only the studies with the sample size N ≥ 90 were included → Metformin outperformed glimepiride only on LDL (0.41 [0.21, 0.61], P < 0.0001) in the studies with sample size N ≥ 90. Other outcomes such as FPG, BMI, TC and TG did not show significant difference between glimepiride and metformin. ⇒ In *12-24 weeks subgroup,* metformin performed better than glimepiride on both BMI (0.47 [0.24, 0.69], P < 0.0001) and TC (0.50 [0.27, 0.72], P < 0.0001). ⇒ In *48-60 weeks subgroup*, metformin performed better only on LDL (0.48 [0.29, 0.67], P < 0.00001). ⇒ Eight out of 15 studies reported **adverse events**:

	Table 9 Adverse events Adverse events | No. of studies | Pooled sample size | Heterogeneity: T^2 | I^2 | P-value | Overall effect: OR [95% CI] | P-value All side effects | 8 | 1003 | 4.70 | 81% | <0.00001 | 0.35 [0.06, 2.01] | 0.24 Hypoglycemia | 5 | 542 | 0.00 | 0% | 0.77 | 4.94 [2.03, 11.99] | 0.0004 Gastrointestinal upset | 5 | 763 | 2.27 | 61% | 0.04 | 0.07 [0.01, 0.37] | 0.002
	Anmerkungen/Fazit der Autoren ⇒ This meta-analysis supported that both metformin and glimepiride was effective in treating T2DM for glycemic control. Metformin performed better than glimepiride in management of BMI and lipid metabolism indices but the advantages of metformin were only significant in short follow-up periods. ⇒ Metformin and glimepiride were not significantly different in glycemic control of T2DM, suggesting that glimepiride would be a good choice second to metformin in the monotherapy of T2DM.
Zhang, 2013 **[108]** **The effects of sulfonylureas plus metformin on lipids, blood pressure, and adverse events in type 2 diabetes: a meta-analysis of randomized controlled trials**	**Fragestellung** meta-analysis of randomized controlled trials (RCTs) on the effects of metformin plus sulfonylureas on lipids profiles, blood pressure, glucose control, insulin, and adverse events
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: metformin and sulfonylureas (glimepiride, glipizide, glibenclamide, gliclazide, etc.), compared to metformin alone in control group Endpunkt: **Primär:** blood pressure, lipid parameters, adverse events; **Sekundär:** HbA1c, fasting insulin Suchzeitraum: Syst. Literaturrecherche (bis August 2012) Anzahl eingeschlossene Studien/Patienten (Gesamt): 20 RCTs (n= 3,633 participants) Quality Assessment/Risk of bias: Cochrane Handbook risk of bias tool

Table 2 Risk of bias assessment of the included trials

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Free from other bias
Cheng [25]	Adequate	Adequate	Adequate	Unclear	Unclear	Adequate
Ning et al. [26]	Unclear	Unclear	Adequate	Unclear	Adequate	Unclear
Dai [7]	Unclear	Unclear	Adequate	Adequate	Adequate	Unclear
Nauck et al. [29]	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate
Bermudez-Pirela et al. [6]	Unclear	Unclear	Adequate	Adequate	Unclear	Unclear
Charpentier et al. [20]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Su et al. [32]	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate
Li et al. [22]	Unclear	Adequate	Adequate	Adequate	Adequate	Adequate
Zhang [28]	Unclear	Adequate	Adequate	Unclear	Unclear	Unclear
Yao et al. [31]	Unclear	Adequate	Adequate	Adequate	Unclear	Adequate
Yao et al. [21]	Unclear	Adequate	Adequate	Adequate	Adequate	Adequate
Ji [30]	Adequate	Adequate	Adequate	Unclear	Adequate	Adequate
Feinglos et al. [19]	Unclear	Unclear	Adequate	Adequate	Unclear	Unclear
Goldstein et al. [33]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Garber et al. [18]	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate
Chien et al. [5]	Unclear	Unclear	Adequate	Adequate	Unclear	Unclear
Garber et al. [35]	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate
Blonde et al. [34]	Unclear	Unclear	Adequate	Adequate	Adequate	Unclear
Marre et al. [36]	Unclear	Unclear	Adequate	Adequate	Unclear	Adequate
Luo et al. [27]	Unclear	Unclear	Adequate	Unclear	Unclear	Unclear

Ergebnisdarstellung

Lipid parameters

⇒ the combination therapy of sulfonylureas and metformin did not change LDL-C significantly when compared with metformin (95 % CI -0.03 to 0.24, P>0.05) (n=4 RCTs)

⇒ the combination therapy reduced HDL-C significantly compared with control treatment (-0.03, 95 % CI -0.06 to -0.01, **P<0.05**) (n=5 RCTs)

⇒ the combination therapy of sulfonylureas and metformin did not change TG significantly when compared with metformin alone (95 % CI -0.21 to -0.03, P>0.05) (n=7 RCTs)

⇒ no significant increase in TC in the groups given sulfonylurea plus metformin compared with the metformin alone groups (0.02, 95 % CI -0.08 to 0.13, P>0.05) (n=6 RCTs)

Hypoglycemia

⇒ the combination therapy groups were associated with a significant increase in the proportion of patients with hypoglycemia (RR = 4.09, 95 % CI 2.13–7.89, **P<0.05**) (n=17 RCTs)

⇒ In subgroup analyses, combination therapy significantly increased hypoglycemia in glipizide group (RR = 3.36, 95 % CI 1.40–8.08) and in glibenclamide group (RR = 16.05, 95 % CI 6.22–41.39).

⇒ No correlation was found between dose and the incidence of hypoglycemia.

Adverse events

⇒ the combination therapy significantly increased the incidence of nervous system reactions (RR = 1.27, 95 % CI 1.03–1.57, **P<0.05**) (n=11 RCTs)

⇒ metformin plus sulfonylureas compared to metformin showed a significant decrease in digestive system side effects (RR = 0.75, 95 %

	CI 0.67–0.84, **P<0.05**) (n=18 RCTs) ⇒ Thirteen studies reported diarrhea. The results indicated that a significant decrease in diarrhea (RR = 0.70, 95 % CI 0.58–0.86, **P<0.05**) (n=13 RCTs) ⇒ Ten studies reported nausea or vomiting. The pooled analysis showed that a significant decrease was seen in the combination therapy groups (RR = 0.58, 95 % CI 0.42–0.80, **P<0.05**) (n=10 RCTs) <u>HbA1c</u> ⇒ The combination of sulfonylureas and metformin was associated with a significant reduction of HbA1c versus metformin alone (-0.79, 95 % CI -0.96 to -0.63, **P<0.001**) (n=15 RCTs) ⇒ Subgroup analyses also showed reductions of HbA1c in glimepiride group (-0.84, 95 % CI -1.23 to -0.45), as well as those in glipizide group (-0.66, 95 % CI -0.89 to -0.42). <u>Fasting insulin</u> ⇒ no significantly increase in FINS compared with metformin (WMD = 1.26 mU/L, 95 % CI -0.78 to 3.30) (n=10 RCTs) ⇒ In glipizide group, the level of FINS was significantly increased in the combination therapy (WMD = 2.33 mU/ L, 95 % CI 1.94–2.73).
	Anmerkungen/Fazit der Autoren ⇒ HDL-C in the combination therapy groups was decreased, but none of the other lipid parameters and BP showed any significant change compared with the controlled groups ⇒ The combination of sulfonylureas and metformin reduced HbA1c by 0.79 %, compared with metformin monotherapy. However, hypoglycemic events increased when sulfonylurea was added (RR = 4.09, 95 % CI 2.13–7.89, **P<0.05)** ⇒ In conclusion, adding sulfonylureas to patients with T2DM inadequately controlled with metformin monotherapy has no clinically significant effect on BP and metabolic effects except for HDL-C. ⇒ The combination therapy can reduce the incidence of digestive symptoms, but it is associated with high risk of hypoglycemia and nervous system adverse events.
Yin, 2014 [107] **Comparison of repaglinide and metformin versus metformin alone for type 2**	**Fragestellung** we conducted a meta-analysis of RCTs which compared combination therapy and metformin monotherapy
	Methodik Population: Pat. mit DM Typ II

diabetes: a meta-analysis of randomized controlled trials	Intervention/ Komparator: repaglinide plus metformin combination therapy group (with or without additional medication) and metformin monotherapy group (with or without the same additional medication) Endpunkt: HbA1c, FBG, PBG (postprandial blood sugar), TG (triglycerides), TC (total cholesterol), LDL (low-density lipoprotein), HDL (high-density lipoprotein) Suchzeitraum: Syst. Literaturrecherche (bis November 2013) Anzahl eingeschlossene Studien/Patienten (Gesamt): 22 Quality Assessment/Risk of bias: Jadad scale

Table 1 – Characteristics of included studies.

Author (year)	N (R + M/M)	Age[a] (R + M/M)	Sex (male/female)	Treatment				Trail duration	Jaded score
				R + M		M (mg/day)	Additional medication		
				R (mg/day)	M (mg/day)				
Ma 2003 [3]	81 (29/27/25)	53.17 (8.11)/ 52.53 (7.24)	26/26	1.5–3	750–1500	750–1500	NO	12 weeks	3
Liu 2005 [4]	40 (20/20)	NR	NR	1.5–3	1500	1500	NO	8 weeks	1
Chen 2006 [5]	52 (27/25)	53.17 (8.11)/ 52.53 (7.24)	26/26	1.5–3	750–1500	750–1500	NO	12 weeks	2
Chen 2007 [6]	78 (40/38)	35–73	46/32	1.5–3	500	500	NO	8 weeks	1
Davies 2007 [7]	51 (26/29)	56.1 (10.8)/ 57.9 (10.5)	24/30	1.5–4	Maximum dose tolerated	Maximum dose tolerated	NPH insulin	4 months	3
Civera 200 8 [8]	24 (12/12)	60.3 (7.7)/ 61.6 (9.2)	13/11	6	1700	1700	NPH insulin	6 months	2
Lin 2008 [9]	36 (18/18)	62.8 (8. 7)	20/16	1.5	750	1500	NO	12 weeks	1
Zhang 2008 [10]	80 (28/26/26)	30-65	NR	1–2	750–1000	750–1000	NO	12 weeks	1
Xu 2009 [11]	120 (68/52)	41–72	58/62	NR			NO	12 weeks	1
Chen 2010 [12]	62 (32/30)	47.5 (13.9)/ 47.1 (11.9)	33/29	1.5–3	750–1500	750–1500	NO	12 weeks	2
Cha 2011 [13]	60 (20/20/20)	51.78 (5.71)/ 51.65 (4.26)	22/18	1.5–3	750–1500	750–1500	NO	8 weeks	1
Jing 2011 [14]	156 (52/52/52)	42.67 (8.52)	71/85	1.5	1500	1500	NO	12 weeks	1
We 2011 [15]	50 (25/25)	40–70	36/14	1.5–3	1500	1500	NO	8 weeks	1
Zhu 2012 [16]	60 (30/30)	40–70	33/27	6	750	750	NO	12 weeks	1
Bai 2012 [17]	90 (30/30/30)	47	48/42	1.5–3	750–1500	750–1500	NO	8 weeks	1
Jin 2012 [18]	65 (32/33)	53.2	38/27	3	1500	1500	NO	12 weeks	3
Zhao [19]	135 (45/45/45)	40.7 (18.3)	74/61	1.5	750	750	NO	12 weeks	2
Dong 2012 [20]	94 (47/47)	49.7 (8.9)	58/36	1.5	1500	1500	NO	8 weeks	1
Lin 2013 [21]	96 (32/32/32)	65.6 (3.2)	56/40	3	750–1500	750–1500	NO	8 weeks	1
Li 2013 [22]	186 (62/62/62)	56.9	102/84	1.5–3	750–1500	750–1500	NO	8 weeks	2
He 2013 [23]	148 (74/74)	47.27	76/72	1.5	750–1500	1500	NO	3 months	1
Xu 2013 [24]	840 (280/280/ 280)	38.7	560/280	1.5	1500	1500	NO	3 months	1

Notes: R + M, repaglinide + metformin; M, metformin; NR, not reported.
[a] Presented in range or mean (standard deviation).

