Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-133-z Insulin Icodec

Stand: Juni 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Insulin Icodec
Diabetes mellitus Typ 2 bei Erwachsenen

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Biguanide Sulfonylharnstoffe Alpha-Glukosidasehemmer GLP-1-Rezeptor Agonisten (Glutide; Inkretinmimetika) DPP-4-Hemmer (Gliptine) SGLT-2-Inhibitoren (Gliflozine) Glinide Thiazolidindione (Glitazone) Insuline und Analoga
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	– Beschlüsse über die Nutzenbewertung nach § 35a SGB V: o Linagliptin vom 21.02.2013 (erneute Nutzenbewertung) sowie Linagliptin (neues AWG) vom 16.05.2013 o Lixisenatid vom 05.09.2013 o Vildagliptin sowie Vildagliptin/Metformin vom 01.10.2013; Vildagliptin (erneute Nutzenbewertung) vom 21.05.2015 o Canagliflozin vom 04.09.2014 sowie Canagliflozin/Metformin vom 05.02.2015 o Insulin degludec vom 16.10.2014, Insulin degludec (neues AWG) vom 20.08.2015 sowie Insulin degludec (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) vom 16.05.2019 o Albiglutid vom 19.03.2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Insulin Icodec **Diabetes mellitus Typ 2 bei Erwachsenen** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
	○ Insulin degludec/Liraglutid vom 15.10.2015 sowie Insulin degludec/Liraglutid (neues AWG) vom 04.02.2016 ○ Empagliflozin (erneute Nutzenbewertung) sowie Empagliflozin/Metformin vom 01.09.2016 ○ Sitagliptin, Sitagliptin/Metformin vom 15.12.2016 (erneute Nutzenbewertung nach Fristablauf) sowie Sitagliptin vom 22.3.2019 (erneute Nutzenbewertung nach Fristablauf) ○ Saxagliptin (erneute Bewertung nach Fristablauf) vom 15.12.2016 ○ Saxagliptin/Metformin vom 15.12.2016 sowie Saxagliptin/Metformin (neues AWG) vom 01.02.2018 ○ Insulin glargin/Lixisenatid vom 16.08.2018 und Insulin glargin/Lixisenatid (nAWG) vom 15.10.2020 ○ Ertugliflozin/Sitagliptin vom 01.11.2018 ○ Empagliflozin/Linagliptin vom 22.11.2019 ○ Dapagliflozin sowie Dapagliflozin/Metformin (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) jeweils vom 19.12.2019 ○ Dulaglutid vom 16.07.2020 (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) und Dulaglutid (nAWG) vom 21.09.2023 ○ Semaglutid vom 15.04.2021 ○ Ertugliflozin vom 19.05.2022 ○ Tirzepatid vom 02.05.2024 – Bestehender Verordnungsausschluss (AM-RL, Anlage III): Glitazone – Bestehende Verordnungseinschränkungen (AM-RL, Anlage III): schnell wirkende/lang wirkende Insulinanaloga, Glinide, orale Antidiabetika, Harn- und Blutzuckerteststreifen

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Insulin Icodec **Diabetes mellitus Typ 2 bei Erwachsenen** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
	– Beschluss des G-BA vom 16. Juni 2016 über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung: Kontinuierliche interstitielle Glukosemessung mit Real-Time-Messgeräten (rtCGM) zur Therapiesteuerung bei Patientinnen und Patienten mit insulinpflichtigem Diabetes mellitus – IQWiG- Rapid-Report zur LEADER Studie (Studie zu Liraglutid, Auftrag A17-09, Stand 23.08.2017) – DMP Diabetes mellitus Typ 2 (Anforderungen an strukturierte Behandlungsprogramme für Diabetes mellitus Typ 2)
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:	
Insulin Icodec	**Zugelassenes Anwendungsgebiet:** Behandlung des Diabetes mellitus bei Erwachsenen. <u>Vorliegend zu betrachtendes Anwendungsgebiet:</u> Behandlung des **Diabetes mellitus Typ 2** bei Erwachsenen
Biguanide	
Metformin A10BA02 generisch	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 Glucophage in Form einer Monotherapie oder in Kombination mit anderen oralen Antidiabetika bzw. Insulin angewendet werden. - Bei Kindern ab 10 Jahren und bei Jugendlichen kann Glucophage in Form einer Monotherapie oder in Kombination mit Insulin angewendet werden. Bei übergewichtigen erwachsenen Patienten mit Diabetes mellitus Typ 2 konnte nach Versagen diätetischer Maßnahmen eine Senkung der Häufigkeit von diabetesbedingten Komplikationen unter Behandlung mit Metformin als Therapie der ersten Wahl nachgewiesen werden. (siehe Abschnitt 5.1) *[FI Glucophage, Stand 09/2022]*
Sulfonylharnstoffe	
Glibenclamid A10BB01 generisch	Nicht insulinabhängiger Diabetes mellitus bei Erwachsenen (NIDDM, Typ 2), wenn andere Maßnahmen wie konsequente Einhaltung der Diabetes-Diät, Gewichtsreduktion bei Übergewicht, ausreichende körperliche Betätigung nicht zu einer befriedigenden Einstellung des Blutglukosespiegels geführt haben. Glibenclamid AbZ® kann als Monotherapie oder in Kombination mit Metformin verwendet werden. *[FI Glibenclamid AbZ, Stand 07/2018]*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Glimepirid A10BB12 z.B. Amaryl®	Amaryl ist angezeigt zur Behandlung des Diabetes mellitus Typ 2, wenn eine Diät, körperliche Aktivität und Gewichtsreduktion allein nicht ausreichen. *[FI Amaryl, Stand 10/2022]*
Gliquidon A10BB08 Glurenorm®	Glurenorm wird angewendet bei nicht-insulinabhängigem Diabetes mellitus bei Erwachsenen (NIDDM, Typ 2), wenn andere Maßnahmen wie konsequente Einhaltung der Diabetes-Diät, Gewichtsreduktion bei Übergewicht, ausreichende körperliche Betätigung nicht zu einer befriedigenden Einstellung des Blutglucosespiegels geführt haben. Glurenorm kann als Monotherapie oder in Kombination mit Metformin verwendet werden. *[FI Glurenorm, Stand 02/2022]*
Gliclazid A10BB09 Diamicron Uno®	Nicht insulinabhängiger Diabetes mellitus (Typ II) bei Erwachsenen, sofern eine Diät, körperliche Aktivität und Gewichtsreduzierung alleine nicht ausreichend sind, um den Blutzuckerspiegel einzustellen. *[FI Diamicron, Stand 02/2020]*
Alpha-Glucosidase-Inhibitoren	
Acarbose A10BF01 Acarbose AbZ®	Acarbose AbZ Tabletten sind angezeigt als Zusatztherapie bei Patienten mit Diabetes mellitus in Verbindung mit Diät. *[FI Acarbose, Stand 12/2022]*
GLP-(Glucagon-like Peptide)-1-Rezeptor-Agonisten (Inkretinmimetika)	
Exenatide A10BJ01 Byetta®	Byetta 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 Arzneimitteln keine angemessene Blutzuckerkontrolle erreicht haben. *[FI Byetta, Stand 07/2022]*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Liraglutid A10BJ02 Victoza®	Victoza wird zur Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 10 Jahren als Zusatz zu Diät und körperlicher Aktivität angewendet - als Monotherapie, wenn die Anwendung von Metformin aufgrund einer Unverträglichkeit oder Kontraindikation ungeeignet ist - zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus. Für Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse, sowie die untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. *[FI Victoza, Stand 07/2023]*
Insulin glargin/Lixisenatid A10AE54 Suliqua®	Suliqua wird als Ergänzung zu Diät und Bewegung zusätzlich zu Metformin mit oder ohne Natrium-Glucose-Cotransporter-2-(SGLT-2-)Inhibitoren zur Behandlung von erwachsenen Patienten mit unzureichend kontrolliertem Diabetes mellitus Typ 2 zur Verbesserung der Blutzuckerkontrolle angewendet. Zu Studienergebnissen hinsichtlich Wirkung auf die Blutzuckerkontrolle sowie der untersuchten Populationen siehe Abschnitt 4.4 und 5.1. *[FI Suliqua, Stand 05/2023]*
Dulaglutid A10BJ05 Trulicity®	<u>Typ 2-Diabetes mellitus</u> Trulicity ist angezeigt zur Behandlung von Patienten ab 10 Jahren mit unzureichend kontrolliertem Typ 2-Diabetes mellitus unterstützend zu Diät und Bewegung: - als Monotherapie, wenn die Einnahme von Metformin wegen Unverträglichkeit oder Kontraindikationen nicht angezeigt ist. - zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus. Für Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse, sowie untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. *[FI Trulicity: Stand 03/2023]*
Semaglutid A10BJ06 Ozempic®	Ozempic wird zur Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität angewendet - als Monotherapie, wenn die Anwendung von Metformin aufgrund einer Unverträglichkeit oder Kontraindikationen ungeeignet ist - zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus. Für Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse, sowie untersuchte Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. *[FI Ozempic, Stand 03/2023]*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Mounjaro A10BX16 Tirzepatid	Typ-2-Diabetes mellitus Mounjaro® ist angezeigt zur Behandlung von Erwachsenen mit unzureichend eingestelltem Typ-2-Diabetes mellitus als Ergänzung zu Diät und Bewegung - als Monotherapie, wenn die Einnahme von Metformin wegen Unverträglichkeiten oder Kontraindikationen nicht angezeigt ist, - zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes mellitus. Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle, sowie auf die untersuchten Populationen, sind in den Abschnitten 4.4, 4.5 und 5.1 zu finden. […] *[FI Mounjaro, Stand 12/2023]*
Gliptine (DPP (Dipeptidylpeptidase)-4 Hemmer)	
Saxagliptin A10BH03 Onglyza®	Onglyza ist bei erwachsenen Patienten mit Typ-2-Diabetes mellitus in Ergänzung zu einer Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle indiziert: - Als Monotherapie, wenn Metformin aufgrund von Unverträglichkeit oder Kontraindikationen ungeeignet ist. - In Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes einschließlich Insulin, wenn diese den Blutzucker nicht ausreichend kontrollieren (siehe Abschnitte 4.4, 4.5 und 5.1 bezüglich vorhandener Daten für verschiedene Kombinationen) *[FI Onglya, Stand 11/2021]*
Saxagliptin/Metformin A10BD10 Komboglyze®	Komboglyze ist als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten mit Typ-2-Diabetes mellitus zu verbessern: - Bei Patienten, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind. - In Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes einschließlich Insulin, bei Patienten, die mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert sind (siehe Abschnitte 4.4, 4.5 und 5.1 bezüglich vorhandener Daten für verschiedene Kombinationen). - Bei Patienten, die bereits mit der Kombination von Saxagliptin und Metformin als separate Tabletten behandelt werden. *[FI Komboglyze, Stand 02/2024]*
Sitagliptin A10BH01 Januvia®	Bei erwachsenen Patienten mit Typ-2-Diabetes mellitus ist Januvia indiziert zur Verbesserung der Blutzuckerkontrolle: Als 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. Als orale Zweifachtherapie in Kombination mit:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	- Metformin, wenn Diät und Bewegung plus eine Monotherapie mit Metformin den Blutzucker nicht ausreichend senken. - einem 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. - einem Peroxisomal Proliferator-activated Receptor gamma(PPARγ)-Agonisten (d. h. einem Thiazolidindion), wenn die Anwendung eines PPARγ-Agonisten angebracht ist und Diät und Bewegung plus Monotherapie mit einem PPARγ-Agonisten den Blutzucker nicht ausreichend senken. <u>Als orale Dreifachtherapie in Kombination mit</u>: - einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken. - einem PPARγ-Agonisten und Metformin, wenn die Anwendung eines PPARγ-Agonisten angebracht ist und Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken. Januvia ist auch zusätzlich zu Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung sowie eine stabile Insulindosis den Blutzucker nicht ausreichend senken. *[FI Januvia, Stand 09/2023]*
Sitagliptin/Metformin A10BD07 z.B. Janumet®	Für erwachsene Patienten mit Typ-2-Diabetes mellitus: Janumet 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. Janumet ist in Kombination mit einem Sulfonylharnstoff (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(PPARγ)-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. Janumet ist auch zusätzlich zu Insulin (d. h. als Dreifachtherapie) indiziert als Ergänzung zu Diät und Bewegung bei Patienten, bei denen eine stabile Insulindosis und Metformin allein den Blutzucker nicht ausreichend senken. *[FI Janumet, Stand 08/2023]*
Ertugliflozin/Sitagliptin A10BD24 Steglujan®	Steglujan ist bei Erwachsenen ab 18 Jahren mit Typ-2 Diabetes mellitus zusätzlich zu Diät und Bewegung angezeigt: - zur Verbesserung der Blutzuckerkontrolle bei Patienten, deren Blutzucker unter Metformin und/oder einem Sulfonylharnstoff und einem der in Steglujan enthaltenen Einzelwirkstoffe nicht ausreichend

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	- gesenkt werden kann. - bei Patienten, die bereits mit der Kombination aus Ertugliflozin und Sitagliptin in Form von einzelnen Tabletten behandelt werden. (Zu Studienergebnissen für die Kombinationen und die Wirkung auf die Blutzuckerkontrolle, siehe Abschnitte 4.4, 4.5 und 5.1.) *[FI Steglujan, Stand 09/2023]*
Vildagliptin A10BH02 Jalra®	Vildagliptin wird angewendet bei Erwachsenen mit Typ-2-Diabetes-mellitus als Ergänzung zu Diät und Bewegung zur Verbesserung der glykämischen Kontrolle: - als Monotherapie bei Patienten, für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist. - in Kombination mit anderen Arzneimitteln zur Behandlung von Diabetes, einschließlich Insulin, wenn diese zu keiner ausreichenden glykämischen Kontrolle führen (siehe Abschnitte 4.4, 4.5 und 5.1 für verfügbare Daten zu verschiedenen Kombinationen). *[FI Jalra: Stand 10/2022]*
Vildagliptin/Metformin A10BD08 z.B. Eucreas®	Eucreas wird angewendet bei Erwachsenen mit Typ-2-Diabetes-mellitus als Ergänzung zu Diät und Bewegung zur Verbesserung der glykämischen Kontrolle: - bei Patienten, die mit Metforminhydrochlorid allein unzureichend eingestellt sind. - bei Patienten, die bereits mit einer Kombination von Vildagliptin und Metforminhydrochlorid als separate Tabletten behandelt werden. - in Kombination mit anderen Arzneimitteln zur Behandlung von Diabetes, einschließlich Insulin, wenn diese zu keiner ausreichenden glykämischen Kontrolle führen (siehe Abschnitte 4.4, 4.5 und 5.1 für verfügbare Daten zu verschiedenen Kombinationen). *[FI Eucreas: Stand 07/2022]*
Selektive Natrium-Glucose-Cotransport-Inhibitoren (SGLT-2-Inhibitoren)	
Dapagliflozin A10BK01 Forxiga®	<u>Typ-2-Diabetes mellitus</u> Forxiga ist bei Erwachsenen und Kindern im Alter von 10 Jahren und älter indiziert zur Behandlung von unzureichend kontrolliertem Typ-2-Diabetes mellitus in Ergänzung zu einer Diät und Bewegung - als Monotherapie, wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird. - zusätzlich zu anderen Arzneimitteln zur Behandlung des Typ-2-Diabetes. Zu Studienergebnissen im Hinblick auf Kombinationen von Behandlungen, die Wirkung auf die Blutzuckerkontrolle, kardiovaskuläre und renale Ereignisse sowie die untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. […] *[FI Forxiga, Stand 01/2024]*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Dapagliflozin/Metformin A10BD15 z.B. Xigduo®	Xigduo ist bei erwachsenen Patienten für die Behandlung des Typ-2-Diabetes mellitus indiziert als Ergänzung zu Diät und Bewegung: - bei Patienten, bei denen der Blutzucker mit der maximal verträglichen Dosis von Metformin allein unzureichend kontrolliert wird - in Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes bei Patienten, die mit Metformin und diesen Arzneimitteln unzureichend kontrolliert sind - bei Patienten, die bereits mit der Kombination aus Dapagliflozin und Metformin als separate Tabletten behandelt werden. Zu Studienergebnissen im Hinblick auf Kombinationen von Behandlungen, die Wirkung auf die Blutzuckerkontrolle und kardiovaskuläre Ereignisse sowie die untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. *[FI Xigduo, Stand 02/2024]*
Empagliflozin A10BK03 Jardiance®	Jardiance wird angewendet bei Erwachsenen und Kindern ab 10 Jahren zur Behandlung von nicht ausreichend behandeltem Typ-2-Diabetes mellitus als Ergänzung zu Diät und Bewegung - als Monotherapie, wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird - zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes Zu Studienergebnissen im Hinblick auf Kombinationstherapien, die Wirkung auf Blutzuckerkontrolle, kardiovaskuläre und renale Ereignisse sowie die untersuchten Populationen siehe Abschnitte 4.4, 4.5 und 5.1. […] *[FI Jardiance, Stand 12/2023]*
Empagliflozin/Linagliptin A10BD19 Glyxambi®	Glyxambi, eine Fixdosiskombination aus Empagliflozin und Linagliptin, wird angewendet bei Erwachsenen ab 18 Jahren mit Typ-2-Diabetes mellitus: - zur Verbesserung der Blutzuckerkontrolle, wenn Metformin und/oder Sulfonylharnstoff (SH) und eine der Monosubstanzen von Glyxambi zur Blutzuckerkontrolle nicht ausreichen - wenn der Patient bereits mit der freien Kombination von Empagliflozin und Linagliptin behandelt wird. (Siehe Abschnitte 4.2, 4.4, 4.5 und 5.1 für verfügbare Daten zu untersuchten Kombinationen) *[FI Glyxambi, Stand 03/2023]*
Ertugliflozin A10BK04 Steglatro®	Steglatro ist zur Behandlung von Erwachsenen mit unzureichend kontrolliertem Typ-2 Diabetes mellitus als Ergänzung zu Diät und Bewegung angezeigt: - Als Monotherapie, wenn Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen nicht geeignet ist. - Zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes. Zu Studienergebnissen im Hinblick auf die Kombinationen von Therapien, die Wirkung auf die Blutzuckerkontrolle, die kardiovaskulären Ereignisse und die untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. *[FI Steglatro, Stand 11/2022]*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Glinide	*Verordnungseinschränkung Anlage III – AM-RL*
Nateglinid A10BX03 Starlix 120 mg Filmtabletten	Nateglinid ist indiziert für die Kombinationstherapie mit Metformin bei Patienten mit Typ-2-Diabetes, die nicht ausreichend mit einer maximal tolerierbaren Metformin-Dosis eingestellt werden können. *[AMIce Datenbank, Stand 04/2024]*
Repaglinid A10BX02 z.B. Repaglinid AbZ®	Repaglinid ist indiziert bei Erwachsenen mit 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. *[FI Repaglinid, Stand 02/2022]*
Glitazone	*Verordnungsausschluss Anlage III – AM-RL*
Humaninsuline	
Insulin human A10AC01 Berlinsulin H	Zur Behandlung von Patienten mit Diabetes mellitus, die Insulin für die Aufrechterhaltung einer normalen Glukosehomöostase benötigen. *[FI Berlinsulin, Stand 02/2024]*
Insulinanaloga	*Verordnungseinschränkung Anlage III – AM-RL*
Insuline schnell wirkend: Insulin lispro, Insulin aspart, Insulin glulisin A10AB01-06 NovoRapid 100 I.E./ml	Insulin aspart: NovoRapid wird angewendet zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr. *[FI Novorapid, Stand 09/2020]*
Insuline lang wirkend: Insulin detemir, Insulin glargin, Insulin degludec A10AE01-06 Lantus 100 I.E./ml	Insulin glargin: Zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern im Alter von 2 Jahren und älter. *[FI Lantus, Stand 07/2020]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-133-z (Insulin Icodec)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. Mai 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACP	American College of Physicians
AGI	Alpha-glucosidase inhibitor
AHA	Antihyperglycaemic agent
AHRQ	U.S. Agency for Healthcare Research and Quality
AMSTAR	A Measurement Tool to Assess systematic Reviews
ASCVD	Atherosclerotic cardiovascular disease
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BB	Basal-bolus
BI	Basal insulin
BMI	Body mass index
BP	Basal-plus
CKD	Chronic kidney disease
CV(D)	Cardiovascular (disease)
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
DPP-4(i)	Dipeptidyl peptidase-4 (inhibitor)
eGFR	the estimated glomerular filtration rate
EMA	European Medicines Agency
EMPA	Empagliflozin
ESRD	End-stage renal disease
FBG	Fasting blood glucose
FDA	U.S. Food and Drug Administration
FE	Fixed effects
FPG	Fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GLP-1 (RA)	Glucagon-like peptide-1 (receptor agonits)
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTI	Genital tract infection
HbA1c	Haemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HR	Hazard Ratio

INS	Insulin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LDL-C	Low-density lipoprotein cholesterol
LoE	Level of Evidence
MACE	Major adverse cardiovascular events
MET	Metformin
MD	Mean difference
NAFLD	Non alcoholic fatty liver disease
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NPH	Neutral protamine Hagedorn
NVL	Nationale VorsorgungsLeitlinie
OAD	Oral antidiabetic agent
OR	Odds Ratio
PBG	Postprandial blood glucose
PBO	Placebo
PPG	Postprandial glucose
RCT	Randomised controlled trial
RE	Random effects
RR	Relatives Risiko
SAE	(Serious) adverse events
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SGLT-2(i)	Sodium–glucose cotransporter 2 (inhibitor)
SIGN	Scottish Intercollegiate Guidelines Network
SMPG	Self-monitored plasma glucose
SU	Sulfonylureas
T2DM	Type 2 diabetes mellitus
TRIP	Turn Research into Practice Database
TZD	Thiazolidinediones
UACR	Urine Albumin-to-Creatinine Ratio
UTI	Urinary tract infection
WHO	World Health Organization
WMD	Weighted mean difference

1 Indikation

Behandlung von Erwachsenen mit Typ 2 Diabetes mellitus.

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Diabetes mellitus Typ 2* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 15.04.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 3442 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 75 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Systematische Reviews zu DPP-4 Inhibitoren

Li J et al., 2023 [30].

Effect of new glucose-lowering drugs on stroke in patients with type 2 diabetes: A systematic review and Meta-analysis

Fragestellung

The effects of glucagon-like peptide-1 (GLP-1) agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors on stroke risk were evaluated in published RCTs

Methodik

Population:

- Type 2 Diabetes

Intervention:

- GLP-1, SGLT-2, DPP-4

Komparator:

- Placebo + Hintergrundtherapie

Endpunkte:

- Stroke

Recherche/Suchzeitraum:

- Embase, Cochrane Library, and PubMed from inception through to December 3, 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of bis

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 19 eligible studies involving 155,027 T2DM patients published were identified, which included 5 RCTs of SGLT-2 inhibitors (CANVAS, CREDENCE, DECLARE-TIMI 58, EMPA-REG, VERTIS CV), 8 RCTs of GLP-1 agonists (AMPLITUDE-O, ELIXA,, EXSCEL, Harmony, LEADER, PIONEER 6, REWIND, SUSTAIN), and 6 RCTs of DPP-4 inhibitors (CARMELINA, EXAMINE, Omarigliptin, SAVOR, TIMI 53, TECOS, VIVIDD).

Charakteristika der Population/Studien:

- Of the 19 studies included, the number of subjects in the range 254-16.492 and the median follow-up was from 1.3 to 10.5 years. The percentage of the male participants was 66.5 %. The percentage of patients with a history of stroke ranged from 5.5 % to 22.4 %. HARMONY had a higher proportion of stroke patients, with about a quarter having a hjstory of stroke at baseline.

Qualität der Studien:

- Of the 19 studies included, 16 had low risk of bias in all areas, 2 were at unclear risk in terms of random sequence generation, and 1 was at high risk for other bias

Studienergebnisse:

- Total Stroke
  - DPP-4 Inhibitors: RR = 0.95, 95%CI [0.81-1.11], P = 0.484
  - GLP-1 agonists: RR = 0.84, 95%CI [0.77-0.93], P = 0,000
  - SGLT-2 inhibitors: RR= 0.96, 95%CI [0.84-1.09], P = 0.504
- Non-fatal stroke:
  - DPP-4: RR=0.98, 95%CI [0.85-1.12], P = 0.762
  - GLP-1 agonists: RR = 0.851 95%CI [0.77-0.94] P = 0.002
  - SGLT-2 inhibitors: RR = 0,98, 95%CI [0.88-1.10], P = 0.776
- Fatal Stroke: no drug calls showed a beneficial effect.

Anmerkung/Fazit der Autoren

In conclusion, this meta-analysis demonstrates the beneficial effect of GLP-1 agonists on stroke, especially for non-fatal stroke and total stroke. SGLT-2 inhibitors and DPP-4 inhibitors do not increase the risk of stroke events.

Pan Z et al., 2020 [53].

Efficacy and safety of DPP-IV inhibitors combined with basal insulin in the treatment of type 2 diabetes

Fragestellung

To evaluate the efficacy and safety of dipeptidyl peptidase IV (DPP-IV) inhibitors when added to insulin therapy in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- T2DM

Intervention:

- DPP-IVi/INS
- duration ≥12 weeks

Komparator:

- insulin-alone (with or without placebo)

Endpunkte:

- glycemic control

Recherche/Suchzeitraum:

- PubMed, EMBASE, the Web of Science, and the Cochrane Library published through May 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 16

Charakteristika der Population:

TABLE 1 Characteristics of the included studies

Number	First author (publication)	country	Study duration, wk	Single-center or multicenter	Diabetes duration, y	Number of baseline samples		Sex (male/female)		Age		Intervention measures		Relevant variables	Drug treatment sequence
						Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
No.1	Vilsboll (2010) [16]	USA	24	100 clinical sites	12.5	322	319	157/49	169/53	58.3 ± 9.1	57.2 ± 9.3	Saxagliptin +insulin	placebo +insulin	HbA1c (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.2	Barnett (2012) [17]	USA	24	multicenter	12	304	151	120/184	68/83	57.2 ± 9.43	57.3 ± 9.27	Saxagliptin + insulin	placebo +insulin	HbA1c (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.3	Hong (2012) [18]	Korean	24	single-center	15.8	61	63	33/28	32/31	58.8 ± 14.3	59.6 ± 13.0	Saxagliptin +insulin	placebo + insulin	HbA1c (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia	DPP-IVi therapy was added on to insulin
No.4	Yki-Jarvinen (2013) [19]	19 countries	24	19 dinical sites	>5	631	630	329/302	329/301	59.7 ± 6 9.9	60.4 ± 10.0	Linagliptin +insulin	placebo +insulin	HbA1c (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
NO.5	Kadowaki (2013) [20]	Japan	16	60 dinical sites	14	129	137	53/76	57/80	59.3 ± 9.9	59.1 ± 10.1	Sitagliptin +insulin	placebo +insulin	HbA1c (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.6	Kaku (2014) [21]	Japan	12	37 dinical sites	14.5	90	89	50/40	47/40	62.9 ± 8.22	62.4 ± 9.88	Alogliptin + insulin	placebo +insulin	HbA1c (%), FBG (mmol/L), Hypoglycemia, AEs	DPP-IVi therapy was added on to insulin
No.7	Hirose (2015) [22]	Japan	12	28 dinical sites	12.9	44	44	55/23	56/22	58.5 ± 9.6	60.1 ± 9.1	Vildagliptin +insulin	placebo +insulin	HbA1c (%)	DPP-IVi therapy was added on to insulin
No.8	Sato (2015) [23]	Japan	24	single-center	19.5	25	24	16/9	18/6	66 ± 8	66 ± 13	Sitagliptin +insulin	placebo +insulin	HbA1c (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia	DPP-IVi therapy was added on to insulin

TABLE 1 (Continued)

Number	First author (publication)	country	Study duration, wk	Single-center or multicenter	Diabetes duration, y	Number of baseline samples		Sex (male/female)		Age		Intervention measures		Relevant variables	Drug treatment sequence
						Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
No.9	Mathieu (2015) [24]	USA	24	multicenter	13.5	329	329	151/178	164/165	59.3 ± 8.9	58.3 ± 9.7	Sitagliptin +insulin	placebo +insulin	HbA1c (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.10	Ning (2016) [25]	China	24	22 clinical sites	11.3	146	147	61/85	66/81	57.8 ± 9.1	58.4 ± 9.6	Vildagliptin +insulin	placebo +insulin	HbA1c (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.11	Mita (2016) [26]	Japan	104	12 clinical sites	NA	137	137	83/61	82/30	63.8 ± 9.7	63.6 ± 1.0	Sitagliptin +insulin	placebo +insulin	HbA1c (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.12	Kadowaki (2017) [27]	Japan	16	62 clinical sites	NA	117	115	69/44	70/45	63.1 ± 10.3	63.7 ± 10.1	Saxagliptin +insulin	placebo +insulin	HbA1c (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.13	Cao (2017) [28]	China	16	single-center	6	33	32	18/15	18/14	52.1 ± 9.6	49.8 ± 11.2	Sitagliptin +insulin	Insulin	HbA1c (%), Hypoglycemia	NA
No.14	Chen (2018) [29]	China	24	22 clinical sites	NA	234	232					Saxagliptin +insulin	placebo +insulin	2hPPG (mmol/L), FBG (mmol/L), Hypoglycemia	DPP-IVi therapy was added on to insulin
No.15	Ledesma (2019) [30]	Japan	24	multicenter	NA	151	151	92/59	91/60	72.5 ± 5.1	72.5 ± 5.6	Linagliptin +insulin	placebo +insulin	FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.16	Munch (2020) [31]	France	12	6 clinical sites	23.5	32	33	17/16	15/18	69.7 ± 9.6	71.3 ± 7.3	Vildagliptin +insulin	Insulin	HbA1c (%), Hypoglycemia, SAEs	DPP-IVi therapy was added on to insulin

Abbreviations: 2hPPG, 2-hour postprandial blood glucose; AE, adverse event; FBG, fasting blood glucose; DPP-IVi, dipeptidyl peptidase IV inhibitor; HbA1c, glycosylated hemoglobin; NA, not available; SAE, serious adverse event.

Qualität der Studien:

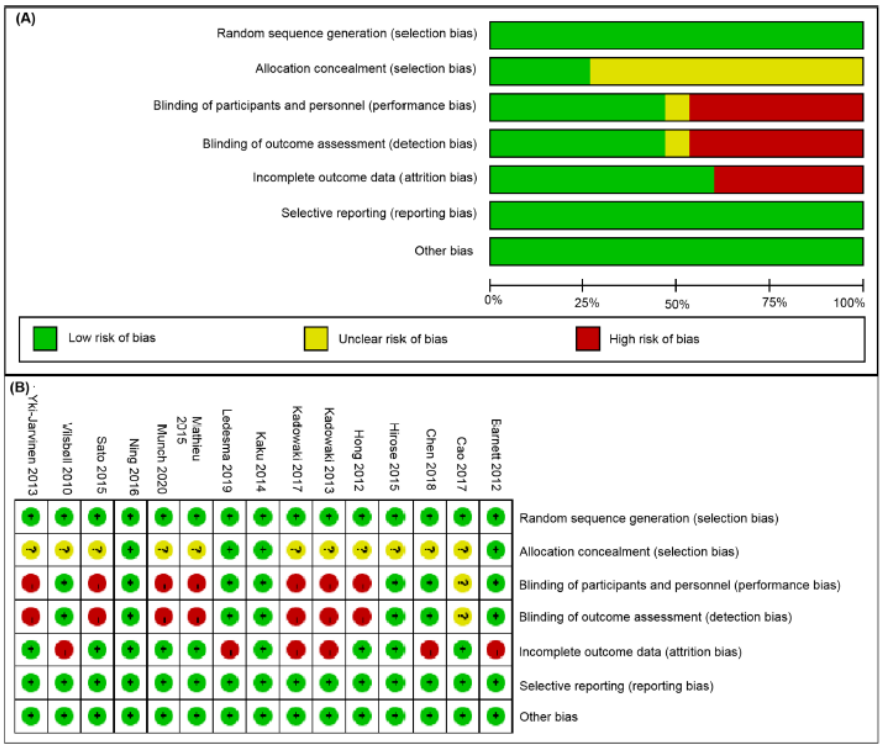


FIGURE 2 Risk of bias graph (A) and summary (B). In Figure 2B, green represents a low risk of bias, while red represents a high risk of bias. Yellow represents unclear risk of bias

Studienergebnisse:

- Glycosylated hemoglobin (HbA1c) was significantly decreased in the DPP-IV inhibitors with insulin (DPP-IVi/INS) group compared with the insulin-alone (with or without placebo) group (WMD = −0.62%; 95% CI: −0.74, −0.49; P < .05).

- Consistent with this finding, the fasting blood glucose (FBG)-lowering effect (WMD = −0.61 mmol/L; 95% CI: −0.77, −0.45; P < .05) and 2-hour postprandial glucose (2hPPG)-lowering efficacy (WMD = −2.39 mmol/L; 95% CI: −2.81, −1.97; P < .05) in the DPP-IVi/INS group were also significantly better than in the insulin-alone group.
- Regarding safety indicators, compared with the insulin-alone group, DPP-IVi/INS treatments had no association with the risk of adverse effects, including hypoglycemia, adverse events (AEs), and serious adverse events (SAEs).

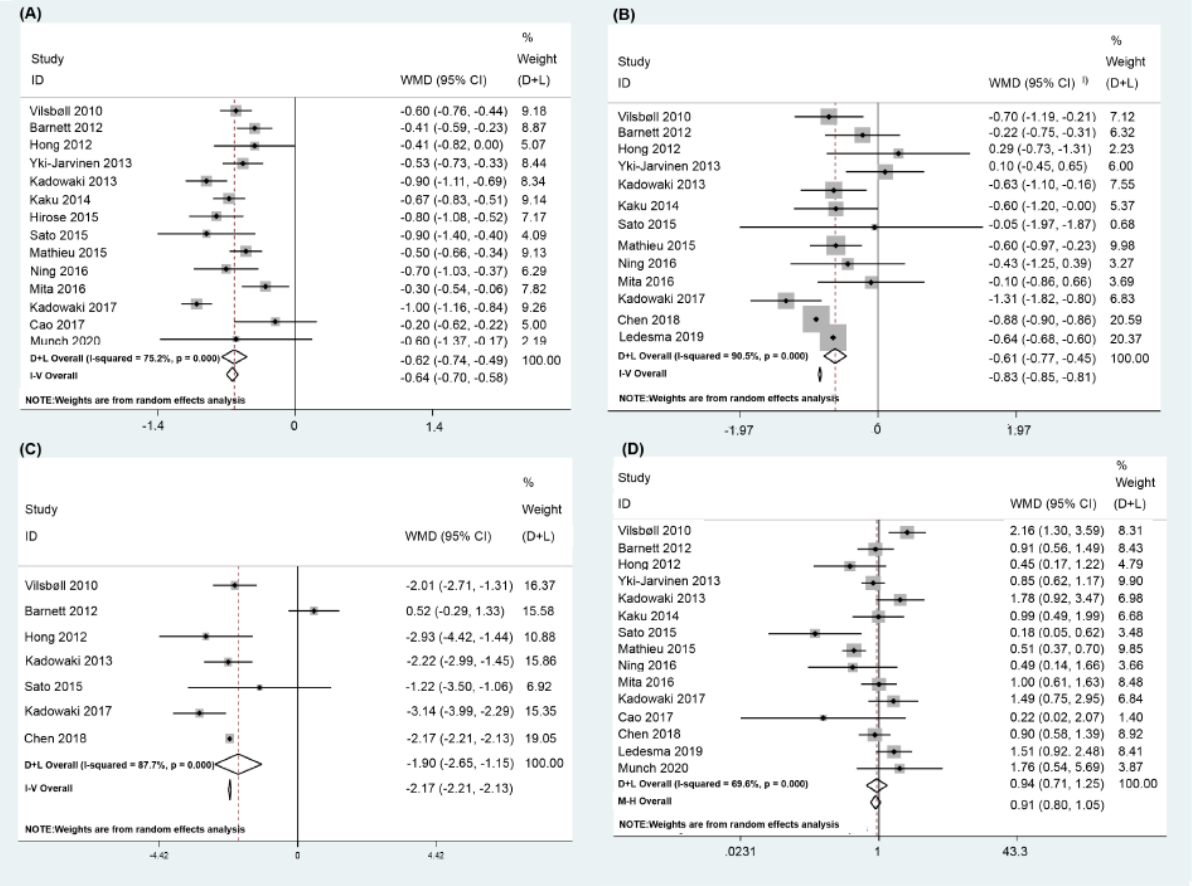
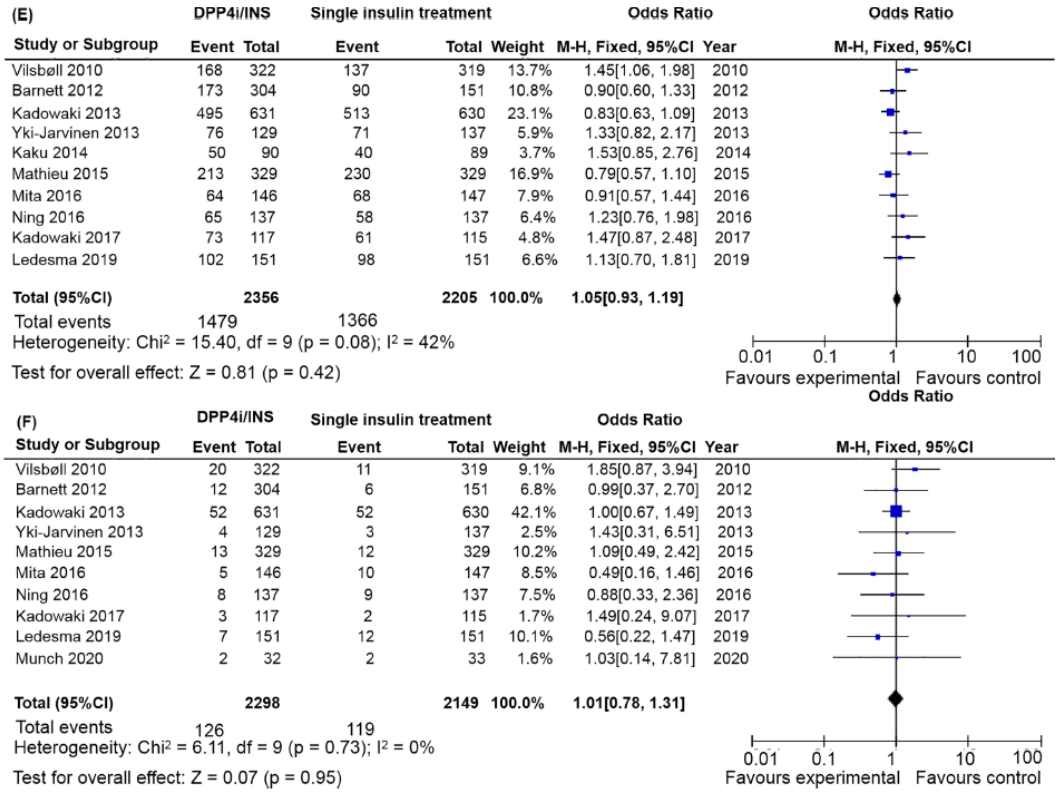


FIGURE 3 Outcomes of the comparison of the HbA1c (A), FBG (B), 2hPPG (C), hypoglycemia (D), adverse events (F) and severe adverse reactions (E) of the DPP4i/INS group with those of the insulin alone group in patients with T2DM by forest plots



Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis demonstrated that compared with the insulin-alone group, DPP-IVi/INS improved glycemic control without leading to any known AEs or SAEs. We recommend that T2DM patients have DPP-IVi/INS therapy for improved glycemic control, especially T2DM patients with inadequate glycemic control who are on insulin treatment alone.

Dalui SK et al., 2021 [10].

Effects of DPP4 inhibitors on renal outcomes in diabetes mellitus: a systematic review and meta-analysis

Fragestellung

This meta-analysis of randomized clinical trials (RCT) intends to evaluate the efficacy of DPP4 Inhibitors (DPP4I) compared with placebo, other antidiabetics (or DPP4I) on renal outcomes, adverse events (AEs), and all-cause mortality.

Methodik

<u>Population:</u>

- type 2 diabetes

<u>Intervention:</u>

- DPP-4 inhibitors

<u>Komparator:</u>

- placebo or other antidiabetic agents

Endpunkte:

- primary outcomes: changes in eGFR (estimated glomerular filtration rate), UACR (urine albumin creatinine ratio) at 24 weeks and 52 weeks
- secondary outcomes: incidence of adverse events and all-cause mortality

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE to identify RCT of DPP4I published from inception to February 2021

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs (n=39,040)

Charakteristika der Population:

- The number of participants in individual studies ranged from 36 to 16,492.
- The study duration of two studies lasted up to 4 years [12,14], and one study reported results with a median duration of 2.1 years [11]. The remaining studies had 12 to 160 weeks of study duration.
- Baseline eGFR of participants was ≥60 mL/min/1.73 m2 in five studies [30-34] and ≥30 mL/min/1.73 m2 in five studies [12,14,15,23,35]. Two studies did not describe inclusion or exclusion criteria for baseline eGFR or serum creatinine levels [36,37].

Qualität der Studien:

The quality of evidence was high for progression of albuminuria but ranged from moderate to very low for all other outcomes.

Studienergebnisse:

Table 2: Summary of findings of the results

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Plain language summary
	Risk with intervention	Risk with comparator				
A: Intervention: DPP4 inhibitors, Comparator: Placebo						
Changes in eGFR at 24 weeks from baseline	MD 1.53 lower (3.34 lower to 0.29 higher)	The mean changes in eGFR at 24 weeks from baseline was 0	-	652 (3 RCTs)	⊕⊕◯◯ LOW[b,c]	We are uncertain of the effect of DPP4I on changes of eGFR at 24 weeks from baseline
Changes in eGFR at 52 weeks	MD 0.08 higher (3.4 lower to 3.55 higher)	The mean changes in eGFR at 52 weeks was 0	-	14661 (2 RCTs)	⊕◯◯◯ VERY LOW[a,b,c,d,e]	We are very uncertain of the effect of DPP4I on changes of eGFR at 52 weeks from baseline
Adverse events within 1 year	465 per 1,000	500 per 1,000	RR 0.93 (0.80 to 1.08)	700 (3 RCTs)	⊕⊕⊕◯ MODERATE[b]	Probably there is little or no difference in adverse events within 1 year
Albuminuria progression at EOT (more than 1 year)	208 per 1,000 (189 to 226)	236 per 1,000	RR 0.88 (0.80 to 0.96)	14741 (2 RCTs)	⊕⊕⊕⊕ HIGH	We are certain that DPP4I results in delayed progression of albuminuria at more than 1 year
Adverse events – long-term	483 per 1,000 (478 to 493)	493 per 1,000	RR 0.98 (0.97 to 1.00)	38011 (3 RCTs)	⊕⊕◯◯ LOW[b,e]	There may be little or no difference in adverse events
All-cause mortality	70 per 1,000 (65 to 76)	68 per 1,000	RR 1.04 (0.96 to 1.12)	38142 (3 RCTs)	⊕◯◯◯ VERY LOW[b,e,f]	We are very uncertain of the effect of DPP4I on all-cause mortality
B: Intervention: Alogliptin, Comparator: Vildagliptin						
Changes in eGFR at 24 weeks	MD 0.21 lower (2.53 lower to 2.1 higher)	The mean eGFR changes at 24 weeks was 0	-	180 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,e,g]	We are very uncertain of the effects of alogliptin compared to vildagliptin on changes of eGFR at 24 weeks from baseline
Changes inUACR at 24 weeks	MD 19.45 higher (7.68 lower to 46.58 higher)	The mean UACR changes at 24 weeks was 0	-	180 (2 RCTs)	⊕⊕◯◯ LOW[a,b,g]	We are uncertain of the effects of alogliptin compared to vildagliptin on changes of UACR at 24 weeks from baseline
AE at 24 weeks	22 per 1,000 (4 to 128)	22 per 1,000	RR 1.00 (0.17 to 5.81)	180 (2 RCTs)	⊕⊕◯◯ LOW[b,e,g]	We are uncertain about the difference in adverse events between alogliptin and vildagliptin at 24 weeks

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; RR: Risk ratio a. CI of studies did not overlap with each other b. CI includes null effect c. eGFR is a surrogate marker d. High I^2 value e. Variation in effect size of the studies f. It does not reflect the actual number of deaths due to renal causes g. Small sample size h. Bias was detected in studies

<u>eGFR</u>

- DPP-4 inhibitors showed a small but significant decline in eGFR compared with controls ([WMD, −1.11 mL/min/1.73 m2; 95% CI, −1.78 to −0.44; P=0.001], [SMD, −0.07; 95% CI, −0.12 to −0.02; P= 0.009]).
- The test for heterogeneity showed moderate heterogeneity across the studies (I2=40.5%, P=0.064 on the test of WMD; I2=43.2%, P=0.048 on the test of SMD).

<u>Development, progression, and regression of albuminuria</u>

- DPP-4 inhibitors significantly reduced the risk of developing microalbuminuria (RR, 0.89; 95% CI, 0.80 to 0.98; P=0.022) and macroalbuminuria (RR, 0.77; 95% CI, 0.61 to 0.97; P=

0.027) compared with controls. However, the effects of DPP-4 inhibitors on incident albuminuria were mainly driven by one large trial (Supplemental Fig. S3) [11]. There was no heterogeneity across the studies on both microalbuminuria (I2=0.0%, P=0.471) and macroalbuminuria (I2=1.3%, P=0.363) (Fig. 4A, B).

Development of ESRD

- DPP-4 inhibitors did not reduce the risk of developing ESRD in patients with type 2 diabetes compared with controls (RR, 0.93; 95% CI, 0.76 to 1.14; P=0.475) (Fig. 4D). There was no heterogeneity across the studies (I2=0.0%, P=0.853).

Anmerkung/Fazit der Autoren

DPP4I did not show any significant improvement in eGFR or mortality compared to placebo, though there is an indication for retarding albuminuria progression with 52 weeks of use in patients with type 2 diabetes mellitus. The available evidence for supporting the use of DPP4I for improving renal outcomes and mortality in type 2 diabetes mellitus patients seem rather inconsistent and weak. A head-to-head comparison of different DPP4Is is required to generate conclusive evidence of the effects of individual agents on the above investigated outcomes.

Yoshiji S et al., 2022 [71]

Effects of glucagon-like peptide-1 receptor agonists on cardiovascular and renal outcomes: A meta-analysis and meta-regression analysis

Fragestellung

To evaluate the cardiovascular and renal outcomes of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the associations between these outcomes and HbA1c or weight reduction.

Methodik

Population:

- type 2 diabetes

Intervention:

- GLP-1 RAs

Komparator:

- Placebo (background therapy – table 1)

Endpunkte:

- Primary: MACE
- Secondary: individual components of MACE, all-cause mortality, hospitalization because of heart failure, composite renal outcome, and renal function outcome

Recherche/Suchzeitraum:

- 23 January 2022 in PubMed/MEDLINE, EMBASE, and CENTRAL

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs

Charakteristika der Population:

TABLE 1 Study characteristics

Study name	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER 6	AMPLITUDE-O
Published year	2015	2016	2016	2017	2018	2019	2019	2021
Sample size	6068	9340	3297	14 752	9463	9901	3183	4076
GLP-1 RAs	Lixisenatide 20 µg/day	Liraglutide 1.8 mg/day	Semaglutide 0.5 or 1 mg/week	Exenatide 2 mg/week	Albiglutide 30 or 50 mg/week	Dulaglutide 1.5 mg/week	Oral semaglutide 14 mg/day	Efpeglenatide 4 or 6 mg/week
Follow-up period (median year)	2.1	3.8	2.1	3.2	1.5	5.4	1.3	1.8
Age	59.9 ± 9.7	64.2 ± 7.2	64.6 ± 7	61.9 ± 9.4	64.1 ± 8.7	66.2 ± 6.5	66.0 ± 7.0	64.5 ± 8.2
Sex (% female)	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)	2894 (31%)	4589 (46%)	1007 (32%)	1344 (33%)
Body mass index (kg/m^2)	30.1 ± 5.6	32.5 ± 6.3	32.8 ± 6.2	32.7 ± 6.4	32.3 ± 5.9	32.3 ± 5.7	32.3 ± 6.5	32.7 ± 6.2
White ethnicity	4576 (75%)	7238 (77%)	2736 (83%)	11 175 (76%)	6583 (70%)	7498 (76%)	2300 (72%)	3534 (87%)
Duration of diabetes (y)	9.2 ± 8.2	12.8 ± 8.0	13.9 ± 8.1	13.1 ± 8.3	14.1 ± 8.7	10.5 ± 7.3	14.9 ± 8.5	15.4 ± 8.8
HbA1c (%)	7.7 ± 1.3	8.7 ± 1.6	8.7 ± 1.5	8.1 ± 1.0	8.7 ± 1.5	7.3 ± 1.1	8.2 ± 1.6	8.9 ± 1.5
eGFR ($mL/min/1.73m^2$)[a]	78 ± 21	80 (NA)	80 (61–92)	77 (61–92)	79 ± 25	75 ± 24	74 ± 21	72.4 ± 9.7
Previous cardiovascular disease	6068 (100%)	7598 (81.3%)	2735 (83%)	10 782 (73%)	9463 (100%)	3114 (31%)	2695 (85%)	3650 (90%)
Previous heart failure	1358 (22%)	1667 (18%)	777 (24%)	2389 (16%)	1922 (20%)	853 (9%)	388 (12%)	737 (18%)
Other treatments								
Insulin	2734 (39%)	4159 (45%)	1913 (58%)	6368 (46%)	5597 (59%)	2363 (24%)	1930 (61%)	2560 (63%)
Metformin	4021 (66%)	7136 (76%)	2414 (73%)	11 295 (77%)	6968 (74%)	8037 (81%)	2463 (77%)	2985 (72%)
Sulphonylurea	2004 (33%)	4721 (51%)	1410 (43%)	5401 (37%)	2725 (29%)	4552 (46%)	1027 (77%)	1036 (25%)
Thiazolidinedione	95 (2%)	573 (6%)	76 (2%)	579 (4%)	194 (2%)	168 (2%)	118 (4%)	–
DPP4 inhibitor	–	6 (<1%)	5 (<1%)	2203 (15%)	1437 (15%)	564 (6%)	2 (<1%)	
SGLT2 inhibitor	–	–	5 (<1%)	77 (1%)	575 (6%)	620 (6%)	305 (10%)	

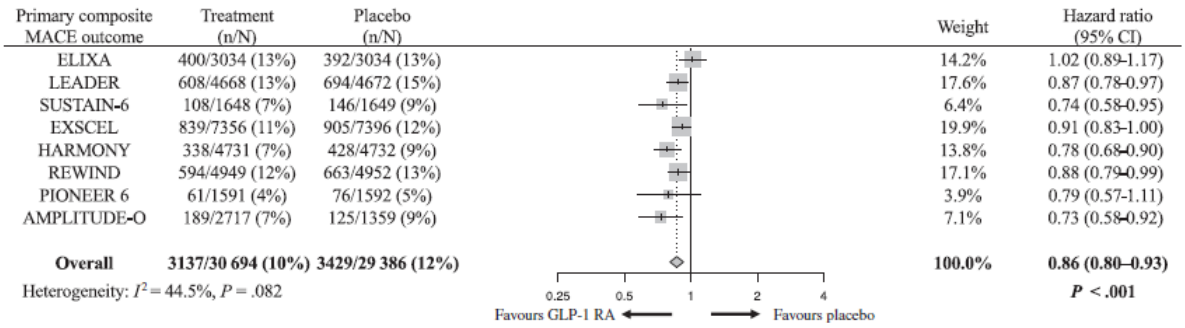
Note: Continuous variables are presented as mean ± standard deviation (except for EXSCEL), and categorical variables are presented as number (%). Continuous data of EXSCEL are presented as median (interquartile range [IQR]).
Abbreviations: DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SGLT2, sodium-glucose co-transporter-2.
[a]eGFR data of SUSTAIN-6, EXSCEL, and REWIND are expressed as median (IQR). The standard deviation of eGFR in LEADER was not available (NA).

Qualität der Studien:

- Low risk of bias for all studies in all domains

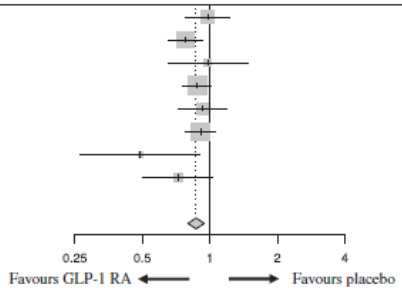
Studienergebnisse:

- MACE



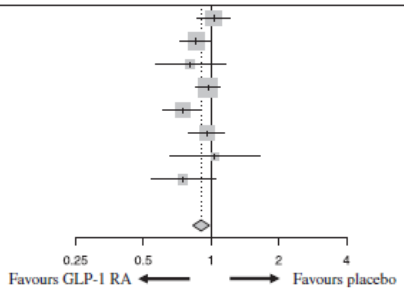
- Cardiovascular Mortality

Cardiovascular mortality	Treatment (n/N)	Placebo (n/N)	Weight	Hazard ratio (95% CI)
ELIXA	156/3034 (5%)	158/3034 (5%)	12.3%	0.98 (0.78-1.22)
LEADER	219/4668 (5%)	278/4672 (6%)	19.2%	0.78 (0.66-0.93)
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	4.0%	0.98 (0.65-1.48)
EXSCEL	340/7356 (5%)	383/7396 (5%)	24.3%	0.88 (0.76-1.02)
HARMONY	122/4731 (3%)	130/4732 (3%)	10.5%	0.93 (0.73-1.19)
REWIND	317/4949 (6%)	346/4952 (7%)	22.8%	0.91 (0.78-1.06)
PIONEER 6	15/1591 (1%)	30/1592 (2%)	1.8%	0.49 (0.27-0.92)
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	5.1%	0.72 (0.50-1.03)
Overall	**1288/30 694 (4%)**	**1421/29 386 (5%)**	**100.0%**	**0.87 (0.80–0.94)**
Heterogeneity: $I^2 = 12.8\%$, $P = .330$				**$P = .001$**



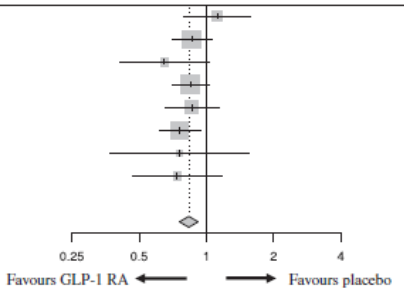
- Myocardial infarction

Myocardial infraction	Treatment (n/N)	Placebo (n/N)	Weight	Hazard ratio (95% CI)
ELIXA	270/3034 (9%)	261/3034 (9%)	16.6%	1.03 (0.87-1.22)
LEADER	292/4668 (6%)	339/4672 (7%)	18.2%	0.86 (0.73-1.00)
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	5.1%	0.81 (0.57-1.16)
EXSCEL	483/7356 (7%)	493/7396 (7%)	22.9%	0.97 (0.85-1.10)
HARMONY	181/4731 (4%)	240/4732 (5%)	13.7%	0.75 (0.61-0.90)
REWIND	223/4949 (5%)	231/4952 (5%)	14.4%	0.96 (0.79-1.15)
PIONEER 6	37/1591 (2%)	35/1592 (2%)	3.2%	1.04 (0.66-1.66)
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	5.8%	0.75 (0.54-1.05)
Overall	**1631/30 694 (5%)**	**1724/29 386 (6%)**	**100.0%**	**0.90 (0.83–0.98)**
Heterogeneity: $I^2 = 27.4\%$, $P = .210$				**$P = .020$**



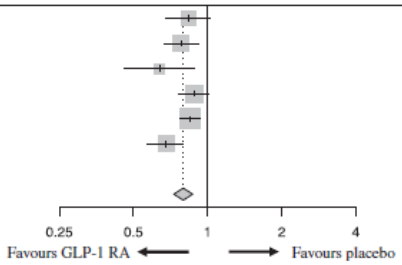
- Stroke

Stroke	Treatment (n/N)	Placebo (n/N)	Weight	Hazard ratio (95% CI)
ELIXA	67/3034 (2%)	60/3034 (2%)	7.7%	1.12 (0.79-1.58)
LEADER	173/4668 (4%)	199/4672 (4%)	23.1%	0.86 (0.71-1.06)
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	4.4%	0.65 (0.41-1.03)
EXSCEL	187/7356 (3%)	218/7396 (3%)	24.8%	0.85 (0.70-1.03)
HARMONY	94/4731 (2%)	108/4732 (2%)	12.4%	0.86 (0.66-1.14)
REWIND	158/4949 (3%)	205/4952 (4%)	21.4%	0.76 (0.62-0.94)
PIONEER 6	13/1591 (1%)	17/1592 (1%)	1.8%	0.76 (0.37-1.56)
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	4.5%	0.74 (0.47-1.17)
Overall	**769/30 694 (3%)**	**884/29 386 (3%)**	**100.0%**	**0.83 (0.76–0.92)**
Heterogeneity: $I^2 = 0\%$, $P = .639$				**$P < .001$**



- Composite renal outcome: HARMONY and PIONEER 6 did not report renal outcomes and were excluded from the analysis of renal outcomes.

Composite renal outcome	Treatment (n/N)	Placebo (n/N)	Weight	Hazard ratio (95% CI)
ELIXA	172/2647 (6%)	203/2639 (8%)	12.8%	0.84 (0.68-1.02)
LEADER	268/4668 (6%)	337/4672 (7%)	17.4%	0.78 (0.67-0.92)
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	6.3%	0.64 (0.46-0.88)
EXSCEL	366/6256 (6%)	407/6222 (7%)	19.5%	0.88 (0.76-1.01)
REWIND	848/4949 (17%)	970/4952 (20%)	27.1%	0.85 (0.77-0.93)
AMPLITUDE-O	335/2717 (13%)	250/1359 (18%)	16.8%	0.68 (0.57-0.79)
Overall	**2051/22 885 (9%)**	**2267/21 493 (11%)**	**100.0%**	**0.80 (0.73–0.87)**
Heterogeneity: $I^2 = 45.0\%$, $P = .106$				**$P < .001$**



- Further GLP-1 RAs reduced all-cause mortality (HR: 0.88; 95% CI: 0.82-0.94; P < .001; I2 = 10.5%), hospitalization because of heart failure (HR: 0.89; 95% CI: 0.82-0.98; P = .013; I2 = 2.5%), and renal function outcome (HR: 0.84; 95% CI: 0.73-0.97; P = .016; I2 = 31.4%).
- Subgroup analysis
  - In a subgroup analysis of MACE stratified by the structural backbone of GLP-1 RAs, exendin-based GLP-1 RAs did not reduce MACE with high heterogeneity (HR: 0.90; 95% CI: 0.78-1.04; P = .163; I2 = 67.2%). On the contrary, human GLP-1–based GLP-1 RAs reduced MACE with low heterogeneity (HR: 0.84; 95% CI: 0.79-0.90; P < .001).

- In another subgroup analysis of MACE stratified by the history of established cardiovascular disease (Figure S3), GLP-1 RAs reduced MACE in individuals with established cardiovascular disease (HR: 0.85; 95% CI: 0.79-0.92; P < .001; I2 = 48.0%), but not in those without established cardiovascular disease (HR: 0.94; 95% CI: 0.83-1.06; P = .303; I2 = 0.0%).

Anmerkung/Fazit der Autoren

In conclusion, GLP-1 RAs reduce MACE, its components, all-cause mortality, hospitalization because of heart failure, the composite renal outcome, and the renal function outcome. The meta-regression analysis showed that the reduction in HbA1c, but not body weight, is associated with the cardiovascular and renal outcomes of GLP-1 RAs. The magnitude of HbA1c reduction can be a surrogate for the cardiovascular and renal benefits of treatment with GLP-1 RAs.

Kommentare zum Review

Es liegen weitere SRs zu ähnlichen Fragestellungen mit derselben Schlussfolgerung vor:

- Li, X. et al., 2022 [32]
- Simental-Mendía, M. et al., 2021 [61]

Evans, M et al., 2023 [17].

Cardiovascular and renal outcomes of GLP-1 receptor agonists vs. DPP-4 inhibitors and basal insulin in type 2 diabetes mellitus: A systematic review and meta-analysis.

Fragestellung

To compare the cardiovascular and renal outcomes of GLP-1 RA versus DPP4i and basal insulin in the management of T2DM.

Methodik

Population:

- adults aged 18 years and older with T2DM

Intervention:

- GLP-1 RA

Komparator:

- DPP4i or basal insulin

Endpunkte:

- cardiovascular outcomes ofinterest were composite cardiovascular outcomes such as major adverse cardiovascular events (MACEs); and single endpoints, such as non-fatal stroke, non-fatal myocardial infarction, peripheral artery disease, heart failure, cardiovascular death, and all-cause mortality.
- Renal outcomes included composite kidney endpoints, comprising new-onset macroalbuminuria, doubling of serum creatinine, reduction in eGFR, dialysis, renal-replacement therapy, hospitalisation, and death due to renal causes.
- short- and long-term safety and tolerability outcomes

Recherche/Suchzeitraum:

- Embase, MEDLINE (via PubMed), Cochrane Library (including the Cochrane Central Register ofControlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE)), https://ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) from 2008 (when the first formulation of FDA guidance called for evaluating the cardiovascular safety of glucose-lowering therapies) to date.

Qualitätsbewertung der Studien:

- Non-randomised Studies of Interventions (ROBINS-I) tool for nonrandomised, cohort-type interventional studies and Cochrane Risk of Bias Tool for randomised controlled trials

Ergebnisse

Anzahl eingeschlossener Studien:

- 22 studies involving over 200,000 participants

Charakteristika der Population/Studien:

- Studies were conducted between 2014 and 2022 in 21 countries; Australia, Brazil, Denmark, Hungary, Italy, Japan, Mexico, Norway, Poland, Puerto Rico, Romania, Russia, Slovenia, South Africa, South Korea, Spain, Sweden, Taiwan, Ukraine, the United Kingdom and United States. In terms of study design, 20 studies were longitudinal (cohort-type) observational studies (19 of which were retrospective while one was prospective) and two were RCTs. Most (16/20) cohort studies employed a propensity score matching design. 16 ofthe included studies reported on cardiovascular but no renal outcomes (eight comparing GLP-1 RA with DPP4i, five comparing GLP-1 RAwith basal insulin and three comparing GLP-1 RA with both DPP4i and basal insulin), while four studies reported on renal but no cardiovascular outcomes. Two studies reported on both cardiovascular and renal outcomes. Observational studies were mostly based on patient data from hospitalbased medical and health administrative databases.

Qualität der Studien:

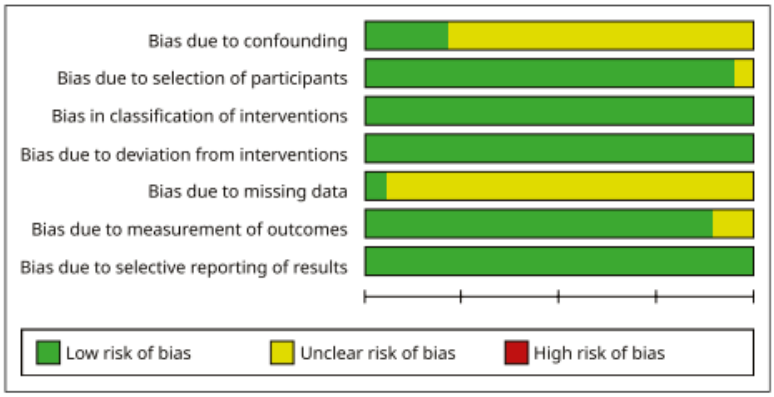


Figure 2. Outcomes of risk of bias assessment of studies included in the meta-analysis.

Studienergebnisse:

- Compared with DPP4i, treatment with GLP-1 RA was associated with a greater benefit on composite cardiovascular outcomes (HR:0.77, 95% CI:0.69–0.87), myocardial infarction (HR:0.82, 95% CI:0.69–0.97), stroke (HR:0.83, 95% CI: 0.74–0.93), cardiovascular mortality (HR:0.76, 95% CI:0.68–0.85) and all-cause mortality (HR:0.65, 95% CI:0.48– 0.90).

- There was no difference in effect on heart failure (HR:0.97, 95% CI:0.82–1.15). Compared with basal insulin, GLP-1 RA was associated with better effects on composite cardiovascular outcomes (HR:0.62, 95% CI:0.48–0.79), heart failure (HR:0.57, 95% CI:0.35–0.92), myocardial infarction (HR:0.70, 95% CI:0.58–0.85), stroke (HR:0.50, 95% CI:0.40–0.63) and all-cause mortality (HR:0.31, 95% CI:0.20–0.48).
- Evidence from a small number of studies suggests that GLP-1 RA had better effects on composite and individual renal outcomes, such as eGFR, compared with either DPP4i and basal insulin.

Fazit der Autoren

Available evidence from studies investigating cardiovascular outcomes suggests that treating T2DM people with GLP-1 RA can yield better benefits on composite and individual cardiovascular outcomes such as myocardial infarction, stroke, cardiovascular mortality and all-cause mortality, compared with DPP4i. However, there was no difference in effect between GLP-1 RA and DPP4i on heart failure. GLP-1 RA compares better against basal insulin, with better effects on both composite cardiovascular and specific cardiovascular outcomes such as myocardial infarction, stroke, cardiovascular mortality and all-cause mortality. Evidence from a small number of studies investigating renal outcomes suggests that GLP-1 RA had better effects on composite and individual renal outcomes such as eGFR, than either DPP4i and basal insulin.

Nreu, B et al., 2020 [52].

Major cardiovascular events, heart failure, and atrial fibrillation in patients treated with glucagon-like peptide-1 receptor agonists: An updated meta-analysis of randomized controlled trials

Fragestellung

Aim of the present meta-analysis is the assessment of the effect of GLP1-RA treatment on the incidence of MACE, heart failure, major amputation, and mortality, collecting all available evidence from randomized controlled trials.

Methodik

Population:

- patients with type 2 diabetes

Intervention:

- GLP-1 RA

Komparator:

- placebo or any other non-GLP-1 receptor agonist drug

Endpunkte:

- The principal endpoints were MACE and individual components of MACE (i.e. non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality), reported as adjudicated events, or as serious adverse events if a formal adjudication was not available.
- Heart failure, atrial fibrillation, major amputation, total (fatal + nonfatal) myocardial infarction and total stroke, and all-cause mortality were considered as secondary endpoints.

Recherche/Suchzeitraum:

- A MEDLINE, Cochrane database and clinicaltrials.gov search was performed to identify all clinical trials (English only), up to June 15th, 2019, with duration of follow-up of at least 52 weeks, in which GLP-1 RA (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide).

Qualitätsbewertung der Studien:

- The quality of trials was assessed using the parameters proposed by the Cochrane Collaboration.

Ergebnisse

Anzahl eingeschlossener Studien:

- 43 studies

Charakteristika der Population/Studien:

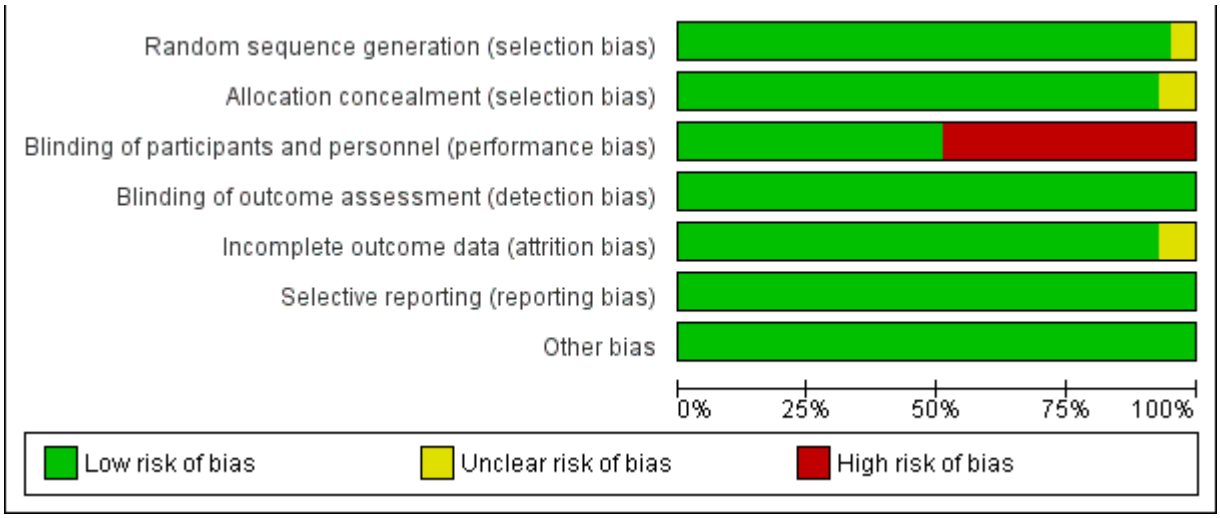
Table 1 Principal characteristics of the included trials.

Study name (Pub year)	Drug	Comparator	Trial durat. (weeks)	Patients (n)	Age (years)	BMI (kg/m^2)	Durat. of DM (yrs)	HbA1c (%)
Cardiovascular outcome trials								
ELIXA [15]	Lixisenatide	Placebo	109	6068	60.3	30.1	9.0	7.6
LEADER [1]	Liraglutide	Placebo	198	9340	64.3	32.5	13.0	8.7
SUSTAIN-6 [2]	Semaglutide	Placebo	109	3297	64.6	32.8	14.0	8.7
EXSCEL [5]	Exenatide LA	Placebo	166	14,752	62.0	31.7	12.0	8.0
HARMONY [4]	Albiglutide	Placebo	83	9463	64.1	32.3	14.0	8.7
REWIND [3]	Dulaglutide	Placebo	281	9901	66.2	32.3	10.5	7.3
PIONEER-6 [6]	Oral semaglutide	Placebo	68	3183	66.0	32.0	15.0	8.2
Non-cardiovascular outcome trials								
Ahrén [33]	Albiglutide	Placebo	104	1012	54.0	32.6	6.0	8.1
Home [34]	Albiglutide	Placebo	52	386	55.0	32.2	9.0	8.2
Nauck [35]	Albiglutide	Placebo	52	301	53.0	33.5	4.0	8.1
Reusch [36]	Albiglutide	Placebo	156	301	55.0	34.1	8.0	8.1
Leiter [37]	Albiglutide	Sitagliptin	52	495	63.3	30.4	11.2	8.2
Weissman [38]	Albiglutide	Glargine	52	745	55.0	33.0	9.0	8.3
Leiter [17]	Albiglutide	Lispro	52	566	55.6	NR	11.1	8.5
Miyagawa [39]	Dulaglutide	Placebo	52	351	58.0	25.0	6.5	8.1
Umpierrez [40]	Dulaglutide	Metformin	52	537	56.0	33.3	3.0	7.6
Weinstock [41]	Dulaglutide	Sitagliptin	104	783	54.0	31.0	7.0	8.1
Blonde [42]	Dulaglutide	Glargine	52	884	59.5	32.5	12.3	8.5
Tuttle 2018 [66]	Dulaglutide	Glargine	52	577	64.5	32.3	18.0	8.6
NCT01648582[a]	Dulaglutide	Glargine	52	526	55.0	NR	NR	NR
Giorgino [43]	Dulaglutide	Glargine	78	537	57.0	31.3	9.0	8.1
Sathyanarayana [44]	Exenatide	None	52	24	52.0	32.0	NR	8.2
Derosa [45]	Exenatide	Placebo	52	171	57.0	31.8	8.0	8.0
Liang [46]	Exenatide	Placebo	52	70	51.0	30.3	7.0	10.7
Derosa [47]	Exenatide	Glibenclamide	52	128	56.0	28.6	NR	8.8
Derosa [48]	Exenatide	Glimepiride	52	101	55.0	28.4	NR	8.7
Gallwitz [49]	Exenatide	Glimepiride	208	977	56.0	32.4	6.0	7.4
Nauck [50]	Exenatide	Aspart	52	501	59.0	30.2	10.0	8.6
Bunck [51]	Exenatide	Glargine	64	69	58.0	30.6	5.0	7.5
Jaiswal [52]	Exenatide	Glargine	78	46	52.0	36.0	7.0	8.3
Jabbour [53]	Exenatide LAR	Placebo	52	464	54.0	32.7	7.4	9.3
Diamant [54]	Exenatide LAR	Glargine	156	467	58.0	32.3	7.9	8.3
Inagaki [55]	Exenatide LAR	Glargine	52	427	57.0	26.2	9.0	8.5
De Wit [56]	Liraglutide	None	52	50	58.0	33.0	NR	7.3
Davies [57]	Liraglutide	Placebo	56	423	55.0	37.4	7.0	7.9
Nauck [58]	Liraglutide	Placebo	104	221	57.0	31.2	7.0	8.4
Pratley [59]	Liraglutide	Sitagliptin	52	658	55.0	32.8	6.0	8.4
Arturi [60]	Liraglutide	Sitagliptin	52	20	60.0	31.8	NR	8.1
Gouch [61]	Liraglutide	Degludec	52	827	55.0	31.2	7.0	8.3
Garber [62]	Liraglutide	Glimepiride	104	746	53.0	33.0	5.0	8.3
Kaku 2018 [63]	Semaglutide	None	56	601	58.0	27.4	8.8	8.1
Ahren [64]	Semaglutide	Sitagliptin	56	1225	55.0	32.5	6.5	8.1
Rosenstok 2019 [65]	Semaglutide	Sitagliptin	78	1864	58.0	32.5	8.5	8.3

NR: Not reported. LAR: Long-Acting Release.
[a] See www.clinicaltrials.gov.

Qualität der Studien:

Figure 1S – Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Studienergebnisse:

- A significant reduction of MACE was observed in patients treated with GLP-1 RA in comparison with control (MH-OR 0.87 [0.83, 0.92]), even when applying a fixed-effect model (MH-OR 0.87 [0.83, 0.92], p < 0.001).
- A significant reduction in the risk of nonfatal myocardial infarction was observed in patients treated with GLP-1 RA (MH-OR 0.90 [0.84, 0.97])
- GLP-1 RA treatment was associated with a reduced risk of nonfatal stroke (MH-OR 0.83 [0.75, 0.93])
- A significant reduction with GLP1-RA was observed for all-cause mortality (MH-OR 0.89 [0.83, 0.96])
- GLP1-RA did not increase the risk of heart failure (MH-OR 0.93 [0.85, 1.01], pZ 0.09) with no difference between different groups
- GLP1-RA did not increase the risk of atrial fibrillation (MH-OR 0.94 [0.84, 1.04]), with no difference between different groups of trials.

Fazit der Autoren

The present meta-analysis confirms the favorable effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events, cardiovascular and all-cause mortality, stroke, and possibly myocardial infarction. Conversely, the effects on heart failure remain uncertain. Available data on atrial fibrillation seems to exclude any major safety issues in this respect.

Patel T et al., 2023 [54].

Comparative efficacy and safety profile of once-weekly Semaglutide versus once-daily Sitagliptin as an add-on to metformin in patients with type 2 diabetes: a systematic review and meta-analysis.

Fragestellung

We conducted a systematic review and meta-analysis because there is a limited number of clinical trials with a restricted scope that assessed the safety and efficacy of semaglutide compared to sitagliptin, a frequently prescribed DPP-4 inhibitor, as adjunctive therapy for patients with type 2 diabetes who had suboptimal glycemic control with metformin.

Methodik

Population:

- Type 2 diabetes

Intervention:

- Semaglutide 0.5 mg and 1.0 mg

Komparator:

- Sitagliptin 100mg

Endpunkte:

- Primär: HbA1c levels, changes in both systolic (SBP) and diastolic (DBP) blood pressures, fluctuations in pulse rate, shifts in body weight, variations in waist circumference, and modifications in body mass index (BMI)
- secondary outcomes, which included the total occurrence of adverse events (AEs) and the severity levels of these events categorized as serious, severe, moderate, or mild

Recherche/Suchzeitraum:

- PubMed, the Cochrane Library and Elsevier's ScienceDirect until April 2023

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTs with 2401 participants

Charakteristika der Population:

- 800 (33.3%) subjects assigned to the Semaglutide 0.5 mg group, 801 (33.4%) to the Semaglutide 1 mg group, and 800 (33.3%) to the Sitagliptin 100 mg group.

Table 1. Baseline characteristics of the included participants.

			No. of participants			Age, years (mean ± SD)			Males No. (%)			Females No. (%)		
Study and year	Study design	Total No. of participants	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg
Ahrén (2017) [14]	RCT	1225	409	409	407	54.8 ± 10.2	56.0 ± 9.4	54.6 ± 10.4	209 (51)	205 (50)	208 (50)	200 (49)	204 (50)	199 (49)
Seino (2018) [10]	RCT	308	103	102	103	58.8 ± 10.4	58.1 ± 11.6	57.9 ± 10.1	207 (76.7)	205 (73.5)	208 (78.6)	202 (23.3)	204 (26.5)	199 (21.4)
Linong (2021) [15]	RCT	868	288	290	290	53.0 ± 11.4	53.0 ± 10.6	53.1 ± 10.4	160 (55.6)	154 (53.1)	185 (63.8)	128 (44.4)	136 (46.9)	105 (36.2)

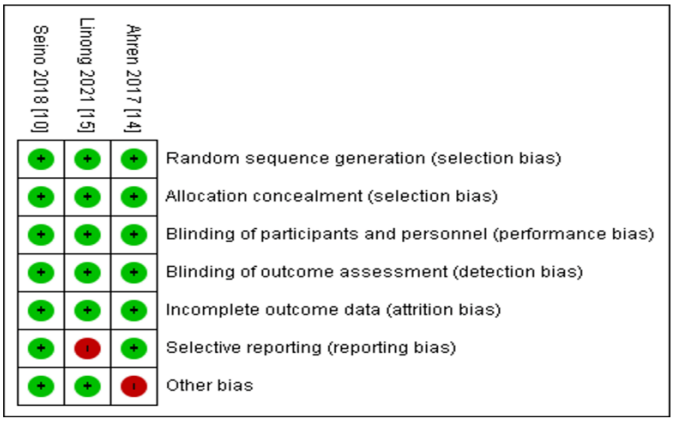
SD: standard deviation; RCT: randomized controlled trial.

Table 2. Baseline Demographics of the included participants.

	HbA1c, % (mean ± SD)			FPG, mmol/L (mean ± SD)			BMI, kg/m2 (mean ± SD)			Diabetes duration, years (mean ± SD)			Body weight, kg (mean ± SD)		
Study and year	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Sitagliptin 100 mg
Ahrén (2017) [14]	8.0 ± 0.9	8.0 ± 0.9	8.2 ± 0.9	9.3 ± 2.4	9.3 ± 2.2	9.6 ± 2.2	32.4 ± 6.2	32.5 ± 6.6	32.5 ± 5.8	6.4 ± 4.7	6.7 ± 5.6	6.6 ± 5.1	89.9 ± 20.4	89.2 ± 20.7	89.3 ± 19.7
Seino (2018) [10]	8.2 ± 1.0	8.0 ± 0.9	8.2 ± 0.9	9.2 ± 2.1	9.2 ± 1.8	9.5 ± 2.0	25.1 ± 3.8	26.1 ± 5.2	25.1 ± 3.6	8.0 ± 5.2	7.8 ± 6.9	8.1 ± 6.7	67.8 ± 11.7	70.8 ± 16.4	69.4 ± 12.9
Linong (2021) [15]	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 0.9	9.30 ± 2.67	9.29 ± 2.22	9.05 ± 2.21	28.2 ± 5.0	27.9 ± 5.0	27.3 ± 4.7	6.3 ± 5.4	6.7 ± 4.9	6.1 ± 5.2	77.6 ± 16.4	76.1 ± 16.3	75.5 ± 14.7

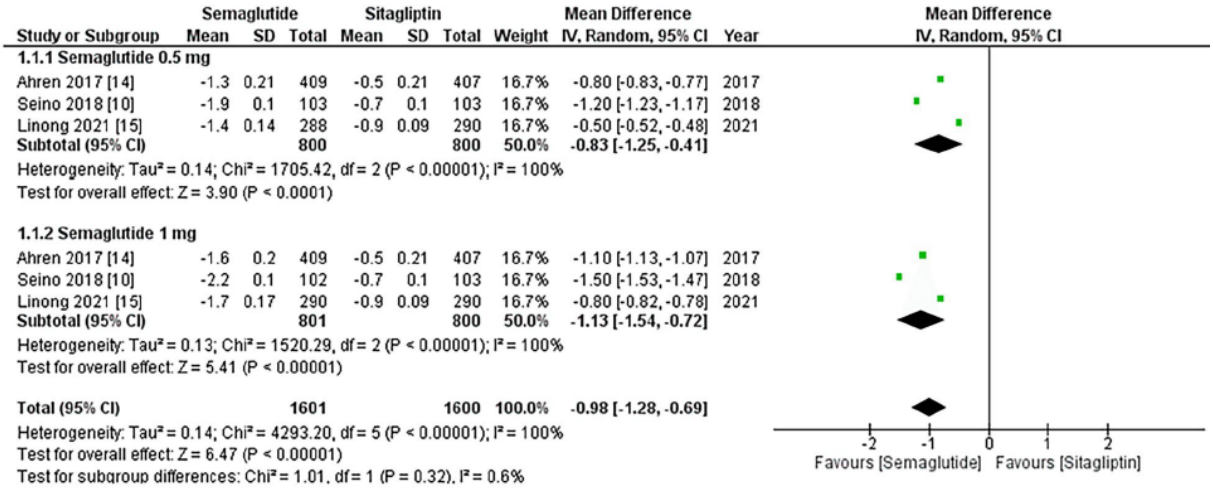
SD: Standard deviation; HbA1C: glycated hemoglobin; FPG: Fasting plasma glucose; BMI: body mass index.