Ergebnisdarstellung

⇒ combination therapy induced a greater reduction of HbA1c (pooled mean difference -1.2% (-13 mmol/mol); 95% CI -1.5 to 0.83, P < 0.00001) than metformin alone

⇒ In both subgroups, the level of HbA1c was significantly lower in the combination therapy group than in the metformin monotherapy group (pooled mean difference -1.1% (-12 mmol/mol); 95% CI -1.50 to 0.78; P < 0.00001, pooled mean difference -1.4% (-15 mmol/mol); 95% CI -1.91 to 0.86; P < 0.00001, respectively)

⇒ Combination therapy significantly reduced FBG (95% CI -1.99 to 0.93, P < 0.00001), PBG level (95% CI -2.38 to -1.42, P < 0.00001) and TC (95% CI -0.41 to -0.04, P = 0.02) compared with metformin alone.

⇒ Combination therapy did not change TG (95% CI -0.85 to 0.01, P = 0.06); LDL (95% CI -0.30 to 0.04, P = 0.13) and HDL (95% CI -0.19 to

	0.14, P = 0.76) compared with metformin alone ⇒ compared with metformin alone, there was no increased hypoglycaemia episode with the combination therapy (RR = 1.21, 95% CI 0.72 to 2.04, P = 0.48) ⇒ Only one serious treatment-related hypoglycemia was reported in combination therapy group. As for gastrointestinal incidents, most of studies did not report these events in detail, so we did not compare the rates of gastrointestinal upset.
	Anmerkungen/Fazit der Autoren ⇒ the combination therapy resulted in better improvement in glucose control, but not most of lipid parameters compared with metformin alone. Moreover, the meta-analysis showed that the combination therapy caused no increase in the risk of hypoglycemia ⇒ In conclusion, our meta-analysis shows that combination therapy is safe and can gain better outcomes in glycemic control. However, due to the poor methodological quality of the studies included in this meta-analysis and the short study duration, well-designed multicenter RCTs are required to confirm these findings.
Yang, 2014 **[106]** **Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis**	**Fragestellung** We conduct a systematic review and meta-analysis to summarize the benefits and harms of canagliflozin in T2DM either as monotherapy or as add-on treatment.
	Methodik Population: Pat. mit DM Typ II Intervention/ Komparator: any use of canagliflozin in dual or triple therapy or monotherapy/ placebo or active comparator Endpunkt: HbA1c, FPG, body weight, HOMA2-%β, blood pressure, plasma lipids, AEs Suchzeitraum: Syst. Literaturrecherche (bis Januar 2014) Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 RCTs Quality Assessment/Risk of bias: Cochrane Handbook risk of bias tool ⇒ alle Studien haben ein geringes Bias-Risiko ⇒ 2 RCTs: random sequence generation and allocation concealment unclear ⇒ All studies were funded by industry
	Ergebnisdarstellung (Darstellung ausschließlich von Canagliflozin vs. active comparator)

HbA1c

Compared with active comparator, canagliflozin significantly reduced HbA1c by −0.21 % (WMD, 95 %CI [−0.33 to −0.08], p=0.001) (Fig. 3). When compared with each active hypoglycemic agents, HbA1c was also reduced with canagliflozin compared with sitagliptin (WMD −0.24 %, 95 %CI [−0.40 to −0.09], p=0.002) and glimepiride (WMD −0.12 %, 0.95 %CI [−0.23 to −0.01], p=0.03) (Fig. 3).

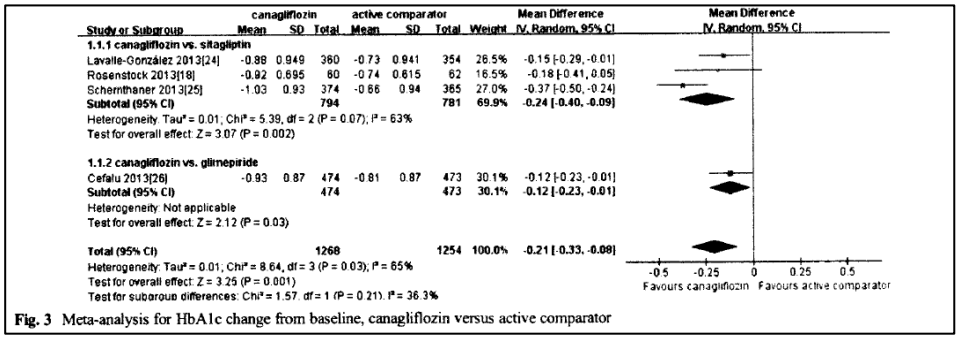


Fig. 3 Meta-analysis for HbA1c change from baseline, canagliflozin versus active comparator

and Fig. 3). Compared with placebo or active comparator, canagliflozin provided a significant greater reduction in FPG (vs. placebo, WMD −33.50 mg/dl, 95 %CI [−39.22 to −27.78], p<0.00001; vs. active comparators, WMD −15.86 mg/dl, 95 %CI [−23.17 to −8.56], p<0.00001).

Body weight

Treatment with canagliflozin was associated with a significant reduction in body weight. Compared with placebo, body weight was reduced by −2.81 kg (WMD, 95 %CI [−3.26 to −2.37], p<0.00001) (Supplementary Fig. 4). Similarly, canagliflozin had a superior effect on body weight reduction compared with active comparator (WMD −3.49 kg, 95 %CI [−4.86 to −2.12], p<0.00001) (Supplementary Fig. 5), with WMD vs. sitagliptin of −2.84 kg (95 %CI [−3.21 to −2.48], p<0.00001). When compared canagliflozin with glimepiride, weight loss occurred much greater with canagliflozin (WMD −5.40 kg, 95 %CI [−5.95 to −4.85], p<0.00001) (Supplementary Fig. 5).

HOMA2-%β

Canagliflozin was associated with a greater significant improvement in HOMA2-%β, the pooled WMD with canagliflozin vs. placebo for HOMA2-%β was 15.07 (WMD, 95 %CI [7.14 to 23.00], p=0.0002) and vs. active comparator 11.33 (WMD, 95 %CI [5.31 to 17.34], p=0.0002), respectively (Table 2).[a]p<0.05, there was a statistical significance between two groups

Blood-pressure

Compared with placebo, treatment with canagliflozin produced a significant higher reduction in systolic blood pressure (SBP) (WMD −5.05, 95 %CI [−6.81 to −3.28], p<0.00001) (Supplementary Fig. 6 and Table 2) and diastolic blood pressure (DBP) (WMD −2.43, 95 %CI [−3.29 to −1.57], p<0.0001) (Supplementary Fig. 8 and Table 2).

When compared with other antidiabetic agents, canagliflozin provided higher reduction in SBP by −4.34 mmHg (WMD, 95 %CI [−5.31 to −3.36], p<0.00001)

Plasmalipids

No significant differences were seen in plasma lipids levels between canagliflozin and sitagliptin in our meta-analysis (all $p>0.05$) (Supplementary Table 2). Canagliflozin relative to glimepiride was associated with an increase in LDL-C (WMD 0.20, 95 %CI [0.09 to 0.31], $p=0.0004$) (Supplementary Fig. 11) and HDL-C levels (WMD 0.11, 95 %CI [0.08 to 0.14], $p<0.00001$); a similar decreases in triglycerides levels (WMD −0.09, 95 %CI [−0.23 to 0.05], $p=0.2$), with smaller increases in LDL-C/HDL-C ratio (WMD −0.03, 95 %CI [−0.11 to 0.05], $p=0.48$) across groups (Supplementary Table 2).

AEs: Hpoglycemia

When compared canagliflozin with sitagliptin, there was no significant difference in all types of hypoglycemia between two groups (RR 1.29, 95 %CI [0.82 to 2.03], $p=0.28$) (Fig. 5). In the RCT comparing canagliflozin to glimepiride [26], the hypoglycemic rates were significantly lower with canagliflozin 100 mg (6 %) and 300 mg (5 %) than with glimepiride (34 %) ($p<0.0001$ for both). The frequency of severe hypoglycemia was also lower with canagliflozin (<1 % for both doses) than with glimepiride (3 %). The pooled RR of hypoglycemia of canagliflozin relative to glimepiride was 0.15 (95 %CI [0.10 to 0.22], $p<0.00001$) (Fig. 5).

AEs: urinary tract infections and genital tract infections

Overall, there was no significant difference in the rate of urinary tract infections (UTIs) when compared canagliflozin with placebo or other antidiabetic agents, the pooled RRs were 1.19(95 %CI [0.82 to 1.73], $p=0.36$) and 1.18 (95 %CI [0.84 to 1.64], $p=0.34$), respectively (Table 2). However, a significant increase, with a non-dose-dependent manner, was seen in canagliflozin group in the incidence of genital tract infections (vs. placebo, RR 3.76, 95 %CI [2.23 to 6.35], $p<0.00001$; vs. active comparators, RR 4.95, 95 %CI [3.25 to 7.52], $p<0.00001$) (Table 2).

AEs: others

Compared with placebo or active comparator, the incidence of any AE, serious AEs or discontinuation due to AEs did not differ between the two groups (all $p>0.05$) (Supplementary Table 3). However, the risks of osmotic diuresis-related AEs (ie., pollakiuria and diarrhea) were slightly higher with canagliflozin (vs. placebo, RR 3.93, 95 %CI [2.25 to 6.86], $p<0.00001$; vs. active comparators, RR 2.57, 95 %CI [1.26 to 5.25], $p=0.009$). Volume-related AEs (ie., postural dizziness, orthostatic hypotension) were similar among patients treated with canagliflozin and those receiving placebo or active comparator (all $p>0.05$) (Supplementary Table 3).

Anmerkungen/Fazit der Autoren

Treatment with canagliflozin provided clinically and statistically significant reductions in HbA1c levels in patients with T2DM. These effects were associated with significant improvements in FPG levels, body weight as well as β-cell function. However, due to the higher rates of genital infections, increase in LDL-C levels and unclear cardiovascular risks, careful patient selection, and ongoing monitoring will be important.

Wojciechowski, 2015 **[104]** **Clinical efficacy and safety of insulin aspart compared with regular human insulin in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis**	**Fragestellung** a systematic review to summarize and update the evidence on relative efficacy and safety of IAsp and RHI in both types of diabetes in patients receiving prandial insulin treatment.
	Methodik Population: Pat. mit DM Typ I & II Intervention/ Komparator: compare IAsp with RHI Endpunkt: HbA1c Suchzeitraum: Syst. Literaturrecherche (bis Mai 2013) Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 RCTs included in the analysis: 11 RCTs T1DM + **5 RCTs T2DM (n= 451 participants)** Quality Assessment/Risk of bias: Jadad scale

Bretzel, 2004	pg, ol	75	80	61.4	62	59	50	> 1		7.82 (62)	7.83 (62)	29.2	29.3	MDI/NPH	12	2/5
Herrmann, 2013	pg, ol	18	11	58	60	61	73	n/a		8.7 (72)	8.7 (72)	31.5	32.8	MDI/NPH or LAA	104	1/5
Maiti, 2012	pg, ol	30	30	54.0	50.2	53	60	5.42	4.93	8.3 (67)	8.1 (65)	24.9	25.2	MDI/ NA	52	3/5
Pala, 2007	co, ol	25		65		28		17.5		7.3 (56)		27.7		MDI/no basal	2×12	1/5
Raskin, 1999	pg, ol	91	91	NA		NA		≥2		8.1 (65)	7.9 (63)	NA		MDI/NPH	26	1/5

Ergebnisdarstellung

<u>HbA1c</u>

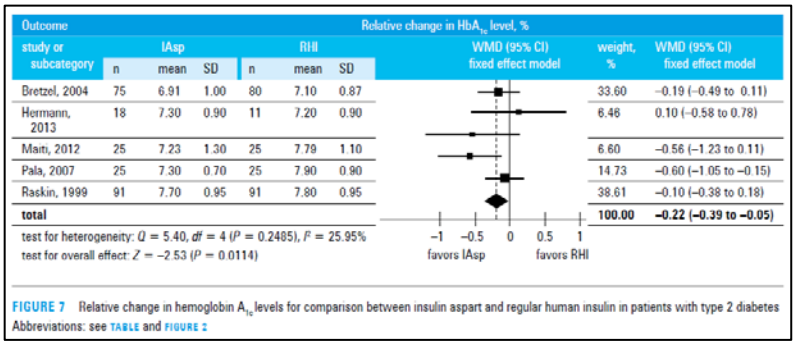


FIGURE 7 Relative change in hemoglobin A_{1c} levels for comparison between insulin aspart and regular human insulin in patients with type 2 diabetes
Abbreviations: see TABLE and FIGURE 2

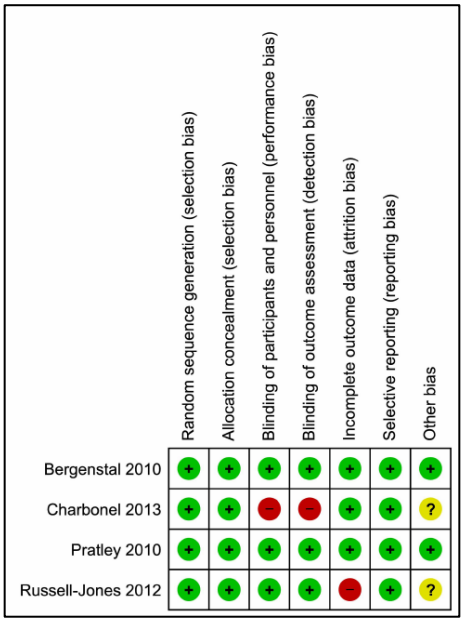
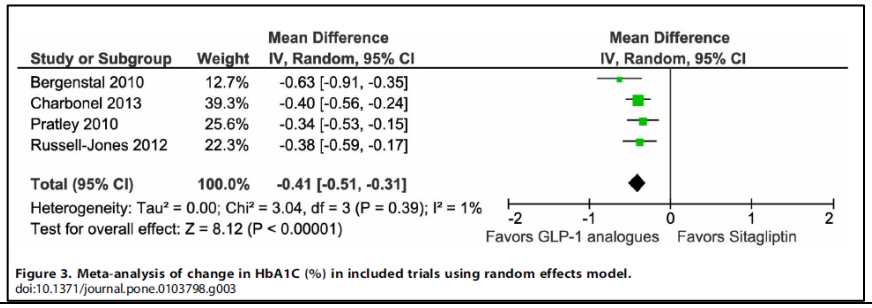
<u>Hypoglycemia</u>

⇒ Pooled results demonstrated no significant between-group differences in the risk of overall hypoglycemia (RR, 1.00 [0.70, 1.44]).

Anmerkungen/Fazit der Autoren

⇒ In summary, IAsp demonstrates better glycemic control with respect to HbA1c and prandial glucose fluctuations compared with RHI in patients with both T1DM and T2DM receiving a prandial insulin regimen therapy.

Wang, 2014 [103] **Comparison of GLP-1 Analogues versus Sitagliptin in**	**Fragestellung** The main objective of this meta-analysis was to assess the efficacy and safety of GLP-1 analogues compared to the DPP-4 inhibitors in the management of patients with T2DM

the Management of Type 2 Diabetes: Systematic Review and Meta-Analysis of Head-to-Head Studies	**Methodik** Population: Pat. mit DM Typ II Intervention/ Komparator: GLP-1 analogues and DPP-4 inhibitors as monotherapy or add-on therapy to metformin Endpunkt: HbA1c; Sekundär: body weight, fasting and postprandial plasma glucose values, percentage of patients achieving a HbA1C ,7%, blood pressure (systolic and diastolic) and lipid parameters (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels). Safety outcomes extracted included withdrawal rates from any adverse events that documented incidence of hypoglycemia, nausea, vomiting, diarrhea, constipation, urinary tract infection (UTI), upper respiratory infection (URTI), nasopharyngitis, and headache Suchzeitraum: Syst. Literaturrecherche (bis Januar 2014) Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs Quality Assessment/Risk of bias: Cochrane Collaboration's risk of bias tool 
	Ergebnisdarstellung ⇒ All 4 trials directly compared GLP-1 analogues groups with sitagliptin  **Figure 3. Meta-analysis of change in HbA1C (%) in included trials using random effects model.** doi:10.1371/journal.pone.0103798.g003

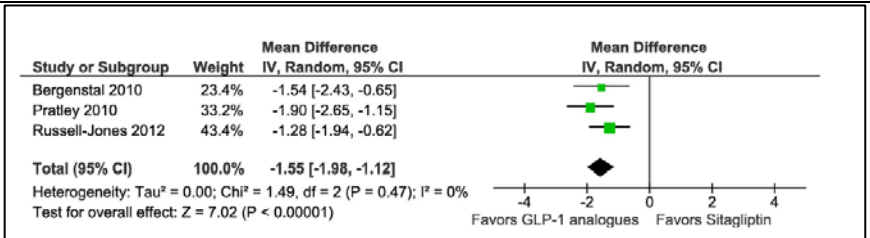


Figure 5. Meta-analysis of change in body weight (kg) of included trials using random effects model.
doi:10.1371/journal.pone.0103798.g005

Table 3. Summary of meta-analyses of adverse events in patients with type 2 diabetes treated with GLP-1 analogues vs Sitagliptin.

Adverse event	No. of studies contributing data	Relative risk (95% CI)	I^2 Heterogeneity, %	Comparator group (Event/Total)	
				GLP-1 analogues	Sitagliptin
Withdrawal	3	2.89 (1.42 to 5.87)	0	31/629	10/548
Hypoglycemia	4	1.35 (0.71 to 2.58)	16	33/956	22/874
Nausea	3	3.14 (2.15 to 4.59)	1	112/629	32/548
Vomiting	3	2.60 (1.48 to 4.56)	0	47/629	16/548
Diarrhea	3	1.82 (1.24 to 2.69)	0	72/629	35/548
Constipation	3	2.50 (1.33 to 4.70)	0	40/629	13/548
Urinary tract infection	1	1.15 (0.48 to 2.76)	N/A	10/160	9/166
Upper respiratory tract infection	1	0.41 (0.17 to 1.04)	N/A	6/160	15/166
Nasopharyngitis	2	0.83 (0.57 to 1.22)	0	46/469	47/382
Headache	3	0.87 (0.61 to 1.23)	0	56/629	57/548

Anmerkungen/Fazit der Autoren

⇒ The results demonstrate that compared to sitagliptin, GLP-1 analogues are more efficacious for glycemic control and weight loss, but not better in reducing blood pressure and lipid profile; and GLP-1 analogues have a higher incidence of gastrointestinal adverse events and similar hypoglycemic events compared to sitagliptin.

⇒ For less common adverse events, GLP-1 analogues and sitagliptin have a similar incidence of headache, UTI, URTI, and nasopharyngitis. If weight loss is not a particular concern and only a small decrease in A1C is required, a DPP-4 inhibitor may be better choice.

Vasilakou, 2013

[102]

Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes A Systematic Review and Meta-analysis

Fragestellung

To assess the efficacy and safety of SGLT2 inhibitors in adults with type 2 diabetes.

Methodik

Population: Adults with type 2 diabetes

Intervention: SGLT2 inhibitors

Komparator:

- placebo
- another antidiabetic medication

Endpunkt:

	• change from baseline in hemoglobin A1c (HbA1c) level (primary outcome), • body weight, • systolic and diastolic blood pressures. • all-cause mortality and cardiovascular events (myocardial infarction, stroke, death due to cardiovascular disease, or hospitalization for unstable angina). • AEs (any hypoglycemia, urinary tract infections, genital tract infections, hypotension, any serious adverse event, bladder cancer, or breast cancer) Suchzeitraum (Aktualität der Recherche): up to April 201 Anzahl eingeschlossene Studien/Patienten (Gesamt): 55 (49 primary and 9 extension studies Qualitätsbewertung: • Cochrane Risk of bias for each study • Assessment of publication bias: Eggers test • Assessment of overall quality of evidence (GRADE) for following outcomes: change in HbA1c level, change in body weight, change in systolic blood pressure, hypoglycemia, cardiovascular events, urinary and genital tract infections. Heterogeneity assessment with I2 This study received no funding
	Ergebnisdarstellung (*hier: Vergleiche mit aktiven Kontrollen* • 13 studies: Comparison of SGLT2 inhibitors with o metformin in 6 studies (22, 23, 25, 30, 48), o sitagliptin in 5 studies (7, 59, 60, 62, 63), o a sulfonylurea in 2 studies (43, 57). • Overall risk of bias for the primary outcome was high in almost all studies, primarily because of incomplete outcome data (high discontinuation rate or use of inadequate imputation method to handle missing data) • The Egger test did not reveal any evidence of publication bias *Efficacy results (siehe auch Tab.)* <u>Gycemic efficacy:</u> • Compared with other hypoglycemic agents, SGLT2 inhibitors had similar glycemic efficacy when used as monotherapy (WMD, 0.05% [CI, -0.06% to 0.16%]; I2 =0%) or add-on treatment (WMD, -0.16% [CI, -0.32% to 0.00%]; I2 =82%) • overall risk of bias was high