Qualität der Studien:



Studienergebnisse:

- HbA1c: All three studies reported change in HbA1c levels, and upon pooled analysis, it was found that once-weekly Semaglutide treatment resulted in a significant decrease in HbA1c values after treatment (WMD: −0.98; 95% CI: −1.28, −0.69, p-value: < 0.0001; I2: 100%) compared to once daily Sitagliptin, particularly the 1 mg dose (WMD: −1.13; 95% CI: −1.54, −0.72, p-value: <0.00001; I2: 100%)



- Adverse Events: After analyzing the combined data, it was found that using a once-weekly Semaglutide treatment was associated with a significantly higher risk of total adverse events and premature treatment discontinuation. The risk of serious, severe, moderate, and mild adverse events also increased in the group receiving once-weekly Semaglutide, but the results were not statistically significant.

Table 3. Secondary outcomes.

Outcomes	Effect size (RR or WMD)	95% CI	p-value	I2
Total AE	**RR: 1.05**	**1.00, 1.09**	**0.04**	**0%**
Semaglutide 0.5 mg Vs. Sitagliptin	RR: 1.06	1.00, 1.12	0.07	0%
Semaglutide 1 mg Vs. Sitagliptin	RR: 1.04	0.97, 1.10	0.25	0%
Serious AE	**RR: 1.20**	**0.91, 1.58**	**0.21**	**0%**
Semaglutide 0.5 mg Vs. Sitagliptin	RR: 1.24	0.83, 1.86	0.29	3%
Semaglutide 1 mg Vs. Sitagliptin	RR: 1.16	0.78, 1.72	0.47	0%
Severe AE	**RR: 1.08**	**0.77, 1.53**	**0.64**	**0%**
Semaglutide 0.5 mg Vs. Sitagliptin	RR: 1.07	0.66, 1.76	0.78	0%
Semaglutide 1 mg Vs. Sitagliptin	RR: 1.10	0.67, 1.78	0.71	0%
Moderate AE	**RR: 1.10**	**0.96, 1.28**	**0.18**	**8%**
Semaglutide 0.5 mg Vs. Sitagliptin	RR: 1.15	0.95, 1.38	0.14	0%
Semaglutide 1 mg Vs. Sitagliptin	RR: 1.08	0.81, 1.45	0.60	36%
Mild AE	**RR: 1.05**	**1.00, 1.10**	**0.07**	**0%**
Semaglutide 0.5 mg Vs. Sitagliptin	RR: 1.06	0.99, 1.13	0.12	0%
Semaglutide 1 mg Vs. Sitagliptin	RR: 1.04	0.96, 1.11	0.33	0%
Premature treatment discontinuation	**RR: 3.27**	**2.31, 4.63**	**< 0.00001**	**0%**
Semaglutide 0.5 mg Vs. Sitagliptin	RR: 2.64	1.59, 4.38	0.0002	0%
Semaglutide 1 mg Vs. Sitagliptin	RR: 3.97	2.45, 6.42	< 0.00001	0%

AE: Adverse events; RR: relative risk, CI: confidence interval; I2: heterogeneity.

Anmerkung/Fazit der Autoren

In summary, the administration of once-weekly Semaglutide led to a significant reduction in HbA1c, average systolic blood pressure (SBP), mean diastolic blood pressure (DBP), body weight, waist circumference, and BMI, as well as an increase in pulse rate, compared to the once-daily administration of Sitagliptin. Moreover, Semaglutide demonstrated a favorable safety profile similar to other GLP-1 receptor agonists. Based on these findings, we conclude that once-weekly Semaglutide shows great promise as an adjunctive treatment to metformin when monotherapy fails to achieve adequate glycemic control in individuals with type 2 diabetes.

Kommentare zum Review

Ergebnisse zur Veränderung des Blutdrucks, Puls, Gewichts und BMI wurden nicht dargestellt

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Patoulias D et al., 2020 [55].

Glucagon-like peptide-1 receptor agonists or sodium–glucose cotransporter-2 inhibitors as add-on therapy for patients with type 2 diabetes? A systematic review and meta-analysis of surrogate metabolic endpoints

Fragestellung

Our study sought to provide precise effect estimates (safety and efficacy) regarding the role of GLP-1RAs vs SGLT-2is as add-on treatments in patients uncontrolled by metformin monotherapy.

Methodik

Population:

- adult patients with T2DM inadequately controlled by metformin monotherapy

Intervention:

- GLP-1RA

Komparator:

- SGLT-2i

Endpunkte:

- primary efficacy outcome: glycaemic efficacy of GLP-1RAs vs SGLT-2is, as estimated by absolute changes in HbA1c (%) levels
- Secondary efficacy outcomes: body weight (kg), fasting plasma glucose (FPG) levels (mmol/L), and achievement of HbA1c < 7% and body weight loss > 5% of baseline body weight, renal function, lipid profiles and blood pressure.
- Safety outcomes: hypoglycaemia (as defined by ADA guidelines), gastrointestinal adverse events (nausea, diarrhoea), acute pancreatitis, genital and urinary tract infections, diabetic ketoacidosis, diabetic retinopathy, amputation and malignancy.

Recherche/Suchzeitraum:

- PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov website and European Union Drug-Regulating Authorities Clinical Trials Database (EudraCT) and grey literature until December 2019

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool for randomized trials (RoB version 2)

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTs

Charakteristika der Population:

Table 2
Patients' baseline characteristics in three selected randomized clinical trials [reference].

Study	PIONEER 2 [29]	DURATION-8 [30]	SUSTAIN 8 [31]
Patients (*n*)	821	685	788
Assigned treatment of interest	Oral semaglutide 14 mg (*n* = 411) Empagliflozin 25 mg (*n* = 410)	Exenatide 2 mg OW + placebo (*n* = 227) Dapagliflozin 10 mg + placebo (*n* = 230)	Semaglutide 1.0 mg (*n* = 394) Canagliflozin 300 mg (*n* = 394)
Gender	Oral semaglutide 14 mg (M/F = 206/205) Empagliflozin 25 mg (M/F = 209/201)	Exenatide 2 mg OW + placebo (M/F = 116/111) Dapagliflozin 10 mg + placebo (M/F = 110/120)	Semaglutide 1.0 mg (M/F = 223/171) Canagliflozin 300 mg (M/F = 201/193)
Mean age (years)	Oral semaglutide 14 mg [57 (10)] Empagliflozin 25 mg [58 (10)]	Exenatide 2 mg OW + placebo [54.2 (9.6)] Dapagliflozin 10 mg + placebo [54.5 (9.2)]	Semaglutide 1.0 mg [55.7 (11.1)] Canagliflozin 300 mg [57.5 (10.7)]
Body weight (kg)	Oral semaglutide 14 mg [91.9 (20.5)] Empagliflozin 25 mg [91.3 (20.1)]	Exenatide 2 mg OW + placebo [89.8 (20.2)] Dapagliflozin 10 mg + placebo [91.1 (19.7)]	Semaglutide 1.0 mg [90.6 (22.6)] Canagliflozin 300 mg [89.8 (22.6)]
Body mass index (kg/m^2)	Oral semaglutide 14 mg [32.9 (6.3)] Empagliflozin 25 mg [32.8 (5.9)]	Exenatide 2 mg OW + placebo [32.0 (5.9)] Dapagliflozin 10 mg + placebo [33.0 (6.1)]	Semaglutide 1.0 mg [32.2 (6.8)] Canagliflozin 300 mg [32.5 (6.9)]
Diabetes duration (years)	Oral semaglutide 14 mg [7.2 (5.8)] Empagliflozin 25 mg [7.7 (6.3)]	Exenatide 2 mg OW + placebo [7.4 (5.5)] Dapagliflozin 10 mg + placebo [7.1 (5.5)]	Semaglutide 1.0 mg [7.5 (5.9)] Canagliflozin 300 mg [7.2 (5.4)]
HbA1c (%)	Oral semaglutide 14 mg [8.1 (0.9)] Empagliflozin 25 mg [8.1 (0.9)]	Exenatide 2 mg OW + placebo [9.3 (1.1)] Dapagliflozin 10 mg + placebo [9.3 (1.0)]	Semaglutide 1.0 mg [8.3 (1.0)] Canagliflozin 300 mg [8.2 (1.0)]
Baseline antidiabetic medication	Metformin monotherapy	Metformin monotherapy	Metformin monotherapy
Follow-up period (weeks)	52	52	52
Registration number at ClinicalTrials.gov	NCT02863328	NCT02229396	NCT03136484

Data are presented as n (absolute number) or as means (standard deviation); dosages are once daily unless otherwise stated.
M/F: male/female; OW: once weekly.

Qualität der Studien:

Table 1
Assessment of bias risk related to primary efficacy outcomes.

Randomized clinical trial [reference]	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Overall grade
PIONEER 2 [29]	Low	Low	Low	Low	Low	Low
DURATION-8 [30]	Low	Low	Low	Low	Low	Low
SUSTAIN 9 [31]	Low	Low	Low	Low	Low	Low

Studienergebnisse:

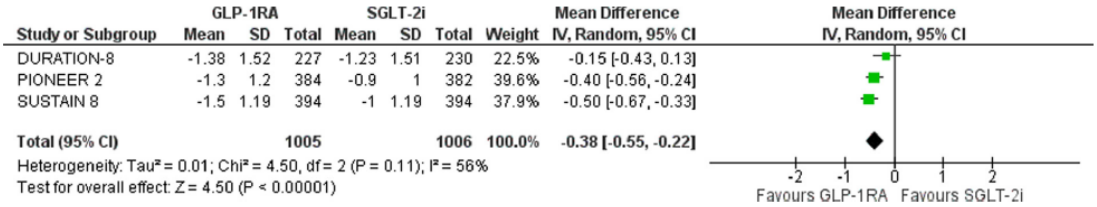


Fig. 2. Effect of glucagon-like peptide-1 receptor agonists (GLP-1RA) vs sodium–glucose cotransporter-2 inhibitors (SGLT-2i) on HbA1c levels. IV: inverse variance.

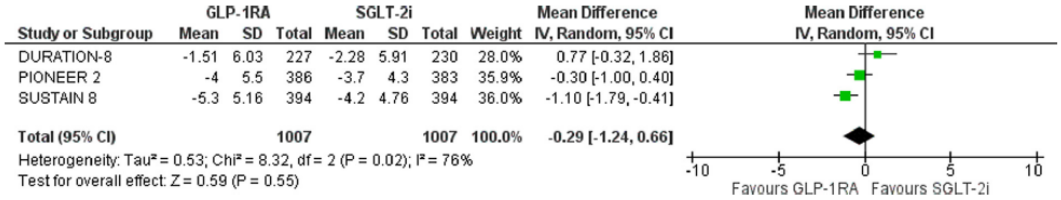


Fig. 3. Effect of glucagon-like peptide-1 receptor agonists (GLP-1RA) vs sodium–glucose cotransporter-2 inhibitors (SGLT-2i) on body weight. IV: inverse variance.

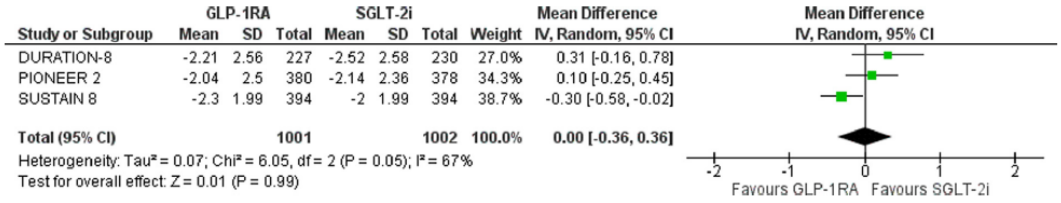


Fig. 4. Effect of glucagon-like peptide-1 receptor agonists (GLP-1RA) vs sodium–glucose cotransporter-2 inhibitors (SGLT-2i) on fasting plasma glucose. IV: inverse variance.

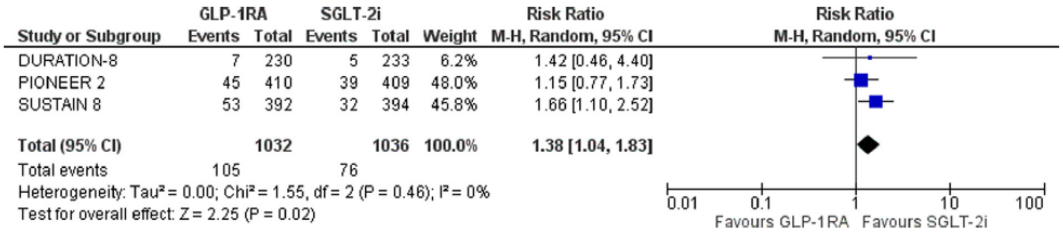


Fig. 5. Effect of glucagon-like peptide-1 receptor agonists (GLP-1RA) vs sodium–glucose cotransporter-2 inhibitors (SGLT-2i) on any hypoglycaemia risk. M–H: Mantel–Haenszel.

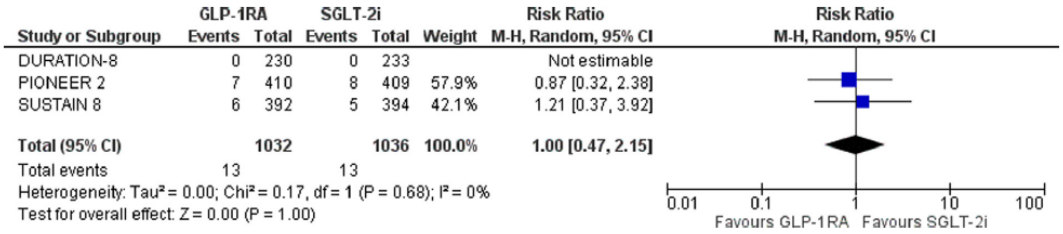


Fig. 6. Effect of glucagon-like peptide-1 receptor agonists (GLP-1RA) vs sodium–glucose cotransporter-2 inhibitors (SGLT-2i) on risk of severe hypoglycaemia. M–H: Mantel–Haenszel.

- HbA1c:
  - GLP-1RAs led to a significantly greater reduction in HbA1c of 0.38% (95% CI: -0.55 to -0.22, I2 = 56%) compared with SGLT2is (Fig. 2). GRADE analysis indicated that the quality of evidence concerning the primary efficacy outcome was moderate, given the observed high heterogeneity, which downgraded the score due to inconsistency.
- Body weight:
  - Similar body weight reduction was found with both drug classes. Compared with SGLT-2is, GLP-1RAs resulted in a nonsignificant reduction in body weight of 0.29 kg (95% CI: -1.24 to 0.66, I2 = 76%), as shown in Fig. 3 (GRADE: low).
- Fasting plasma glucose:

- FPG changes also showed that GLP-1RAs and SGLT-2is exhibited similar reductions (mean D: 0.00, 95% CI: -0.36 to 0.36, I2 = 67%), as depicted in Fig. 4.

- Other efficacy outcomes:
  - patients receiving GLP-1RAs had significantly greater odds of achieving an HbA1c < 7% than those receiving SGLT-2is (OR: 2.40, 95% CI: 1.99– 2.90, I2 = 0%; GRADE: high; see supplementary materials associated with this article online).
  - In contrast, it was also found that patients administered GLP-1RAs had equal odds of achieving a body weight reduction > 5% compared with those receiving SGLT- 2is (OR: 0.96, 95% CI: 0.70–1.33, I2 = 64%; GRADE: moderate
  - As for blood pressure, our results have shown that GLP-1RAs are not superior to SGLT-2is in terms of either systolic (mean D: 0.98, 95% CI: -1.00 to 2.97, I2 = 62%) or diastolic (mean D: 1.01, 95% CI: -0.25 to 2.27, I2 = 49%) blood pressure ()
- Safety Outcomes:
  - Our results showed that patients administered GLP-1RAs presented with significantly greater risk of experiencing any hypoglycaemia (Fig. 5) compared with those given SGLT-2is (RR: 1.38, 95% CI: 1.04–1.83, I2 = 0%; GRADE: high)
  - It was also revealed that both classes of antidiabetic agents exert the same risk for severe hypoglycaemia (RR: 1.00, 95% CI: 0.47–2.15, I2 = 0%) (Fig. 6)
  - Patients receiving GLP-1RAs had significantly greater risk of experiencing nausea than patients taking SGLT-2is (RR: 4.12, 95% CI: 2.18–7.77, I2 = 71%; GRADE: moderate).
  - In addition, GLP-1RA-treated patients had greater risk of diarrhoea compared with patients taking SGLT-2is (RR: 1.93, 95% CI: 1.34– 2.78, I2 = 22%; GRADE: moderate).
  - GLP-1RA treatment was associated with a significantly lower risk of genital infections, primarily mycotic ones, compared with SGLT-2i treatment (RR = 0.21, 95% CI: 0.12–0.34, I2 = 0%; GRADE: high)
  - Data were inconclusive regarding the impact of the assessed treatment options on other safety outcomes, namely, urinary tract infections, diabetic ketoacidosis, diabetic retinopathy, amputation, malignancy and acute pancreatitis.
  - Finally, it was found that patients given GLP-1RAs had a non-significant increase in risk of treatment discontinuation (RR: 1.16, 95% CI: 0.63–2.12, I2 = 78%)

Anmerkung/Fazit der Autoren

The present meta-analysis suggests that GLP-1RAs may provide better glycaemic results in patients with T2DM uncontrolled by metformin monotherapy compared with SGLT-2is, but at the cost of increasing risk for hypoglycaemia and gastrointestinal adverse events. Nevertheless, no significant differences in body weight loss or treatment discontinuation were identified. Choosing between the two drug classes should be made after meticulous evaluation of the patient's comorbidities (for example, heart failure). In future, head-to-head trials of surrogate cardiovascular and renal outco-mes should shed further light on the best add-on treatment for T2DM patients uncontrolled by metformin monotherapy.

Patoulias D et al., 2023 [56].

Effect of semaglutide versus other glucagon-like peptide-1 receptor agonists on cardio-metabolic risk factors in patients with type 2 diabetes: A systematic review and meta-analysis of head-to-head, phase 3, randomized controlled trials

Fragestellung

The aim of the present meta-analysis was to assess whether semaglutide exerts greater effects on glycemia and other cardio-metabolic risk factors compared to other GLP-1RAs.

Methodik

Population:

- type 2 diabetes

Intervention:

- semaglutide

Komparator:

- other GLP-1RAs

Endpunkte:

- HbA1c
- body weight, BMI (in kg/m2), fasting plasma glucose (FPG, in mmol/1, or mg/dL), office systolic blood pressure (SBP, in mm Hg), office diastolic blood pressure (DBP1 in mm Hg) office pulse rate, total cholesterol levels, LDL-C, HDL-C, and triglycerides levels (TRG, in mmol/ L).

Recherche/Suchzeitraum:

- PubMed and Cochrane Library databases were searched form inception to 8th February 2023 to retrieve eligible head-to-head phase 3 RCTs

Qualitätsbewertung der Studien:

- Risk of bias tool 2 (RoB 2)

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Population/Studien:

Participants' baseline characteristics across the eligible RCTs, included in the present meta-analysis.

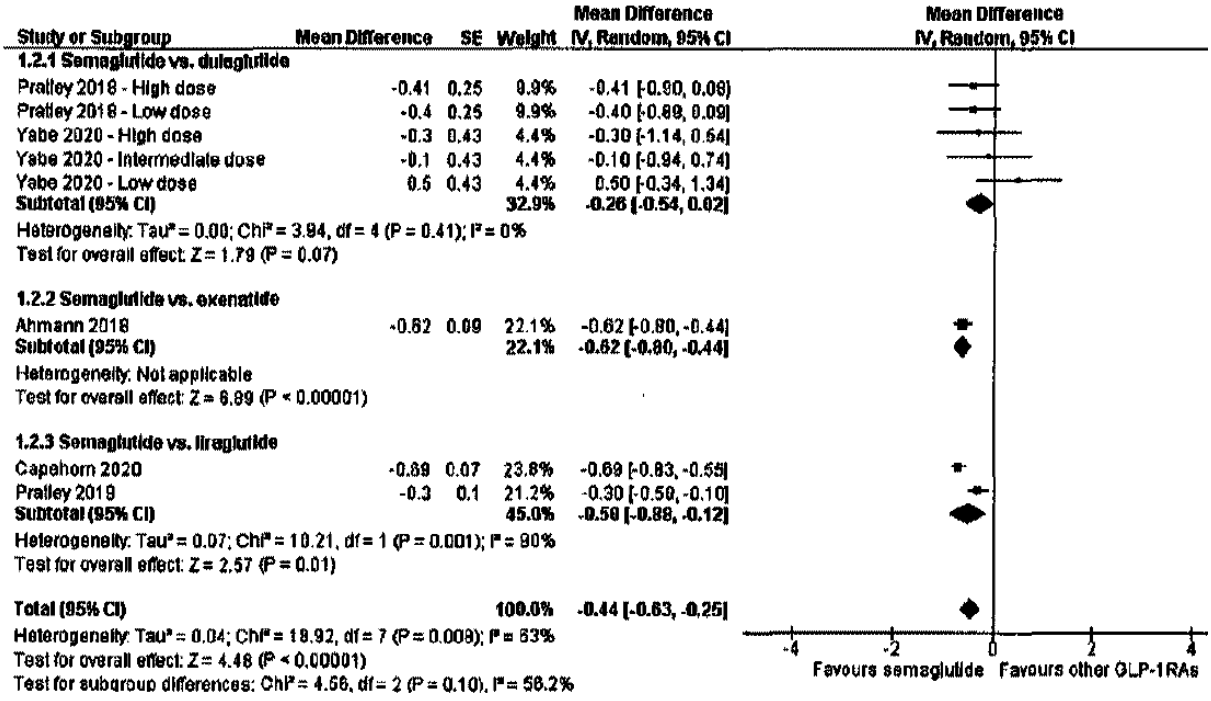
	Ahmann et al[14]	Capehorn et al[15]	Pratley et al[10]	Pratley et al[16]	Yabe et al[17]
Study design	Parallel group	Parallel group	Parallel group	Parallel group	Parallel group
Number of randomized subjects (n)	813	577	1201	711	458
Treatment duration (weeks)	56	30	40	26	52
Route of semaglutide administration	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Oral
Dose of semaglutide	1.0 mg	1.0 mg	0.5 mg & 1.0 mg	14 mg	3 mg, 7 mg & 14 mg
Comparator	Exenatide 2 mg	Liraglutide 1.2 mg	Dulaglutide 0.75 mg & 1.5 mg	Liraglutide 1.8 mg	Dulaglutide 0.75 mg
Age (years)	Semaglutide: 56.4 (20–82)	Semaglutide: 60.1 (10.5)	Semaglutide 0.5 mg: 56 (10.9) Semaglutide 1.0 mg: 55 (10.6)	Semaglutide: 56 (10)	Semaglutide 3 mg: 59 (10) Semaglutide 7 mg: 58 (11) Semaglutide 14 mg: 57 (10)
	Exanatide: 56.7 (21–83)	Liraglutide: 58.9 (10.0)	Dulaglutide 0.75 mg: 55 (10.4) Dulaglutide 1.5 mg: 56 (10.6)	Liraglutide: 56 (10)	Dulaglutide: 61 (9)
Male to female ratio	Semaglutide: 319/185	Semaglutide: 160/130	Semaglutide: 331/270	Semaglutide: 147/138	Semaglutide: 290/103
	Exenatide: 228/177	Liraglutide: 167/120	Dulaglutide: 331/267	Liraglutide: 149/135	Dulaglutide: 51/14
Type 2 diabetes duration (years)	Semaglutide: 9.0 (0.4–37.1)	Semaglutide: 9.6 (6.1)	Semaglutide 0.5 mg: 7.7 (5.9) Semaglutide 1.0 mg: 7.3 (5.7)	Semaglutide: 7.8 (5.7)	Semaglutide 3 mg: 9.4 (6.3) Semaglutide 7 mg: 9.3 (6.3) Semaglutide 14 mg: 9.1 (6.4)
	Exenatide: 9.4 (0.3–54.0)	Liraglutide: 8.9 (5.7)	Dulaglutide 0.75 mg: 7.0 (5.5) Dulaglutide 1.50 mg: 7.6 (5.6)	Liraglutide: 7.3 (5.3)	Dulaglutide: 9.9 (6.3)
Body mass index (kg/m^2)	Semaglutide: 34.0 (21.0–72.8)	Semaglutide: 33.7 (6.6)	Semaglutide 0.5 mg: 33.7 (7.1) Semaglutide 1.0 mg: 33.6 (6.5)	Semaglutide: 32.5 (5.9)	Semaglutide 3 mg: 25.8 (4.5) Semaglutide 7 mg: 26.8 (5.0) Semaglutide 14 mg: 26.3 (5.2)
	Exenatide: 33.6 (21.2–55.8)	Liraglutide: 33.7 (7.0)	Dulaglutide 0.75 mg: 33.6 (6.9) Dulaglutide 1.50 mg: 33.1 (6.6)	Liraglutide: 33.4 (6.7)	Dulaglutide: 26.0 (4.0)
HbA1c (%)	Semaglutide: 8.4 (6.7–11.1)	Semaglutide: 8.2 (0.9)	Semaglutide 0.5 mg: 8.3 (0.9) Semaglutide 1.0 mg: 8.2 (0.9)	Semaglutide: 8.0 (0.7)	Semaglutide 3 mg: 8.2 (0.9) Semaglutide 7 mg: 8.3 (0.9) Semaglutide 14 mg: 8.4 (1.0)
	Exenatide: 8.3 (6.5–11.2)	Liraglutide: 8.3 (1.0)	Dulaglutide 0.75 mg: 8.2 (0.9) Dulaglutide 1.50 mg: 8.2 (0.9)	Liraglutide: 8.0 (0.7)	Dulaglutide: 8.4 (0.9)

Qualität der Studien:

- Overall risk of bias was assessed as low across RCTs included in the present systematic review and metaanalysis

Studienergebnisse:

- HbA1c:



- In addition, semaglutide use was associated with a significantly greater reduction in FPG by 0.48 mmol/L (MD -0.48, 95 % Cl; -0.80 to -0.15, I2 - 82 %, p -0.004). For this

comparison semaglutide was not superior to dulaglutide; however, semaglutide produced a significantly greater reduction in FPG compared to either exenatide or liraglutide

- Body weight: Semaglutide was shown to provide a significantly greater reduction in body weight compared to other GLP1-RAs among subjects with T2DM, equal to 2.53 kg (MD -2.53, 95 % CI; -3.31 to -1.75, I2 = 86 %, p < 0.00001), as depicted in Fig. 6. In addition, we documented that semaglutide compared to other GLP1-RAs resulted in a significantly greaterreductioninBMiby0.91 kg/m2 (MD= -0.91, 95%CI; -1.18 to -0.63, I2 = 85 %, p < 0.0001)
- Safety: Semaglutide use compared to other GLP1-RAs was linked to a significant increase in the odds for nausea (OR - 1.43; 95 % CI 1.08 to 1.88, I2 = 55 %, p = 0.01) and vomiting (OR= 1.49, 95 % CI; 1.10 to 2.01, I2 = 19 %, p = 0.01). However, semaglutide was not associated with significantly increased odds for diarrhea, compared with other GLP1-RAs (OR= 1.23, 95 % CI; 0.89 to 1.70, 12 = 54 %, p = 0.21). Semaglutide use was also not associated with a significant increase in the odds for acute pancreatitis (OR = 0.45, 95 % CI 0.11 to 1.82, I2 = 0 % p = 0.26) and diabetic retinopathy (OR 1.36, 95 % CI 0.68 to 2.75, 12 = 0 %, p = 0.39). Importantly, subjects randomized to Semaglutide compared to other GLP1-RAs had significantly increased odds for premature treatment discontinuation, mainly due to gastrointestinal adverse events (OR= 1.481 95 % CI; 1.15 to 1.91, I2 = 0 %, p = 0.002).

Anmerkung/Fazit der Autoren

Semaglutide seems to be more efficacious compared with the rest of commercially available GLP-1 RAs, in terms of improvement in glycemia and other cardio-metabilik risk factors, among individuals with T2DM. However, it is also associated with significantly greater odds for treatment discontinuation, due to gastrointestinal adverse events, mainly nausea and vomiting. No other major safety issues emerged in the present meta-analysis. Generated results from relevant RCTs should be incorporated into daily clinical practice, by amending treatment algorithms used by involved physicians and proposing appropriate treatment combinations, especially for subjects with concomitant cardiorenal disease. The impact of semaglutide compared with other GLP1-RAs on surrogate endpoints, including all-cause mortality and cardiovascular morbidity and mortality, compared to other GLP1-RAs, remains unclear, and should be the focus of future RCTs.

Stretton B et al., 2023 [62].

Effect of semaglutide versus other glucagon-like peptide-1 receptor agonists on cardio-metabolic risk factors in patients with type 2 diabetes: A systematic review and meta-analysis of head-to-head, phase 3, randomized controlled trials

Fragestellung

This review was conducted with the aim of summarising direct comparisons between subcutaneous semaglutide and other GLP-1 RAs in individuals with type 2 diabetes (T2D), particularly with respect to efficacy for inducing weight loss and improving other markers of metabolic health.

Methodik

Population:

- individuals with a diagnosis of T2D

Intervention:

- semaglutide

Komparator:

- other GLP-1RAs or the dual GLP-1/GIP RA tirzepatide

Endpunkte:

- The primary outcome: weight loss.
- Secondary outcomes: body mass index (BMI), waist circumference, systolic blood pressure (BP), glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG).

Recherche/Suchzeitraum:

- PubMed (incorporating MEDLINE) and Embase were searched from database inception on 15 January 2022.

Qualitätsbewertung der Studien:

- Risk of bias tool 2 (RoB 2)

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Population/Studien:

Table 1 Study characteristics

First author	Year	Design	Country	Total cohort size	Men/women (%)	Duration of intervention	Comparator	Risk of bias
Ahmann[15]	2018	RCT	International	813	55.3/44.7	56 weeks	Exenatide	Low
Capehorn[16]	2020	RCT	International	577	56.7/43.3	30 weeks	Liraglutide	Low
Frias[17]	2021	RCT	International	1879	47/53	40 weeks	Tirzepatide	Low
Nauck[19]	2016	RCT	International	415	65/35	12 weeks	Liraglutide	Low
Pratley[18]	2018	RCT	International	1201	55/45	40 weeks	Dulaglutide	Low

RCT, randomized controlled trial.

Qualität der Studien:

- There was a low risk of bias for the included studies (Table 1).

Studienergebnisse:

- Weight loss:
  - In direct comparisons, 1.0–mg semaglutide resulted in significantly greater weight loss than 2.0–mg exenatide (-3.78 kg [95% confidence interval (CI), –4.58 to -2.98], P < 0.0001), 1.2–mg liraglutide (-3.83 kg [95% CI, -4.57 to _3.09], P < 0.0001) and 1.5–mg dulaglutide (-3.55 kg [95% CI, _4.32 to _2.78], P < 0.0001). Conversely, all doses of tirzepatide were associated with greater reductions in weight than 1.0–mg semaglutide (5 mg: _1.9 kg [95% CI: _2.8 to _1.0], P < 0.001), (10 mg: -3.6 kg [95% CI, -4.5 to _2.7], P < 0.001) and (15 mg: -5.5 kg [95% CI, _6.4 to _4.6], P < 0.001).
- BMI:
  - When direct comparisons were undertaken, 1.0 mg of semaglutide resulted in a greater reduction in BMI than 1.5 mg of dulaglutide (-1.25 [95% CI, –1.52 to -0.98], P < 0.0001); 1.2 mg of liraglutide (-1.35 [95% CI, – 1.61 to -1.09], P < 0.0001) and exenatide (-1.36 [95% CI, –1.64 to -1.07], P < 0.0001).
- Waist circumference.

  - In direct comparisons, semaglutide 1.0 mg resulted in a greater reduction in mean waist circumference than 2.0 mg exenatide (-2.76 [95% CI, –3.63 to -1.89], P < 0.0001), 1.2–mg liraglutide (-2.73 [95% CI, –3.62 to -1.84], P < 0.0001) and 1.5–mg dulaglutide (-2.27 [95% CI, –3.21 to -1.33], P < 0.0001).
- Blood pressure:
  - In direct comparisons, 1.0–mg semaglutide resulted in a greater reduction in systolic BP than 2.0–mg exenatide (-2.37 [95% CI, –4.29 to -0.45], P = 0.0158) but was not superior to 1.5–mg dulaglutide (-2.02 [95% CI, – 4.14 to 0.09], P = 0.0607). No doses of semaglutide were superior to 1.2– or 1.8–mg liraglutide16,19 for systolic BP reduction.
- Fasting glucose:
  - In direct comparisons, 1.0–mg semaglutide demonstrates greater reductions in FPG than 1.2–mg daily subcutaneous liraglutide (-1.24 mmol/L [95% CI, -1.54 to -0.93], P < 0.0001)16 and 1.5–mg dulaglutide (-0.58 mmol/L [95% CI, –0.91 to -0.26], P = 0.0005). Tirzepatide, however, at doses of 5, 10 and 15 mg appeared superior in FPG reduction than 1.0–mg semaglutide; no P values were reported.
- HbA1c:
  - Direct comparisons indicate that semaglutide 1.0 mg was associated with greater reductions in HbA1c when compared with exenatide 2.0 mg (-0.62 [95% CI, –0.80 to -0.44], P < 0.0001), liraglutide 1.2 mg (0.69 [95% CI, 0.82–0.56], P < 0.0001) and 1.5–mg dulaglutide (-0.41 [95% CI, –0.57 to -0.25], P < 0.0001). However, semaglutide was inferior to tirzepatide across all doses (-0.15 [95% CI, -0.28 to -0.03], P = 0.02) with tirzepatide 5 mg (-0.39 [95% CI, -0.51 to -0.26], P < 0.001) with tirzepatide 10 mg and (-0.45 [95% CI, -0.57 to -0.32], P < 0.001) with tirzepatide 15 mg.

Anmerkung/Fazit der Autoren

This systematic review synthesised the existing evidence base to examine the effects of semaglutide on body weight in patients with T2D compared with other GLP-1 RAs. There is evidence to support the superiority of semaglutide over comparator GLP–1 RAs, with respect to weight loss and glycaemic control but not to tirzepatide, a dual mechanism of GLP-1/GIP RA. This review provides a comprehensive assessment of currently available GLP-1 RAs, demonstrating their therapeutic benefit and potential for large contributions to the reduction in morbidity and mortality related to T2D worldwide. The results suggest that when unable to prescribe tirzepatide, 1.0 mg of semaglutide per week confers a good balance between significant results and tolerance of adverse effects. Further direct comparisons between tirzepatide and a higher range of semaglutide doses should now be considered. It will also be important to achieve greater mechanistic understanding of why tirzepatide appears more effective than all existing GLP-1RA comparators, including the contribution of GIP receptor agonism.

Nauck MA et al., 2023 [51].

Meta-analysis of head-to-head clinical trials comparing incretin-based glucose-lowering medications and basal insulin: An update including recently developed glucagon-like peptide-1 (GLP-1) receptor agonists and the glucose-dependent insulinotropic polypeptide/GLP-1 receptor co-agonist tirzepatide

Fragestellung

To assess comparative efficacy, safety and tolerability of injectable incretin-based glucose-lowering medications (IBGLMs) versus basal insulin treatment in patients with type 2 diabetes

Methodik

Population:

- insulin-naïve type 2 diabetes patients on a background of a well-defined therapy with single or combined oral glucose-lowering agents

Intervention:

- Short- and long-acting glucagon-like peptide-1 [GLP-1] receptor agonists [GLP-1RAs] and glucose-dependent insulinotropic polypeptide [GIP]/GLP-1 receptor co-agonist tirzepatide)

Komparator:

- basal insulin

Endpunkte:

- primary endpoint: HbA1c
- Secondary endpoints: fasting plasma glucose, body weight, HbA(1c) target achievement, hypoglycaemia, blood pressure and lipids.

Recherche/Suchzeitraum:

- PubMed database search (April 2022)

Qualitätsbewertung der Studien:

- Jadad scores and the Cochrane Collection Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 20 publications were retrieved for the present analysis, reporting on comparisons of exenatide twice daily (n = 5; the only short-acting compound), liraglutide (n = 5), exenatide once weekly (n = 3), dulaglutide (n = 3), albiglutide (n = 1), semaglutide for injection (n = 1) and tirzepatide (n = 2), representing a total of 6869 patients treated with incretin-based medications and 4974 patients treated with basal insulin preparations

Charakteristika der Population:

TABLE 1 Patient and study characteristics of publications used for the meta-analysis comparing clinical consequences of treating type 2 diabetic patients with either GLP-1RAs or basal insulin added to oral glucose-lowering medications

Characteristic	Unit	GLP-1RAs			Basal insulin		
		Short-acting GLP-1RAs	Long-acting GLP-1RAs	GIP/ GLP-1 R Co-Ag tirzepatide	Short-acting GLP-1RAs	Long-acting GLP-1RAs	GIP/ GLP-1 receptor co-agonist tirzepatide
Number of studies/arms	n	5/5	13/16	2/6	5/5	13/13	2/2
Number of patients	n	526	4210	2073	510	3033	1365
Proportion female	%	41.8	45.0	42.2	42.7	44.0	37.8
Age	Years	58 ± 9	56 ± 10	60 ± 9	57 ± 9	56 ± 10	62 ± 9
Duration of diabetes	Years	9 ± 6	8 ± 7	9 ± 6	8 ± 5	9 ± 8	10 ± 7
HbA_{1c}	%	8.3 ± 0.9	8.4 ± 1.0	8.4 ± 0.9	8.4 ± 0.9	8.4 ± 1.0	8.4 ± 0.9
Fasting plasma glucose	mmol/L	10.4 ± 2.6	9.4 ± 2.6	9.6 ± 2.7	10.4 ± 2.8	9.5 ± 2.5	9.3 ± 2.7
Body mass index	kg/m^2	31.9 ± 5.5	30.9 ± 5.0	33.1 ± 5.8	31.5 ± 4.4	30.7 ± 4.8	32.7 ± 5.7
Study duration	Weeks	25.1	39.4	52.0			
Patient years of observation	Years	349.5	3315.8	2497.5	354.8	2111.3	1844.0
Proportion taking							
Metformin	%	93.7	97.7	97.3	93.1	98.0	96.6
Sulphonylureas	%	69.2	59.0	26.5	69.0	52.1	39.3
Thiazolidinediones	%	12.7	3.4	0.0	12.7	3.3	0.0
SGLT2 inhibitors	%	0.0	0.0	28.3	0.0	0.0	27.3

Note: Weighted means ± pooled standard deviations or proportions (%) for predefined subgroups. Short-acting GLP-1RAs: exenatide twice daily; long-acting GLP-1 RAs: liraglutide, exenatide q.w. (once weekly), dulaglutide, albiglutide, semaglutide; GIP/GLP-1 receptor co-agonist: tirzepatide. Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-1 R Co-Ag, glucagon-like peptide-1 receptor co-agonist; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2.

Qualität der Studien:

- The quality of the studies was found to be sufficient for the inclusion of all retrieved publications and relevant study arms. All studies included in the present analysis were open label comparisons

Studienergebnisse:

- Primary Endpoint HbA1c: As shown in Figure 1, based on the results of fixed-effects meta-analysis, IBGLMs lowered HbA1c more than basal insulin preparations did, by 0.50 (0.46; 0.53)% (P < 0.001). Looking at pooled subgroups, shortacting GLP-1RAs did not perform significantly better than basal insulin (Δ0.01 [-0.13; 0.12]%), but with long-acting GLP-1RAs the reduction in HbA1c was greater by 0.27 (0.12; 0.42)%. The largest difference was seen for tirzepatide (all doses pooled) versus basal insulin (Δ0.90 [0.75; 1.06]%).
- The comparison of effects of IBGLMs and basal insulin regarding fasting plasma glucose led to a different pattern of results. Overall, basal insulin reduced fasting plasma more than did pooled IBGLMs (Δ0.30 [0.23;0.37] mmol/L; P < 0.001). This difference was greatest for short-acting GLP-1RAs (Δ1.50 [1.08; 1.92] mmol/L; P < 0.001) and was smaller and nonsignificant (P = 0.17) for long-acting GLP-1RAs (Δ0.32 [-0.14; 0.78] mmol/L). Tirzepatide (pooled doses), in contrast to selective GLP-1RAs, was equally effective compared to basal insulin (Δ0.06 [-0.04; 0.18]; P = 0.19), but the high dose of tirzepatide lowered fasting plasma glucose significantly more than did insulin glargine in the study by Del Prato et al
- Body weight, generally speaking, was reduced by all IBGLMs, and increased slightly with basal insulin. This led to an overall difference between changes in body weight with IBGLMs and basal insulin of 4.6 (4.5; 4.7) kg (P < 0.001), with no significant difference between shortbvand long-acting agents. Tirzepatide was exceptionally effective in this

respect and led to a difference in body weight of 12.0 (10.1; 13.9) kg (P < 0.001), which was significantly different from the body weight difference observed with both short- and long-acting GLP-1RAs

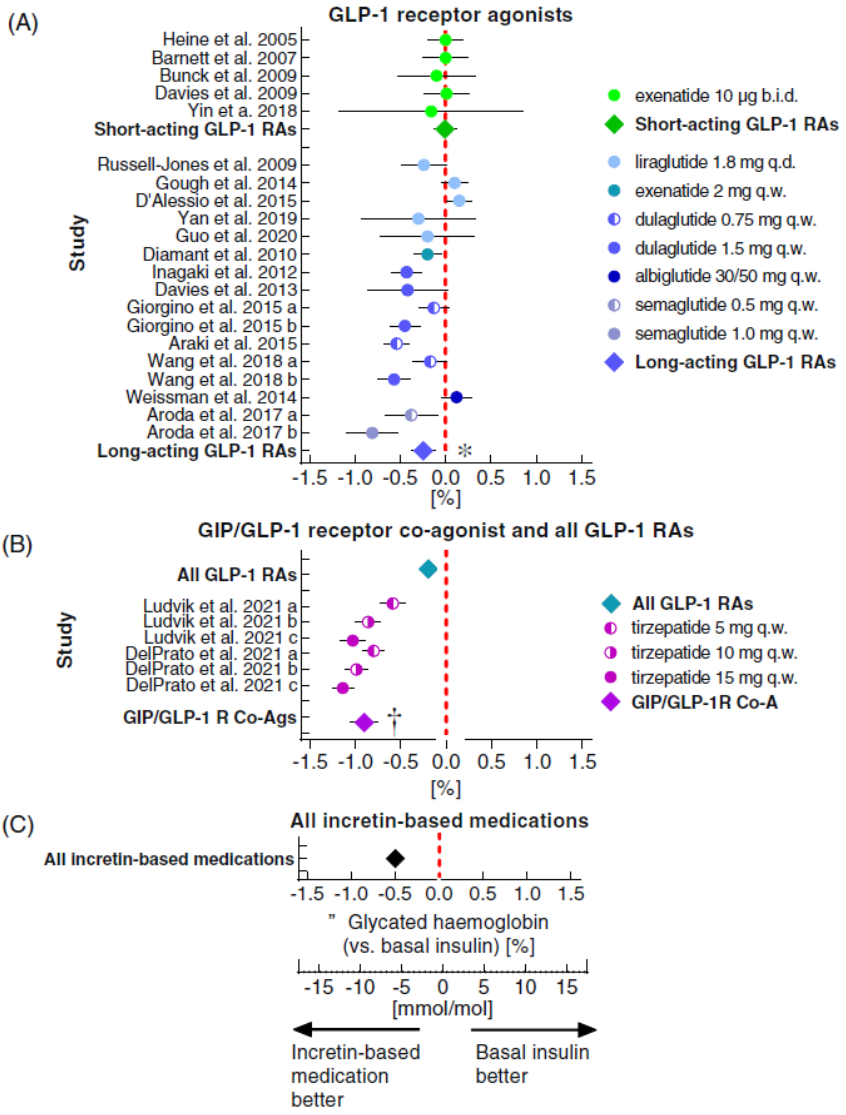


FIGURE 1 Forrest plots of mean differences (and their 95% confidence intervals) for glycated haemoglobin (HbA_{1c}) reductions elicited by treatment with incretin-based medications. (A) Glucagon-like peptide-1 receptor agonists (GLP-1RAs) grouped as short-acting and long-acting compounds; (B) glucose-dependent insulinotropic polypeptide (GIP)/ glucagon-like peptide-1 (GLP-1) receptor co-agonist tirzepatide and pooled GLP-1RAs; and (C) pooled incretin-based medications compared with basal insulin treatment. For the meta-analysis, three categories of subgroups of incretin-based medications were defined: short-acting compared to long-acting GLP-1RAs (A), pooled long-acting GLP-1RAs compared with the GIP/GLP-1 receptor co-agonist tirzepatide (B), and twice-daily, once-daily and once-weekly administered GLP-1RAs (ie, by injection interval; Table S2). For all incretin-based medications pooled, results of fixed-effects meta-analysis are shown. For the comparison of subgroups, results from random-effects meta-analysis are presented. *$P = 0.063$, short- versus long-acting GLP-1RAs; heterogeneity indicators: Q value = 7.1, $P = 0.008$; $\tau = 0.898$, $I^2 = 85.7\%$) or †$P < 0.0001$, pooled GLP-1RAs versus GIP/GLP-1 receptor co-agonist tirzepatide (heterogeneity indicators: Q value = 45.6, $P < 0.001$; $\tau = 0.426$; $I^2 = 95.7$). b.i.d., twice daily; GLP-1 co-A, GLP-1 receptor co-agonist; q.d., once daily; q.w., once weekly

- Adverse Events
  - The proportion of patients reporting any hypoglycaemia was lower with IBGLMs as compared with basal insulin, as was the proportion reporting severe hypoglycaemia. Both risks were reduced by approximately 50%. There was a significant relationship between the proportion of patients treated with sulphonylureas and the proportion reporting any hypoglycaemia, while a similar relationship for severe hypoglycaemia was not significant.
  - The proportions of patients with nausea, vomiting, or diarrhoea were sixfold, three- to fourfold, and two- to fourfold higher with various subcategories of IBGLMs as compared with basal insulin. Medication discontinuation was 60% to 71% higher with IBGLMs than with basal insulin

Anmerkung/Fazit der Autoren

In conclusion, a meta-analysis of head-to-head comparisons of IBGLMs and basal insulin treatment shows better fasting glucose control with basal insulin, except when compared to semaglutide or tirzepatide, but overall equivalent (short-acting GLP-1RA exenatide twice

daily) or better (long-acting GLP-1RAs, tirzepatide) glycaemic control (HbA1c reduction and target achievement) with IBGLMs, which also uniformly result in a reduced body weight and are associated with a lower risk for any or severe hypoglycaemic episodes. The recently developed, highly effective agents (eg, semaglutide and tirzepatide) outperform earlier representatives of the class of GLP-1RAs. Our results emphasize the recommendation to preferentially recommend IBGLMs when a patient with type 2 diabetes needs injectable treatment because of a failure to achieve individual treatment targets with lifestyle modifications and oral glucose-lowering medications.

Yang, X. Y. et al., 2023 [69].

Is tirzepatide 15 mg the preferred treatment strategy for type 2 diabetes? A meta-analysis and trial-sequence-analysis

Fragestellung

The study aims to evaluate tirzepatide's efficacy and safety in treating type 2 diabetes by meta-analysis and trial-sequential-analysis (TSA).

Methodik

Population:

- Participants in line with the basic diagnosis of type 2 diabetes

Intervention:

- once-weekly tirzepatide 5, 10 or 15 mg

Komparator:

- placebo or other hypoglycemic agents

Endpunkte:

- Outcomes: hemoglobin-type-A1C (HbA1c), fasting-serum-glucose (FSG), and weight were treated as efficacy endpoints.
- Total adverse events (AEs), serious AEs, gastrointestinal (GI) AEs, major adverse cardiovascular events-4 (MACE-4), and hypoglycaemia (<54 mg/dl) were used as safety endpoints.

Recherche/Suchzeitraum:

- China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), VIP, Wanfang, Embase, PubMed, the Cochrane Library, and Web of Science with a time limit to November 2022

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

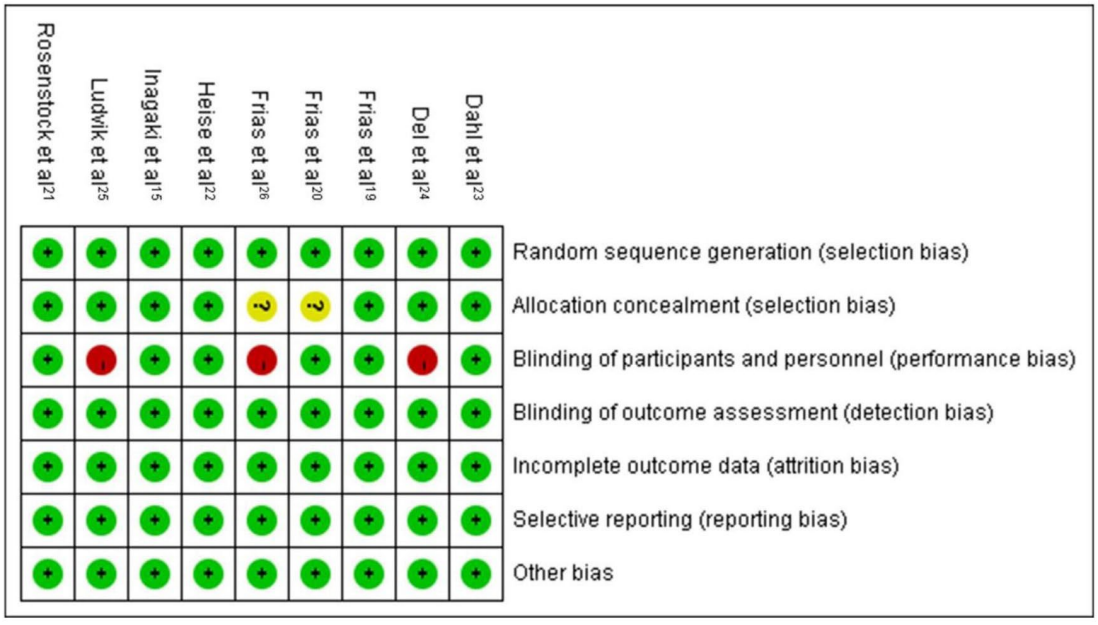
- nine trials (4.148 participants)

Charakteristika der Population/Studien:

Author Name	Research Center	Patient Number	Treatment Duration (weeks)	Intervention	Number Randomized	Male N (%)	Age (Years)	Disease Duration (years)	HbA1c (%)	Body weight (kg)
Frias et al[19]	Poland, Slovakia, Puerto Rico, USA	158	26	TZP 15 mg	53	22 (42%)	56.0	8.5	8.1	89.1
				dulaglutide 1.5 mg	54	24 (44%)	58.7	9.3	8.1	89.8
				Placebo	51	29 (57%)	56.6	8.6	8.0	91.5
Frias et al[20]	USA	82	12	TZP 15 mg-1	28	16 (57%)	55.5	8.2	8.5	88.7
				TZP 15 mg-2	28	23 (82%)	56.6	8.9	8.4	89.6
				Placebo	26	12 (46%)	56.0	8.8	8.2	89.6
Rosenstock et al[21]	India, Japan, Mexico, USA	236	40	TZP 15 mg	121	63 (52%)	52.9	4.8	7.9	85.4
				Placebo	115	56 (49%)	53.6	4.5	8.1	84.8
Heise et al[22]	Germany	117	28	TZP 15 mg	45	31 (69%)	61.1	10.2	7.8	94.2
				Semaglutide 1 mg	44	34 (77%)	63.7	12.7	7.7	92.7
				Placebo	28	21 (75%)	60.4	11.0	7.9	98.7
Dahl et al[23]	USA, Japan, Czech Republic, Germany, Poland, Slovakia, Puerto Rico, Spain	240	40	TZP 15 mg	120	65 (54%)	61.0	13.7	8.2	96.2
				Placebo	120	66 (55%)	60.0	12.9	8.4	94.1
Del et al[24]	Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania, Russia, Slovakia, Spain, Taiwan, USA	1338	52	TZP 15 mg	338	203 (60%)	63.7	10.4	8.5	90.0
				Insulin glargine	1,000	636 (64%)	63.8	10.7	8.5	90.2
Ludvik et al[25]	Argentina, Austria, Greece, Hungary, Italy, Poland, Puerto Rico, Romania, South Korea, Spain, Taiwan, Ukraine, USA	719	52	TZP 15 mg	359	194 (54%)	57.5	8.5	8.2	94.9
				Insulin degludec	360	213 (59%)	57.5	8.1	8.1	94.0
Frias et al[26]	USA, UK, Argentina, Australia, Brazil, Canada, Israel, Mexico	939	40	TZP 15 mg	470	214 (45%)	55.9	8.7	8.3	93.8
				Semaglutide 1 mg	469	225 (48%)	56.9	8.3	8.3	93.7
Inagaki et al[15]	Japan	319	52	TZP 15 mg	160	132 (83%)	56.0	5.1	8.2	78.9
				dulaglutide 0.75 mg	159	117 (74%)	57.5	5.0	8.2	76.5

*N: number; HbA1c: hemoglobin-type-A1C; TZP: tirzepatide.

Qualität der Studien:



Studienergebnisse:

- Efficacy

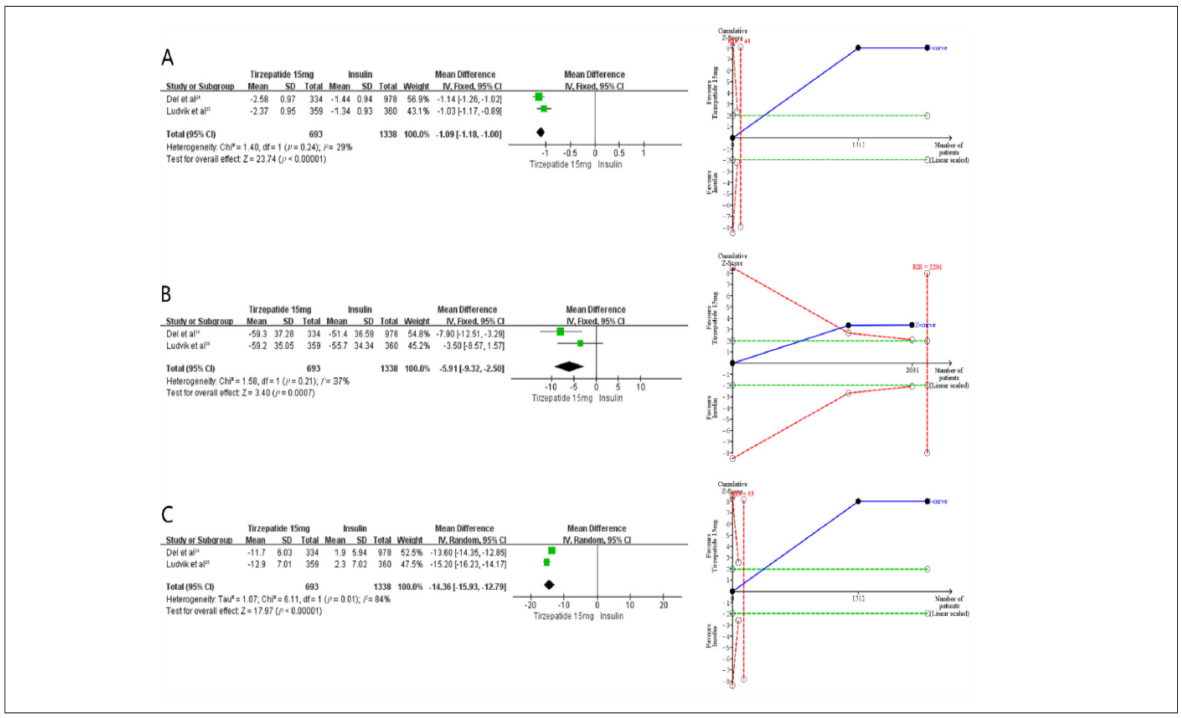


Figure 4. Meta-analysis and TSA results of efficacy endpoint in tirzepatide 15 mg *vs.* insulin in treating type 2 diabetes. **A**, Meta-analysis and TSA results of HbAlc in tirzepatide 15 mg *vs.* insulin in the treatment of type 2 diabetes. **B**, Meta-analysis and TSA results of FSG in tirzepatide 15 mg *vs.*. insulin in the treatment of type 2 diabetes. **C**, Meta-analysis and TSA results of weight in tirzepatide 15 mg *vs.*. insulin in the treatment of type 2 diabetes.

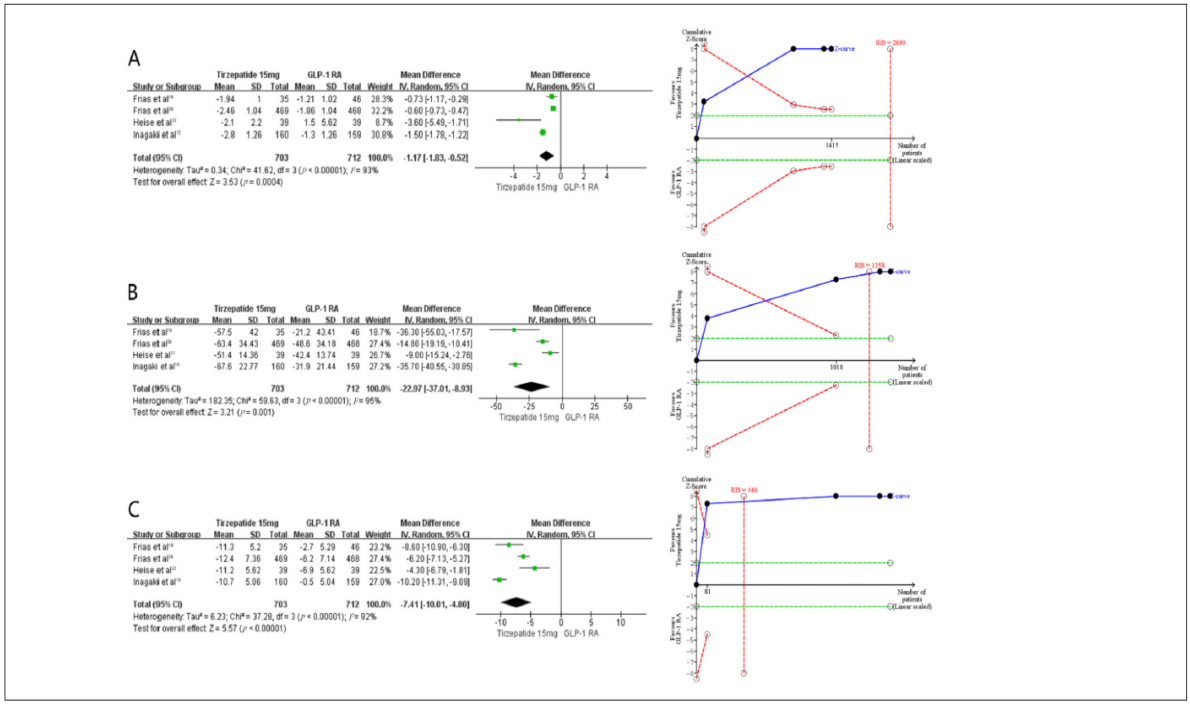


Figure 5. Meta-analysis and TSA results of efficacy endpoint in tirzepatide 15 mg *vs.* GLP-1 RA in treating type 2 diabetes. **A**, Meta-analysis and TSA results of HbAlc in tirzepatide 15 mg *vs.* GLP-1 RA in the treatment of type 2 diabetes. **B**, Meta-analysis and TSA results of FSG in tirzepatide 15 mg *vs.* GLP-1 RA in the treatment of type 2 diabetes. **C**, Meta-analysis and TSA results of weight in tirzepatide 15 mg *vs.* GLP-1 RA in the treatment of type 2 diabetes.

- Tirzepatide 15 mg vs. insulin: Two studies [24,25] were included to evaluate the efficacy endpoint of "tirzepatide 15 mg vs. insulin". Meta-analysis revealed that HbA1c (MD -1.09, 95% CI -1.18 – -1.00, p<0.00001), FSG (MD -5.91, 95% CI -9.32 – -2.50, p<0.00007), and weight (MD -14.36, 95% CI -15.93 – -12.79, p<0.00001) were dramatically lower in tirzepatide 15 mg compared with the insulin. TSA displayed

that the HbA1c, FSG, and weight observed in the current information set were conclusive (Figure 4).

- Tirzepatide 15 mg vs. GLP-1 RA: Four studies [15,19,22,26] were included to analyze "tirzepatide 15 mg *vs.* GLP-1 RA". Meta-analysis suggested that HbA1c (MD -1.17, 95% CI -1.83 – -0.52, *p*=0.00004), FSG (MD -22.97, 95%CI -37.01 – -8.93, p=0.001), and weight (MD -7.41, 95% CI -10.01 - -4.80, *p*<0.00001) were significantly lower in tirzepatide 15 mg than GLP-1 RA. TSA demonstrated that the HbA1c, FSG, and weight improvements observed in the current data set were conclusive for each group. Sensitivity analysis showed that the combined sensitivity of HbA1c, FSG, and weight was low, and the results were robust (Figure 5).

- Safety

Table II. Meta-analysis and TSA results of tirzepatide 15mg *vs.* placebo, insulin, and GLP-1 RA for AEs.

Outcome	TZP arm	Control arm	I^2	RR (95% CI)	TSA
TZP 15 mg *vs.* Placebo					
Total AEs	302/395	219/340	63	1.22 (1.04, 1.44)	No
Serious AEs	13/395	17/340	0	0.72 (0.36, 1.45)	No
GI AEs	85/174	27/166	82	3.59 (1.16, 11.17)	No
Hypoglycemia (<54 mg/dl)	17/297	16/216	0	1.06 (0.56, 1.98)	No
TZP 15 mg *vs.* Insulin					
Total AEs	522/697	872/1360	87	1.24 (1.02, 1.50)	No
Serious AEs	67/697	215/1360	74	0.83 (0.45, 1.53)	No
MACE-4	12/697	65/1,360	0	0.51 (0.28, 0.93)	Yes
Hypoglycemia (<54 mg/dl)	35/697	217/1,360	0	0.39 (0.28, 0.56)	Yes
TZP 15 mg *vs.* GLP-1 RA					
Total AEs	546/728	507/726	50	1.05 (0.97, 1.13)	No
Serious AEs	37/728	30/726	59	1.06 (0.41, 2.76)	No
GI AEs	257/683	217/682	75	1.43 (0.87, 2.34)	No
Hypoglycemia (<54 mg/dl)	10/630	2/628	0	4.19 (1.06, 16.56)	No

*TZP: tirzepatide; RR: Risk ratio; TSA: Trial sequential analysis; AEs: adverse events; GI: gastrointestinal; MACE-4: major adverse cardiovascular events-4.

- Tirzepatide 15 mg vs. insulin: Two studies [24, 25] were included to compare the safety endpoints of "tirzepatide 15 mg vs. insulin". Meta-analysis indicated that the MACE-4 (RR 0.51, 95% CI 0.28-0.93, p=0.03) and hypoglycaemia (<54 mg/dl) (RR 0.39, 95% CI 0.28- 0.56, p<0.00001) were significantly lower in the tirzepatide 15 mg. The total AEs (RR 1.24, 95% CI 1.02-1.50, p=0.03) were significantly higher for tirzepatide 15 mg than insulin, while the serious AEs (RR 0.83, 95% CI 0.45-1.53, p=0.55) in tirzepatide 15 mg were comparable to insulin. TSA showed that the MACE-4 and hypoglycemia benefits of tirzepatide 15 mg were conclusive, while the total AEs and serious AEs were inconclusive (Table II).
- Tirzepatide 15 mg vs. GLP-1 RA: Four studies [15,19,22,26] were included to compare the safety endpoints of "tirzepatide 15 mg vs. GLP-1 RA". Meta-analysis revealed that, compared with the GLP-1 RA, hypoglycemia (<54 mg/ dl) (RR 4.19, 95% CI 1.06-16.56, p=0.04) in tirzepatide 15 mg was dramatically higher, while the total AEs (RR 1.05, 95% CI 0.97-1.13, p=0.20), serious AEs (RR 1.06, 95% CI 0.41-2.76, p=0.90) and GI AEs (RR 1.43, 95% CI 0.87-2.34, p=0.15) were comparable. TSA showed that the results obtained from the current amount of information need more research and demonstration. Sensitivity analysis showed that the combined sensitivity of serious AEs was low, and the result was robust. The combined sensitivity of total AEs was high, and the result was labile, and the sensitivity analysis showed that the heterogeneity of total AEs was derived from Heise et al22. When the study of Heise et al [22] was excluded from the total AEs, the heterogeneity disappeared, and the combined results suggested that the total AEs of tirzepatide

15 mg were significantly higher than that of GLP-1 RA (RR 1.09 95 CI% 1.02-1.16, p=0.01) (Table II).

Fazit der Autoren

Tirzepatide 15 mg has excellent hypoglycemic and weight loss effects superior to insulin and GLP-1 RA. GI AEs are the major AEs for tirzepatide 15 mg, significantly higher than placebo and insulin and comparable to GLP-1 RA. Tirzepatide 15 mg can also reduce the risk of hypoglycemia and cardiovascular risk relative to insulin. Ultimately, tirzepatide 15 mg is a better therapeutic strategy for type 2 diabetes. However, its GI AEs must be investigated.

Kommentare zum Review

- Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Bhagavathula, A. S. et al., 2021 [5]
  - Dutta, D. et al., 2021 [15]
  - Tang, Y. et al., 2022 [63]
  - Permana, H. et al., 2022 [57]
  - Karagiannis, T. et al., 2022 [24]

Luan, S. et al., 2022 [38].

Impact of glucagon-like peptide 1 analogs on cognitive function among patients with type 2 diabetes mellitus: A systematic review and meta-analysis.

Fragestellung

To assess the impact of GLP-1 analogs on the general cognitive functioning among patients with T2DM.

Methodik

Population:

- adult subjects diagnosed with T2DM

Intervention:

- GLP-1 analogs

Komparator:

- no use of GLP-1 analogs, placebo, or self-control before treatment

Endpunkte:

- cognitive functioning was assessed by Mini-mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA)

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases from their inception till June 30, 2022

Qualitätsbewertung der Studien:

- Newcastle-Ottawa Quality Assessment Scale criteria (NOS) / RoB Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Five studies including 7,732 individuals

Charakteristika der Population/Studien:

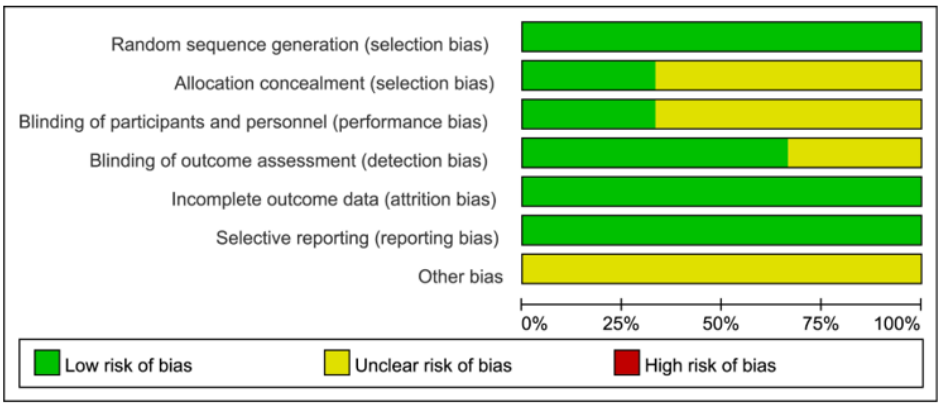
TABLE 1 Characteristics of the five prospective studies.

Author, year	Sample number	GLP-1 RA category	Control	Age	History of cardio-cerebrovascular disease	Treatment duration	General cognitive assessments
Cheng et al., 19	36	Liraglutide	Self-control, non-GLP-1 analog treated	GLP-1 analog group: 51.9 ± 10.2	No	16 weeks	MMSE, MoCA
Li et al., 21	47	Liraglutide	Self-control, non-GLP-1 analog treated	GLP-1 analog group: 55.0 ± 11.9	No	12 weeks	MMSE
Cukierman-Yaffe et al., 18	7570	Dulaglutide	Self-control, non-GLP-1 analog treated	GLP-1 analog group: 65.5 ± 6.4	Yes	60 months	MoCA
Wang et al., 20	60	Liraglutide	Self-control, non-GLP-1 analog treated	GLP-1 analog group: 66.1 ± 5.9	Yes	6 months	MMSE, MoCA
Zhang et al., 22	19	Liraglutide, Exenatide	Self-control	52.1 ± 10.2	No	3 months	MoCA

Qualität der Studien:

STable2. Risk of bias assessment (Newcastle-Ottawa Quality Assessment Scale criteria).

Study	Selection	Comparability	Outcome	Quality score
Li, 2021	****	*	***	8
Zhang, 2019	****	**	***	9



SFigure1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Studienergebnisse:

- The use of GLP-1 analogs exerted no significant effects on the general cognitive functioning in self-controlled studies (SMD 0.33, 95% CI -0.03 to 0.69).
- Subgroup analyses among the self-controlled studies based on age and history of cardio-cerebrovascular disease showed that GLP-1 analogs significantly improved the general cognitive functioning in T2DM patients younger than 65 years (SMD 0.69, 95% CI 0.31 to 1.08) or those without cardio-cerebrovascular diseases (SMD 0.69, 95% CI 0.31 to 1.08).

- Similarly, differences in the general cognitive functioning for GLP-1 analogs between treated and non-treated patients with T2DM were significant in subgroups with patients younger than 65 years (SMD 1.04, 95% CI 0.61 to 1.47) or those with no history of cardio-cerebrovascular diseases (SMD 1.04, 95% CI 0.61 to 1.47).

Fazit der Autoren

Based on the existing limitedevidence, our findings indicated that the use of GLP-1 analogs had no significant effects on the general cognitive functioning among patients with T2DM but may be beneficial for those younger than 65 years or without a history of cardio-cerebrovascular diseases, and thus, might be dependent on the extent of neuropathy. Nevertheless, multicenter, multi-regional, and large-sample studies are needed to complement and further validate these findings in the future.

Alexander JT et al., 2022 [1].

The longer-term benefits and harms of glucagon-like peptide-1 receptor agonists: a systematic review and meta-analysis

Fragestellung

we conducted a meta-analysis of all randomized trials of GLP1RAs compared to placebo or other anti-hyperglycemic medications for patients with T2D, with at least 52-week study duration, and that reported cardiovascular risk factor changes, microvascular or macrovascular complications, all-cause mortality, or treatment-related adverse events.

Methodik

Population:

- adults age 18 years or older with T2D

Intervention:

- GLP1RA

Komparator:

- placebo and/or other anti-hyperglycemic medications

Endpunkte:

- Outcomes of interest included cardiovascular risk factors, microvascular and macrovascular complications, all-cause mortality, and treatment-related adverse events

Recherche/Suchzeitraum:

- PubMed, Scopus, and clinicaltrials.gov from inception to July 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias in randomized trials tool with five bias domains (sequence generation, blinding, attrition, detection, and reporting).

Ergebnisse

Anzahl eingeschlossener Studien:

- 55 articles comprising 45 trials (n=71,517) met inclusion criteria. Among the included trials, 17 trials (n=61,330) compared GLP1RAs vs. placebo and 30 trials (n=19,785)

compared GLP1RAs vs. other anti-hyperglycemic medications. Two trials had comparisons with both placebo and another anti-hyperglycemic medication.

Charakteristika der Population:

- Among placebo-controlled trials, six of the 17 placebo-controlled trials required participants to have a high risk for or pre-existing ASCVD. Patients tended to be in their fifth or sixth decade of life, white, male, and obese (mean BMI ranged from30 to 35 in 14 of 16 trials that reportedmean BMI), with a baseline HbA1c ranging from 7 to 9% and median diabetes duration of more than 6 years.
- In trials comparing GLP1RAs vs. other antihyperglycemic medications, patient characteristics were similar to placebo-controlled trials; however, Asian race was more common because five trials were conducted exclusively in Asia. The comparison group was insulin in 12 trials, a DPP4I in nine trials, a sulfonylurea in five trials, and other drugs in four trials. Only two of these trials required pre-existing ASCVD. These trials more often included cardiovascular risk factors, mortality, and adverse event outcomes compared to placebo-controlled trials.

Qualität der Studien:

- In general, the risk of bias due to sequence generation, detection, and reporting was judged as low for the majority of the included studies. For studies in which the overall risk of bias was judged as moderate or high risk, the most common reason was due to attrition.
- Among placebocontrolled trials, the overall quality of evidence was judged as high for six of the seven outcomes, with HbA1c receiving a moderate overall rating due to the presence of attrition bias.
- In trials comparing GLP1RAs to other antihyperglycemic medications, the overall quality of evidence ratings was more variable. In particular, risk of bias and imprecision led to low quality of evidence ratings for the outcomes of myocardial infarction, stroke, and any renal event.

Studienergebnisse:

	Summary of findings							
	No. of participants (studies)	Effect (RR/ MD)						
GLP1RA vs. placebo								
Cardiovascular risk factors								
HbA_{1c} (%)	48575 (15)	−0.67 (−0.76 to −0.58)						
Mortality								
All-cause mortality	59338 (16)	0.89 (0.84 to 0.94)						
Macrovascular outcomes								
3-component MACE	49936 (6)	0.87 (0.82 to 0.93)						
Any myocardial infarction	53136 (7)	0.93 (0.84 to 1.03)						
Stroke	53134 (7)	0.86 (0.78 to 0.95)						
Microvascular outcomes								
Any renal event	51001 (8)	0.85 (0.80 to 0.90)						
Adverse events								
Any GI event leading to treatment discontinuation	21732 (9)	3.84 (2.59 to 5.7)						
GLP1RA vs. other								
Cardiovascular risk factors								
HbA_{1c} (%)	11832 (28)	−0.37 (−0.53 to −0.22)						
Mortality								
All-cause mortality	11171 (22)	0.66 (0.40 to 1.12)						
Macrovascular outcomes								
3-component MACE	NA	NA						
Any myocardial infarction	2713 (4)	0.86 (0.2 to 3.71)						
Stroke	2011 (3)	2.48 (0.48 to 12.83)						
Microvascular outcomes								
Any renal event	2679 (5)	0.61 (0.29 to 1.28)						
Adverse events								
Any GI event leading to treatment discontinuation	7146 (15)	3.61 (2.11 to 6.18)						

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; MACE, major adverse cardiovascular event; GI, gastrointestinal; NA, not applicable
[a]Risk of bias detailed review of evidence found in eTables 11–23. Overall risk of bias was determined as follows: If all five domains had low bias, then overall bias was low. If more than 60% of domains had some concern, then overall bias was high. If less than 60% of domains had some concern, then overall bias was some concern. If more than 20% of domains had high bias, then overall bias was high
[b]Used I^2 and forest plots (75% of study effects in the same direction) to determine inconsistency
[c]Studies required (1) pre-existing CVD; (2) pre-existing CVD or older age and high CVD risk; (3) enrolled 70% patients with CVD
[d]Optimal information size (OIS) at Relative risk reduction (RRR) 20%, α 0.05, and β 0.2

Anmerkung/Fazit der Autoren

Our systematic review and meta-analysis is the first to synthesize findings related to long-term use of GLP1RAs compared to placebo and other anti-hyperglycemic medications. GLP1RAs compared to placebo were associated with significant reductions in cardiovascular risk factors, renal events, stroke, 3-component MACE, and mortality. GLP1RAs compared to other anti-hyperglycemic medications were associated with reductions in cardiovascular risk factors. Insufficient evidence exists to evaluate the long-term effects of GLP1RAs compared to other anti-hyperglycemic medications on microvascular or macrovascular outcomes. These findings inform decisions on benefits and tradeoffs when prescribing GLP1RAs for individual patients with T2D.

Kommentare zum Review

Es liegen weitere SRs zu ähnlichen Fragestellungen mit derselben Schlussfolgerung vor:

- Guo X et al., 2023 [22]
- Banerjee M et al., 2023 [4]

Xu J et al., 2021 [68].

Efficacy and safety of dulaglutide compared with glargine in patients with type 2 diabetes: a systematic review and meta-analysis

Fragestellung

Therefore, the present meta-analysis with updated data aims to evaluate the efficacy and safety of two different doses of dulaglutide versus insulin glargine for the treatment of T2DM.

Methodik

Population:

- patients with T2DM

Intervention:

- dulaglutide

Komparator:

- insulin glargine

Endpunkte:

- The primary efficacy outcome was glycaemic efficacy assessed by the absolute change in HbA1c levels (%).
- Secondary efficacy outcome was the absolute change in body weight (kg). Safety outcomes were as follows: adverse events (AEs), severe adverse events (SAEs), hypoglycaemia, gastrointestinal events, infection, headache and abnormality of pancreatic enzymes.

Recherche/Suchzeitraum:

- PubMed, Embase and Cochrane Library
- until December 2020

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

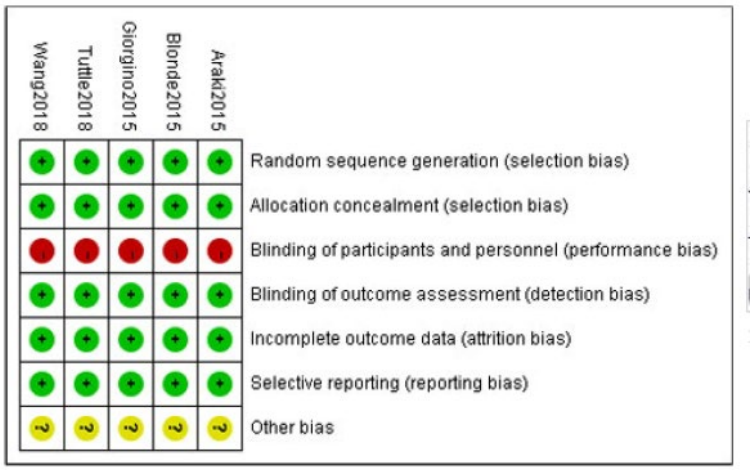
- Finally, we included 5 studies with 3383 randomized participants in total

Charakteristika der Population:

- All these studies were open-label and parallel-group. The duration ranged from 34 to 78 weeks. In four studies, patients were randomized 1:1:1 to receive dulaglutide 0.75 mg or 1.5 mg once a week, or matched insulin glargine once daily, whereas in the remaining study patients were 1:1 randomized to receive either dulaglutide 0.75 mg once a week or insulin glargine once daily.