	<u>Body weight</u> • SGLT2 inhibitors had a favorable effect compared with other antihyperglycemic agents in absolute change (WMD, -1.80 kg [CI, -3.50 to -0.11 kg]; I2 = 97%)and percentage of change (WMD, -2.14% [CI, -3.02% to -1.25%]; I2 = 67%) in body weight • absolute body weight reduction for SGLT2 inhibitors versus other active comparators was less evident and heterogeneity was eliminated in a post hoc sensitivity analysis that excluded 1 sulfonylurea-controlled study (57) (WMD, -1.11 kg [CI, -1.46 to -0.76 kg]; I2 = 0%). • Overall risk of bias for body weight analyses was high. <u>Blood pressure</u> • SGLT2 inhibitors associated with a reduction in systolic (WMD, -4.45 mm Hg [CI, -5.73 to -3.18 mm Hg]; I2 =34%) and diastolic blood pressure (WMD,-2.01 mm Hg [CI, -2.62 to -1.39 mm Hg]; I2 =0%) compared to active control • Risk of bias was high for both systolic and diastolic blood pressure analyses. <u>Hypoglycemia</u> • Incidence of hypoglycemia was low in most treatment groups, except for among patients receiving a sulfonylurea or insulin as allocation treatment or background therapy • OR compared to active control 0.44 (CI, 0.35 to 0.54; I2= 93%) • Exclusion of 1 sulfonylurea-controlled study (57) in a post hoc sensitivity analysis resulted in similar hypoglycemic risk compared with other antidiabetic agents and removed heterogeneity (OR, 1.01 [CI, 0.77 to 1.32]; I2= 0%) <u>Death and SAEs</u> • All-cause mortality did not differ between SGLT2 inhibitors and placebo or active comparators, although relatively few deaths have been reported <u>Genitourinary Tract Infections and Hypotension</u> • SGTL2 inhibitors vs other antidiabetic drugs: higher risk for urinary tract infection (OR, 1.42 [CI, 1.06 to 1.90]; I2 =25%); genital tract infections (OR, 5.06 [CI, 3.44 to 7.45]; I2 = 0%), hypotension (OR, 2.68 [CI, 1.14 to 6.29]; I2=2%) <u>Cardiovascular Outcomes</u> • No stat. sign differences between SGTL2 inhibitors and placebo or active control

	Table 2. Quality of Evidence for Clinically Relevant Outcomes* Illustrative Comparative Risks† Outcome | Follow-up, wk | Assumed Risk (Active Comparator) | Corresponding Risk (SGLT2 Inhibitor) Mean change in HbA_{1c} level (%) from baseline | 12–52 | The mean change in HbA_{1c} level ranged across control groups from −0.37% to 0.16% | The mean change in HbA_{1c} level in the intervention groups was 0.06% lower§ (95% CI, 0.18% lower to 0.05% higher) Mean absolute change in body weight (kg) from baseline | 12–24 | The mean change in body weight ranged across control groups from −1.37 to −0.71 kg | The mean change in body weight in the intervention groups was 1.11 kg lower§ (CI, 1.46 to 0.76 kg lower) Mean percentage of change in body weight from baseline | 12–52 | The mean change in body weight ranged across control groups from −2.80% to −1.00% | The mean change in body weight in the intervention groups was 2.14 percentage points lower§ (CI, 3.02 to 1.25 percentage points lower) Mean change in systolic blood pressure (mm Hg) from baseline | 12–52 | The mean change in systolic blood pressure ranged across control groups from −6.00 to −2.40 mm Hg | The mean change in systolic blood pressure in the intervention groups was 4.45 mm Hg lower§ (CI, 5.73 to 3.18 mm Hg lower) Incidence of any hypoglycemia | 12–52 | 16 cases per 100 patients | 16 cases per 100 patients (CI, 13 to 20 cases per 100 patients) Incidence of cardiovascular events | 12–102 | 2 cases per 100 patients | 2 cases per 100 patients (CI, 1 to 2 cases per 100 patients) Incidence of urinary tract infections | 12–52 | 6 cases per 100 patients | 8 cases per 100 patients (CI, 6 to 10 cases per 100 patients) Incidence of genital tract infections | 12–52 | 2 cases per 100 patients | 10 cases per 100 patients (CI, 7 to 14 cases per 100 patients) HbA_{1c} = hemoglobin A_{1c}; SGLT2 = sodium–glucose cotransporter 2. * Among studies that compared SGLT2 inhibitors with active comparators (any antidiabetic medication) in adults with type 2 diabetes mellitus. † The assumed risk is based on the median risk in the control group across studies. The corresponding risk is based on the assumed risk in the comparison group and the relative effect of the intervention. ‡ Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation guidelines (16, 17). Evidence could be rated as high quality (further research is very unlikely to change our confidence in the estimate of effect), moderate quality (further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate), or very low quality (we are very uncertain about the estimate). § Lower change indicates better outcome. ‖ Downgraded for inconsistency due to heterogeneity of effect estimate. ¶ Downgraded because most of the studies had high risk of bias. ** The monotherapy subgroup included SGLT2 inhibitors as first-line antidiabetic treatment. The add-on therapy subgroup included SGLT2 inhibitors as add-on therapy to existing antidiabetic treatment. †† Downgraded because most of the studies had unclear risk of bias. ‡‡ Downgraded for imprecision due to wide CIs in results.
	Anmerkungen/Fazit der Autoren Sodium–glucose cotransporter 2 inhibitors may improve short-term outcomes in adults with type 2 diabetes, but effects on long-term outcomes and safety are unclear.
Tricco, 2014 [101] **Safety and effectiveness of dipeptidyl peptidase-4 inhibitors versus intermediate-acting insulin or placebo for**	**Fragestellung** To evaluate the effectiveness and safety of dipeptidyl peptidase-4 (DPP-4) inhibitors versus intermediate-acting insulin for adults with type 2 diabetes mellitus (T2DM) and poor glycaemic control despite treatment with two oral agents.
	Methodik Population: third-line treatment of adults with T2DM and HbA1c ≥6.5% third-line treatment defined as when the study examined the use of two oral antihyperglycaemic agents among all patients, plus the addition of a DPP-4 inhibitor,

patients with type 2 diabetes failing two oral antihyperglycaemic agents: a systematic review and network meta-analysis	intermediate-acting insulin or placebo (ie, three agents in total per group). Intervention: DPP-4 inhibitors (eg, sitagliptin, vildagliptin, saxagliptin and linagliptin) Komparator: • intermediate-acting insulin (eg, NPH) • no treatment or placebo Endpunkte • HbA1c • healthcare utilisation (eg, emergency department visits), • body weight, • fractures, • quality of life, • microvascular complications (retinopathy, neuropathy, nephropathy), • macrovascular complications (cardiovascular disease,stroke/transient ischaemic attack, peripheral vascular disease), • all-cause mortality, • harms (including infection, pancreatic cancer, severe hypoglycaemia, serious hyperglycaemia and body weight), • cost and cost-effectiveness Suchzeitraum (Aktualität der Recherche): 12/2012Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 (n=2967) Qualitätsbewertung der Studien: • Cochrane risk of bias tool • McMaster Quality Assessment Scale of Harms (McHarm) tool Clinical, methodological and statistical (eg, I2 statistic) heterogeneity were considered. Bayesian random effects network meta-analysis (NMA) for HbA1c *Sonstige methodische Hinweise* Protocol registered with PROSPERO registry (CRD42013003624)
	Ergebnisdarstellung *Studienqualität:*

Table 3 Appraisal of risk of bias of the included studies using the Cochrane risk-of-bias tool[12]

Study	1	2	3	4	5	6	7
Fonseca *et al*[25]	Unclear	Low	Low	Low	High	Low	High
Gilman*[26]	Unclear	Unclear	Low	Low	High	Unclear	High
Abdulwahid*[27]	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear
Lukashevich*[28]	Unclear	Unclear	Low	Low	Low	Low	Unclear
Makdissi *et al*[29]	Unclear	Unclear	Low	Low	Unclear	Low	Low
Moses *et al**[30]	Unclear	Unclear	Low	Low	High	Unclear	Unclear
Nogueira*[31]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Violante *et al*[32]	Unclear	Unclear	Low	Low	High	Low	High
Owens *et al*[33]	Unclear	Unclear	Low	Low	Low	Low	High
Hermansen *et al*[34]	Low	Low	Low	Low	High	Unclear	High

Items:
1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective reporting.
7. Other bias.
*Unpublished data.
High, high risk; Low, low risk; Unclear, unclear risk.

Results:

Reduction in HbA1c: network meta-analysis (based on 8 RCTs

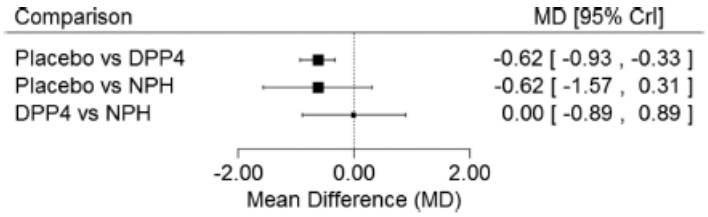


Figure 2 Glycosylated haemoglobin network meta-analysis results. This is the forest plot for the glycosylated haemoglobin network meta-analysis. CrI, credit limit; DPP-4, dipeptidyl peptidase-4 inhibitors; NPH, neutral protamine Hagedorn; MD, mean difference.

- ➔ Addition of DPP-4 inhibitors vs placebo significantly reduced HbA1c
- ➔ No sign. differences in HbA1c for neutral protamine Hagedorn (NPH) insulin versus placebo and DPP-4 inhibitors versus NPH

Meta-analysis

Reduction in HbA1c:

superiority of DPP-4 inhibitor plus metformin + a sulfonylurea/ exenatide vs placebo plus metformin and a sulfonylurea/exenatide (5 RCTs, MD −0.61%, 95% CI −0.81% to −0.41%, I2=87%).

microvascular complications:

no differences in neuropathy between saxagliptin plus metformin and a sulfonylurea vs placebo plus metformin + a sulfonylurea after 24 weeks of follow-up (1 RCT; RR 6.95, 95% CI 0.36 to 133.13).

macrovascular complications

no differences in cardiovascular disease (unspecified or acute myocardial infarction26) between DPP-4 inhibitor plus metformin and a sulfonylurea/ exenatide versus placebo plus metformin and asulfonylurea/exenatide (2 RCTs, 22 w median follow up, RR 0.18, 95% CI 0.02 to 1.63, I2=0%)

all-cause mortality

	no differences in all-cause mortality between sitagliptin plus metformin and a sulfonylurea/ pioglitazone versus placebo plus metformin and a sulfonylurea/ pioglitazone (2 RCTs, 25w median follow up; RR 0.98, 95% CI 0.10 to 9.41, I2=0%). Harms • no differences in any harm (5 RCTs, RR 1.07, 95% CI 0.96 to 1.19, I2=22%) or overall harms that were treatment related (4 RCTs, RR 1.38, 95% CI 0.92 to 2.09, I2=67%) between DPP-4 inhibitor plus metformin and a sulfonylurea/exenatide/ pioglitazone versus placebo plus metformin and a sulfonylurea/exenatide/pioglitazone • no differences in severe hypoglycemia (2 RCTs, RR 0.69, 95% CI 0.16 to 2.94, I2=0% • lower risk for infections with DPP-4 inhibitor plus metformin and a sulfonylurea/ pioglitazone compared with those receiving placebo plus metformin and a sulfonylurea/pioglitazone (4 RCTs, RR 0.72, 95% CI 0.57 to 0.91, I2=0%M subgroup analyses for specific type of infections revealed no diff. • body weight: no differences after a median of 24 weeks of follow-up between DPP-4 inhibitor plus metformin and a sulfonylurea/exenatide/pioglitazone vs placebo plus metformin and a sulfonylurea/exenatide/pioglitazone (4 RCTs, MD 0.23 kg, 95% CI −1.58 to 2.04, I2=0%).; no differences for sitagliptin plus metformin and a sulfonylurea versus NPH insulin plus metformin and a sulfonylurea (1 RCT; MD −4.10 kg, 95% CI −11.32 to 3.12).
	Anmerkungen/Fazit der Autoren DPP-4 inhibitors are superior to placebo and have similar effectiveness as NPH insulin in reducing HbA1c as a third-line therapy. This literature base can be improved by ensuring less patient dropouts, adequate reporting of patient characteristics and harms, and examining important diabetes outcomes, including healthcare utilisation, fractures, quality of life, cost and cost-effectiveness.

Qaseem A., 2012 **American College of Physicians** **[93]** Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians	The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the comparative effectiveness and safety of type 2 diabetes medications.
	Methodik Grundlage der Leitlinie The evidence report informing this guideline reviewed data for 11 FDA-approved, unique classes of drugs for the treatment of hyperglycemia in type 2 diabetes Key question 1: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options for the intermediate outcomes of glycemic control (in terms of hemoglobin A1c [HbA1c]), weight, or lipids? Key question 2: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options in terms of the following long-term clinical outcomes: all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity (for example, myocardial infarction and stroke), retinopathy, nephropathy, and neuropathy? Key question 3: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of these treatment options in terms of the following adverse events and side effects: hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and gastrointestinal side effects? Key question 4: Do safety and effectiveness of these treatment options differ across subgroups of adults with type 2 diabetes, in particular for adults aged 65 years or older, in terms of mortality, hypoglycemia, and cardiovascular and cerebrovascular outcomes? (no sufficient evidence available) Literature search: Update systematic search done by Johns Hopkins Evidence-based Practice Center. This review updates a 2007 systematic review on the

same topic in MEDLINE, EMBASE,
and the Cochrane Central Register of Controlled Trials until 2010

– *Quality of RCTs judged by Jadad scale*

LoE/GoR:
This guideline rates the recommendations by using the American College of Physicians guideline grading system, which is based on the GRADE system

Table 1. **The American College of Physicians Guideline Grading System***

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) workgroup.

Details of the ACP guideline development process can be found in ACP's methods paper

Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).

Initiation of oral pharmacologic therapy is an important approach to effective management of type 2 diabetes. There are no data on the best time to add oral therapies to lifestyle modifications; thus, to avoid an unacceptable burden on patients, other complicating factors should be considered, such as life expectancy of the patient, presence or absence of microvascular and macrovascular complications, risk for adverse events related to glucose control, and patient preferences. The goal for HbA1c should be based on individualized assessment of risk for complications from diabetes, comorbidity, life expectancy, and patient preferences. An HbA1c level less than 7% based on individualized assessment is a reasonable goal for many but not all patients. (Based on 104 RCTs)

Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat

	most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence). Physicians and patients should discuss adverse event profiles before selecting a medication. Compared with baseline values, most diabetes medications (metformin, thiazolidinediones, and sulfonylureas) reduced baseline HbA1c by about 1 percentage point 3 or more months after the initiation of treatment. For adverse effects, metformin is associated with an increased risk for gastrointestinal side effects, sulfonylureas and meglitinides are associated with an increased risk for hypoglycemia, and thiazolidinediones are associated with an increased risk for heart failure (with no conclusive evidence for an increase in ischemic cardiovascular risk). However, in comparing the effectiveness of various agents, the evidence shows that metformin is the most efficacious agent as monotherapy and in combination therapy. (based on 66 RCTs) **Recommendation 3:** ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence). All dual-therapy regimens were more efficacious than monotherapies in reducing the HbA1c level in patients with type 2 diabetes by about 1 additional percentage point. Combination therapies with more than 2 agents were not included in the evidence review. No good evidence supports one combination therapy over another, even though some evidence shows that the combination of metformin with another agent generally tends to have better efficacy than any other monotherapy or combination therapy. However, combination therapies are also associated with an increased risk for adverse effects compared with monotherapy. […] adverse effects are generally worse with combination therapies that include a sulfonylurea. Although this guideline addresses only oral pharmacological therapy, patients with persistent hyperglycemia despite oral agents and lifestyle interventions may need insulin therapy.
Nationale VersorgungsLeitlinie: Therapie des Typ-2-Diabetes [86] Langfassung Version 3 (Stand April. 2014)	Herausgeber der NVL „THERAPIE DES TYP-2-DIABETES“: Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Arzneimittelkommission der deutschen Ärzteschaft, Deutsche Diabetes Gesellschaft (DDG) , Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM) , Deutsche Gesellschaft für Innere Medizin (DGIM) (vertreten durch die DDG) , Verband der Diabetesberatungs- und Schulungsberufe Deutschland (VDBD) – Diese Leitlinie … ist bis zur nächsten Überarbeitung bzw. spätestens bis 01. August 2018 gültig.
	Methodik (Details zur Methodik im Leitlinien-Report, Version 1, Jan 2014) Grundlage der Leitlinie: Systematische Recherche nach Leitlinien,

Konsensusverfahren, Bewertung von ausgewählten, aktuellen RCT

Suchzeitraum: inkl. 2012

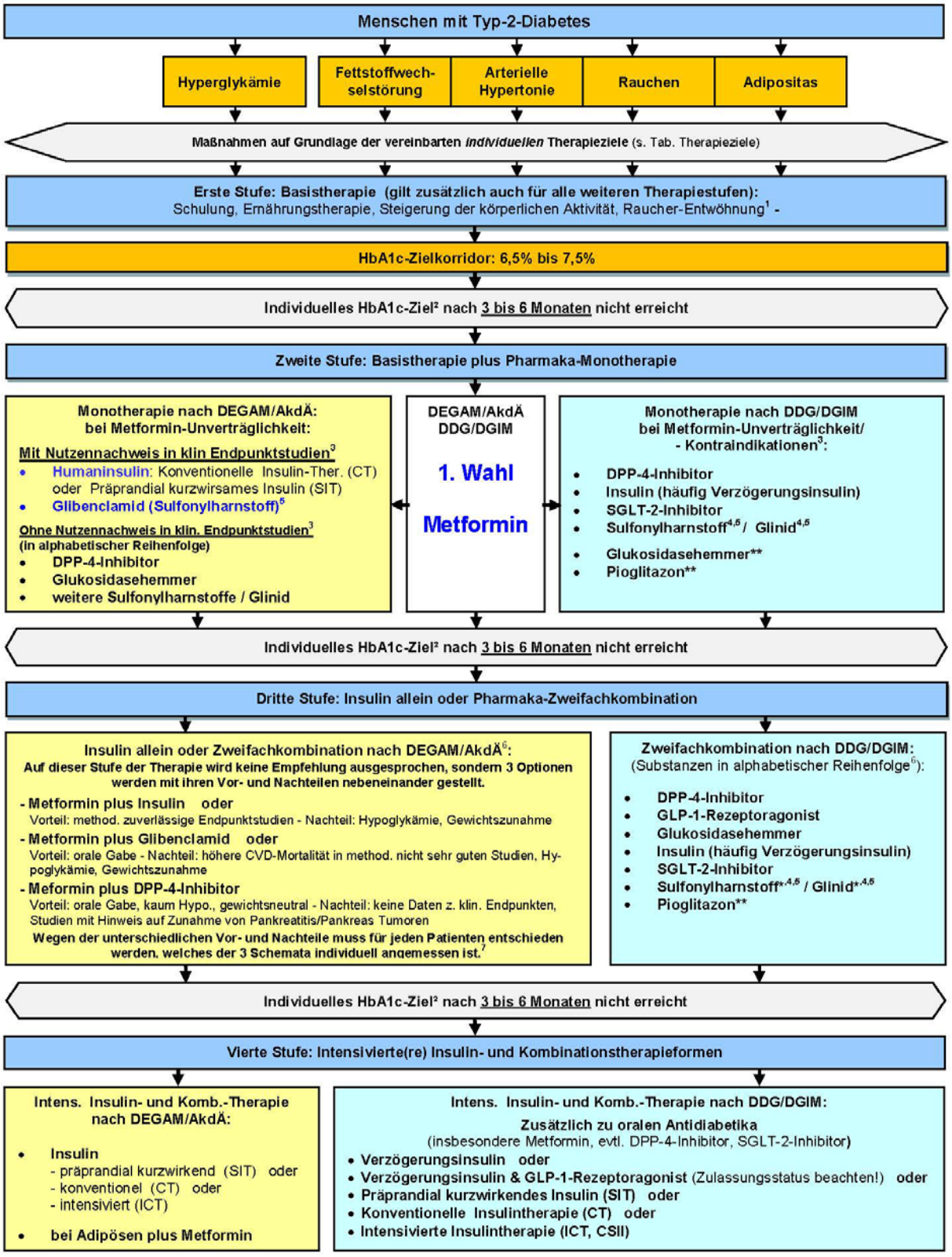
Die in der NVL Therapie des Typ-2-Diabetes verwendeten Empfehlungsgrade orientieren sich, wie im aktuellen Methodenreport zum Programm für Nationale VersorgungsLeitlinien beschrieben (www.versorgungsleitlinien.de), soweit möglich an der Einteilung nach GRADE (http://www.gradeworkinggroup.org/).“

Empfehlungs-grad	Beschreibung	Formulierung	Symbol
A	Starke Empfehlung	„soll“	⇑⇑
		„soll nicht“	⇓⇓
B	Empfehlung	„sollte“	⇑
		„sollte nicht“	⇓
0	Offen	„kann“	⇔

Empfehlungen - **Pharmakotherapie**

Bei der Behandlung von Menschen mit Typ-2-Diabetes sollte einem der beiden Algorithmen – von AkdÄ und DEGAM (gelb unterlegt in Therapie-Algorithmus A. 5) bzw. von DDG und DGIM (türkis unterlegt in Therapie-Algorithmus A. 5) gefolgt werden.

⇑ (starker Konsens)



(Hinweis: Weitere Details bzw. Ausführungen zum Algorithmus finden sich in der LL)

Fortsetzung NVL	Aufgrund unterschiedlicher Konzepte der Experten der die Inhalte der NVL verantwortenden Organisationen – inklusive unterschiedlicher Interpretation und unterschiedlicher klinischer Gewichtung der berücksichtigten Evidenz – konnte bei einzelnen Schritten der Pharmakotherapie des Typ-2-Diabetes keine Einigung erreicht werden. DDG und DGIM empfehlen ab Stufe 2 des Therapiealgorithmus ein in einigen Punkten vom gemeinsamen Vorschlag der AkdÄ und der DEGAM abweichendes therapeutisches Vorgehen. Die diesbezüglichen Divergenzen der DDG/DGIM und DEGAM/AkdÄ sind transparent in einem Algorithmus getrennt (farblich sichtbar) dargestellt und kommentiert. ---------- Orale Antidiabetika **<u>Orale Antidiabetika mit gesicherter günstiger Beeinflussung klinischer Endpunkte</u>** • Metformin Aufgrund der belegten Wirksamkeit hinsichtlich Stoffwechseleinstellung, makrovaskulärer Risikoreduktion sowie weiterer günstiger Eigenschaften, insbesondere des geringen Einflusses auf Gewicht und Hypoglykämierate, wird heute Metformin als Antidiabetikum der ersten Wahl angesehen. Bei nicht ausreichender Senkung der Plasmaglukose sollte die Medikation mit Metformin fortgesetzt und mit Insulin kombiniert werden (Algorithmus von AkdÄ und DEGAM) oder es kann mit anderen oralen Antidiabetika kombiniert werden (Algorithmus von DDG und DGIM). Als sehr häufige Nebenwirkungen treten gastrointestinale Beschwerden auf, Geschmacksveränderungen werden als häufige Nebenwirkungen genannt. Kontraindikationen sind wegen des Risikos von letalen Laktatazidosen besonders sorgfältig zu beachten. • Sulfonylharnstoffe (SH) Die dosisabhängige Senkung der Plasmaglukose und des HbA1c durch SH ist gut belegt. Die Wirksamkeit einer Sulfonylharnstofftherapie hinsichtlich der Reduktion des mikrovaskulären Risikos konnte für bestimmte Sulfonylharnstoffe (Glibenclamid und Gliclazid) nachgewiesen werden…. Sulfonylharnstoffe sind für Patienten zu empfehlen, die Metformin nicht vertragen oder Kontraindikationen für diesen Wirkstoff aufweisen. Als häufige unerwünschte Nebenwirkungen sind Hypoglykämien und Gewichtszunahme zu nennen, gelegentlich kommt es zu gastrointestinalen Beschwerden und allergischen Hautreaktionen. **<u>Orale Antidiabetika ohne gesicherte günstige Beeinflussung klinischer Endpunkte</u>**