Trial name and year	Duration (weeks)	Intervention and included patients	Mean age (SD) (years)	Female (%)	Mean disease duration (SD) (years)	Mean HbA1c(SD) (%)	Mean body weight (SD) (kg)	Mean BMI(SD) (kg/m^2)
Giorgino 2015[16] (AWARD–2)	78	Dulaglutide 0.75 mg (*n* = 272)	57.0 (9.0)	50.0	9.0 (6.0)	8.1 (1.0)	86.0 (8.0)	32.0 (5.0)
		Dulaglutide 1.5 mg (*n* = 273)	56.0 (10.0)	47.0	9.0 (6.0)	8.2 (1.0)	85.0 (18.0)	31.0 (5.0)
		Glargine (*n* = 262)	57.0 (9.0)	49.0	9.0 (6.0)	8.1 (1.0)	88.0 (20.20)	32.0 (6.0)
Araki 2015[17]	34	Dulaglutide 0.75 mg (*n* = 181)	57.5 (10.5)	31.0	8.9 (6.7)	8.1 (0.8)	70.9 (13.7)	26.1 (3.6)
		Glargine (*n* = 180)	56.1 (11.3)	26.0	8.8 (6.1)	8.0 (0.9)	71.1 (13.8)	25.9 (3.9)
Blonde 2015[18] (AWARD–4)	52	Dulaglutide 0.75 mg (*n* = 293)	59.3 (9.0)	50.0	12.4 (6.9)	8.40 (1.03)	91.7 (18.0)	33.1 (5.2)
		Dulaglutide 1.5 mg (*n* = 295)	58.9 (9.6)	46.0	12.8 (7.2)	8.46 (1.08)	91.0 (18.2)	32.0 (5.1)
		Glargine (*n* = 296)	59.9 (9.1)	44.0	13.0 (6.8)	8.53 (1.03)	90.8 (18.9)	32.4 (5.3)
Wang 2016[19]	52	Dulaglutide 0.75 mg (*n* = 252)	54.5 (10.0)	43.3	8.1 (5.3)	8.3 (1.1)	74.6 (12.7)	27.0 (3.8)
		Dulaglutide 1.5 mg (*n* = 253)	55.0 (9.6)	46.6	7.9 (4.8)	8.5 (1.2)	73.6 (13.0)	26.6 (3.7)
		Glargine (*n* = 250)	55.4 (9.2)	44.4	8.4 (5.3)	8.3 (1.1)	73.4 (13.1)	26.7 (3.5)
Tuttle 2018[20] (AWARD–7)	52	Dulaglutide 0.75 mg (*n* = 190)	64.7 (8.6)	45	18.0 (8.8)	8.6 (1.1)	90.9 (18.3)	33.0 (5.5)
		Dulaglutide 1.5 mg (*n* = 192)	64.7 (8.8)	46	17.6 (8.7)	8.6 (0.9)	88.1 (16.0)	32.1 (4.8)
		Glargine (*n* = 194)	64.3 (8.4)	52	18.7 (8.7)	8.6 (1.0)	88.2 (18.5)	32.4 (5.3)

Qualität der Studien:



Studienergebnisse:

Efficacy outcomes

- All the studies reported the data of mean change from baseline in HbA1c.16-20Compared with insulin glargine, the mean difference in HbA1c change was −0.21% (95% CI, −0.43, 0.01) with dulaglutide 0.75 mg and −0.33% (95% CI, −0.52, −0.15) with dulaglutide 1.5 mg.
- All the studies included also reported the data of mean change from baseline in body weight.16-20 Compared with insulin glargine, the mean difference in body weight change was −2.23 kg (95% CI, −2.85, −1.61) with dulaglutide 0.75 mg and −3.15 kg (95% CI, −3.84, −2.47) with dulaglutide 1.5 mg (Figures 5 and 6).

Safety outcomes

- Dulaglutide slightly increased the rate of treatment-emergent adverse events compared with insulin glargine, whereas there was no difference in severe adverse events between dulaglutide 0.75 mg and insulin glargine or between dulaglutide 1.5 mg and insulin glargine.
- The most frequent adverse events, arising significantly more often with dulaglutide than glargine, were gastrointestinal adverseevents, including nausea, diarrhoea and vomiting.

- Compared with insulin glargine, the rate of total hypoglycaemia in patients was reduced by 3.91 (95% CI, −6.63, −1.19) and 3.80 (95% CI, −6.55, −1.05) events/patient/year for dulaglutide 0.75 mg and 1.5 mg, respectively.
- The incidence of clinically relevant increases in lipase (≥3 × upper limit of normal) was higher with dulaglutide 1.5 mg (RR = 3.28, 95% CI, 1.87, 5.76) and dulaglutide 0.75 mg (RR = 2.09, 95% CI, 1.17, 3.76) than with glargine. Three cases of pancreatitis, two with dulaglutide 1.5 mg and one with dulaglutide 0.75 mg, were reported by Blonde. Three cases of pancreatitis, two with dulaglutide 1.5 mg and one with insulin glargine, were reported by Tuttle, as well. No pancreatitis events were confirmed in the rest of three studies.
- Compared with insulin glargine, dulaglutide 1.5 mg and 0.75 mg were associated with decreases in mean systolic blood pressure of 1.88 mm Hg (95% CI, −3.17, −0.58) and 1.21 mm Hg (95% CI, −2.35, −0.07), respectively. And dulaglutide 1.5 mg slightly increased heart rate compared with insulin glargine.

Anmerkung/Fazit der Autoren

In summary, the present meta-analysis indicates that, compared with insulin glargine, dulaglutide is an effective and generally well-tolerated treatment for patients with T2DM, with beneficial effects on glycaemic control and body weight, low risk of hypoglycaemia and a convenient once-weekly regimen.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Qie S et al., 2020 [58]

Li A et al. 2023 [27].

Efficacy and safety of oral semaglutide in type 2 diabetes mellitus: A systematic review and meta-analysis

Fragestellung

we conducted a systematic review and meta-analysis to assess semaglutide at different dosages in terms of glycemic control, body weight, some safety and tolerability outcomes in patients with T2DM.

Methodik

Population:

- Patients with T2DM

Intervention:

- Semaglutide 7 mg, 14 mg and 25 mg

Komparator:

- Placebo or other antidiabetic agents + Background therapy

Endpunkte:

- HbA1c, body weight, changes in fasting plasma glucose (FPG), SMPG-Mean 7-Point Profile (SMPG), systolic and diastolic blood pressure (SBP and DBP), participants who

achieved HbAlc < 7.0% and HbAlc < 7.0% without hypoglycemia and without body weight gain.

- adverse events (AE), serious adverse events (SAE), hypoglycemic episodes, AE resulting in premature trial drug discontinuation and gastrointestinal disorders (nausea, diarrhea, vomiting).

Recherche/Suchzeitraum:

- RCTs were PubMed, EMBASE (Ovid - Technologies), Cochrane Library, ClinicalTrials.gov, Science Direct, Springer, CNKI, Wang Fang Data and VIP

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 11

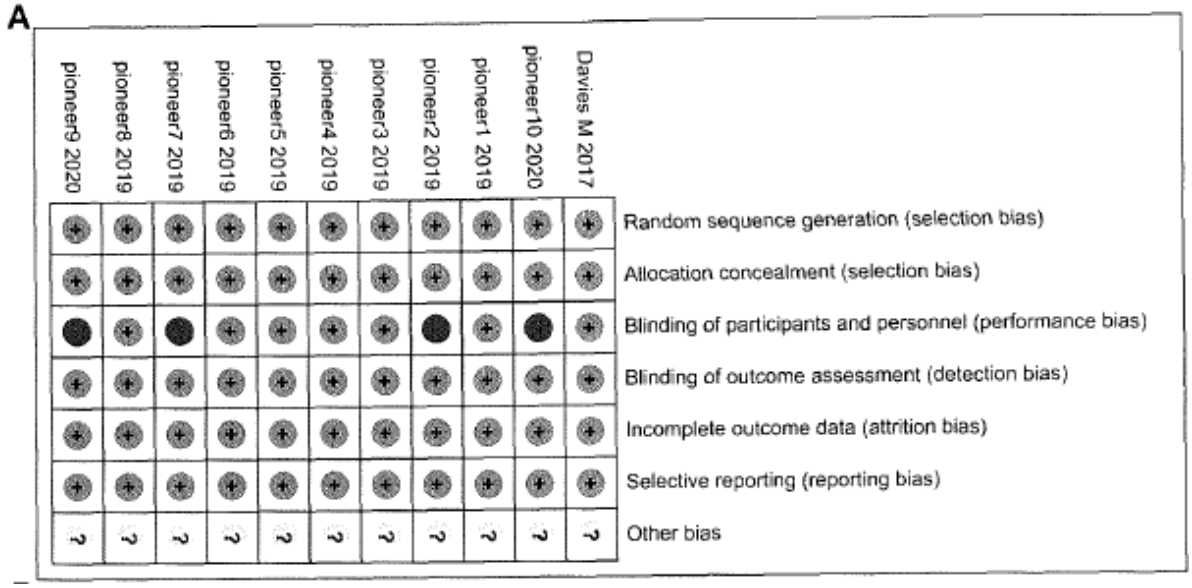
Charakteristika der Population/Studien:

Baseline characteristics and summary of included trials.

Study ID	Time of primary outcome measure, week	Background therapy	Study arms	Patients randomized, n	Mean age, y	Mean diabetes duration, y	Mean HbA1c, %	Mean body weight, kg	FPG, mmol/L
Aroda VR2019 (pioneer1) NCT02906930	26	diet and exercise	Semaglutide 7 mg QD	175	56	3.6	8	89	8.98
			Semaglutide 14 mg QD	175	54	3.4	8	88.1	8.77
			Placebo	178	54	3.4	7.9	88.6	8.88
Rodbard HW 2019 (pioneer2) NCT02863328	26	MET	Semaglutide 14 mg QD	411	57	7.2	8.1	91.9	9.5
			Empagliflozin 25 mg QD	410	58	7.7	8.1	91.3	9.7
Rosenstock J 2019 (pioneer3) NCT02607865	26	MET ± SU	Semaglutide 7 mg QD	465	58	8.3	8.4	91.3	9.45
			Semaglutide 14 mg QD	465	57	8.7	8.3	91.2	9.32
			Sitagliptin 100 mg QD	467	58	8.8	8.3	90.9	9.54
Pratley R 2019 (pioneer4) NCT02863419	26	MET ± SGLT-2i	Semaglutide 14 mg QD	285	56	7.8	8	92.9	9.27
			Liraglutide 1.8 mg QD	284	56	7.3	8	95.5	9.3
			Placebo	142	57	7.8	7.9	93.2	9.25
Mosenzon O 2019 (pioneer5) NCT02827708	26	MET, SU, Insulin,(1–2)	Semaglutide 14 mg QD	163	71	14.1	8.0	91.3	9.1
			Placebo	161	70	13.9	7.9	90.4	9.1
Husain M2019 (pioneer6) NCT02692716	82	standard care	Semaglutide 14 mg QD	1591	66	14.7	8.2	91	8.6
			Placebo	1592	66	15.1	8.2	90.8	8.73
Pieber TR 2019 (pioneer7) NCT02849080	52	MET, SU, TZD, SGLT-2i (1–2)	Semaglutide flex QD	253	56.9	8.6	8.3	88.9	9.8
			Sitagliptin 100 mg QD	251	57.9	9	8.3	88.4	9.8
Zinman B2019 (pioneer8) NCT03021187	26	MET + Insulin	Semaglutide 7 mg QD	182	60	16.2	8.2	87.1	8.5
			Semaglutide 14 mg QD	181	61	14.1	8.2	84.6	8.3
			Placebo	184	60	14.8	8.2	86	8.3
Yamada Y2020 (pioneer9) NCT03018028	26	diet and exercise or MET, SU, GLI, αGL-I, DPP-4i, SGLT-2i	Semaglutide 7 mg QD	49	60	71.3	7.7	8.3	8.93
			Semaglutide 14 mg QD	48	61	68	7.9	8	8.88
			Liraglutide 0.9 mg QD	48	59	74.7	6.7	8.3	9.68
			Placebo	49	59	70.3	8.4	8.3	9
Yabe D 2020 (pioneer10) NCT03015220	26	MET, SU, GLI, TZD, αGL-i, SGLT-2i	Semaglutide 7 mg QD	132	58	9.3	8.3	72.7	9.17
			Semaglutide 14 mg QD	130	57	9.1	8.4	72.6	9.35
			Dulaglutide 0.75 mg QW	65	61	9.9	8.4	71.2	9.5
Davies M 2017 NCT01923181	26	diet and exercise ± MET	Semaglutide 5 mg QD	70	55.7	5.3	7.8	93.1	9.6
			Semaglutide 10 mg QD	69	56.5	5.8	7.8	91.8	9.2
			Placebo	71	58.9	6.7	8	93.8	9.5

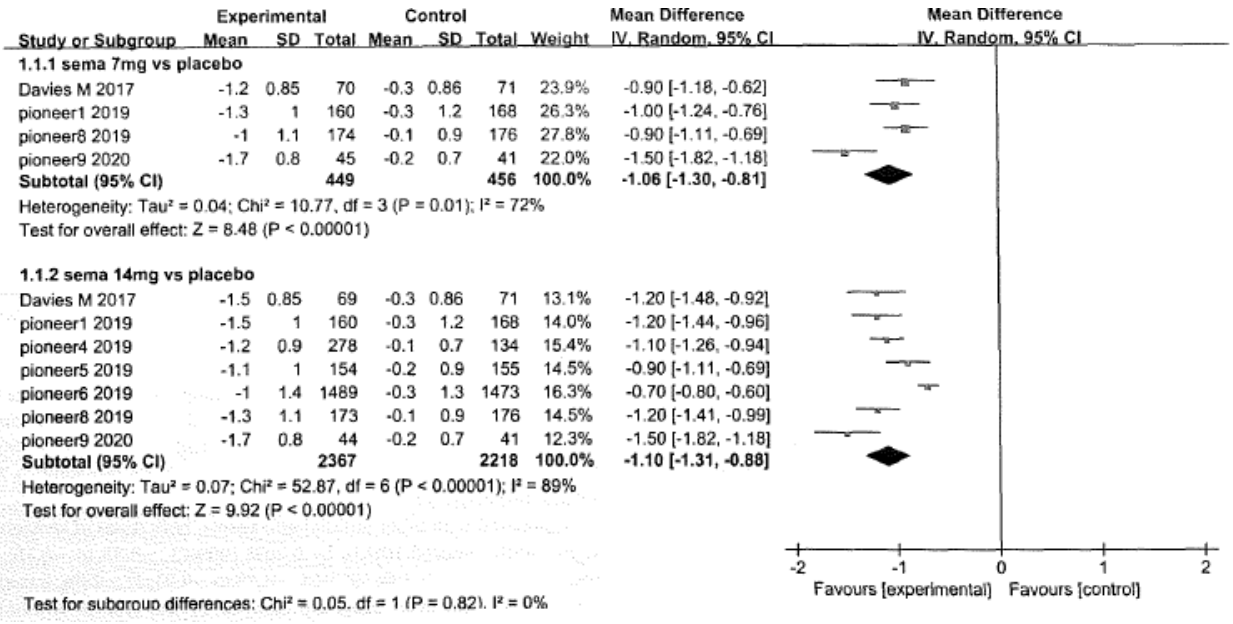
Abbreviations: HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; MET, metformin; TZD, thiazolidinediones; SU, sulphonylurea; SGLT-2i, sodium-dependent glucose transporters-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors.

Qualität der Studien:

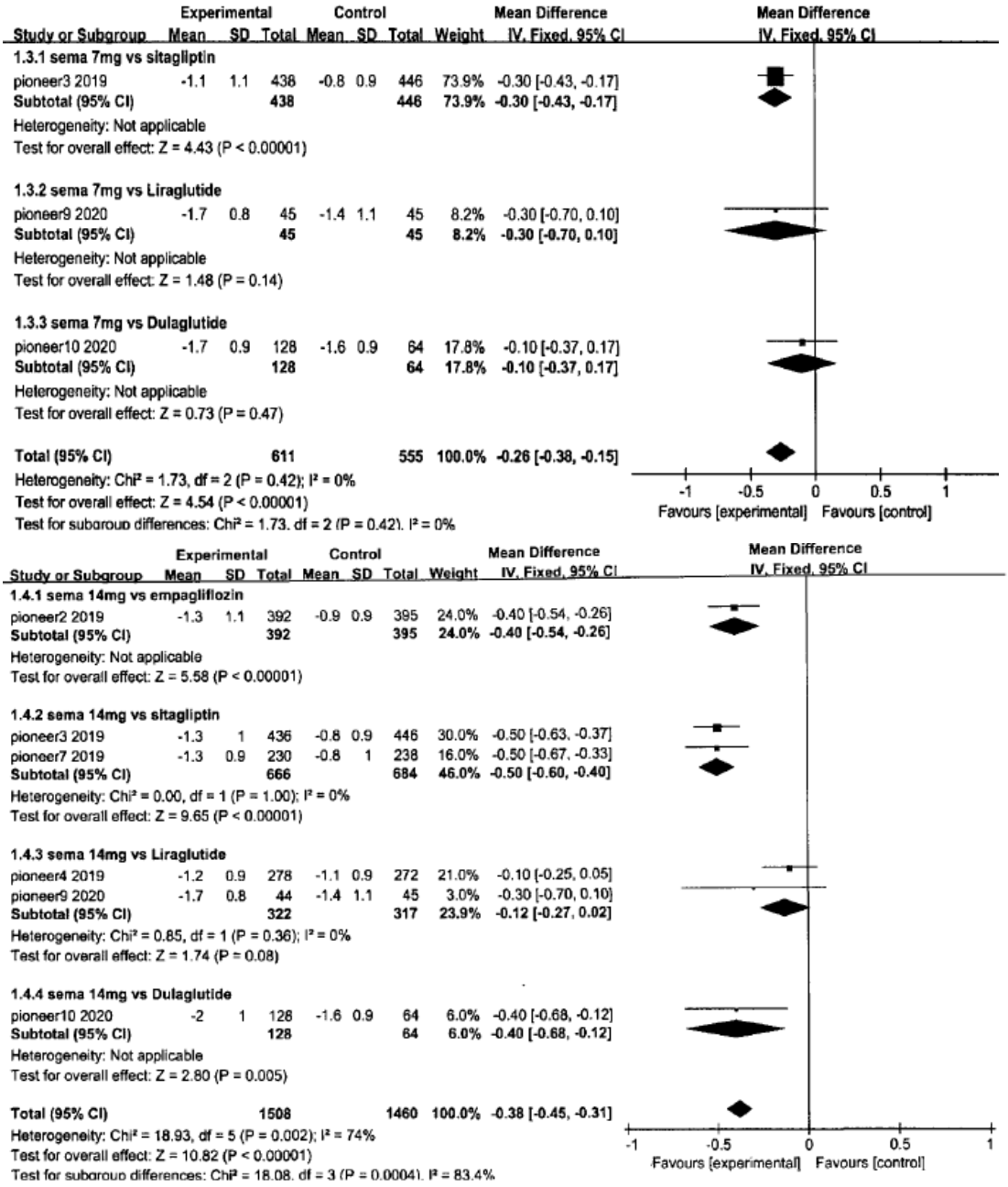


Studienergebnisse:

- HbA1c



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 sema 7mg vs placebo								
Davies M 2017	-1.2	0.85	70	-0.3	0.86	71	23.9%	-0.90 [-1.18, -0.62]
pioneer1 2019	-1.3	1	160	-0.3	1.2	168	26.3%	-1.00 [-1.24, -0.76]
pioneer8 2019	-1	1.1	174	-0.1	0.9	176	27.8%	-0.90 [-1.11, -0.69]
pioneer9 2020	-1.7	0.8	45	-0.2	0.7	41	22.0%	-1.50 [-1.82, -1.18]
Subtotal (95% CI)			**449**			**456**	**100.0%**	**-1.06 [-1.30, -0.81]**
Heterogeneity: Tau² = 0.04; Chi² = 10.77, df = 3 (P = 0.01); I² = 72%								
Test for overall effect: Z = 8.48 (P < 0.00001)								
1.1.2 sema 14mg vs placebo								
Davies M 2017	-1.5	0.85	69	-0.3	0.86	71	13.1%	-1.20 [-1.48, -0.92]
pioneer1 2019	-1.5	1	160	-0.3	1.2	168	14.0%	-1.20 [-1.44, -0.96]
pioneer4 2019	-1.2	0.9	278	-0.1	0.7	134	15.4%	-1.10 [-1.26, -0.94]
pioneer5 2019	-1.1	1	154	-0.2	0.9	155	14.5%	-0.90 [-1.11, -0.69]
pioneer6 2019	-1	1.4	1489	-0.3	1.3	1473	16.3%	-0.70 [-0.80, -0.60]
pioneer8 2019	-1.3	1.1	173	-0.1	0.9	176	14.5%	-1.20 [-1.41, -0.99]
pioneer9 2020	-1.7	0.8	44	-0.2	0.7	41	12.3%	-1.50 [-1.82, -1.18]
Subtotal (95% CI)			**2367**			**2218**	**100.0%**	**-1.10 [-1.31, -0.88]**
Heterogeneity: Tau² = 0.07; Chi² = 52.87, df = 6 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 9.92 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%								



- FPG: Compared with placebo, semaglutide 7 mg and 14 mg reduced FPG by 1.43 mmol/L and 1.65 mmol/L. Semaglutide 7 mg did not show a significant difference in decreasing FPG when compared to other antidiabetic agents, however semaglutide 14 mg did. Subgroup analysis revealed that semaglutide 14 mg was only slightly greater than sitagliptin.
- Body weight: Compared with placebo, treatment with oral semaglutide 7 and 14 mg significantly reduced body weight by 1.18 kg (95% CI, -2.13 to -0.23; P = 76%, 4 studies) and 2.96 kg (95% CI, -3.49 to -2.42; I2 = 72%, 7 studies), respectively. Compared with other antidiabetic agents, treatment with oral semaglutide 7 and 14 mg significantly reduced body weight by 1.47 kg (95% CI, -1.81 to -1.12; I2 = 0%, 3 studies) and 1.78 kg (95% CI, -2.64 to -0.93; I2 = 90%, 6 studies), respectively.
- AE and SAE: The number of adverse events and the proportion of individuals who had adverse events were high, and oral semaglutide 14 mg had a greater risk of adverse events than placebo, but oral semaglutide 7 mg showed no significant differences.

Futhermore, according to the results of semaglutide 14 mg arms, the main cause of adverse events was related to the gastrointestinal tract. Nausea, diarrhea, vomiting, decreased appetite, nasopharyngitis and headache were the top six most common adverse effects. Compared with other antidiabetic agents, both dosages of semaglutide demonstrated no significant difference in the risk of adverse events and serious adverse events. There was no significant difference between such arms in subgroup analysis.

- Semaglutide 7 and 14 mg had significantly more adverse events resulting in discontinuation than placebo. Semaglutide 14 mg caused a higher rate of adverse events leading to discontinuation when compared to other antidiabetic agents, whereas 7 mg had no effect. It is worth mentioning that this outcome was mainly attributed to gastrointestinal symptoms in eight RCTs. Further subgroup analysis showed that as compared to sitagliptin and empagliflozin, oral semaglutide 14 mg had a significantly greater rate of discontinuation due to adverse events, but no difference between liraglutide and duraglutide.
- Gastrointestinal adverse events: The top three most commonly reported adverse events (5%) in the 10 included RCTs (except for PIONEER6, which was not reported) were gastrointestinal adverse events. The top three most frequent adverse events, according to the semaglutide 14 mg arm statistics, was nausea, vomiting and diarrhea. There was no significant difference between semaglutide 7 mg and placebo or other antidiabetic agents in terms of nausea, diarrhea or vomiting. However, semaglutide 14 mg considerably increased the occurrence of these three outcomes, as compared to placebo and other antidiabetic agents. However, further subgroup analysis found that semaglutide 14 mg occurred more in nausea, vomiting and diarrhea, mainly due to the comparison of sitagliptin and empagliflozin, while there was no difference in the incidence of liraglutide and duraglutide.
- Hypoglycemic episode: Severe or blood glucose confirmed symptomatic hypoglycemic episodes were not significantly different between semaglutide 7 and 14 mg and placebo, or between both dosages of semaglutide and other antidiabetic agents

Anmerkung/Fazit der Autoren

In conclusion, once-daily 14 mg oral semaglutide can significantly reduce HbAlc, body weight and a higher proportion of patients achieving blood glucose goals when compared to either placebo or other antidiabetic agents. In addition, as previously mentioned, oral semaglutide has been shown to reduce cardiovascular risk in patients with T2DM. To minimize gastrointestinal discomfort, the dosage of oral semaglutide should be strictly increased from 3 mg to 7 mg, 7 mg to 14 mg in increasing dosages, and the time of administration should be carefully monitored. Therefore, if patients can endure gastrointestinal side effects and do not wish to utilize injectable medications, oral semaglutide gives advantages, allowing for early incretin use in the treatment of T2DM.

Kommentare zum Review

Es liegen weitere SRs zu ähnlichen Fragestellungen mit derselben Schlussfolgerung vor:

- Avgerinos I et al. 2020 [3]
- Hu S et al., 2023 [23]
- Li J et al., 2021 [29]

Wu W et al. 2024 [66].

The effect of semaglutide on blood pressure in patients with type-2 diabetes: a systematic review and meta-analysis

Fragestellung

Therefore, this review analyzed the results of multiple RCTs to further investigate the effect of semaglutide on BP levels in individuals with T2D.

Methodik

Population:

- participants were 18 years of age or older with T2D

Intervention:

- Semaglutide

Komparator:

- other antihyperglycemic agents (AHAs) or placebo

Endpunkte:

- primary outcome: systolic and/or diastolic BP
- Secondary outcomes: HbA1c and body weight

Recherche/Suchzeitraum:

- Web of Science, Embase, the Cochrane Library, PubMed and Clinicaltrials.gov were systematically searched from inception until March 18, 2023.

Qualitätsbewertung der Studien:

- Cochrane Risk of bias (RoB)

Ergebnisse

Anzahl eingeschlossener Studien:

- 29 studies (n = 26985 participants)

Charakteristika der Population/Studien:

Table 1 (continued)

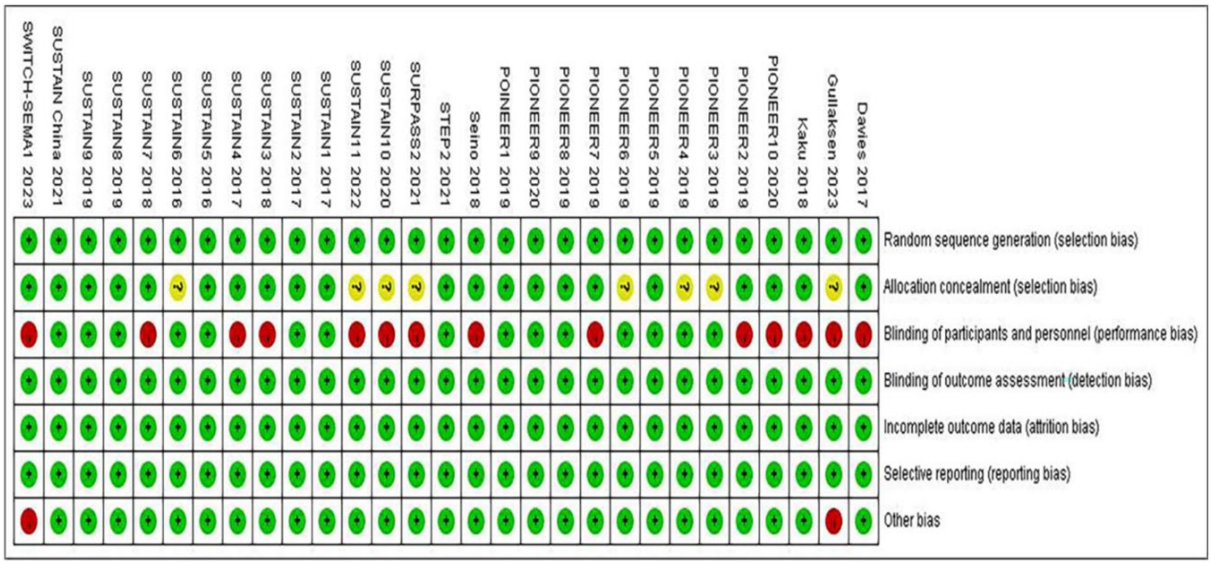
Author	Study	Year	Study duration	Study arms	Sample size	Average age (years)	Female (%)	Diabetes duration	HbA1c (%)	Body weight (kg)
Pratley et al. [14]	SUSTAIN 7	2018	40-week	Semaglutide 0.5 mg	301	56 (10.9)	44	7.7 (5.9)	8.3 (0.9)	96.4 (24.4)
				Semaglutide 1.0 mg	300	55 (10.6)	46	7.3 (5.7)	8.2 (0.9)	95.5 (20.9)
				Dulaglutide 0.75 mg	299	55 (10.4)	46	7.0 (5.5)	8.2 (0.9)	95.6 (23.0)
				Dulaglutide 1.5 mg	299	56 (10.6)	43	7.6 (5.6)	8.2 (0.9)	93.4 (21.8)
Seino et al. [28]		2018	30-week	Semaglutide 0.5 mg	103	58.8 (10.4)	23.3	8.0 (5.2)	8.2 (1.0)	67.8 (11.7)
				Semaglutide 1.0 mg	102	58.1 (11.6)	26.5	7.8 (6.9)	8.0 (0.9)	70.8 (16.4)
				Sitagliptin 100 mg	103	57.9 (10.1)	21.4	8.1 (6.7)	8.2 (0.9)	69.4 (12.9)
Kaku et al. [29]		2018	56-week	Semaglutide 0.5 mg	239	58.0 (10.6)	30.5	8.1 (6.0)	8.0 (0.9)	71.0 (15.4)
				Semaglutide 1.0 mg	241	58.7 (10.2)	27.8	9.4 (6.5)	8.1 (1.0)	71.7 (15.9)
				Additional OAD	120	59.2 (10.1)	25.8	9.3 (7.0)	8.1 (0.9)	72.2 (14.9)
Aroda et al. [35]	PIONEER 1	2019	26-week	Semaglutide 3 mg	175	55 (11)	49.1	3.8 (5.3)	7.9 (0.7)	86.9 (21.0)
				Semaglutide 7 mg	175	56 (11)	46.9	3.6 (5.1)	8.0 (0.6)	89.0 (21.8)
				Semaglutide 14 mg	175	54 (11)	50.9	3.4 (4.4)	8.0 (0.7)	88.1 (22.1)
				Placebo	178	54 (11)	50.0	3.4 (4.6)	7.9 (0.7)	88.6 (23.4)
Rodbard et al. [37]	PIONEER 2	2019	52-week	Semaglutide 14 mg	411	57 (10)	49.9	7.2 (5.8)	8.1 (0.9)	91.9 (20.5)
				Empagliflozin 25 mg	410	58 (10)	49.0	7.7 (6.3)	8.1 (0.9)	91.3 (20.1)
Rosenstock et al. [13]	PIONEER 3	2019	78-week	Semaglutide 3 mg	466	58 (10.0)	45.5	8.4 (6.1)	8.3 (1.0)	91.6 (22.0)
				Semaglutide 7 mg	465	58 (10.0)	47.3	8.3 (5.8)	8.4 (1.0)	91.3 (20.8)
				Semaglutide 14 mg	465	57 (10.0)	46.9	8.7 (6.1)	8.3 (0.9)	91.2 (21.7)
				Sitagliptin 100 mg	467	58 (10.0)	49.0	8.8 (6.0)	8.3 (0.9)	90.9 (21.0)
Pratley et al. [16]	PIONEER 4	2019	52-week	Semaglutide 14 mg	285	56 (10)	48	7.8 (5.7)	8.0 (0.7)	92.9 (20.6)
				Liraglutide 1.8 mg	284	56 (10)	48	7.3 (5.3)	8.0 (0.7)	95.5 (21.9)
				Placebo	142	57 (10)	48	7.8 (5.5)	7.9 (0.7)	93.2 (20.0)
Mosenzon et al. [21]	PIONEER 5	2019	26-week	Semaglutide 14 mg	163	71 (8)	49	14.1 (8.6)	8.0 (0.7)	91.3 (17.8)
				Placebo	161	70 (8)	55	13.9 (7.4)	7.9 (0.7)	90.4 (17.5)
Husain et al. [12]	PIONEER 6	2019	69-week	Semaglutide 14 mg	1591	66 ± 7	31.9	14.7 ± 8.5	8.2 ± 1.6	91.0 ± 21.4
				Placebo	1592	66 ± 7	31.4	15.1 ± 8.5	8.2 ± 1.6	90.8 ± 21.0
Pieber et al. [27]	PIONEER 7	2019	52-week	Semaglutide	253	56.9 (9.7)	43	8.6 (6.3)	8.3 (0.6)	88.9 (19.6)
				Sitagliptin 100 mg	251	57.9 (10.1)	44	9.0 (6.2)	8.3 (0.6)	88.4 (20.1)
Zinman et al. [34]	PIONEER 8	2019	26/52-week	Semaglutide 3 mg	184	61 (9)	44.6	15.1 (7.9)	8.2 (0.7)	85.9 (21.5)
				Semaglutide 7 mg	182	60 (10)	43.3	16.2 (8.6)	8.2 (0.7)	87.1 (23.6)
				Semaglutide 14 mg	181	61 (10)	53.0	14.1 (8.0)	8.2 (0.7)	84.6 (21.0)
				Placebo	184	60 (10)	42.9	14.8 (7.9)	8.2 (0.7)	86.0 (21.4)

Table 1 (continued)

Author	Study	Year	Study duration	Study arms	Sample size	Average age (years)	Female (%)	Diabetes duration	HbA1c (%)	Body weight (kg)
Lingvay et al. [23]	SUSTAIN 8	2019	52-week	Semaglutide 1.0 mg	394	55.7 (11.1)	43	7.5 (5.9)	8.3 (1.0)	90.6 (22.6)
				Canagliflozin300 mg	394	57.5 (10.7)	49	7.2 (5.4)	8.2 (1.0)	89.8 (22.6)
Zinman et al. [25]	SUSTAIN 9	2019	30-week	Semaglutide 1.0 mg	151	57.5 (8.9)	41.1	9.8 (6.3)	8.0 (0.8)	89.6 (19.5)
				Placebo	151	56.6 (10.1)	42.4	9.6 (5.9)	8.1 (0.8)	93.8 (22.3)
Capehorn et al. [15]	SUSTAIN10	2020	30-week	Semaglutide 1.0 mg	290	60.1 (10.5)	44.8	9.6 (6.1)	8.2 (0.9)	96.6 (21.0)
				Liraglutide 1.2 mg	287	58.9 (10.0)	41.8	8.9 (5.7)	8.3 (1.0)	97.2 (21.7)
Yamada et al. [24]	PIONEER 9	2020	52-week	Semaglutide 3 mg	49	58 (9)	27	7.4 (5.5)	8.1 (0.8)	71.4 (14.3)
				Semaglutide 7 mg	49	60 (10)	27	7.4 (5.6)	8.3 (1.0)	71.3 (10.8)
				Semaglutide 14 mg	48	61 (9)	17	7.9 (5.9)	8.0 (0.9)	68.0 (13.0)
				Placebo	49	59 (9)	18	8.4 (6.0)	8.3 (1.1)	70.3 (12.4)
				Liraglutide 0.9 mg	48	59 (10)	19	6.7 (5.2)	8.3 (0.8)	74.7 (15.4)
Yabe et al. [19]	PIONEER10	2020	52-week	Semaglutide 3 mg	131	59 (10)	24	9.4 (6.3)	8.2 (0.9)	71.5 (16.0)
				Semaglutide 7 mg	132	58 (11)	32	9.3 (6.3)	8.3 (0.9)	72.7 (16.4)
				Semaglutide 14 mg	130	57 (10)	23	9.1 (6.4)	8.4 (1.0)	72.6 (15.2)
				Dulaglutide 0.75 mg	65	61 (9)	22	9.9 (6.3)	8.4 (0.9)	71.2 (14.3)
Frías et al. [9]	SURPASS 2	2021	40-week	Semaglutide 1 mg	469	56.9 ± 10.8	52.0	8.3 ± 5.80	8.25 ± 1.01	93.7 ± 21.12
				Tirzepatide 5 mg	470	56.3 ± 10.0	56.4	9.1 ± 7.16	8.32 ± 1.08	92.5 ± 21.76
				Tirzepatide 10 mg	469	57.2 ± 10.5	49.3	8.4 ± 5.90	8.30 ± 1.02	94.8 ± 22.71
				Tirzepatide 15 mg	470	55.9 ± 10.4	54.5	8.7 ± 6.85	8.26 ± 1.00	93.8 ± 21.83
Davies et al. [11]	STEP 2	2021	68-week	Semaglutide 1.0 mg	403	56 (10)	50.4	7.7 (5.9)	8.1 (0.8)	99.0 (21.1)
				Semaglutide 2.4 mg	404	55 (11)	55.2	8.2 (6.2)	8.1 (0.8)	99.9 (22.5)
				Placebo	403	55 (11)	47.1	8.2 (6.2)	8.1 (0.8)	100.5 (20.9)
Ji et al. [18]	SUSTAIN China	2021	30-week	Semaglutide 0.5 mg	288	53.0 (11.4)	44.4	6.3 (5.4)	8.1 (0.9)	77.6 (16.4)
				Semaglutide 1.0 mg	290	53.0 (10.6)	46.9	6.7 (4.9)	8.1 (0.9)	76.1 (16.3)
				Sitagliptin 100 mg	290	53.1 (10.4)	36.2	6.1 (5.2)	8.1 (0.9)	75.5 (14.7)
Kellerer et al. [22]	SUSTAIN 11	2022	52-week	Semaglutide 1.0 mg/0.5 mg	874	60.8 (9.4)	49.1	13.4 (6.8)	8.6 (0.7)	87.6 (18.1)
				Insulin aspart	874	61.5 (9.5)	48.4	13.4 (6.5)	8.5 (0.7)	88.1 (18.4)
Gullaksen et al. [31]		2023	32-week	Semaglutide 1.0 mg	20	70.1 ± 6.8	15	8.5 (3.5–16.0)	7.5 (6.9–7.8)	94.9 (91.5, 98.4)
				Empagliflozin 10 mg	20	69.6 ± 6.0	35	10.0 (5.0–18.5)	7.4 (6.9–7.6)	94.9 (91.5, 98.4)
Takahashi et al. [30]	SWITCH-SEMA 1	2023	24-week	A: Semaglutide (0.25–1.0 mg)	19	59.6 (49.0–72.0)	36.8	NA	NA	NA
				B: Semaglutide (0.25–1.0 mg)	31	64.6 (54.0–75.0)	35.5	NA	NA	NA
				A: Liraglutide	18	60.9 (49.5–72.3)	33.3	NA	NA	NA
				B: Dulaglutide	32	60.8 (49.0–71.8)	59.4	NA	NA	NA

HbA1c glycated hemoglobin A1c, *ER* extended release, *OAD* oral antidiabetic drug, *NA* not available

Qualität der Studien:



Studienergebnisse:

- Systolic (SPB)/diastolic blood pressure (DBP)

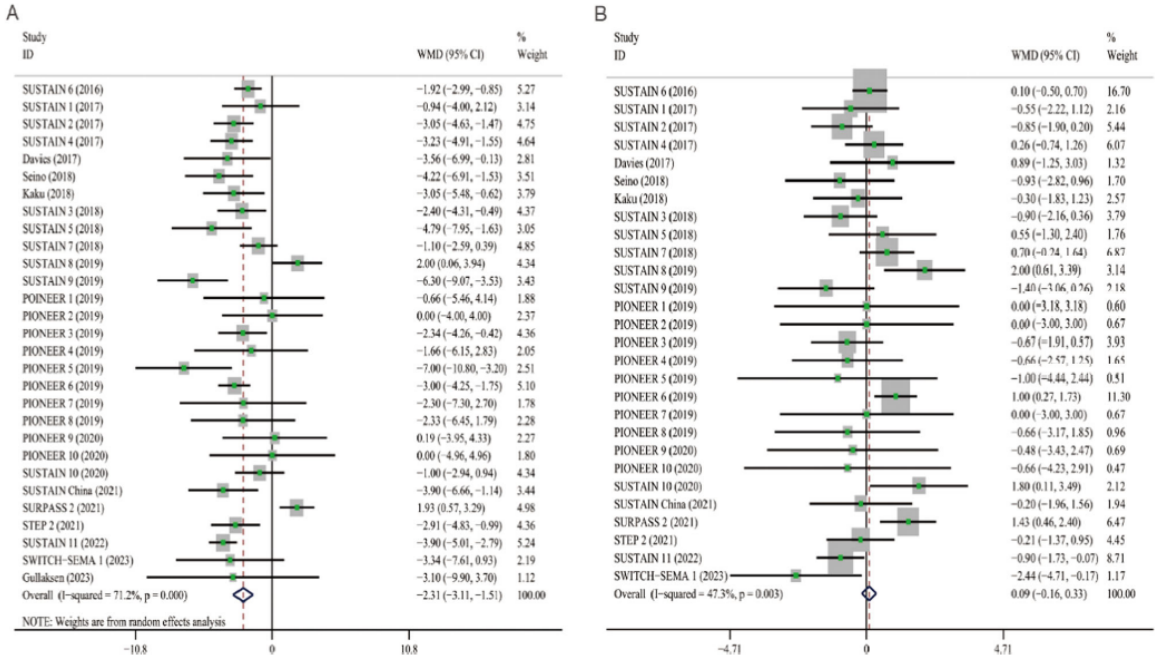


Fig. 2 Forest plot of semaglutide vs. placebo or other antidiabetic drugs showing the pooled WMD for BP. **A** SBP (Random-effects model). **B** DBP (Fix-effects model). Each study is depicted by green squares (WMD) and widths (95% CI). The pooled WMD is presented by dark blue rhombuse and width (95% CI). WMD weighted mean difference, CI confidence interval, BP blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure

- HbA1c und body weight

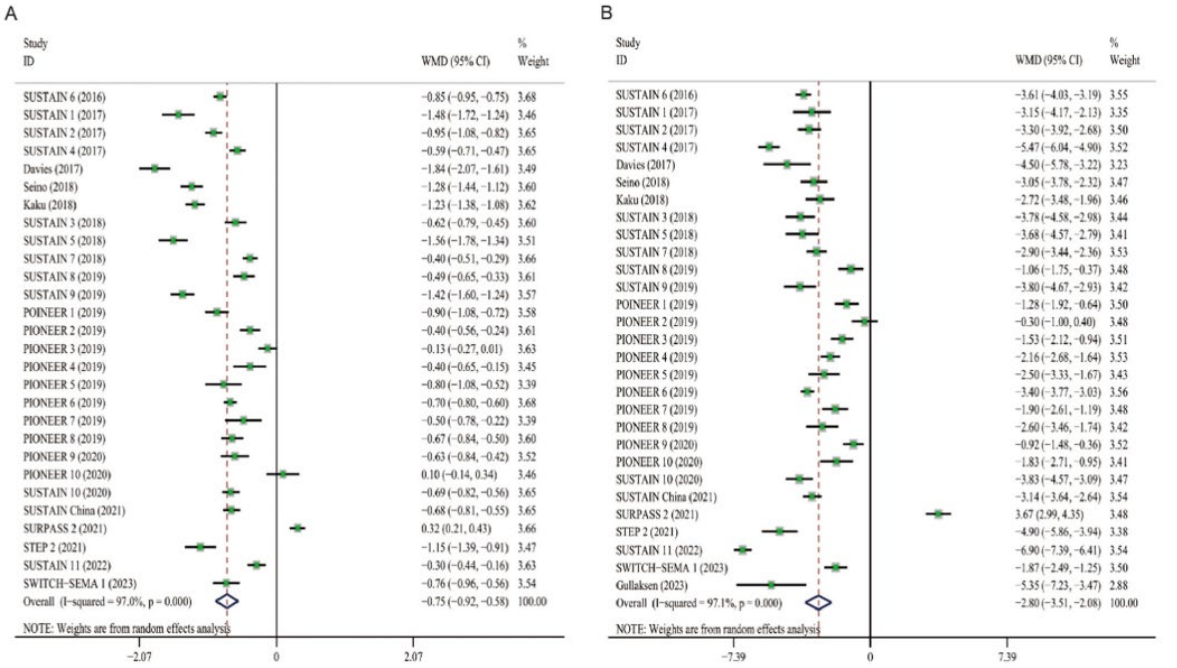


Fig. 3 Forest plot of semaglutide vs. placebo or other antidiabetic drugs showing the pooled WMD for HbA1c and body weight (Random-effects model). **A** HbA1c. **B** Body weight. Each study is depicted by green squares (WMD) and widths (95% CI). The pooled WMD is presented by dark blue rhombuse and width (95% CI). WMD weighted mean difference, CI confidence interval, HbA1c glycated hemoglobin A1c

- SBP/DBP: A mean reduction in SBP from baseline was indicated for semaglutide (WMD: −2.31, 95% CI: −3.11 to −1.51) across all trials (Fig. 2A). The mean difference in DBP from baseline was 0.09 mmHg (95% CI: −0.16 to 0.33) across all studies, which was not statistically significant (Fig. 2B)
- HbA1c und Body weight: In addition, compared to placebo or other AHAs, semaglutide can reduce HbA1c by 0.75% (95% CI: −0.92 to −0.58) and weight by 2.80 kg (95% CI: −3.51 to −2.08), respectively (Fig. 3A, B).

Anmerkung/Fazit der Autoren

Our analysis suggests that semaglutide, either oral or subcutaneous, can significantly reduce SBP in subjects with T2D. For diabetes patients with hypertension, the antihypertensive effect of semaglutide may be greater than the 2.31 mmHg in this paper, but the real-world effect has yet to be determined. We also investigated the changes in HbA1c and body weight after treatment with semaglutide, and found that HbA1c decreased by 0.75% and body weight reduced by 2.80 kg, indicating that weight loss and SBP reduction were synchronized. Future studies to uncover the underlying BP lowering mechanisms of semaglutide will benefit more individuals with diabetes by increasing the understanding these associations.

Marilly E et al., 2022 [45].

SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials balancing their risks and benefits

Fragestellung

The risk/benefit ratio of SGLT2i remains unquantified, and we therefore aimed to provide a quantitative estimation at low risk of bias of the risk/benefit ratio of SGLT2i that could easily be used in routine care of individuals with type 2 diabetes.

Methodik

Population:

- type 2 diabetes, with or without other diseases

Intervention:

- SGLT2i

Komparator:

- placebo- or active-controlled

Endpunkte:

- Primary: overall mortality and the risk/benefit ratio between the key primary efficacy outcomes (MACE, HHF) and the primary safety outcomes (amputation, DKA and genital infection)
- The key secondary efficacy outcome was cardiovascular death and the key secondary safety outcomes were serious adverse events, adverse events leading to withdrawal, hypoglycaemia and urinary-tract infections.

Recherche/Suchzeitraum:

- between 31 December 2014 and 14 September 2021 in PubMed/MEDLINE

Qualitätsbewertung der Studien:

- Cochrane ‘Risk of bias’ assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 Studies

Charakteristika der Population/Studien:

Table 1 Baseline characteristics of included trials

Characteristic	CANVAS [2]	CREDENCE [3]	DECLARE-TIMI 58 [4]	EMPA-REG OUTCOME [5]	VERTIS-CV [41]
Year of publication	2017	2019	2018	2015	2020
Sample size, *n*	10,142	4401	17,160	7020	8246
Follow-up period, years	3.6	2.6	4.2	3.1	3
Blinding	DB	DB	DB	DB	DB
Age, years	63.3 ± 8.3	63.0 ± 9.2	64	63.1 ± 8.6	64.4
Female sex, %	35.8	33.9	37.4	28.5	30.2
eGFR, ml/min per 1.73 m^2	76.5 ± 20.5	56.2 ± 18.2	85.3	74	75.9
BMI, kg/m^2	32.0 ± 5.9	31.3 ± 6.2	32.1	30.6 ± 5.2	32.0
Diabetes duration, years	13.5 ± 7.8	15.8 ± 8.6	10.5	NA	13
HbA_{1c}, mmol/mol	66 ± 14	67 ± 9	67	65 ± 15	66
HbA_{1c}, %	8.2 ± 0.9	8.3 ± 1.3	8.3	8.1 ± 0.8	8.2
Current smoker, %	17.8	14.5	NA	NA	NA
Heart failure, %	14.4	14.8	10.1	10.2	24.0
CVD, %	65.6	50.4	40.6	99.2	75.9[a]
Amputation, %	2.3	5.3	1.4	1.9	NA

Data are shown as mean ± SD from the whole trial (or the mean of the arms if not available)

[a] Coronary artery disease

DB, double-blind; NA, not applicable

Qualität der Studien:

- We judged all studies as having a low risk of selection bias due to sequence generation and allocation concealment, and a low risk of performance or detection bias We judged all studies as having a low risk of selection bias due to sequence generation and allocation concealment, and a low risk of performance or detection bias. We judged the CANVAS Program as having an unclear risk of reporting bias, due to its change in protocol combining two independent trials.

Studienergebnisse:

- Efficacy

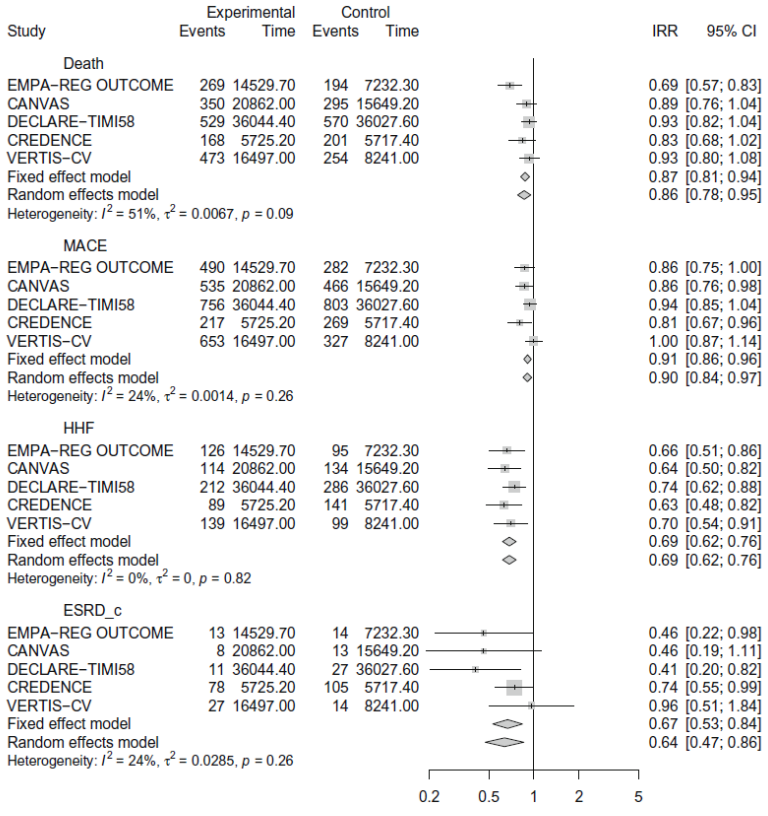
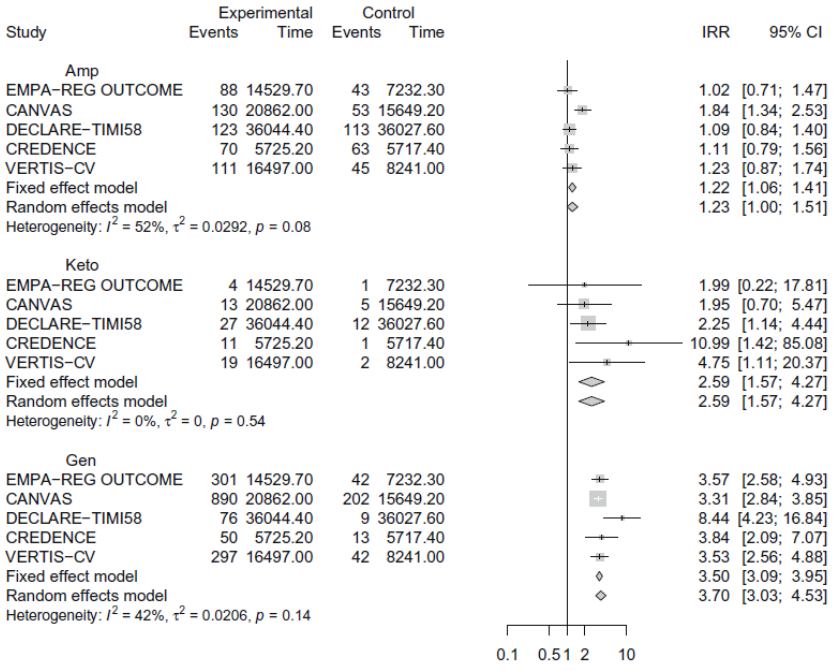


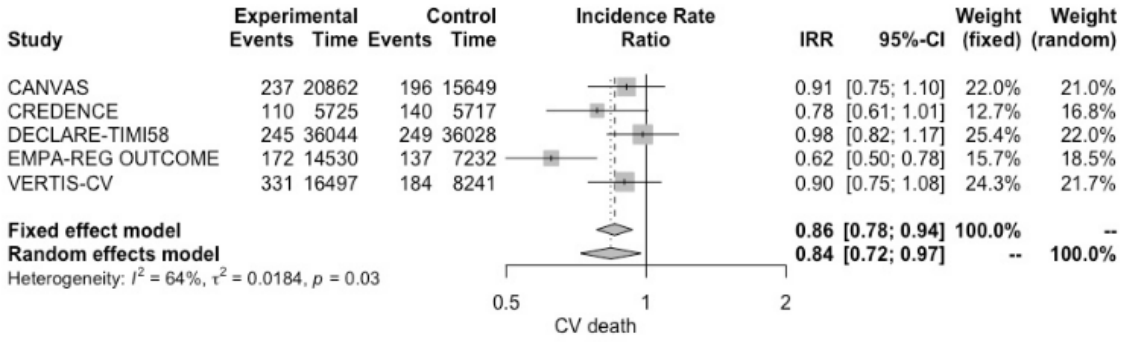
Fig. 2 Forest plot of the primary efficacy outcomes: mortality; MACE; HHF; and ESRD. 'Events' indicates the number of events in each arm. 'Time' indicates person-time at risk in each arm. Death, death from any cause; ESRD_c, ESRD, clinical (defined as a clinical renal outcome or a sustained GFR of <15 ml/min per 1.73 m^2). Squares indicate weighting, diamonds are for pooled results

- Safety

Fig. 3 Forest plot of the primary safety outcomes: amputation; DKA; and genital infection. 'Events' indicates the number of events in each arm. 'Time' indicates person-time at risk in each arm. Amp, amputations; Gen, genital infection; Keto, DKA. Squares indicate weighting, diamonds are for pooled results



- CV-Death (Key Secondary)



- Key Secondary Adverse Events: Overall, SGLT2i were associated with a decreased risk of serious adverse events compared with control treatment (IRR 0.92 [95% CI 0.90, 0.95]). No significant differencewas observed compared with control groups in the risk of adverse events leading to drug withdrawal or hypoglycaemia (IRR 1.05 [95% CI 0.93, 1.19] and IRR 0.93 [95% CI 0.81, 1.07], respectively). However, SGLT2i were associated with an increased risk of urinary-tract infections compared with control treatment (IRR 1.10 [95% CI 1.02, 1.18])
- Secondary Outcomes: total of 3146 cardiovascular deaths or HHF occurred in the trials. SGLT2i decreased the risk of cardiovascular death or HHF (IRR 0.79 [95% CI 0.74, 0.85]; ESM). SGLT2i were associated with an increased risk of volume depletion compared with control treatment (IRR 1.17 [95% CI 1.02, 1.33]). No significant difference was observed in the risk of bladder cancer (IRR 0.74 [95%CI 0.52, 1.06]), breast cancer (IRR 1.18 [95% CI 0.88, 1.58]) or renal-cell carcinoma compared with control treatment (IRR 0.93 [95% CI 0.06, 14.26]). SGLT2i were not associated with a significant increase in the risk of fracture compared with control treatment (IRR 1.08 [95% CI 0.99, 1.18]). However, SGLT2i were associated with a decreased risk of acute kidneyinjury compared with control treatment (IRR 0.76 [95% CI 0.66, 0.87]

- Secondary renal efficacy outcome A total of 1430 participants had a secondary renal efficacy outcome. SGLT2i reduced this risk by 31% (IRR 0.64 [95% CI 0.57, 0.71]; . Heterogeneity was moderate (I2=46%)

Anmerkung/Fazit der Autoren

In a population of individuals with type 2 diabetes and a high CVD risk, the cardiovascular and renal benefits seem to remain greater than the risk of adverse drug reactions. We hope that these results will help inform both clinicians and patients of the effects they can expect when initiating SGLT2i therapy.

Kommentare zum Review

Es liegen weitere SRs zu ähnlichen Fragestellungen mit derselben Schlussfolgerung vor:

- Zou, MD et al., 2019 [75]
- Lo, K. B. et al., 2020 [36]
- Kovil R et al. 2022 [26]

Xu et al., 2022 [67].

The Cardiovascular Benefits and Infections Risk of SGLT2i versus Metformin in Type 2 Diabetes: A Systemic Review and Meta-Analysis

Fragestellung

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and metformin are both widely accepted anti-hyperglycemic agents. However, there is still no systematic review evaluating the cardiovascular benefits and risk of infections of SGLT2i versus metformin.

Methodik

Population:

- Diabetes Mellitus

Intervention:

- SGLT2i

Komparator:

- Metformin

Endpunkte:

- Primary: incidence of infections
- Cardiovascular risk factors enrolled in this analysis included body weight, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, diastolic blood pressure, and systolic blood pressure
- changes in FPG and HbA1c

Recherche/Suchzeitraum:

- Cochrane Library database, Web of Science, Embase, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database to March 1st, 2022

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

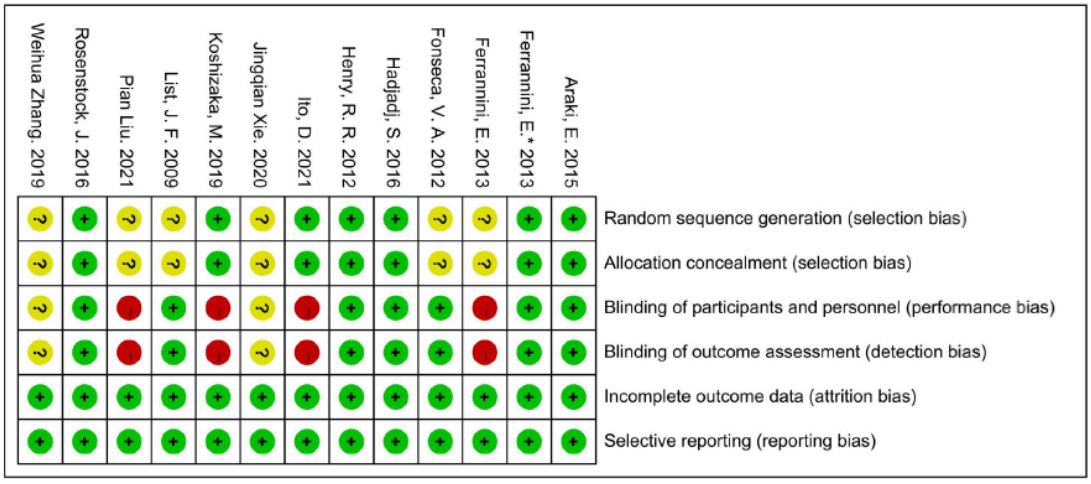
- 13 RCT

Charakteristika der Population/Studien:

Study	Interventions	Study Duration (Weeks)	Number of Participants	Male (N)	Age (Years)	HbA1c (%)	Body Weight (Kg)	BMI (Kg/M)
Araki, E. 2015 [20] (NCT01368081)	EMPA 10 mg EMPA 25 mg MET 1111 mg §	52	136 137 63	99 96 47	61.3 ± 9.9 61.8 ± 9.6 60.0 ± 10.2	8.0 ± 0.7 8.1 ± 0.8 7.9 ± 0.8	65.8 ± 12.2 67.0 ± 13.7 68.2 ± 12.2	24.6 ± 3.8 25.2 ± 4.2 25.2 ± 3.6
Ferrannini, E.* 2013 [21] (NCT00789035)	EMPA 5 mg EMPA 10 mg EMPA 25 mg MET †	12	81 81 82 80	46 40 41 39	59.0 (37–78) * 58.0 (30–76) * 57.0 (30–79) * 58.0 (34–73) *	7.9 ± 0.8 8.0 ± 0.8 7.8 ± 0.8 8.1 ± 0.9	82.8 (51.9–116.0) * 76.8 (45.5–118.0) * 81.2 (49.1–130.0) * 81.1 (42.0–126.0) *	28.5 (20.5–38.8) * 28.1 (21.5–39.3) * 28.3 (20.1–38.8) * 28.6 (18.7–40.6) *
Hadjadj, S. 2016 [22] (NCT01719003)	EMPA 10 mg EMPA 25 mg MET 500 mg MET 1000 mg	24	169 164 168 164	97 83 86 92	53.1 ± 10.7 53.3 ± 10.7 53.4 ± 10.9 51.6 ± 10.8	8.6 ± 1.2 8.9 ± 1.3 8.7 ± 1.0 8.6 ± 1.1	83.8 ± 19.8 83.1 ± 20.3 82.7 ± 21.2 83.7 ± 20.1	30.3 ± 5.2 30.6 ± 5.9 30.3 ± 5.8 30.5 ± 5.9
Ferrannini, E. 2013 [23] (NCT00881530)	EMPA 10 mg EMPA 25 mg MET †	78	106 109 56	49 57 28	59 (30–76) * 59 (35–79) * 58 (35–73) *	7.9 ± 0.9 8.0 ± 0.9 8.2 ± 1.0	82.9 ± 16.4 84.6 ± 18.1 85.8 ± 15.6	28.9 (20.3–39.2) * 28.1 (19.3–40.0) * 28.6 (22.4–39.3) *
Henry, R.R. 2012 [24] (NCT00643851 NCT00859898)	DAPA 5 mg DAPA 10 mg MET 2000 mg	24	203 219 409	92 105 192	52.3 ±10.2 51.1 ± 11.5 52.3 ± 10.1	9.1 ± 1.4 9.1 ± 1.3 9.1 ± 1.3	86.2 ± 21.1 88.5 ± 19.3 86.4 ± 19.7	NO
List, J.F. 2009 [25] (NCT00263276)	DAPA 2.5 mg DAPA 5 mg DAPA 10 mg DAPA 20 mg DAPA 50 mg MET 1500 mg	12	59 58 47 59 56 56	29 28 25 32 25 27	55.0 ± 11.0 55.0 ± 12.0 54.0 ± 9.0 55.0 ± 10.0 53.0 ± 10.0 54.0 ± 9.0	7.6 ± 0.7 8.0 ± 0.9 8.0 ± 0.8 7.7 ± 0.9 7.8 ± 1.0 7.6 ± 0.8	90.0 ± 20.0 89.0 ± 17.0 86.0 ± 17.0 88.0 ± 18.0 92.0 ± 19.0 88.0 ± 20.0	32.0 ± 5.0 32.0 ± 5.0 31.0 ± 5.0 31.0 ± 5.0 32.0 ± 4.0 32.0 ± 5.0
Ito, D. 2021 [26]	DAPA 5 mg MET 1000 mg	12	11 10	8 9	55.9 ± 7.5 57.5 ± 9.6	7.9 ± 0.9 7.9 ± 0.9	77.5 ± 18.1 74.8 ± 8.7	27.7 ± 4.9 26.7 ± 3.4
Pian Liu. 2021 [27]	DAPA 10 mg MET 1000 mg	26	58 59	31 32	66.6 ± 8.4 66.3 ± 9.3	8.1 ± 1.2 8.5 ± 1.1	70.1 ± 7.8 68.6 ± 7.7	24.7 ± 1.8 24.1 ± 2.3
Weihua Zhang. 2019 [28]	DAPA 10 mg MET 1500 mg	12	30 30	19 20	44.9 ± 10.2 44.1 ± 10.8	8.5 ± 1.7 8.3 ± 1.4	76.3 ± 13.6 75.4 ± 14.3	27.9 ± 4.3 27.5 ± 4.5
Rosenstock, J. 2016 [29] (NCT01809327)	CANA 100 mg CANA 300 mg MET 2000 mg	26	237 238 237	105 125 116	54.1 ± 10.7 55.9 ± 9.6 55.3 ± 9.8	8.8 ± 1.2 8.8 ± 1.2 8.8 ± 1.2	90.2 ± 18.6 93.0 ± 19.9 92.1 ± 20.1	32.4 ± 5.4 32.6 ± 5.8 33.0 ± 6.0
Jingqian Xie. 2020 [30]	CANA 100 mg MET (1000–1500 mg)	12	31 31	11 13	63.8 ± 8.6 63.0 ± 9.7	9.1 ± 1.7 8.3 ± 1.5	73.3 ± 10.3 72.5 ± 10.2	NO
Fonseca, V.A. 2012 [31] (NCT01071850)	IPRA 12.5 mg IPRA 50 mg IPRA 150 mg IPRA 300 mg MET 1500 mg	12	70 67 68 68 69	39 34 29 37 40	53.9 ± 9.6 52.6 ± 10.7 54.2 ± 10.3 54.2 ± 10.7 53.1 ± 11.7	8.0 ± 0.8 8.1 ± 0.8 7.8 ± 0.7 7.9 ± 0.7 8.0 ± 0.9	86.0 ± 22.3 90.7 ± 20.8 83.3 ± 21.6 86.7 ± 19.6 84.1 ± 21.8	31.0 ± 5.9 32.2 ± 5.9 30.9 ± 6.3 30.7 ± 5.0 29.8 ± 5.5
Koshizaka, M. 2019 [32]	IPRA 50 mg MET 1124 mg§	12	48 50	31 28	56.6 ± 11.9 55.7 ± 12.2	8.0 ± 0.7 8.1 ± 0.9	73.1 ± 14.2 78.3 ± 18.4	27.6 ± 4.2 28.8 ± 5.3

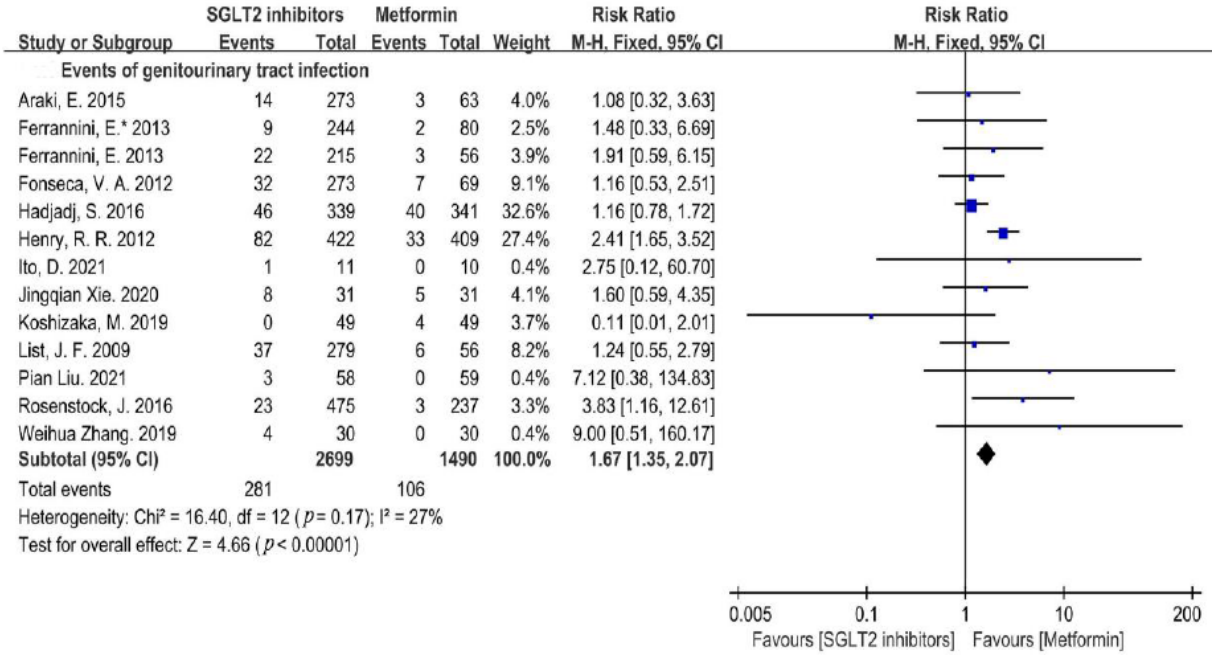
EMPA, empagliflozin; DAPA, dapagliflozin; CANA, canagliflozin; IPRA, ipragliflozin; MET, metformin; BMI, body mass index. Data are mean ± SD (standard deviation) unless indicated otherwise. Ferrannini, E.*: Used to distinguish two articles with the same first author name and publication year (references [21,23]). * Data are median (minimum–maximum). † MET dose < 1000 mg or up to the maximum tolerated dose. § Data are mean dose.

Qualität der Studien:



Studienergebnisse:

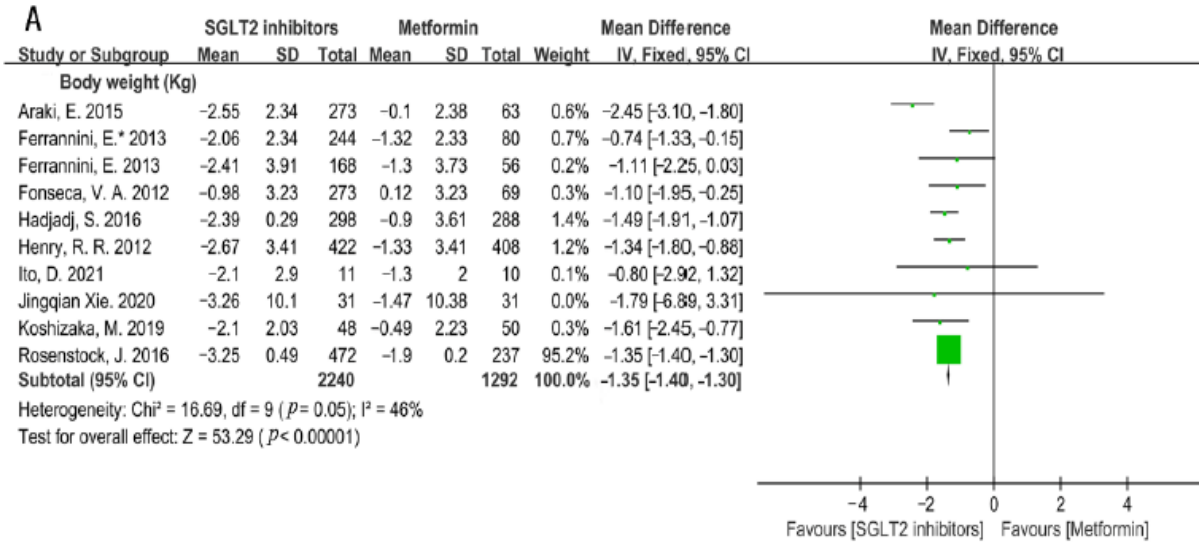
- Infection Incidence Risk
  - Genitourinary tract infections were reported in all of the included RCTs. Compared with metformin, SGLT2i increased the risk of genitourinary tract infections (RR = 1.67, 95% CI = 1.35 to 2.07, p < 0.00001, I2 = 27%, Q test: p = 0.17)



Study or Subgroup	SGLT2 inhibitors Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Events of genitourinary tract infection						
Araki, E. 2015	14	273	3	63	4.0%	1.08 [0.32, 3.63]
Ferrannini, E.* 2013	9	244	2	80	2.5%	1.48 [0.33, 6.69]
Ferrannini, E. 2013	22	215	3	56	3.9%	1.91 [0.59, 6.15]
Fonseca, V. A. 2012	32	273	7	69	9.1%	1.16 [0.53, 2.51]
Hadjadj, S. 2016	46	339	40	341	32.6%	1.16 [0.78, 1.72]
Henry, R. R. 2012	82	422	33	409	27.4%	2.41 [1.65, 3.52]
Ito, D. 2021	1	11	0	10	0.4%	2.75 [0.12, 60.70]
Jingqian Xie. 2020	8	31	5	31	4.1%	1.60 [0.59, 4.35]
Koshizaka, M. 2019	0	49	4	49	3.7%	0.11 [0.01, 2.01]
List, J. F. 2009	37	279	6	56	8.2%	1.24 [0.55, 2.79]
Pian Liu. 2021	3	58	0	59	0.4%	7.12 [0.38, 134.83]
Rosenstock, J. 2016	23	475	3	237	3.3%	3.83 [1.16, 12.61]
Weihua Zhang. 2019	4	30	0	30	0.4%	9.00 [0.51, 160.17]
Subtotal (95% CI)		**2699**		**1490**	**100.0%**	**1.67 [1.35, 2.07]**
Total events	281		106			

Heterogeneity: Chi² = 16.40, df = 12 (p = 0.17); I² = 27%
Test for overall effect: Z = 4.66 (p < 0.00001)

  - Urinary Tract Infections (UTI): Out analysis showed that the overall occurrence of UTIs was not statistically significant between the SGLT2i and metformin group (RR = 1.20, 95% CI = 0.92 to 1.58, p = 0.18, I2 = 0%, N =12). Dapagliflozin resulted in a higher risk of a UTI compared to that of metformin (RR = 1.67, 95% CI = 1.11 to 2.52, p = 0.01, I2 = 0%, N = 5)
  - Reproductive Tract Infections (RTI): The result showed that SGLT2i significantly increased the incidence of an RTI compared with that of metformin (RR = 3.16, 95% CI = 2.04 to 4.89, p < 0.00001, I2 = 0%, N = 8), and the incidence of an RTI induced by empagliflozin was also higher than of metformin (RR = 2.09, 95% CI = 1.07 to 4.09, p = 0.03, I2 = 0%, N = 4)
- Non-Genitourinary Tract Infections: Four studies contributed to the risk of upper respiratory tract infections, and the result indicated no significant difference between the SGLT2i and metformin monotherapy group (RR = 0.80, 95% CI = 0.53 to 1.20, p = 0.28, I2 = 0%, N = 4).
- Effects on Cardiovascular Risk Factors - Body weight: significantly reduced body weight compared with that of metformin (WMD = -1.35, 95% CI = -1.40 to -1.30, p < 0.00001, N = 10) with a moderate heterogeneity (I2 = 46%, Q test: p = 0.05)



- Glycemic Control
  - HbA1c: The antihyperglycemic effects were evaluated and the results showed that SGLT2i and metformin had a similar effect on the reduction in HbA1c (WMD = 0.01, 95% CI = -0.02 to 0.03, p = 0.71, I2= 49%, N = 13)
  - FPG: Compared tometforminmonotherapy, SGLT2i significantly decreased FPG (WMD = -4.36, 95% CI = -5.33 to -3.40, p < 0.00001, I2 = 39%, N = 12) (Figure 15C). The subgroup analysis indicated that empagliflozin and dapagliflozin were more effective than metformin in the reduction in FPG (empagliflozin: WMD = -4.52, 95% CI = -7.67 to -1.38, p = 0.005, I2 = 62%, N = 4; dapagliflozin: WMD = -4.39, 95% CI = -5.42 to -3.36, p < 0.00001, I2 = 52%, N = 5)

Anmerkung/Fazit der Autoren

In summary, SGLT2i showed significant benefits in the reduction in cardiovascular risk factors, such as body weight, blood pressure, triglycerides, and increasing HDL cholesterol level, and had similar antihyperglycemic efficacy, including lowering blood glucose and HbA1c without the significant elevation of UTIs compared with metformin monotherapy, especially in obese T2DM patients. In short-term trials, SGLT2i provided the similar antihyperglycemic effect with metformin and induced additional cardiovascular benefits and the potential risk of an RTI. Additional long-term trials are needed to confirm the longterm safety of SGLT2i, which is expected to be the first choice for patients with metformin intolerance.

Kommentare zum Review

Ergebnisse zu Blutwerten (LDL, HDL, Triglyceride), ausgenommen der glykämischen Kontrolle, wurden nicht dargestellt.

Zhang Q et al., 2023 [73].

Renal, cardiovascular, and safety outcomes of adding sodium-glucose cotransporter-2 inhibitors to insulin therapy in patients with type-2 diabetes: a meta-analysis

Fragestellung

Due to the mechanism of SGLT2is, combination therapy with SGLT2is and insulin is expected to have complementary effects, i.e., not only better glucose control but also renal

and cardiovascular benefits. However, there has been no large trial or meta-analysis on this topic. Therefore, this meta-analysis investigated the renal, cardiovascular, and safety outcomes of adding SGLT2is to insulin therapy in patients with T2DM.

Methodik

Population:

- T2DM

Intervention:

- SGLT2i + insulin therapy

Komparator:

- insulin therapy

Endpunkte:

- urinary albumin/creatinine ratio (UACR), blood urea nitrogen (BUN), serum creatinine, estimated glomerular filtration rate (eGFR), uric acid, renal-related adverse events, HbA1c, insulin dosage, hypoglycemic response, blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP]), body weight, lipid parameters (high-density lipoprotein cholesterol [HDL-c], low-density lipoprotein cholesterol [LDL-c], total cholesterol [TC], triglyceride [TG]), urinary tract infection, genital infection, death or cancer.

Recherche/Suchzeitraum:

- February 2023 by searching PubMed, Embase, and the Cochrane Library

Qualitätsbewertung der Studien:

- Cochrane Risk of bias

Ergebnisse

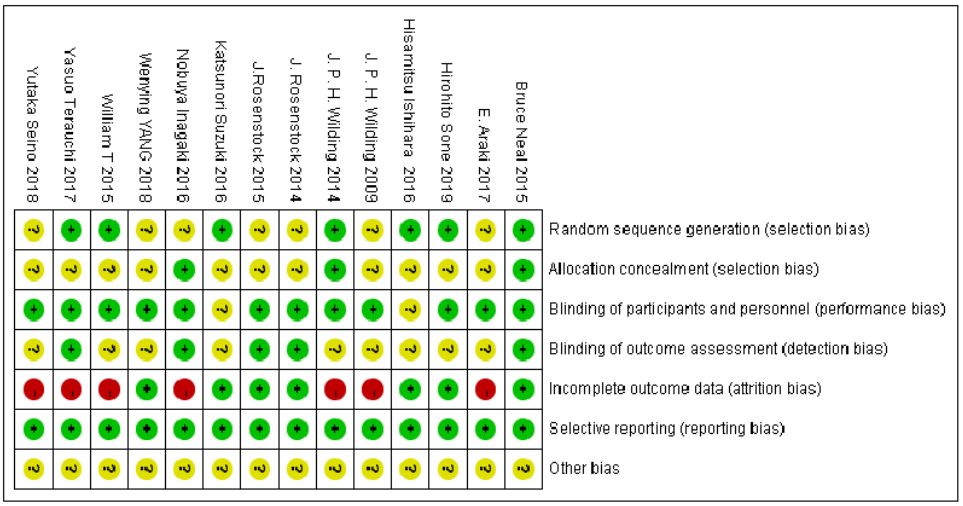
Anzahl eingeschlossener Studien:

- 14 RCTs

Charakteristika der Population/Studien:

- Siehe Anhang

Qualität der Studien:



Studienergebnisse:

Table 2 Results of meta-analysis: SGLT2i + INS vs. INS

Outcomes	No. studies	Sample size	Overall effect			Heterogeneity test	
			Statistical method	95% CI	*P*	I^2 (%)	*P'*
Effect outcomes							
HbA1c	12	2673	WMD, random	− 0.76 [− 0.96, − 0.57]	< 0.00001	89	< 0.00001
Insulin dosage	8	1567	WMD, random	− 4.76[− 6.80, − 2.72]	< 0.00001	86	< 0.00001
Renal outcomes							
UACR	3	629	WMD, fixed	− 25.42 [− 48.21, − 2.63]	0.03	0	0.64
< = 24 weeks	2	397	WMD, fixed	− 33.65 [− 62.48, − 4.82]	0.02	0	0.8
> = 52 weeks	1	232	WMD, fixed	− 11.70 [− 48.91, 25.51]	0.54	–	–
EGFR	9	1858	WMD, fixed	− 0.89 [− 1.84, 0.06]	0.07	0	0.45
< = 24 weeks	5	748	WMD, fixed	− 1.19 [− 2.55, 0.17]	0.09	0	0.97
> = 52 weeks	4	1110	WMD, fixed	− 0.61 [− 1.94, 0.72]	0.37	57	0.08
Serum creatinine	3	585	SMD, fixed	0.25 [0.08, 0.42]	0.003	0	0.46
BUN	4	723	SMD, fixed	0.52 [0.37, 0.68]	< 0.00001	21	0.29
Uric acid	7	1756	SMD, fixed	− 0.17 [− 0.27, − 0.07]	0.001	46	0.09
Renal-related adverse events	3	3151	RR, fixed	0.95 [0.50, 1.81]	0.88	0	0.71
Cardiovascular outcomes							
SBP	11	2452	WMD, fixed	− 2.56 [− 3.58, − 1.54]	< 0.00001	3	0.42
DBP	10	1978	WMD, fixed	− 1.06 [− 1.76, − 0.36]	0.003	40	0.09
TC	10	1844	SMD, random	− 0.18 [− 0.77, 0.41]	0.55	97	< 0.00001
TG	9	1711	SMD, random	0.21 [− 0.31, 0.73]	0.44	96	< 0.00001
HDL-c	10	1850	SMD, random	0.51 [− 0.08, 1.09]	0.09	97	< 0.00001
LDL-c	10	1839	SMD, random	− 0.36 [− 1.07, 0.35]	0.32	98	< 0.00001
Body weight	12	2789	WMD, random	− 1.82 [− 2.15, − 1.49]	< 0.00001	66	0.001
Safety outcomes							
Hypoglycemia	13	5613	RR, fixed	1.14 [1.08, 1.22]	< 0.00001	43	0.05
Severe hypoglycemia	9	4905	RR, fixed	1.23 [0.84, 1.82]	0.29	0	0.73
Urinary tract infection	10	3324	RR, fixed	1.13 [0.87, 1.47]	0.37	11	0.34
Men	4	1111	RR, fixed	1.77 [0.91, 3.46]	0.09	0	0.51
Women	4	1029	RR, random	1.22 [0.76, 1.97]	0.41	54	0.09
Genital infection	10	5130	RR, fixed	4.78 [3.29, 6.94]	< 0.00001	0	0.99
Men	5	2480	RR, fixed	6.57 [3.41, 12.64]	< 0.00001	0	0.82
Women	5	1732	RR, fixed	3.73 [2.33, 5.95]	< 0.00001	0	0.6
Increased blood ketone	4	884	RR, fixed	1.94 [0.77, 4.86]	0.16	0	0.85
All-cause death	8	4830	RR, fixed	0.73 [0.36, 1.48]	0.39	0	0.77
Cancer	2	1079	RR, fixed	0.75 [0.31, 1.78]	0.51	0	0.69

HbA1c glycated hemoglobin, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *UACR* urine albumin/creatinine ratio, *eGFR* estimated glomerular filtration rate, *BUN* blood urea nitrogen, *WMD* weighted mean difference, *SMD* standard mean difference, *RR* risk ratio

Anmerkung/Fazit der Autoren

In summary, adding SGLT2is to insulin therapy in T2DM patients showed better glucose control and decreased albuminuria, uric acid, blood pressure, and body weight without a reduction in the eGFR. The use of SGLT2is was not associated with increased risks of severe hypoglycemia or urinary tract infection but it was associated with an elevated risk of genital infection. Thus, adding SGLT2is to insulin had renal and cardiovascular benefits diabetic patients.

Fernandes GC et al., 2021 [18].

Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: a meta-analysis of 34 randomized controlled trials

Fragestellung

to perform a systematic review of the literature and meta-analysis of arrhythmia endpoints in randomized controlled trials of SGLT2is use for T2DM or HF.

Methodik

Population:

- adult patients older than 18 years with diagnosed type 2 diabetes, HF, or both

Intervention:

- SGLT2i

Komparator:

- Placebo or active control

Endpunkte:

- incident atrial arrhythmias (atrial fibrillation and atrial flutter), incident ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation, ventricular flutter, ventricular arrhythmia, and torsades de pointes), SCD (sudden cardiac death, sudden death, and cardiac arrest; as these diagnoses may represent different mechanisms and were not adjudicated, data for this outcome are presented individually for each component and cumulatively), and cumulative incidence of events

Recherche/Suchzeitraum:

- MEDLINE (via PubMed) and ClinicalTrials.gov
- The database search was performed on December 31, 2020.

Qualitätsbewertung der Studien:

- Cochrane tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 34 randomized trials, 25 placebo-controlled and 9 active-controlled, totaling 63,166 patients: 35,883 (56.8%) in the SGLT2i group and 27,273 (43.2%) in the control group.

Charakteristika der Population:

- Follow-up ranged from 24 weeks to 5.7 years, providing 177,087 patient-years. The mean age ranged from 53 to 67 years; 63% were male and 75% white.
- SGLT2is used were dapagliflozin (11 studies, 25,210 patients), canagliflozin (10 studies, 19,732 patients), empagliflozin (9 studies, 12,066 patients) and ertugliflozin (4 studies, 3158 patients). The study population had T2DM for all studies except for 1, DAPA-HF,3 which included patients with symptomatic HF and ejection fraction 40% and had 42% of patients with T2DM.
- 16/34 received background therapy

Qualität der Studien:

- There was no study with a high risk of bias.

Studienergebnisse:

Atrial arrhythmias

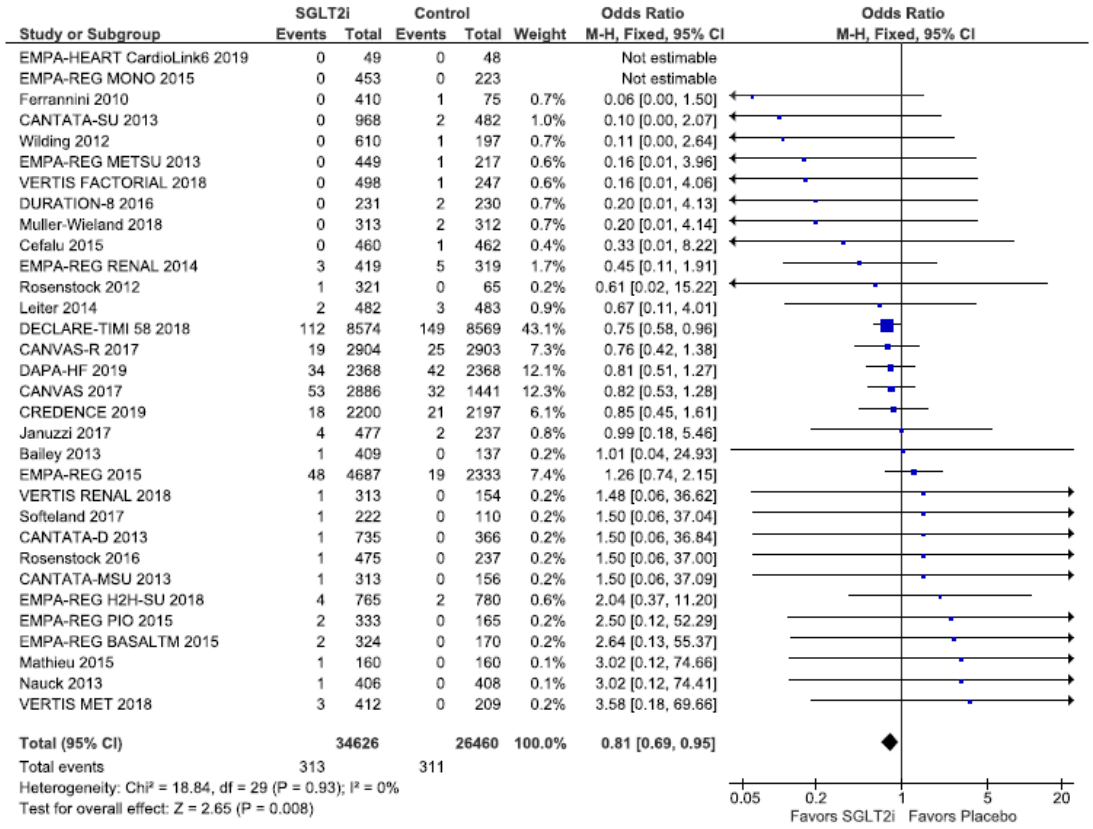


Figure 2 Incident atrial arrhythmias with sodium-glucose cotransporter 2 inhibitors (SGLT2is) vs control in patients with diabetes or heart failure. Summary statistic favors SGLT2is (odds ratio 0.81; 95% confidence interval [CI] 0.69–0.95; $P = .008$) with a significant reduction in incident atrial fibrillation or flutter compared with placebo or active control. M-H = Mantel-Haenszel.

- Subgroup analyses, including only studies of diabetes and only placebo-controlled trials, yielded results similar to overall analysis (OR 0.81; 95% CI 0.68–0.96; P 5 .01 and OR 0.82; 95% CI 0.69–0.96; P 5 .01, respectively). For the 9 active-controlled trials, there were only 7 atrial arrhythmia events in the SGLT2i group and 7 in the control group.
- In subgroup analysis based on SGLT2i used, only dapagliflozin was associated with a significantly reduced risk of atrial arrhythmias (OR 0.74; 95% CI 0.60–0.91; P 5 .005).

Ventricular arrhythmias and SCD

- The risk of incident ventricular arrhythmias was not significantly different between SGLT2is and control. In subgroup analysis, there were 4 trials in the canagliflozin group and 5 trials in each dapagliflozin and empagliflozin groups, and all showed no significant differences between treatment and control groups
- SGLT2i treatment was associated with a significant 28% relative reduction in the odds of the SCD component of this variable when compared with placebo (OR 0.72; 95% CI 0.54–0.97; P 5 .03). The overall analysis of the composite SCD outcome demonstrated no significant difference.

Anmerkung/Fazit der Autoren

SGLT2is are associated with a significantly reduced risk of incident atrial arrhythmias and may be associated with a reduced risk of SCD in patients with type 2 diabetes. More specifically designed studies are needed to confirm these benefits in patients with type 2 diabetes and, in particular, HF. Prospective trials are warranted to confirm the antiarrhythmic effect of SGLT2is and to investigate whether this is related to improvement in HF and a class or drug-specific effect.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Alexander JT et al. 2022 [2]
- Georgiou P et al., 2021 [20]

Gebrie D, et al., 2021 [19].

Cardiovascular safety and efficacy of metformin-SGLT2i versus metformin-sulfonylureas in type 2 diabetes: systematic review and meta-analysis of randomized controlled trials.

Fragestellung

to compare the cardiovascular safety and efficacy of combination therapy of metformin-SGLT2Is and metformin-sulfonylureas in patients with T2DM.

Methodik

Population:

- Patients with T2DM

Intervention:

- A combination of metformin with any of the SGLT2Is, which could be dapagliflozin, canagliflozin, empagliflozin, or ertugliflozin

Komparator:

- A combination of metformin with any of sulfonylureas compounds, which could be gliclazide, glipizide, glyburide, glibenclamide, or glimepiride.

Endpunkte:

- All-cause mortality, Serious adverse events (SAEs), Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hypoglycemia, Changes in HbA1c, Change in body weight, Changes in fasting plasma glucose (FPG), Changes in systolic blood pressure (SBP), Changes in diastolic blood pressure (DBP), Changes in low-density lipoprotein cholesterol (LDL-C), Changes in high-density lipoprotein cholesterol (HDL-C)

Recherche/Suchzeitraum:

- MEDLINE, PubMed, Embase, The Cochrane Library and ClinicalTtrials.gov up to 15 August 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs with 10,974 patients

Charakteristika der Population:

- patients with T2DM who were in either of the two combination therapies at least for a year

Qualität der Studien:

- The studies were found to be “low risk of bias”

Studienergebnisse:

- The pooled analysis showed no significant difference in all-cause mortality (risk ration [RR] = 0.93, 95% CI [0.52, 1.67]), serious adverse events (RR = 0.96, 95% CI [0.79, 1.17]) and adverse events (RR = 1.00, 95% CI [0.99, 1.02]) between the two, but in hypoglycemia (RR = 0.13, 95% CI [0.10, 0.17], $P < 0.001$).

- Participants taking metformin-sodium glucose cotransporter-2 inhibitors showed a significantly greater reduction in HbA1c (mean difference [MD] = − 0.10%, 95% CI [− 0.17, − 0.03], body weight (MD = − 4.57 kg, 95% CI [− 4.74, − 4.39], systolic blood pressure (MD = − 4.77 mmHg, 95% CI [− 5.39, − 4.16]), diastolic blood pressure (MD = − 2.07 mmHg, 95% CI [− 2.74, − 1.40], and fasting plasma glucose (MD = − 0.55 mmol/L, 95% CI [− 0.69, − 0.41]), p < 0.001.

Anmerkung/Fazit der Autoren

Combination therapy of metformin and sodium-glucose cotransporter-2 inhibitors are a safe and efficacious alternative to combination therapy of metformin and sulfonylureas for patients with T2DM who are at risk of cardiovascular comorbidity. However, there remains a need for additional long-term randomized controlled trials as available studies are very limited and heterogeneous.

Liu L et al., 2021 [33].

Efficacy and safety of ertugliflozin in type 2 diabetes: a systematic review and meta-analysis

Fragestellung

To evaluate the efficacy and safety of ertugliflozin in patients with type 2 diabetes.

Methodik

Population:

- adult patients with type 2 diabetes

Intervention/ Komparator:

- ertugliflozin;
- placebo, glimepiride, metformin, sitagliptin;
- Background treatments included diet and exercise, metformin, and other antihyperglycaemic agents

Endpunkte:

- The primary efficacy outcomes comprised glycaemic control [HbA1c, the proportion of participants achieving an HbA1c level < 7%, and fasting plasma glucose (FPG)]; weight loss (body weight); and blood pressure control [systolic blood pressure (SBP) and diastolic blood pressure (DBP)].
- Adverse events (AEs) with different degrees and prespecified AEs of SGLT2 inhibitors were selected to assess the safety and tolerability of ertugliflozin.
- The primary safety outcomes were any AEs, AEs related to study drug, serious AEs, deaths, discontinuations due to AEs, and predetermined AEs of interest for ertugliflozin [genital mycotic infection (GMI), urinary tract infection (UTI), symptomatic hypoglycaemia, and hypovolaemia].

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were systematically searched to identify potentially eligible studies until July 31, 2021

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- nine studies (RCT trials) involving 5638 participants were finally included in the quantitative synthesis
- control: placebo (5 trials), glimepiride (2 trials), metformin (1 trial), sitagliptin (1 trial)

Charakteristika der Population:

- Seven trials mainly focused on Caucasians (ranged from 64.8 to 90.4%), one trial focused on Asians (406 Chinese patients), and one trial did not report races. The duration of the trial follow-up ranged from 12 to 104 weeks. The mean age of participants was 57.6 years, and the mean duration of diabetes was 4.6–14.7 years. The mean HbA1c % ranged from 7.8 to 9.0%.

TABLE 1 | Characteristics of included RCTs of ertugliflozin.

Study	Amin et al. (2015)		Aronson et al. (2018)		Dagogo-Jack et al. (2018)		Gallo et al. (2019)		Grunberger et al. (2018)		Hollander et al. (2019)		Ji et al. (2019)		Miller et al. (2018)		Pratley et al. (2018)	
NCT number	01059825		01958671		02036515		02033889		01986855		01999218		02630706		02226003		02099110	
Follow-up (weeks)	12		52		52		104		52		104		26		26		52	
Background	MET		DE		MET + SIT		DE + MET		DE ± AHA		MET		MET		DE		MET	
Control	PLA/SIT	ERT	PLA/MET	ERT	PLA	ERT	PLA/GLI	ERT	PLA	ERT	GLI	ERT	PLA	ERT	PLA	ERT + SIT	SIT	ERT
Participants	109	219	153	308	153	309	209	412	154	313	437	888	167	339	97	194	247	985
Male sex (%)	64.2	65.3	53.6	58.1	65.4	52.7	46.9	46.2	46.8	50.8	51.3	47.1	52.7	56.9	58.8	56.7	62.3	51.8
Mean age (year)	53.6	54.8	56.1	56.5	58.3	59.4	56.5	56.7	67.5	67.1	57.8	58.4	56.9	56.2	54.3	56.3	54.8	55.2
Mean duration of diabetes (year)	6.3	6.3	4.6	5.2	9.4	9.6	8.0	8.0	13.1	14.7	7.5	7.4	6.4	7.2	6.8	6.1	6.2	7.1
HbA1c (%)	8.2	8.1	8.1	8.3	8.0	8.1	8.2	8.1	8.1	8.2	7.8	7.8	8.1	8.1	9.0	8.9	8.5	8.6
HbA1c (mmol/mol)	NK	NK	65.2	66.7	64.3	64.3	NK	NK	NK	NK	61.3	61.9	NK	NK	74.3	74.1	69.4	70.1
Body weight (kg)	NK	NK	94.2	92.3	86.4	87.1	84.5	85.1	90.4	87.6	86.8	86.8	70.1	70.5	95.0	91.0	89.8	88.4
BMI (kg/m^2)	30.5	30.4	33.3	32.9	30.3	31.1	30.7	30.9	33.2	32.2	31.2	31.5	26.1	25.9	32.7	32.0	31.7	31.9
eGFR (mL/min/1.73 m^2)	NK	NK	86.2	88.4	89.9	87.0	91.6	89.9	46.0	46.8	86.6	87.5	99.9	99.0	92.6	89.8	92.6	92.3
SBP (mmHg)	126.6	126.3	129.8	130.1	130.2	131.9	129.3	130.4	NK	NK	129.9	130.5	NK	NK	127.4	130.0	128.3	129.5
DBP (mmHg)	79.2	78.6	78.1	78.5	78.5	78.6	77.5	78.3	NK	NK	NK	NK	NK	NK	77.8	77.6	NK	NK
FPG (mmol/L)	9.2	9.1	10.0	10.0	9.4	9.4	9.4	9.3	8.7	8.8	8.8	9.0	9.2	9.4	11.5	10.7	9.8	10.1
Race (%)																		
Asian	NK	NK	9.8	7.8	21.6	19.8	14.8	16.7	5.8	11.5	16.7	18.7	100.0	100.0	0	0	11.7	10.4
Black or African American	NK	NK	5.9	6.5	2.0	1.9	9.1	10.9	2.6	4.8	5.7	4.0	0	0	4.1	4.6	4.5	3.5
White	NK	NK	82.4	84.4	70.6	74.1	68.9	64.8	87.0	78.6	72.8	73.0	0	0	92.8	89.2	78.1	80.8
Others*	NK	NK	2.0	1.3	5.9	4.2	7.2	7.5	4.5	5.1	4.8	4.2	0	0	3.1	6.2	5.6	5.3

*MET, metformin; DE, diet and exercise; SIT, sitagliptin; AHA, antihyperglycaemic agent; PLA, placebo; ERT, ertugliflozin; GLI, glimepiride; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; NK, not known. * Others includes American Indian or Alaska Native, multiple, and Native Hawaiian or other Pacific Islander.*

Qualität der Studien:

- Seven trials used an interactive voice response system/integrated web response system when allocating concealment; two trials that did not report a similar system were evaluated as unclear. One trial that did not report the personnel assessing the outcomes was unclear. According to the bias tool item, nine trials were assessed to have a low risk of bias

Studienergebnisse:

Overall Efficacy Outcomes

- We evaluated the effects of ertugliflozin on glycaemic variables, body weight, and blood pressure, as shown in Figure 2. Meta-analysis results revealed that ertugliflozin significantly decreased HbA1c levels (%) (WMD −0.452%; 95% CI −0.774 to −0.129; I2 =96.2%), HbA1c (mmol/mol) (WMD −7.722 mmol/mol; 95% CI −14.691 to −0.753; I2 =98.3%), FPG (WMD −0.870 mmol/L; 95% CI −1.418 to −0.322; I2 =96.6%), consequently increasing the rate of patients achieving target HbA1c (< 7%) (RR: 1.152; 95% CI: 1.073–1.951; I2 =80.7%), compared with other hypoglycaemic agents or placebo. For body weight and blood pressure, the reduction in body weight from baseline was more considerable in ertugliflozin than non-ertugliflozin (WMD −1.774 kg; 95% CI −2.601 to −0.946; I2 =97.6%). A greater reduction in blood pressure levels was also observed in patients receiving ertugliflozin compared with other treatments (SBP: WMD −2.572 mmHg; 95% CI −3.573 to −1.571; I2 = 93.8% and DBP: WMD −1.152 mmHg; 95% CI −2.002 to −0.303; I2 = 85.5%).

Safety Outcomes

- The analysis assessed the tolerability of type 2 diabetes patients, as presented in Figure 2. The incidence of any AEs was 63.58% (2517/3959) in ertugliflozin group and 65.73% (1097/1669) in non-ertugliflozin group (Supplementary Table S5), indicating a similar risk between the two therapies (RR: 0.983; 95% CI 0.944–1.023; I2 = 0%). […]
- Also, no significant differences between ertugliflozin group and control group were observed in terms of serious AEs (RR: 1.132; 95% CI 0.909–1.409; I2 = 0%), death (RR: 1.174; 95% CI 0.054–2.739; I2 = 0%), and AEs leading to discontinuation (RR: 1.140; 95% CI 0.858–1.515; I2 = 0%). There were no notable differences between groups in the incidence of AEs related to study drug (1.158; 95% CI 0.963–1.391; I2 = 45.4%), although the incidence was higher when using ertugliflozin (19.22%) compared with other therapies (17.14%).
- Regarding GMI, ertugliflozin use increased the 3-fold risk compared with other medications (RR: 4.004; 95% CI 2.504–6.402; I2 = 13.7%), with a higher incidence in ertugliflozin group (6.59%) versus in control group (1.44%). However, when the follow-up was less than 26 weeks, no correlation of higher GMI risk was observed with ertugliflozin treatment (RR: 1.977; 95% CI 0.756–5.165; I2 = 0%).
- AEs related to symptomatic hypoglycaemia were more common in non-ertugliflozin group (10.84%) than in ertugliflozin group (5.35%). However, there was no evidence that ertugliflozin use had a lower risk of symptomatic hypoglycaemia than other therapies (RR: 0.781; 95% CI 0.418–1.459; I2 = 83.7%).
- In the subgroup analysis by follow-up, a higher risk of symptomatic hypoglycaemia in ertugliflozin group was found in less than 26 weeks compared with in non-ertugliflozin group (RR: 3.896; 95% CI 1.058–14.337; I2 = 0%). We failed to find a higher risk of UTI in ertugliflozin treatment group compared with the control (RR: 0.906; 95% CI 0.737–1.113; I2 = 0%), with a lower incidence (6.92% in ertugliflozin group, 7.67% in control group, respectively). Also, there was no meaningful difference between the two groups in hypovolemia (RR: 1.296; 95% CI 0.577–2.910; I2 = 35.6%), with a comparable incidence (1.66% in ertugliflozin group, 1.18% in control group). Further, the results were similar in fixed-effect model sensitive analysis

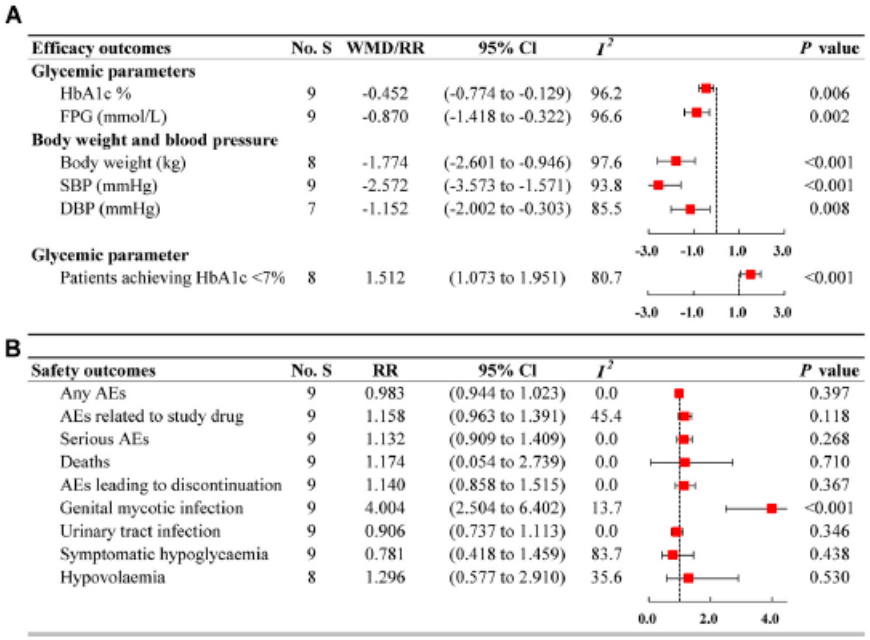


FIGURE 2 | Forest plots of ertugliflozin on efficacy **(A)** and safety **(B)** outcomes. No. S, numbers of studies; WMD, weighted mean difference; CI, confidence interval; I2, heterogeneity; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, risk ratio; AEs, adverse events.

Anmerkung/Fazit der Autoren

Our meta-analysis illustrated that ertugliflozin performed well in glycaemic control, weight loss, and blood pressure reduction. Ertugliflozin was relatively effective and tolerated in patients with type 2 diabetes, except for a high GMI risk. Given that, ertugliflozin may be a good alternative to other SGLT2 inhibitors. Further studies with head-to-head comparisons among SGLT2 inhibitors are needed to explore whether ertugliflozin would present a better profile of glycaemic control and safety outcomes.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Zhang F et al. 2022 [72].
- Cheng Q et al. 2023 [9].

Katsiki N et al., 2020 [25].

Fixed-dose combination of empagliflozin and linagliptin for the treatment of patients with type 2 diabetes mellitus: a systematic review and meta-analysis

Fragestellung

The present meta-analysis evaluated the efficacy and safety of empagliflozin + linagliptin combination compared with either monotherapy.

Methodik

Population:

- patients with T2DM aged ≥18 years

Intervention:

empagliflozin + linagliptin

Komparator:

- Either drug alone (empagliflozin or linagliptin)

Endpunkte:

- change in FPG, HBA1c, weight, BMI, SBP and DBP

Recherche/Suchzeitraum:

- Medline, Embase, CINAHL, PsycINFO and Cochrane CENTRAL,
- until October 20, 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool for randomized trials

Ergebnisse

Anzahl eingeschlossener Studien:

- six RCTs (n = 2857 patients)

Charakteristika der Population:

- The studies altogether enrolled 2,857 patients with T2DM aged ≥18 years on diet + exercise ± metformin.
- Across all studies, the mean age of the patients ranged from 54.6 to 59.9 years, 39.7% of the participants were women and 47.6% had been diagnosed over 5 years prior to their enrolment in the RCTs. Empagliflozin + linagliptin combination was administered as a fixed-dose regimen (in 2 trials) or free combination (in 4 trials).

Qualität der Studien:

Supplementary Table 2. Quality of bias assessment of the included studies according to the Cochrane guidelines.

First Author, Year of Publication	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Other Bias
Søfteland 2017	L	L	L	H	L	H	L
Kawamori 2017	L	L	L	L	L	L	L
Kaku 2019	L	H	L	L	L	L	L
Tinahones 2017	L	L	L	L	L	L	H
Lewin 2015	L	L	L	L	L	H	L
DeFronzo 2015	L	L	L	L	L	L	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

Studienergebnisse:

- Significantly higher reductions in HbA1c, body weight and fasting plasma glucose (FPG) were observed with the combination therapy (either empagliflozin 10 mg + linagliptin 5 mg or empagliflozin 25 mg + linagliptin 5 mg) compared with linagliptin 5 mg over 24 weeks.
- Furthermore, HbA1c and FPG were significantly more decreased with the combination (either empagliflozin 10 mg + linagliptin 5 mg or empagliflozin 25 mg + linagliptin 5 mg) compared with empagliflozin (10 or 25 mg) monotherapy; body weight was lowered equally.
- Patients with T2DM on combination therapy had a significantly greater likelihood of attaining HbA1c <7% over 24 weeks than those on monotherapies.
- In relation to blood pressure (BP), with empagliflozin 10 mg + linagliptin 5 mg systolic BP was lower than with linagliptin 5 mg, but the difference fell just short of statistical significance (P = 0.084, Table 1), probably because of the rather large heterogeneity (I2 = 61%).
- Furthermore, no differences were found in adverse events between the combination and monotherapy groups. The findings were robust to leave-one-out sensitivity analyses.

TABLE 1 Pooled results comparing empagliflozin + linagliptin fixed dose combination with linagliptin or empagliflozin monotherapies over 24 weeks

Outcomes	Summary of studies	Empagliflozin 10 mg + linagliptin 5 mg vs. linagliptin 5 mg	Empagliflozin 25 mg + linagliptin 5 mg vs. linagliptin 5 mg	Empagliflozin 10 mg + linagliptin 5 mg vs. empagliflozin 10 mg	Empagliflozin 25 mg + linagliptin 5 mg vs. empagliflozin 25 mg
HbA1c (%)	No. of studies pooled	4	3	4	3
	Sample size	561/462	378/371	500/505	379/380
	WMD (95% CI)	[−0.72 (−1.04, −0.40), $P < 0.001$; $I^2 = 90.0\%$]	[−0.52 (−0.68, −0.37), $P < 0.001$; $I^2 = 43.0\%$]	[−0.50 (−0.73, −0.26), $P < 0.001$; $I^2 = 85.4\%$]	[−0.40 (−0.66, −0.14), $P < 0.001$; $I^2 = 82.2\%$]
Percentage of patients with HbA1c ≥7% at baseline who achieve HbA1c <7%	No. of studies pooled	4	3	4	3
	Sample size	561/462	378/371	500/505	379/380
	OR (95% CI)	[3.89 (2.79, 5.41), $P < 0.001$; $I^2 = 0.0\%$]	[3.20 (2.25, 4.55), $P < 0.001$; $I^2 = 0.0\%$]	[3.70 (2.58, 5.32), $P < 0.001$; $I^2 = 0.0\%$]	[3.18 (1.81, 5.59), $P < 0.001$: $I^2 = 58.9\%$]
Weight (kg)	No. of studies pooled	4	3	3	3
	Sample size	561/462	378/371	393/397	379/380
	WMD (95% CI)	[−2.08 (−2.62, −1.53), $P < 0.001$; $I^2 = 55.7\%$]	[−1.96 (−2.59, −1.33), $P < 0.001$ $I^2 = 37.4\%$]	[0.07 (−0.57, 0.71), $P = 0.826$; $I^2 = 43.1\%$]	[0.00 (−0.47, 0.48), $I^2 = 43.1\%$]
Fasting plasma glucose (mmol/L)	No. of studies pooled	4	3	4	3
	Sample size	561/462	378/371	500/505	379/380
	WMD (95% CI)	[−1.60 (−2.21, −1.00), $P < 0.001$; $I^2 = 88.1\%$]	[−1.52 (−2.02, −1.02), $P < 0.001$; $I^2 = 74.7\%$]	[−0.60 (−0.78, −0.41), $P < 0.001$; $I^2 = 0.0\%$]	[−0.54 (−0.93, −0.15), $P < 0.001$; $I^2 = 61.5\%$]
Systolic blood pressure (mmHg)	No. of studies pooled	2	—[a]	2	—[a]
	Sample size	291/201		229/231	
	WMD (95% CI)	[−3.02 (−6.45, 0.41), $P = 0.084$; $I^2 = 61.0\%$]		[−1.24 (−3.26, 0.78), $P = 0.230$; $I^2 = 0.0\%$]	
Diastolic blood pressure (mmHg)	No. of studies pooled	2	—[a]	2	—[a]
	Sample size	291/201		229/231	
	WMD (95% CI)	[−0.67 (−2.04, 0.69), $P = 0.333$; $I^2 = 0.0\%$]		[−1.30 (−2.60, 0.00), $P = 0.051$, $I^2 = 0.0\%$]	
All adverse events (%)	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[0.93 (0.84, 1.03), $P = 0.163$; $I^2 = 24.5\%$]	[0.96 (0.80, 1.14), $P = 0.610$; $I^2 = 70.2\%$]	[0.91 (0.84, 1.00), $P = 0.038$; $I^2 = 0.0$]	[1.02 (0.92, 1.13), $P = 0.779$; $I^2 = 14.2\%$]
Drug-related adverse events (%)	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.48 (0.79, 2.77), $P = 0.223$; $I^2 = 57.2\%$]	[1.41 (0.96, 2.08), $P = 0.083$; $I^2 = 0.0\%$]	[0.95 (0.69, 1.30), $P = 0.732$; $I^2 = 0.0\%$]	[1.01 (0.67, 1.50), $P = 0.980$; $I^2 = 27.9\%$]
Adverse events leading to discontinuation (%)	No. of studies pooled	4	3	1.034	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.28 (0.47, 3.46), $P = 0.632$; $I^2 = 16.0\%$]	[1.15 (0.22, 5.94), $P = 0.864$; $I^2 = 52.9\%$]	[0.69 (0.30, 1.55), $P = 0.362$; $I^2 = 29.7\%$]	[1.26 (0.59, 2.69), $P = 0.554$; $I^2 = 0.0\%$]

Confirmed hypoglycaemia (%)	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[0.55 (0.17, 1.83), $P = 0.331$ $I^2 = 0.0\%$]	[1.54 (0.50, 4.70), $P = 0.452$; $I^2 = 0.0\%$]	[0.83 (0.22, 3.12), $P = 0.629$; $I^2 = 0.0\%$]	[0.71 (0.25, 2.06), $P = 0.530$; $I^2 = 0.0\%$]
Urinary tract infections	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.04 (0.69, 3.47), $P = 0.866$; $I^2 = 0.0\%$]	[0.87 (0.53, 1.43), $P = 0.584$; $I^2 = 3.8\%$]	[0.96 (0.66, 1.40), $P = 0.841$; $I^2 = 0.0\%$]	[1.11 (0.72, 1.71), $I^2 = 13.6\%$]
Genital infections	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.53 (0.68, 1.56), $P = 0.306$; $I^2 = 0.0\%$]	[1.73 (0.77, 3.92), $P = 0.186$; $I^2 = 0.0\%$]	[0.74 (0.40, 1.38), $P = 0.342$; $I^2 = 0.0\%$]	[0.51 (0.18, 1.48), $P = 0.216$; $I^2 = 58.2\%$]

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; OR, odds ratio; RR, risk ratio; WMD, weighted mean difference.
[a]No pooled data (<2 studies with available data).

Anmerkung/Fazit der Autoren

The present meta-analysis demonstrated superior efficacy and similar safety of empagliflozin (10 or 25 mg) + linagliptin 5 mg compared with empagliflozin (10 or 25 mg) or linagliptin 5 mg monotherapies in patients with T2DM inadequately controlled with diet + exercise ± metformin, facilitating the achievement of their glycaemic control. The available FDCs of these drugs (i.e. empagliflozin 10 mg + linagliptin 5 mg, empagliflozin 25 mg + linagliptin 5 mg) can simplify drug dosing regimen, decrease pill burden and enhance treatment adherence, which might represent an important therapeutic option in routine clinical practice.

Mantsiou C et al., 2020 [44].

Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors as combination therapy for type 2 diabetes: a systematic review and meta-analysis

Fragestellung

To evaluate the efficacy and safety of combination therapy with a GLP-1RA and an SGLT2i in patients with type 2 diabetes

Methodik

Population:

- adults with type 2 diabetes

Intervention:

- combination of a GLP-1RA and an SGLT2i (GLP-1RA/SGLT2i)

Komparator:

- placebo or an active control (including individual GLP-1RAs or SGLT2is)

Endpunkte:

- HbA1c, body weight, systolic blood pressure, diastolic blood pressure and estimated glomerular filtration rate (eGFR)
- all-cause mortality and cardiovascular mortality, and the numbers of patients who experienced at least one event of severe hypoglycaemia (as defined in each study), myocardial infarction, stroke and hospitalization for heart failure.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and the Cochrane library up to 2 December 2019

Qualitätsbewertung der Studien:

- revised Cochrane Collaboration's Risk of Bias Tool version 2.0 for change in HbA1c, body weight and systolic blood pressure
- GRADE) approach to rate the certainty of evidence in effect estimates for the three aforementioned outcomes

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 trials

Charakteristika der Studien/Population:

Comparisions

- 3 studies evaluated the combination of GLP-1RA/SGLT2i as simultaneous initiation therapy versus isolated GLP-1RA and SGLT2i.
- 3 studies compared a GLP-1RA with placebo as add-on therapy in patients already treated with an SGLT2i,
- 1 study was a post hoc subgroup analysis of the CANVAS (CANagliflozin cardioVascular Assessment Study) trial programme comparing an SGLT2i with placebo as add-on therapy in patients already treated with a GLP-1RA.

Population

- In all RCTs, patients continued receiving their background antidiabetic treatment, which was mostly metformin or metformin plus a sulphonylurea.
- Across the included trials, mean baseline HbA1c ranged from 8.0% to 8.2% in all studies, except for the DURATION-8 trial, in which mean HbA1c at baseline was 9.3%.
- Mean body weight, body mass index and systolic blood pressure at baseline ranged from 90.9 to 91.7 kg, 31.9 to 37.4 kg/m2 and 127.9 to 136.7 mmHg, respectively.
- Across all trials, mean participant's age ranged from 52.3 to 61.0 years

Qualität der Studien:

Overall risk of bias for change in HbA1c was deemed to be of some concern in three studies and low in four studies. .

GRADE Assessment:

Supplementary table S3. Summary of GRADE assessment.

Outcome	Comparator	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall
HbA_{1c}	GLP-1 RA	serious	very serious	serious	not serious	undetected	very low
	SGTL2i	serious	very serious	serious	not serious	undetected	very low
Body weight	GLP-1 RA	serious	serious	serious	not serious	undetected	very low
	SGLT2i	serious	very serious	serious	not serious	undetected	very low
Systolic blood pressure	GLP-1 RA	serious	serious	serious	not serious	undetected	very low
	SGLT2i	serious	very serious	serious	not serious	undetected	very low

Abbreviations: GLP-1 RA, glucagon-like peptide 1 receptor agonist; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HbA_{1c}, glycated hemoglobin; SGLT2i, sodium glucose co-transporter 2 inhibitor.

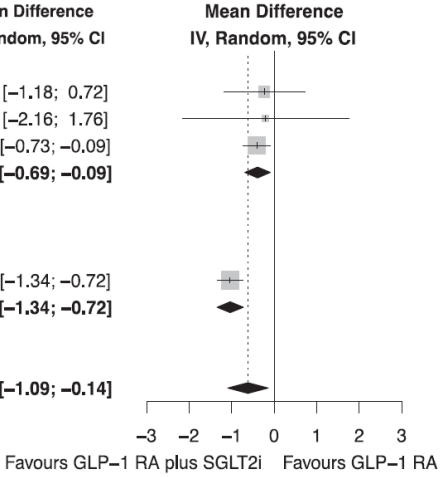
Studienergebnisse:

Change from baseline in HbA1c (%)

GLP-1RA/SGLT2i vs GLP-1RA:

(A)

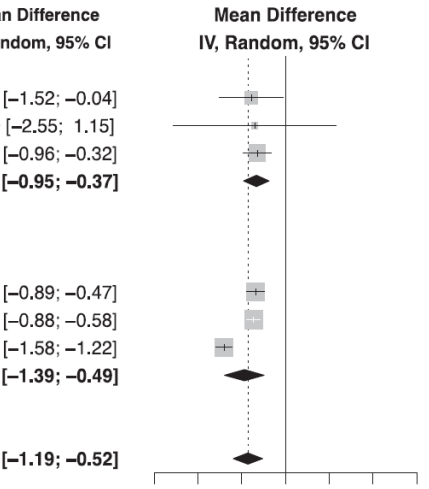
Study or Subgroup	GLP–1 RA plus SGLT2i Mean	SD	Total	GLP–1 RA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP–1 RA plus SGLT2i								
Ali 2020[36]	–1.67	1.12	15	–1.44	1.51	15	16.3%	–0.23 [–1.18; 0.72]
Ikonomidis 2018[28]	–1.50	3.58	20	–1.30	2.68	20	5.2%	–0.20 [–2.16; 1.76]
Jabbour 2018[21]	–1.70	1.66	228	–1.29	1.81	227	39.0%	–0.41 [–0.73; –0.09]
Total (95% CI)			**263**			**262**	**60.5%**	**–0.39 [–0.69; –0.09]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.16$, df = 2 ($P = 0.92$); $I^2 = 0\%$								
Sequential addition of SGLT2i to GLP–1 RA								
Fulcher 2016[24]	–0.86	0.71	65	0.17	0.71	30	39.5%	–1.03 [–1.34; –0.72]
Total (95% CI)			**65**			**30**	**39.5%**	**–1.03 [–1.34; –0.72]**
Heterogeneity: not applicable								
Total (95% CI)			**328**			**292**	**100.0%**	**–0.61 [–1.09; –0.14]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.79$, df = 3 ($P = 0.03$); $I^2 = 66\%$								



GLP-1RA/SGLT2i vs SGLT2i.:

(B)

Study or Subgroup	GLP–1 RA plus SGLT2i Mean	SD	Total	SGLT2i Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP–1 RA plus SGLT2i								
Ali 2020[36]	–1.67	1.12	15	–0.89	0.93	15	11.0%	–0.78 [–1.52; –0.04]
Ikonomidis 2018[28]	–1.50	3.58	20	–0.80	2.24	20	2.9%	–0.70 [–2.55; 1.15]
Jabbour 2018[21]	–1.70	1.66	228	–1.06	1.82	230	19.5%	–0.64 [–0.96; –0.32]
Total (95% CI)			**263**			**265**	**33.4%**	**–0.66 [–0.95; –0.37]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.12$, df = 2 ($P = 0.94$); $I^2 = 0\%$								
Sequential addition of GLP–1 RA to SGLT2i								
Blonde 2020[33]	–1.00	0.86	195	–0.32	0.83	95	21.8%	–0.68 [–0.89; –0.47]
Ludvik 2018[34]	–1.27	0.74	266	–0.54	0.74	133	22.6%	–0.73 [–0.88; –0.58]
Zinman 2019[35]	–1.50	0.74	151	–0.10	0.86	151	22.2%	–1.40 [–1.58; –1.22]
Total (95% CI)			**612**			**379**	**66.6%**	**–0.94 [–1.39; –0.49]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 38.05$, df = 2 ($P < 0.01$); $I^2 = 95\%$								
Total (95% CI)			**875**			**644**	**100.0%**	**–0.85 [–1.19; –0.52]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 41.09$, df = 5 ($P < 0.01$); $I^2 = 88\%$								



Severe hypoglycaemia

- Combination treatment with GLP-1RA /SGLT2i did not increase the incidence of severe hypoglycaemia compared with
  - GLP-1RA (OR = 1.38, 95% CI 0.14 to 13.14, I2 = 0%, three studies) or
  - SGLT2i (OR = 2.39, 95% CI 0.47 to 12.27, I2 = 0%, five studies)

Mortality and cardiovascular outcomes

Supplementary table S5. Effect of GLP-1 RA plus SGLT2i on incidence of all-cause mortality, cardiovascular mortality, myocardial infarction and stroke compared to GLP-1 RA and SGLT2i.

Outcome	Comparator	Studies contributing data, n	Participants analyzed, n		Participants with outcome, n		Overall effect estimate, OR (95% CI)	I^2, %
			GLP-1 RA plus SGLT2i	Comparator	GLP-1 RA plus SGLT2i	Comparator		
Incidence of all-cause mortality	GLP-1 RA	3	311	275	3	1	1.98 (0.33; 11.85)	0
	SGLT2i	5	881	639	5	2	1.51 (0.40; 5.68)	0
Incidence of cardiovascular mortality	GLP-1 RA	3	311	275	1	1	1.00 (0.13; 7.42)	0
	SGLT2i	5	881	639	1	1	1.00 (0.19; 5.16)	0
Incidence of myocardial infarction	GLP-1 RA	2	246	245	0	3	0.28 (0.03; 3.06)	0
	SGLT2i	4	679	539	0	4	0.31 (0.06; 1.58)	0
Incidence of stroke	GLP-1 RA	2	246	245	1	1	1.00 (0.10; 9.73)	0
	SGLT2i	4	679	539	2	2	0.97 (0.20; 4.82)	0

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide 1 receptor agonist; OR, odds ratio; SGLT2i, sodium glucose co-transporter 2 inhibitor.

Anmerkung/Fazit der Autoren

In conclusion, based on data from a limited number of RCTs, combination therapy with a GLP-1RA and an SGLT2i seems to reduce HbA1c and systolic blood pressure without increasing the risk of severe hypoglycaemia compared with either GLP-1RA or SGLT2i alone. Combination therapy with GLP-1RA/SGLT2i can also reduce body weight compared with either GLP-1RA or SGLT2i in the short term, while long-term data from one trial suggest that combination therapy was similar to SGLT2i in terms of body weight reduction. Currently, the available research evidence does not allow for a valid assessment of the long-term effectiveness, effect on cardiovascular outcomes or differences between types of GLP-1RA/SGLT2i combinations.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung (Vergleich von GLP-1RA/SGLT2i vs SGLT2i) mit derselben Schlussfolgerung vor:

- Li C et al. 2022 [28]

Zhang X et al., 2020 [74].

Long-term renal outcomes associated with sodium glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a systematic review and meta-analysis.

Fragestellung

to investigate the renal outcomes associated with SGLT2 inhibitors in patients with type 2 diabetes (T2DM) in the long term.

Methodik

Population:

- Adult patients with T2DM

Intervention/Komparator:

- SGLT2 inhibitors with placebo or other kinds of anti-diabetic treatments

Endpunkte:

- Renal outcomes

Recherche/Suchzeitraum:

- PubMed and ClinicalTrials.gov up to August 2, 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 39 studies involving 35 trials. The total number of participants was 60 656, ranging from 180 to 17 160 across different trials

Charakteristika der Population:

- The mean age of patients in all trials included was over 50 years old. Large proportion of participants was obese according to the relatively high BMI (>28 kg/m2) in most studies. All patients were previously diagnosed with T2DM and most patients received background anti-diabetic medications except for the intervention therapies. Four trials included patients with impaired renal function

Qualität der Studien:

- Most trials were rated at low risk of bias for all items assessed. All trials were RCTs, but the process of random sequence generation, allocation concealment, and blinding were not clearly described in several trials. The interventions were slightly adjusted in the early phase in one trial.

Studienergebnisse:

- Compared with placebo or other anti-diabetic medications, SGLT2 inhibitors were associated with significant lower incidence of composite renal outcome and acute renal failure or injury in patients with T2DM.
- The risk of progression of albuminuria also appeared to be decreased.
- No significant changes of estimated glomerular filtration rate levels or urine albumin-creatinine ratios were found in patients receiving SGLT2 inhibitors.

Anmerkung/Fazit der Autoren

In conclusion, this meta-analysis indicated overall renal safety and beneficial effects of SGLT2 inhibitors in patients with T2DM in the long term. Future trials and real-world studies are warranted to further clarify the renal effects of SGLT2 inhibitors, both in the general population with T2DM and in patients with T2DM and CKD.

Dehghani, M. et al., 2024 [11].

Efficacy and safety of basal insulins in people with type 2 diabetes mellitus: a systematic review and network meta-analysis of randomized clinical trials.

Fragestellung

determining the benefits (efficacy) and risks (safety) of basal insulins in T2D and determining the best treatment alternative (preferred or with a high priority to choose) among basal insulins in terms of glycemic control, weight gain, and hypoglycemic events.

Methodik

Population:

- adults with T2D

Intervention/Komparator:

- basal insulins (long and ultra-long-acting insulins) with each other

Endpunkte:

- glycemic control, weight gain, and hypoglycemia

Recherche/Suchzeitraum:

- MEDLINE, Embase, Cochrane Library, ISI, and Scopus, was performed through November 2023,

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool (ROB-2) / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 44 RCTs (23,699 participants)

Charakteristika der Population/Studien:

- The included trials were published between 2000 and 2021. Most trials were multicenter and multinational from most to all continents and with relatively large sample sizes. Only five studies had a total sample size of smaller than 100 participants, i.e., less than 50 patients in each group (31, 45, 61, 70, 71), and about 80% oftrials had included more than 100 patients in each study arm (Supplementary Table 1). Three studies were conducted as a crossover clinical trial design (39, 42, 61), and the rest were parallel clinical trials.
- Both men and women were included in all studies. The mean age of patients with T2D was 58.7 years (range 54 to 66 years). The mean treatment period (follow-up period) was 38 weeks, and the mean duration of T2D was 10.8 (range 6.8 to 16) years. The mean HbA1c level and body mass index (BMI) at baseline were 8.5% (range 7.1% to 9.5%) and 30.2 (range 24.6 to 36.6), respectively. Moreover, the qualitative synthesis revealed a diverse range of pretreatment backgrounds among patients initiating basal insulins in included studies, with 27 RCTs specifically comparing efficacy and/or safety in insulin-naive patients (solely using oral antidiabetic therapy), six assessing those already using basal insulin, three examining a population comprised of both insulin-naive individuals

and those already using basal insulins, and eight RCTs focusing on patients utilizing a basal-bolus regimen before the commencement of the trial.

Qualität der Studien:

- 44 randomized clinical trials were assessed for methodological quality. Based on the assessment, two RCTs (4.5% of studies) were at high risk of bias, nine RCTs (19.5% of studies) posed some concerns at risk of bias, and 35 RCTs (76% of the studies) were placed in the low risk of bias category. More than two-thirds of the studies had a low risk of bias because of their standard design, conduct, analysis, and reporting. Most of the studies suffered from two domains: deviations from intended interventions and the measurement of the outcome. Deviation from the intervention was almost balanced among the groups in most of the studies, and the outcome assessors were aware of the type of insulin received by the patients in some studies.

Studienergebnisse:

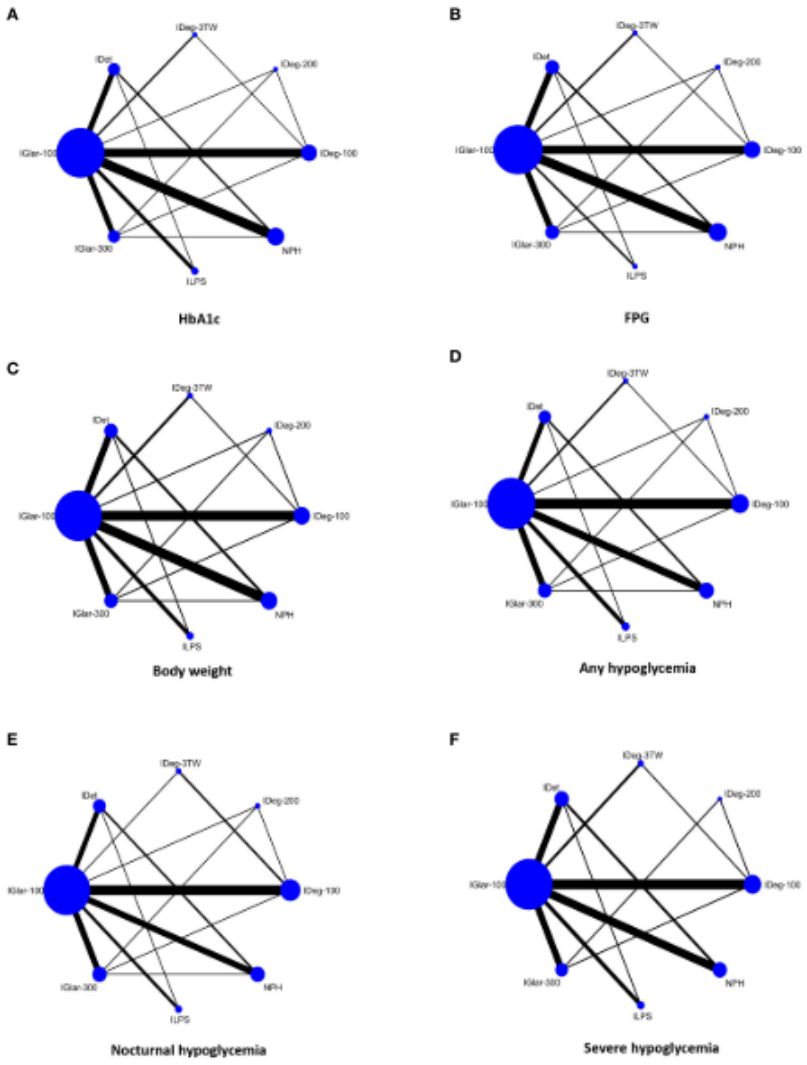


FIGURE 2
Network plots comparing basal insulins for change in HbA1c level **(A)**, FPG **(B)**, body weight **(C)**, overall/any hypoglycemia **(D)**, nocturnal hypoglycemia **(E)**, and severe hypoglycemia **(F)** in people with T2DM. Each node (circle) represents a basal insulin regimen, and its size is proportional to the number of participants randomly assigned to each treatment. The width of the line joining two nodes is proportional to the number of trials that directly compare the two respective treatments. Glargine, 100 U/mL (IGlar-100); Glargine, 300 U/mL (IGlar-300); Determir (IDet); Degludec, 100 U/mL (IDeg-100); Degludec, 200 U/mL (IDeg-200); Thrice-weekly degludec (IDeg-3TW).

- no significant difference among various basal insulins (including Neutral Protamine Hagedorn (NPH), ILPS, insulin glargine, detemir, and degludec) in reducing HbA1c.
- Insulin glargine, 300 U/mL (IGlar-300) was significantly associated with less weight gain (mean difference ranged from 2.9 kg to 4.1 kg) compared to other basal insulins, namely thrice-weekly insulin degludec (IDeg-3TW), insulin degludec, 100 U/mL (IDeg-100), insulin degludec, 200 U/mL (IDeg-200), NPH, and insulin detemir (IDet), but with low to very low certainty regarding most comparisons.
- IDeg-100, IDeg-200, IDet, and IGlar-300 were associated with significantly lower odds of overall, nocturnal, and severe hypoglycemic events than NPH and insulin lispro protamine (ILPS) (moderate to high certainty evidence).
- NPH was associated with the highest odds of overall and nocturnal hypoglycemia compared to others.
- Network meta-analysis models were robust, and findings were consistent in sensitivity analyses.

Fazit der Autoren

Findings of the combination of direct and indirect evidence with acceptable quality indicate that basal insulin regimens are comparable in glycemic control in people with T2D. Insulin glargine, 300 U/mL, may be associated with a slightly less severe weight gain than other basal insulins. Insulin degludec 100 U/mL, degludec 200 U/mL, detemir, and glargine 300 U/mL are preferred options when hypoglycemia is the primary concern.

Liu, Y. et al., 2024 [34].

IDegLira for type 2 diabetes: a systematic review and meta-analysis.

Fragestellung

to evaluate the efficacy and safety of IDegLira for T2D.

Methodik

Population:

- DM Typ 2 patients

Intervention:

- IDegLira

Komparator:

- placebo or conventional treatment like degludec, liraglutide

Endpunkte:

- HbA1c, change in body weight, percentage of patients achieving HbA1c < 7%, percentage of patients achieving HbA1c < 6.5%, HbA1c < 7.0% without weight gain and without severe or blood glucose (BG)-confirmed hypoglycaemia episodes, HbA1c < 6.5% without weight gain and without severe or BG-confirmed hypoglycaemia episodes, change in fasting plasma glucose (FPG), change in self-measured plasma glucose (SMPG), change in systolic pressure, change in diastolic pressure, total daily insulin dose, severe or BG confirmed symptomatic hypoglycaemia, nocturnal severe or BG-confirmed symptomatic hypoglycaemia, adverse events (AEs) and serious adverse events (SAEs)

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Library and ClinicalTrials.gov were searched from inception to August 15, 2023

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 eligible trials, enroling 7773 patients

Charakteristika der Population/Studien:

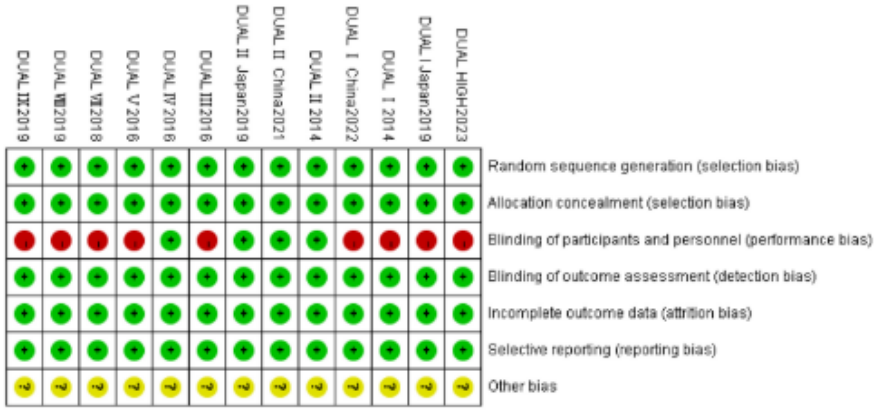
Table 1 Characteristics of the included studies and patients

Trial name	Country	Study arms	Patients	Age (years)	Male, *n* (%)	Body weight (kg)	Body-mass index (kg/m^2)	HbA1c (%)	Duration of diabetes (years)	Treatment duration (weeks)
DUAL I China2022	China	IDegLira	361	54.5 ± 10.3	219 (60.7)	74.8 ± 14.3	27.0 ± 3.9	8.20 ± 0.83	8.00 ± 5.33	26
		Degludec	179	55.7 ± 10.2	100 (55.9)	73.2 ± 13.2	26.5 ± 3.6	8.31 ± 0.84	8.63 ± 5.55	
		Liraglutide	180	54.1 ± 10.2	108 (60.0)	73.8 ± 13.3	26.5 ± 3.6	8.21 ± 0.77	8.05 ± 5.28	
DUAL I Japan2019	Japan	IDegLira	275	56.9 ± 10.2	194 (70.5)	70.7 ± 12.4	26.1 ± 3.7	8.5 ± 1.1	9.2 ± 6.2	52
		Degludec	271	57.8 ± 9.9	195 (72.0)	72.6 ± 14.5	26.6 ± 4.8	8.5 ± 1.1	9.7 ± 6.0	
		Liraglutide	273	56.8 ± 10.1	192 (70.3)	72.2 ± 15.0	26.5 ± 4.5	8.3 ± 1.0	9.4 ± 5.9	
DUAL I2014	UK, USA, Canada, et al.	IDegLira	833	55.1 ± 9.9	435(52.2)	87.2 ± 19.0	31.2 ± 5.2	8.3 ± 0.9	6.6 ± 5.1	26
		Degludec	413	54.9 ± 9.7	200(48.4)	87.4 ± 19.2	31.2 ± 5.3	8.3 ± 1.0	7.0 ± 5.3	
		Liraglutide	414	55.0 ± 10.2	208(50.2)	87.4 ± 18.0	31.3 ± 4.8	8.3 ± 0.9	7.2 ± 6.1	
DUAL II China2021	China	IDegLira	302	54.5 ± 9.8	183 (60.6)	76.8 ± 13.0	27.5 ± 3.3	8.93 ± 1.20	11.52 ± 5.9	26
		Degludec	151	55.3 ± 10.0	91 (60.3)	74.3 ± 11.4	27.0 ± 2.9	8.96 ± 1.17	11.33 ± 6.3	
DUAL II Japan2019	Japan	IDegLira	105	56.6 ± 10.4	70(66.7)	73.9 ± 11.9	27.3 ± 3.1	8.61 ± 0.88	14.33 ± 7.79	26
		Degludec	105	55.5 ± 10.0	63(60)	75.5 ± 14.0	28.1 ± 4.4	8.56 ± 0.80	13.77 ± 7.46	
DUAL II2014	Denmark, Bulgaria, Switzerland, et al.	IDegLira	199	57 ± 9	111(56)	95.4 ± 19	33.6 ± 6	8.7 ± 0.7	10 ± 6	26
		Degludec	199	58 ± 11	105(53)	93.5 ± 20	33.8 ± 6	8.8 ± 0.7	11 ± 7	
DUAL III2016	Australia, France, Hungary, et al.	IDegLira	292	58.3 ± 9.9	153(52.4)	95.6 ± 16.6	32.9 ± 4.4	7.8 ± 0.6	10.4 ± 5.8	26
		Liraglutide or exenatide	146	58.4 ± 8.8	71(48.6)	95.5 ± 17.3	33.0 ± 4.1	7.7 ± 0.6	10.4 ± 5.8	
DUAL IV2016	Bulgaria, Canada, Germany, et al.	IDegLira	289	60.0 ± 9.6	154(53.3)	87.2 ± 18.6	31.2 ± 4.8	7.9 ± 0.6	9.0 ± 5.5	26
		Placebo	146	59.4 ± 10.8	73(50.0)	89.3 ± 17.5	32.0 ± 4.5	7.9 ± 0.6	9.3 ± 6.5	
DUAL V2016	Argentina, Australia, Greece, et al.	IDegLira	278	58.4 ± 9.8	143(51.4)	88.3 ± 17.5	31.7 ± 4.4	8.4 ± 0.9	11.64 ± 7.44	26
		Glargine	279	59.1 ± 9.3	137(49.1)	87.3 ± 15.8	31.7 ± 4.5	8.2 ± 0.9	11.33 ± 6.59	
DUAL VII2018	Argentina, Czech republic, France, et al.	IDegLira	252	58.6 ± 9.0	110(43.7)	87.2 ± 16.0	31.7 ± 4.4	8.2 ± 0.8	13.2 ± 7.0	26
		Glargine and Aspart	254	58.0 ± 8.6	117(46.1)	88.2 ± 17.2	31.7 ± 4.5	8.2 ± 0.8	13.3 ± 6.8	
DUAL VIII2019	USA, Mexico, Denmark, et al.	IDegLira	506	56.8 ± 10.0	280(55)	89.7 ± 20.5	32.0 ± 6.2	8.4 ± 1.0	10.0 ± 6.2	104
		Glargine	506	56.4 ± 10.1	275(54)	89.0 ± 20.1	31.9 ± 5.8	8.6 ± 1.0	10.2 ± 6.1	
DUAL IX2019	Spain, India, Denmark, et al.	IDegLira	210	56.1 ± 10.4	121 (57.6)	89.3 ± 17.6	31.5 ± 4.8	8.2 ± 0.9	9.8 ± 6.2	26
		Glargine	210	57.2 ± 10.2	126 (60.0)	87.2 ± 17.2	30.9 ± 4.8	8.4 ± 1.1	9.3 ± 6.3	
DUAL HIGH2023	USA	IDegLira	72	54.5 ± 10.1	28 (39)	93.1 ± 20.5	32.4 ± 6.5	10.8 ± 1.4	NA	26
		Basal-bolus insulin	73	53.8 ± 9.7	35 (48)	91.9 ± 19.5	31.5 ± 6.2	10.7 ± 1.3	NA	

Qualität der Studien:

- According to the Cochrane criteria, all studies were parallel group studies with high quality.

Fig. 2 Quality assessment of included studies



Studienergebnisse:

- Compared with the control groups, IDegLira was optimal in change in HbA1c, percentage of patients achieving HbA1c < 7%, percentage of patients achieving HbA1c < 6.5%, HbA1c < 7.0% without weight gain and without severe or blood glucose (BG)-confirmed hypoglycaemia episodes, HbA1c < 6.5% without weight gain and without severe or BG-confirmed hypoglycaemia episodes, change in fasting plasma glucose, change in self-measured plasma glucose, change in systolic pressure, and total daily insulin dose.
- No difference was found between the IDegLira and control groups in terms of change in body weight, change in diastolic pressure, severe or BG-confirmed symptomatic hypoglycaemia, nocturnal severe or BG-confirmed symptomatic hypoglycaemia, adverse events or serious adverse events

Fazit der Autoren

In conclusion, IDegLira treatment can improve glycaemic control whilst balancing out risk for hypoglycaemia and gastrointestinal side effects. It could be considered a reliable treatment option for patients with T2D. Due to the limitations imposed by the data quality of the original studies, more studies are needed for further verification to draw a more accurate conclusion.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Wang, R. et al., 2024 [65]

Gerardo González-González J et al., 2022 [21].

Effect of metformin on microvascular outcomes in patients with type 2 diabetes: a systematic review and meta-analysis

Fragestellung

In order to address this important knowledge gap and establish the impact of metformin therapy on microvascular disease outcomes among adults with type 2 diabetes, we performed a systematic review and meta-analysis of studies that examined surrogate and patient-important microvascular endpoints.

Methodik

Population:

- adults (18 years or older) with T2DM

Intervention:

- any dose of metformin

Komparator:

- another active glucose-lowering treatment or placebo

Endpunkte:

- Kidney-related surrogate outcomes were the urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate(eGFR), and serum creatinine. Kidney-related patient-important outcomes were kidney-related death, adverse events (including elevated blood creatinine, reduction in glomerular filtration rate, and renal impairment), and advanced kidney disease defined as the need for continuous renal replacement therapy or kidney transplant, or chronic kidney disease stage 3 or greater.
- Retinopathy-related surrogate outcomes were onset of retinal neo-vascularization, cataract extraction, events reported as general retinopathy, retinal photocoagulation, and treatment with intravitreal agents. Retinopathy-related patient-important outcomes were diabetes-related blindness, vitreous hemorrhage, retinal detachment, severe macular edema, and retinal artery occlusion.
- Neuropathic surrogate outcomes were changes from baseline in tendon reflex and electrophysiologic parameters. Neuropathic patient-important outcomes were diabetic foot ulcer, diabetic peripheral neuropathy, pain, numbness, sensory loss (touch or vibration), and quality of life related to neuropathy.

Recherche/Suchzeitraum:

- comprehensive search was conducted in MEDLINE, EMBASE, Web of Science, and Scopus to find eligible studies. All databases were searched from inception to May 30, 2020.

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool for randomized trials (RoB2)

Ergebnisse

Anzahl eingeschlossener Studien:

- We included 21 studies published between 1998 and 2019, however, two were post-hoc analyses of the Hyperinsulinaemia

Charakteristika der Population:

- Included patients were 56.2 (SD 3.7) years old with a mean hemoglobin A1c (HbA1c) of 7.8% (SD 0.6). Six of the 19 studies included patients with established cardiovascular disease [29,34–41]. Four studies compared metformin with thiazolidinediones [29,39,42,43], two with insulin [39,41], four with SGLT-2 inhibitors [44–47], three with sulfonylureas [34,41,43], five with Dipeptidyl peptidase-4(DPP-4) inhibitors [38,48–50,52], one with an alpha-glucosidase inhibitor [48], five with placebo [44,49–52], one with a meglitinide [53], and one did not specify the comparator [55]. Twelve studies included patients naïve to glucose-lowering therapy in whom metformin was initiated

as first-line therapy. None of the studies reported microvascular outcomes as their primary outcome.

Qualität der Studien:

- We found an overall moderate risk of bias

Studienergebnisse:

Kidney-related outcomes

- Fifteen studies evaluated at least one kidney-related outcome, most of them surrogate endpoints. Meta-analyses of eGFR, UACR, serum creatinine, and advanced kidney disease were performed(13,33–43).
- In the eGFR meta-analysis, metformin increased the eGFR by mean difference (MD) of 1.08 (95% CI 0.84 to 1.33 ml/min/1.73 mts2; I2 = 0%). However, after excluding studies reporting calculated change scores (47), this relationship lost statistical significance (MD −0.59, 95% CI −3.0 to 1.83 ml/min/1.73 mts2; I2 = 0%). Conversely, no effect was seen on UACR (MD 1.28; 95% CI −0.43 to 2.98 mg/g; I2 = 100%). In a sensitivity analysis excluding studies at high risk of bias), there was no impact of metformin therapy on UACR (MD 1.16; 95% CI −0.57 to 2.89 mg/g; I2 = 100%). Metformin did not have a statistically significant effect on serum creatinine with a MD −1.16 (95% CI −2.43 to 0.10 mmol/l; I2 = 0%) at 6 months follow-up or at longest follow-up with a MD −0.93 (95% CI −2.11 to 0.25 mmol/l; I2 = 3%). Similarly, the incidence of advanced kidney disease (OR 0.79; 95% CI 0.28 to 2.21; I2 = 40%) did not change with metformin therapy.
- Four studies evaluated kidney-related patient-important outcomes including, death from kidney causes, progression of nephropathy, and kidney adverse events [6,45,46,52] with no impact of metformin on these outcomes.

Retinal outcomes

- Only two studies evaluated the effect of metformin on retinal complications [36,57] for which a meta-analysis could not be performed. Results from the UKPDS trial [41] showed a non-significant effect on retinal photocoagulation and vitreous hemorrhage (0.69; 95% CI 0.34 to 1.89 and 0.75; CI 0.07 to 7.82 respectively). There was also no effect on blindness (relative risk reduction (RRR) 1.07; 95% CI 0.38 to 2.99). The HOME trial [35] only reported one event of progression of retinopathy in the metformin group.

Neuropathy outcomes

- Five studies presented neuropathic outcomes, primarily paresthesia or pain in an extremity [37,38,50,52,58]. Variable definitions and scarce information on neuropathic endpoints precluded data synthesis and meta-analysis. Additionally, none of the outcomes showed a statistically significant difference between metformin and the control groups. The only study directly evaluating progression of neuropathic symptoms using a formal scale was the HOME trial [35], where the intervention group used metformin as add-on therapy to insulin, and when compared to placebo showed the same rate of progressive neuropathy

Anmerkung/Fazit der Autoren

In adult patients with T2DM, there is no evidence of clinically significant beneficial effect of metformin therapy as compared to other glucose-lowering medications or placebo on microvascular complications. Importantly, the majority of studies focused on surrogate rather than patient-important outcomes. These results can help patients and clinicians engage in shared decision making about preferred choices for pharmacologic management of T2DM.

Long T et al., 2022 [37].

Comparative efficiency and safety of insulin degludec/aspart with insulin glargine in type 2 diabetes: a metaanalysis of randomized controlled trials

Fragestellung

In this context, the purpose of this randomized controlled trial meta-analysis was to appraise the efficiency and safety of the IDeg/Asp combination compared with basal insulin glargine in T2DM.

Methodik

Population:

- Type 2 diabetes participants (adults with an HbA1c of 7–11%)

Intervention:

- Insulin degludec/aspart (IDeg/Asp)

Komparator:

- Insulin glargine (IGlar (100 units/mL or 300 units/mL))

Endpunkte:

- Efficiency assessments: mean HbA1c end-of trail, mean FPG end-of-trial, nine-point SMPG;
- Safety assessments: confirmed hypoglycemia, nocturnal confirmed hypoglycemia, adverse events (AEs), and serious adverse events

Recherche/Suchzeitraum:

- May 16, 2021
- PubMed, Embase, Scopus, Cochrane library

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool and Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 studies

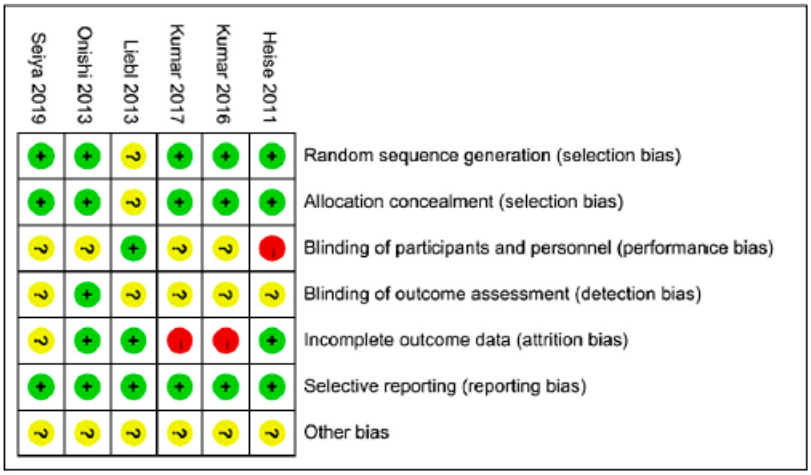
Charakteristika der Population:

Table 1 Characteristic of included studies

Trials	Country	NCT No.	Patients	Time Range (weeks)	Sample size			Intervention measure		Injection time		Age (Years)		Gender (Male/Female)		Duration of diabetes (Years)		BMI (Kg/m²)		HbA1C (%)		FPG (mmol/L)	
					IGlar	IDegAsp	Total	IGlar	IDegAsp	IGlar	IDegAsp	IGlar	IDeg/Asp	IGlar	IDeg/Asp	IGlar	IDeg/Asp	IGlar	IDeg/Asp	IGlar	IDeg/Asp	IGlar	IDeg/Asp
Heise (2011) [14]	Europe	NCT00614055	T2D (insulin naïve)	16	55	55	110	once-daily*	once-daily*	before the evening meal	before the evening meal	58.4 (±8.4)	58.7 (±8.8)	40/15	35/20	8.5 (±4.8)	9.1 (±8.0)	30.5 (±3.5)	30.2 (±3.4)	8.4 (±1.3)	8.3 (±1.2)	12.1 (±3.5)	11.1 (±3.3)
Kumar (2016) [15]	Country[a]	NCT01169766	T2D (insulin naïve)	52	209	179	388	once-daily*	once-daily*	either with breakfast or with the largest meal of the day	either with breakfast or with the largest meal of the day	56.5 (±8.6)	57.4 (±9.2)	118/103	91/101	9.6 (±6.1)	8.7 (±6.2)	30.4 (±5.2)	30.9 (±4.9)	8.9 (±1.0)	8.9 (±1.0)	10.2 (±2.8)	10.2 (±2.7)
Kumar (2017) [16]	Country[b]	NCT01045447	T2D	26	205	196	401	once-daily#	once-daily#	the largest meal of the day	the largest meal of the day	58.4 (±10.1)	57.8 (±9.5)	127/106	135/95	11.4 (±7.3)	11.6 (±6.8)	30.1 (±5.3)	30.1 (±5.1)	8.4 (±1.0)	8.3 (±0.8)	7.8 (±2.8)	8.0 (±2.5)
Liebl (2013) [17]	Europe	NA	T2D (insulin naïve)	16	57	55	112	once-daily*	once-daily*	before the evening meal	before the evening meal	—	—	36/21	40/15	—	—	25–37 (–)	25–37 (–)	7–11 (–)	7–11 (–)	—	—
Onishi (2013) [18]	Japan	NCT01272193	T2D (insulin naïve)	26	149	147	296	once-daily	once-daily	either before breakfast or at bedtime at the discretion of each subject	before the largest meal of the day	61 (±9.6)	60 (±10.0)	99/50	90/57	12.4 (±8.6)	10.9 (±7.3)	25.0 (±3.8)	25.2 (±3.8)	8.5 (±0.8)	8.3 (±0.8)	9.1 (±1.9)	9.0 (±1.6)
Seiya (2019) [19]	Japan	NA	T2D (insulin naïve)	12	13	26	39	once-daily	once-daily	before breakfast or dinner	before breakfast or dinner	49 (–)	64 (–)	7/6	17/9	5.0 (–)	11.0 (–)	25.9 (–)	26.0 (–)	9.7 (–)	8.9 (–)	—	—

Country*: Austria, India, Korea, Poland, Russia, Spain, Turkey, and America; Country[b]: includes Croatia, France, India, Poland, South Africa, South Korea, Sweden, Turkey, and America; T2D, Type 2 diabetes; Values are mean (±SD); (—) devotes unclear; (*) means all in combination with metformin; (#) means combination with metformin ± pioglitazone ± dipeptidyl peptidase-4 inhibitors

Qualität der Studien:



Studienergebnisse:

Efficiency outcome

Meta-analysis of mean HbA1c end-of-trail

- The pooled analysis showed that there was a pronounced significant difference in mean HbA1c endof- trail between IDeg/Asp and IGlar [MD = –0.16; 95% CI (–0.31, –0.00); p = 0.04], with low heterogeneity (I2 = 0%). Egger's test showed no publication bias, suggesting that IDeg/Asp has better control in mean HbA1c level than IGlar.

Meta-analysis of mean FPG end-of-trail

- The pooled analysis showed that mean FPG end-of- trail was similar in patients between IDeg/Asp and IGlar, with no significant difference [MD = –0.01; 95% CI (–0.36, 0.34); p = 0.95]. The heterogeneity was very low (I2 = 0%). No publication bias was found after analysis.

Meta-analysis of nine-point SMPG (self-measured plasma glucose)

- The pooled analysis showed that there was no significant difference in patients among IDeg/Asp to IGlar [MD = –0.12; 95% CI (–0.31, 0.08); p = 0.25], with low heterogeneity (I2 = 0%). No publication bias was found after analysis.

Safety outcome

Meta-analysis of confirmed hypoglycemia

- The pooled analysis showed that confirmed hypoglycemia was similar in patients between IDeg/Asp and IGlar that was no significant difference [OR = 1.59; 95% CI (0.97, 2.61); p = 0.07], with moderate heterogeneity (I2 = 66%). Throughout the subgroup analysis, we tend to found that the group of IDeg/Asp (duration of diabetes ≤11 years) considerably had a higher risk than IGlar (p < 0.0001) in confirmed hypoglycemia, with lower heterogeneity (I2 = 0%). No publication bias was found after analysi.

Meta-analysis of nocturnal confirmed hypoglycemia

- There was no significant distinction in nocturnal confirmed hypoglycemia [OR = 0.54; 95% CI (0.31, 0.94); p = 0.49], with moderate heterogeneity (I2 = 57%). Compared with alternative studies, the research by Kumar revealed in 2017 manifested prominent heterogeneity. After deleting this study, heterogeneity was low (I2 = 0%), and the comprehensive effects revealed that the nocturnal confirmed hypoglycemia of IDeg/Asp group was lower than IGlar group [OR = 0.40; 95% CI (0.26, 0.62); p < 0.0001]. No publication bias was found after analysis.

Meta-analysis of adverse events

- There was no significant distinction in adverse events [OR = 0.98; 95% CI (0.68, 1.41); p = 0.92], with moderate heterogeneity. Compared with alternative studies, the research by Heise revealed in 2011 manifested prominent heterogeneity. After deleting this study, heterogeneity was low (I2 = 0%), but the comprehensive effects revealed that adverse events still had no significant difference in the two groups [OR = 0.87; 95% CI (0.68, 1.13); p = 0.30]. It may be that the experimental cycle of the study by Heise is relatively short, and the adverse events of insulin may be more likely to occur in the late stage when it is used for a long time. No publication bias was found after analysis.

Meta-analysis of serious AEs

- The pooled analysis indicated that there was a pronounced significant difference in serious AEs among IDeg/Asp to IGlar [OR = 2.09; 95% CI (1.27, 3.45); p = 0.004], with low heterogeneity (I2 = 0%). Egger's test showed no publication bias was detected, suggesting that IDeg/Asp has a higher risk of serious AEs than IGlar.

Anmerkung/Fazit der Autoren

Our pooled analysis suggested that compared with IGlar, IDeg/Asp had a tremendous advantage in controlling mean HbA1c level but had no significant difference in controlling mean FPG level and nine-point SMPG. Furthermore, we found that there was no significant difference in the occurrence of hypoglycemia overall, but our subgroup analysis of confirmed hypoglycemia revealed the population in this subgroup (duration of diabetes ≤11 years) might has its particularity effecting the hypoglycemia outcome, which emphasized the significance of personalized treatment for different patients. In contrast, IGlar may increase the risk of hypoglycemia confirmed at night, which suggested that in the future use of IDeg/Asp. It is worth noting that the vast majority of the studies we included were patients who received insulin treatment for the first time based on oral hypoglycemic drugs. We reached conclusions through data collection and analysis. Therefore, it is necessary for us to limit our conclusions to patients treated with insulin for the first time. As for whether it can be applied to non-insulin primary treatment and long-term efficacy, further research is needed.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Moon S et al 2021 [48]
- Edina BC et al 2022 [16]

Mannucci E et al., 2022 [43].

Effects of insulin on cardiovascular events and all-cause mortality in patients with type 2 diabetes: a meta-analysis of randomized controlled trials

Fragestellung

Thus, this systematic review and meta-analysis of randomized controlled trials (RCTs) testing the effects of insulin on the risk of MACE, all-cause mortality, and HHF was performed as a part of the development of the aforementioned new Italian guidelines for the treatment of T2DM

Methodik

Population:

- patients with established T2DM

Intervention:

- insulin

Komparator:

- either placebo/no therapy, current care, or other active glucose-lowering comparators

Endpunkte:

- MACE, defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death
- All-cause mortality (including also RCTs not reporting MACE within the primary outcome, or as pre-defined secondary outcome)
- Hospital admission for heart failure

Recherche/Suchzeitraum:

- A MEDLINE, SCOPUS and EMBASE database search was performed to identify all available RCTs published in English up to June 1st, 2021

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 RCTs

Charakteristika der Population:

Table S2 – Principal characteristics and outcomes of the included trials.

Study Name *(Reference)*	MACE within presp. endp.	Investigational drug	Comparator	Trial duration (weeks)	Patients (ID/C)		Age (years)	MACE		ALL-CAUSE MORTALITY		HEART FAILURE	
					ID	C		ID	C	ID	C	IC	C
Alvarsson 2008(1)	NO	Human Insulin	Glibenclamide	330	23	26	53	NR	NR	2	1	NR	NR
Arturi 2017(2)	YES	Glargine	Sitagliptin	52	12	10	60	0	0	0	0	0	0
Blonde 2015(3)	YES	Glargine	Dulaglutide	52	296	588	60	12	11	3	2	1	2
Bunck 2009(4)	NO	Glargine	Exenatide	52	33	36	58	0	0	0	0	NR	NR
Diamant 2014(5)	NO	Glargine	Exenatide LAR	156	233	234	58	NR	NR	1	1	NR	NR
Giorgino 2015(6)	NO	Glargine	Dulaglutide	78	262	275	57	NR	NR	2	1	NR	NR
Gough 2015(7)	YES	Degludec	Liraglutide	52	414	413	55	1	1	0	0	5	7
Inagaki 2012(8)	NO	Glargine	Exenatide LAR	52	212	215	57	NR	NR	0	1	NR	NR
jaiswal 2015(9)	NO	Glargine	Exenatide	78	24	22	52	NR	NR	0	0	NR	NR
Klein 1991(10)	NO	NPH	Metformin	52	25	25	67	0	2	0	0	NR	NR
Ko 2006(11)	NO	NPH	Rosiglitazone	52	56	56	58	0	1	0	0	NR	NR
Lingvay 2009(12)	NO	BiAsp	Pioglit.+Gliben.	156	29	29	45	NR	NR	1	1	NR	NR
Nauck 2007(13)	NO	BiAsp	Exenatide	52	248	253	58	NR	NR	1	2	NR	NR
NCT01648582	NO	Glargine	Dulaglutide	52	263	263	55	NR	NR	0	1	NR	NR
ORIGIN 2012(14)	YES	Glargine	OAD	322	6264	6273	63	1041	1013	951	965	310	343
Tuttle 2018(15)	YES	Glargine	Dulaglutide	52	194	383	65	4	8	6	9	1	0
UKPDS 1998(16)	YES	Human Insulin	Met+SU	572	911	2472	54	211	502	184	497	25	77
Weng 2008(17)	NO	Human insulin	Gliclazide e/o Metf	52	261	121	51	0	0	0	0	NR	NR

Presp. Endp.: prespecified endpoints; MACE: Major Adverse Cardiovascular Events; Pioglit.: Pioglitazone; Gliben.: Glibenclamide. ID: Investigational Drug; C: Comparator.

Qualität der Studien:

- The overall quality of eligible RCTs was satisfactory for the majority of the items of the Cochrane Collaboration's tool, except for “performance bias” (i.e., blinding of participants and personnel) due to the open-label design of all included trials.