	• Alpha-Glukosidasehemmer Diese Substanzen haben eine relativ schwache plasmaglukose-senkende Wirkung. • DPP-4-Inhibitoren (Dipeptidyl-Peptidase-4-Inhibitoren, Gliptine) Im Gegensatz zu Sulfonylharnstoffen besitzen DPP-4-Inhibitoren aufgrund ihres Wirkmechanismusses kein intrinsisches Hypoglykämierisiko. • SGLT2-Inhibitoren (Gliflozine) Dapagliflozin, als erster Vertreter der SGLT2-Inhibitoren, wirkt antihyperglykämisch durch Hemmung der renalen Glukosereabsorption. Auf Grund dieses Wirkmechanismus kommt es neben der Blutglukosesenkung (Senkung des HbA1c im Vergleich mit Placebo um 0,54 bis 0,68 %) zu einem Gewichtsverlust (im Mittel um 2 bis 3 kg) sowie zur Reduktion des Blutdrucks (im Mittel 4 mmHg systolisch, 2 mmHg diastolisch). Die antihyperglykämische Effektivität ist abhängig von der Nierenfunktion (eGFR). Bei Nierenfunktionseinschränkung (eGFR < 60 ml/min/1,73 m²) wird der Einsatz von Dapagliflozin wegen nachlassender Effektivität nicht mehr empfohlen. Die Gabe von Dapagliflozin wird bei mit Schleifendiuretika therapierten Patienten nicht empfohlen, um eine Volumendepletion zu vermeiden. Insbesondere danach sowie bei gleichzeitiger Einnahme von Schleifendiuretika können die Patienten durch Flüssigkeitsverlust und Kreatininanstieg (bei über 65-Jährigen in 2,5 % vs. 1,1 % unter Placebo) bedroht werden. Glinide Glinide haben eine den Sulfonylharnstoffen ähnliche Wirkung. Der Wirkungseintritt ist jedoch rascher und die Wirkungsdauer kürzer. Die Nebenwirkungen der Glinide sind denjenigen der Sulfonylharnstoffe (Hypoglykämien, leichte Gewichtszunahme) ähnlich. Hinsichtlich des Auftretens von Hypoglykämien, Gewichtszunahme, Lebensqualität und Therapiezufriedenheit findet sich kein gesicherter Vorteil gegenüber Vergleichsmedikamenten. Sie sind deshalb als Langzeittherapie des Typ-2-Diabetes nicht vorteilhaft gegenüber Sulfonylharnstoffen und ihr Einsatz kann derzeit nur in Ausnahmen (z. B. Unverträglichkeit von Vergleichsmedikamenten) empfohlen werden. • Glitazone (Thiazolidendione) Der Vertrieb von Rosiglitazon wurde aufgrund des ungünstigen Nutzen-Schaden-Profils am 01.11.2010 eingestellt. Pioglitazon kann nach einem Beschluss des Gemeinsamen Bundesausschusses seit April 2011 nur noch in begründeten Ausnahmefällen zu Lasten der GKV verordnet werden. Die Therapie mit Glitazonen führt zu einer Senkung der prä- und postprandialen Plasmaglukosespiegel sowie zu einer signifikanten Senkung des HbA1c. In Anbetracht des Nebenwirkungsspektrums und des unzureichenden Wirksamkeitsnachweises im Hinblick auf klinische

Endpunkte ist Pioglitazon nur in Ausnahmen (z. B. Unverträglichkeit von Vergleichsmedikamenten) zu empfehlen.

Insulintherapie: Indikation und Schemata

Die Indikation zur Insulintherapie besteht, wenn durch alleinige Lebensstiländerungen und eine Therapie mit oralen Antidiabetika das individuelle Therapieziel nicht erreicht wird oder wenn Kontraindikationen gegen orale Antidiabetika bestehen. Bei initialer Stoffwechseldekompensation kann eine primäre Insulintherapie, gegebenenfalls temporär, erforderlich sein.

Empfehlungen/Statements	Empfehlungsgrad
Da bei der Insulintherapie keine Daten vorliegen, die die konsistente Überlegenheit einer bestimmten Insulinart belegen, kann diese deshalb nur individuell für jeden Patienten gewählt werden.	⇔
Grundsätzlich sollte die Insulintherapie in der niedrigsten, wirksamen Dosierung begonnen werden. Die Dosis ist stufenweise bis zum Erreichen des individuellen Therapieziels zu steigern.	⇑

Insulintherapieschemata

Es stehen fünf Formen der Insulintherapie zur Wahl:

• BOT: Basalunterstützte orale Therapie = Basalinsulin z. B. vor dem Schlafengehen unter Beibehaltung oraler Antidiabetika;

• CT: Konventionelle Insulintherapie mit 1 bis 2 Injektionen eines Mischinsulins (ggf. unter Beibehaltung oraler Antidiabetika);

• SIT: Supplementäre Insulintherapie mit präprandialen Injektionen ohne Basalinsulin (ggf. unter Beibehaltung oraler Antidiabetika);

• ICT: Intensivierte konventionelle Insulintherapie mit präprandialen Injektionen mit Basalinsulin, (ggf. unter Beibehaltung oraler Antidiabetika);

• BOT mit GLP-1-Rezeptoragonisten.

Die bei Typ-1-Diabetes eingesetzte kontinuierliche subkutane Insulininfusion (CSII) kann im Rahmen einer Einzelfallentscheidung eine Rolle spielen.

Vor Einleitung einer Insulintherapie muss der Patient in jedem Fall besonders geschult und die zuverlässige Selbstkontrolle der Plasmaglukose praktiziert und dokumentiert werden.

Kombinationstherapie von Insulin und oralen (bzw. parenteralen)

	<u>Antidiabetika</u> Wenn die Möglichkeiten der Basistherapie (körperliche Bewegung, ausgewogene Ernährung, Gewichtsabnahme, Stressbewältigung) für das Individuum ausgeschöpft sind, ist bei entsprechender Verträglichkeit und unter Berücksichtigung der Kontraindikation die Behandlung mit Metformin effektiv und effizient. Wegen der chronischen Progression der Erkrankung ist häufig zur Erreichung des individuellen Therapieziels und zur Minimierung schwerer Nebenwirkungen eine Kombination mit oralen Antidiabetika oder der Injektion plasmaglukosesenkender Pharmaka notwendig. Im Verlauf der Erkrankung benötigen viele Menschen mit Typ-2-Diabetes zur Erreichung ihres Therapieziels Insulin als Monotherapie oder in Kombination mit anderen plasmaglukosesenkenden Prinzipien. Die Wahl der Therapiekombinationen oder der verschiedenen Insulintherapiemöglichkeiten ist nicht mit klinischen Endpunkten belegt. Daher richtet sich die Auswahl von Kombinationstherapie oder Insulinmonotherapie nach Patientenpräferenzen, individueller Verträglichkeit und Kontraindikationen, Hypoglykämierisiko, Körpergewicht, und der Heterogenität der Erkrankung. Jede Therapieform ist häufig zeitlich begrenzt und bedarf einer Therapieeskalation oder Modifikation im Laufe der Erkrankung und sollte stets die Reduktion des gesamten kardiovaskulären Risikos des Einzelnen berücksichtigen. **<u>Parenterale Antidiabetika ohne gesicherte günstige Beeinflussung klinischer Endpunkte</u>** **GLP-1-Rezeptorgonisten (Inkretinmimetika, GLP-1-Analoga)** Die plasmaglukosesenkende Wirkung und die Verminderung des HbA1c ist für die GLP-1- Rezeptoragonisten (Exenatide, Exenatide LAR, Liraglutid und Lixisenatide) in klinischen Studien gezeigt worden. GLP-1-Rezeptoragonisten besitzen aufgrund ihres Wirkmechanismusses kein intrinsisches Hypoglykämierisiko. Wirksamkeitsbelege zur Reduktion klinischer Endpunkte liegen nicht vor.
SIGN, 2010 [96] Management of diabetes - A national clinical guideline	SIGN=Scottish Intercollegiate Guidelines Network Fragestellung This guideline provides recommendations based on current evidence for best practice in the management of diabetes.
	Methodik Grundlage der Leitlinie: Literaturrecherche Suchzeitraum: 2004-2008 (als Update der Version 55; Angaben zur Literaturrecherche in einem Extradokument auf der Webseite)

	LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies; High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies 1^{++}or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

Pharmacological management of glycaemic control in people with type 2 diabetes

<u>Metformin:</u>

- Für übergewichtige Patienten mit Diabetes Mellitus Typ 2 sollte eine Behandlung mit Metformin die erste Wahl sein (Empfehlungsgrad A)

<u>Sulfonylharnstoffe:</u>

- Sulfonylharnstoffe sollten bei nicht übergewichtigen Patienten als Behandlung erster Wahl in Betracht gezogen werden wenn Metformin wegen Unverträglichkeit oder Kontraindikation nicht eingesetzt werden kann (Empfehlungsgrad A).

(<u>Thiazolidinedione:</u> *Verordnungsausschluss, nicht weiter betrachtet (Kommentar FBMed))*

	DPP-4 Inhibitoren: • DPP-4 Inhibitoren sollte bei Patienten mit Diabetes Typ 2 gegeben werden um die Blutglukose Kontrolle zu verbessern (Empfehlungsgrad A) Alpha-glukosidase Inhibitoren: • Alpha-Glukosidase Inhibitoren können als Monotherapie bei Patienten mit Diabetes Typ 2 gegeben werden, wenn sie vertragen werden (Empfehlungsgrad B). Meglitinide: *Keine Empfehlung dazu in der Leitlinie angegeben.* Glucagon Like Peptide (GLP)-1: • Zur Verbesserung der glykämischen Kontrolle bei übergewichtigen Patienten (BMI ≥ 30 kg/m2) die bereits eine Metformin und/oder Sulfonylharnstoff Behandlung bekommen. GLP-1 Agonisten werden normalerweise als Drittlinientherapie gegeben, bei Patienten bei denen eine Zweifachkombinationstherapie mit Metformin und Sulfonylharnstoffen nicht zu einer ausreichenden Blutzuckersenkung geführt hat (Empfehlungsgrad A). • Liraglutid kann als Drittlinientherapie nach unzureichender Blutzuckersenkung unter Metformin und Thiazolidinedione gegeben werden, um eine Verbesserung der glykämischen Kontrolle bei übergewichtigen Patienten (BMI ≥ 30 kg/m2) zu erzielen (Empfehlungsgrad A). Insulin: • Die Gabe von oralem Metformin und Sulfonylharnstoffe sollte fortgeführt werden, wenn eine Insulintherapie angezeigt ist (Ziel: Verbesserung/Beibehaltung glykämische Kontrolle) (Empfehlungsgrad A). • Einmal tägliches NPH Insulin zur Nacht sollte gegeben werden, wenn zusätzlich zu einer Metformin und/oder Sulfonylharnstoff Behandlung gegeben wird. Die Gabe von Basal Insulin Analoga sollte in Betracht gezogen werden wenn Bedenken auf ein Hyoglykämie Risiko besteht (Empfehlungsgrad A). • Lösliches Insulin oder schnellwirksame Insulin Analoga können bei einer Intensivierung der Insulin Therapie gegeben werden, um die glykämische Kontrolle beizubehalten oder zu verbessern (Empfehlungsgrad A).
NICE, 2009 [85] Type 2 diabetes The management of type 2 diabetes NICE clinical guideline 87 Issued: May 2009 last modified: July 2014	Suchzeitraum bis 2009 (Zulassungrelevante Informationen wie „withdrawal of market authorisation“ wurden auch nach 2009 ergänzt; Detaillierte Angaben zur Methodik und Suchstrategie finden sich in Online-Appendices) Teilweise wurden die Empfehlungen in der „clinical guideline Type 2 diabetes newer agents for blood glucose control in type 2 diabetes” aktualisiert. (The guideline gives details of the methods and the evidence used to develop the recommendations.)
	Empfehlungen zu den einzelnen Antidiabetika ohne Einstufung: **Metformin** • Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body-weight-associated risk according to ethnic group) and whose blood glucose is