Studienergebnisse:

3.1. 3-Point MACE

Out of six RCTs reporting information on adjudicated cardiovascular events, one [23] reported zero events. Overall, these RCTs included 8091 T2DM patients treated with insulin (with a total of 1269 MACE) and 10,139 T2DM patients treated with placebo or any other active comparators (with a total of 1535 MACE). No publication bias was detected at the visual analysis of the Funnel plot (Supplementary Figure S3) and at Egger's test (Kendall's tau without continuity correction: −0.03; p = 0.71). Treatment with insulin was not associated with significant differences in the incidence of MACE (MH-OR: 1.09 [0.97, 1.23], with a random-effect model), as shown in Fig. 1. Similar results were obtained using a fixed-effect model (MH-OR: 1.07 [0.99, 1.16], p = 0.11). Another sensitivity analysis, imputing one case per arm in RCTs reporting zero events, was also performed (MH-OR: 1.07 [0.99, 1.16], p = 0.11). A subgroup analysis considering different comparators was performed: MH-OR for RCTs comparing insulin with GLP-1 receptor agonists [24–26] and with oral antidiabetic drugs [13,23,27] was 1.64 [0.85, 3.15], p = 0.14 and 1,06 [0.98, 1.16], p = 0.15, respectively.

3.2. All-cause mortality

Out of 18 studies included in the meta-analysis (9760 and 11,694 patients in the insulin and control group, respectively; Table S2), 13 reported at least one death (1151 vs. 1481 in insulin and control group, respectively) and were therefore included in the meta-analysis. Possible publication bias was detected at a visual analysis of the Funnel plot (Figure S3), but it was not confirmed by Kendall's tau (Tau: 0.24, p = 0.13).

As shown in Fig. 2, treatment with insulin was not associated with significant changes in all-cause mortality (MH-OR: 0.99 [0.91, 1.08]; I^2 = 0%).

A sensitivity analysis, imputing one case per arm in RCTs reporting zero events, was performed (MH-OR: 0.99 [0.91, 1.08], p = 0.86). Two post-hoc analyses excluding RCTs with adjudicated cardiovascular endpoints and using rosiglitazone as comparator showed similar results (MH-OR: 0.94 [0.34, 2.61], p = 0.91 and MH-OR: 0.99 [0.91, 1.08], p = 0.87, respectively). A subgroup analysis considering different comparators was performed: MH-OR for RCTs comparing insulin with GLP-1 receptor agonists [24–26,28–33] and sulfonylureas [14,34–36] was 1.23 [0.60, 2.55], p = 0.57 and 1.01 [0.84, 1.22], p = 0.91, respectively.

3.3. Hospitalizations for heart failure

Out of six RCTs reporting information on adjudicated cardiovascular events, one [23] did not report any case of HHF. The total number of HHF was 871 (342 and 429 in the insulin and control group, respectively). No publication bias was detected both at Egger's test (Kendall's tau without continuity correction: Tau: 0.02, p = 0.90) and at the visual analysis of the Funnel plot (Figure S3).

Overall, as shown in Fig. 3, treatment with insulin was not associated with a significant increase in the risk of HHF (MH-OR 0.90 [0.78, 1.04]).

A sensitivity analysis, imputing one case per arm in RCTs reporting zero events, was performed (MH-OR: 0.90 [0.78, 1.04], p = 0.15). A subgroup analysis considering different comparators was performed: MH-OR for RCTs comparing insulin with GLP-1 receptor agonists [24–26] and with oral antidiabetic drugs [13,23,27] was 0.92 [0.34, 2.48], p = 0.87 and 0.90 [0.77, 1.04], p = 0.15, respectively.

Anmerkung/Fazit der Autoren

In conclusion, the present meta-analysis performed on RCTs reporting adjudicated MACE within their endpoints showed no significant effects of insulin on incident MACE, HHF, and mortality in patients with established T2DM.

Rezaei S et al., 2022 [59].

Efficacy and safety of insulin detemir versus glargine in patients with diabetes: a systematic review and meta-analysis

Fragestellung

The objective of the current study is to compare the safety and efficacy of insulin glargine and insulin detemir in adults with DM1 and DM2 based on available evidence from RCTs.

Methodik

Population:

- patients diagnosed with DM1 or DM2

Intervention:

- insulin detemir

Komparator:

- insulin glargine

Endpunkte:

- efficacy outcomes namely HbA1c and FPG levels; and safety outcomes including weight gain and hypoglycemia (overall hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia).

Recherche/Suchzeitraum:

- PubMed, Embase, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) up to 18 August 2021

Qualitätsbewertung der Studien:

- JADAD Scale (Oxford quality scoring system) and the Cochrane risk-of-bias tool for randomized trials (RoB 2).

Ergebnisse

Anzahl eingeschlossener Studien:

- Finally, we included 12 RCTs for this systematic review and meta-analysis
- 9 studies in patients with DM2, 3 studies in patients with DM1
- A total of 5,794 DM2 patients were involved in these studies, of which 2,070 received insulin detemir and 3,724 received insulin glargine.

Charakteristika der Population:

- In the DM2 studies, the mean age of patients was 58.13 ± 9.79 years, 61.56% were male, and the mean duration of follow-up was 30.31 ± 15.35 weeks.

Table 1. Characteristics of the included studies.

Study	Type of diabetes	Country	Age, years, mean (SD)	Male, n (%)	Mean duration of follow-up, weeks
Meneghini et al., 2020 [20]	2	USA	59.2 (10.9)	1826(55.3)	26
Elisha et al., 2016 [21]	2	Canada	59.7 (2.7)	24 (66.7)	26
Meneghini et al., 2013 [22]	2	USA	57.3 (10.3)	113(56.5)	26
Swinnen et al., 2010 [23]	2	Netherland	58.4 (8.3)	532 (54.7)	24
Raskin et al., 2009 [24]	2	USA	55.8 (10.3)	210 (54.5)	26
Fadini et al., 2011 [25]	2	Italy	66.2 (1.8)	34 (79.1)	26
Rosenstock et al., 2008 [26]	2	UK	58.9 (9.9)	337 (57.9)	26
Hollander et al., 2008 [27]	2	UK	58.5 (11.0)	185 (58.0)	52
Bhosle et al., 2014 [28]	2	India	54.6 (7.7)	28 (70.0)	24
Renard et al., 2011 [29]	1	France	46.8 (13.7)	54 (61.4)	16
Heller et al., 2009 [30]	1	UK	42 (12.0)	248(56.0)	52
Pieber et al., 2007 [31]	1	Germany	40.46 (14.8)	164(51.3)	26

Qualität der Studien:

- Siehe Studienergebnisse für HbA1c (forest plots)

Studienergebnisse:

*Hinweis FBMed: Es werden lediglich Ergebnisse für DM2 Patient*innen dargestellt.*

HbA1c

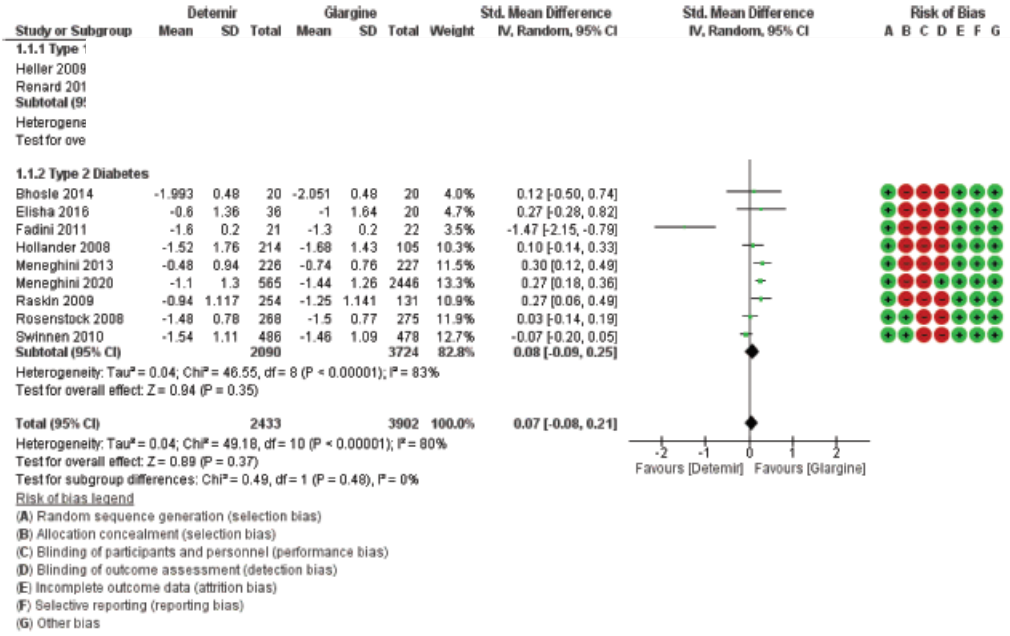


Figure 2. Forest plot of pooled SMD of HbA1c, comparing detemir vs. glargine. SMD, standardized mean difference.

FPG

- Five RCTs involving 2,523 DM2 patients compared the effects of insulin detemir and insulin glargine on FPG levels. The pooled SMD was 0.05 (95% CI −0.03 to 0.13; P = 0.26, I2 = 0%)

Weight gain

- Eight RCTs involving 5,754 DM2 patients compared the effects of insulin detemir and insulin glargine on weight gain. The pooled SMD was −0.18 (95% CI −0.67 to 0.32; P = 0.48; I2 = 98%)

Hypoglycemia

- The pooled RRs of hypoglycemic events were 0.96 (95% CI 0.91 to 1.02; P = 0.20; I2 = 8%). Based on seven trials in DM2 patients (involving 2,788 patients).
- four trials in DM2 patients (involving 1,741 patients), compared the risk of nocturnal hypoglycemia: The pooled RRs were 1.05 (95% CI 0.92 to 1.19; P = 0.49; I2 = 10%)

- five trials in DM2 patients (involving 1,784 patients), compared the risk of severe hypoglycemia: The pooled RRs were 0.73 (95% CI 0.41 to 1.28; P = 0.27; I2 = 0%)

Anmerkung/Fazit der Autoren

Our meta-analysis study shows that insulin detemir and insulin glargine provide similar glycemic control in diabetic patients. We found no statistically significant differences in HbA1c and FPG values between the two insulin treatment groups. Similarly, we observed a not statistically significant difference in the overall incidence of hypoglycemia in DM1 and DM2 patients. The only statistically significant differences between groups were in the weight change in DM2 (P = 0.01) and severe hypoglycemia in DM1 (P = 0.002) variables. According to the results of our sensitivity analysis, DM2 patients achieved the same glycemic control on insulin detemir with less weight gain compared with those on insulin glargine. Collectively, our study suggests that there is no clinically considerable difference in the safety and efficacy outcomes between the two long-acting insulin analogs of detemir and glargine based on the available RCTs.

Dong ZY et al., 2022 [14].

Efficacy and Tolerability of Insulin Degludec Versus Other Long-acting Basal Insulin Analogues in the Treatment of Type 1 and Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis

Fragestellung

The goal of this study was to compare the efficacy and tolerability of insulin degludec with those of other long-acting insulin analogues (insulin glargine and insulin detemir) in patients with type 1 or 2 diabetes mellitus (T1D or T2D)

Methodik

Population:

- patients with T1D or T2D

Intervention:

- insulin degludec

Komparator:

- insulin glargine (IGlar300)

Endpunkte:

- changes from baseline in HbA1c and FPG.
- prevalences of hypoglycemia (any 24-hour glucose level of ≤3.9 mmol/L)
- overall, nocturnal (12 am to < 6 am), and severe (< 2.9 mmol/L) hypoglycemic events

Recherche/Suchzeitraum:

- Studies before August 21, 2022 from PubMed, Web of Science, the Cochrane Library, and EMBASE

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

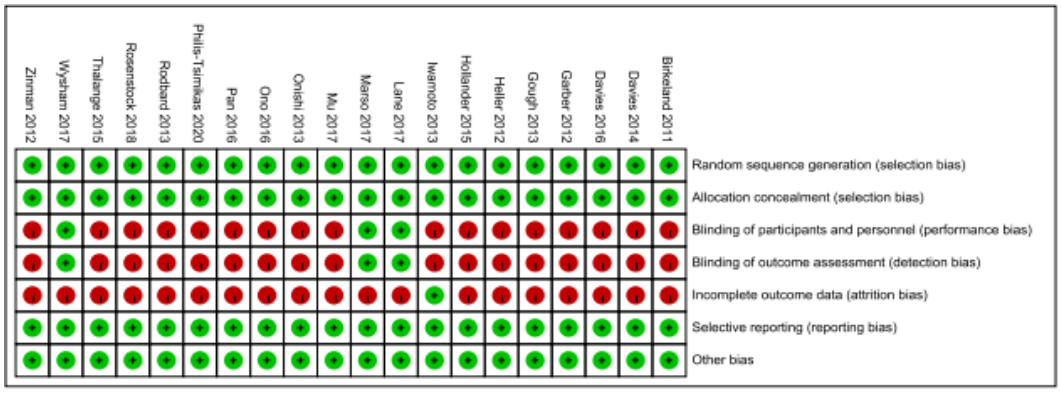
- 20 trials (19,048 patients)
- 12 trials with T2D patients

Charakteristika der Population/Studien:

Study	Year	No.of Patients	F/U,wk	Study Popula-tion	Intervention	Control	Age, mean (SD), y	Female, %	Duration of Diabetes, mean (SD), y		HbA_{1c}, mean (SD), %		Baseline FPG, mean (SD), mmol/L	
									IDeg	Control	IDeg	Control	IDeg	Control
Garber et al[15]	2012	992	52	T2D	IDeg100 + IAsp ± Met ± Pio	IGlar100 + IAsp ± Met ± Pio	52.9 (9.1)	45.8	13.6 (7.4)	13.4 (6.9)	8.3 (0.8)	8.4 (0.9)	9.2 (3.0)	9.2 (3.2)
Gough et al[16]	2013	457	26	T2D	IDeg200 + OAD(s)	IGlar100 + OAD(s)	57.8 (9.0)	46.8	8.4 (6.7)	8.0 (5.6)	8.3 (1.0)	8.2 (0.9)	9.6 (2.9)	9.7 (2.6)
Heller et al[17]	2012	629	52	T1D	IDeg100 + IAsp	IGlar100 + IAsp	43.0 (13.6)	41.5	19.1 (12.2)	18.2 (11.4)	7.7 (0.9)	7.7 (1.0)	9.1 (4.0)	9.7 (4.4)
Hollander et al[18]	2015	757	26	T2D	IDeg100 + IAsp TID ± Met + Pio	IGlar100 + IAsp TID ± Met + Pio	58.9 (8.6)	44.9	13.4 (7.2)	13.7 (6.8)	8.2 (0.8)	8.3 (0.9)	9.2 (3.0)	9.2 (3.2)
Marso et al[21]	2017	7637	104	T2D	IDeg100 + IAsp + OAD(s)	IGlar100 + IAsp TID + OAD(s)	65.0 (7.4)	37.4	16.6 (8.8)	16.2 (8.9)	8.4 (1.6)	8.4 (1.7)	9.4 (3.9)	9.6 (3.9)
Mu et al[22]	2017	560	26	T2D	IDeg100 + Met	IGlar100 + Met	55.2 (9.4)	47.3	6.7 (4.7)	7.9 (5.4)	8.2 (0.8)	8.2 (0.9)	9.2 (2.3)	9.3 (2.5)
Onishi et al[23]	2013	435	26	T2D	IDeg100 + OAD(s)	IGlar100 + OAD(s)	58.6 (9.9)	46.4	11.8 (6.5)	11.1 (6.5)	8.4 (0.8)	8.5 (0.8)	8.4 (2.1)	8.6 (1.9)
Ono et al[24]	2016	186	26	T1D	IDeg100 + IAsp	IDet100 + IAsp	48.6 (14.0)	57.5	12.5 (9.6)	12.9 (8.6)	7.9 (0.9)	8.2 (0.9)	9.7 (3.7)	9.5 (3.1)
Pan et al[25]	2016	833	26	T2D	IDeg100 + Met	IGlar100 + Met	55.9 (9.7)	49.5	7.6 (5.3)	8.3 (5.5)	8.3 (0.9)	8.3 (0.8)	9.4 (2.4)	9.4 (2.5)
Philis-Tsimikas et al[26]	2020	1609	88	T2D	IDeg200 + OADs	IGlar300 + OADs	62.9 (10.0)	43.6	15.1 (8.2)	15.0 (8.4)	7.6 (1.0)	7.6 (0.9)	7.9 (2.6)	8.0 (2.6)
Rodbard et al[27]	2013	725	52	T2D	IDeg100 + OAD(s)	IGlar100 + OAD(s)	59.7 (9.3)	36.6	9.7 (6.3)	9.0 (5.6)	8.1 (0.8)	8.2 (0.8)	9.7 (2.4)	9.5 (2.4)
Rosenstock et al[28]	2018	929	24	T2D	IDeg100 + OAD(s)	IGlar300 + OAD(s)	60.5 (9.7)	46	10.5 (6.1)	10.7 (6.5)	8.6 (0.8)	8.7 (0.8)	10.1 (2.8)	10.6 (2.7)
Thalange et al[29]	2015	350	52	T1D	IDeg100 + IAsp	IDet100 + IAsp	10.0 (4.4)	44.5	3.9 (3.6)	4.0 (3.4)	8.2 (1.1)	8.0 (1.1)	9.0 (5.2)	8.4 (4.9)
Wysham et al[30]	2017	720	32	T2D	IDeg100 + OAD(s)	IGlar100 + OAD(s)	61.4 (10.5)	46.9	14.2 (8.3)	13.9 (8.0)	7.6 (1.1)	7.6 (1.1)	7.7 (3.0)	7.5 (2.9)
Zinman et al[31]	2012	1030	52	T2D	IDeg100 + OAD(s)	IGlar100 + OAD(s)	59.3 (9.7)	38.1	9.4 (6.3)	8.6 (5.7)	8.2 (0.8)	8.2 (0.8)	9.6 (2.6)	9.7 (2.6)

FPG = fasting plasma glucose; F/U = follow-up; Hb = hemoglobin; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; IGlar = insulin glargine; Met = metformin; OAD = oral antidiabetic; Pio = pioglitazone; T1D = type 1 diabetes; T2D = type 2 diabetes.

Qualität der Studien:



Studienergebnisse:

estimated rate ratio (ERR) was calculated, based on hypoglycemic rate, as the number of hypoglycemic events exposed per patient-year.

- HbA 1c. There was no heterogeneity of the T2D group (I^2 = 0; P = 0.447). The fixed-effects model was selected, obtaining a combined effect size of –0.014 (–0.043 to 0.072). In the treatment of patients with T2D, the HbA 1c with insulin degludec had no statistical significance (z = 0.50; P = 0.621).
- FPG. There was no heterogeneity of the T2D group (I^2 = 13.4%; P = 0.328). The fixed-effects model was selected, obtaining a combined effect size of -0.343 (-0.448 to -0.239). In the treatment of patients with T2D, the FPG with insulin degludec was significantly lower, by 0.343 mmol/L, which was statistically significant (z = 6.43; P < 0.001).
- All Confirmed Hypoglycemia. The heterogeneity of the T2D group (I^2 = 15.7%; P = 0.294) was not statistically significant. The fixed-effects model was selected to combine the effect size, obtaining an ERR = 0.809 (95% CI, 0.762 to 0.857). In the treatment of patients with T2D, the overall prevalence of hypoglycemia with insulin degludec was 80.9% of that in the control group, which was statistically significant (z = 6.58; P < 0.001).
- Nocturnal Hypoglycemia. There was mild heterogeneity of the T2D group (I^2 = 37.9%; P = 0.088). The random-effects model was selected (ERR = 0.664; 95% CI, 0.575 to 0.753). In the treatment of patients with T2D, the prevalence of nocturnal hypoglycemia with insulin degludec was 66.4% of that in the control group, which was statistically significant (z = 5.05; P < 0.001).
- Severe Hypoglycemia. There was moderate heterogeneity of the T2D group (I^2 = 66.2%; P = 0.007). The random-effects model was selected to combine the effect size, obtaining an ERR = 0.515 (95% CI, 0.306 to 0.724). In the treatment of patients with T2D, the prevalence of severe hypoglycemia with insulin degludec was 51.5% of that in the control group, with no statistical significance (z = 1.23; P = 0.218).

Anmerkung/Fazit der Autoren

In the treatment of T2D, FPG and the prevalences of overall and nocturnal hypoglycemia were significantly lower with insulin degludec compared with first- and second- generation insulin glargine (IGlar100 and IGlar300).

Kommentare zum Review

- Es werden lediglich Ergebnisse für DM2 Patient*innen dargestellt.

Yang Y et al., 2022 [70].

Insulin degludec versus insulin glargine on glycemic variability in diabetic patients: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

This study aimed to determine whether insulin degludec (IDeg) or insulin glargine (IGla) was more beneficial for reducing glycemic fluctuations.

Methodik

Population:

- All diabetic patients were included, irrespective of the types of diabetes mellitus;

Intervention/Komparator:

- IDeg versus IGla

Endpunkte:

- standard deviation of blood glucose (SDBG), mean amplitude of glycemic excursions (MAGE), mean blood glucose (MBG), time in the range (TIR), amean of daily differences (MODD), the coefficient of variation (CV), area under the glucose curve (AUC), and Mvalue;

Recherche/Suchzeitraum:

- Eight common databases were searched from their inception to 30 November 2021, specifically including the Cochrane Library, PubMed, Embase, Web of Science, Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), VIP database, and Wanfang database. Besides, Clinical Trials (ClinicalTrials.gov), unpublished gray literature, and references cited in the eligible studies were also searched.

Qualitätsbewertung der Studien:

- The Cochrane Collaboration tool was used to assess the risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies involving 8,683 patients were included in this research.

Charakteristika der Population:

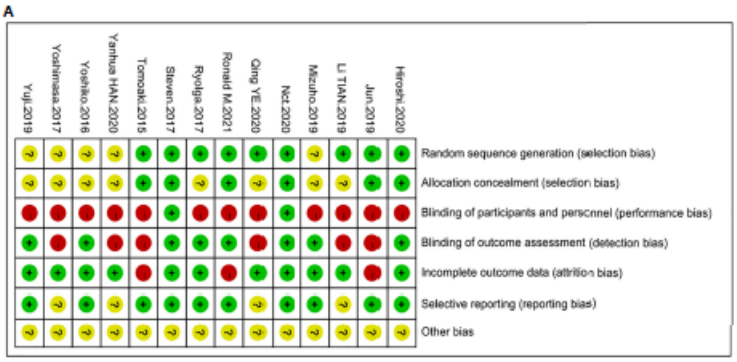
TABLE 1 | Baseline characteristics of included studies.

First author and year	Design	Country	Follow-up	Patients	Male (%)	Total cases	Sample size		Treatment		Age (years)		Disease duration (years)		HbA1c (%)		Outcomes
							IDeg	IGla	Group1	Group2	IDeg	IGla	IDeg	IGla	IDeg	IGla	
Yoshiko, 2016 (13)	RCT, C	Japan	8 weeks	T1DM	54%	13	13*	13*	IDeg★	IGla▲	44.9 (7.2)	44.9 (7.2)	15.5 (7.0)	15.5 (7.0)	7.8 (0.54)	7.9 (0.54)	①②③④
Ryolga, 2017 (18)	RCT,O,C	Japan	24 weeks	T1DM	55%	20	10	10	IAsp + IDeg★	IAsp + IGla▲	54 (16)	54 (16)	16 (8)	16 (8)	7.1 (0.9)	7.7 (0.6)	②③⑦
Yuji, 2019 (28)	RCT,O,C	Japan	10 days	T2DM	60%	30	15	15	IDeg★	IGla300	69.5 (11.3)	69.5 (11.3)	18.3 (11.3)	18.3 (11.3)	8.0 (1.5)	8.5 (2.2)	①②③④⑤⑥
Tomoaki, 2015 (17)	RCT,O,M,C	Japan	8 weeks	T1DM	41%	36	17	19	IDeg★	IGla▲	57 (14)	57 (14)	18 (10)	18 (10)	7.4 (0.8)	7.4 (0.8)	①④⑥
Yoshimasa, 2017 (19)	RCT,O,M,P	Japan	24 weeks	T2DM	45%	43	31	12	IDeg★	IGla▲	64.0 (13.6)	64.7 (15.7)	10 (3.5)	14.5 (5.27)	8.88 (1.48)	8.84 (1.46)	⑥
Hiroshi, 2020 (27)	RCT,M,C	Japan	4 weeks	T1DM	30%	46	23	23	IDeg★	IGla300	53.3 (14.7)	53.3 (14.7)	19.4 (11.6)	19.4 (11.6)	7.6 (0.7)	7.6 (0.7)	①②③④⑤⑥
Jun, 2019 (14)	RCT,O,P	Japan	12 days	T2DM	51%	74	36	38	IDeg100	IGla100	58.9 (10.5)	61.8 (9.4)	3.9 (4.6)	6.6 (8.2)	11.3 (1.4)	10.4 (1.9)	①②③④
Yan.Han, 2020 (31)	RCT,P	China	NR	T2DM	58%	64	32	32	IAsp + IDeg★	IAsp + IGla▲	52.38 (6.29)	52.54 (6.07)	10.34 (1.25)	10.29 (1.54)	9.12 (1.46)	9.07 (1.34)	②⑤
LiTian, 2019 (30)	RCT,P	China	NR	T2DM	67%	86	43	43	IAsp+ IDeg300	IAsp + IGla300	53.3 (8.8)	53.9 (8.5)	NR	NR	11.2 (1.8)	11.4 (1.7)	⑤
Qing, 2020 (29)	RCT,P	China	NR	T2DM	59%	100	30	70	IAsp + IDeg300	IAsp + IGla300	57.96 (8.35)	58.74 (8.41)	4.23 (1.05)	4.12 (1.03)	11.29 (1.74)	11.25 (1.85)	⑤
Ronald, 2021 (26)	RCT,O,M,C	Canada	41 weeks	T2DM	48%	498	249	249	IDeg100	IGla100	62.9 (10.0)	62.7 (9.7)	14.5 (7.0)	15.6 (8.3)	7.6 (1.0)	7.6 (1.0)	⑤
Nct, 2020 (25)	RCT,C	Mexico	6 days	T2DM	67%	12	6	6	IDeg★	IGla▲	44.1 (8.8)	44.1 (8.8)	NR	NR	8.2 (1.4)	8.2 (1.4)	③④
Steven, 2017 (33)	RCT,M,D,P	America	2 years	T2DM	63%	7637	3818	3819	IDeg★	IGla100	64.9 (7.3)	65.0 (7.5)	16.6 (8.8)	16.2 (8.9)	8.4 (1.6)	8.4 (1.7)	②
Mizuho, 2019 (32)	RCT,O,C	Japan	8 weeks	T2DM	50%	24	12	12	IDeg★	IGla300	71.9 (5.2)	69.5 (9.5)	16.5 (9.1)	11.6 (9.1)	6.83 (0.34)	6.78 (0.33)	①②③⑥⑦

Data are shown as numbers or means (standard deviation) unless otherwise stated.

☆The article did not report sample size of each group. Because it was a crossover study, all participants completed the experiment. So the values in each group are the total sample size; ★These studies did not report the type of insulin degludec;▲These studies did not report the type of insulin glargine; NR, not report; RCT, randomized controlled trial; O, open-label; M, multicenter; C, crossover; P, parallel; D, double-blind; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IDeg, insulin degludec; IGla, insulin glargine; IAsp, insulin aspart; IGla300, insulin glargine 300 U/ml; IDeg100, insulin degludec 100 U/ml; IDeg300, insulin degludec 300U/ml; IGla100, insulin glargine 100 U/ml; HbA1c, hemoglobin A1c; ①, SDBG (standard deviation of blood glucose); ②, MBG (mean blood glucose); ③, MAGE (mean amplitude of glycemic excursion); ④, AUC (area under the curve of glucose); ⑤, TIR (time in range); ⑥, CV (coefficient of variation); ⑦, MODD (mean of daily difference); ⑧, M-value.

Qualität der Studien:



Studienergebnisse:

*Hinweis FBMed: Es werden lediglich Ergebnisse für DM2 Patient*innen dargestellt. Es wurde sich auf drei Endpunkte fokussiert.*

Effect of Standard Deviation of Blood Glucose (SDBG)

- Three studies were conducted on patients with T2DM. There were also no significant differences in pooled results between IDeg and IGla (MD: 1.07, 95% CI −2.66 to 4.80, P = 0.57, I2 = 0%), and no heterogeneity was identified (Phe = 0.91, I2 = 0%).

Effect of Mean Blood Glucose (MBG)

- Four studies (14, 28, 31, 32) were conducted in patients with T2DM. Similarly, no significant differences were found in the pooled results (MD: −3.04, 95% CI −10.53 to 4.44, P = 0.43), with no heterogeneity (Phe = 0.44, I2 = 0%).
- One study (33) enrolling 7,637 patients with a baseline HbA1c of <9% comparing IDeg with IGla100 in T2DM also showed IDeg was more beneficial than IGla100 (P <0.001).

Effect of Time in Range (TIR)

- Seven studies (14, 26, 28–32) were conducted in T2DM. Two studies (14, 26) comparing IDeg with IGla100 demonstrated that IDeg maintained TIR longer than IGla100 (SMD: 0.15, 95% CI 0.02 to 0.27, P = 0.02) while four studies (28–30, 32) comparing IDeg with IGla300 revealed a comparable effect (SMD: −0.15, 95% CI −0.44 to 0.14, P = 0.30). No significant heterogeneity was observed in two subgroup analyses. Another study (31), without specifying the type of IGla, also showed no difference in TIR compared to IDeg (P >0.05).

Anmerkung/Fazit der Autoren

In people with T1DM, IDeg was related to a lower mean and SD in FBG compared to IGla. There was comparable efficacy between IDeg and IGla in MAGE, SDBG of 24 h, TIR, MBG of 24 h, CV, MODD, AUC, and M-value. In patients with T2DM, IDeg was associated with a lower mean of FBG versus IGla100. Concerning the CV of FBG, IDeg was also more stable than IGla. Moreover, IDeg achieved TIR longer than IGla100. However, compared with IGla300, IDeg showed similar efficacy in TIR. In terms of MAGE, SDBG, mean of 24 h, CV of 24 h, MODD, AUC, and M-value, there was comparable efficacy between IDeg and IGla.

In conclusion, IDeg was found to be superior to IGla in reducing fasting glucose variability in both T1DM and T2DM, but due to the limitations of the original study, it is still unclear whether IDeg is superior to both IGla100 and IGla300. Moreover, studies comparing the efficacy of IDeg and IGla in fasting glucose fluctuations are still needed. In T2DM, IDeg had a longer TIR than IGla100 but not longer than IGla300. For other indicators of blood glucose variation, including SD of 24 h, MAGE, MBG of 24 h, CV of 24 h, MODD, AUC, and M-value, no significant differences were identified between IDeg and IGla, regardless of T1DM or T2DM.

Monami M et al., 2021 [47].

Effect of metformin on all-cause mortality and major adverse cardiovascular events: an updated meta-analysis of randomized controlled trials.

Fragestellung

to perform a systematic review and meta-analysis on the effect of metformin on on major adverse cardiovascular events (MACEs) and all-cause mortality.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- metformin

Komparator:

- current care or other active comparators or placebo

Endpunkte:

- MACE and all-cause mortality at ≥52 weeks

Recherche/Suchzeitraum:

- MEDLINE and EMBASE search on August 31st, 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- GRADE for overall quality of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 trials fulfilling the inclusion criteria was identified for MACE and 13 for all-cause mortality.

Charakteristika der Studien/ Population:

All-cause mortality

- Mean trial duration: 131 weeks;
- most of the trials with active comparators
- mean age 55 years

MACE

- the 2 trials compared metformin vs active comparators
- trial duraion were 256 and 577 weeks;

Qualität der Studien:

- Risk of bias was generally low, with the exception of blinding procedures.

Studienergebnisse:

MACE:

- Metformin was associated with a lower risk of MACEs compared with comparator treatments (n = 2 RCTs; MH-OR 0.52 [0.37, 0.73]), p < 0.001 (moderate quality of evidence)

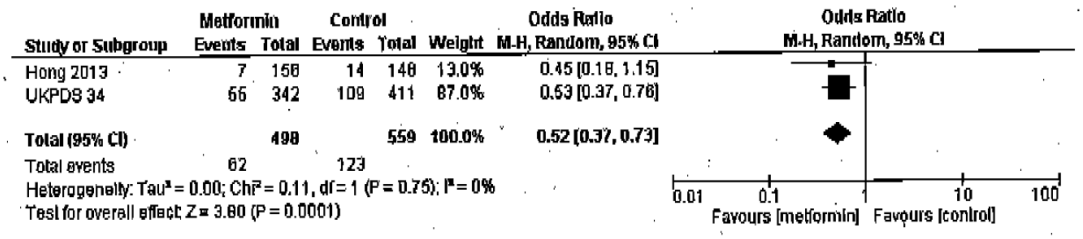


Figure 1 Risk of major adverse cardiovascular events (MACE) with metformin *versus* other active comparators approved by EMA and currently used in Europe (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

All-cause mortality

- Overall: no sign. stat. difference:

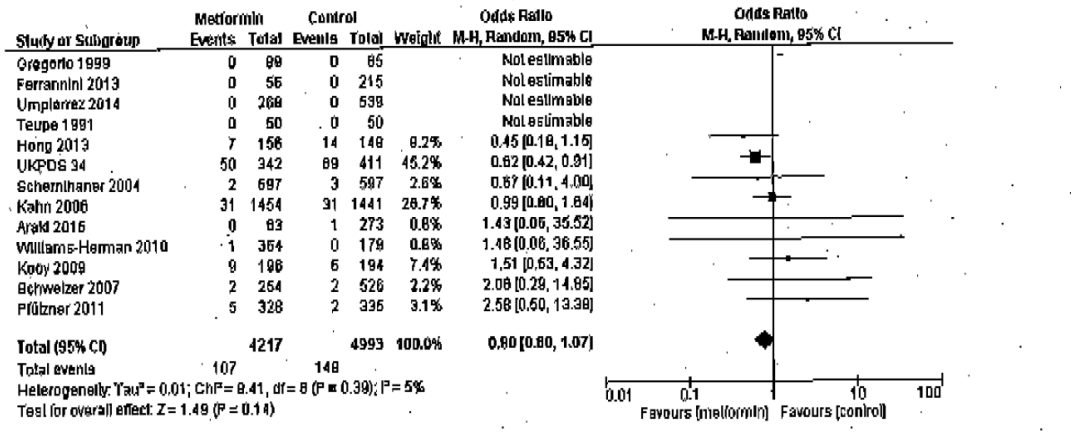


Figure 2 Risk of all-cause mortality with metformin *versus* other active comparators approved by EMA and currently used in Europe (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

- No significant stat. Difference in risk of all-cause mortality for metformin in comparison with different classes of anti-hyperglycaemic drugs

Anmerkung/Fazit der Autoren

This meta-analysis suggests that metformin is associated with a lower risk of MACE, when compared with other anti-hyperglycaemic drugs.

Mannucci E et al., 2020 [42].

Effect of insulin secretagogues on major cardiovascular events and all-cause mortality: a meta-analysis of randomized controlled trials.

Fragestellung

to perform a systematic review and meta-analysis on the effect of insulin secretagogues (sulfonylureas and glinides) on on major adverse cardiovascular events (MACEs) and all-cause mortality.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- insulin secretagogues (glibenclamide, gliclazide, glimepiride, glipizide, chlorpropamide, repaglinide, nateglinide)

Komparator:

- active comparators or placebo

Endpunkte:

- MACE and all-cause mortality at ≥52 weeks

Recherche/Suchzeitraum:

- MEDLINE up to January 1st, 2020.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

- GRADE for overall quality of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- 46 RCTs for all-cause mortality, 14 for MACE

Charakteristika der Studien/ Population:

All-cause mortality

- Mean trial duraion 140 weeks; all trials with active comparators
- mean 58 years

MACE

- all trials on sulfonylureas and none on glinides
- Mean trial duraion 162 weeks; all trials with active comparators
- Mean age 56 years

Qualität der Studien:

- The overall quality of all included RCTs was high for all items, with the exception of performance bias in 11 open-label trials (all cause mortality) / in 2 open-label trials (MACE).

Studienergebnisse:

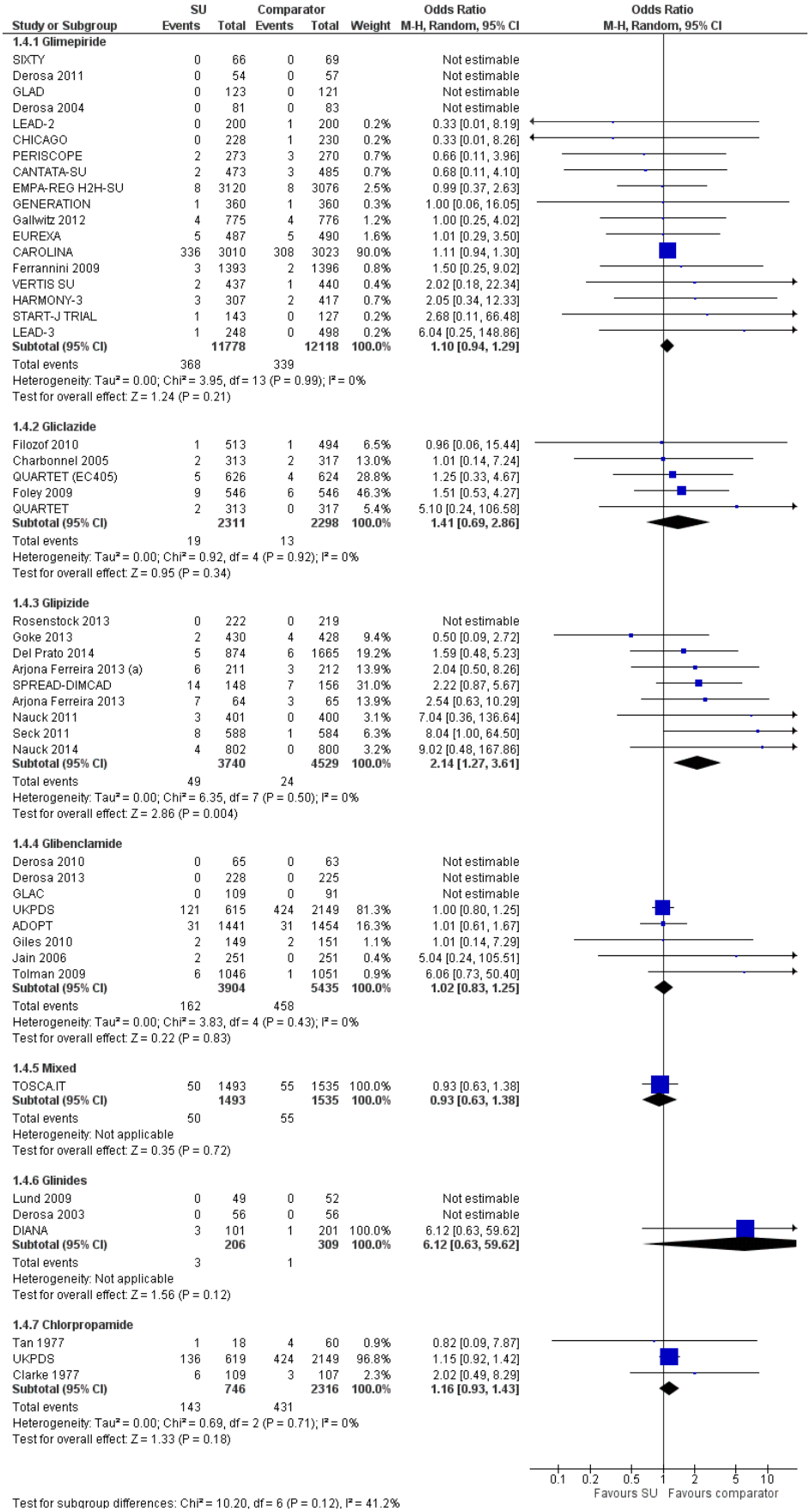
MACE (14 RCTs)

- Insulin secretagogues were not significantly associated with an increased risk of MACEs in comparison with controls (MH-OR 1.08 [95% CI 0.96, 1.22] I^2=11%, p = 0.20), quality of evicence: high

When considering trials in which insulin secretagogues were given as first-line treatment (i.e. monotherapy) [9,11–14] the MH–OR was 1.08 [0.95, 1. 22], p = 0.27, whereas in those in which *insulin secretagogues* were administered as add-on therapy the MH–OR *was* 0.87 [0.59, 1. 30], p = 0.51.

All-cause mortality

- insulin secretagogues were associated with a significantly increased risk of all-cause mortality (MH-OR 1.11 [1.00, 1.23] I^2=0%, p = 0.04), quality of evicence: high
- Risk of all-cause mortality with individual insulin secretagogues versus other comparators approved by EMA and currently used in Europe (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, 95% of Confidence Intervals):


SU
Comparator
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.4.1 Glimepiride
SIXTY 0 66 0 69 Not estimable
Derosa 2011 0 54 0 57 Not estimable
GLAD 0 123 0 121 Not estimable
Derosa 2004 0 81 0 83 Not estimable
LEAD-2 0 200 1 200 0.2% 0.33 [0.01, 8.19]
CHICAGO 0 228 1 230 0.2% 0.33 [0.01, 8.26]
PERISCOPE 2 273 3 270 0.7% 0.66 [0.11, 3.96]
CANTATA-SU 2 473 3 485 0.7% 0.68 [0.11, 4.10]
EMPA-REG H2H-SU 8 3120 8 3076 2.5% 0.99 [0.37, 2.63]
GENERATION 1 360 1 360 0.3% 1.00 [0.06, 16.05]
Gallwitz 2012 4 775 4 776 1.2% 1.00 [0.25, 4.02]
EUREXA 5 487 5 490 1.6% 1.01 [0.29, 3.50]
CAROLINA 336 3010 308 3023 90.0% 1.11 [0.94, 1.30]
Ferrannini 2009 3 1393 2 1396 0.8% 1.50 [0.25, 9.02]
VERTIS SU 2 437 1 440 0.4% 2.02 [0.18, 22.34]
HARMONY-3 3 307 2 417 0.7% 2.05 [0.34, 12.33]
START-J TRIAL 1 143 0 127 0.2% 2.68 [0.11, 66.48]
LEAD-3 1 248 0 498 0.2% 6.04 [0.25, 148.86]
Subtotal (95% CI) 11778 12118 100.0% 1.10 [0.94, 1.29]
Total events 368 339
Heterogeneity: Tau² = 0.00; Chi² = 3.95, df = 13 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.21)
1.4.2 Gliclazide
Filozof 2010 1 513 1 494 6.5% 0.96 [0.06, 15.44]
Charbonnel 2005 2 313 2 317 13.0% 1.01 [0.14, 7.24]
QUARTET (EC405) 5 626 4 624 28.8% 1.25 [0.33, 4.67]
Foley 2009 9 546 6 546 46.3% 1.51 [0.53, 4.27]
QUARTET 2 313 0 317 5.4% 5.10 [0.24, 106.58]
Subtotal (95% CI) 2311 2298 100.0% 1.41 [0.69, 2.86]
Total events 19 13
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
1.4.3 Glipizide
Rosenstock 2013 0 222 0 219 Not estimable
Goke 2013 2 430 4 428 9.4% 0.50 [0.09, 2.72]
Del Prato 2014 5 874 6 1665 19.2% 1.59 [0.48, 5.23]
Arjona Ferreira 2013 (a) 6 211 3 212 13.9% 2.04 [0.50, 8.26]
SPREAD-DIMCAD 14 148 7 156 31.0% 2.22 [0.87, 5.67]
Arjona Ferreira 2013 7 64 3 65 13.9% 2.54 [0.63, 10.29]
Nauck 2011 3 401 0 400 3.1% 7.04 [0.36, 136.64]
Seck 2011 8 588 1 584 6.3% 8.04 [1.00, 64.50]
Nauck 2014 4 802 0 800 3.2% 9.02 [0.48, 167.86]
Subtotal (95% CI) 3740 4529 100.0% 2.14 [1.27, 3.61]
Total events 49 24
Heterogeneity: Tau² = 0.00; Chi² = 6.35, df = 7 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)
1.4.4 Glibenclamide
Derosa 2010 0 65 0 63 Not estimable
Derosa 2013 0 228 0 225 Not estimable
GLAC 0 109 0 91 Not estimable
UKPDS 121 615 424 2149 81.3% 1.00 [0.80, 1.25]
ADOPT 31 1441 31 1454 16.3% 1.01 [0.61, 1.67]
Giles 2010 2 149 2 151 1.1% 1.01 [0.14, 7.29]
Jain 2006 2 251 0 251 0.4% 5.04 [0.24, 105.51]
Tolman 2009 6 1046 1 1051 0.9% 6.06 [0.73, 50.40]
Subtotal (95% CI) 3904 5435 100.0% 1.02 [0.83, 1.25]
Total events 162 458
Heterogeneity: Tau² = 0.00; Chi² = 3.83, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)
1.4.5 Mixed
TOSCA.IT 50 1493 55 1535 100.0% 0.93 [0.63, 1.38]
Subtotal (95% CI) 1493 1535 100.0% 0.93 [0.63, 1.38]
Total events 50 55
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)
1.4.6 Glinides
Lund 2009 0 49 0 52 Not estimable
Derosa 2003 0 56 0 56 Not estimable
DIANA 3 101 1 201 100.0% 6.12 [0.63, 59.62]
Subtotal (95% CI) 206 309 100.0% 6.12 [0.63, 59.62]
Total events 3 1
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
1.4.7 Chlorpropamide
Tan 1977 1 18 4 60 0.9% 0.82 [0.09, 7.87]
UKPDS 136 619 424 2149 96.8% 1.15 [0.92, 1.42]
Clarke 1977 6 109 3 107 2.3% 2.02 [0.49, 8.29]
Subtotal (95% CI) 746 2316 100.0% 1.16 [0.93, 1.43]
Total events 143 431
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Chi² = 10.20, df = 6 (P = 0.12), I² = 41.2%
0.1 0.2 0.5 1 2 5 10
Favours SU Favours comparator

Anmerkung/Fazit der Autoren.

This meta-analysis suggests that insulin secretagogues are associated with an increased risk of all-cause mortality when compared with placebo or other anti-hyperglycaemic drugs.

Netzwerk-Metaanalysen

Ding, Y. et al., 2024 [13].

Evaluation and comparison of efficacy and safety of tirzepatide and semaglutide in patients with type 2 diabetes mellitus: A Bayesian network meta-analysis

Fragestellung

to evaluate and compare the efficacy and safety of Tir and Sem in treating type 2 diabetes mellitus (T2DM).

Methodik

Population:

- T2DM patients

Intervention/Komparator

- Tir and Sem with placebo or the other antidiabetic drugs in treating

Endpunkte:

- glycated hemoglobin (HbA1c), body weight (BW), body mass index (BMI), and the proportion of participants with HbA1c< 7 %, gastrointestinal adverse events (GIAEs)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Web of Science, Cochrane Library and ClinicalTrials.gov were systematically searched from inception to April 3rd, 2023

Qualitätsbewertung der Studien:

- Cochrane ROB 2

Ergebnisse

Anzahl eingeschlossener Studien:

- 38 studies with 34166 participants

Qualität der Studien:

- The assessment results for the risk of bias of HbA1c: Out of the total studies, 14 studies were evaluated as having low risks of bias, while two studies were deemed to have high risks of bias.
- The risk of bias in the proportion of participants with HbA1c< 7 % was assessed, and the results are shown in Fig. 7. Among the studies, 11 were deemed to have low risks of bias, while the remaining studies presented some concerns regarding the risk of bias.
- The risk studies on BW were assessed: 13 studies were deemed to have low risks of bias. One study was deemed to have a high risk of bias, and the remaining studies presented some concerns regarding the risk of bias.

- The risk of bias of BMI was assessed: 9 studies were deemed to have a low risk of bias, while the remaining studies presented some concerns regarding the risk of bias.
- The risk of bias of GIAEs was assessed: 16 studies were deemed to have a low risk of bias, while the remaining studies presented some concerns regarding the risk of bias.

Studienergebnisse:

- Compared to 1 mg of subcutaneous Sem (Sem SC), 5 mg, 10 mg and 15 mg of Tir demonstrated superior efficacy in reducing HbA1c (mean difference (MD), [95 % CI], −0.22 [−0.40, −0.03] %, −0.42 [−0.60, −0.24] % and −0.53 [−0.71, −0.35] %, respectively) and BW (MD [95 % CI], −1.48 [−2.53, −0.43] kg, −4.00 [−5.05, −2.95] kg and −5.71 [−6.73, −4.68] kg, respectively).
- Conversely, 7 mg and 14 mg of oral Sem (Sem PO) displayed inferior efficacy in reducing HbA1c (MD [95 % CI], 0.47 [0.26, 0.68] % and 0.35 [0.16, 0.54] %, respectively) and BW (MD [95 % CI], 2.36 [1.24, 3.48] kg and 1.11 [0.10, 2.13] kg).
- However, 20 mg and 40 mg of Sem PO were non-inferior in reducing HbA1c (MD [95 % CI], 0.13 [−0.29, 0.55] % and 0.01 [−0.38, 0.40] %, respectively) and BW (MD [95 % CI], −0.41 [−2.71, 1.90] kg and −1.32 [−3.58, 0.92] kg).
- In terms of safety, compared to 1 mg of Sem SC, 5 mg, 10 mg and 15 mg of Tir did not significantly increase the incidence of GIAEs (odd ratio (OR) [95 % CI], 0.70 [0.42, 1.10], 0.87 [0.52, 1.36] and 0.99 [0.60, 1.54], respectively), while 7 mg of Sem PO showed a lower incidence of GIAEs (OR [95 % CI], 0.48 [0.25, 0.83]).
- Compared to insulin, 0.5 mg of Sem SC, 1 mg of Sem SC, 5 mg of Tir, 10 mg of Tir and 15 mg of Tir displayed better efficacy in lowering HbA1c (MD [95 % CI], −0.40 [−0.63, −0.18] %, −0.69 [−0.90, −0.48] %, −0.91 [−1.10, −0.72] %, −1.11 [−1.30, −0.92] % and −1.22 [−1.41, −1.03] %, respectively) and BW (MD [95 % CI], −5.34[−6.60, −4.09] kg, −6.70 [−7.90,−5.51] kg, −8.18 [−9.27, −7.10] kg, −10.70 [−11.79, −9.61] kg and −12.41 [−13.49,−11.33] kg, respectively).
- According to the surface under the cumulative ranking curve (SUCRA) value, among all the included interventions, 15 mg of Tir exhibited the most potent effect in reducing HbA1c (99.81 %) and BW (99.98 %), followed by 10 mg of Tir (96.83 % and 95.72 %), 5 mg of Tir (92.88 % and 86.04 %), 1 mg of Sem SC (85.85 % and 74.97 %), 40 mg of Sem PO (83.66 % and 84.31 %), 20 mg of Sem PO (76.98 % and 77.12 %), 300 mg of Can (49.93 % and 60.89 %), insulin (36.38 % and 0.22 %) and 100 mg of Sit (12.28 % and 18.51 %) respectively.
- Meanwhile, 5 mg, 10 mg, and 15 mg of Tir (48.32 %, 30.96 %, and 21.07 %, respectively), 0.5 mg and 1 mg of Sem SC (33.54 % and 24.77 %, respectively) significantly increased the incidence of GIAEs.

Fazit der Autoren

In summary, Tir and Sem demonstrate favorable antidiabetic effects and acceptable safety profiles, and are especially suitable for T2DM patients with obesity or overweight. Overall, the antidiabetic and BW loss efficacy of Sem SC was superior to that of Sem PO, although the safety of Sem SC was marginally inferior to Sem PO. Tir was the best option among all included interventions.

Shi Q et al., 2023 [60].

Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials

Fragestellung

To compare the benefits and harms of drug treatments for adults with type 2 diabetes

Methodik

Population:

- adults with type 2 diabetes

Intervention/Komparator:

- SGLT-2 inhibitors, GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, sulfonylureas, metformin, α-glucosidase inhibitors, meglitinides, insulins, dual GIP/GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists

Endpunkte:

- Critical:
  - All cause death,
  - cardiovascular death,
  - non-fatal stroke,
  - end stage kidney disease, and
  - amputation;
- Important:
  - non-fatal myocardial infarction,
  - admission to hospital for heart failure,
  - body weight change,
  - health related quality of life,
  - severe hypoglycaemia,
  - severe gastrointestinal events,
  - genital infection,
  - ketoacidosis due to diabetes,
  - and hyperkalaemia leading to admission to hospital.

Recherche/Suchzeitraum:

- Ovid Medline, Embase, and Cochrane Central to 14 October 2022

Qualitätsbewertung der Studien:

- Cochrane risk-of bias tool, modified by the CLARITY group at McMaster University

NMA-Methodik/Überprüfung der zentralen Annahmen für eine NMA

- The evidence did not suggest global publication bias and intransitivity for any outcome (appendix 4.7), nor did the results suggest relevant global inconsistency or incoherence in outcomes except for health related quality of life, body weight change, and amputation (appendices 4.4, 4.5, and 4.6).

  Supplements:

  https://www.bmj.com/content/bmj/suppl/2023/04/06/bmj-2022-074068.DC1/shiq074068.ww.pdf

  Hinweis: Siehe „Kommentare zum Review“ unten.

Ergebnisse

Anzahl eingeschlossener Studien:

- 816

Charakteristika der Population/Studien:

Table 1 | Baseline characteristics of included trials and participants

Characteristic	No/median/pooled mean*	Interquartile or 95% CI	Range or 95% PI
Study settings (of eligible studies)			
Total No of trials	816	—	—
No of participants	471 038	—	—
Follow-up (months)†	6.0	5.5 to 12.0	5.5 to 212.0
Study characteristics (of participants)			
Age (years)‡	57.7	57.4 to 58.1	47.6 to 68.0
No of men (%)‡	56.6	55.8 to 57.5	34.1 to 76.7
Body mass index‡	29.5	29.3 to 29.8	22.7 to 36.4
HbA1c (%)‡	8.1	8.1 to 8.2	6.5 to 9.7
Cardiovascular disease (%)‡	58.9	40.9 to 74.9	0.0 to 100.0
Duration of diabetes (years)*	7.4	5.2 to 10.1	0.0 to 20.7

CI=confidence interval; HbA1c=haemoglobin A1c; PI=prediction interval.
*Pooled mean was estimated using the single mean/proportion meta-analyses via a random effect model.
†Data are median, interquartile, and range.
‡Data are pooled mean, 95% confidence interval, and 95% prediction interval.

Supplements:

https://www.bmj.com/content/bmj/suppl/2023/04/06/bmj-2022-074068.DC1/shiq074068.ww.pdf

Qualität der Studien:

- Of the 816 trials, 223 proved at high risk of bias for at least one of six domains, most commonly because of lack of blinding (62%), missing outcome data (26%), and allocation concealment (25%) (appendix 3).

  Supplements:

  https://www.bmj.com/content/bmj/suppl/2023/04/06/bmj-2022-074068.DC1/shiq074068.ww.pdf

Studienergebnisse:

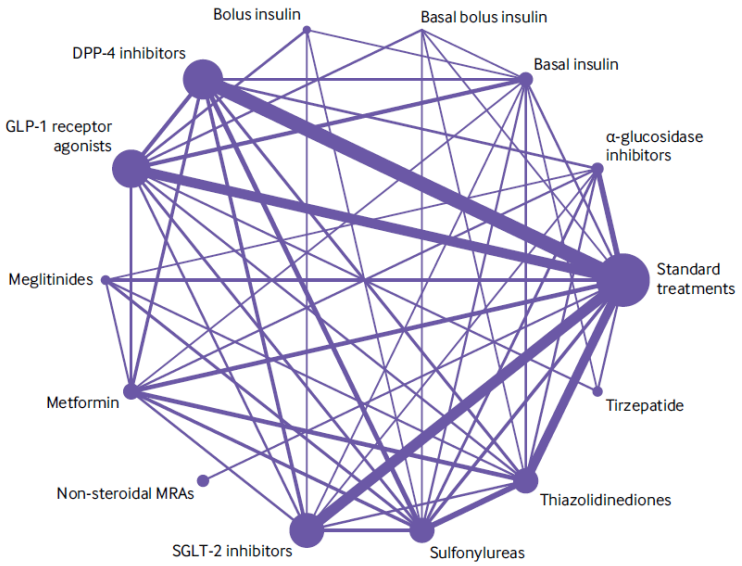


Fig 2 | Network plot for all included studies, by drug treatments. Drug treatments were grouped by their drug classes. Network plots consist of the drug nodes with node size being proportional to the sample size and the comparison edges with line thickness being proportional to the number of trials. MRA=non-steroidal mineralocorticoid receptor antagonists; GLP-1=glucagon-like peptide-1; SGLT-2=sodium glucose cotransporter-2; DPP-4=dipeptidyl peptidase-4

- All cause death and cardiovascular death

  The analysis included 257 trials with 342 237 participants and 15 371 events for all cause mortality, and 144 trials with 275 679 participants and 9120 events for cardiovascular death. SGLT-2 inhibitors (odds ratio 0.88, 95% confidence interval 0.83 to 0.94; high certainty) and GLP-1 receptor agonists (0.88, 0.82 to 0.93; high certainty) reduce all cause mortality, and cardiovascular death (SGLT-2 inhibitors: 0.86, 0.80 to 0.94; GLP-1 receptor agonists: 0.87, 0.81 to 0.94; both high certainty). Non-steroidal mineralocorticoid receptor antagonists probably reduce all cause mortality (0.89, 0.79 to 1.00; moderate certainty) and possibly reduce cardiovascular death (0.88, 0.75 to 1.02; low certainty). Metformin possibly reduces all cause mortality (0.84, 0.67 to 1.04; low certainty) and might have little or no effect on cardiovascular death. DPP-4 inhibitors probably have little or no effect on cardiovascular death (moderate certainty). Sulfonylureas possibly increase all cause mortality (low certainty) and might have little or no effect on cardiovascular death. Other drugs might have little or no or uncertain effect on mortal outcomes (low to very low certainty; fig 3 and appendix 5).
- Non-fatal myocardial infarction and non-fatal stroke

  This analysis included 209 trials with 293 042 participants and 8906 events for non-fatal myocardial infarction, and 178 trials with 283 728 participants and 4878 events for non-fatal stroke. SGLT-2 inhibitors reduce non-fatal myocardial infarction (odds ratio 0.90, 95% confidence interval 0.82 to 0.98; high certainty)—as, probably, do GLP- 1 receptor agonists (0.91, 0.85 to 0.98; moderate certainty) and, possibly, metformin (0.86, 0.68 to 1.09; low certainty). GLP-1 receptor agonists are the only drug class that convincingly reduces non-fatal stroke (0.85, 0.77 to 0.94; high certainty). Other drugs might have little or no or uncertain effects on non-fatal myocardial infarction or stroke, relative to standard treatments (low to very low certainty; fig 3 and appendix 5).
- Admission to hospital for heart failure
- The analysis included 142 trials with 252 055 participants and 6681 events. SGLT-2 inhibitors (odds ratio 0.66, 95% confidence interval 0.60 to 0.73; high certainty) decrease admission to hospital for heart failure as, probably, do GLP-1 receptor agonists (0.91, 0.83 to 0.99; moderate certainty) and finerenone (0.78, 0.66 to 0.92; moderate certainty). SGLT-2 inhibitors and finerenone are among the most effective drugs in this regard and SGLT-2 inhibitors are probably superior to GLP-1 receptor agonists (moderate certainty). Thiazolidinediones probably increase admission to hospital due to heart failure (1.54, 1.27 to 1.88; moderate certainty). Metformin and other drugs might have little or no effect, or uncertain effects (low or very low certainty; fig 3 and appendix 5).
- End stage kidney disease

  The analysis included 54 trials with 209 754 participants and 6972 events. Compared with standard treatments, SGLT-2 inhibitors (odds ratio 0.61, 95% confidence interval 0.55 to 0.67; moderate certainty), GLP-1 receptor agonists (0.83, 0.75 to 0.92; moderate certainty), and finerenone (0.83, 0.75 to 0.92; moderate certainty) probably reduce end stage kidney disease. We rated down the certainty of evidence to moderate owing to indirectness, a result of our composite outcome of end stage kidney disease driven by variable reporting of kidney outcomes in the trials. SGLT-2 inhibitors are among the most effective drugs and are possibly superior to GLP-1 receptor agonists and finerenone (low certainty). Other drugs might have little or no effect, or uncertain effects on end stage kidney disease, relative to standard treatment (very low to low certainty; fig 3 and appendix 5).
- Health related quality of life

We analysed 33 trials with 18 588 participants using 13 types of questionaries (appendix 1.2). SGLT-2 inhibitors, GLP-1 receptor agonists, and tirzepatide probably improve health related quality of life with standardised mean differences ranging from 0.17 to 0.39 (moderate certainty), which did not surpass the minimal important difference (1.7 to 3.9 points in the 36-item short form survey; minimal important difference 10 points). DPP-4 inhibitors probably have little or no effect, and other drugs might have little or uncertain impact on health related quality of life (low or very low certainty; fig 3 and appendix 5).

- Body weight change

  We analysed 531 trials with 279 118 participants. Figure 5 shows that tirzepatide is the most effective drug for reducing body weight (mean reduction 8.57 kg, 95% confidence interval 7.75 to 9.40), followed by individual GLP-1 receptor agonists, SGLT-2 inhibitors (class effect), and metformin with intermediate effects (mean reduction, range 4.62 to 0.72 kg), all high to moderate certainty). Two classes of drugs probably have the biggest effect size in increasing body weight: thiazolidinediones (2.81 kg, moderate certainty) and basal insulin (2.15 kg, moderate certainty). A third, basal bolus insulin, may have a similar effect (increase 3.26 kg, low certainty). Another four drugs have intermediate effects on body weight: sulfonylureas probably increase body weight by 1.78 kg (moderate certainty), meglitinides may increase body weight by 1.26 kg (low certainty), bolus insulin probably increases body weight by 1.01 kg (moderate certainty), and DPP-4 inhibitors probably increase body weight minimally by 0.28 kg (moderate certainty). Other drugs might have little or no effect on body weight (low to very low certainty; fig 5 and appendix 5).

- Severe hypoglycaemia

  We analysed 202 trials with 302 457 participants and 5595 events. Sulfonylureas (odds ratio 5.22, 95% confidence interval 3.88 to 7.01) and basal bolus insulin (4.94, 1.06 to 22.96) probably increase the risk of severe hypoglycaemic events (moderate certainty), with likely smaller increases in risk with basal insulin (2.38, 1.82 to 3.12), bolus insulin (2.46, 1.31 to 4.63), and DPP-4 inhibitors (1.11, 1.00 to 1.23), with and without the contamination of other treatments. Meglitinides and thiazolidinediones may increase the risk of severe hypoglycaemic events (low certainty). SGLT-2 inhibitors and GLP-1 receptor agonists do not increase the risk of severe hypoglycaemic events (high certainty). Finerenone is probably associated with fewer severe hypoglycaemia than the standard treatments (0.64, 0.43 to 0.96, moderate certainty). Other drugs might have little to no effect compared with standard treatments (low to very low certainty; fig 3 and appendix 5).

- Severe gastrointestinal events

  We analysed 37 trials with 65 283 participants and 1661 events. Tirzapetide (odds ratio 4.59, 95% confidence interval 1.89 to 11.14) and GLP-1 receptor agonists (1.97, 1.39 to 2.80) probably increase the risk of severe gastrointestinal adverse events (moderate certainty). Other drugs might have little or no effects compared with standard treatments (low to very low certainty; fig 3 and appendix 5).

- Genital infection

  We analysed 94 trials with 103 111 participants and 2396 events. SGLT-2 inhibitors increase genital infection (odds ratio 3.30, 95% confidence interval 2.88 to 3.78; high certainty). Sulfonylureas may reduce the risk of a genital infection (0.52, 0.36 to 0.75; low certainty). Other drugs might have little to no effect compared with standard treatments (low to very low certainty; fig 3 and appendix 5).

- Amputation

We analysed 18 trials with 107 503 participants and 1150 events. SGLT-2 inhibitors probably increase the risk of amputation (odds ratio 1.27, 95% confidence interval 1.01 to 1.61, moderate certainty); other drugs do not (high to very low certainty; fig 3 and appendix 5). With an estimated baseline risk of 1%, treatment with SGLT-2 inhibitors in 1000 patients for five years probably results in three additional amputations (95% confidence interval 0 to 6; fig 4 and appendix 6). Ketoacidosis due to diabetes We analysed 36 trials with 138 322 participants and 265 events. SGLT-2 inhibitors increase the risk of ketoacidosis due to diabetes (odds ratio 2.07, 95% confidence interval 1.44 to 2.98; high certainty); other drugs do not (high to very low certainty; fig 3 and appendix 5). With an estimated baseline risk of 0.2%, treatment with SGLT-2 inhibitors in 1000 patients for five years probably results in two more events with ketoacidosis due to diabetes (95% confidence interval 1 to 4; fig 4 and appendix 6).

- Hyperkalaemia leading to admission to hospital

  We analysed two trials with 12 999 participants and 71 events for the non-steroidal mineralocorticoid receptor antagonists, which probably increase the risk of hyperkalaemia leading to admission to hospital (odds ratio 5.92, 95% confidence interval 3.02 to 11.62; moderate certainty). With an estimated baseline risk of 0.2%, treatment with non-steroidal mineralocorticoid receptor antagonists in 1000 patients for five years probably results in 10 additional events (95% confidence interval 4 to 21; fig 4 and appendix 6).

- Subgroup analyses and sensitivity analyses

  Our study did not identify any credible subgroup effects (appendix 7) and all sensitivity analyses confirmed the robustness of our findings (appendix 8).

Interventions	All cause death (OR, 95%CI)	Cardiovascular death (OR, 95%CI)	Non-fatal myocardial infarction (OR, 95%CI)	Non-fatal stroke (OR, 95%CI)	Admission to hospital for heart failure (OR, 95%CI)	End stage kidney disease* (OR, 95%CI)	Health related quality of life score (OR, 95%CI)	Severe hypoglycaemia (OR, 95%CI)	Drug specific adverse events (OR, 95%CI)
SGLT-2 inhibitors	**0.88 (0.83 to 0.94)**	**0.86 (0.80 to 0.94)**	**0.90 (0.82 to 0.98)**	0.99 (0.88 to 1.11)	**0.66 (0.60 to 0.73)**	**0.61 (0.55 to 0.67)**	**0.30 (0.10 to 0.49)**	0.90 (0.79 to 1.02)	Genital infection 3.30 (2.88 to 3.78) Amputation 1.27 (1.01 to 1.61) Ketoacidosis 2.07 (1.44 to 2.98)
GLP-1 receptor agonists	**0.88 (0.82 to 0.93)**	**0.87 (0.81 to 0.94)**	**0.91 (0.85 to 0.98)**	**0.85 (0.77 to 0.94)**	0.91 (0.83 to 0.99)	0.83 (0.75 to 0.92)	**0.17 (0.07 to 0.27)**	0.98 (0.90 to 1.06)	Severe gastrointestinal events 1.97 (1.39 to 2.80)
Non-steroidal MRAs	**0.89 (0.79 to 1.00)**	0.88 (0.75 to 1.02)	0.91 (0.74 to 1.12)	1.00 (0.82 to 1.22)	**0.78 (0.66 to 0.92)**	0.83 (0.75 to 0.92)	-	**0.64 (0.43 to 0.96)**	Hyperkalaemia leading to hospital admission 5.92 (3.02 to 11.62)
Tirzepatide	0.83 (0.48 to 1.44)	1.00 (0.35 to 2.85)	0.69 (0.08 to 6.10)	-	0.63 (0.16 to 2.39)	0.68 (0.09 to 4.84)	**0.39 (0.13 to 0.65)**	1.13 (0.42 to 3.02)	Severe gastrointestinal events 4.59 (1.89 to 11.14)
Metformin	0.84 (0.67 to 1.04)	0.95 (0.48 to 1.88)	0.86 (0.68 to 1.09)	0.97 (0.71 to 1.33)	1.45 (0.28 to 7.36)	1.61 (0.36 to 7.24)	0.04 (-0.25 to 0.33)	1.73 (0.89 to 3.37)	Severe gastrointestinal events 2.22 (0.64 to 7.71)
α-glucosidase inhibitors	0.89 (0.30 to 2.61)	0.99 (0.21 to 4.70)	0.33 (0.06 to 1.92)	9.44 (0.76 to 116.58)	3.25 (0.13 to 82.49)	-	0.03 (-0.34 to 0.39)	1.30 (0.31 to 5.43)	Severe gastrointestinal events 3.40 (0.30 to 38.15)
Thiazolid-inediones	0.95 (0.83 to 1.09)	0.93 (0.77 to 1.12)	0.97 (0.81 to 1.15)	0.85 (0.70 to 1.03)	**1.54 (1.27 to 1.88)**	0.69 (0.37 to 1.28)	0.20 (-0.13 to 0.52)	1.42 (0.97 to 2.10)	-
DPP-4 inhibitors	1.01 (0.95 to 1.08)	1.00 (0.92 to 1.09)	1.01 (0.92 to 1.11)	0.91 (0.80 to 1.03)	1.05 (0.95 to 1.16)	1.04 (0.93 to 1.16)	0.03 (-0.12 to 0.17)	1.11 (1.00 to 1.23)	-
Sulfonylureas	1.10 (0.97 to 1.26)	1.01 (0.83 to 1.23)	1.00 (0.83 to 1.22)	1.05 (0.84 to 1.32)	0.99 (0.79 to 1.23)	0.68 (0.37 to 1.24)	0.23 (-0.19 to 0.64)	**5.22 (3.88 to 7.01)**	-
Meglitinides	1.58 (0.51 to 4.92)	0.64 (0.11 to 3.69)	0.28 (0.05 to 1.60)	1.71 (0.26 to 11.40)	-	-	0.17 (-0.29 to 0.63)	3.21 (0.96 to 10.75)	-
Basal insulin	1.10 (0.81 to 1.49)	1.28 (0.83 to 1.99)	0.98 (0.47 to 2.06)	0.76 (0.33 to 1.77)	0.94 (0.62 to 1.43)	1.20 (0.62 to 2.30)	0.00 (-0.25 to 0.24)	2.38 (1.82 to 3.12)	-
Basal bolus insulin	0.79 (0.19 to 3.32)	2.23 (0.23 to 21.92)	0.33 (0.03 to 3.27)	0.58 (0.10 to 3.35)	-	-	-	**4.94 (1.06 to 22.96)**	-
Bolus insulin	0.48 (0.15 to 1.59)	1.05 (0.11 to 10.26)	1.18 (0.40 to 3.50)	0.86 (0.16 to 4.48)	0.64 (0.07 to 6.22)	2.55 (0.10 to 62.86)	-0.11 (-0.29 to 0.07)	2.46 (1.31 to 4.63)	-
Standard treatments	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate effective	Possibly among the intermediate effective
Not convincingly different from standard treatment	Possibly not convincingly different from standard treatment
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

Fig 3 | Benefits and harms of drug treatments for type 2 diabetes. Figure shows benefits and harms of the drugs for diabetes with the estimates that represent the comparative effects of the drugs compared with standard treatments. The GRADE (grading of recommendations, assessment, development, and evaluations) approach was used with a null effect threshold to rate and categorise drugs from among the most effective to among the most harmful. Any 95% confidence intervals touching but not crossing the decision threshold (ie, the null effect), were not rated down for imprecision. Drugs that were superior to (or inferior to) standard treatments (ie, point estimate exceeding (or falling below) the null effect and the 95% confidence interval not crossing) were first categorised into the most effective group (or the most harmful group). Drugs among the most effective (or most harmful) but inferior to (ie, point estimate falling below and 95% confidence interval not crossing) at least one drug in that group were then categorised into the intermediate effective group (or the intermediate harmful group). Non-steroidal mineralocorticoid receptor antagonists (MRAs) mainly refer to finerenone. *End stage kidney disease was defined as a composite of a long term dialysis, kidney transplantation, sustained estimated glomerular filtration rate <15 mL per min per 1.73 m^2 for ≥30 days, sustained percent decline in estimated glomerular filtration rate of at least 40% for ≥30 days or a doubling of serum creatinine, or renal death; effects on end stage kidney disease were rated down owing to indirectness. CI=confidence interval; GLP-1=glucagon-like peptide-1; OR=odds ratio; SGLT-2=sodium glucose cotransporter-2

Interventions	All cause death	Cardiovascular death	Non-fatal myocardial infarction	Non-fatal stroke	Admission to hospital for heart failure	End stage kidney disease	Severe hypoglycaemia	Drug specific adverse events
Baseline risks	170 per 1000 patients	112 per 1000 patients	120 per 1000 patients	120 per 1000 patients	105 per 1000 patients	92 per 1000 patients	30 per 1000 patients	-
SGLT-2 inhibitors	**17 fewer (25 fewer to 9 fewer)**	**14 fewer (20 fewer to 6 fewer)**	**11 fewer (19 fewer to 2 fewer)**	1 fewer (13 fewer to 11 more)	**33 fewer (39 fewer to 26 fewer)**	**34 fewer (39 fewer to 28 fewer)**	3 fewer (6 fewer to 1 more)	Genital infection 133 more (112 more to 156 more) Amputation 3 more (0 to 6 more) Ketoacidosis 2 more (1 more to 4 more)
GLP-1 receptor agonists	**17 fewer (26 fewer to 10 fewer)**	**13 fewer (19 fewer to 6 fewer)**	**10 fewer (16 fewer to 2 fewer)**	**16 fewer (25 fewer to 6 fewer)**	9 fewer (16 fewer to 1 fewer)	14 fewer (21 fewer to 7 fewer)	1 fewer (3 fewer to 2 more)	Severe gastrointestinal events 40 more (16 more to 72 more)
Non-steroidal MRAs	**16 fewer (31 fewer to 0)**	12 fewer (26 fewer to 2 more)	10 fewer (28 fewer to 12 more)	0 (19 fewer to 23 more)	**21 fewer (33 fewer to 8 fewer)**	14 fewer (21 fewer to 7 fewer)	**11 fewer (17 fewer to 1 fewer)**	Hyperkalaemia leading to admission to hospital 10 more (4 more to 21 more)
Tirzepatide	25 fewer (80 fewer to 58 more)	0 (70 fewer to 152 more)	34 fewer (109 fewer to 334 more)	-	36 fewer (87 fewer to 114 more)	28 fewer (83 fewer to 237 more)	4 more (17 fewer to 55 more)	Severe gastrointestinal events 133 more (37 more to 299 more)
Metformin	23 fewer (49 fewer to 6 more)	5 fewer (55 fewer to 80 more)	15 fewer (35 fewer to 9 more)	3 fewer (32 fewer to 34 more)	40 more (73 fewer to 358 more)	48 more (57 fewer to 331 more)	21 more (3 fewer to 64 more)	Severe gastrointestinal events 50 more (16 fewer to 221 more)
α-glucosidase inhibitors	16 fewer (112 fewer to 178 more)	1 fewer (86 fewer to 260 more)	77 fewer (112 fewer to 87 more)	443 more (26 fewer to 821 more)	171 more (90 fewer to 801 more)	-	9 more (21 fewer to 114 more)	Severe gastrointestinal events 93 more (31 fewer to 598 more)
Thiazolid-inediones	7 fewer (25 fewer to 13 more)	7 fewer (23 fewer to 12 more)	3 fewer (21 fewer to 16 more)	16 fewer (33 fewer to 3 more)	48 more (25 more to 76 more)	27 fewer (56 fewer to 23 more)	12 more (1 fewer to 31 more)	-
DPP-4 inhibitors	1 more (7 fewer to 11 more)	0 (8 fewer to 9 more)	1 more (9 fewer to 11 more)	10 fewer (22 fewer to 3 more)	5 more (5 fewer to 15 more)	3 more (6 fewer to 13 more)	3 more (0 to 7 more)	-
Sulfonylureas	14 more (4 fewer to 35 more)	1 more (17 fewer to 22 more)	0 (18 fewer to 23 more)	5 more (17 fewer to 33 more)	1 fewer (20 fewer to 21 more)	28 fewer (56 fewer to 20 more)	109 more (77 more to 148 more)	-
Meglitinides	74 more (75 fewer to 332 more)	37 fewer (98 fewer to 206 more)	83 fewer (113 fewer to 59 more)	69 more (86 fewer to 489 more)	-	-	60 more (1 fewer to 220 more)	-
Basal insulin	14 more (28 fewer to 64 more)	27 more (17 fewer to 89 more)	2 fewer (60 fewer to 99 more)	26 fewer (77 fewer to 74 more)	6 fewer (37 fewer to 39 more)	16 more (33 fewer to 97 more)	39 more (23 more to 58 more)	-
Basal bolus insulin	31 fewer (133 fewer to 235 more)	108 more (84 fewer to 622 more)	77 fewer (116 fewer to 188 more)	47 fewer (107 fewer to 194 more)	-	-	103 more (2 more to 385 more)	-
Bolus insulin	80 fewer (140 fewer to 76 more)	5 more (98 fewer to 452 more)	19 more (68 fewer to 203 more)	15 fewer (99 fewer to 259 more)	35 fewer (97 fewer to 317 more)	113 more (82 fewer to 772 more)	41 more (9 more to 95 more)	-
Standard treatments	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate effective	Possibly among the intermediate effective
Not convincingly different from standard treatment	Possibly not convincingly different from standard treatment
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

Fig 4 | Anticipated absolute effects for patients with type 2 diabetes and chronic kidney disease, by drug treatment. Figure shows absolute benefits and harms of the drugs for patients with type 2 diabetes and chronic kidney disease. Estimates represent risk differences per 1000 patients in five years compared with standard treatments. Absolute effects were anticipated by applying the relative effects to the baseline risks adopted from a previous guideline panel. Figure is restricted to adults with type 2 diabetes and chronic kidney disease as an example, with the full populations in appendix 6 and the online tool (https://qingys.shinyapps.io/data_visualization) or the MATCH-IT tool (https://matchit.magicevidence.org/230125dist-diabetes). Non-steroidal mineralocorticoid receptor antagonists (MRAs) mainly refer to finerenone. GLP-1=glucagon-like peptide-1 SGLT-2=sodium glucose cotransporter-2

Interventions	Bodyweight change (kg, MD, 95%CI)
Tirzepatide	-8.57 (-9.40 to -7.75)
Semaglutide (subcutaneous)	-4.62 (-5.22 to -4.03)
Semaglutide (oral)	-2.98 (-3.66 to -2.29)
Efpeglenatide	-2.59 (-4.40 to -0.78)
Liraglutide	-2.21 (-2.58 to -1.85)
SGLT-2 inhibitors	-1.98 (-2.18 to -1.78)
Exenatide immediate release	-1.77 (-2.47 to -1.07)
Dulaglutide	-1.40 (-1.93 to -0.88)
Exenatide extended release	-1.05 (-1.67 to -0.42)
Lixisenatide	-0.83 (-1.40 to -0.26)
Metformin	-0.83 (-1.16 to -0.51)
Albiglutide	-0.72 (-1.35 to -0.08)
α-glucosidase inhibitors	-0.38 (-0.80 to 0.04)
Loxenatide	0.16 (-1.72 to 2.04)
DPP-4 inhibitors	0.28 (0.11 to 0.46)
Bolus insulin	1.01 (0.24 to 1.79)
Meglitinides	1.26 (0.58 to 1.94)
Sulfonylureas	1.78 (1.50 to 2.06)
Basal insulin	2.15 (1.74 to 2.56)
Thiazolidinediones	2.81 (2.55 to 3.07)
Basal bolus insulin	3.26 (2.10 to 4.41)
Standard treatments	Reference

High to moderate certainty evidence

Among the most effective
Among the intermediate effective
Not convincingly different from standard treatment
Among the intermediate harmful
Among the most harmful

Low to very low certainty evidence

Possibly among the most effective
Possibly among the intermediate effective
Possibly not convincingly different from standard treatment
Possibly among the intermediate harmful
Possibly among the most harmful

Fig 5 | Body weight impact of drug treatment for type 2 diabetes by drug treatment. Figure shows body weight changes of the drugs for diabetes with the estimates that represent the comparative effects of the drugs compared with standard treatments. The GRADE (grading of recommendations, assessment, development, and evaluations) approach was used with a null effect threshold to rate and categorise drugs from among the most effective to among the most harmful. Any 95% confidence intervals touching but not crossing the decision threshold (ie, the null effect) were not rated down for imprecision. Drugs that were superior to (or inferior to) standard treatments (ie, point estimate exceeding (or falling below) the null effect and the 95% confidence interval not crossing) were first categorised into the most effective group (or the most harmful group). Drugs among the most effective (or the most harmful) but inferior to (ie, point estimate falling below and 95% confidence interval not crossing) at least one drug in that group were then categorised into the intermediate effective group (or the intermediate harmful group). CI=confidence interval; DPP-4=dipeptidyl peptidase-4; MD=mean difference; SGLT-2=sodium glucose cotransporter-2

Anmerkung/Fazit der Autoren

Among all drug classes, SGLT-2 inhibitors, GLP-1 receptor agonists, and finerenone show benefits in reducing all cause mortality, admission to hospital due to heart failure (SGLT-2 inhibitors and—probably— finerenone are the most effective drug treatments), and end stage kidney disease (SGLT-2 inhibitors are the most effective drug treatments). Only GLP-1 receptor agonists convincingly reduce non-fatal stroke. SGLT-2 inhibitors, GLP-1 receptor agonists, and tirzepatide improve health related quality of life, but did not reach the threshold for minimal important differences, suggesting trivial effects. As illustrated in the MATCH-IT tool, the absolute benefits of these drugs vary greatly in people with type 2 diabetes depending on baseline risks for cardiovascular and kidney outcomes 23 (appendix 6).