	inadequately controlled by lifestyle interventions (nutrition and exercise) alone. • Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight. • Continue with metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added. • Step up metformin therapy gradually over weeks to minimise risk of gastrointestinal (GI) side effects. Consider a trial of extended-absorption metformin tablets where GI tolerability prevents continuation of metformin therapy. • The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that: - due consideration can be given to the cardiovascular-protective effects of the drug; - an informed decision can be made on whether to continue or stop the metformin. **Insulin secretagogues** • Consider a sulfonylurea as an option for first-line glucose-lowering therapy if: • the person is not overweight • the person does not tolerate metformin (or it is contraindicated) • **or** a rapid response to therapy is required because of hyperglycaemic symptoms. • Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin. • Continue with a sulfonylurea if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added. • Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated. • When drug concordance is a problem, offer a once-daily, long-acting sulfonylurea. • Educate a person being treated with an insulin secretagogue, particularly if renally impaired, about the risk of hypoglycaemia. **Rapid-acting insulin secretagogues** • Consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle. **Acarbose** • Consider acarbose for a person unable to use other oral glucose-lowering medications. **DPP-4 inhibitors (sitagliptin, vildagliptin)** Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

	• the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), • or the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if: • the person does not tolerate metformin, or metformin is contraindicated. Consider adding sitagliptin as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate. Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months). Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision. **GLP-1 mimetic (exenatide)** Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has: • a body mass index (BMI) ≥ 35.0 kg/m2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological • or medical problems associated with high body weight, or a BMI < 35.0 kg/m2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months. **Glucose control: insulin therapy** **Oral agent combination therapy with insulin** When starting basal insulin therapy: • continue with metformin and the sulfonylurea (and acarbose, if used) • review the use of the sulfonylurea if hypoglycaemia occurs.

When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):

- continue with metformin
- continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs.

Insulin therapy

- Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees.
- For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification not to.
- When starting insulin therapy, use a structured programme employing active insulin dose titration

Initiate insulin therapy from a choice of a number of insulin types and regimens:

- Begin with human NPH insulin injected at bed-time or twice daily according to need.
    - Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if:
    - the person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily,
    - or the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes,
    - or the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs,
    - or the person cannot use the device to inject NPH insulin.

- Consider twice-daily pre-mixed (biphasic) human insulin (particularly if HbA1c ≥ 9.0%). A once-daily regimen may be an option.
- Consider pre-mixed preparations that include short-acting insulin analogues, rather than pre-mixed preparations that include short-acting human insulin preparations, if:a person prefers injecting insulin immediately before a meal, or hypoglycaemia is a problem, or blood glucose levels rise markedly after meals.

- Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin in people: who do not reach their target HbA1c because of significant hypoglycaemia, or who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached, or who cannot use the device needed to inject NPH insulin but

	who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made, or who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.
American Diabetes Association, 2015 [3] Standards of Medical Care in Diabetes – 2015. (Jährliches update siehe auch 2014 [2]).	**Absicht/Ziel:** The American Diabetes Association's (ADA's) Standards of Care are intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care. Methodik: • Standards of Care: ADA position statement that provides key clinical practice recommendations. • ADA position statements are typically based on a systematic review or other review of published literature. Position statements undergo a formal review process. They are updated annually or as needed. • Professional Practice Committee (PPC) is a multidisciplinary expert committee comprised of physicians, diabetes educators, registered dietitians, and others who have expertise in a range of areas, including adult and pediatric endocrinology, epidemiology, public health, lipid research, hypertension, and preconception and pregnancy care. • PPC members systematically searched MEDLINE for human studies related to each section and published since 1 January 2014. Recommendations were revised based on new evidence or, in some cases, to clarify the prior recommendation or match the strength of the wording to the strength of the evidence. • Feedback from the larger clinical community was valuable for the 2015 revision of the Standards of Care. Readers who wish to comment on the Standards of Medical Care in Diabetesd2015 are invited to do so. LoE

Table 1—ADA evidence-grading system for "Standards of Medical Care in Diabetes"

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence; i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

GoR: nicht dargestellt

Pharmacological Therapy for Hyperglycemia in Type 2 Diabetes Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. (A)
    - In patients with metformin intolerance or contraindications, consider an initial drug from other classes depicted in Fig. 7.1 under "Dual therapy" and proceed accordingly.
- In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset. (E)
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin. (A)
- A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. (E)
- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. (B)

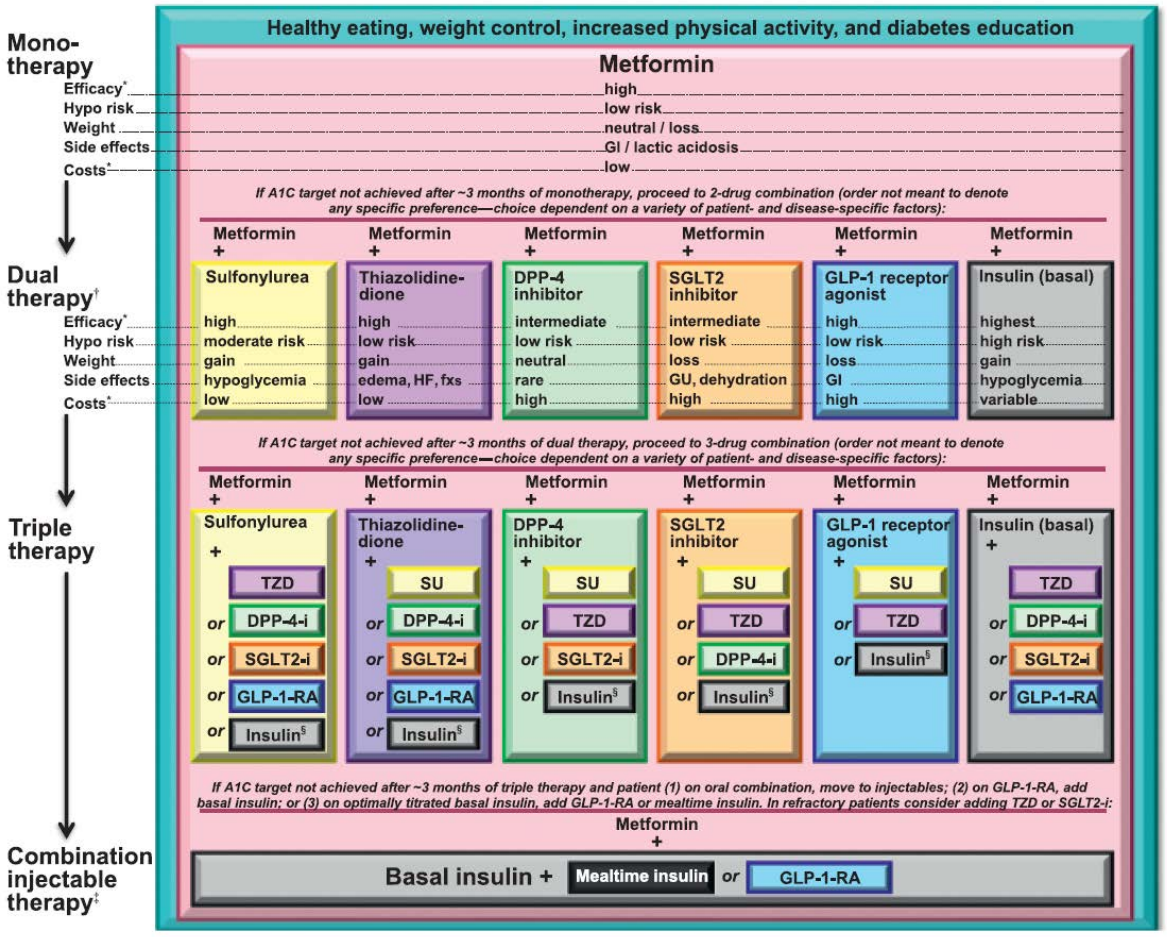


Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (15). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. *See ref. 15 for description of efficacy categorization. †Consider starting at this stage when A1C is ≥9%. ‡Consider starting at this stage when blood glucose is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12%, especially if symptomatic or catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (15).

Combination therapy:

A comparative effectiveness meta-analysis (17) suggests that overall each new class of noninsulin agents added to initial therapy lowers A1C around 0.9–1.1%.

17. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–613

If the A1C target is not achieved after approximately 3 months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin (Fig. 7.1).

For all patients, consider initiating therapy with a dual combination when A1C is ≥9% to more expeditiously achieve the target A1C level. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms are present or any catabolic features (weight loss, ketosis) are in evidence. Consider initiating combination insulin injectable therapy when blood glucose Is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12%. As the patient's glucose toxicity resolves, the regimen can, potentially, be subsequently simplified.

Insulin therapy:

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 U or 0.1–0.2 U/kg, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and possibly one additional noninsulin agent.
If basal insulin has been titrated to an acceptable fasting blood glucose level, but A1C remains above target, consider advancing to combination injectable therapy (Fig. 7.2) to cover postprandial glucose excursions. Options include adding a GLP-1 receptor agonist or mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (lispro, aspart, or glulisine) administered just before eating.

Once an insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the prevailing blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control) → see figure below.

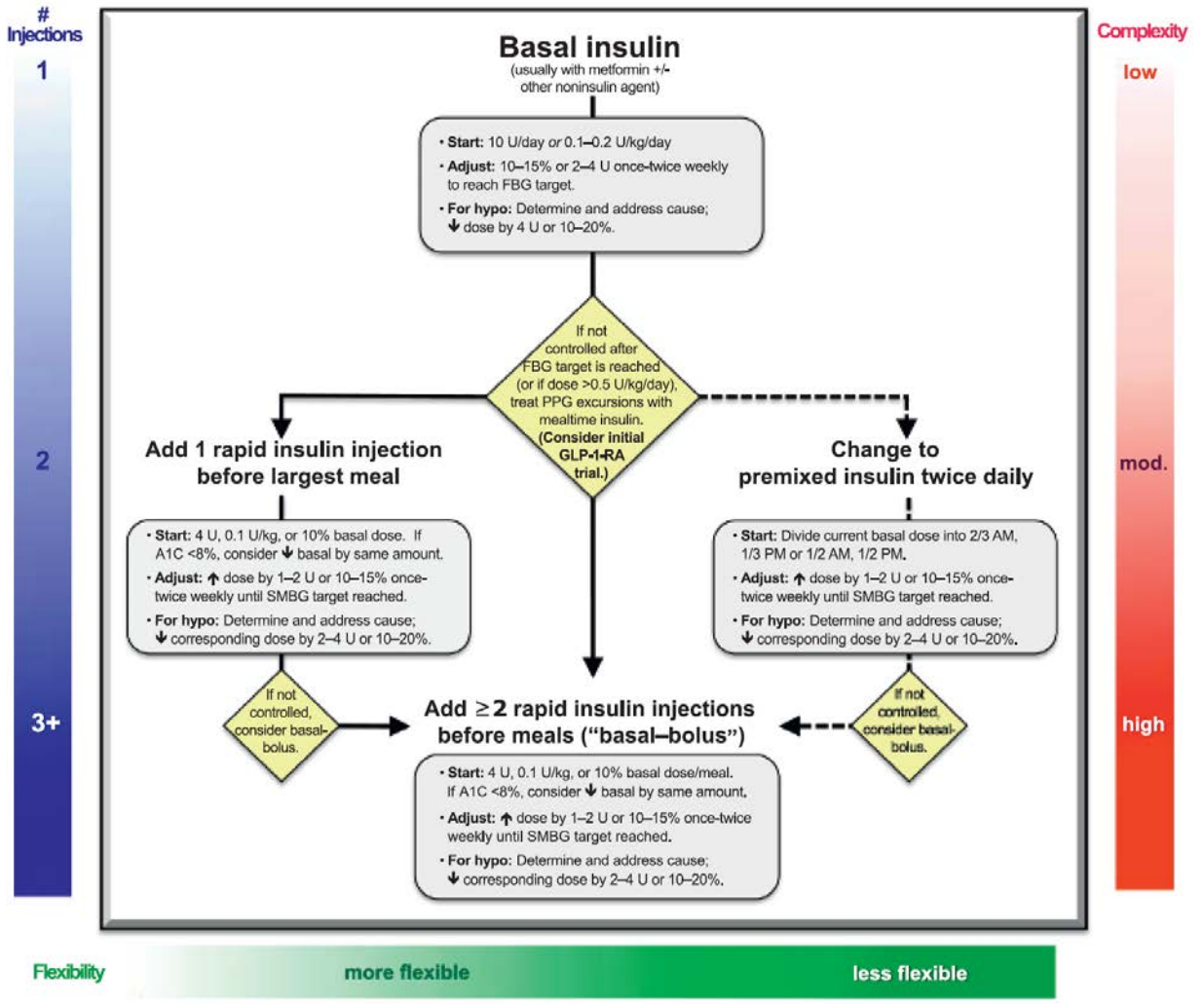


Figure 7.2—Approach to starting and adjusting insulin in type 2 diabetes (15). FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo, hypoglycemia; mod., moderate; PPG, postprandial glucose; #, number. Adapted with permission from Inzucchi et al. (15).

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

CADTH, 2013 **[8]** **Third-line pharmacotherapy for type 2 diabetes — Update** **Siehe auch CADTH, 2014 [9] Erratum [9]**	Fragestellung 1. What is the comparative efficacy and safety of third-line antidiabetes drugs in adults with type 2 diabetes experiencing inadequate glycemic control on metformin and a sulfonylurea? Update zu: “Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and a Sulfonylurea” siehe [10]
	Methodik Population: patients inadequately controlled with metformin and sulfonylurea combination therapy Intervention/ Komparator: Metformin and a sulfonylurea plus any one of the following: placebo/no treatment, GLP-1 analogue, DPP-4 inhibitor, meglitinide, TZD, alpha-glucosidase inhibitor, insulin (basal, bolus, biphasic). Agents within each drug class were included in the review only if they were approved for marketing in one or more of the following countries: Canada, the United States (US), or the European Union (EU). Endpunkt: mortality, diabetes-related complications, A1C, bodyweight, hypoglycemia, and serious adverse events Beobachtungszeitraum: mind. 4 Wochen Suchzeitraum: 2009- May 2012 (als Update zur Recherche 1980-2009) Anzahl eingeschlossene Studien/Patienten (Gesamt): 46 articles describing 40 RCT (n=k.A.)
	Evidence was available for the following 8 drug classes: alpha-glucosidase inhibitors (5 RCTs), meglitinides (1 RCT), TZDs (10 RCTs), DPP-4 inhibitors (3 RCTs), GLP-1 analogues (7 RCTs), basal insulin (20 RCTs), bolus insulin (1 RCT), and biphasic insulin (12 RCTs). **Network meta-analyses were conducted for change from baseline in A1C and change from baseline in body weight.** **Hb A1C**; 24 RCTs (n = 8,517). With the exception of alpha-glucosidase inhibitors and meglitinides, all classes achieved statistically significant reductions in A1C (range –0.72% to –1.15%) relative to metformin and a sulfonylurea alone. The addition of a basal or biphasic insulin resulted in mean differences of –15% (95% credible interval [CrI], –1.49% to –0.83%) and –1.12% (95% CrI: –1.52% to –0.75%) respectively, and resulted in the most favourable rankings for reducing A1C. (*Anmerkung FBMed: An dieser Stelle werden die korrigierten Ergebnisse dargestellt, siehe Erratum [9]*) Estimates for basal insulin, TZDs, DPP-4 inhibitors, alpha-

	glucosidase inhibitors, GLP-1 analogues, and meglitinides were largely unchanged in the revised analysis of A1C, with the effect sizes shifting by no more than –0.07% from the original estimates. The result for biphasic insulin changed from –1.12% to –1.29% and the result for bolus insulin changed from –1.02% to –1.51%. The relatively large change in the bolus insulin estimate is not surprising as the 4T study was the only randomized controlled trial (RCT) that investigated this drug class. **body weight;** 18 RCTs (n = 7,907). When added to metformin and a sulfonylurea, basal insulin, biphasic insulin, a rapid-acting insulin analogue, or a thiazolidinedione was associated with a significantly greater increase in body weight than occurred with metformin and a sulfonylurea alone (range 1.9 kg to 5.0 kg). DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral; whereas, GLP-1 analogues were associated with statistically significant weight loss (–1.6 kg, 95% CrI, –2.8 to –0.4). Meglitinides appeared to be trending toward an increase in body weight; however, the wide confidence intervals (CIs) indicate considerable uncertainty in the estimate of effect (2.6 kg [95% CrI, –0.7 to 6.0]). **Overall Hypoglycemia,** 28 RCT (n= 8,553); An NMA was not performed for this outcome due to the large variation in the control group event rates of overall hypoglycemia There was a degree of variability in the clinical definitions of this outcome across RCTs. The most common differences were the specific blood glucose threshold for hypoglycemia (range ≤ 3.0 mmol/L to ≤ 4.0 mmol/L), and whether or not patients were required to validate symptoms of hypoglycemia with self-monitoring of blood glucose. The studies demonstrated that basal insulin, TZDs, DPP-4 inhibitors, and GLP-1 analogues were associated with a significantly greater risk of overall hypoglycemia than placebo when given in combination with metformin and a sulfonylurea. **Severe Hypoglycemia;** 25 RCTs (n=15,111) Severe hypoglycemia was typically defined as an event requiring third-party assistance. Events of severe hypoglycemia were relatively rare for all drug classes including the insulins, limiting the ability to conduct comparisons across drug classes. Six RCTs compared treatment strategies involving the use of biphasic or basal insulin. The largest was a three-arm trial that randomized patients to treatment with biphasic insulin (BiAsp30), basal insulin (determir), or bolus insulin (aspart), each in addition to continued metformin and sulfonylurea. This RCT reported a statistically significant increase in risk of severe hypoglycemia with bolus insulin versus basal insulin (OR [95% CI], 4.14 (1.36 to 12.59]) and a trend toward more events with biphasic versus basal insulin (OR [95% CI], 2.82 [0.89 to 9.00]). **Long-term complications of diabetes:** There were no RCTs designed to assess differences in long-term

	diabetes-related complications.
	Anmerkung FBMed: An error was identified in the CADTH report *Third-Line Pharmacotherapy for Type 2 Diabetes —Update* published in July 2013. A data entry error occurred in the conduct of CADTH's network meta-analyses for glycated hemoglobin (A1C) for third-line pharmacotherapy. Specifically, the effect size for basal insulin against biphasic insulin from the 4T trial (Holman et al, 2007)[2] was incorrectly entered as –0.5%, when it should have been entered as 0.5%. This document provides a summary of the corrected results for the network meta-analyses. The correction of this error did not alter the overall conclusions regarding the comparative efficacy of the third-line drugs studied with respect to A1C.
CADTH 2010 **[7]** **Canadian Agency for Drugs and Technologies in Health (CADTH)** **Optimal Theapy Report; Second-Line Therapy for Patients With Diabetes Inadequately Controlled on Metformin: A Systematic Review and Cost-Effectiveness Analysis**	*Objective:* To conduct a systematic review of the clinical evidence pertaining to second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy. *Methods:* Active and placebo-controlled randomized controlled trials (RCTs) of antihyperglycemic agents used in patients with type 2 diabetes inadequately controlled or intolerant to metformin monotherapy were identified through electronic databases, grey literature, reference lists, conference abstracts, and stakeholder consultation. Outcomes of interest included glycosylated hemoglobin (A1C), hypoglycemia, long-term complications of diabetes, mortality, quality of life, and serious adverse effects. Mixed treatment comparison (MTC) and pairwise meta-analyses were conducted to pool trial results, when appropriate. Numerous sensitivity analyses were performed to examine robustness of meta-analytic results. *Clinical:* Evidence for eight classes of second-line antidiabetes therapies in adults with type 2 diabetes inadequately controlled with metformin monotherapy was identified. The methodological quality of the evidence was generally low. All agents achieved statistically significant reductions in A1C, and there were no statistically significant differences between drug classes. Events of severe hypoglycemia were very rare for all agents; however, the insulins and insulin secretagogues were associated with a higher risk for overall hypoglycemia than the other agents. A modest increase in body weight was observed with most second-line therapies, the exceptions being dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors, and glucagon-like peptide-1 (GLP-1) analogues. There was little evidence regarding the effect of second-line antidiabetes drugs on the long-term complications of diabetes or mortality. *Conclusion:* Sulfonylureas are equally efficacious as other agents when used as second-line treatment after inadequate control with metformin monotherapy

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 01.06.2015

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#3	(diabetes mellitus type 2) or (type 2 diabet*) or (diabetes mellitus type II) or (type II diabet*) or DMT2:ab (Word variations have been searched)
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#29	#28 and #6
#30	#29 Publication Year from 2010 to 2015

Recherche nach Systematischen Reviews und HTA in MEDLINE (PubMed) am 01.06.2015

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#9	Search (Insulins[MeSH Terms] OR Insulin[MeSH Terms])
#10	Search (((insulin*[Title/Abstract]) OR hyperglycemia*[Title/Abstract]) OR hyperglycemic*[Title/Abstract])
#11	Search ((#10) OR #9)
#12	Search ((“sglt*2”[Title/Abstract]) OR “sglt2”[Title/Abstract])
#13	Search ((“sodium glucose cotransporter2”[Title/Abstract]) OR “sodium glucose co*transporter*2”[Title/Abstract])
#14	Search (((sodium AND glucose AND cotransporter AND 2[Title/Abstract])) OR (sodium AND glucose AND co*transporter AND 2[Title/Abstract]))
#15	Search ((#12) OR #13) OR #14)
#16	Search ((((#4) OR #7) OR #8) OR #11 OR #15)
#17	Search ((#3) AND #16)
#18	Search ((#17) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title])) Filters: published in the last 5 years

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