Summary

- Compared with standard treatments, adding finerenone probably reduces all cause mortality, admission to hospital for heart failure, and end stage kidney disease, while adding tirzepatide could reduce body weight
- Compared with standard treatments, findings indicate that adding SGLT-2 inhibitors or GLP-1 receptor agonists reduces all cause mortality, cardiovascular death, non-fatal

myocardial infarction, admission to hospital for heart failure, and end stage kidney disease, while adding only GLP-1 receptor agonists reduces non-fatal stroke

- Compared with standard treatments, adding metformin possibly reduces all cause mortality and non-fatal myocardial infarction, adding sulfonylureas possibly increases all cause mortality, and adding thiazolidinediones probably increases admission to hospital due to heart failure

Limitations

Firstly, for many outcomes that are important to patients, we found low to very low certainty evidence for the oldest as well as the newest classes of drugs, including metformin, sulfonylureas, tirzepatide, and non-steroidal mineralocorticoid receptor antagonists. […] Thirdly, owing to sparse direct evidence and limited reporting of outcomes important to patients, we adopted a composite outcome definition for end stage kidney disease that included a surrogate component. This resulted in moderate certainty of evidence for the effects of all drugs on end stage kidney disease, given the inherent indirectness. Fourthly, this study did not consider the dose-response of each drug.

Kommentare zum Review

Hinsichtlich der Grundlagen für die Durchführung einer Netzwerkmetaanalyse, kann aufgrund begrenzter Information nicht abschließend beurteiltet werden, ob die zentrale Annahme der Transitivität erfüllt ist. Dies ist als wesentliche Limitation bei der Interpretation der Ergebnisse zu berücksichtigen.

Tsapas A et al., 2020 [64].

Comparative effectiveness of glucose-lowering drugs for type 2 diabetes. A systematic review and network meta-analysis.

Fragestellung

This systematic review and network meta-analysis of randomized controlled trials assesses the long-term effects of antidiabetic drugs on clinically important outcomes in clinically relevant subpopulations.

Methodik

Population:

- adults with type 2 diabetes

Intervention/ Komparator:

- glucose-lowering drugs that had been approved or had pending applications for regulatory authorization in Europe or the United States.
- Comparisons among the following single interventions were included:
  - metformin,
  - sulphonylureas,
  - pioglitazone,
  - dipeptidyl peptidase-4 (DPP-4) inhibitors,
  - GLP-1 RAs,
  - SGLT-2 inhibitors,

- basal insulin, basal–bolus insulin regimens (including basal-plus insulin), premixed insulins,
- a-glucosidase inhibitors,
- meglitinides,
- or placebo.

In each comparison, background treatment was defined as the antidiabetic medication therapy used in both the intervention and control groups after randomization. Eligible background therapy was either no background treatment (monotherapy) or metformin-based background treatment (metformin only or metformin plus any other antidiabetic medication).

Endpunkte:

- primary outcomes: change from baseline in HbA1c level and all-cause mortality
- Secondary outcomes: severe hypoglycemia, cardiovascular death, stroke, myocardial infarction, hospitalization for heart failure, diabetic retinopathy, and amputation
- data for end-stage renal disease

Recherche/Suchzeitraum:

- We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception through 18 December 2019 (without language restrictions)

Qualitätsbewertung der Studien

revised Cochrane Collaboration Risk of Bias tool RoB2.0.

NMA-Methodik/Überprüfung der zentralen Annahmen für eine NMA

- Initially, we did pairwise meta-analyses and then explored the transitivity assumption that a network meta-analysis approach was appropriate by comparing the distribution of potential effect modifiers across treatment comparisons (duration of diabetes, age, hemoglobin A1c level at baseline, and body mass index)
- We did frequentist random-effects network metaanalyses and calculated mean differences (MDs) for the change in hemoglobin A1c level and odds ratios (ORs) and 95% CIs for dichotomous outcomes, assuming a common heterogeneity variable across all comparisons. In case of sparse networks, we used a fixed-effects model, given that the common between-study heterogeneity cannot be estimated reliably in such networks
- We evaluated heterogeneity by comparing the magnitude of the common between-study variance for each outcome with empirical distributions of heterogeneity variances
- We evaluated consistency in the networks both locally by comparing direct with indirect evidence and globally by using the design-by-treatment interaction mode

Ergebnisse

Anzahl eingeschlossener Studien:

- 453 trials assessing 21 antidiabetic interventions from 9 drug classes

Charakteristika der Studien/Population:

- In 134 trials (41 862 patients), treatment interventions were used as monotherapy, of which 101 studies were in drug-naive patients, whereas the remaining studies recruited patients who had received antidiabetic treatment in the past but had all prior medication withdrawn at randomization.

- In 296 trials (264 087 patients), treatment interventions were used as an add-on to metformin-based therapy (metformin only or metformin plus any other antidiabetic medication). The remaining 23 studies (14 525 patients) included both groups that evaluated treatments as monotherapy and groups with patients receiving background metformin-based therapy. The median duration of trials was 26 weeks (interquartile range, 24 to 52 weeks).
- Three hundred studies had a double-blind design, 127 were open label, and 5 were single-blind; blinding status was unclear in the remaining studies.
- Mean hemoglobin A1c level at baseline was 8.3% (SD, 0.76%), and mean body weight was 85.1 kg (SD, 9.17).
- The median HbA1c level was 8.2% (interquartile range, 7.9% to 8.7%) in monotherapy trials and 8.2% (interquartile range, 8.0% to 8.5%) in trials with drugs as an add-on to metformin-based therapy.
- The median duration of diabetes across all trials was 6.9 years (interquartile range, 4.6 to 9.3 years).

Qualität der Studien:

- Regarding change in hemoglobin A1c level, 224 trials (58%) had low overall risk of bias.
- For allcause mortality, overall risk of bias was low in 80 trials(20%), whereas 292 trials (74%) had high risk of bias

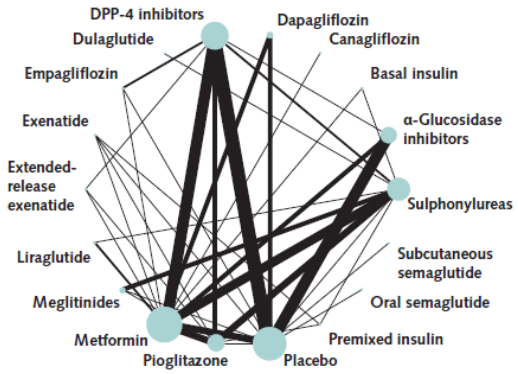
NMA

- On the basis of the distribution of potential effect modifiers (duration of diabetes, age, hemoglobin A1c level at baseline, and body mass index) across all treatment comparisons, eligible trials were deemed sufficiently similar to assume that a network meta-analysis was appropriate
- There was no evidence of heterogeneity for any outcome except for change in hemoglobin A1c level in both subnetworks and for diabetic retinopathy and amputation in the subnetwork of patients at increased cardiovascular risk receiving metformin-based background therapy
- The design-by-treatment interaction model did not identify global inconsistency in any of the networks, except for change in hemoglobin A1c level in the network of drug-naive patients. Local inconsistency in all analyses was generally low

Drug-Naive Patients

Glycemic Outcomes

Netzwerkgeometrie HbA1c



Results

- All treatments reduced HbA1c level compared with placebo, with MDs ranging from -1.48% (95% CI, -2.15% to -0.81%) for subcutaneous semaglutide to -0.60% (CI, -0.75% to -0.46%) for DPP-4 inhibitors (moderate confidence).

12.1.1. Change in HbA1c

aGIs										
0.39 (-0.23, 1.01)	Basal insulin									
-0.12 (-0.33, 0.08)	-0.51 (-1.12, 0.09)	DPP-4i								
0.40 (0.12, 0.69)	0.02 (-0.62, 0.65)	**0.53 (0.28, 0.78)**	GLP-1 RAs							
0.04 (-0.29, 0.36)	-0.35 (-1.01, 0.31)	0.16 (-0.14, 0.47)	**-0.37 (-0.73, -0.01)**	Meglitinides						
0.19 (-0.01, 0.38)	-0.20 (-0.79, 0.39)	**0.31 (0.17, 0.45)**	-0.22 (-0.47, 0.03)	0.15 (-0.15, 0.45)	Metformin					
0.17 (-0.07, 0.41)	-0.22 (-0.83, 0.39)	**0.29 (0.10, 0.48)**	-0.24 (-0.51, 0.03)	0.13 (-0.19, 0.45)	-0.02 (-0.19, 0.16)	Pioglitazone				
0.36 (-0.21, 0.93)	-0.03 (-0.83, 0.78)	0.49 (-0.07, 1.04)	-0.04 (-0.59, 0.50)	0.32 (-0.28, 0.93)	0.18 (-0.37, 0.72)	0.19 (-0.35, 0.74)	Premixed insulin			
0.11 (-0.16, 0.37)	-0.28 (-0.91, 0.35)	**0.23 (0.01, 0.45)**	-0.30 (-0.60, 0.01)	0.07 (-0.28, 0.42)	-0.08 (-0.29, 0.13)	-0.06 (-0.32, 0.20)	-0.25 (-0.83, 0.33)	SGLT-2i		
0.12 (-0.10, 0.33)	-0.27 (-0.88, 0.33)	**0.24 (0.06, 0.42)**	**-0.29 (-0.55, -0.03)**	0.08 (-0.20, 0.36)	-0.07 (-0.24, 0.10)	-0.05 (-0.25, 0.15)	-0.25 (-0.80, 0.30)	0.01 (-0.25, 0.26)	SU	
-0.73 (-0.91, -0.56)	**-1.12 (-1.73, -0.52)**	**-0.61 (-0.75, -0.47)**	**-1.14 (-1.38, -0.89)**	**-0.77 (-1.06, -0.48)**	**-0.92 (-1.06, -0.77)**	**-0.90 (-1.10, -0.70)**	**-1.09 (-1.65, -0.54)**	**-0.84 (-1.06, -0.63)**	**-0.85 (-1.03, -0.67)**	Placebo

Treatments are reported in alphabetical order. Treatment estimates are MDs and 95% CIs in the column-defining treatment compared to the row-defining treatment. MDs lower than 0 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- All treatments reduced HbA1c level to a similar extent with metformin, except for DPP-4 inhibitors (MD, 0.32% [CI, 0.17% to 0.46%]), which were also inferior to liraglutide, subcutaneous semaglutide, pioglitazone, and sulphonylureas.

12.2. Mean differences for comparisons between drug classes and individual GLP-1 RAs and SGLT-2 inhibitors

12.2.1. Change in HbA1c

aGIs																
0.39 (-0.24, 1.02)	Basal insulin															
0.28 (-0.39, 0.96)	-0.11 (-0.99, 0.78)	Canagliflozin														
0.09 (-0.23, 0.42)	-0.30 (-0.96, 0.37)	-0.19 (-0.89, 0.51)	Dapagliflozin													
-0.13 (-0.34, 0.08)	-0.52 (-1.14, 0.10)	-0.42 (-1.07, 0.24)	-0.22 (-0.52, 0.08)	DPP-4i												
0.55 (-0.12, 1.23)	0.16 (-0.73, 1.05)	0.27 (-0.65, 1.19)	0.46 (-0.25, 1.18)	**0.68 (0.02, 1.35)**	Dulaglutide											
0.08 (-0.31, 0.47)	-0.31 (-1.01, 0.39)	-0.20 (-0.94, 0.53)	-0.01 (-0.46, 0.44)	0.21 (-0.14, 0.57)	-0.47 (-1.22, 0.27)	Empagliflozin										
0.25 (-0.22, 0.71)	-0.14 (-0.89, 0.60)	-0.04 (-0.81, 0.74)	0.16 (-0.35, 0.67)	0.38 (-0.06, 0.82)	-0.31 (-1.09, 0.48)	0.17 (-0.39, 0.72)	Exenatide									
0.18 (-0.39, 0.74)	-0.21 (-1.02, 0.60)	-0.11 (-0.94, 0.73)	0.09 (-0.51, 0.69)	0.31 (-0.23, 0.85)	-0.37 (-1.22, 0.47)	0.10 (-0.54, 0.74)	-0.07 (-0.75, 0.61)	Exenatide ER								
0.72 (-0.02, 1.45)	0.33 (-0.61, 1.26)	0.43 (-0.53, 1.39)	0.62 (-0.14, 1.39)	**0.85 (0.12, 1.57)**	0.16 (-0.80, 1.13)	0.64 (-0.16, 1.43)	0.47 (-0.37, 1.30)	0.54 (-0.36, 1.43)	Liraglutide							
0.04 (-0.29, 0.37)	-0.35 (-1.02, 0.32)	-0.24 (-0.96, 0.47)	-0.05 (-0.45, 0.35)	0.17 (-0.14, 0.48)	-0.51 (-1.21, 0.19)	-0.04 (-0.50, 0.42)	-0.21 (-0.72, 0.31)	-0.14 (-0.75, 0.47)	-0.67 (-1.45, 0.10)	Meglitinides						
0.18 (-0.02, 0.39)	-0.21 (-0.81, 0.40)	-0.10 (-0.74, 0.54)	0.09 (-0.19, 0.38)	**0.32 (0.17, 0.46)**	-0.37 (-1.03, 0.30)	0.10 (-0.26, 0.47)	-0.06 (-0.50, 0.37)	0.01 (-0.53, 0.54)	-0.53 (-1.25, 0.18)	0.14 (-0.16, 0.45)	Metformin					
0.15 (-0.10, 0.40)	-0.24 (-0.86, 0.39)	-0.13 (-0.80, 0.53)	0.06 (-0.27, 0.39)	**0.28 (0.09, 0.48)**	-0.40 (-1.07, 0.27)	0.07 (-0.32, 0.46)	-0.09 (-0.54, 0.35)	-0.03 (-0.57, 0.52)	-0.56 (-1.30, 0.17)	0.11 (-0.22, 0.44)	-0.03 (-0.21, 0.15)	Pioglitazone				
0.29 (-0.31, 0.89)	-0.10 (-0.93, 0.74)	0.01 (-0.86, 0.87)	0.20 (-0.44, 0.84)	0.42 (-0.16, 1.01)	-0.26 (-1.13, 0.60)	0.21 (-0.46, 0.89)	0.04 (-0.55, 0.64)	0.11 (-0.67, 0.89)	-0.42 (-1.34, 0.49)	0.25 (-0.39, 0.89)	0.11 (-0.47, 0.69)	0.14 (-0.43, 0.71)	Premixed insulin			
0.37 (-0.31, 1.04)	-0.02 (-0.92, 0.88)	0.08 (-0.85, 1.01)	0.27 (-0.44, 0.99)	0.50 (-0.17, 1.17)	-0.19 (-1.12, 0.75)	0.29 (-0.46, 1.03)	0.12 (-0.67, 0.90)	0.19 (-0.67, 1.04)	-0.35 (-1.33, 0.63)	0.33 (-0.39, 1.04)	0.18 (-0.49, 0.85)	0.21 (-0.47, 0.90)	0.07 (-0.80, 0.95)	Semaglutide PO		
0.75 (0.06, 1.44)	0.36 (-0.55, 1.27)	0.46 (-0.48, 1.40)	0.65 (-0.07, 1.38)	**0.88 (0.20, 1.56)**	0.19 (-0.75, 1.14)	0.67 (-0.09, 1.42)	0.50 (-0.30, 1.29)	0.57 (-0.29, 1.43)	0.03 (-0.96, 1.02)	0.71 (-0.02, 1.44)	0.56 (-0.12, 1.24)	0.59 (-0.10, 1.29)	0.45 (-0.43, 1.34)	0.38 (-0.55, 1.31)	Semaglutide SC	
0.12 (-0.10, 0.35)	-0.27 (-0.89, 0.35)	-0.16 (-0.83, 0.50)	0.03 (-0.29, 0.35)	**0.25 (0.06, 0.45)**	-0.43 (-1.07, 0.21)	0.04 (-0.34, 0.43)	-0.12 (-0.58, 0.33)	-0.06 (-0.61, 0.50)	-0.59 (-1.32, 0.13)	0.08 (-0.21, 0.37)	-0.06 (-0.24, 0.11)	-0.03 (-0.24, 0.18)	-0.17 (-0.75, 0.42)	-0.24 (-0.92, 0.44)	-0.62 (-1.32, 0.07)	SU

Treatments are reported in alphabetical order. Treatment estimates are MDs and 95% CIs in the column-defining treatment compared to the row-defining treatment. MDs lower than 0 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os, SC=subcutaneous. SU=sulphonylureas.

- For all treatments, there was no difference versus placebo or metformin in the incidence of severe hypoglycemia (59 studies; 24 479 patients).

12.1.2. Severe hypoglycemia

aGIs										
0.83 (0.04, 19.11)	Basal insulin									
1.15 (0.26, 4.99)	1.39 (0.07, 26.45)	DPP-4i								
1.53 (0.25, 9.25)	1.85 (0.08, 41.48)	1.34 (0.32, 5.63)	GLP-1 RAs							
1.25 (0.06, 27.72)	1.51 (0.03, 89.20)	1.09 (0.06, 20.91)	0.81 (0.04, 18.04)	Meglitinides						
1.12 (0.27, 4.66)	1.36 (0.08, 23.43)	0.98 (0.41, 2.34)	0.73 (0.18, 2.91)	0.90 (0.05, 17.51)	Metformin					
1.20 (0.17, 8.41)	1.45 (0.06, 34.64)	1.04 (0.24, 4.57)	0.78 (0.13, 4.59)	0.96 (0.04, 24.18)	1.06 (0.24, 4.74)	Pioglitazone				
0.95 (0.05, 18.81)	1.15 (0.02, 54.94)	0.83 (0.05, 13.18)	0.62 (0.04, 9.88)	0.76 (0.01, 39.17)	0.85 (0.06, 12.93)	0.80 (0.05, 13.17)	Premixed insulin			
1.47 (0.25, 8.63)	1.78 (0.08, 39.33)	1.28 (0.34, 4.90)	0.96 (0.17, 5.50)	1.18 (0.05, 26.15)	1.31 (0.37, 4.61)	1.23 (0.19, 7.94)	1.55 (0.08, 29.52)	SGLT-2i	.	
0.59 (0.12, 2.89)	0.72 (0.04, 12.39)	0.52 (0.16, 1.71)	0.39 (0.09, 1.72)	0.48 (0.02, 10.00)	0.53 (0.19, 1.44)	0.50 (0.09, 2.60)	0.62 (0.04, 9.20)	0.40 (0.09, 1.88)	SU	
0.88 (0.22, 3.45)	1.06 (0.05, 20.96)	0.77 (0.28, 2.07)	0.57 (0.15, 2.24)	0.70 (0.04, 11.36)	0.78 (0.28, 2.19)	0.73 (0.14, 3.77)	0.92 (0.06, 14.97)	0.60 (0.15, 2.33)	1.48 (0.43, 5.10)	Placebo

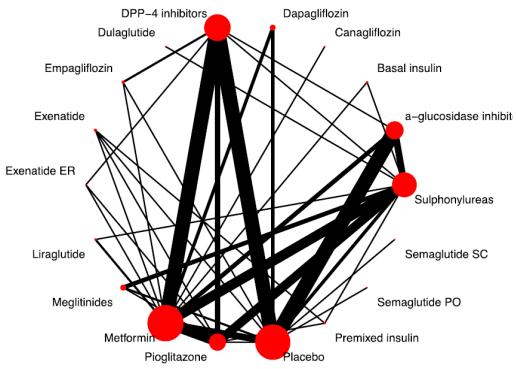
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

Mortality and Vascular Outcomes

- We did not identify any trials exclusively recruiting drug-naive patients at increased cardiovascular risk; hence, for mortality and vascular outcomes, all trials in drug-naive patients were analyzed in a single network. Of note, patients in these trials likely had low underlying cardiovascular risk given that no cardiovascular deaths were reported among patients in the placebo groups.

Netzwerkgeometrie All cause mortality (P: at low cardiovascular risk)

5.2.1. All-cause mortality



Results

- All medications had a neutral effect on all-cause mortality (97 studies; 31 489 patients), cardiovascular death (91 studies; 24 212 patients), stroke (16 studies; 10 744 patients), myocardial infarction (27 studies; 15 286 patients), or hospitalization for heart failure (8 studies; 2560 patients). The confidence in these estimates was generally deemed very low

14.1.1. All-cause mortality

aGIs										
1.07 (0.06, 20.65)	Basal insulin									
1.40 (0.52, 3.83)	1.31 (0.08, 22.80)	DPP-4i								
1.18 (0.27, 5.07)	1.10 (0.05, 23.14)	0.84 (0.23, 3.01)	GLP-1 RAs							
1.12 (0.19, 6.75)	1.04 (0.04, 26.20)	0.80 (0.15, 4.19)	0.95 (0.13, 6.79)	Meglitinides						
1.08 (0.41, 2.82)	1.00 (0.06, 16.63)	0.77 (0.43, 1.38)	0.91 (0.27, 3.07)	0.96 (0.19, 4.83)	Metformin					
1.19 (0.36, 3.95)	1.11 (0.06, 20.38)	0.85 (0.34, 2.10)	1.01 (0.26, 4.01)	1.06 (0.19, 5.99)	1.11 (0.50, 2.48)	Pioglitazone				
0.62 (0.07, 5.70)	0.58 (0.02, 18.26)	0.44 (0.05, 3.56)	0.53 (0.06, 4.93)	0.55 (0.04, 7.12)	0.58 (0.07, 4.45)	0.52 (0.06, 4.30)	Premixed insulin			
1.55 (0.39, 6.12)	1.44 (0.07, 29.24)	1.10 (0.35, 3.47)	1.31 (0.27, 6.44)	1.38 (0.20, 9.33)	1.44 (0.48, 4.31)	1.30 (0.34, 4.91)	2.49 (0.25, 24.88)	SGLT-2i		
1.05 (0.40, 2.77)	0.98 (0.06, 16.30)	0.75 (0.40, 1.39)	0.89 (0.26, 3.05)	0.94 (0.19, 4.61)	0.98 (0.64, 1.49)	0.88 (0.39, 2.01)	1.70 (0.23, 12.76)	0.68 (0.22, 2.15)	SU	
0.91 (0.37, 2.23)	0.85 (0.05, 15.33)	0.65 (0.31, 1.35)	0.77 (0.22, 2.76)	0.81 (0.16, 4.23)	0.85 (0.41, 1.77)	0.77 (0.28, 2.10)	1.47 (0.18, 12.34)	0.59 (0.18, 1.91)	0.87 (0.41, 1.85)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

14.1.2. Cardiovascular mortality

aGIs										
1.13 (0.06, 21.93)	Basal insulin									
1.08 (0.36, 3.31)	0.96 (0.05, 17.90)	DPP-4i								
1.24 (0.28, 5.54)	1.10 (0.05, 23.74)	1.15 (0.28, 4.67)	GLP-1 RAs							
1.17 (0.19, 7.18)	1.03 (0.04, 26.12)	1.08 (0.18, 6.48)	0.94 (0.13, 7.02)	Meglitinides						
1.12 (0.39, 3.18)	0.99 (0.06, 16.91)	1.03 (0.45, 2.37)	0.90 (0.24, 3.31)	0.96 (0.17, 5.42)	Metformin					
1.28 (0.36, 4.56)	1.13 (0.06, 21.46)	1.18 (0.39, 3.61)	1.03 (0.24, 4.40)	1.09 (0.18, 6.49)	1.14 (0.42, 3.15)	Pioglitazone				
0.61 (0.05, 7.97)	0.54 (0.01, 21.55)	0.57 (0.04, 7.12)	0.49 (0.04, 6.35)	0.52 (0.03, 9.04)	0.55 (0.05, 6.53)	0.48 (0.04, 5.64)	Premixed insulin			
1.73 (0.36, 8.28)	1.53 (0.07, 34.35)	1.60 (0.38, 6.70)	1.39 (0.23, 8.24)	1.48 (0.18, 12.12)	1.55 (0.42, 5.76)	1.35 (0.27, 6.67)	2.83 (0.18, 44.79)	SGLT-2i		
1.13 (0.37, 3.39)	1.00 (0.06, 17.06)	1.04 (0.35, 3.09)	0.91 (0.23, 3.61)	0.96 (0.19, 4.82)	1.01 (0.40, 2.57)	0.88 (0.32, 2.44)	1.84 (0.17, 20.17)	0.65 (0.14, 3.04)	SU	
0.90 (0.36, 2.22)	0.79 (0.04, 14.61)	0.83 (0.35, 1.94)	0.72 (0.19, 2.69)	0.77 (0.14, 4.19)	0.80 (0.34, 1.87)	0.70 (0.23, 2.14)	1.47 (0.12, 17.90)	0.52 (0.13, 2.07)	0.80 (0.29, 2.17)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

14.1.3. Myocardial infarction

DPP-4i						
0.79 (0.10, 6.34)	GLP-1 RAs					
0.82 (0.34, 2.01)	1.04 (0.13, 8.41)	Metformin				
0.68 (0.21, 2.16)	0.86 (0.10, 7.21)	0.83 (0.28, 2.42)	Pioglitazone			
1.06 (0.26, 4.32)	1.34 (0.15, 12.28)	1.29 (0.36, 4.57)	1.55 (0.32, 7.45)	SGLT-2i		
0.99 (0.35, 2.78)	1.25 (0.15, 10.67)	1.20 (0.67, 2.16)	1.45 (0.48, 4.41)	0.93 (0.23, 3.74)	SU	
0.70 (0.17, 2.86)	0.89 (0.13, 5.85)	0.85 (0.20, 3.57)	1.03 (0.21, 4.96)	0.66 (0.15, 2.88)	0.71 (0.15, 3.25)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

14.1.4. Stroke

DPP-4i					
2.07 (0.17, 25.55)	GLP-1 RAs				
0.99 (0.31, 3.18)	0.48 (0.04, 5.32)	Metformin			
1.08 (0.16, 7.45)	0.52 (0.04, 7.74)	1.10 (0.17, 7.27)	SGLT-2i		
1.14 (0.30, 4.29)	0.55 (0.05, 6.10)	1.16 (0.60, 2.22)	1.06 (0.15, 7.64)	SU	
0.51 (0.10, 2.67)	0.25 (0.02, 2.63)	0.52 (0.09, 2.92)	0.47 (0.09, 2.36)	0.45 (0.07, 2.75)	Placebo

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14.1.5. Hospitalization for heart failure

DPP-4i						
0.93 (0.01, 127.86)	GLP-1 RAs					
1.23 (0.15, 10.06)	1.32 (0.01, 180.78)	Metformin				
1.19 (0.08, 17.22)	1.28 (0.01, 171.38)	0.97 (0.07, 14.15)	Pioglitazone			
2.00 (0.04, 101.15)	2.14 (0.00, 1161.53)	1.63 (0.02, 140.12)	1.68 (0.01, 193.37)	SGLT-2i		
1.21 (0.02, 64.30)	1.30 (0.00, 446.64)	0.99 (0.02, 39.39)	1.01 (0.03, 40.52)	0.61 (0.00, 161.39)	SU	
0.47 (0.02, 9.26)	0.51 (0.01, 25.77)	0.39 (0.02, 7.57)	0.40 (0.02, 7.47)	0.24 (0.00, 32.65)	0.39 (0.01, 29.77)	Placebo

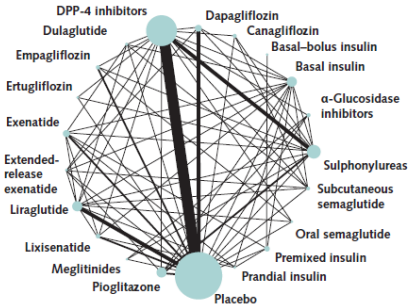
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

We did not do meta-analyses for diabetic retinopathy and amputation because of a paucity of pertinent data.

Patients on Metformin-Based Background Therapy

Glycemic Outcomes

Netzwerkgeometrie HbA1C



Results

- The greatest placebo-subtracted reductions in HbA1c level were seen with GLP-1 RAs, premixed insulin, and basal–bolus insulin regimens. Subcutaneous semaglutide was more efficacious in lowering HbA1c level than all other treatments (MD vs. placebo, -1.33% [CI, -1.50% to -1.16%]). The confidence in effect estimates for change in HbA1c level was high to moderate.

16.1.1. Change in HbA_{1c}

aGIs											
0.21 (0.01, 0.41)	Basal insulin										
0.42 (0.09, 0.75)	0.20 (-0.07, 0.48)	Basal-bolus insulin									
0.02 (-0.16, 0.19)	**-0.20 (-0.32, -0.08)**	**-0.40 (-0.69, -0.11)**	DPP-4i								
0.27 (0.09, 0.45)	0.06 (-0.05, 0.16)	-0.15 (-0.43, 0.13)	**0.25 (0.18, 0.33)**	GLP-1 RAs							
0.14 (-0.12, 0.39)	-0.08 (-0.31, 0.16)	-0.28 (-0.64, 0.07)	0.12 (-0.09, 0.34)	-0.13 (-0.35, 0.09)	Meglitinides						
0.10 (-0.09, 0.29)	-0.11 (-0.26, 0.03)	**-0.32 (-0.62, -0.02)**	0.08 (-0.03, 0.19)	**-0.17 (-0.29, -0.05)**	-0.04 (-0.27, 0.19)	Pioglitazone					
0.25 (-0.01, 0.51)	0.04 (-0.16, 0.24)	-0.17 (-0.50, 0.16)	**0.24 (0.03, 0.44)**	-0.02 (-0.21, 0.17)	0.11 (-0.18, 0.40)	0.15 (-0.07, 0.37)	Prandial insulin				
0.42 (0.18, 0.67)	0.21 (0.04, 0.38)	0.01 (-0.21, 0.22)	**0.41 (0.22, 0.60)**	0.16 (-0.03, 0.34)	**0.29 (0.01, 0.57)**	**0.33 (0.11, 0.54)**	0.17 (-0.07, 0.42)	Premixed insulin			
0.04 (-0.14, 0.22)	**-0.17 (-0.30, -0.04)**	**-0.38 (-0.67, -0.08)**	0.03 (-0.06, 0.11)	**-0.23 (-0.32, -0.13)**	-0.10 (-0.32, 0.13)	-0.06 (-0.19, 0.07)	-0.21 (-0.42, 0.00)	**-0.38 (-0.58, -0.19)**	SGLT-2i		
0.07 (-0.11, 0.25)	**-0.15 (-0.28, -0.01)**	**-0.35 (-0.65, -0.05)**	0.05 (-0.04, 0.14)	**-0.20 (-0.30, -0.10)**	-0.07 (-0.28, 0.14)	-0.03 (-0.15, 0.08)	-0.18 (-0.40, 0.03)	**-0.36 (-0.56, -0.16)**	0.03 (-0.08, 0.14)	SU	
-0.50 (-0.67, -0.34)	**-0.72 (-0.83, -0.61)**	**-0.92 (-1.21, -0.64)**	**-0.52 (-0.58, -0.46)**	**-0.77 (-0.84, -0.71)**	**-0.64 (-0.86, -0.43)**	**-0.60 (-0.71, -0.50)**	**-0.75 (-0.95, -0.56)**	**-0.93 (-1.12, -0.74)**	**-0.55 (-0.62, -0.47)**	**-0.57 (-0.66, -0.48)**	Placebo

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16.2.1. Change in HbA_{1c}

aGIs																			
0.21 (0.01, 0.41)	Basal insulin																		
0.38 (0.06, 0.71)	0.17 (-0.10, 0.44)	Basal-bolus insulin																	
0.12 (-0.10, 0.35)	-0.08 (-0.27, 0.10)	-0.26 (-0.58, 0.06)	Canagliflozin																
0.01 (-0.19, 0.21)	**-0.20 (-0.36, -0.04)**	**-0.37 (-0.68, -0.07)**	-0.12 (-0.31, 0.08)	Dapagliflozin															
0.02 (-0.15, 0.19)	**-0.18 (-0.30, -0.07)**	**-0.36 (-0.64, -0.07)**	-0.10 (-0.26, 0.06)	0.02 (-0.11, 0.14)	DPP-4i														
0.39 (0.15, 0.62)	0.18 (0.00, 0.36)	0.01 (-0.31, 0.32)	**0.26 (0.04, 0.49)**	**0.38 (0.18, 0.58)**	**0.36 (0.19, 0.53)**	Dulaglutide													
0.06 (-0.16, 0.28)	-0.15 (-0.33, 0.04)	-0.32 (-0.64, 0.00)	-0.06 (-0.28, 0.15)	0.05 (-0.13, 0.24)	0.04 (-0.12, 0.19)	**-0.33 (-0.55, -0.11)**	Empagliflozin												
0.07 (-0.20, 0.34)	-0.14 (-0.38, 0.11)	-0.31 (-0.66, 0.05)	-0.05 (-0.32, 0.21)	0.06 (-0.18, 0.31)	0.05 (-0.17, 0.27)	**-0.31 (-0.59, -0.04)**	0.01 (-0.25, 0.27)	Ertugliflozin											
0.10 (-0.11, 0.31)	-0.11 (-0.26, 0.04)	-0.28 (-0.57, 0.01)	-0.03 (-0.23, 0.17)	0.09 (-0.08, 0.26)	0.08 (-0.06, 0.21)	**-0.29 (-0.49, -0.09)**	0.04 (-0.16, 0.23)	0.03 (-0.22, 0.28)	Exenatide										
0.30 (0.05, 0.54)	0.09 (-0.11, 0.29)	-0.08 (-0.41, 0.25)	0.17 (-0.06, 0.41)	**0.29 (0.08, 0.50)**	**0.28 (0.09, 0.46)**	-0.09 (-0.33, 0.15)	0.24 (0.00, 0.47)	0.23 (-0.06, 0.51)	0.20 (-0.02, 0.42)	Exenatide ER									
0.29 (0.10, 0.48)	0.08 (-0.05, 0.22)	-0.09 (-0.38, 0.20)	0.17 (-0.01, 0.35)	**0.29 (0.14, 0.43)**	**0.27 (0.17, 0.37)**	-0.09 (-0.27, 0.09)	**0.23 (0.06, 0.41)**	0.22 (-0.02, 0.46)	**0.19 (0.04, 0.34)**	-0.01 (-0.20, 0.19)	Liraglutide								
-0.07 (-0.29, 0.14)	**-0.28 (-0.45, -0.11)**	**-0.45 (-0.76, -0.14)**	-0.20 (-0.40, 0.01)	-0.08 (-0.26, 0.10)	-0.10 (-0.24, 0.05)	**-0.46 (-0.67, -0.25)**	-0.13 (-0.33, 0.07)	-0.14 (-0.40, 0.11)	-0.17 (-0.35, 0.01)	**-0.37 (-0.60, -0.14)**	**-0.36 (-0.53, -0.20)**	Lixisenatide							
0.13 (-0.12, 0.39)	-0.07 (-0.31, 0.16)	-0.25 (-0.60, 0.10)	0.01 (-0.25, 0.27)	0.13 (-0.11, 0.36)	0.11 (-0.10, 0.32)	-0.25 (-0.52, 0.01)	0.07 (-0.18, 0.33)	0.06 (-0.24, 0.36)	0.03 (-0.21, 0.28)	-0.17 (-0.44, 0.11)	-0.16 (-0.39, 0.07)	0.21 (-0.04, 0.46)	Meglitinides						
0.10 (-0.08, 0.28)	-0.11 (-0.25, 0.04)	-0.28 (-0.58, 0.02)	-0.02 (-0.21, 0.16)	0.09 (-0.06, 0.25)	0.08 (-0.03, 0.19)	**-0.29 (-0.48, -0.09)**	0.04 (-0.14, 0.22)	0.03 (-0.21, 0.27)	0.00 (-0.16, 0.16)	-0.20 (-0.40, 0.01)	**-0.19 (-0.33, -0.05)**	0.17 (0.00, 0.34)	-0.03 (-0.26, 0.19)	Pioglitazone					
0.16 (-0.09, 0.42)	-0.04 (-0.24, 0.16)	-0.22 (-0.54, 0.10)	0.04 (-0.21, 0.29)	0.16 (-0.07, 0.38)	0.14 (-0.06, 0.34)	-0.22 (-0.47, 0.02)	0.10 (-0.14, 0.35)	0.09 (-0.20, 0.38)	0.06 (-0.14, 0.27)	-0.14 (-0.40, 0.13)	-0.13 (-0.33, 0.07)	**0.24 (0.01, 0.46)**	0.03 (-0.26, 0.32)	0.06 (-0.16, 0.28)	Prandial insulin				
0.39 (0.14, 0.64)	**0.18 (0.02, 0.35)**	0.01 (-0.21, 0.22)	**0.26 (0.02, 0.50)**	**0.38 (0.17, 0.60)**	**0.37 (0.18, 0.55)**	0.00 (-0.23, 0.24)	**0.33 (0.09, 0.56)**	**0.32 (0.03, 0.60)**	**0.29 (0.09, 0.49)**	0.09 (-0.16, 0.34)	0.10 (-0.10, 0.29)	**0.46 (0.24, 0.68)**	0.25 (-0.02, 0.53)	**0.29 (0.08, 0.50)**	0.23 (-0.05, 0.51)	Premixed insulin			
0.39 (0.13, 0.65)	0.18 (-0.04, 0.41)	0.01 (-0.34, 0.35)	**0.27 (0.02, 0.52)**	**0.38 (0.15, 0.61)**	**0.37 (0.17, 0.57)**	0.00 (-0.25, 0.26)	**0.33 (0.10, 0.56)**	**0.32 (0.02, 0.61)**	**0.29 (0.06, 0.53)**	0.09 (-0.18, 0.36)	0.10 (-0.12, 0.31)	**0.46 (0.22, 0.70)**	0.26 (-0.03, 0.54)	**0.29 (0.07, 0.51)**	0.23 (-0.05, 0.51)	0.00 (-0.27, 0.27)	Semaglutide PO		
0.83 (0.59, 1.07)	**0.62 (0.43, 0.81)**	**0.45 (0.12, 0.77)**	**0.70 (0.49, 0.92)**	**0.82 (0.62, 1.03)**	**0.81 (0.63, 0.98)**	**0.44 (0.22, 0.66)**	0.77 (0.54, 0.99)	**0.76 (0.48, 1.03)**	**0.73 (0.52, 0.94)**	**0.53 (0.30, 0.76)**	**0.54 (0.35, 0.72)**	**0.90 (0.68, 1.12)**	**0.69 (0.42, 0.96)**	**0.73 (0.53, 0.93)**	**0.67 (0.41, 0.92)**	**0.44 (0.20, 0.68)**	**0.44 (0.18, 0.70)**	Semaglutide SC	
0.06 (-0.12, 0.24)	**-0.15 (-0.28, -0.01)**	**-0.32 (-0.61, -0.03)**	-0.06 (-0.23, 0.11)	0.05 (-0.09, 0.20)	0.04 (-0.05, 0.13)	**-0.32 (-0.51, -0.14)**	0.00 (-0.16, 0.17)	-0.01 (-0.24, 0.22)	-0.04 (-0.18, 0.11)	-0.24 (-0.44, -0.04)	**-0.23 (-0.35, -0.11)**	0.13 (-0.03, 0.30)	-0.07 (-0.27, 0.13)	-0.04 (-0.15, 0.07)	-0.10 (-0.31, 0.11)	-0.33 (-0.53, -0.13)	**-0.33 (-0.54, -0.11)**	**-0.77 (-0.96, -0.58)**	SU
-0.50 (-0.67, -0.34)	**-0.71 (-0.82, -0.60)**	**-0.89 (-1.17, -0.60)**	**-0.63 (-0.78, -0.47)**	**-0.51 (-0.63, -0.40)**	**-0.53 (-0.58, -0.47)**	**-0.89 (-1.05, -0.73)**	**-0.57 (-0.71, -0.42)**	**-0.58 (-0.79, -0.36)**	**-0.60 (-0.73, -0.47)**	**-0.80 (-0.99, -0.62)**	**-0.80 (-0.89, -0.70)**	**-0.43 (-0.57, -0.29)**	**-0.64 (-0.85, -0.43)**	**-0.60 (-0.71, -0.50)**	**-0.67 (-0.86, -0.47)**	**-0.89 (-1.08, -0.71)**	**-0.89 (-1.09, -0.70)**	**-1.33 (-1.50, -1.16)**	**-0.57 (-0.66, -0.48)**	Placebo

Treatments are reported in alphabetical order. Treatment estimates are MDs and 95% CIs in the column-defining treatment compared to the row-defining treatment. MDs lower than 0 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os. SC=subcutaneous. SU=sulphonylureas.

- Sulphonylureas, premixed insulin, and basal–bolus insulin were associated with an increase in the incidence of severe hypoglycemia (252 studies; 261 559 patients)., the confidence for severe hypoglycemia was generally moderate to low.

16.1.2. Severe hypoglycemia

aGIs												
0.97 (0.28, 3.37)	Basal insulin											
0.59 (0.15, 2.31)	0.61 (0.34, 1.10)	Basal-bolus insulin										
1.34 (0.41, 4.40)	1.39 (0.92, 2.10)	**2.27 (1.15, 4.50)**	DPP-4i									
1.41 (0.43, 4.65)	1.46 (0.99, 2.16)	**2.40 (1.23, 4.68)**	1.05 (0.90, 1.23)	GLP-1 RAs								
1.18 (0.17, 8.11)	1.23 (0.24, 6.25)	2.01 (0.36,11.17)	0.88 (0.18, 4.29)	0.84 (0.17, 4.08)	Meglitinides							
0.99 (0.28, 3.58)	1.03 (0.53, 1.99)	1.68 (0.71, 3.97)	0.74 (0.43, 1.28)	0.70 (0.41, 1.22)	0.84 (0.16, 4.43)	Pioglitazone						
0.71 (0.18, 2.83)	0.73 (0.35, 1.55)	1.20 (0.50, 2.86)	0.53 (0.25, 1.09)	0.50 (0.24, 1.02)	0.60 (0.11, 3.39)	0.71 (0.29, 1.75)	Prandial insulin					
0.66 (0.18, 2.44)	0.68 (0.43, 1.08)	1.11 (0.78, 1.59)	**0.49 (0.27, 0.88)**	**0.46 (0.26, 0.82)**	0.55 (0.10, 2.97)	0.66 (0.30, 1.44)	0.93 (0.42, 2.05)	Premixed insulin				
1.72 (0.52, 5.73)	**1.78 (1.15, 2.77)**	**2.92 (1.45, 5.89)**	**1.28 (1.03, 1.61)**	1.22 (0.98, 1.52)	1.46 (0.30, 7.14)	1.73 (0.98, 3.07)	**2.44 (1.15, 5.14)**	**2.63 (1.44, 4.80)**	SGLT-2i			
0.26 (0.07, 0.87)	**0.26 (0.15, 0.45)**	**0.43 (0.20, 0.93)**	**0.19 (0.13, 0.27)**	**0.18 (0.12, 0.26)**	0.22 (0.04, 1.05)	**0.26 (0.14, 0.48)**	**0.36 (0.16, 0.81)**	0.39 (0.20, 0.77)	**0.15 (0.10, 0.22)**	SU		
1.42 (0.43, 4.65)	1.47 (0.99, 2.19)	**2.41 (1.23, 4.73)**	1.06 (0.94, 1.20)	1.01 (0.91, 1.11)	1.20 (0.25, 5.84)	1.43 (0.83, 2.45)	2.01 (0.98, 4.13)	**2.17 (1.23, 3.84)**	0.83 (0.68, 1.01)	**5.57 (3.84, 8.08)**	Placebo	

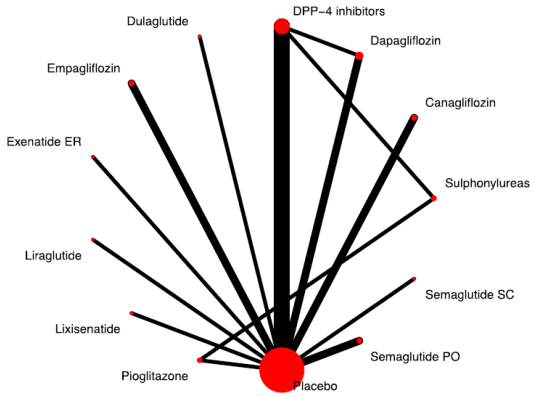
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os. SC=subcutaneous. SU=sulphonylureas.

Mortality and Cardiovascular Outcomes

a) Patients at Increased Cardiovascular Risk

Netzwerkgeometrie all-cause mortality

6.2.1 All-cause mortality



Results

- **all-cause mortality:** Compared with placebo, all-cause mortality (21 studies; 145 694 patients) was reduced with oral semaglutide (OR, 0.50 [CI, 0.31 to 0.83]), empagliflozin (OR, 0.67 [CI, 0.55 to 0.81]), liraglutide (OR, 0.84 [CI, 0.73 to 0.97]), extended-release exenatide (OR, 0.86 [CI, 0.76 to 0.98]), and dapagliflozin (OR, 0.89 [CI, 0.80 to 0.99]) The confidence in these effect estimates was high to moderate.

18.1.1. All-cause mortality

DPP-4i					
1.15 (0.99, 1.33)	GLP-1 RAs				
0.99 (0.77, 1.27)	0.86 (0.67, 1.11)	Pioglitazone			
1.16 (0.99, 1.35)	1.01 (0.87, 1.17)	1.17 (0.91, 1.51)	SGLT-2i		
0.94 (0.76, 1.15)	0.82 (0.64, 1.05)	0.95 (0.72, 1.25)	0.81 (0.63, 1.04)	SU	
1.00 (0.89, 1.11)	**0.87 (0.79, 0.96)**	1.01 (0.80, 1.27)	**0.86 (0.77, 0.96)**	1.06 (0.85, 1.34)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i,=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

  - On the basis of indirect comparisons, oral semaglutide and empagliflozin also had a favorable effect compared with canagliflozin, dapagliflozin, DPP-4 inhibitors, dulaglutide, extended-release exenatide, lixisenatide, pioglitazone, subcutaneous semaglutide, and sulphonylureas.

18.2.1. All-cause mortality

Canagliflozin												
1.10 (0.93, 1.30)	Dapagliflozin											
0.97 (0.83, 1.12)	0.88 (0.77, 1.00)	DPP-4i										
1.09 (0.91, 1.30)	0.99 (0.84, 1.17)	1.13 (0.98, 1.30)	Dulaglutide									
1.45 (1.15, 1.83)	**1.32 (1.06, 1.65)**	**1.50 (1.22, 1.85)**	**1.33 (1.06, 1.67)**	Empagliflozin								
1.13 (0.95, 1.35)	1.03 (0.87, 1.21)	**1.17 (1.01, 1.35)**	1.04 (0.87, 1.23)	**0.78 (0.62, 0.98)**	Exenatide ER							
1.16 (0.96, 1.41)	1.06 (0.88, 1.26)	**1.20 (1.02, 1.41)**	1.06 (0.88, 1.29)	0.80 (0.63, 1.02)	1.03 (0.85, 1.24)	Liraglutide						
1.04 (0.82, 1.31)	0.94 (0.75, 1.18)	1.07 (0.87, 1.32)	0.95 (0.75, 1.20)	**0.71 (0.54, 0.94)**	0.92 (0.73, 1.15)	0.89 (0.70, 1.14)	Lixisenatide					
0.97 (0.77, 1.22)	0.88 (0.71, 1.10)	1.01 (0.82, 1.23)	0.89 (0.71, 1.12)	**0.67 (0.51, 0.88)**	0.86 (0.69, 1.08)	0.84 (0.66, 1.06)	0.94 (0.71, 1.23)	Pioglitazone				
1.94 (1.16, 3.24)	**1.76 (1.06, 2.93)**	**2.00 (1.21, 3.31)**	**1.78 (1.06, 2.96)**	1.33 (0.78, 2.27)	**1.71 (1.03, 2.86)**	1.67 (0.99, 2.80)	**1.87 (1.10, 3.19)**	**1.99 (1.17, 3.39)**	Semaglutide PO			
0.94 (0.64, 1.38)	0.86 (0.59, 1.25)	0.98 (0.67, 1.41)	0.86 (0.59, 1.27)	**0.65 (0.43, 0.98)**	0.83 (0.57, 1.22)	0.81 (0.55, 1.20)	0.91 (0.60, 1.37)	0.97 (0.64, 1.46)	**0.49 (0.26, 0.90)**	Semaglutide SC		
0.90 (0.73, 1.11)	**0.81 (0.67, 0.99)**	0.93 (0.80, 1.08)	0.82 (0.67, 1.01)	**0.62 (0.48, 0.80)**	**0.79 (0.64, 0.98)**	**0.77 (0.62, 0.96)**	0.87 (0.67, 1.12)	0.92 (0.73, 1.16)	0.46 (0.27, 0.78)	0.95 (0.64, 1.42)	SU	
0.98 (0.86, 1.11)	**0.89 (0.80, 0.99)**	1.01 (0.94, 1.09)	0.89 (0.79, 1.01)	**0.67 (0.55, 0.81)**	**0.86 (0.76, 0.98)**	**0.84 (0.73, 0.97)**	0.94 (0.77, 1.15)	1.00 (0.83, 1.21)	**0.50 (0.31, 0.83)**	1.04 (0.72, 1.49)	1.09 (0.92, 1.29)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors, ER=extended release, PO=per os, SC=subcutaneous, SU=sulphonylureas.

- **cardiovascular death**
  - Compared with placebo, oral semaglutide, empagliflozin, and liraglutide were associated with lower odds of cardiovascular death (21 studies; 145 694 patients) The confidence in these effect estimates was high to moderate

10.1.2. Cardiovascular mortality

DPP-4i					
1.12 (0.93, 1.34)	GLP-1 RAs				
0.98 (0.70, 1.37)	0.88 (0.63, 1.23)	Pioglitazone			
1.14 (0.94, 1.38)	1.02 (0.85, 1.23)	1.16 (0.83, 1.63)	SGLT-2i		
1.05 (0.78, 1.40)	0.94 (0.67, 1.32)	1.07 (0.70, 1.64)	0.92 (0.65, 1.30)	SU	
0.97 (0.85, 1.11)	**0.87 (0.77, 0.99)**	0.99 (0.73, 1.35)	**0.85 (0.74, 0.97)**	0.93 (0.67, 1.27)	Placebo

- Empagliflozin had a favorable effect on cardiovascular death compared with several other treatments, including canagliflozin, dapagliflozin, DPP-4 inhibitors, dulaglutide, extended-release exenatide, pioglitazone, and sulphonylureas (Figure 3).

Figure 3. Network meta-analysis results for cardiovascular death (left lower half) and hospitalization for heart failure (right upper half) in patients at increased cardiovascular risk receiving metformin-based background therapy:

Canagliflozin	0.97† (0.76–1.22)	***0.68†*** ***(0.55–0.84)***	0.76† (0.59–1.00)	1.10† (0.80–1.54)	***0.76†*** ***(0.58–0.98)***	0.82† (0.63–1.07)	0.75† (0.55–1.03)	***0.51†*** ***(0.37–0.69)***	0.85‡ (0.46–1.56)	0.66† (0.43–1.00)	0.83† (0.58–1.17)	***0.72**** ***(0.60–0.87)***
1.05† (0.85–1.30)	**Dapagliflozin**	***0.70**** ***(0.59–0.84)***	0.79† (0.62–1.01)	1.14† (0.84–1.56)	***0.78†*** ***(0.62–0.99)***	0.85† (0.67–1.08)	0.78† (0.58–1.04)	***0.53†*** ***(0.39–0.70)***	0.88‡ (0.48–1.60)	0.68† (0.45–1.02)	0.86† (0.61–1.19)	***0.75**** ***(0.64–0.86)***
0.98† (0.82–1.16)	0.92† (0.78–1.10)	**DPP-4 inhibitors**	1.13† (0.91–1.40)	***1.63†*** ***(1.22–2.18)***	1.12† (0.90–1.38)	1.22† (0.98–1.50)	1.11† (0.84–1.46)	***0.75†*** ***(0.57–0.98)***	1.25‡ (0.70–2.26)	0.97‡ (0.66–1.43)	1.22† (0.92–1.62)	1.06† (0.96–1.17)
1.06† (0.85–1.32)	1.00‡ (0.81–1.24)	1.08† (0.90–1.30)	**Dulaglutide**	***1.45†*** ***(1.04–2.01)***	0.99† (0.76–1.29)	1.08† (0.82–1.41)	0.98‡ (0.71–1.35)	***0.66†*** ***(0.48–0.91)***	1.11‡ (0.60–2.05)	0.86‡ (0.56–1.31)	1.08‡ (0.76–1.54)	0.94‡ (0.78–1.14)
1.57† ***(1.19–2.08)***	***1.49†*** ***(1.14–1.96)***	***1.62†*** ***(1.26–2.07)***	***1.49†*** ***(1.13–1.97)***	**Empagliflozin**	***0.68†*** ***(0.49–0.95)***	0.74† (0.54–1.03)	***0.68†*** ***(0.47–0.98)***	***0.46†*** ***(0.32–0.67)***	0.77‡ (0.41–1.46)	***0.59†*** ***(0.37–0.94)***	0.75† (0.50–1.12)	***0.65**** ***(0.50–0.85)***
1.09† (0.88–1.34)	1.03‡ (0.83–1.27)	1.11† (0.94–1.33)	1.03‡ (0.83–1.28)	***0.69†*** ***(0.52–0.91)***	**Extended-release exenatide**	1.09† (0.84–1.42)	0.99‡ (0.72–1.36)	***0.67†*** ***(0.49–0.92)***	1.12‡ (0.61–2.07)	0.87‡ (0.57–1.32)	1.09‡ (0.77–1.56)	0.95‡ (0.79–1.15)
1.24† (0.98–1.57)	1.17† (0.93–1.48)	***1.27†*** ***(1.04–1.55)***	1.17† (0.92–1.49)	0.79† (0.59–1.05)	1.14† (0.90–1.44)	**Liraglutide**	0.91† (0.67–1.25)	***0.62†*** ***(0.45–0.84)***	1.03‡ (0.56–1.90)	0.80† (0.52–1.21)	1.00‡ (0.71–1.43)	0.87† (0.73–1.05)
0.98† (0.74–1.28)	0.93† (0.71–1.21)	1.00‡ (0.78–1.28)	0.92† (0.70–1.22)	***0.62†*** ***(0.45–0.86)***	0.90† (0.69–1.18)	0.79† (0.59–1.05)	**Lixisenatide**	***0.68†*** ***(0.47–0.97)***	1.13‡ (0.60–2.13)	0.87‡ (0.56–1.38)	1.10‡ (0.74–1.63)	0.96† (0.74–1.24)
0.99‡ (0.74–1.32)	0.94† (0.71–1.25)	1.01† (0.78–1.31)	0.94† (0.70–1.25)	***0.63†*** ***(0.45–0.88)***	0.91† (0.69–1.21)	0.80† (0.59–1.08)	1.01‡ (0.73–1.41)	**Pioglitazone**	1.68† (0.89–3.16)	1.29† (0.82–2.04)	***1.63†*** ***(1.10–2.41)***	1.42† (1.10–1.83)
1.88† (1.00–3.52)	1.78† (0.95–3.33)	***1.93†*** ***(1.04–3.57)***	1.78† (0.95–3.34)	1.19‡ (0.62–2.29)	1.73† (0.93–3.24)	1.52† (0.80–2.87)	1.93† (1.01–3.69)	1.90† (0.99–3.66)	**Oral semaglutide**	0.77‡ (0.39–1.54)	0.97‡ (0.51–1.87)	0.85‡ (0.47–1.51)
1.01‡ (0.64–1.57)	0.96‡ (0.61–1.49)	1.03‡ (0.67–1.59)	0.95‡ (0.61–1.49)	0.64† (0.40–1.03)	0.93‡ (0.59–1.45)	0.81† (0.52–1.29)	1.03‡ (0.64–1.66)	1.02‡ (0.63–1.65)	0.54† (0.26–1.12)	**Subcutaneous semaglutide**	1.26† (0.78–2.04)	1.10‡ (0.75–1.60)
1.00‡ (0.76–1.33)	0.95† (0.72–1.25)	1.03‡ (0.83–1.28)	0.95† (0.72–1.26)	***0.64†*** ***(0.46–0.88)***	0.92† (0.70–1.22)	0.81† (0.60–1.09)	1.03‡ (0.74–1.42)	1.01‡ (0.73–1.41)	0.53† (0.28–1.02)	1.00‡ (0.62–1.61)	**Sulphonylureas**	0.87† (0.65–1.17)
0.96† (0.83–1.12)	0.91† (0.79–1.06)	0.99* (0.90–1.08)	0.91† (0.78–1.07)	***0.61**** ***(0.49–0.77)***	0.89† (0.76–1.03)	***0.78†*** ***(0.65–0.93)***	0.99‡ (0.79–1.24)	0.97† (0.76–1.24)	***0.51†*** ***(0.28–0.94)***	0.96‡ (0.63–1.45)	0.96† (0.76–1.21)	**Placebo**

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs of the column-defining treatment compared with the row-defining treatment for cardiovascular death. Treatment estimates are ORs and 95% CIs of the row-defining treatment compared with the column-defining treatment for hospitalization for heart failure. Odds ratios less than 1 favor the column-defining treatment for cardiovascular death and the row-defining treatment for hospitalization for heart failure. Significant results are italicized and highlighted in light green. DPP-4 = dipeptidyl peptidase-4; OR = odds ratio.
* High level of confidence in effect estimate.
† Moderate level of confidence in effect estimate.
‡ Low level of confidence in effect estimate.

- **hospitalization for heart failure:**

18.1.5. Hospitalization for heart failure

DPP-4i					
1.14 (0.99, 1.31)	GLP-1 RAs				
0.75 (0.57, 0.98)	**0.66 (0.50, 0.86)**	Pioglitazone			
1.47 (1.27, 1.70)	**1.29 (1.12, 1.49)**	**1.97 (1.49, 2.59)**	SGLT-2i		
1.22 (0.92, 1.62)	1.07 (0.79, 1.47)	**1.63 (1.10, 2.41)**	0.83 (0.60, 1.14)	SU	
1.06 (0.96, 1.17)	0.93 (0.85, 1.03)	**1.42 (1.10, 1.83)**	**0.72 (0.65, 0.80)**	0.87 (0.65, 1.17)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i,=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- The odds of hospitalization for heart failure were increased with pioglitazone compared with placebo (OR, 1.42 [CI, 1.10 to 1.83]) or other treatments (Figure 3).
- The confidence in effect estimates for hospitalization for heart failure was moderate.

Stroke / Myocardial infarction

- Compared with placebo, GLP-1 RAs reduced the incidence of stroke (OR, 0.84 [CI, 0.75 to 0.93]).

18.1.4. Stroke

DPP-4i					
1.18 (0.99, 1.39)	GLP-1 RAs				
1.21 (0.90, 1.61)	1.03 (0.77, 1.37)	Pioglitazone			
0.98 (0.82, 1.17)	**0.83 (0.71, 0.98)**	0.81 (0.60, 1.09)	SGLT-2i		
0.87 (0.68, 1.12)	**0.74 (0.55, 0.99)**	0.72 (0.51, 1.02)	0.89 (0.66, 1.20)	SU	
0.99 (0.87, 1.12)	**0.84 (0.75, 0.93)**	0.82 (0.63, 1.07)	1.01 (0.89, 1.14)	1.14 (0.86, 1.50)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i,=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- In terms of individual agents, the odds of stroke were lower with subcutaneous semaglutide (OR, 0.61 [CI, 0.37 to 0.99]) and dulaglutide (OR, 0.76 [CI, 0.62 to 0.94]). The confidence in these effect estimates was high to moderate.

18.2.3. Stroke

Canagliflozin												
0.91 (0.70, 1.19)	Dapagliflozin											
0.94 (0.74, 1.19)	1.03 (0.82, 1.29)	DPP-4i										
1.21 (0.91, 1.62)	**1.33 (1.01, 1.76)**	**1.29 (1.01, 1.66)**	Dulaglutide									
0.78 (0.55, 1.10)	0.86 (0.61, 1.20)	0.83 (0.61, 1.14)	**0.64 (0.45, 0.92)**	Empagliflozin								
1.08 (0.82, 1.43)	1.18 (0.90, 1.55)	1.15 (0.91, 1.46)	0.89 (0.67, 1.19)	1.38 (0.98, 1.96)	Exenatide ER							
1.07 (0.80, 1.43)	1.18 (0.89, 1.55)	1.14 (0.89, 1.46)	0.88 (0.66, 1.19)	1.37 (0.97, 1.95)	0.99 (0.75, 1.32)	Liraglutide						
0.83 (0.55, 1.24)	0.91 (0.61, 1.35)	0.88 (0.61, 1.28)	0.68 (0.45, 1.03)	1.06 (0.68, 1.67)	0.77 (0.51, 1.15)	0.77 (0.51, 1.16)	Lixisenatide					
1.13 (0.81, 1.58)	1.24 (0.90, 1.72)	1.21 (0.90, 1.61)	0.93 (0.66, 1.31)	1.45 (0.98, 2.15)	1.05 (0.75, 1.47)	1.06 (0.75, 1.49)	1.37 (0.88, 2.13)	Pioglitazone				
1.19 (0.58, 2.48)	1.31 (0.63, 2.71)	1.27 (0.62, 2.60)	0.98 (0.47, 2.05)	1.53 (0.72, 3.27)	1.11 (0.53, 2.30)	1.11 (0.54, 2.32)	1.44 (0.66, 3.16)	1.05 (0.50, 2.23)	Semaglutide PO			
1.53 (0.90, 2.57)	1.67 (1.00, 2.81)	1.62 (0.98, 2.68)	1.26 (0.74, 2.13)	**1.96 (1.12, 3.43)**	1.41 (0.84, 2.38)	1.42 (0.84, 2.41)	**1.84 (1.01, 3.35)**	1.35 (0.77, 2.34)	1.28 (0.54, 3.00)	Semaglutide SC		
0.82 (0.58, 1.15)	0.90 (0.64, 1.25)	0.87 (0.68, 1.12)	**0.67 (0.47, 0.95)**	1.05 (0.70, 1.56)	0.76 (0.54, 1.06)	0.76 (0.54, 1.08)	0.99 (0.63, 1.54)	0.72 (0.51, 1.02)	0.68 (0.32, 1.45)	**0.53 (0.31, 0.93)**	SU	
0.93 (0.76, 1.13)	1.02 (0.85, 1.22)	0.99 (0.87, 1.12)	**0.76 (0.62, 0.94)**	1.19 (0.89, 1.58)	0.86 (0.70, 1.05)	0.87 (0.70, 1.07)	1.12 (0.79, 1.59)	0.82 (0.63, 1.07)	0.78 (0.38, 1.57)	**0.61 (0.37, 0.99)**	1.14 (0.86, 1.50)	Placebo

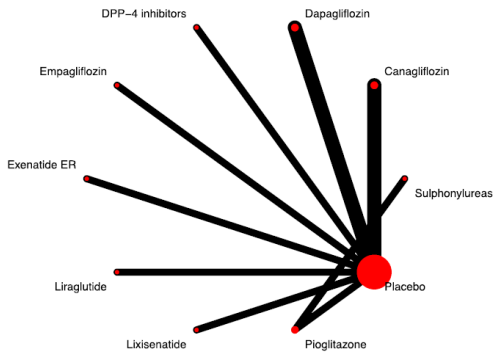
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os. SC=subcutaneous. SU=sulphonylureas.

- No differences were evident among any treatments for myocardial infarction.

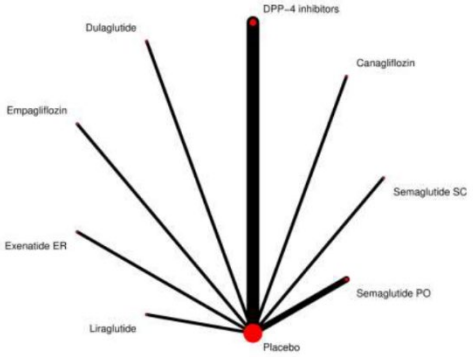
Diabetic retinopathy, amputation, end-stage renal disease

Netwerkgeometrie

6.2.7. Amputation



6.2.6. Diabetic retinopathy



Results

- The odds of diabetic retinopathy (12 studies; 95 664 patients) were similar to placebo for all treatments, except for subcutaneous semaglutide (OR, 1.75 [CI, 1.10 to 2.78]).

- The odds of amputation (11 studies; 93 922 patients) versus placebo were increased with canagliflozin (OR, 1.61 [CI, 1.27 to 2.05]) and reduced with liraglutide (OR, 0.65 [CI, 0.45 to 0.96]).
- The network for end-stage renal disease included 11 studies with 98 379 patients. Compared with placebo, SGLT-2 inhibitors reduced the odds of end-stage renal disease (OR, 0.63 [CI, 0.50 to 0.79]). This effect was consistent for dapagliflozin (OR, 0.32 [CI, 0.13 to 0.79]), empagliflozin (OR, 0.46 [CI, 0.22 to 0.98]), and canagliflozin (OR, 0.69 [CI, 0.54 to 0.88]).
- The confidence in effect estimates for diabetic retinopathy, amputation, and end-stage renal disease was low.

b) Patients at Low Cardiovascular Risk

Results

- **all-cause mortality:** When treatments were analyzed as drug classes, GLP-1 RAs were associated with reduced odds of all-cause mortality (292 studies; 136 942 patients) versus placebo (OR, 0.64 [CI, 0.45 to 0.91]).

20.1.1. All-cause mortality

aGIs											
1.26 (0.38, 4.14)	Basal insulin										
0.59 (0.10, 3.50)	0.46 (0.12, 1.84)	Basal-bolus insulin									
1.16 (0.40, 3.36)	0.92 (0.49, 1.72)	1.98 (0.45, 8.66)	DPP-4i								
1.42 (0.48, 4.24)	1.13 (0.65, 1.98)	2.44 (0.57, 10.34)	1.23 (0.82, 1.83)	GLP-1 RAs							
0.72 (0.16, 3.32)	0.57 (0.15, 2.22)	1.23 (0.18, 8.28)	0.62 (0.18, 2.16)	0.51 (0.14, 1.80)	Meglitinides						
1.13 (0.35, 3.63)	0.90 (0.39, 2.05)	1.93 (0.40, 9.32)	0.98 (0.51, 1.87)	0.79 (0.39, 1.59)	1.57 (0.40, 6.10)	Pioglitazone					
0.81 (0.21, 3.17)	0.64 (0.29, 1.44)	1.38 (0.32, 5.94)	0.70 (0.28, 1.75)	0.57 (0.24, 1.34)	1.12 (0.25, 5.09)	0.71 (0.24, 2.09)	Prandial insulin				
0.88 (0.24, 3.32)	0.70 (0.36, 1.37)	1.51 (0.45, 5.05)	0.76 (0.33, 1.78)	0.62 (0.28, 1.38)	1.23 (0.28, 5.35)	0.78 (0.29, 2.15)	1.10 (0.48, 2.49)	Premixed insulin			
0.96 (0.31, 2.94)	0.76 (0.38, 1.55)	1.64 (0.36, 7.46)	0.83 (0.52, 1.34)	0.67 (0.40, 1.13)	1.33 (0.37, 4.81)	0.85 (0.41, 1.79)	1.19 (0.45, 3.16)	1.09 (0.44, 2.71)	SGLT-2i		
1.03 (0.34, 3.08)	0.82 (0.41, 1.61)	1.76 (0.39, 7.88)	0.89 (0.60, 1.31)	0.72 (0.45, 1.17)	1.43 (0.42, 4.89)	0.91 (0.47, 1.78)	1.27 (0.49, 3.32)	1.16 (0.48, 2.83)	1.07 (0.65, 1.76)	SU	
0.92 (0.32, 2.60)	0.73 (0.40, 1.32)	1.57 (0.36, 6.78)	0.79 (0.58, 1.08)	**0.64 (0.45, 0.91)**	1.27 (0.37, 4.36)	0.81 (0.43, 1.54)	1.14 (0.46, 2.79)	1.04 (0.45, 2.38)	0.95 (0.62, 1.48)	0.89 (0.59, 1.36)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- incidence of **myocardial infarction** (131 studies; 91 152 patients) was lower with GLP-1 RAs and SGLT-2 inhibitors than placebo,

20.1.3. Myocardial infarction

aGIs											
0.33 (0.03, 3.61)	Basal insulin										
0.23 (0.01, 3.87)	0.69 (0.14, 3.25)	Basal-bolus insulin									
0.43 (0.05, 3.94)	1.28 (0.50, 3.30)	1.87 (0.31, 11.25)	DPP-4i								
0.61 (0.06, 5.73)	1.82 (0.79, 4.23)	2.66 (0.47, 15.18)	1.42 (0.85, 2.37)	GLP-1 RAs							
1.14 (0.06, 21.58)	3.43 (0.33, 36.10)	5.00 (0.30, 82.65)	2.67 (0.30, 23.65)	1.88 (0.21, 17.20)	Meglitinides						
0.38 (0.03, 4.72)	1.15 (0.26, 5.18)	1.68 (0.20, 14.32)	0.90 (0.27, 3.04)	0.63 (0.18, 2.26)	0.34 (0.03, 4.02)	Pioglitazone					
0.31 (0.03, 3.84)	0.95 (0.34, 2.67)	1.38 (0.24, 8.03)	0.74 (0.22, 2.49)	0.52 (0.17, 1.60)	0.28 (0.02, 3.28)	0.82 (0.15, 4.43)	Prandial insulin				
0.23 (0.02, 3.10)	0.71 (0.25, 1.98)	1.03 (0.32, 3.29)	0.55 (0.14, 2.16)	0.39 (0.11, 1.42)	0.21 (0.02, 2.65)	0.61 (0.10, 3.70)	0.75 (0.20, 2.81)	Premixed insulin			
0.72 (0.08, 6.80)	2.18 (0.82, 5.83)	3.18 (0.52, 19.54)	1.70 (1.04, 2.78)	1.20 (0.68, 2.10)	0.64 (0.07, 5.74)	1.89 (0.53, 6.73)	2.31 (0.66, 8.02)	3.09 (0.77, 12.46)	SGLT-2i		
0.31 (0.03, 2.84)	0.94 (0.35, 2.50)	1.36 (0.22, 8.37)	0.73 (0.48, 1.10)	**0.51 (0.29, 0.90)**	0.27 (0.03, 2.33)	0.81 (0.23, 2.85)	0.99 (0.29, 3.44)	1.33 (0.33, 5.34)	**0.43 (0.26, 0.71)**	SU	
0.39 (0.04, 3.57)	1.17 (0.47, 2.93)	1.71 (0.29, 10.14)	0.92 (0.63, 1.34)	**0.64 (0.42, 0.99)**	0.34 (0.04, 3.06)	1.02 (0.30, 3.42)	1.24 (0.38, 4.09)	1.66 (0.43, 6.39)	**0.54 (0.35, 0.84)**	1.25 (0.79, 2.00)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- odds of diabetic retinopathy (38 studies; 25 151 patients) were increased with sulphonylureas (OR versus placebo, 2.48 [CI, 1.02 to 6.07]).

20.1.6. Diabetic retinopathy

aGIs									
15.20 (0.48, 485.76)	Basal insulin								
11.01 (0.41, 298.56)	0.72 (0.24, 2.19)	DPP-4i							
16.71 (0.61, 459.01)	1.10 (0.39, 3.14)	1.52 (1.00, 2.29)	GLP-1 RAs						
2.97 (0.12, 73.13)	0.20 (0.00, 12.26)	0.27 (0.00, 14.77)	0.18 (0.00, 9.83)	Meglitinides					
6.10 (0.17, 212.35)	0.40 (0.08, 2.06)	0.55 (0.14, 2.17)	0.36 (0.10, 1.38)	2.05 (0.03, 138.19)	Pioglitazone				
11.72 (0.39, 356.27)	0.77 (0.20, 2.93)	1.06 (0.42, 2.68)	0.70 (0.31, 1.60)	3.94 (0.07, 237.02)	1.92 (0.40, 9.21)	Prandial insulin			
10.55 (0.36, 306.86)	0.69 (0.19, 2.48)	0.96 (0.42, 2.20)	0.63 (0.30, 1.33)	3.55 (0.06, 205.66)	1.73 (0.39, 7.77)	0.90 (0.30, 2.74)	SGLT-2i		
5.99 (0.24, 147.32)	0.39 (0.11, 1.48)	0.54 (0.25, 1.21)	0.36 (0.15, 0.84)	2.02 (0.04, 101.72)	0.98 (0.21, 4.56)	0.51 (0.16, 1.67)	0.57 (0.20, 1.63)	SU	
14.88 (0.54, 413.39)	0.98 (0.34, 2.83)	1.35 (0.77, 2.37)	0.89 (0.56, 1.41)	5.01 (0.09, 279.26)	2.44 (0.70, 8.50)	1.27 (0.49, 3.27)	1.41 (0.61, 3.26)	**2.48 (1.02, 6.07)**	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- All drug classes were similar to placebo in terms of cardiovascular death (263 studies; 118 419 patients), stroke (106 studies; 76 660 patients), hospitalization for heart failure (27 studies; 12 570 patients), and amputation (16 studies; 8921 patients).
- When GLP-1 RAs and SGLT-2 inhibitors were analyzed as individual agents, all treatments were similar to placebo in terms of all-cause mortality and cardiovascular outcomes.
- The confidence in most effect estimates in this subnetwork was very low because of imprecision and within-study bias

Anmerkung/Fazit der Autoren

In conclusion, the use of metformin as first-line treatment of drug-naive patients at low cardiovascular risk seems justified. Given the lack of pertinent evidence, we could not reach a conclusion about the optimal initial treatment of drug-naive patients at increased cardiovascular risk. In patients at low cardiovascular risk receiving metformin-based background therapy, choice among available agents should be based on their effect on other efficacy and safety outcomes because of lack of difference in vascular outcomes. For patients at increased cardiovascular risk receiving metformin-based background therapy, the optimal choice between specific GLP-1 RAs and SGLT-2 inhibitors should be based on the cardiovascular profile of individual agents and guided by patients' personal preferences and therapeutic priorities.

Kommentare zum Review

Hinsichtlich der Grundlagen für die Durchführung einer Netzwerkmetaanalyse, kann aufgrund begrenzter Information nicht abschließend beurteiltet werden, ob die zentrale Annahme der Transitivität erfüllt ist. Dies ist als wesentliche Limitation bei der Interpretation der Ergebnisse zu berücksichtigen.

3.3 Leitlinien

Bundesärztekammer et al., 2023 [7,8].

Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF),

Nationale VersorgungsLeitlinie: Typ-2-Diabetes; Teilpublikation der Langfassung; 2. Auflage; Version 3

Zielsetzung/Fragestellung

Auf diesem Weg soll die Qualität der Versorgung verbessert und die Stellung der Menschen mit Typ-2-Diabetes gestärkt werden. Zudem kann die Berücksichtigung der Empfehlungen zu einer Effizienzsteigerung und damit zur Kostendämpfung im Gesundheitswesen beitragen.

Die Überarbeitung der NVL Typ-2-Diabetes erfolgt modular. Sie ist Teil eines späteren Gesamtdokumentes. Weitere Themen werden im Rahmen der nächsten Versionen bearbeitet und veröffentlicht.

In der 2. Auflage der NVL Typ-2-Diabetes waren die Kapitel Partizipative Entscheidungsfindung (PEF) und Teil-habe in allen relevanten Lebensbereichen und Medikamentöse Therapie des Glukosestoffwechsels veröffentlicht worden. Während der Vorbereitung der Version 3 hat die Leitliniengruppe diese Kapitel überprüft und bestätigt. Anpassungen, die sich aus der Prüfung ergeben haben, sind im Anhang des Leitlinienreports zu finden [8]. Die Leitliniengruppe bestätigt die Gültigkeit der Empfehlungen, Abbildungen und Tabellen aus dem Kapitel Medikamentöse Therapie des Glukosestoffwechsels aus der 2. Auflage der NVL Typ-2-Diabetes aus 2021

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche und Auswahl der Literatur – trifft zu;
- systematische Bewertung der Evidenz – trifft zu;
  - Übersichtsarbeiten: AMSTAR-Tool
  - Randomisierten kontrollierten Studien: Cochrane-Risk-of-Bias-Tool
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

<u>Recherche/Suchzeitraum:</u>

- initialen Recherche: März 2018; Up-Date-Recherche: Dezember 2019
- Medline, Cochrane-Datenbank, U.S. Agency for Healthcare Research and Quality (AHRQ)

<u>LoE</u>

- endpunktbezogene Bewertung: GRADE

GoR

Empfehlungsgrad	Beschreibung	Formulierung	Symbol
A	Starke Positiv-Empfehlung	soll	⇑⇑
B	Abgeschwächte Positiv-Empfehlung	sollte	⇑
0	Offene Empfehlung	kann	⇔
B	Abgeschwächte Negativ-Empfehlung	sollte nicht	⇓
A	Starke Negativ-Empfehlung	soll nicht	⇓⇓

Sonstige methodische Hinweise

- Die Vorgehensweise zur Erstellung der NVL ist im Leitlinienreport beschrieben.

Empfehlungen: 2 Medikamentöse Therapie des Glukosestoffwechsels

2.2 Allgemeine Therapieprinzipien für nicht-medikamentöse und medikamentöse Therapie

- **2-1:** ⇑⇑ Vor jeder Therapie-Eskalation sollen Ursachen für die Nicht-Erreichung bisher vereinbarter Therapieziele evaluiert und berücksichtigt werden.
- **2-2:** ⇑⇑ Bei Menschen mit Typ-2-Diabetes soll eine Therapie-Deeskalation oder eine Veränderung der Therapiestrategie regelmäßig geprüft werden, insbesondere:
  - wenn die negativen Effekte der Therapie auf die Sicherheit und die Lebensqualität der/des Betroffenen überwiegen;
  - wenn die individuelle Situation dafür spricht, dass prognostische Aspekte eine geringere Rolle spielen als die aktuelle Lebensqualität;
  - wenn das individuelle Therapieziel unterschritten wird;
  - bei Multimorbidität und Polymedikation;
  - bei Auftreten von akuten Erkrankungen.
- Die Empfehlungen 2-1 und 2-2 beruhen auf einem Expert*innenkonsens und beschreiben gute klinische Praxis.

2.3 Algorithmus Medikamentöse Therapie des Typ-2-Diabetes

- **2-3:** ⇑⇑ Ist bei Menschen mit Typ-2-Diabetes, unter Berücksichtigung der individuellen Therapieziele und nach Ausschöpfung der nicht-medikamentösen Basistherapie, eine medikamentöse Therapie des Glukosestoffwechsels indiziert, soll der Therapie-Algorithmus angewendet werden.
- Die in Empfehlung 2-3 genannten Voraussetzungen, die erfüllt sein sollen, um den Algorithmus anzuwenden, beruhen auf einem Expert*innenkonsens und beschreiben gute klinische Praxis.

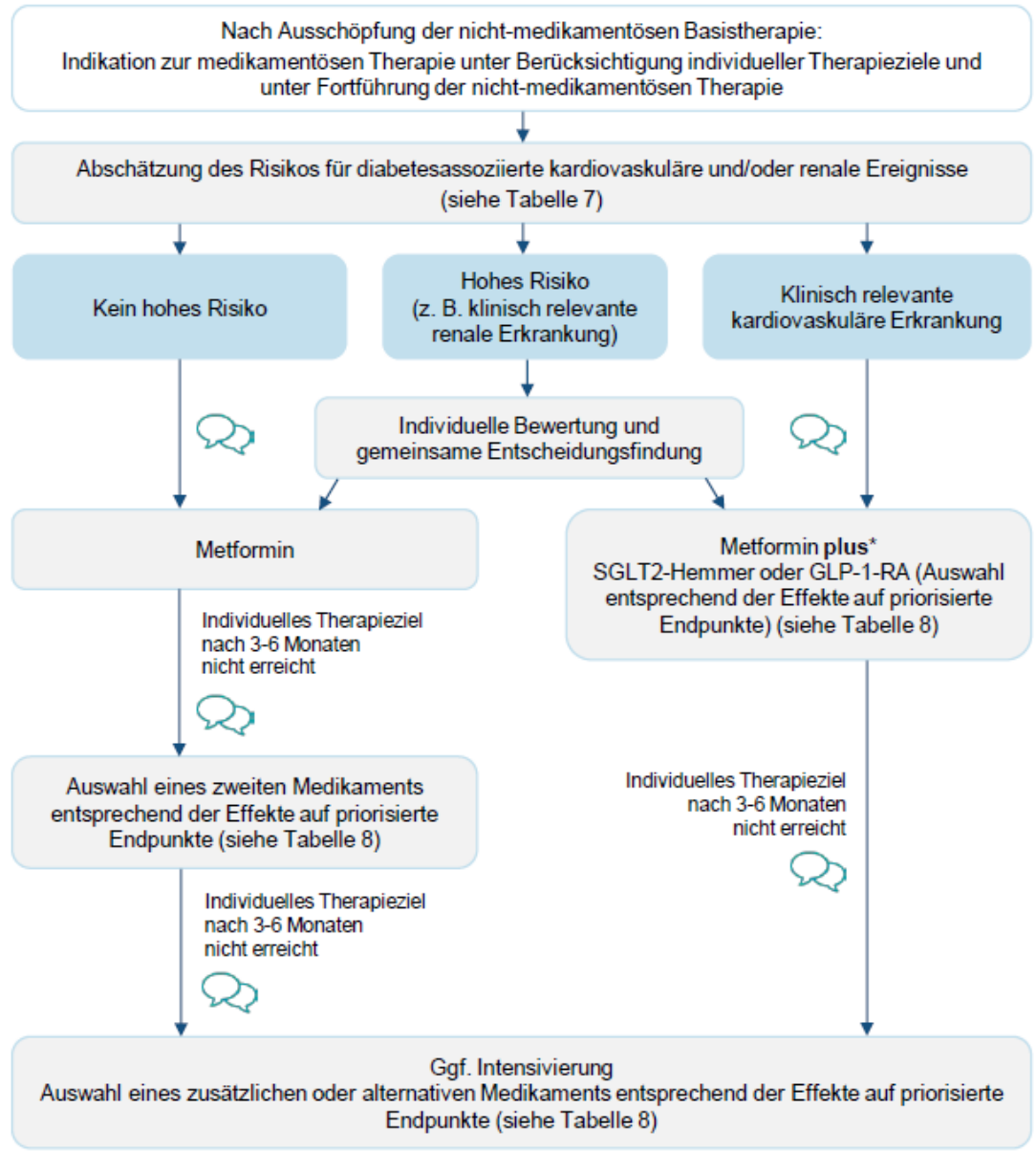


Abbildung 1: Algorithmus medikamentöse Therapie des Typ-2-Diabetes

- Beispiele kardiovaskulärer Risikofaktoren (Tabelle 7)
  - (biologisches) Alter, Geschlecht (männlich > weiblich), Diabetesdauer, Lebensstil/Ernährung/Bewegungsmangel, familiäre/genetische Disposition, Hypertonie, Dyslipidämie, Adipositas, Niereninsuffizienz, Albuminurie, Raucherstatus, starke Stoffwechselinstabilität und schwere Hypoglykämien, linksventrikuläre Hypertrophie, subklinische Arteriosklerose bzw. subklinische kardiovaskuläre Erkrankung

- Die hier aufgeführten Risikofaktoren beruhen auf einem Expert*innenkonsens. Für mehrere Faktoren wurden von einzelnen Fachgesellschaften an anderer Stelle Grenzwerte für ein erhöhtes Risiko festgelegt (Gewicht, Blutdruck, Lipide). Da einzelne geringgradige Grenzwertüberschreitungen keine große Risikoerhöhung zur Folge haben, ist eine umfassende integrative Beurteilung der beeinflussenden Risikofaktoren wichtig. Es ist zu bedenken, dass mit steigendem Alter und zunehmender Schwere der Komorbiditäten die Wahrscheinlichkeit abnimmt, von einer zusätzlichen Intervention zu profitieren. Die Reihenfolge der Aufzählung stellt keine Gewichtung dar.

2.4 Rationale für den Algorithmus

2.4.1 Stellenwert der nicht-medikamentösen Therapie

- Die nicht-medikamentöse Basistherapie (siehe noch zu erstellendes Kapitel nicht-medikamentöse Therapie) bietet eine wirkungsvolle Therapieoption und ist die Grundlage der Behandlung. Erst wenn nicht-medikamentöse Maßnahmen ausgeschöpft sind, sieht die Leitliniengruppe die Indikation zur medikamentösen Therapie.

2.4.2 Priorisierung des Therapieziels auf Basis des persönlichen Risikoprofils

- Leitend für die Wahl der geeigneten Therapiestrategie sind die gemeinsam priorisierten Therapieziele sowie die Wahrscheinlichkeit, aufgrund der persönlichen Krankheitsfaktoren von einer bestimmten Therapie zu profitieren. Auf Grundlage der derzeit vorliegenden Evidenz eröffnen sich dabei prinzipiell zwei Wege:
  - Reduktion von Folgeerkrankungen des Diabetes primär durch die Kontrolle des HbA1c als Surrogat für die Stoffwechseleinstellung;
  - primäre Reduktion der Wahrscheinlichkeit eines speziell kardiovaskulären und renalen Ereignisses durch die Gabe von Medikamenten, die diese Endpunkte reduzieren

2.4.3 Patientengruppen

- Es folgt zur Erläuterung des Algorithmus eine auf die Wirkstoffgruppen SGLT2-Inhibitoren und GLP-1-RA verkürzte Darstellung zur Verdeutlichung der Rationale; dabei sind Gruppeneffekte zu diskutieren. Die detaillierte Darstellung der Evidenz nach Wirkstoffen folgt im Kapitel 2.5 Wirkstoffe (Evidenzdarstellung):
- *Kardiovaskuläre Erkrankung*: Konsistente Ergebnisse zur Reduktion relevanter Endpunkte zeigten sich in einer Metaanalyse zu SGLT2-Inhibitoren [35] für Patient*innen mit manifester kardiovaskulärer Erkrankung, wobei Ergebnisse teilweise stark durch die EMPA-REG OUTCOME-Studie [36] beeinflusst wurden. Aus den präspezifizierten Subgruppenanalysen stratifiziert nach vorbestehender kardiovaskulärer Erkrankung in den Einzelstudien zu den GLP-1-RA ergaben sich ähnliche Hinweise. Diese Aussage wird gestützt durch eine nach Abschluss der Recherche erschienene, selektiv eingebrachte Metaanalyse [37].
- *Multiple Risikofaktoren:* Bei Patient*innen mit mehreren Risikofaktoren für kardiovaskuläre Ereignisse (Einschlusskriterien der Studien siehe Evidenztabelle [15]) waren die Effekte geringer, weniger konsistent und betrafen weniger Endpunkte.
- *Nierenfunktion/renale Erkrankung*: Gleiches galt für Patient*innen mit eingeschränkter Nierenfunktion. Beide Wirkstoffgruppen reduzierten zwar renale Endpunkte, welche Patientengruppen aber am ehesten profitieren, lässt sich auf Basis der Subgruppenanalysen stratifiziert nach Nierenfunktion nicht ableiten (siehe Evidenztabelle [15]).
- *Patient*innen ohne relevante Risikofaktoren:* Menschen ohne relevante kardiovaskuläre Risikofaktoren wurden in die Studien, die Wirksamkeit in Bezug auf kardiovaskuläre oder

renale Endpunkte zeigten, nicht eingeschlossen. Die Leitliniengruppe geht davon aus, dass diese im Rahmen der Beobachtungszeiträume der zitierten Studien eher nicht von einer sofortigen Kombinationstherapie mit SGLT2-Inhibitoren oder GLP-1-RA profitiert hätten, weil die Wahrscheinlichkeit, zeitnah ein kardiovaskuläres oder renales Ereignis zu entwickeln, hier als geringer anzusehen ist.

- *HbA1c-Wert:* Die Endpunktstudien zu SGLT2-Hemmern und GLP-1-RA wurden mit bereits medikamentös vorbehandelten Patient*innen durchgeführt. Der HbA1c-Wert lag im Mittel in den Studien zu SGLT2-Inhibitoren jeweils bei etwa 8% (zwischen 8,0 bis 8,3%). In den Studien zu den GLP-1-RA lag der durchschnittliche HbA1c-Wert zwischen etwa 8,0% und 8,7%, in der REWIND- [38] und der ELIXA-Studie [39] war er etwas niedriger (ca. 7,3% und 7,7%). Allerdings hatten z. B. in der Subgruppenanalyse bei der EMPA-REG OUTCOME-Studie [36] vor allem Patient*innen mit einem niedrigeren HbA1c (< 8,5%) profitiert. Ab welchem HbA1c-Schwellenwert sich eine Indikation für die sofortige Kombinationsbehandlung ergeben könnte, lässt sich aus den vorliegenden Daten nicht ableiten. Für Patient*innen ohne Herzinsuffizienz und mit einem HbA1c von ≤ 7% liegen keine ausreichenden Daten zur Wirksamkeit vor, weil diese Gruppe nicht an den vorliegenden Studien, die eine Wirksamkeit dieser Medikamente zeigten, teilgenommen hat. Die DAPA-HF-Studie [40] wird als begründende Evidenz für den Algorithmus ausgeklammert und in der NVL Herzinsuffizienz diskutiert [41], da das Haupt-Einschlusskriterium für diese Studie eine vorbestehende Herzinsuffizienz war und ein großer Teil der Patient*innen keinen Diabetes hatte.
- *Insulinsekretion:* Bei einem Teil der Menschen mit Typ-2-Diabetes liegt ein schweres Insulindefizit (reduzierte Insulinsekretion) vor. Nach Analyse einer schwedischen Arbeitsgruppe an einer Kohorte von 8 980 Menschen mit neu diagnostiziertem Diabetes lag dieser Anteil bei ca. 17,5% [42]. Je nach Ausprägung der Insulinsekretionsstörung kann ein initialer oder frühzeitiger Einsatz einer Insulintherapie notwendig sein (siehe auch Kapitel 2.5.6. Insuline).
- *Priorisierung der Therapieziele nach Risikoprofil:* Entsprechend sieht der Algorithmus vor, dass Menschen mit Diabetes und einer klinisch relevanten kardiovaskulären Erkrankung eine Kombinationstherapie aus Metformin und einem SGLT2-Inhibitor oder einem GLP-1-RA angeboten wird, wenn Patient*innen nach Abwägung der Wirkungen und Nebenwirkungen dazu bereit sind. Bei Patient*innen mit mehreren Risikofaktoren für das Auftreten eines renalen oder kardiovaskulären Ereignisses gemäß Tabelle 7 gibt es Gründe für eine primär HbA1c-orientierte Strategie, wie auch für eine sofortige Kombinationstherapie. Wer wovon eher profitiert, ist unklar, deshalb wird hier eine kritische individuelle Beurteilung und die partizipative Entscheidung auf Basis der verfügbaren Daten empfohlen. Unterstützende Materialien für das Gespräch zwischen Ärzt*innen und Patient*innen werden mit der NVL zur Verfügung gestellt (siehe „Patientenblätter“ und „Vorbereitung für das Gespräch mit der Ärztin/dem Arzt“ im Anhang). In den betrachteten Endpunktstudien wurden Patient*innen untersucht, die bereits eine glukosesenkende Therapie erhielten. Es besteht eine gewisse Unsicherheit, ob die Ergebnisse auf Therapie-naive Patient*innen übertragen werden können und diese von einer initialen Kombinationstherapie profitieren. Zu Therapie-naiven Patient*innen wurde keine Evidenz identifiziert. Die Bewertung der vorliegenden Evidenz durch die verschiedenen Fachgesellschaften werden im Anhang anhand von Auszügen aus den entsprechenden Anwenderversionen bzw. Praxisempfehlungen dargestellt (siehe „Abweichende Einschätzungen von DDG/DGIM/DGK/DGfN und DEGAM/AkdÄ/DGP“). Für Betroffene, bei denen die Kontrolle des Glukosestoffwechsels im Vordergrund steht, empfiehlt der Algorithmus wie bisher zunächst eine Monotherapie mit Metformin.

2.4.4 Wirkstoffwahl

- Leitend bei der Wirkstoffwahl sind die Effekte auf priorisierte klinische Outcomes, die in Tabelle 8 dargestellt sind. Nach Einschätzung der Leitliniengruppe liegen die belastbarsten Daten sowie Hinweise auf die Beeinflussung der Gesamtsterblichkeit in der Gruppe SGLT2-Inhibitoren für Empagliflozin vor und in der Gruppe der GLP-1-RA für Liraglutid. Beide Substanzen werden inzwischen auch vom G-BA als zweckmäßige Vergleichstherapie in der Kombinationstherapie anerkannt [43]. Die Entscheidung, diese beiden Substanzen nicht explizit im Algorithmus zu nennen, ist der derzeitigen Dynamik geschuldet, mit der neue Ergebnisse für bestimmte Wirkstoffe zu erwarten sind, die eine Einschätzung möglicherweise revidieren könnten.

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2.5 Wirkstoffe

Tabelle 8: Orientierende, vergleichende Betrachtung der Substanzklassen (als Ergänzung zum Algorithmus Medikamentöse Therapie des Typ-2-Diabetes)

Diese Tabelle ist eine zusammenfassende Interpretation der Evidenz. Für die ausführliche Darstellung der Evidenz zu den einzelnen Wirkstoffgruppen siehe Evidenztabellen [15].

Medikament	Gesamt-mortalität	Kardiovaskuläre Endpunkte	Mikrovaskuläre Endpunkte[1]	Renale Endpunkte	Hypoglykämien	HbA1c, Gewicht	Anmerkungen/ Ausgewählte Sicherheitshinweise
Metformin	(↓)	(↓)	(0)	(0)	↔	HbA1c ↓↓ Gewicht: ↔↓	▪ Risiko der Laktatazidose ▪ bei Krankheit („sick days“) pausieren
SGLT2-Inhibitoren							▪ Risiko genitaler Infektionen, atypischer Ketoazidose, Fournier-Gangrän ▪ bei Krankheit („sick days“) pausieren ▪ Gewichtsreduktion (bei Frailty unerwünscht)
Empagliflozin	↓ senkt*	MACE: ↓ senkt CV-Tod: ↓ senkt HHI: ↓ senkt	k. A.	↓ senkt	↔	HbA1c ↓↓ Gewicht: ↓	
Canagliflozin	0	MACE: ↓ senkt CV-Tod: 0 HHI: ↓ senkt	k. A.: Retinopathie, Neuropathie Amputationen 0 bis ↑	↓ senkt	↔	HbA1c ↓↓ Gewicht: ↓	
Dapagliflozin	0*	MACE: 0 CV-Tod: 0 HHI: ↓ senkt	k. A.: Retinopathie, Neuropathie; Amputationen: 0.	↓ senkt	↔	HbA1c ↓↓ Gewicht: ↓	

Medikament	Gesamt-mortalität	Kardiovaskuläre Endpunkte	Mikrovaskuläre Endpunkte[1]	Renale Endpunkte	Hypoglykämien	HbA1c, Gewicht	Anmerkungen/ Ausgewählte Sicherheitshinweise
GLP-1-RA							▪ gastrointestinale Nebenwirkungen, Gallensteine ▪ bei den meisten Wirkstoffen Injektionen notwendig ▪ Gewichtsreduktion (bei Frailty unerwünscht)
Liraglutid	↓ senkt*	MACE: ↓ senkt CV-Tod: ↓ senkt HHI: 0	Retinopathie: 0 k. A.: Neuropathie, Amputationen	↓ senkt	↔	HbA1c: ↓↓ Gewicht: ↓	
Exenatid	↓ senkt*	MACE: 0 CV-Tod: 0 HHI: 0	k. A.: Retinopathie, Neuropathie Amputationen: 0	k. A.	↔	HbA1c: ↓↓ Gewicht: ↓	
Semaglutid s.c.	0*	MACE: ↓ senkt CV-Tod: 0 HHI: 0	Retinopathie: ↑ k. A.: Neuropathie, Amputationen	↓ senkt	↔	HbA1c: ↓↓ Gewicht: ↓	
Semaglutid oral	↓ senkt*	MACE: 0 CV-Tod: ↓ senkt HHI: 0	k. A.: Retinopathie, Neuropathie, Amputationen	k. A.	k. A.	HbA1c: ↓↓ Gewicht: ↓	
Lixisenatid	0*	MACE: 0 CV-Tod: 0 HHI: 0	k. A.: Retinopathie, Amputationen, Neuropathie	k. A.	↔	HbA1c: ↓↓ Gewicht: ↓	
Albiglutid	0*	MACE: ↓ senkt CV-Tod: 0 HHI: k. A.	Retinopathie: 0 k. A.: Neuropathie, Amputationen	k. A.	↔	HbA1c: ↓↓ Gewicht: ↓	
Dulaglutid	0	MACE: ↓ senkt CV-Tod: 0 HHI: 0	Retinopathie: 0 k. A.: Amputationen, Neuropathie	↓ senkt	↔	HbA1c: ↓↓ Gewicht: ↓	

Medikament	Gesamt-mortalität	Kardiovaskuläre Endpunkte	Mikrovaskuläre Endpunkte[1]	Renale Endpunkte	Hypoglykämien	HbA1c, Gewicht	Anmerkungen/ Ausgewählte Sicherheitshinweise
Sulfonylharnstoffe	(0)	MACE: k. A. CV-Tod: (0) HHI: (0)	(0 bis ↓)	(0 bis ↓)	↑↑	HbA1c: ↓↓ Gewicht: ↑	▪ Risiko schwerer prolongierter Hypoglykämien
DPP-4-Inhibitoren	(0)	MACE: k. A. CV-Tod: (0) HHI: (0)	(0)	(0)	↔	HbA1c: ↓ Gewicht: ↔	▪ Risiko für Pankreatitis, entzündliche Darmerkrankungen
Ggf. ab Stufe 3 des Algorithmus							
Insulin	(0)	(0)	(↓)	(0)	↑↑	HbA1c: ↓↓ (dosisabhängig) Gewicht: ↑↑	▪ Risiko für Hypoglykämien, besonders zu Therapiebeginn ▪ Lipohypertrophien ▪ Injektionen nötig

Legende

Effektangaben: ↓: positiver Effekt (Endpunkt wurde in den Studien seltener erreicht); ↑: negativer Effekt (Endpunkt wurde in den Studien häufiger erreicht); 0: der Endpunkt wurde nicht beeinflusst; k. A.: keine Angabe (die Effektgrößen wurden in der Hauptpublikation nicht, oder ohne Konfidenzintervall angegeben); renale Endpunkte: bei SGLT2-Inhibitoren und GLP-1-RA bezogen auf renale Kompositendpunkte.
Annahmen in Klammern () stammen aus Studien mit niedriger methodischer Qualität, oder es lag keine ausreichende Evidenz zur Beurteilung vor.

Hypoglykämien: ↑: erhöhtes Risiko; ↔: geringes Risiko, k. A.: keine Angabe (Hypoglykämien: Intervention > Placebo, Angabe ohne Konfidenzintervall)

HbA1c: ↓: Senkung

Gewicht: ↑: Gewichtszunahme; ↓: Gewichtsabnahme

Gesamtmortalität: *: Die Studie war nicht für den Endpunkt Gesamtmortalität gepowert

Abkürzungen: MACE: i. d. R. kardiovaskulärer Tod, Schlaganfall, Myokardinfarkt (Definitionen teils heterogen); CV-Tod: kardiovaskulärer Tod; HHI: Herzinsuffizienz-bedingte Hospitalisierung.

[1]Mikrovaskuläre Endpunkte: Retinopathie, Neuropathie, Amputationen

Daten zu renalen Endpunkten zu Empagliflozin aus [44]

Evidenzdarstellung

2.5.1 Metformin

- Cochrane-Review [45], AHRQ-Review [46], Cochrane-Review [47], NVL von 2014 [2]

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2.5.2 SGLT2-Inhibitoren (Gliflozine)

- 4 RCTs [36,40,44,52,53,54,56], Metanalyse [35]

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2.5.3 GLP-1-Rezeptoragonisten (GLP-1-RA)

- RCTs [69-73,38,39], Marktrücknahme Albiglutid [74,75]

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2.5.4 Sulfonylharnstoffe (Glibenclamid, Gliclazid, Glimepirid)

- Cochrane-Review [85], AHRQ-Review [46] RCTs [86-88], NVL von 2014 [2]

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2.5.5 DPP-4-Hemmer

- AHRQ-Review [46], RCTs [86], Cochrane Review [89]

Referenzen aus Leitlinien

46. Agency for Healthcare Research and Quality (AHRQ). Diabetes Medications for Adults With Type 2 Diabetes: An Update. 2016 (Comparative Effectiveness Reviews; 173) [cited: 2019-07-04]. https://www.ncbi.nlm.nih.gov/books/NBK362863/.

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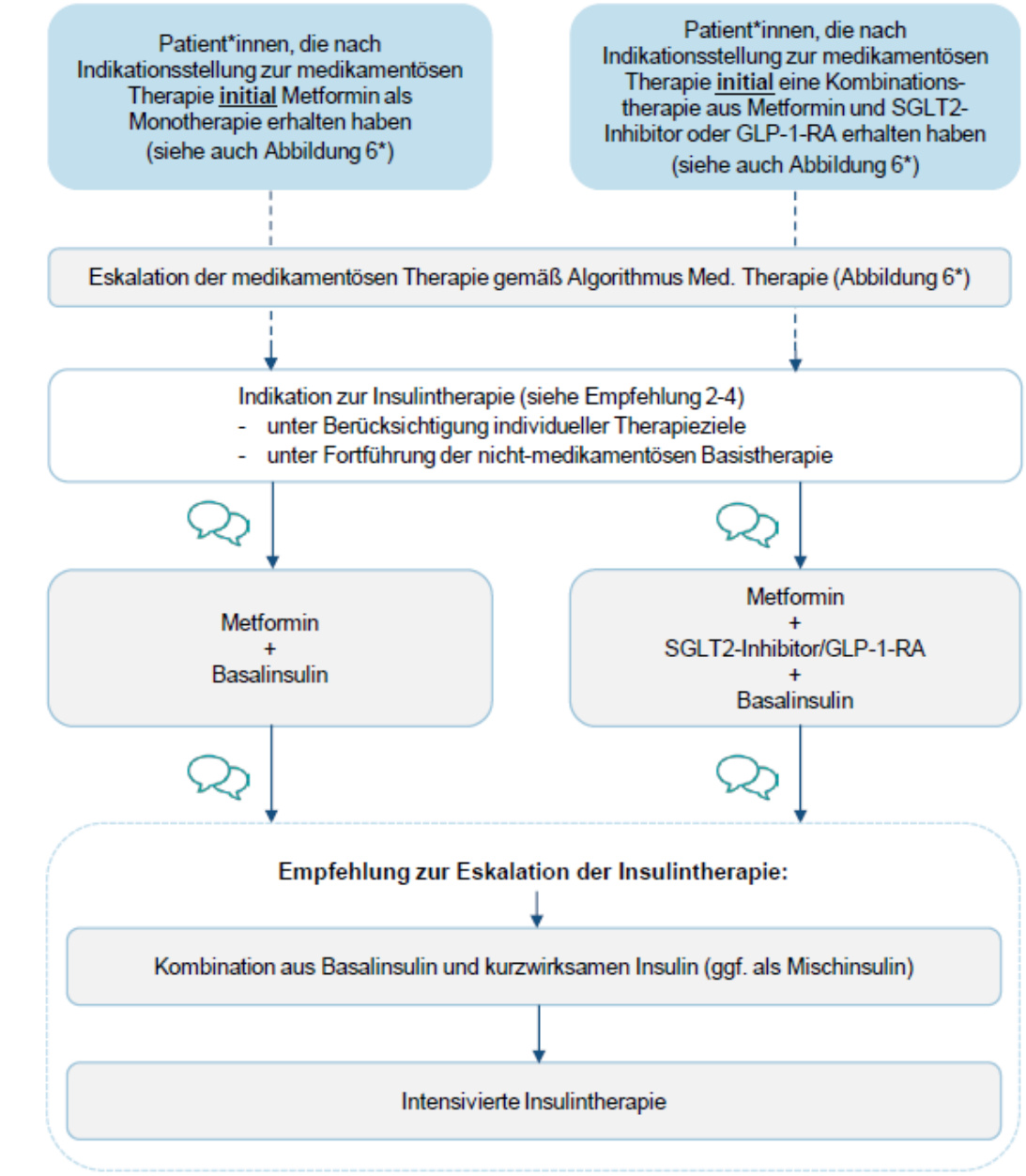
2.5.6 Insuline

- **2-4:** ⇑⇑ Bei Menschen mit Typ-2-Diabetes soll die Indikation zur Insulintherapie in folgenden Situationen geprüft werden:
  - bei Nicht-Erreichen des individuellen Therapieziels trotz Ausschöpfung der nicht-medikamentösen Maßnahmen und medikamentösen Therapie (Kombination aus oralen Antidiabetika mit/ohne s.c. zu verabreichenden GLP-1-RA gemäß Abbildung 1);
  - bei metabolischen Entgleisungen, z. B. bei Erstdiagnose (unklare diagnostische Situation, Typ-1-Diabetes nicht sicher ausgeschlossen);
  - bei Gabe von diabetogenen Medikamenten (z. B. Glukokortikoide), bei schweren Infekten, Traumata oder größeren Operationen, (eventuell nur temporär);
  - bei stark eingeschränkter Nierenfunktion (in Abhängigkeit vom individuellen Therapieziel).
- **2-5:** ⇑⇑ Die Deeskalation der Insulintherapie soll bei Menschen mit Typ-2-Diabetes in folgenden Situationen geprüft werden: Wenn
  - die Indikation (z. B. akute Erkrankung, metabolische Entgleisung, Verschlechterung der Nierenfunktion) nicht mehr besteht;
  - die Zielwerte des Glukosestoffwechsels erreicht sind oder unterschritten werden;
  - Hypoglykämien auftreten;
  - sich das individuelle Therapieziel ändert (z. B. in Folge von Multimorbidität).

  Die Empfehlungen [2-4 & 2-5] basieren auf einem Expert*innenkonsens sowie indirekt auf der Evidenz zur Wirksamkeit der Insulinbehandlung und beschreiben gute klinische Praxis.

  Die Leitliniengruppe nimmt aus ihrer klinischen Erfahrung als Versorgungsproblem wahr, dass die Indikation zur Insulintherapie bei Menschen mit Typ-2-Diabetes teilweise zu zeitig gestellt wird und eine einmal begonnen Insulintherapie nicht wieder deeskaliert wird, auch wenn die Indikation nicht mehr besteht. In anderen Situationen, in denen eine Insulintherapie ggf. auch nur temporär sinnvoll ist, wird sie zu zögerlich initiiert.

  Rationale: Der Nutzen in Bezug auf patientenrelevante Langzeit-Endpunkte ist nicht belastbar nachgewiesen. Gleichzeitig kann die Insulintherapie zu Hypoglykämien und Gewichtszunahme führen, sowie eine Belastung der Patient*innen (Injektionen, Anpassung des Alltags) darstellen. Die Indikation für die dauerhafte Insulintherapie sieht die Leitliniengruppe daher erst dann gegeben, wenn andere, im Nutzen besser belegte Handlungsoptionen ausgeschöpft sind. Sie spricht daher eine starke Empfehlung für die Bedingungen aus, unter denen die Indikation zur Insulintherapie geprüft werden soll. Situationen, in denen eine Insulintherapie notwendig ist, sind hiervon ausgenommen und werden zusätzlich genannt. Aus denselben Überlegungen und um Belastungen durch unerwünschte Wirkungen möglichst gering zu halten, spricht die Leitliniengruppe eine starke Empfehlung für die Prüfung der Deeskalation in spezifischen Situationen aus
- Algorithmus der Insulintherapie:



= Überprüfung der Therapiestrategie und des Therapieziels in partizipativer Entscheidungsfindung
Die Kontraindikationen der eingesetzten Wirkstoffe sind zu beachten (z. B. bei stark eingeschränkter Nierenfunktion).

* Abbildung 6: Algorithmus Medikamentöse Therapie des Typ-2-Diabetes

Abbildung 2: Algorithmus Insulintherapie

- Der Algorithmus schließt an den Algorithmus zur Medikamentösen Therapie des Typ-2-Diabetes (siehe Abbildung 1) an und ist als dessen Fortführung beim Einsatz von Insulin zu verstehen.
- **2-6:** ⇑⇑ Die Wahl der Insulinart und des Insulinschemas soll sich an der Lebenssituation der Patient*innen orientieren.

Evidenzbasis des Algorithmus zur Insulintherapie und der Empfehlung 2-6

- Der Algorithmus bezieht sich vorrangig auf eine längerfristige Therapie bei Menschen mit Typ-2-Diabetes, bei denen das individuelle Therapieziel durch die vorherigen Eskalationsstufen nicht erreicht wurde. Bei anderen Situationen, die in Empfehlung 2-4

beschrieben werden (z. B. größere Operationen oder bei schweren Infekten, akuten Dekompensationen oder initial unklaren diagnostischen Situationen), sollte ein anderes Therapiekonzept überlegt werden. Es ist zu berücksichtigen, dass beispielsweise die Therapie mit Metformin bei einer eGFR < 30 ml/min/1,73 m^2 kontraindiziert ist.

- Cochrane-Reviews [99,100,102,103], Beobachtungsstudie [104]
- Für weitere Evidenzbeschreibung und Erwägungen, die die Empfehlungen begründen, wird auf die Teilpublikation der NVL verwiesen.

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103. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007(2):CD005613. DOI: 10.1002/14651858.CD005613.pub3. http://www.ncbi.nlm.nih.gov/pubmed/17443605.
104.Mertes B, Gödde S, Piorkowski M, et al. Successful Treatment with Bedtime Basal Insulin Added to Metformin without Weight Gain or Hypoglycaemia over Three Years. Journal of clinical medicine 2020; 9(4). DOI: 10.3390/jcm9041153. http://www.ncbi.nlm.nih.gov/pubmed/32316649

2.6 Therapiemöglichkeiten bei höhergradiger Niereninsuffizienz (eGFR < 30 ml/min/1,73 m^2)

- Bei Patient*innen mit einer eGFR < 30 ml/min/1,73 m^2 ist eine Therapie mit Metformin kontraindiziert [51]. In Abhängigkeit der metabolischen Situation ist bei dieser Patientengruppe initial häufig eine Insulintherapie indiziert. Dies kann auch nur vorübergehend sein. Es ist wichtig, regelmäßig zu prüfen, ob die Therapie an die Nierenfunktion angepasst ist.
- Die Leitliniengruppe schlägt vor, Patient*innen mit höhergradiger Niereninsuffizienz, bei denen die individuellen Therapieziele nach Ausschöpfung der nicht-medikamentösen Therapie nicht erreicht worden sind, unter Berücksichtigung des jeweiligen Zulassungsstatus und der Fachinformation mit einem der folgenden Wirkstoffen zu behandeln (alphabetische Reihenfolge): DPP-4-Inhibitoren oder Glinide oder GLP-1-RA oder Insulin.
- Werden die individuellen Therapieziele nicht erreicht, schließt sich eine Kombination aus Basalinsulin mit einem der oben genannten Wirkstoffe an (immer unter Berücksichtigung der Nierenfunktion). Die nächste Eskalationsstufe sieht eine Kombination von Basalinsulin mit kurzwirksamem Insulin bzw. eine Intensivierung der Insulintherapie vor. Die Auswahl der Medikamente erfolgt im Sinne der partizipativen Entscheidungsfindung unter Berücksichtigung der individuellen Therapieziele, Kontextfaktoren, sowie Vor- und Nachteile der Wirkstoffe. Bei dialysepflichtigen Patient*innen kann eine Anpassung des Insulinschemas an die Behandlungstage mit und ohne Nierenersatztherapie erforderlich sein

51. European Medicines Agency (EMA). Anwendung von Metformin zur Behandlung von Diabetes nun auf Patienten mit mittel-schwerer Nierenfunktionsbeeinträchtigung ausgeweitet. Empfehlungen für Patienten mit Nierenfunktionsbeeinträchtigung in den Produktinformationen aktualisiert. EMA/868987/2016. 2016 [cited: 2020-06-04]. https://www.ema.europa.eu/en/docu-ments/referral/metformin-article-31-referral-use-metformin-treat-diabetes-now-expanded-patients-moderately-re-duced_de.pdf.

2.7 Weitere Blutglukose-senkende Wirkstoffe

- Neben den oben genannten Wirkstoffgruppen wurden in der NVL Therapie des Typ-2-Diabetes aus 2014 [2] alpha-Glukosidasehemmer, Glinide und Glitazone genannt. Diese Wirkstoffe sind seltenen Sondersituationen vorbehalten und wurden im Rahmen der Leitlinienarbeit nicht näher betrachtet

2.Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medi-zinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes - Langfassung, 1. Auflage. Version 4. 2014 [cited: 2017-01-12]. DOI: 10.6101/AZQ/000213. http://doi.org/10.6101/AZQ/000213.

National Institute for Health and Care Excellence (NICE), 2015 [49,50].

Type 2 diabetes in adults: management - Clinical Guideline Update

Zielsetzung/Fragestellung

This guideline contains recommendations for managing type 2 diabetes in adults, and focuses on patient education, dietary advice, managing cardiovascular risk, managing blood glucose levels, and identifying and managing long-term complications.

Methodik

Grundlage der Leitlinie

2022 Update der Leitlinie von 2015 → Last updated: 29 June 2022

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- Recherche für die LL Version von 2015:
  - searches undertaken between July 2012 and June 2013; re-run searches in June 2014
  - Cochrane Database of Systematic Reviews –CDSR (Wiley); Cochrane Central Register of Controlled Trials –CENTRAL (Wiley); Database of Abstracts of Reviews of Effects – DARE (Wiley); Health Technology Assessment Database –HTA (Wiley); EMBASE (Ovid); MEDLINE (Ovid); MEDLINE In-Process (Ovid)
- Recherche für die Updates von 2022:
  - Search updates for “Pharmacological therapies with cardiovascular and other benefits in people with type 2 diabetes” on 30th November 2020 in Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Embase, Medline, MEDLINE In Process, MEDLINE ePubs
  - Search updates for “continuous glucose monitoring in adults with type 2 diabetes” on 11th May 2021 in Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Embase, DARE, MEDLINE, MEDLINE In Process, MEDLINE ePubs, PsycINFO

LoE

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

GoR

- Interventions that must (or must not) be used: We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
- Interventions that should (or should not) be used – a 'strong' recommendation: We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer...') when we are confident that an intervention will not be of benefit for most patients.
- Interventions that could be used: We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Sonstige methodische Hinweise

- Die ursprüngliche LL ist von 2009 und wurde 2015 überarbeitet bzw. ersetzt. Seitdem erfolgten verschiedene Updates. Das letzte Update war im Februar und März 2022:
  - March 2022: We have reviewed the evidence on continuous glucose monitoring for adults with type 2 diabetes.
  - February 2022: We have reviewed the evidence and made new recommendations on drug treatment for adults with type 2 diabetes.

Empfehlungen

Algorithmus siehe Anhang

1.3 Dietary advice and bariatric surgery

- 1.3.1 Provide individualised and ongoing nutritional advice from a healthcare professional with specific expertise and competencies in nutrition. [2009]
- 1.3.2 Provide dietary advice in a form sensitive to the person's needs, culture and beliefs, being sensitive to their willingness to change and the effects on their quality of life. [2009]
- 1.3.3 Encourage adults with type 2 diabetes to follow the same healthy eating advice as the general population, which includes:
  - eating high-fibre, low-glycaemic-index sources of carbohydrate, such as fruit, vegetables, wholegrains and pulses
  - choosing low-fat dairy products
  - eating oily fish
  - controlling their intake of saturated and trans fatty acids. [2009]
- 1.3.4 Integrate dietary advice with a personalised diabetes management plan, including other aspects of lifestyle modification such as increasing physical activity and losing weight. [2009]
- 1.3.5 For adults with type 2 diabetes who are overweight, discuss and agree an initial body weight loss target of 5% to 10%. Remember that a small amount of weight loss

may still be beneficial, and a larger amount will have advantageous metabolic impact in the long term. [2009]

- 1.3.6 Individualise recommendations for carbohydrate and alcohol intake, and meal patterns. Make reducing the risk of hypoglycaemia a particular aim for people using insulin or an insulin secretagogue. [2009]
- 1.3.7 Advise adults with type 2 diabetes that they can substitute a limited amount of sucrose-containing foods for other carbohydrate in the meal plan but should take care to avoid excess energy intake. [2009]
- 1.3.8 Discourage adults with type 2 diabetes from using foods marketed specifically for people with diabetes. [2009]
- 1.3.9 When adults with type 2 diabetes are admitted as inpatients to hospital or any other care setting, implement a meal planning system that provides consistency in the carbohydrate content of meals and snacks. [2009]
- 1.3.10 For recommendations on lifestyle advice, see the NICE guidelines on preventing excess weight gain, weight management, obesity, physical activity and tobacco. [2015]
  - https://www.nice.org.uk/guidance/ng7
  - https://www.nice.org.uk/guidance/ph53
  - https://www.nice.org.uk/guidance/cg189
  - https://www.nice.org.uk/guidance/ph44
  - https://www.nice.org.uk/guidance/ng209
- 1.3.11 For recommendations on bariatric surgery for people with recent-onset type 2 diabetes, see the section on bariatric surgery for people with recent-onset type 2 diabetes in the NICE guideline on obesity. [2015]

National Institute for Health and Care Excellence (NICE). Obesity: identification, assessment and management [online]. London (GBR): NICE; 2014. [Zugriff: 25.07.2022]. (NICE guidelines; Band CG189). URL: https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925.

1.11 Bariatric surgery for people with recent-onset type 2 diabetes

- For the recommendations in this section, the GDG considered that recent-onset type 2 diabetes would include those people whose diagnosis has been made within a 10-year time frame.
- 1.11.1Offer an expedited assessment for bariatric surgery to people with a BMI of 35 or over who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent). [new 2014]
- 1.11.2Consider an assessment for bariatric surgery for people with a BMI of 30 to 34.9 who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent). [new 2014]
- 1.11.3Consider an assessment for bariatric surgery for people of Asian family origin who have recent-onset type 2 diabetes at a lower BMI than other populations (see recommendation 1.2.8) as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent). [new 2014]

1.7 Drug treatment

Rescue therapy at any phase of treatment

- 1.7.2 If an adult with type 2 diabetes is symptomatically hyperglycaemic, consider insulin (see the section on insulin-based treatments) or a sulfonylurea, and review treatment when blood glucose control has been achieved. [2015]

First-line drug treatment

- 1.7.3 Offer standard-release metformin as first-line drug treatment to adults with type 2 diabetes. [2015]
- 1.7.4 Assess the person's cardiovascular status and risk to determine whether they have chronic heart failure or established atherosclerotic cardiovascular disease or are at high risk of developing cardiovascular disease. See the recommendations on using risk scores and QRISK2 to assess cardiovascular disease risk in adults with type 2 diabetes in NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification (https://www.nice.org.uk/guidance/cg181/chapter/recommendations). [2022]
- 1.7.5 Based on the cardiovascular risk assessment for the person with type 2 diabetes:
  - If they have chronic heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor with proven cardiovascular benefit in addition to metformin.
  - If they are at high risk of developing cardiovascular disease, consider an SGLT2 inhibitor with proven cardiovascular benefit in addition to metformin. [2022]
- 1.7.6 When starting an adult with type 2 diabetes on dual therapy with metformin and an SGLT2 inhibitor as first-line therapy, introduce the drugs sequentially, starting with metformin and checking tolerability. Start the SGLT2 inhibitor as soon as metformin tolerability is confirmed. [2022]
- 1.7.7 Gradually increase the dose of standard-release metformin over several weeks to minimise the risk of gastrointestinal side effects in adults with type 2 diabetes. [2015]
- 1.7.8 If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. [2015]
- 1.7.9 For first-line drug treatment in adults with type 2 diabetes, if metformin is contraindicated or not tolerated:
  - If they have chronic heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor with proven cardiovascular benefit.
  - If they are at high risk of developing cardiovascular disease, consider an SGLT2 inhibitor with proven cardiovascular benefit. [2022]
- 1.7.10 For first-line drug treatment in adults with type 2 diabetes, if metformin is contraindicated or not tolerated and if they are not in either of the groups in recommendation 1.7.9, consider:
  - a DPP-4 inhibitor or
  - pioglitazone or
  - a sulfonylurea or
  - an SGLT2 inhibitor for people who meet the criteria in NICE's technology appraisal guidance on canagliflozin, dapagliflozin and empagliflozin as monotherapies (https://www.nice.org.uk/guidance/ta390) or ertugliflozin as monotherapy or with metformin for treating type 2 diabetes (https://www.nice.org.uk/guidance/ta572). [2015, amended 2022]
- 1.7.11 Before starting an SGLT2 inhibitor, check whether the person may be at increased risk of diabetic ketoacidosis (DKA), for example if:
  - they have had a previous episode of DKA

  - they are unwell with intercurrent illness
  - they are following a very low carbohydrate or ketogenic diet. [2022]
- 1.7.12 Address modifiable risks for DKA before starting an SGLT2 inhibitor. For example, for people who are following a very low carbohydrate or ketogenic diet, they may need to delay treatment until they have changed their diet. [2022]
- 1.7.13 Advise adults with type 2 diabetes who are taking an SGLT2 inhibitor about the need to minimise their risk of DKA by not starting a very low carbohydrate or ketogenic diet without discussing it with their healthcare professional, because they may need to suspend SGLT2 inhibitor treatment. [2022]

Adding an SGLT2 inhibitor at any stage after first-line treatment has been started

- 1.7.15 For adults with type 2 diabetes at any stage after they have started first-line treatment:
  - If they have or develop chronic heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor with proven cardiovascular benefit in addition to current treatment or replace an existing drug with the SGLT2 inhibitor.
  - If they are or become at high risk of developing cardiovascular disease, consider adding an SGLT2 inhibitor with proven cardiovascular benefit to current treatment or replacing an existing drug with the SGLT2 inhibitor.
  - Take into account the person's current treatment regimen and preferences and make a shared decision about switching treatments or adding an SGLT2 inhibitor, as appropriate (also see recommendations 1.7.12 and 1.7.13 on starting an SGLT2 inhibitor). [2022]
  - In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off-label. See NICE's information on prescribing medicines.

Treatment options if further interventions are needed

- 1.7.16 Introduce drugs used in combination therapy in a stepwise manner, checking for tolerability and effectiveness of each drug. [2015]
- 1.7.17 For adults with type 2 diabetes, if monotherapy has not continued to control HbA1c to below the person's individually agreed threshold for further intervention, consider adding:
  - a DPP-4 inhibitor or
  - pioglitazone or
  - a sulfonylurea or
  - an SGLT2 inhibitor for people who meet the criteria in NICE's technology appraisal guidance on canagliflozin in combination therapy (https://www.nice.org.uk/guidance/ta315), ertugliflozin as monotherapy or with metformin (https://www.nice.org.uk/guidance/ta572), or dapagliflozin (https://www.nice.org.uk/guidance/ta288) or empagliflozin (https://www.nice.org.uk/guidance/ta336) in combination therapy. [2015, amended 2022]
- 1.7.18 For adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for further intervention consider either:
  - triple therapy by adding a DPP-4 inhibitor, pioglitazone or a sulfonylurea or an SGLT2 inhibitor for people who meet the criteria in NICE's technology appraisal guidance on canagliflozin in combination therapy (https://www.nice.org.uk/guidance/ta315), dapagliflozin in triple therapy (https://www.nice.org.uk/guidance/ta418), empagliflozin in combination therapy (https://www.nice.org.uk/guidance/ta336), or

ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor (https://www.nice.org.uk/guidance/ta583) or

- starting insulin-based treatment (see the section on insulin-based treatments) [2015, amended 2022]

- 1.7.19 In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and dual therapy with 2 oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intervention, consider insulinbased treatment (see the section on insulin-based treatments). [2015, amended 2022]
- 1.7.20 If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:
  - have a body mass index (BMI) of 35 kg/m2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
  - have a BMI lower than 35 kg/m2 and: — for whom insulin therapy would have significant occupational implications or — weight loss would benefit other significant obesity-related comorbidities. [2015, amended 2022]
- 1.7.21 Only continue GLP-1 mimetic therapy if the adult with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and weight loss of at least 3% of initial body weight in 6 months). [2015]
- 1.7.22 For adults with type 2 diabetes, only offer combination therapy with a GLP-1 mimetic and insulin along with specialist care advice and ongoing support from a consultant-led multidisciplinary team. [2015]

Insulin-based treatments

- 1.7.23 For adults with type 2 diabetes starting insulin therapy, provide a structured programme using active insulin dose titration that encompasses:
  - injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites
  - continuing telephone support
  - self-monitoring
  - dose titration to target levels
  - dietary advice
  - the DVLA's Assessing fitness to drive: a guide for medical professionals
  - managing hypoglycaemia
  - managing acute changes in plasma glucose control
  - support from an appropriately trained and experienced healthcare professional. [2015]
- 1.7.24 For adults with type 2 diabetes starting insulin therapy, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. [2015]
- 1.7.25 Start insulin therapy for adults with type 2 diabetes from a choice of the following insulin types and regimens:
  - Offer neutral protamine Hagedorn (NPH) insulin injected once or twice daily according to need.
  - Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either: — separately or — as a pre-mixed (biphasic) human insulin preparation.

  - Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: — the person needs help from a carer or healthcare professional to inject insulin, and use of insulin detemir or 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.
  - Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: — the person prefers injecting insulin immediately before a meal or — hypoglycaemia is a problem or — blood glucose levels rise markedly after meals. [2015]
- 1.7.26 Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes:
  - 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 could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or
  - who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. [2015]
- 1.7.27 Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). [2015]
- 1.7.28 Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal-bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. [2015]
- 1.7.29 When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost. [2021]
- 1.7.30 Ensure the risk of medication errors with insulins is minimised by following the Medicines and Healthcare products Regulatory Agency (MHRA) guidance on minimising the risk of medication error with high strength, fixed combination and biosimilar insulin products, which includes advice for healthcare professionals when starting treatment with a biosimilar. [2021]
- 1.7.31 When people are already using an insulin for which a lower cost biosimilar is available, discuss the possibility of switching to the biosimilar. Make a shared decision with the person after discussing their preferences. [2021]
- For guidance on using insulin in combination with SGLT2 inhibitors, see:
  - the section on drug treatment (1.7)
  - NICE's technology appraisal guidance on canagliflozin, dapagliflozin, and empagliflozin in combination therapy:

    Canagliflozin in combination therapy for treating type 2 diabetes

National Institute for Health and Care Excellence (NICE). Canagliflozin in combination therapy for treating type 2 diabetes [online]. London (GBR): NICE; 2014. [Zugriff: 25.07.2022]. (Technology appraisal guidance; Band TA315). URL: https://www.nice.org.uk/guidance/ta315/resources/canagliflozin-in-combination-therapy-for-treating-type2-diabetes-pdf-82602428123077.

1.1 Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated **or**
- the person is at significant risk of hypoglycaemia or its consequences.

1.2 Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- metformin and a sulfonylurea **or**
- metformin and a thiazolidinedione.

1.3 Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

1.4 People currently receiving treatment initiated within the NHS with canagliflozin that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Dapagliflozin in combination therapy for treating type 2 diabetes

National Institute for Health and Care Excellence (NICE). Dapagliflozin in combination therapy for treating type 2 diabetes [online]. London (GBR): NICE; 2013. [Zugriff: 25.07.2022]. (Technology appraisal guidance; Band TA288). URL: https://www.nice.org.uk/guidance/ta288/resources/dapagliflozin-in-combination-therapy-for-treating-type2-diabetes-pdf-82600679642821.

1.1 Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated **or**
- the person is at significant risk of hypoglycaemia or its consequences.

1.2 Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

1.3 This recommendation has been updated and replaced by NICE's technology appraisal guidance on dapagliflozin in triple therapy for treating type 2 diabetes.

1.4 People currently receiving dapagliflozin in a dual therapy regimen that is not recommended for them in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

Empagliflozin in combination therapy for treating type 2 diabetes

National Institute for Health and Care Excellence (NICE). Empagliflozin in combination therapy for treating type 2 diabetes [online]. London (GBR): NICE; 2015. [Zugriff: 25.07.2022]. (Technology appraisal guidance; Band TA336). URL: https://www.nice.org.uk/guidance/ta336/resources/empagliflozin-in-combination-therapy-for-treating-type2diabetes-pdf-82602550735045.

1.1	Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if: • a sulfonylurea is contraindicated or not tolerated, or • the person is at significant risk of hypoglycaemia or its consequences.
1.2	Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with: • metformin and a sulfonylurea or • metformin and a thiazolidinedione.
1.3	Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.
1.4	People currently receiving treatment initiated within the NHS with empagliflozin that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Mannucci E et al., 2023 [40].

2023 update on Italian guidelines for the treatment of type 2 diabetes

Zielsetzung/Fragestellung

This guideline, aimed at providing a reference for pharmacological and non-pharmacological treatment of type 2 diabetes in adults, was directed to physicians, nurses, dietitians and educators working in Diabetes specialist clinics, general practitioners, nurses and dietitian working in territorial services or private offices, and patients with diabetes. In this first update, the guideline panel verified the need to modify, update, add or remove clinical questions, and the opportunity of modifying the outcomes of interest and their relative relevance.

Methodik

Grundlage der Leitlinie

Update der 2022 Leitlinie “Italian guidelines for the treatment of type 2 diabetes” Mannucci E et al., 2022 [39,41];

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;

- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials (Wiley), MEDLINE (OVID), Embase (OVID), Clinicaltrials.gov
- In case of changes in clinical questions and/or critical outcomes, the whole process of evidence review and development of recommendation was performed anew. In all other cases, the evidence review team reviewed and updated all systematic reviews (using the same search strings) for each outcome of individual question previously published in Manucci E et al., 2022 [41]
- Last search date/ Update of meta-analysis: 20/05/2022

LoE

- HIGH: Highly reliable results. It is very unlikely that further studies modify the confidence in estimated effects.
- MODERATE: Moderately reliable results. It is possible that further studies modify the confidence in estimated effects.
- LOW: Results are still uncertain. Further research is needed for a reliable assessment of positive and negative effects of the intervention.
- VERY LOW: Available data are not reliable, and estimates of effects should be considered with caution.

GoR

- Strong recommendation
  - for clinicians: the majority of patients must receive the recommended intervention;
  - for patients: almost all properly informed patients follow the recommendation and only a small fraction choses different options;
  - for policy makers: the recommendation can be used for planning the use of available resources.
- Weak recommendation
  - for clinicians: the final choice should include a careful consideration of patients' values and preferences;
  - for patients: the majority of properly informed patients follow the recommendation, but a minority choses different options;
  - for policy makers: a discussion involving stakeholder should be developed

Empfehlungen

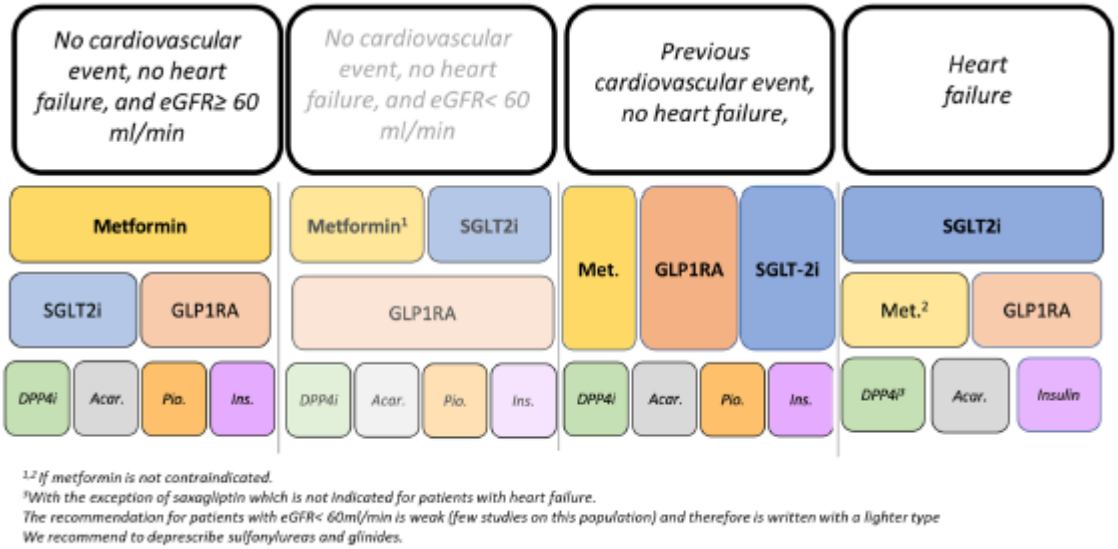


Fig. 1 Therapeutic algorithm for the pharmacological treatment of type 2 diabetes

5. Pharmacological treatment

5.1 We recommend the use of metformin as a first-line long-term treatment in patients with type 2 diabetes without previous cardiovascular events and chronic renal failure. SGLT-2 inhibitors or GLP-1 receptor agonists are recommended as second-line treatments. Pioglitazone, DPP-4 inhibitors, acarbose, and insulin should be considered as third-line treatments. Sulfonylureas and glinides should not be recommended for the treatment of type 2 diabetes (Fig. 1)

MODIFIED RECOMMENDATION *Strength of the recommendation: strong. Quality of evidence: moderate.*

5.2. We suggest the use of metformin and SGLT-2 inhibitors as a first-line long-term treatment in patients with type 2 diabetes and eGFR < 60 ml/min, without previous cardiovascular events/heart failure. GLP-1 receptor agonists are recommended as second-line treatments. Pioglitazone, DPP-4 inhibitors, acarbose, and insulin should be considered as third-line treatments. Sulfonylureas and glinides should not be recommended for the treatment of type 2 diabetes (Fig. 1)**.**

NEW RECOMMENDATION *Strength of the recommendation: weak. Quality of evidence: very low.*

5.3. We recommend the use of metformin, SGLT-2 inhibitors, or GLP-1 receptor agonists as first-line long-term treatment in patients with type 2 diabetes with previous cardiovascular events and without heart failure. DPP-4 inhibitors, pioglitazone, acarbose, and insulin should be considered as second-line treatments. Sulfonylureas and glinides should not be recommended for the treatment of type 2 diabetes (Fig. 1)**.**

MODIFIED RECOMMENDATION *Strength of the recommendation: strong. Quality of evidence: moderate.*

5.4. We recommend the use of metformin, SGLT-2 inhibitors, or GLP-1 receptor agonists as first-line long-term treatment in patients with type 2 diabetes with previous cardiovascular events and without heart failure. DPP-4 inhibitors, pioglitazone, acarbose, and insulin should be considered as second-line treatments. Sulfonylureas and glinides should not be recommended for the treatment of type 2 diabetes (Fig. 1)**.**

MODIFIED RECOMMENDATION *Strength of the recommendation: strong. Quality of evidence: moderate.*

5.5 We suggest the use of prandial insulin analogues for patients with type 2 diabetes needing treatment with prandial insulin.

Strength of the recommendation: weak. Quality of evidence: very low.

5.6 We recommend the use of long-acting basal insulin with longer, instead or shorter duration, for all patients with type 2 diabetes needing treatment with basal insulin.

NEW RECOMMENDATION *Strength of the recommendation: weak. Quality of evidence: very low.*

5.7 We suggest the use of prandial insulin analogues for patients with type 2 diabetes needing treatment with prandial insulin.

Strength of the recommendation: weak. Quality of evidence: very low.

5.8 The routine use of continuous subcutaneous insulin infusion in inadequately controlled patients with type 2 diabetes is not recommended.

Strength of the recommendation: weak. Quality of evidence: very low.

Living Evidence for Diabetes Consortium, 2024 [35].

Australian evidence-based clinical guidelines for diabetes; living guideline, v2.2

Zielsetzung/Fragestellung

The Living Evidence for Diabetes program was developed with the objective of applying the methods of living evidence to several specific clinical questions within two priority areas of diabetes prevention, diagnosis and treatment. This focused approach precludes the analysis of broad topics within diabetes and instead involves the selection and prioritization of a small subset of individual clinical questions.

The clinical guidelines cover: 1. Medical device technology for the management of type 1 diabetes; and 2. Medication for blood glucose management in adults with type 2 diabetes.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – unklar (Multidisciplinary panels are convened);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu (living guideline: The topics will be prioritised and evidence will be reviews and updated regularly to capture any significant changes at the time they are published.). → Last updated: 26.3.2024

Recherche/Suchzeitraum:

- MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to 1st May 2020

LoE/GoR

- Risk of bias assessment was conducted within Covidence using the Cochrane Risk of Bias (RoB) tool for randomized controlled trials
- the certainty of evidence (high certainty indicates that the true effect probably lies close to the effect estimate, whereas very low certainty indicates that the true effect probably does not lie close to the effect estimate)
- GRADE

The following criteria are used in determining the strength of recommendations:

1. **Strong for**: moderate to high certainty evidence suggests that benefits in critical outcomes clearly outweigh the reported harms; a strong recommendation can be made in the absence of high-certainty evidence if patients are expected to highly desire such practice and there are no potential harms in providing it.
2. **Strong against**: moderate to high certainty evidence suggests harms outweigh benefits; high certainty evidence suggests lack of benefits.
3. **Conditional for**: moderate to high certainty evidence suggests equivalent benefits and harms, patients would mostly want to receive the practice, and there is no significant resources implication in doing so; low certainty evidence suggests benefits outweigh harms and there are no significant implications in patients' preferences or resources implications.
4. **Conditional against**: moderate to high certainty evidence suggests equivalent benefits and harms, but there is expected large variation in patients' preference to receive this practice or important resource implications; low certainty evidence suggests harms outweigh benefits and there are no significant implications in patients' preferences or resource implications.
5. **Consensus statement**: evidence is absent or of insufficient certainty; unclear balance between benefits and harms, and there is expected large variation in patients' preferences. No formal method of reaching consensus was used but this was addressed in internal reviews.

Recommendations: Medications for blood glucose management in adults with type 2 diabetes

Optimal initial medication

Conditional recommendation

We suggest the use of metformin as first-line monotherapy in adults with type 2 diabetes.

This recommendation is based on the relative low cost and ease of administration of metformin. There is no convincing evidence of clinically significant differences in treatment effectiveness, serious adverse outcomes or all-cause mortality between the different classes when used as monotherapy. For individuals, there may be other factors that require consideration such as adverse effect potential, weight management strategy, frailty or comorbidities, which may contribute to clinician decision making when prescribing an alternative initial medication.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

There were no clinically relevant differences in any outcome when comparing SGLT-2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, sulphonylureas or thiazolidinediones as monotherapies to metformin alone.

No studies reported results with regards to the major adverse cardiovascular events (MACE) composite outcome.

Certainty of the Evidence

Low

There was no evidence of serious heterogeneity or inconsistency in the network with the exception of HbA1c, in which severe inconsistency was observed. For all outcomes, there was no evidence of incoherence in direct and indirect estimates or evidence of serious small-study effects.

Certainty of the evidence for all outcomes was low or moderate due to serious or very serious imprecision (based on wide confidence intervals and/or estimates not overlapping), with the exception of HbA1c, in which certainty was low due to very serious inconsistency within the network.

Optimal add-on medication

Recommended

In review

We recommend the addition of an SGLT-2 inhibitor to other glucose lowering medication(s) in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.

This recommendation applies to adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease and for whom effective diabetes management remains suboptimal despite the use of one or more existing therapies. We define multiple cardiovascular risk factors as men 55 years of age or older or women 60 years of age or older with type 2 diabetes who have one or more additional traditional risk factors, including hypertension, dyslipidaemia, or smoking. The evidence base for this recommendation includes studies on people with kidney disease who had an estimated glomerular filtration rate of 30 mL per minute per 1.73 m^2 of body-surface area or higher, although a few studies included participants with lower eGFR.

A summary of the network meta-analysis on which this recommendation is based can be found here.

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

When added to other glucose lowering medications, SGLT-2 inhibitors resulted in clinically significant reductions in all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, heart failure and end-stage kidney disease among people with type 2 diabetes and multiple cardiovascular risk factors, established cardiovascular disease and/or established kidney disease. No clinically relevant differences were observed when adding SGLT-2 inhibitors to other glucose lowering medications with regard to severe hypoglycaemia and incidence of non-fatal stroke.

Certainty of the Evidence

Moderate

With regard to the addition of SGLT-2 inhibitors to other glucose lowering medication, there was no evidence of serious heterogeneity or inconsistency in the network or incoherence in the direct and indirect estimates across all outcomes.

The certainty of the evidence for SGLT-2 inhibitors added to other glucose lowering medication was high across all outcomes.

Recommended

In review

We recommend the addition of a GLP-1 receptor agonist to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication.

This recommendation applies to adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, for whom effective management of diabetes and/or associated sequalae remains suboptimal despite the use of one or more existing therapies, and have an intolerance or contra-indication to SGLT-2 inhibitors. We define multiple cardiovascular risk factors as men 55 years of age or older or women 60 years of age or older with type 2 diabetes who have one or more additional traditional risk factors, including hypertension, dyslipidaemia, or smoking. The evidence base for this recommendation includes studies on people with kidney disease who had an estimated glomerular filtration rate of 30 mL per minute per 1.73 m^2 of body-surface area or higher, although a few studies included participants with lower eGFR.

A summary of the network meta-analysis on which this recommendation is based can be found here.

Benefits and harms

Substantial net benefits of the recommended alternative

When added to other glucose lowering medications, GLP-1 receptor agonists resulted in clinically relevant reductions in all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke and end-stage kidney disease among people with type 2 diabetes and multiple cardiovascular risk factors or established cardiovascular disease.

When added to other glucose lowering medications, the use of GLP-1 receptor agonists resulted in greater reductions in the incidence of non-fatal stroke compared with SGLT-2 inhibitors, however, the use of SGLT-2 inhibitors resulted in clinically relevant reductions in hospitalisation due to heart failure and end-stage kidney disease compared with GLP-1 receptor agonists.

Certainty of the Evidence

High

With regard to the addition of a GLP-1 receptor agonist to other glucose lowering medications, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects for all outcomes.

The certainty of evidence for GLP-1 receptor agonists was high for all outcomes. As a result, we are confident that the true effect reflects the data used to formulate the recommendation.

Conditional recommendation

In review

We suggest the addition of a DPP-4 inhibitor to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor or a GLP-1 receptor agonist due to either intolerance or contraindication.

This recommendation applies to individuals with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease and are unable to achieve optimal blood glucose levels on their current baseline therapy. DPP-4 inhibitors were inferior to SGLT-2 inhibitors and GLP-1 receptor agonists with regard to cardiovascular and renal benefits and all-cause mortality. However, certain people are unable to tolerate SGLT-2 inhibitors due to side effects such as genitourinary infections, or GLP-1 receptor agonists due to gastrointestinal upset. Similarly, these medications may be contraindicated in people with kidney failure. In these instances, people with type 2 diabetes would benefit from the addition of a DPP-4 inhibitor as an alternative add on therapy.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

When added to other glucose lowering medication, DPP-4 inhibitors provided clinically significant reductions in HbA1c compared to baseline medications alone. There were no differences in all-cause mortality, heart failure, 3-item MACE, severe hypoglycaemia, kidney failure or serious adverse events. There were no data comparing DPP-4 inhibitors to other glucose lowering medications with regard to 4-item MACE.

When added to other glucose lowering medications, SGLT-2 inhibitors demonstrated superior safety for all-cause mortality, heart failure, 4-item MACE, kidney failure and serious adverse events, and GLP-1 demonstrated superior safety for all-cause mortality, 3-item MACE and kidney failure, and clinically significant improvements in HbA1c compared to DPP4 inhibitors.

When added to metformin only, DPP-4 inhibitors had better safety profiles compared with sulphonylureas (clinically relevant increase in severe hypoglycaemia) and thiazolidinediones (clinically relevant increase in heart failure).

Certainty of the Evidence

High

With regard to the addition of a DPP-4 inhibitor to other glucose lowering medications, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects for all outcomes.

The certainty of evidence for DPP-4 inhibitors was high for all outcomes. As a result, we are confident that the true effect reflects the data used to formulate the recommendation.

Conditional recommendation

In review

We suggest the addition of either an SGLT-2 inhibitor, GLP-1 receptor agonist or a DPP-4 inhibitor to metformin in adults with type 2 diabetes who do not have cardiovascular disease, multiple cardiovascular risk factors or kidney disease, and are unable to achieve optimal blood glucose levels.

This recommendation applies to people without established cardiovascular disease, multiple cardiovascular risk factors or kidney disease. In these people, the addition of an SGLT-2 inhibitor, GLP-1 receptor agonist or DPP-4 inhibitor is equally efficacious in lowering blood glucose. The choice of agent should be based on personal preference, side effect tolerance and comorbidities.

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

When added to metformin, SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors all resulted in clinically relevant reductions in mean HbA1c. In people without cardiovascular disease, multiple cardiovascular risk factors or kidney disease, no clinically relevant differences were observed between SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors with regard to all-cause mortality, heart failure, severe hypoglycaemia and serious adverse events. There were no data comparing SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors with regard to 3-item MACE, 4-item MACE or kidney failure. SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors had better safety profiles compared with sulphonylureas (clinically relevant increase in severe hypoglycaemia) and thiazolidinediones (clinically relevant increase in heart failure).

When added to any other glucose lowering medications, SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors all resulted in clinically relevant reductions in mean HbA1c. In people without multiple

cardiovascular risk factors, no clinically relevant differences were observed between SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-1 inhibitors with regard to all-cause mortality, heart failure, severe hypoglycaemia, serious adverse events, 3-item MACE or kidney failure. SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors had better safety profiles compared with sulphonylureas (clinically relevant increase in severe hypoglycaemia).

Certainty of the Evidence Moderate

With regard to the addition of SGLT-2 inhibitors, GLP-1 receptor agonists or DPP-4 inhibitors to any other glucose lowering medications including metformin, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects for all outcomes.

When added to metformin, the certainty of evidence was high for SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors with regard to change in mean HbA1c and serious adverse events, and moderate for severe hypoglycaemia due to imprecision. Certainty was low for all-cause mortality, heart failure and kidney failure due to serious imprecision with the exception of GLP-1 receptor agonists and DPP-4 inhibitors, for which certainty was moderate due to imprecision.

When added to any other glucose lowering medications, the certainty of evidence was moderate for SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors for all outcomes due to indirectness. The exception was 3-item MACE in people treated with SGLT-2, in which certainty was low due to both indirectness and suspicion of selective outcome reporting.

Conditional recommendation against

We suggest that a sulphonylurea should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of severe hypoglycaemia.

Evidence to decision

Benefits and harms Important harms

When added to metformin as dual therapy, sulphonylureas resulted in a clinically relevant increase in severe hypoglycaemia and decrease in mean HbA1c compared to metformin alone. No clinically relevant differences were observed between sulphonylurea plus metformin compared with metformin alone with regard to all-cause mortality, heart failure or serious adverse events. There were no data comparing sulphonylurea plus metformin to metformin alone within the network meta-analysis for 3-item MACE, 4-item MACE or kidney failure.

Certainty of the Evidence Moderate

For all outcomes, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects.

Certainty of evidence was high for mean change in HbA1c and serious adverse events, moderate for severe hypoglycaemia and all-cause mortality due to imprecision, and low for heart failure and kidney failure due to serious imprecision.

Conditional recommendation against

We suggest that a thiazolidinedione should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of hospitalisation for heart failure.

Evidence to decision

Benefits and harms Important harms

When added to metformin as dual therapy, thiazolidinediones resulted in a clinically relevant increase in hospitalisation due to heart failure and a decrease in mean HbA1c compared to metformin alone. No clinically relevant differences were observed between thiazolidinediones plus metformin compared with metformin alone with regard to all-cause mortality, severe hypoglycaemia or serious adverse events. There were no data comparing thiazolidinediones plus metformin to metformin alone within the network meta analysis with regard to severe hypoglycaemia, 3-item MACE, 4-item MACE or kidney failure.

Certainty of the Evidence Moderate

For all outcomes, there was no evidence of serious heterogeneity or inconsistency in the network, incoherence in the direct and indirect estimates or evidence of serious small-study effects.

Certainty of evidence was high for mean change in HbA1c, and moderate for all-cause mortality, heart failure and serious adverse events due to imprecision.

Blonde L et al., 2022 [6].

American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update

Zielsetzung/Fragestellung

Developing a Comprehensive Diabetes Mellitus Care Plan includes revised and new recommendations for clinical practice based on evidence published since the previous edition of this clinical practice guideline (CPG) in 2015

Methodik

- Repräsentatives Gremium – unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz aber keine detaillierten Angaben oder Informationen zu Datenbanken oder Suchstrategien bzw. zu einer möglichen Systematik – trifft teilweise zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft teilweise zu (keine formalen Konsensusprozesse beschrieben, aber Begutachtungsverfahren durch: Task-Force Mitglieder, AACE CPG Oversight Committee, AACE Board of Directors und Peer Reviewers);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

<u>Recherche/Suchzeitraum:</u>

- literature searches for relevant scientific papers published from January 1, 2015, through May 15, 2022

LoE

Appendix Table A. Table 5 from AACE Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists – 2017 Update

Table 5 Revised Logical Ranking of Scientific Methodologies (Step I: Evidence Rating)[a]		
Numerical Descriptor[b]	**Semantic Descriptor**	**Methodology Descriptor**
STRONG EVIDENCE		
1 (1)	RCT	Randomized controlled trial[c]
1 (1)	MRCT	Meta-analysis of only randomized controlled trials
INTERMEDIATE EVIDENCE		
2 (2)	MNRCT	Meta-analysis including nonrandomized prospective or case-controlled trials
2 (new)	NMA	Network meta-analysis (44, 45)
2 (2)	NRCT	Nonrandomized controlled trial (or unconfirmed randomization)
2 (2)	PCS	Prospective cohort study (does not include open-label extension study)
2 (2)	RCCS	Retrospective case-control study
2 (new)	NCCS	Nested case-control study
2 (3; reassigned)	CSS	Cross-sectional study
2 (3; reassigned)	ES	Epidemiological study (hypothesis driven; includes survey, registry, data mining, with or without retrospective uni-multivariate analyses or propensity matching)
2 (new)	OLES	Open-label extension study (46)
2 (new)	PHAS	Post hoc analysis study (47)
WEAK EVIDENCE		
3 (new)	DS	Discovery science (explorative/inductive; includes -omics, "big data," network analysis, systems biology, Bayesian inference, modeling) (48)
3 (new)	ECON	Economic study (includes Markov models, pharmaco-economics) (49-53)
3 (3)	CCS	Consecutive case series (N > 1)
3 (3)	SCR	Single case report (N = 1)
3 (new)	PRECLIN	Preclinical study (e.g., feasibility, safety)
3 (new)	BR	Basic research (must be high impact and relevant)
NO EVIDENCE		
4 (4)	NE	No evidence (theory, opinion, consensus, review, position, policy, guideline)
4 (new)	O	Other (e.g., lower impact/relevant basic research; any highly flawed study)

Abbreviations: **EBM** = evidence-based methodology; **EL** = evidence level.

[a] Based on principle that interventions, scientific control, generalizability, methodological flaws, and evidentiary details determine strength (54), consistent with other EBM systems (reviewed in Table 2 in reference (2)). Numerical and semantic descriptors of ELs provided in on-line supplementary material.

[b] The original numerical description from G4GAC 2004, 2010, and 2014 are provided in parentheses.

[c] The superiority of RCT over all other studies, and in particular MRCT, is discussed in reference (55). MRCTs are inferior to RCTs due to the bias introduced by being a retrospective analysis (56).

GoR

Appendix Table D. Table 8 from AACE Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists – 2017 Update

Table 8
Revised and Detailed Mapping Protocol (Step IV: Creating Initial Recommendation Grades)[a]

Best Evidence Level	Predominantly Negative SF and/or RQ	Predominantly Positive SF and/or RQ	Consensus for Recommendation and for Grade	EL to Grade Mapping	Map to Final Recommendation Grade
1	No	No	>66%	Direct	1 → A
Any[b]	No	No	100%	Rule	Any → A (new)
2	No	Yes	>66%	Adjust up	2 → A
2	No	No	>66%	Direct	2 → B
1	Yes	No	>66%	Adjust down	1 → B
3	No	Yes	>66%	Adjust up	3 → B
3	No	No	>66%	Direct	3 → C
2	Yes	No	>66%	Adjust down	2 → C
4	No	Yes	>66%	Adjust up	4 → C
4	No	No	>66%	Direct	4 → D
3	Yes	No	>66%	Adjust down	3 → D
Any[b]	Yes/no	Yes/no	≤66%	Rule	Any → D (new)

Abbreviations: **BEL** = best evidence level; **EL** = evidence level; **RQ** = recommendation qualifiers; **SF** = subjective factors.
[a]See Table 6 for SF and Table 7 for RQ. Recommendation Grade A = "Very Strong"; B = "Strong"; C = "Not Strong"; D = "Primarily Based on Expert Opinion." Mappings are provided in on-line supplementary material.
[b]Rule-based adjustment wherein any recommendation can be a "Very Strong" Grade A if there is 100% consensus to use this designation. Similarly, if >66% consensus is not reached, even with some degree of scientific substantiation, a "Primarily Based on Expert Opinion" Grade D designation is assigned. The reasons for downgrading to D may be an inconclusive or inconsistent evidence base or simply failure of the expert writing committee to sufficiently agree. Note that any formulated recommendation is omitted from the document if sufficiently flawed, so any Grade D recommendation in the final document must be deemed sufficiently important. Rule-based adjustments are provided in online supplementary material.

Summary of Recommendations

Q 9: How should antihyperglycemic agents be prioritized in persons with type 2 diabetes at high risk for or with established cardiovascular disease?	
R 9.1	In persons with T2D and established ASCVD or at high risk for ASCVD, use GLP-1 RAs with proven CV benefits to reduce the risk of myocardial infarction, stroke, or CV death regardless of other glucose-lowering or CV therapies and independent of A1C. Grade A; BEL 1
R 9.2	In persons with T2D and established ASCVD or very high ASCVD risk, use SGLT2is with proven CV benefits to reduce the risk of hospitalization for HF, major adverse CV events, or CV death regardless of background glucose-lowering therapy, cardiovascular therapy, or A1C. Grade A; BEL 1
R 9.3	In persons with T2D and established HF (regardless of ejection fraction, background glucose-lowering or HF therapies, or A1C), use SGLT2is with proven HF benefits to reduce the risk of hospitalization for HF or CV death, and to improve HF–related symptoms. Grade A; BEL 1
R 9.4	In persons with T2D and ASCVD or at high risk for ASCVD, use GLP-1 RAs with proven benefit for reduction in the risk of stroke. In persons with insulin resistance, prediabetes, or T2D and a prior transient ischemic attack or stroke, pioglitazone should be considered to reduce the risk of recurrent stroke. Grade A; BEL 1
12.2 Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes	
R 12.2.1	Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. Grade A; BEL 1
R 12.2.2	Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). Grade B; BEL 2
R 12.2.3	Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability (Table 6). Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. Grade B; BEL 4
R 12.2.4	Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated (see also **R 6.1** to **R 6.6** on DKD or CKD in DM and **R 9.1** to **R 9.4** on ASCVD and HF). Grade A; BEL 1
R 12.2.5	DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. Grade A; BEL 1
R 12.2.6	For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. Grade A; BEL 1
R 12.2.7	For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (eg, weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). Grade A; BEL 1
R 12.2.8	Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. Grade B; BEL 2
R 12.2.9	The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. Grade D; BEL 4
R 12.2.10	Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. Grade B; BEL 2
R 12.2.11	Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). Grade A BEL 1
R 12.2.12	Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. Grade A; BEL 1
R 12.2.13	Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. Grade A; BEL 1
R 12.2.14	Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. Grade A; BEL 1
R 12.2.15	When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin (see Table 18). The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. Grade A; BEL 1
R 12.2.16	Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. Grade A; BEL 1
R 12.2.17	Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (ie, insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. Grade C; BEL 1
R 12.2.18	Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. Grade A; BEL 1
R 12.2.19	In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. Grade A; BEL 1

Li S et al., 2021 [31].

SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline

Zielsetzung/Fragestellung

To evaluate sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes at varying cardiovascular and renal risk.

This review is conducted as part of the BMJ Rapid Recommendations project, a collaborative initiative from the MAGIC (Making GRADE the Irresistible Choice) Evidence Ecosystem Foundation (https://magicevidence.org/) and The BMJ. The aim of the initiative is to provide trustworthy practice guidelines within months of newly released evidence, underpinned by rigorous evidence summaries. This systematic review is part of a forthcoming BMJ Rapid Recommendations cluster and a fuller version on MAGICapp (www.magicapp.org).

Methodik

Grundlage der Leitlinie:

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: – trifft zu.

Recherche/Suchzeitraum:

- A linked systematic review and network meta-analysis (764 randomised trials included 421 346 participants)
- Medline, Embase, and Cochrane CENTRAL up to 11 August 2020

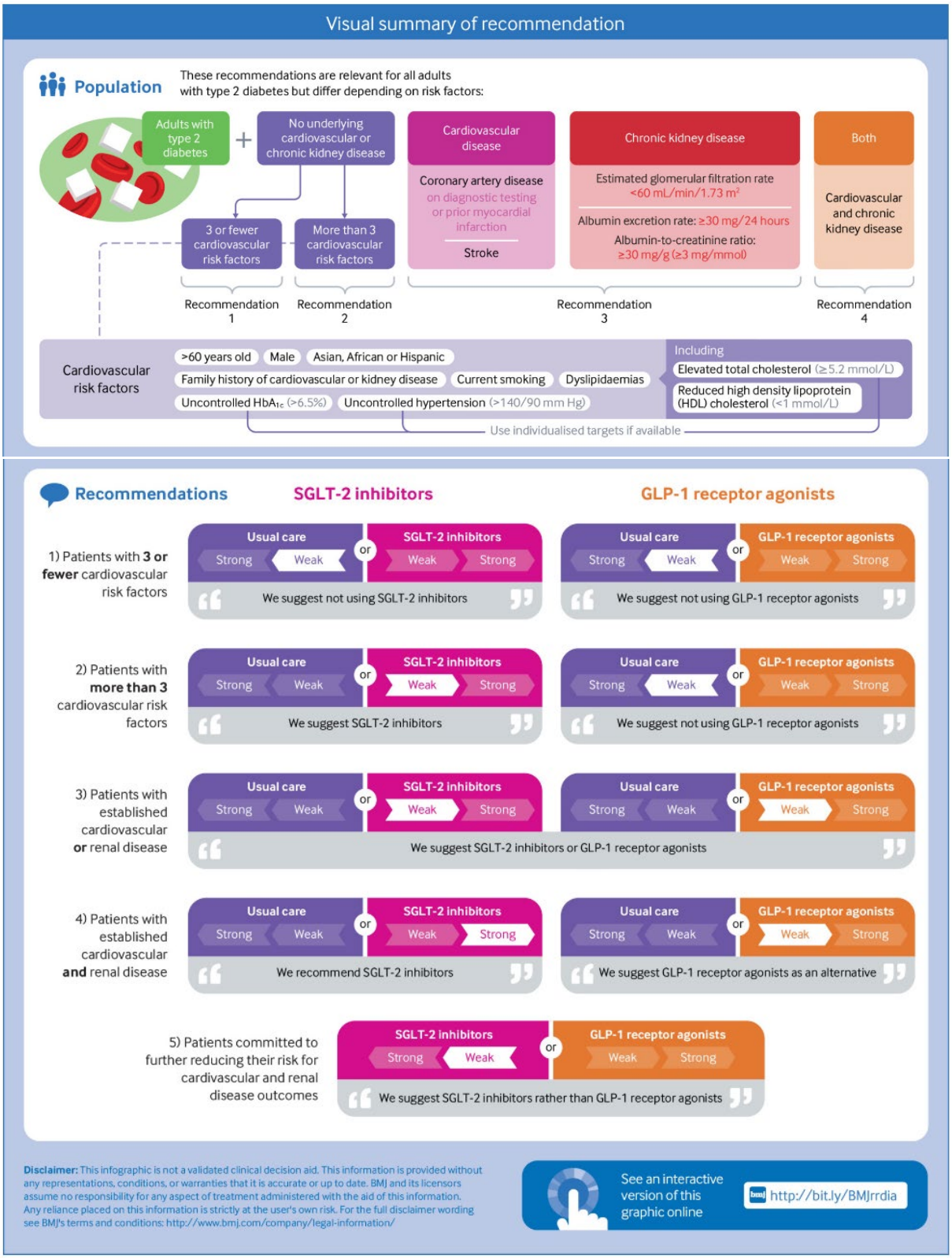
LoE/GoR

- GRADE

Sonstige methodische Hinweise

- Für die spezifische Fragestellung dieser LL wurde eine NMA mit insgesamt 764 RCTs und 421 346 Personen durchgeführt, die den Empfehlungen zugrunde liegt.

Empfehlungen



Diabetes Canada, 2020 [12].

Pharmacologic glycemic management of type 2 diabetes in adults: 2020 update

Zielsetzung/Fragestellung

Based on a careful review of this evidence, the updated recommendations provide more specific treatment guidance for clinicians and people living with type 2 diabetes. We now have more evidence to recommend certain agents over others for patients with CVD, a history of HF, CKD and in those 60 years or older with multiple CV risk factors.

Methodik

Grundlage der Leitlinie

Update der Leitlinie von 2018

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – unklar (wird nicht explizit aufgeführt, dies ist allerding ein update der 2018 Leitlinie, was darauf schließen lässt, dass Empfehlungen aktuell gehalten werden).

Recherche/Suchzeitraum:

- Leveraging the search methods and PICO questions used for the 2018 Canada Clinical Practice Guidelines, a systematic search of the literature for relevant articles published from October 2017 to October 2019 was performed
- MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Trials, and PsycINFO

LoE

Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Non-randomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
Level 4	Other

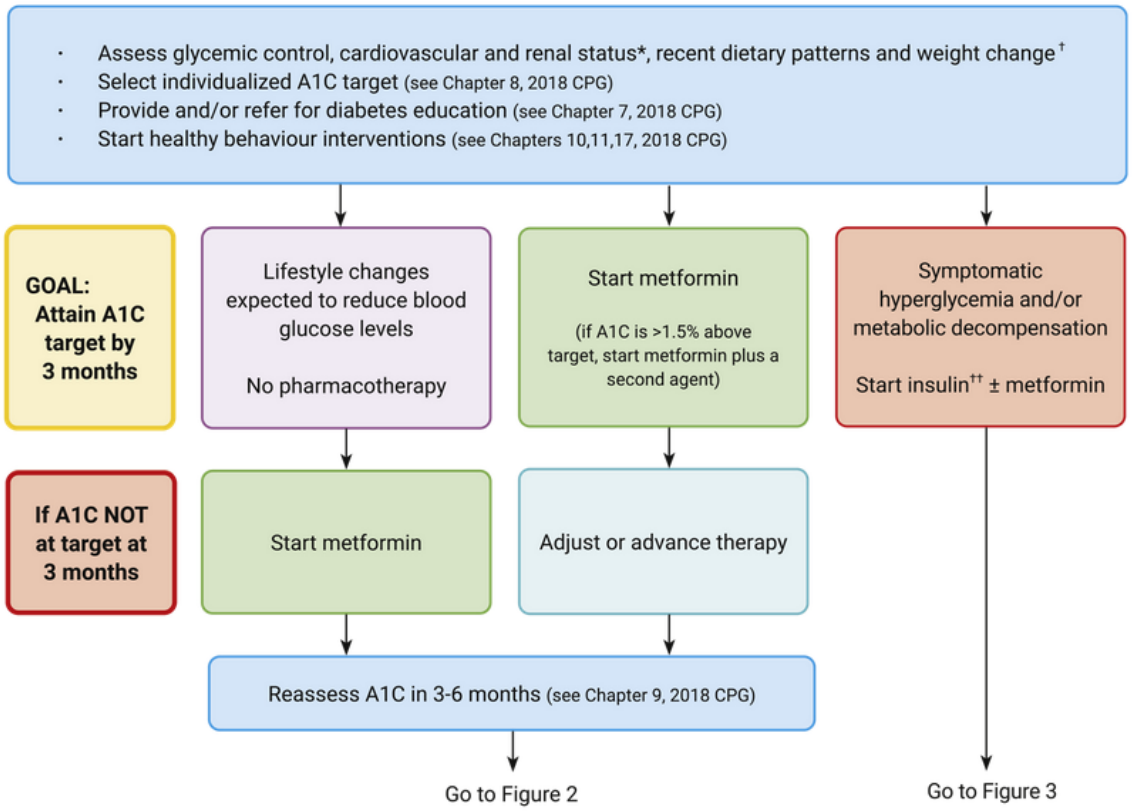
GoR

Table 2
Criteria for assigning grades of recommendations for clinical practice

Grade	Criteria
Grade A	The best evidence was at Level 1
Grade B	The best evidence was at Level 2
Grade C	The best evidence was at Level 3
Grade D	The best evidence was at Level 4 or consensus

Recommendations

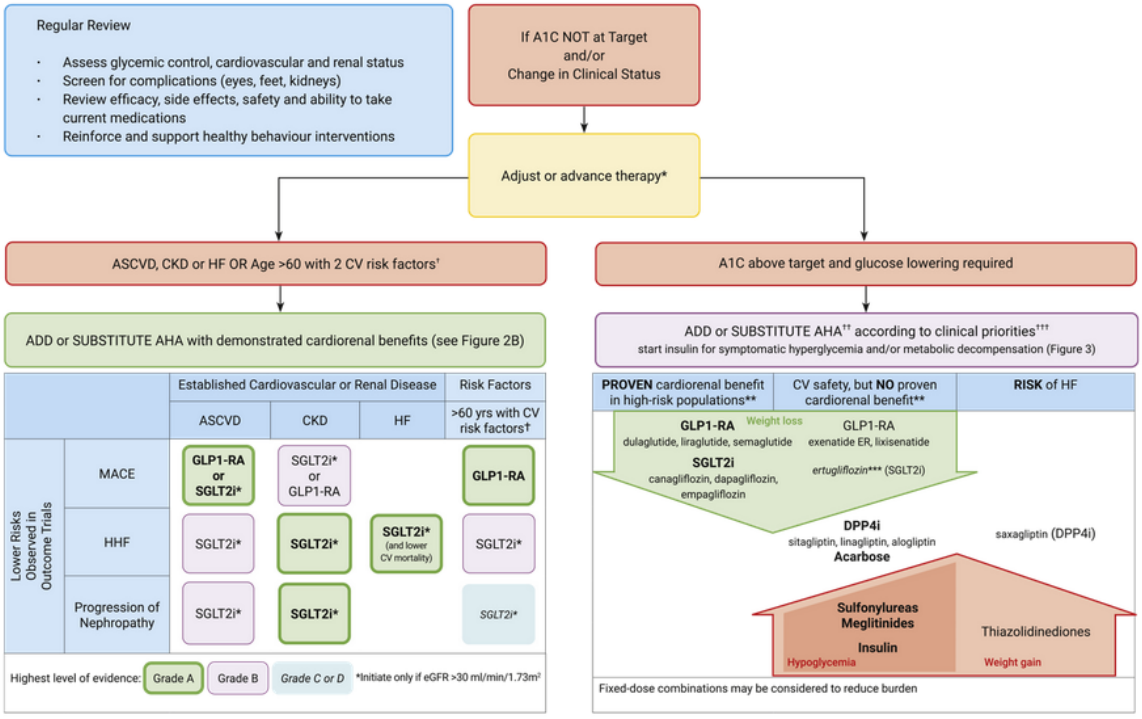
Figure 1
At diagnosis of type 2 diabetes.



* In individuals **with** atherosclerotic cardiovascular disease, history of heart failure (with reduced ejection fraction) or chronic kidney disease, agents with cardiorenal benefits (Figures 2A and 2B) may be considered (see Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update – The User's Guide).
† Unintentional weight loss should prompt consideration of other diagnoses (e.g. type 1 diabetes or pancreatic disease).
†† Reassess need for ongoing insulin therapy once type of diabetes is established and response to health behaviour interventions is assessed.
A1C, glycated hemoglobin; *CPG*, clinical practice guidelines.

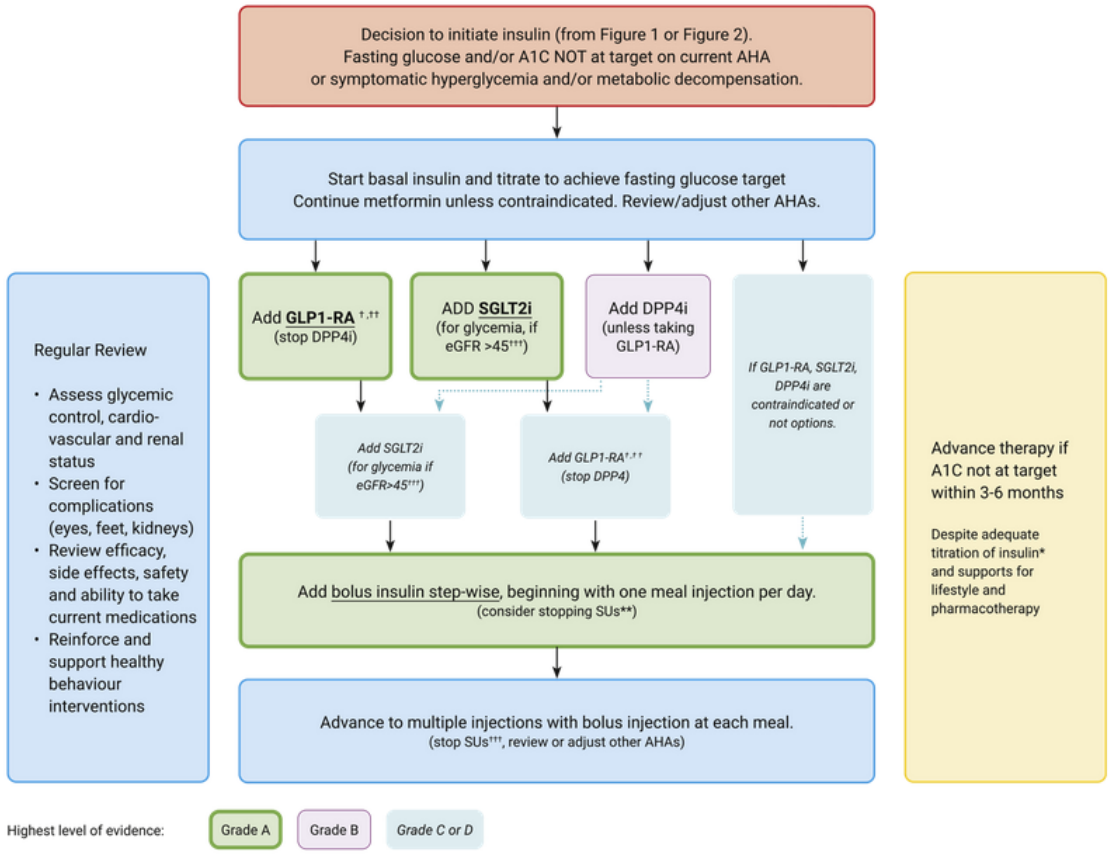
Figure 2A

Reviewing, adjusting or advancing therapy in type 2 diabetes.



* Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing.
† Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) ≥3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women, or triglycerides ≥2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥95 mmHg).
†† All antihyperglycemic agents (AHAs) have Grade A evidence for effectiveness to reduce blood glucose levels.
††† Consider degree of hyperglycemia, costs and coverage, renal function, comorbidity, side effect profile and potential for pregnancy.
** In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk.
*** VERTIS (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing.
A1C, glycated hemoglobin; *DPP4i*, dipeptidyl peptidase-4 inhibitors; *eGFR*, estimated glomerular filtration rate; *GLP1-RA*, glucagon-like peptide-1 receptor agonists; *exenatide ER*, exenatide extended-release; *HHF*, hospitalization for heart failure; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *yrs*, years.

Figure 3
Starting or advancing insulin in type 2 diabetes.



* Titration of basal insulin to achieve FPG target without hypoglycemia.
† And titrate dose of GLP1-RA, as tolerated.
†† Or fixed-ratio combination.
††† If eGFR >30 ml/min/1.73m², may be used for cardiorenal benefit.
** Sulfonylureas or meglitinides.
AHAs, antihyperglycemic agents; *A1C*, glycated hemoglobin; *DPP4i*, dipeptidyl peptidase-4 inhibitors; *eGFR*, estimated glomerular filtration rate; *GLP1-RA*, glucagon-like peptide-1 receptor agonists; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *SU*, sulfonylureas.

Treatment of People With Newly Diagnosed Type 2 Diabetes

- 1) Healthy behaviour interventions should be initiated at type 2 diabetes diagnosis [Grade B, Level 2 (36)] and reinforced and maintained throughout. Metformin may be introduced at the time of diagnosis, in conjunction with healthy behaviour interventions [Grade D, Consensus].
- 2) If glycemic targets are not achieved within 3 months using healthy behaviour interventions alone, antihyperglycemic therapy should be added to reduce the risk of microvascular complications [Grade A, Level 1A (37)]. Metformin should usually be selected before other agents due to its low risk of hypoglycemia and weight gain [Grade A, Level 1A (26)], and long-term experience with this agent [Grade D, Consensus].
- 3) If A1C values are ≥1.5% above target, initiating metformin in combination with a second antihyperglycemic agent should be considered to increase the likelihood of reaching target [Grade B, Level 2 (38-40) for SGLT2i (41); for DPP4i (42,43)].
- 4) Individuals with metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss) should receive insulin with or without metformin, until glycemic control is achieved OR type of diabetes is established [Grade D, Consensus].

Reassessment and Monitoring

- 5) Glycemic control, cardiovascular and renal status should be reviewed regularly (at least annually). Healthy behaviour interventions should be reinforced and supported. Efficacy, side effects and adherence to existing antihyperglycemic therapy should be assessed [Grade D, Consensus].
- 6) Dose adjustments, substitutions and/or addition of antihyperglycemic medications should be made in order to maintain A1C or attain target A1C within 3 to 6 months [Grade D, Consensus].
- 7) If glycemic targets are not achieved with existing antihyperglycemic medication(s), or the individual's clinical status changes, other classes of agents should be used (either by addition or replacement) to reduce cardiorenal outcomes and/or improve glycemic control; or glycemic targets should be reassessed [Grade D, Consensus].
- 8) For adults with type 2 diabetes with metabolic decompensation (e.g. marked or symptomatic hyperglycemia, ketosis or unintentional weight loss), insulin should be used (see #12-16, below) [Grade D, Consensus].

Advancement or Adjustment of Treatment in People With Type 2 Diabetes

- 9) In adults with type 2 diabetes WITH atherosclerotic cardiovascular disease (ASCVD), HF and/or CKD, treatment should include agents from the following classes with demonstrated CV or renal benefits (see Figures 2A).
  - a) In adults with type 2 diabetes and ASCVD, a GLP1-RA or SGLT2i with CV or renal benefit should be used to reduce the risk of:
    - i) MACE [Grade A, Level 1A (6,10) for liraglutide and dulaglutide; Grade B, Level 2 for subcutaneous semaglutide (7); Grade A, Level 1A (12) for empagliflozin; Grade B, Level 2 (15) for canagliflozin].
    - ii) HHF [Grade B, Level 2 (12,15,17) for empagliflozin, canagliflozin and dapagliflozin].
    - iii) Progression of nephropathy [Grade B, Level 2 (44,15,17) for empagliflozin, canagliflozin and dapagliflozin].
  - b) In adults with type 2 diabetes and a history of HF (reduced ejection fraction <40%):
    - i) An SGLT2i should be used to reduce the risk of HHF or CV death, if the eGFR is >30 mL/min/ 1.73m2 [Grade A, Level 1A (19) for dapagliflozin; Grade A, Level 1 (18) for empagliflozin and canagliflozin].
    - ii) TZD and saxagliptin should be avoided due to their higher risk of HF [Grade A, Level 1A (21,45,46)].
  - c) In adults with type 2 diabetes and CKD and an estimated eGFR >30 mL/min/1.73m2:
    - i) An SGLT2i should be used to reduce the risk of: (1) Progression of nephropathy [Grade A, Level 1A (16) for canagliflozin; Grade A, Level 1 (18) for empagliflozin and dapagliflozin]. (2) HHF [Grade A, Level 1 (18) for canagliflozin, dapagliflozin and empagliflozin]. (3) MACE [Grade B, Level 2 for canagliflozin (16), Grade C, Level 3 (12) for empagliflozin].
    - ii) A GLP1-RA may be considered to reduce the risk of MACE (Grade B, Level 2 (6,7) for liraglutide and semaglutide).
- 10) In adults with type 2 diabetes requiring treatment advancement or adjustment to improve glycemic control, the choice of antihyperglycemic medication should be individualized according to clinical priorities (see Figure 2A) [Grade B, Level 2 (26)].

- a) In adults with type 2 diabetes aged 60 years or older with at least 2 CV risk factors, inclusion of the following classes in glycemic management should be considered:
  - i) A GLP1-RA with proven CV outcome benefit to reduce the risk of MACE [Grade A, Level 1A (10) for dulaglutide; Grade B, Level 2 (6) for liraglutide and Grade C, Level 2 (7) subcutaneous semaglutide]; OR
  - ii) An SGLT2i with proven cardiorenal outcome benefit if estimated GFR is >30 mL/min/1.73m2 to reduce the risk of (1) HHF [Grade B Level 2 (15,17) for dapagliflozin and canagliflozin]. (2) Progression of nephropathy [Grade C, Level 3 (15,17) for canagliflozin and dapagliflozin].
- b) If reducing risk of hypoglycemia is a priority: Incretin agents (DPP4i or GLP1-RA), SGLT2i, acarbose and/or pioglitazone should be considered as add-on medication to improve glycemic control with a lower risk of hypoglycemia than other agents [Grade A, Level 1A (26,28,29,47,48,49,74)].
- c) If weight loss is a priority: A GLP1-RA and/or SGLT2i should be considered as add-on medication to improve glycemic control with more weight loss than other agents [Grade A, Level 1A (26,28,29,30,47,48,49].

<u>Initiating Insulin Treatment in Patients With Type 2 Diabetes</u>

- 11) In people not achieving glycemic targets on existing noninsulin antihyperglycemic medication(s), the addition of a basal insulin regimen should be considered over premixed insulin or bolus-only regimens, if lower risk of hypoglycemia and/or preventing weight gain are priorities [Grade B, Level 2 (50)].
- 12) In adults with type 2 diabetes treated with basal insulin therapy, if minimizing risk of hypoglycemia is a priority:
  - a) Long-acting insulin analogues (insulin glargine U-100, glargine U-300, detemir, degludec) should be considered over NPH insulin to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (51-56)].
  - b) Insulin degludec or insulin glargine U-300 (57) may be considered over insulin glargine U-100 to reduce overall and nocturnal hypoglycemia [Grade B, Level 2 for individuals with >1 risk factor for hypoglycemia (58,59)]; [Grade C, Level 3 for other individuals without risk factors for hypoglycemia (56)]; and severe hypoglycemia in patients at high CV risk [Grade C, Level 3 (60)]

<u>Treatment Advancement or Adjustment for People With Type 2 Diabetes Treated With Insulin</u>

- 13) In adults with type 2 diabetes receiving insulin, doses should be adjusted and/or additional antihyperglycemic medication(s) should be added if glycemic targets are not achieved [Grade D, Consensus].
  - a) A GLP1-RA should be considered as add-on therapy [Grade A, Level 1A (61,62)], before initiating bolus insulin or intensifying insulin to improve glycemic controlwith potential benefits ofweight loss and lower hypoglycemia risk compared to single or multiple bolus insulin injections [Grade A, Level 1A (63-71)].
  - b) An SGLT2i should be considered as add-on therapy to improve glycemic control with potential benefits of weight loss and lower hypoglycemia risk compared to additional insulin [Grade A, Level 1A (72-74)].
  - c) A DPP4i may be considered as add-on therapy to improve glycemic control with potential benefits of less weight gain and lower hypoglycemia risk compared to additional insulin [Grade B, Level 2 (72,75-77)].

- 14) When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be considered over shortacting (regular) insulin for greater improvement in glycemic control [Grade B, Level 2 (78,79) for aspart].
- 15) Bolus insulin may be initiated using a stepwise approach (starting with 1 injection at 1 meal and additional mealtime injections as needed) to achieve similar A1C reduction with lower hypoglycemia risk compared to initiating bolus injections at every meal [Grade B, Level 2 (80)].

Safety Considerations for Pharmacotherapy of Type 2 Diabetes

- 16) All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the prevention, recognition and treatment of hypoglycemia [Grade D, Consensus].
- 17) Pharmacotherapy may need to be temporarily adjusted during acute illness or around the time of some investigations:
  - a) Metformin and SGLT2i should be temporarily withheld during acute illnesses associated with risk for dehydration or procedures associated with high risk of acute kidney injury [Grade D, Consensus]
  - b) Insulin and insulin secretagogue doses should be decreased or held to reduce risk for hypoglycemia if oral intake is reduced [Grade D, Consensus].
- 18) SGLT2i should be temporarily withheld prior to major surgical procedures and during acute infections and serious illness to reduce the risk of ketoacidosis [Grade D, Consensus]. Particular caution should be paid to this risk in people following low-carbohydrate eating patterns (81) or with suspected insulin deficiency [Grade D, Consensus].

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McCall AL et al., 2023 [46].

Management of Individuals with Diabetes at High Risk for Hypoglycemia: An Endocrine Society Clinical Practice Guideline

Zielsetzung/Fragestellung

To review and update the diabetes-specific parts of the 2009 Evaluation and Management of Adult Hypoglycemic Disorders: Endocrine Society Clinical Practice Guideline and to address developing issues surrounding hypoglycemia in both adults and children living with diabetes. The overriding objectives are to reduce and prevent hypoglycemia.

Methodik

Grundlage der Leitlinie

Update spezifischer Teile der 2009 Leitlinie "Evaluation and Management of Adult Hypoglycemic Disorders: Endocrine Society Clinical Practice Guideline"

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- Systematic Review to support development of the Endocrine Society Clinical Practice Guideline for management of individuals with diabetes at high risk for hypoglycaemia
- We conducted a comprehensive search of several databases from each database's inception to April 8, 2022. The databases included Ovid MEDLINE; Epub Ahead of Print; In-Process, In-Data-Review & Other Non-Indexed Citations; Daily; Ovid EMBASE; Ovid Cochrane Central Register of Controlled Trials; Ovid Cochrane Database of Systematic Reviews; and Scopus

LoE/GoR

- GRADE

Table 8. Grading of Recommendations Assessment, Development and Evaluation classification of guideline recommendations

Certainty of evidence	Interpretation
High⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate⊕⊕⊕O	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low⊕⊕OO	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low⊕OOO	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Recommendations

Question 7. Should long-acting insulin analogs vs human insulin be used for people on basal insulin therapy who are at high risk for hypoglycemia?

We suggest long-acting insulin analogs be used rather than human neutral protamine Hagedorn (NPH) insulin for adult and pediatric outpatients on basal insulin therapy who are at high risk for hypoglycemia. (2⨁OOO)

Remarks

- Patients who are at high risk for hypoglycemia are defined as those with a history of severe hypoglycemia (requiring assistance to manage), impaired awareness of hypoglycemia (IAH), and/or medical conditions that predispose them to severe hypoglycemia including renal and hepatic dysfunction.
- The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for severe hypoglycemia reduction as an outcome in those using long-acting analog insulins vs NPH insulin. However, the panel acknowledges that most studies of long-acting analog insulins do not assess for significant adverse effects (including cardiovascular outcomes) and that many studies were designed to demonstrate noninferiority of analog insulin compared with human NPH insulin.

Question 8. Should rapid-acting analogs vs regular (short- acting) human insulin be used for people on basal-bolus therapy who are at high risk for hypoglycemia?

We suggest that rapid-acting insulin analogs be used rather than regular (short-acting) human insulins for adult and pediatric patients on basal-bolus insulin therapy who are at high risk for hypoglycemia. (2⨁OOO)

Remarks

- Patients who are at high risk for hypoglycemia are defined as those with a history of severe hypoglycemia (requiring assistance to manage), impaired awareness of hypoglycemia (IAH), and/or medical conditions that predispose them to severe hypoglycemia including renal and hepatic dysfunction.
- The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for reduction of mild-to-moderate and severe hypoglycemia as an outcome in those using rapid-acting analog insulins vs regular (short-acting) insulin. However, the panel acknowledges that many studies were designed to demonstrate noninferiority of analog insulin compared with human regular (short-acting) insulin. Also, many of the data available for review demonstrating reductions in hypoglycemia were in adults with T1D; very few data were available regarding the pediatric population.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2024) am 12.04.2024

#	Suchfrage
1	[mh "diabetes mellitus, type 2"]
2	(t2dm OR dmt2 OR niddm OR mody):ti
3	(diabetes OR dm):ti
4	("adult onset" OR "maturity onset" OR (non NEXT insulin NEXT dependan*) OR (noninsulin NEXT dependan*) OR "slow onset" OR (ketosis NEXT resistan*) OR "type 2" OR "type II" OR t2 OR tII OR (t NEXT 2) OR (t NEXT II)):ti
5	#3 AND #4
6	#1 OR #2 OR #5
7	#6 with Cochrane Library publication date from Apr 2019 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 12.04.2024[1]

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"Diabetes Mellitus, Type 2/drug therapy"[majr]
2	Diabetes Mellitus, Type 2[majr] AND Hypoglycemic Agents[mh]
3	(Diabetes[tiab] OR dm[tiab])
4	"adult onset"[tiab] OR "maturity onset"[tiab] OR (non insulin dependan*[tiab]) OR noninsulin dependan*[tiab] OR "slow onset"[tiab] OR ketosis resistan*[tiab] OR "type 2"[tiab] OR "type II"[tiab] OR "T 2"[tiab] OR T2[tiab] OR TII[tiab] OR "T II"[tiab]
5	#3 AND #4
6	(T2DM[tiab] OR DMT2[tiab] OR NIDDM[tiab] OR MODY[tiab])
7	#5 OR #6
8	(#7) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab] OR therapy[sh]))
9	#8 NOT medline[sb]

[1] Ab 01.2023 preprint [pt] in PubMed eingefügt, durch NOT ausgeschlossen

#	Suchfrage
10	#1 OR #2 OR #9
11	(#10) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
12	(#11) AND ("2019/04/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 12.04.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"Diabetes Mellitus, Type 2/drug therapy"[majr]
2	Diabetes Mellitus, Type 2[majr] AND Hypoglycemic Agents[mh]
3	(Diabetes[tiab] OR dm[tiab])
4	"adult onset"[tiab] OR "maturity onset"[tiab] OR (non insulin dependan*[tiab]) OR noninsulin dependan*[tiab] OR "slow onset"[tiab] OR ketosis resistan*[tiab] OR "type 2"[tiab] OR "type II"[tiab] OR "T 2"[tiab] OR T2[tiab] OR TII[tiab] OR "T II"[tiab]

#	Suchfrage
5	#3 AND #4
6	(T2DM[tiab] OR DMT2[tiab] OR NIDDM[tiab] OR MODY[tiab])
7	#5 OR #6
8	(#7) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab] OR therapy[sh]))
9	#8 NOT medline[sb]
10	#1 OR #2 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
12	(#11) AND ("2019/04/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
14	(#13) NOT ("The Cochrane database of systematic reviews"[Journal])
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 15.04.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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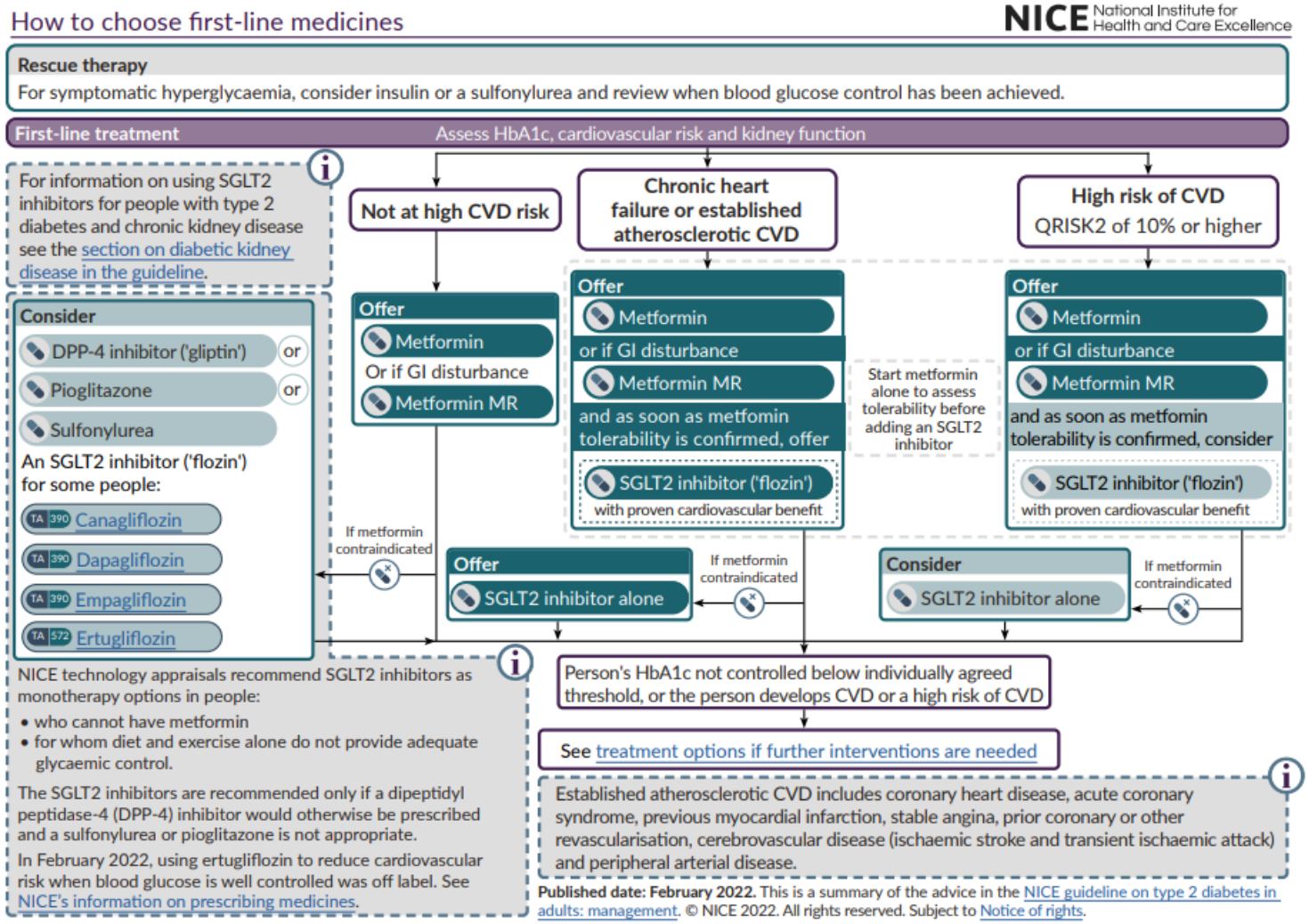
Anhang

Abbildung 3: Algorithm for blood glucose lowering therapy in adults with type 2 diabetes



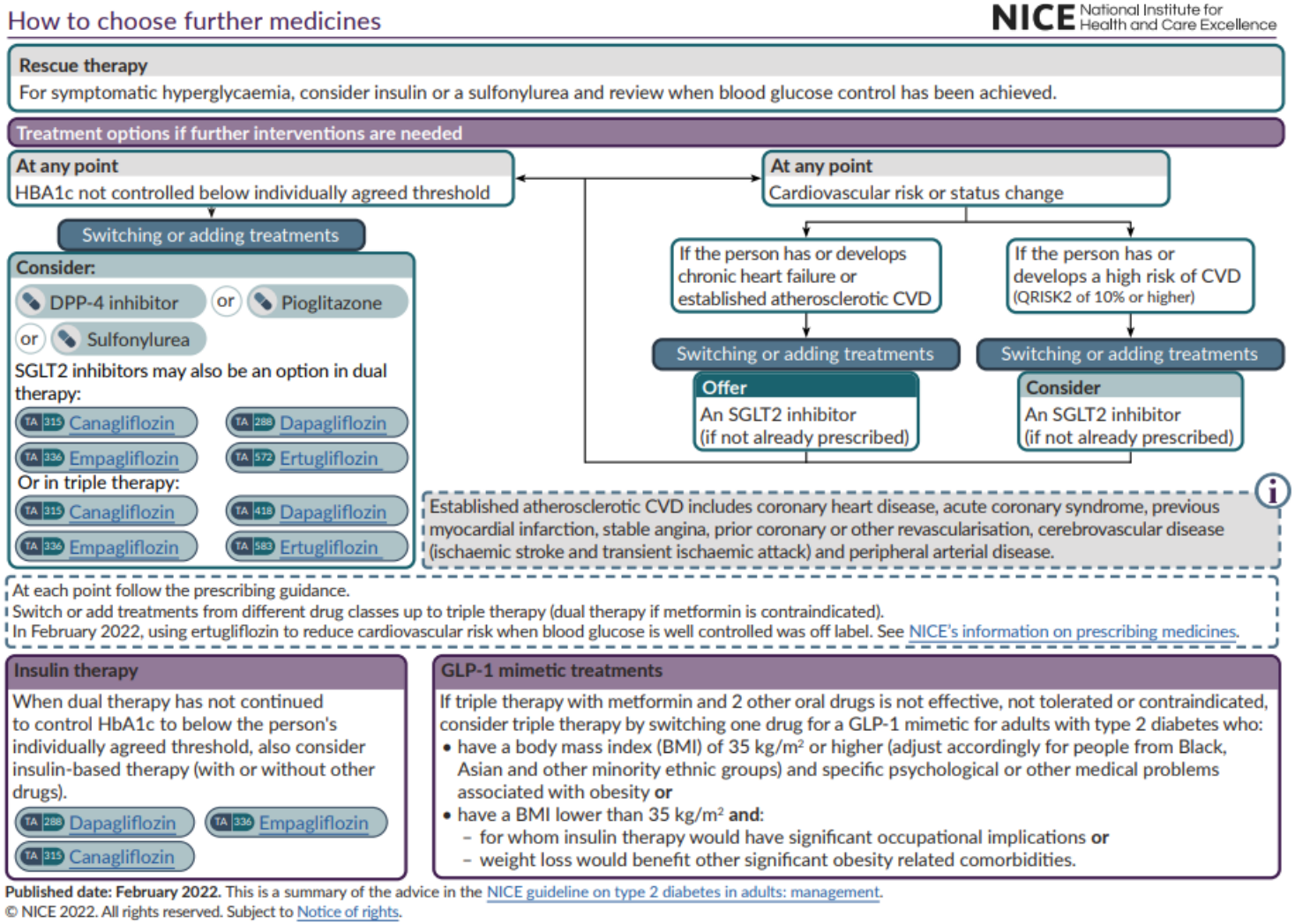

How to choose further medicines
NICE National Institute for Health and Care Excellence
Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.
Treatment options if further interventions are needed
At any point
HBA1c not controlled below individually agreed threshold
Switching or adding treatments
Consider:
DPP-4 inhibitor
or
Pioglitazone
or
Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
TA 315 Canagliflozin
TA 288 Dapagliflozin
TA 336 Empagliflozin
TA 572 Ertugliflozin
Or in triple therapy:
TA 315 Canagliflozin
TA 418 Dapagliflozin
TA 336 Empagliflozin
TA 583 Ertugliflozin
At any point
Cardiovascular risk or status change
If the person has or develops chronic heart failure or established atherosclerotic CVD
If the person has or develops a high risk of CVD (QRISK2 of 10% or higher)
Switching or adding treatments
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)
Consider
An SGLT2 inhibitor (if not already prescribed)
Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.
At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.
Insulin therapy
When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
TA 288 Dapagliflozin
TA 336 Empagliflozin
TA 315 Canagliflozin
GLP-1 mimetic treatments
If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:
• have a body mass index (BMI) of 35 kg/m² or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
• have a BMI lower than 35 kg/m² and:
– for whom insulin therapy would have significant occupational implications or
– weight loss would benefit other significant obesity related comorbidities.
Published date: February 2022. This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.
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Abbildung 4: Tsapas 2020. Pairwise meta-analysis results

Pairwise meta-analysis results for glucose-lowering drugs given as monotherapy in drug naïve patients.

Outcome/Comparison		Number of trials	Effect estimate MD/OR (95% CI)	Heterogeneity I^2 (%)
Change from baseline in HbA_{1c} (all patients)				
aGIs vs	Placebo	12	-0.80 (-0.98, -0.63)	63.7
	SU	4	0.30 (-0.17, 0.77)	82.5
Dapagliflozin vs	Placebo	3	-0.65 (-0.98, -0.32)	87.8
DPP-4i vs	Pioglitazone	4	0.34 (0.22, 0.45)	8.8
	Placebo	14	-0.54 (-0.62, -0.45)	42.4
	SU	2	0.08 (-0.08, 0.24)	0.0
Empagliflozin vs	DPP-4i	2	-0.20 (-0.31, -0.09)	0.0
Meglitinide vs	Placebo	2	-0.40 (-0.62, -0.19)	82.4
	SU	4	-0.19 (-0.41, 0.02)	65.0
Metformin vs	AGIs	4	-0.02 (-0.13, 0.09)	0.0
	Dapagliflozin	3	0.08 (-0.23, 0.38)	74.4
	DPP-4i	12	-0.28 (-0.40, -0.15)	79.9
	Liraglutide	2	0.37 (-0.79, 1.54)	68.0
	Pioglitazone	8	-0.04 (-0.13, 0.06)	26.2
	Placebo	7	-1.22 (-1.98, -0.45)	98.0
	SU	10	0.04 (-0.06, 0.15)	0.0
Pioglitazone vs	SU	7	0.04 (-0.17, 0.25)	35.7
SU vs	Placebo	2	-0.81 (-1.01, -0.60)	55.2
All-cause mortality (patients at low cardiovascular risk)				
aGIs vs.	Placebo	13	1.08 (0.36, 3.25)	0.0
	SU	6	1.00 (0.20, 5.01)	0.0
Dapagliflozin vs	Placebo	3	1.00 (0.09, 10.55)	0.0
DPP-4i vs	Pioglitazone	4	0.79 (0.11, 5.47)	0.0
	Placebo	13	1.00 (0.36, 2.75)	0.0
Empagliflozin vs	DPP-4i	2	1.30 (0.22, 7.78)	46.1
Meglitinide vs	Placebo	2	1.00 (0.06, 17.77)	0.0
	SU	4	1.00 (0.14, 7.20)	0.0
Metformin vs	AGIs	4	1.00 (0.14, 7.18)	0.0
	Dapagliflozin	3	0.77 (0.14, 4.39)	0.0
	DPP-4i	13	1.36 (0.62, 2.98)	0.0
	Liraglutide	2	1.00 (0.06, 16.36)	0.0
	Pioglitazone	8	0.97 (0.32, 2.91)	0.0
	Placebo	6	1.00 (0.20, 5.10)	0.0
	SU	9	0.99 (0.62, 1.59)	0.0
Pioglitazone vs	SU	8	0.66 (0.18, 2.37)	0.0
SU vs	Placebo	3	1.00 (0.10, 10.13)	0.0

Cardiovascular mortality (patients at low cardiovascular risk)				
aGIs vs.	Placebo	13	1.08 (0.36, 3.25)	0.0
	SU	6	1.00 (0.20, 5.01)	0.0
Dapagliflozin vs	Placebo	3	1.00 (0.09 , 10.55)	0.0
DPP-4i vs	Pioglitazone	4	1.00 (0.13, 7.6)	0.0
	Placebo	12	1.18 (0.38, 3.70)	0.0
Meglitinide	Placebo	2	1.00 (0.06, 17.77)	0.0
	SU	4	1.00 (0.14, 7.20)	0.0
Metformin	AGIs	4	1.00 (0.14, 7.18)	0.0
	Dapagliflozin	2	1.02 (0.14, 7.20)	0.0
	DPP-4i	12	1.08 (0.38, 3.09)	0.0
	Liraglutide	2	1.00 (0.06, 16.36)	0.0
	Pioglitazone	7	1.00 (0.22, 4.45)	0.0
	Placebo	6	1.00 (0.20, 5.10)	0.0
	SU	8	1.00 (0.25, 4.04)	0.0
Pioglitazone vs	SU	8	0.80 (0.21, 3.00)	0.0
SU vs	Placebo	3	1.00 (0.10, 10.13)	0.0
Hospitalization for heart failure (patients at low cardiovascular risk)				
Metformin vs	DPP-4i	3	1.00 (0.10, 10.13)	0.0
Myocardial infarction (patients at low cardiovascular risk)				
Metformin vs	DPP-4i	10	1.67 (0.66, 4.19)	0.0
DPP-4i vs	Pioglitazone	3	0.72 (0.14, 3.77)	0.0
	Placebo	3	1.27 (0.23, 6.93)	0.0
Metformin vs	Dapagliflozin	3	0.63 (0.12, 3.28)	0.0
	Pioglitazone	4	0.47 (0.09, 2.49)	0.0
	SU	3	1.26 (0.69, 2.30)	0.0
Pioglitazone vs	SU	3	1.00 (0.20, 5.00)	0.0
Diabetic retinopathy (patients at low cardiovascular risk)				
Metformin vs	DPP-4i	2	1.00 (0.062, 16.27)	0.0
Severe hypoglycemia (all patients)				
aGIs vs.	Placebo	5	1.00 (0.16, 6.23)	0.0
Dapagliflozin	Placebo	2	1.00 (0.06, 17.41)	0.0
Metformin vs	DPP-4i	11	1.00 (0.36, 2.81)	0.0
DPP-4i vs	Pioglitazone	4	1.00 (0.13, 7.6)	0.0
	Placebo	9	1.00 (0.26, 3.89)	0.0
Empagliflozin vs	DPP-4i	2	1.75 (0.11, 26.73)	0.0
Meglitinide vs	Placebo	2	1.00 (0.06, 17.77)	0.0
	AGIs	3	1.00 (0.10, 9.70)	0.0
Metformin vs	Dapagliflozin	3	1.00 (0.10, 9.95)	0.0
	Pioglitazone	3	1.00 (0.10, 9.88)	0.0
	Placebo	3	2.08 (0.28, 15.64)	0.0
	SU	5	0.31 (0.10, 1.02)	0.0
SU vs	Placebo	2	3.52 (0.36, 34.67)	0.0

Stroke				
Dapagliflozin vs	Placebo	2	1.31 (0.22, 7.82)	46.5
Metformin vs	DPP-4i	7	1.26 (0.38, 4.22)	0.0
DPP-4i vs	Placebo	3	0.86 (0.13, 5.52)	0.0

Treatment estimates are mean differences (MDs) and 95% confidence intervals (CIs) for change in glycated hemoglobin (HbA_{1c}) and odds ratios (ORs) and 95% CIs for the remaining outcomes. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. po=per os. sc=subcutaneous.SU=sulphonylureas.

Pairwise meta-analysis results for glucose-lowering drugs given as add-on to metformin-based therapy.

Outcome/Comparison		Number of trials	Effect estimate MD/OR (95% CI)	Heterogeneity I^2 (%)
Glycemic outcomes				
Change from baseline in HbA_{1c}				
aGIs vs.	DPP-4i	2	0.09 (0.00, 0.19)	0.0
	Pioglitazone	2	0.29 (-0.20, 0.77)	83.0
	Placebo	8	-0.59 (-0.74, -0.45)	0.0
Basal insulin vs	DPP-4i	5	0.01 (-0.68, 0.70)	94.5
	Pioglitazone	3	-0.59 (-0.95, -0.23)	0.0
	Placebo	6	-0.75 (-0.88, -0.62)	69.3
	Prandial insulin	3	0.13 (-0.00, 0.26)	0.0
	Premixed insulin	8	0.14 (0.08, 0.20)	0.0
Basal bolus insulin vs	Premixed insulin	8	0.01 (-0.14, 0.16)	61.3
Canagliflozin vs	DPP-4i	2	-0.22 (-0.51, 0.08)	90.3
	Placebo	8	-0.56 (-0.77, -0.36)	95.1
Dapagliflozin vs	DPP-4i	4	-0.07 (-0.34, 0.20)	63.1
	Placebo	15	-0.49 (-0.61, -0.37)	89.0
	SU	2	-0.06 (-0.52, 0.40)	92.3

DPP-4i vs	Pioglitazone	7	0.03 (-0.17, 0.24)	85.4
	Placebo	68	-0.55 (-0.61, -0.47)	93.9
	SU	18	0.04 (-0.12, 0.20)	97.7
Dulaglutide vs	Placebo	5	-0.73 (-0.86, -0.61)	65.8
	Basal insulin	3	-0.25 (-0.36 to -0.13)	14.9
Empagliflozin vs	DPP-4i vs	2	-0.17 (-0.38, 0.03)	0.0
	Placebo	10	-0.55 (-0.66, -0.45)	71.9
Ertugliflozin vs	Placebo	4	-0.57 (-0.83, -0.31)	86.9
Exenatide vs	Basal insulin	3	0.05 (-0.09, 0.18)	0.0
	Placebo	11	-0.68 (-0.87, -0.49)	75.2
	Prandial insulin	3	-0.02 (-0.14, 0.09)	0.0
	Premixed insulin	2	0.44 (-0.20, 1.09)	89.2
	SU	3	0.16 (-0.24, 0.56)	90.6
Exenatide ER vs	Basal insulin	2	-0.30 (-0.52, -0.09)	53.9
	DPP-4i	2	-0.52 (-0.77, -0.28)	22.3
	Placebo	3	-0.66 (-0.82, -0.50)	0.0
Liraglutide vs	Basal insulin	4	0.03 (-0.18, 0.23)	71.7
	DPP-4i	6	-0.39 (-0.61, -0.17)	85.9
	Placebo	20	-0.75 (-0.90, -0.60)	90.1
	Prandial insulin	3	-0.21 (-0.54, 0.11)	75.1
	SU	2	-0.19 (-0.41, 0.04)	64.3
Lixisenatide vs	Placebo	11	-0.44 (-0.55, -0.33)	70.2
Meglitinide vs	Placebo	2	-0.60 (-1.02, -0.18)	74.1
	SU	5	-0.07 (-0.33, 0.18)	92.9
Pioglitazone vs	Placebo	12	-0.65 (-0.84, -0.46)	90.8
	SU	14	-0.08 (-0.21, 0.06)	74.6
Semaglutide po vs	DPP-4i	2	-0.36 (-0.54, -0.18)	39.0
	Placebo	4	-0.84 (-1.02, -0.66)	77.3
Semaglutide sc vs	Placebo	4	-1.34 (-1.76, -0.93)	95.4
SU vs	Placebo	8	-0.66 (-1.04, -0.29)	92.9

Severe hypoglycemia				
aGIs vs.	DPP-4i	2	1.00 (0.06, 16.13)	0.0
	Placebo	6	1.33 (0.30, 6.01)	0.0
Basal insulin vs	DPP-4i	3	2.16 (0.40, 11.81)	0.0
	Pioglitazone	2	1.00 (0.06, 16.74)	0.0
	Placebo	6	1.59 (0.35 , 7.24)	0.0
	Premixed insulin	8	0.75 (0.47, 1.20)	0.0
Basal bolus insulin vs	Premixed insulin	8	1.12 (0.79, 1.60)	0.0
Canagliflozin vs	DPP-4i	3	1.12 (0.55, 2.31)	0.0
	Placebo	5	1.05 (0.65, 1.68)	0.0
Dapagliflozin vs	DPP-4i	2	1.00 (0.06, 16.25)	0.0
	Placebo	10	0.72 (0.53, 1.00)	0.0
	SU	2	0.25 (0.03, 2.24)	0.0
DPP-4i vs	Pioglitazone	6	1.52 (0.43, 5.41)	0.0
	Placebo	57	1.07 (0.95, 1.22)	0.0
	SU	17	0.15 (0.09, 0.23)	0.0
Dulaglutide vs	Basal insulin	3	0.56 (0.29, 1.08)	0.0
	Placebo	5	0.89 (0.64, 1.24)	0.0
Empagliflozin vs	Placebo	9	0.89 (0.61, 1.30)	0.0
Ertugliflozin vs	Placebo	4	1.00 (0.21, 4.83)	0.0
Exenatide vs	Basal insulin	2	0.87 (0.35, 2.17)	0.0
	Placebo	9	1.50 (0.42, 5.41)	0.0
	Prandial insulin	3	0.37 (0.10, 1.39)	0.0
	Premixed insulin	2	0.12 (0.01, 1.23)	21.0
Exenatide ER vs	Basal insulin	2	1.00 (0.06, 16.08)	0.0
	DPP-4i	2	1.00 (0.06, 16.50)	0.0
	Placebo	4	1.13 (0.94, 1.36)	0.0
Liraglutide vs	Basal insulin	4	3.03 (0.90, 10.17)	0.0
	DPP-4i	6	1.20 (0.28, 5.10)	0.0
	Placebo	14	0.78 (0.61, 0.98)	0.0
	Prandial insulin	3	0.70 (0.21, 2.34)	0.0
Lixisenatide vs	Placebo	12	0.89 (0.54, 1.49)	0.0
Meglitinide vs	Placebo	3	1.00 (0.10, 10.15)	0.0
	SU	2	0.26 (0.02, 2.68)	0.0
Pioglitazone vs	Placebo	6	1.96 (1.00, 3.84)	0.0
	SU	5	0.11 (0.03, 0.37)	30.8
Semaglutide po vs	Placebo	2	1.75 (0.89, 3.43)	0.0
Semaglutide sc vs	Placebo	4	1.08 (0.91, 1.27)	0.0
SU vs	Placebo	7	2.42 (0.72, 8.17)	0.0

Mortality and vascular endpoints in patients at increased cardiovascular risk				
All-cause mortality				
Canagliflozin vs	Placebo	2	0.98 (0.86, 1.11)	74.3
Dapagliflozin vs	Placebo	2	0.89 (0.80, 0.99)	47.8
Empagliflozin vs	Placebo	2	0.67 (0.55, 0.81)	0.0
DPP-4i vs	Placebo	4	1.02 (0.94, 1.09)	13.8
Semaglutide po vs	Placebo	2	0.50 (0.31, 0.83)	0.0
Cardiovascular mortality				
Canagliflozin vs	Placebo	2	0.96 (0.83, 1.12)	77.0
Dapagliflozin vs	Placebo	2	0.91 (0.79, 1.06)	49.6
Empagliflozin vs	Placebo	2	0.61 (0.49, 0.77)	0.0
DPP-4i vs	Placebo	4	0.99 (0.91, 1.08)	0.0
Semaglutide po vs	Placebo	2	0.51 (0.28, 0.94)	0.0
Amputation				
Canagliflozin vs	Placebo	2	1.65 (1.30, 2.08)	88.2
Dapagliflozin vs	Placebo	2	1.11 (0.86,1.42)	0.0
Hospitalization for heart failure				
Canagliflozin vs	Placebo	2	0.72 (0.60, 0.86)	58.2
Dapagliflozin vs	Placebo	2	0.74 (0.64, 0.86)	0.0
DPP-4i vs	Placebo	4	1.06 (0.96, 1.18)	53.5
Semaglutide po vs	Placebo	2	0.84 (0.47, 1.50)	0.0
Myocardial infarction				
Canagliflozin vs	Placebo	2	0.96 (0.81, 1.14)	0.0
Empagliflozin vs	Placebo	2	0.92 (0.74, 1.13)	0.0
DPP-4i vs	Placebo	4	1.01 (0.92, 1.10)	0.0
Semaglutide po vs	Placebo	2	1.12 (0.71, 1.76)	0.0
Diabetic retinopathy				
DPP-4i vs	Placebo	4	1.19 (0.99, 1.43)	62.1
Semaglutide po vs	Placebo	2	1.23 (0.91, 1.68)	0.0
Stroke				
Canagliflozin vs	Placebo	2	0.93 (0.76, 1.13)	45.4
Empagliflozin vs	Placebo	2	1.19 (0.89, 1.58)	0.0
DPP-4i vs	Placebo	4	0.99 (0.87, 1.13)	0.0
Semaglutide po vs	Placebo	2	0.78 (0.38, 1.56)	0.0

Mortality and vascular endpoints in patients at low cardiovascular risk				
All-cause mortality				
aGIs vs.	DPP-4i	2	1.00 (0.06, 16.13)	0.0
	Pioglitazone	2	1.00 (0.06, 16.20)	0.0
	Placebo	9	1.00 (0.27, 3.72)	0.0
Basal insulin vs	DPP-4i	5	0.53 (0.11, 2.60)	0.0
	Pioglitazone	3	1.00 (0.10, 9.98)	0.0
	Placebo	6	0.78 (0.20, 3.01)	0.0
	Prandial insulin	3	0.36 (0.11, 1.15)	0.0
	Premixed insulin	8	0.62 (0.31, 1.23)	0.0
Basal bolus insulin vs	Premixed insulin	8	1.68 (0.60, 4.65)	0.0
Canagliflozin vs	DPP-4i	3	1.18 (0.27, 5.22)	0.0
	Placebo	5	1.00 (0.23, 4.27)	0.0
Dapagliflozin vs	DPP-4i	2	3.02 (0.31, 29.09)	0.0
	Placebo	14	1.44 (0.66, 3.15)	0.0
	SU	2	0.45 (0.10, 2.03)	0.0
DPP-4i vs	Pioglitazone	7	0.91 (0.28, 2.96)	0.0
	Placebo	66	0.77 (0.53, 1.12)	0.0
	SU	19	0.76 (0.47, 1.22)	0.0
Dulaglutide vs	Basal insulin	3	0.43 (0.12, 1.50)	0.0
	Placebo	4	1.40 (0.29, 6.73)	0.0
Empagliflozin vs	Placebo	8	1.35 (0.45, 4.08)	0.0
Ertugliflozin vs	Placebo	4	0.76 (0.21, 2.69)	0.0
Exenatide vs	Basal insulin	2	1.00 (0.06, 16.33)	0.0
	Placebo	10	1.00 (0.27, 3.68)	0.0
	Prandial insulin	2	2.00 (0.18, 22.57)	0.0
	Premixed insulin	2	0.59 (0.04, 7.91)	0.0
	SU	3	1.00 (0.32, 3.10)	0.0
Exenatide ER vs	Basal insulin	2	0.97 (0.10, 9.38)	0.0
	DPP-4i	2	0.50 (0.05, 5.51)	0.0
	Placebo	3	1.00 (0.24, 4.13)	0.0
Liraglutide vs	Basal insulin	4	1.00 (0.14, 7.14)	0.0
	DPP-4i	6	0.67 (0.19, 2.33)	0.0
	Placebo	20	0.86 (0.43, 1.72)	0.0
	Prandial insulin	3	1.00 (0.10, 9.68)	0.0
Lixisenatide vs	Placebo	11	0.55 (0.26, 1.18)	0.0
Meglitinide vs	Placebo	3	1.13 (0.20, 6.45)	0.0
	SU	4	1.53 (0.31, 7.50)	0.0
Pioglitazone vs	Placebo	12	1.12 (0.42, 3.00)	0.0

	SU	11	0.64 (0.22, 1.89)	0.0
Semaglutide po vs	DPP-4i	2	0.49 (0.13, 1.76)	0.0
	Placebo	2	2.52 (0.39, 16.21)	0.0
Semaglutide sc vs	Placebo	3	1.00 (0.10, 10.08)	0.0
SU vs	Placebo	8	0.70 (0.22, 2.18)	0.0
Cardiovascular mortality				
aGIs vs.	DPP-4i	2	1.00 (0.06, 16.13)	0.0
	Pioglitazone	2	1.00 (0.06, 16.20)	0.0
	Placebo	9	1.00 (0.27, 3.72)	0.0
Basal insulin vs	DPP-4i	4	1.00 (0.13, 7.49)	0.0
	Pioglitazone	3	1.00 (0.10, 9.98)	0.0
	Placebo	6	1.00 (0.24, 4.21)	0.0
	Prandial insulin	2	0.16 (0.03, 0.88)	0.0
	Premixed insulin	6	0.83 (0.36, 1.93)	0.0
Basal bolus insulin vs	Premixed insulin	8	1.34 (0.46, 3.88)	0.0
Canagliflozin vs	DPP-4i	2	3.13 (0.29, 33.70)	0.0
	Placebo	5	1.00 (0.23, 4.27)	0.0
Dapagliflozin vs	Placebo	10	0.84 (0.27, 2.65)	0.0
	SU	2	0.25 (0.03, 2.24)	0.0
DPP-4i vs	Pioglitazone	7	1.13 (0.29, 4.43)	0.0
	Placebo	59	0.87 (0.56, 1.35)	0.0
	SU	17	0.69 (0.36, 1.33)	0.0
Dulaglutide vs	Basal insulin	2	0.24 (0.04, 1.58)	0.0
	Placebo	4	1.23 (0.16, 9.23)	0.0
Empagliflozin vs	Placebo	7	1.50 (0.40, 5.55)	0.0
Ertugliflozin vs	Placebo	4	0.67 (1.15, 3.01)	0.0
Exenatide vs	Basal insulin	2	1.00 (0.06, 16.33)	0.0
	Placebo	10	1.00 (0.27, 3.68)	0.0
	Prandial insulin	2	2.00 (0.18, 22.57)	0.0
	Premixed insulin	2	0.59 (0.04, 7.91)	0.0
	SU	2	1.00 (0.06, 16.18)	0.0
Exenatide ER vs	DPP-4i	2	1.00 (0.06, 16.50)	0.0
	Placebo	3	1.00 (0.13, 7.63)	0.0
Liraglutide vs	Basal insulin	4	1.00 (0.14, 7.14)	0.0
	DPP-4i	5	0.47 (0.10, 2.15)	0.0
	Placebo	20	0.84 (0.39, 1.79)	0.0
	Prandial insulin	3	1.00 (0.10, 9.68)	0.0
Lixisenatide vs	Placebo	11	0.71 (0.28, 1.80)	0.0
Meglitinide vs	Placebo	3	1.13 (0.20, 6.45)	0.0
	SU	3	1.00 (0.10, 10.08)	0.0

Pioglitazone vs	Placebo	12	1.09 (0.37, 3.15)	0.0
	SU	11	1.00 (0.30, 3.28)	0.0
Semaglutide po vs	DPP-4i	2	0.54 (0.08, 3.57)	7.1
Semaglutide sc vs	Placebo	3	1.00 (0.10, 10.08)	0.0
SU vs	Placebo	8	0.80 (0.21, 2.99)	0.0
Amputation				
Basal insulin vs	DPP-4i	2	0.48 (0.04, 5.38)	0.0
DPP-4i vs	Placebo	2	0.59 (0.08, 4.49)	0.0
	SU	2	1.71 (0.13, 23.08)	0.0
Empagliflozin vs	Placebo	3	1.00 (0.09, 11.10)	0.0
Ertugliflozin vs	Placebo	2	3.27 (0.25, 42.75)	0.0
Liraglutide vs	Placebo	2	1.00 (0.06, 17.93)	0.0
Hospitalization for heart failure				
Basal insulin vs	DPP-4i	2	1.98 (0.17, 22.49)	0.0
DPP-4i vs	Placebo	8	0.81 (0.23, 2.87)	0.0
	SU	3	0.60 (0.08, 4.54)	0.0
Liraglutide vs	Basal insulin	2	0.50 (0.04, 5.54)	0.0
	Placebo	6	0.84 (0.21, 3.44)	0.0
Pioglitazone vs	SU	2	2.00 (0.18, 22.48)	0.0
Semaglutide po vs	DPP4i	2	0.21 (0.03, 1.35)	0.0
Myocardial infarction				
Basal insulin vs	DPP-4i	2	0.51 (0.04, 5.90)	0.0
	Placebo	2	1.00 (0.06, 17.41)	0.0
	Premixed insulin	5	0.57 (0.26, 1.28)	53.2
Basal bolus insulin vs	Premixed insulin	6	1.16 (0.40, 3.33)	0.0
Canagliflozin vs	DPP-4i	2	0.37 (0.05, 2.59)	0.0
	Placebo	2	0.65 (0.18, 2.28)	0.0
Dapagliflozin vs	DPP-4i	3	1.00 (0.17, 5.78)	0.0
	Placebo	10	0.51 (0.21, 1.24)	0.0
	SU	2	0.33 (0.05, 2.12)	0.0
DPP-4i vs	Pioglitazone	2	0.47 (0.06, 3.81)	0.0
	Placebo	37	0.92 (0.60, 1.40)	0.0
	SU	11	0.74 (0.47, 1.16)	22.7
Dulaglutide vs	Basal insulin	3	0.44 (0.14, 1.38)	6.1
	Placebo	3	0.78 (0.18, 3.38)	24.1
Empagliflozin vs	Placebo	6	1.00 (0.35, 2.83)	0.0
Ertugliflozin vs	Placebo	3	0.82 (0.28, 2.42)	0.0
Exenatide ER vs	Placebo	3	0.23 (0.04, 1.37)	0.0
Liraglutide vs	Basal insulin	2	1.00 (0.10, 9.70)	0.0
	DPP-4i	3	1.13 (0.20, 6.43)	0.0

	Placebo	9	1.30 (0.58, 2.93)	0.0
	Prandial insulin	2	0.50 (0.05, 5.53)	0.0
Lixisenatide vs	Placebo	9	0.64 (0.31, 1.32)	0.0
Meglitinide vs	SU	2	0.22 (0.02, 2.24)	0.0
Pioglitazone vs	Placebo	4	1.10 (0.20, 5.89)	0.0
SU vs	Placebo	6	0.87 (0.31, 2.39)	0.0
Diabetic retinopathy				
Basal insulin vs	Placebo	2	0.68 (0.17, 2.83)	0.0
DPP-4i vs	Placebo	7	1.75 (0.67, 4.59)	0.0
	SU	2	0.51 (0.21, 1.26)	0.0
Empagliflozin vs	Placebo	3	1.50 (0.15, 14.54)	0.0
Liraglutide vs	Basal insulin	2	0.56 (0.12, 2.63)	0.0
	DPP-4i	2	1.71 (0.13, 23.36)	0.0
	Placebo	5	0.89 (0.49, 1.64)	0.0
Semaglutide po vs	DPP-4i	2	0.70 (0.44, 1.11)	0.0
Semaglutide sc vs	Placebo	2	0.80 (0.29, 2.21)	68.1
Stroke				
Basal insulin vs	Placebo	4	0.60 (0.13, 2.76)	0.0
	Premixed insulin	7	0.70 (0.27, 1.84)	0.0
Dapagliflozin vs	DPP-4i	2	3.01 (0.31, 29.02)	0.0
	Placebo	4	0.91 (0.21, 3.92)	0.0
	SU	2	3.01 (0.31, 28.99)	0.0
DPP-4i vs	Pioglitazone	4	0.76 (0.18, 3.14)	0.0
	Placebo	29	0.84 (0.50, 1.44)	0.0
	SU	10	0.45 (0.22, 0.91)	0.0
Dulaglutide vs	Basal insulin	3	0.86 (0.25, 2.94)	0.0
	Placebo	2	2.07 (0.17, 25.56)	0.0
Empagliflozin vs	Placebo	5	1.84 (0.51, 6.68)	0.0
Ertugliflozin vs	Placebo	3	0.79 (0.15, 4.10)	0.0
Exenatide ER vs	Placebo	2	1.38 (0.15, 12.86)	0.0
Liraglutide vs	Basal insulin	3	0.60 (0.08, 4.57)	0.0
	DPP-4i	2	0.50 (0.04, 5.61)	0.0
	Placebo	7	0.95 (0.32, 2.81)	0.0
Lixisenatide vs	Placebo	5	0.76 (0.27, 2.16)	0.0
Pioglitazone vs	Placebo	4	1.26 (0.25, 6.51)	0.0
Semaglutide sc vs	Placebo	2	1.71 (0.13, 23.18)	0.0

Treatment estimates are mean differences (MDs) and 95% confidence intervals (CIs) for change in glycated hemoglobin (HbA_{1c}) and odds ratios (ORs) and 95% CIs for the remaining outcomes. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. po=per os. sc=subcutaneous. SU=sulphonylureas.

Abbildung 5: Zhang Q et al., 2023 Studiencharakteristika

Table 1 Characteristics of included studies

Study	Study arms	Duration (weeks)	Population	*n*	Age (years)	Male sex (%)	Country/race
J. P. H. Wilding [15]	Dapagliflozin 10mg + INS	12	Insulin ± OADs as a basic treatment	24	55.7	54.2	White, Asian, Black
	Dapagliflozin 20mg + INS			24	56.1	54.2	
	PBO + INS			23	58.4	69.6	
J. P. H. Wilding [16]	Dapagliflozin 2.5 mg + INS	104	Insulin ± OADs as a basic treatment	202	59.8	49.5	White, Asian, Black
	Dapagliflozin 5/10 mg + INS			211	59.3	47.4	
	Dapagliflozin 10mg + INS			194	59.3	44.8	
	PBO + INS			193	58.8	49.2	
J. Rosenstock [17]	Empagliflozin 10mg + INS	52	Insulin ± metformin as a basic treatment	186	56.7	52	White, Black
	Empagliflozin 25mg + INS			189	58	44	
	PBO + INS			188	55.3	40	
J. Rosenstock [18]	Empagliflozin 10mg + INS	78	Insulin ± OADs as a basic treatment	169	58.6	55	White, Asian, Black
	Empagliflozin 10mg + INS			155	59.9	60	
	PBO + INS			170	58.1	53	
Bruce Neal [19]	Canagliflozin 100mg + INS	52	Insulin as a basic treatment	692	62	67	White, Asian, Black
	Canagliflozin 300mg + INS			690	63	65	
	PBO + INS			690	63	66	
William T [20]	Dapagliflozin 10mg + INS	24	Insulin ± OADs as a basic treatment	455	62.8	68.6	White, Asian, Black
	PBO + INS			459	63	67.9	
Hisamitsu Ishihara [21]	Ipragliflozin 50mg + INS	16	Insulin ± DPP-4 as a basic treatment	168	58.7	62.5	Japan
	PBO + INS			87	59.2	58.6	
Katsunori Suzuki [22]	Tofogliflozin 20mg + INS	24	Insulin ± OADs as a basic treatment	19	54.1	52.6	Japan
	PBO + INS			15	62	66.6	
Nobuya Inagaki [23]	Canagliflozin 100mg + INS	16	Insulin as a basic treatment	76	59.7	57.9	Japan
	PBO + INS			70	56.1	70	
E. Araki [24]	Dapagliflozin 5mg + INS	16	Insulin as a basic treatment	122	58.3	73	Japan
	PBO + INS			60	57.6	66.7	
Yasuo Terauchi [25]	Tofogliflozin 20mg + INS	16	Insulin ± DPP-4 as a basic treatment	141	59.1	63.8	Japan
	PBO + INS			70	56.4	68.6	
Yutaka Seino [26]	Luseogliflozin 2.5 mg + INS	16	Insulin as a basic treatment	159	57.4	70.4	Japan
	PBO + INS			74	57.1	68.9	
Wenying Yang [27]	Dapagliflozin 10mg + INS	24	Insulin ± OADs as a basic treatment	139	56.5	47.5	Asian, Chinese,
	PBO + INS			133	58.6	48.1	Japanese, Korean
Hirohito Sone [28]	Empagliflozin 10mg + INS	52	Insulin as a basic treatment	86	58.3	73.3	Japan
	Empagliflozin 10mg + INS			90	58.6	67.8	
	PBO + INS			90	59.1	76.7	

INS Insulin, *PBO* placebo, *OADs* oral antidiabetic drugs, *DPP-4* dipeptidyl peptidase-4

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

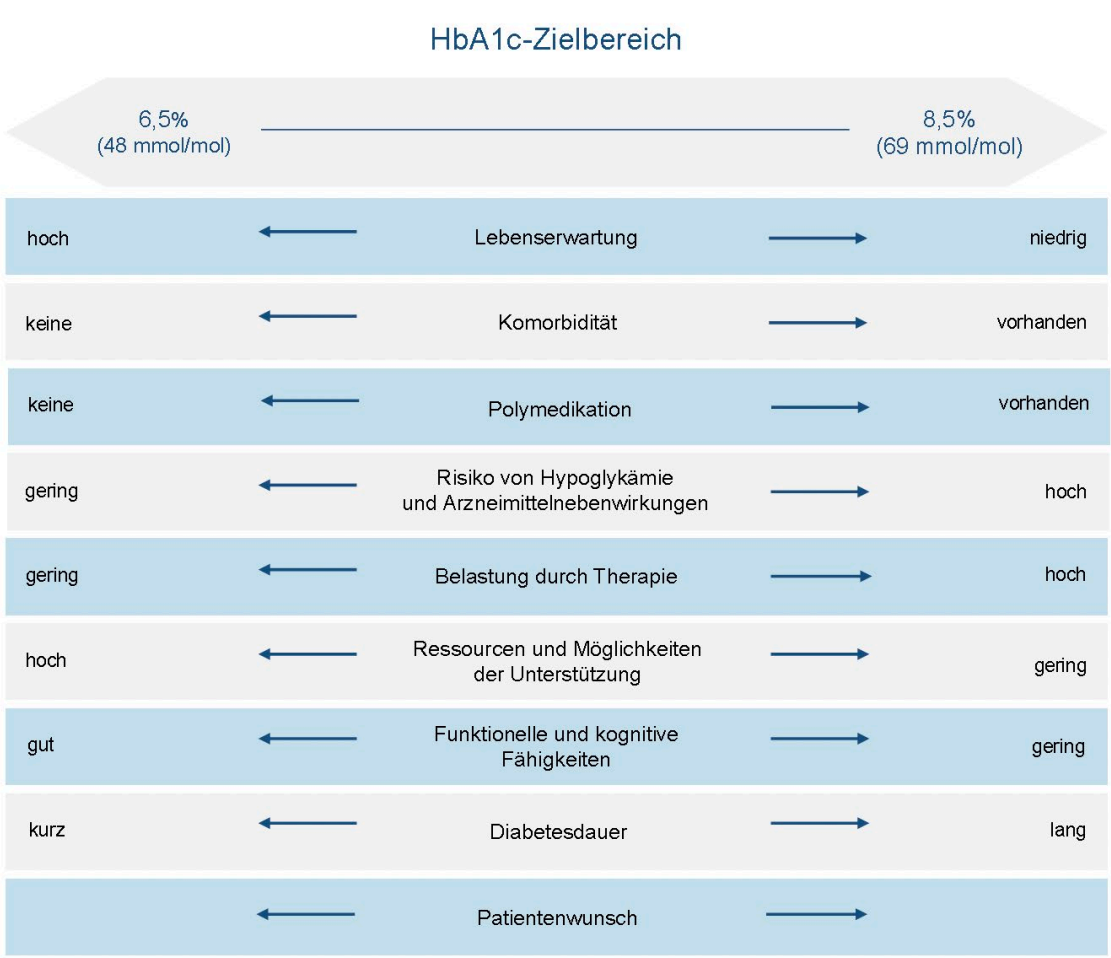
Verfahrens-Nr.: 2024-B-098

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Datum der Erstellung	7. Mai 2024

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Behandlung von erwachsenen Patienten mit Typ 2 Diabetes mellitus.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Die Behandlung von erwachsenen Personen mit einem Typ-2-Diabetes orientiert sich an der aktuellen Version der Nationalen Versorgungsleitlinie Typ 2-Diabetes (1). Diese NVL ist auch Grundlage des Disease-Management-Programs Typ-2-Diabetes, in das der Großteil der in der GKV versicherten Menschen mit Typ-2-Diabetes eingeschrieben ist. Vor Beginn der Behandlung wird zwischen Arzt und Patient im Rahmen einer partizipativen Entscheidungsfindung ein individuelles Therapieziel vereinbart und dokumentiert. Dies beinhaltet sowohl technische Therapieziele (HbA_{1c}, Blutdruck, Lipidwerte u. a.) als auch medizinische Therapieziele (Vermeidung von mikro- und makrovaskulären Komplikationen) sowie der Freiheit von diabetesbezogenen Symptomen. Die Qualität der Stoffwechsellage wird durch die Messung des HbA_{1c}-Wertes beurteilt, der jeweils die mittlere Glykämie der letzten drei Monate repräsentiert. Es lässt sich kein universell gültiger Zielkorridor für den HbA_{1c} festlegen. Vielmehr müssen patientenspezifische Kontextfaktoren berücksichtigt werden. Abbildung 9 der NVL gibt hierzu eine Hilfestellung:

Abbildung 9: HbA1c-Zielkorridor



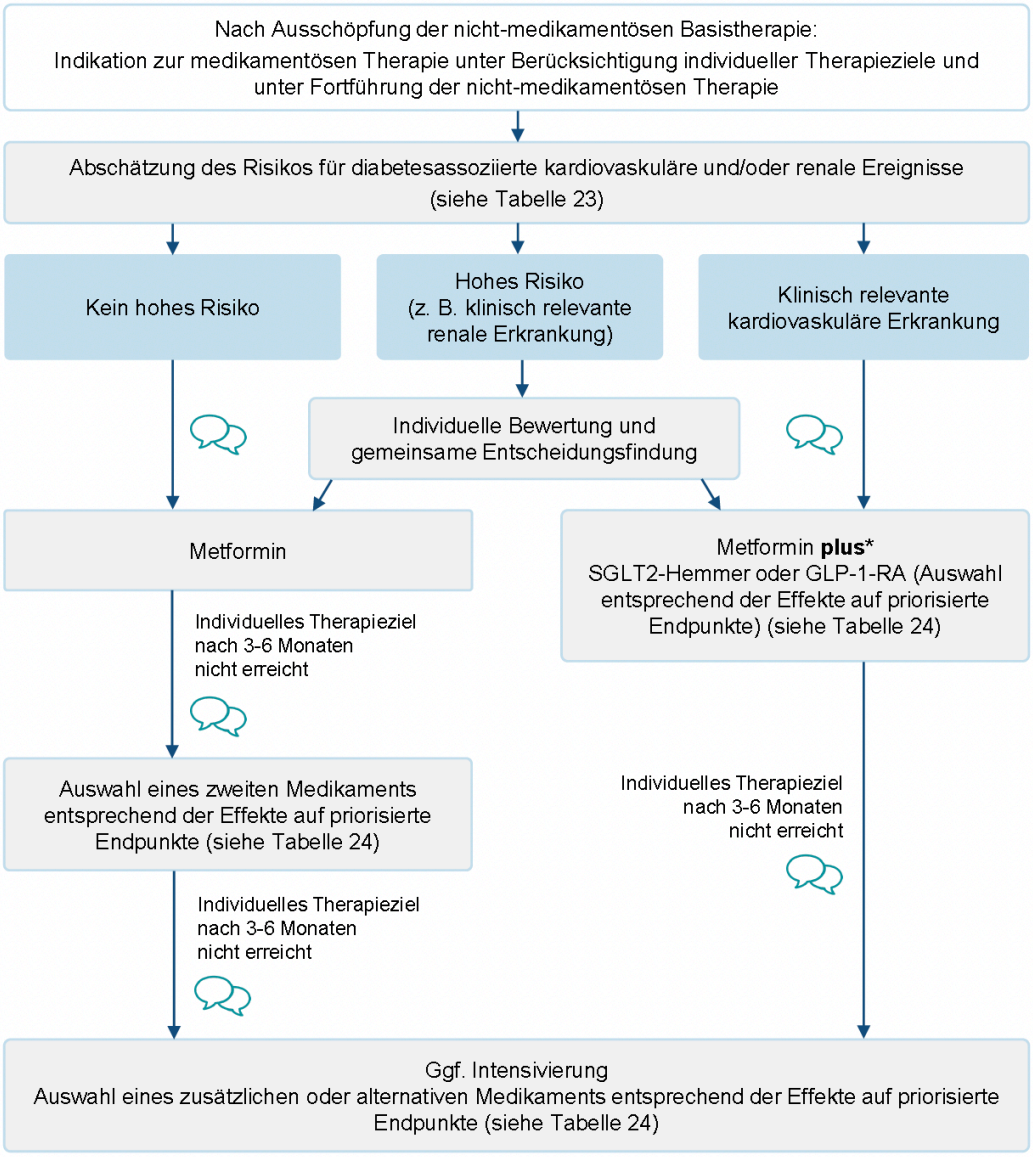
Zu Limitationen der Aussagekraft des HbA1c-Wertes siehe auch Kapitel 4.1.2.2 **Diagnosekriterien**.

Abbildung 9 zum HbA1c-Zielbereich bezieht sich nicht auf Patient*innen mit einer schweren Stoffwechseldekompensation.

Die Behandlung selbst erfolgt als Stufentherapie. Diese beginnt mit nichtmedikamentösen Maßnahmen wie einer Umstellung der Ernährung sowie der Steigerung der körperlichen Aktivität als sogenannte Basismaßnahmen. Diese haben einen hohen Stellenwert und werden auch beim Beginn einer pharmakologischen antidiabetischen Therapie fortgeführt.

In der nächsten Stufe erfolgt zusätzlich zu den Basismaßnahmen eine pharmakologische Behandlung. In der NVL findet sich in Abbildung 7 der zentrale Therapiealgorithmus:

Abbildung 7: Algorithmus Medikamentöse Therapie des Typ-2-Diabetes



= Überprüfung der Therapiestrategie und des Therapieziels in partizipativer Entscheidungsfindung

*Bei einem HbA1c von ≤ 7% (53 mmol/mol) liegen keine Daten für die Wirksamkeit einer Kombinationstherapie bei Menschen mit Typ-2-Diabetes ohne Herzinsuffizienz vor.

Der Algorithmus bezieht sich nicht auf Patient*innen mit schwerer Stoffwechseldekompensation bzw. Notfallsituationen. Aktuelle Fachinformationen sind zu berücksichtigen.

Seit einigen Jahren stehen Medikamente zur Verfügung, die in randomisierten, kontrollierten Studien (RCT) bei bestimmten Patientengruppen – unabhängig von einer blutzuckersenkenden Wirkung – positive Wirkungen auf die kardiovaskuläre Morbidität und Mortalität gezeigt haben. Daher fokussiert der Therapie-Algorithmus nicht mehr primär auf eine Senkung der erhöhten Blutzuckerwerte, sondern schätzt zunächst das Risiko für diabetesassoziierte kardiovaskuläre und/oder renale Ereignisse ab (Abbildung 7 der NVL, zweiter Kasten von oben).

Im Fall von Patienten ohne hohes Risiko (Abbildung 7, linker Kasten in der dritten Zeile von oben) wird der Beginn einer Therapie mit Metformin empfohlen. Diese Patientengruppe ist weniger durch

das Risiko für das Auftreten von kardiovaskulären oder renalen Ereignissen belastet, sondern vielmehr durch das Risiko für mikrovaskuläre Folgeschäden (Retinopathe, Nephropathie) und eine Polyneuropathie. Sollte mit Metformin allein der individuell vereinbarte HbA_{1c}-Zielbereich nicht oder im Verlauf nicht mehr erreicht werden, wird ein zweites Medikament entsprechend der Effekte auf priorisierte Endpunkte (Tabelle 24, Seiten 82–84 der Langversion der NVL) eingesetzt.

Bei Patienten mit einer bereits bestehenden, klinisch manifesten kardiovaskulären Erkrankung (Z. n. Herzinfarkt, Z. n. Schlaganfall, pAVK) (Abbildung 7, rechter Kasten in der dritten Zeile von oben) empfiehlt die NVL den Beginn einer Kombinationstherapie aus Metformin und einem SGLT-2-Inhibitor oder GLP1-Agonisten. Diese Empfehlung basiert auf großen RCT für Empagliflozin, Dapagliflozin und Liraglutid, in denen Vorteile für Morbidität, die kardiovaskuläre Mortalität und teilweise auch für die Gesamtmortalität gezeigt werden konnten. Da in allen diesen Studien die Patienten immer mit der Kombination aus Metformin und einer der genannten Substanzen eingesetzt wurden, hat die NVL dieses Vorgehen in den Therapie-Algorithmus als Kombinations-therapie übernommen. Da in den Studien nur Patienten mit einem HbA_{1c} von ≥ 7,0 % eingeschlossen wurden, wurde dieser Grenzwert ebenfalls übernommen.

Im weiteren Verlauf der Therapie empfiehlt die NVL dann ebenfalls ein weiteres Medikament entsprechend der Effekte auf priorisierte Endpunkte (Tabelle 24, Seiten 82–84 der Langversion der NVL).

Schwieriger, weil kaum durch externe wissenschaftliche Evidenz gesichert, ist die Therapie der Gruppe von Patienten mit einem hohen Risiko, aber ohne ein bereits stattgehabtes kardiovaskuläres Ereignis. Hier empfiehlt die NVL eine individuelle Bewertung und eine gemeinsame Entscheidungsfindung zwischen Patient und Arzt.

Anders als in der vorherigen Version der NVL werden pharmakologische Dreifachtherapien (ohne den Einsatz von Insulin) im Verlauf ermöglicht. Die Insulintherapien wurden in der Stufentherapie zeitlich nach hinten verschoben.

Spätestens wenn das individuell vereinbarte Therapie aber mit drei anderen Substanzklassen nicht erreicht werden kann, wird (zusätzlich) mit einer Insulintherapie begonnen.

Die Art der Insulintherapie ist vielfältig und unterscheidet sich nach der Anzahl der Injektionen:

- eine Injektion: Basalinsulin, zusätzlich zu oralen Antidiabetika.
- zwei Injektionen: konventionelle Insulintherapie (CT) mit einem Mischinsulin vor dem Frühstück und dem Abendessen.
- drei Injektionen: kurzwirksames Insulin, jeweils zu den Hauptmahlzeiten (SIT)
- vier Injektionen: intensivierte Insulintherapie (ICT), kurzwirksames Insulin zu den Hauptmahlzeiten, Basalinsulin zur Nacht.

Beim Beginn einer Insulintherapie wird die Therapie mit Metformin und SGLT-2-Inhibitoren fortgeführt. Sulfonylharnstoffe werden bei der Gabe von Insulin tagsüber (CT, ICT, SIT) abgesetzt.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

Die Therapie des Typ-2-Diabetes ist derzeit sehr viel individueller als noch vor zehn Jahren. Das liegt daran, dass sich das Spektrum der verfügbaren pharmakologischen Therapie durch die Einführung neuer Substanzklassen (vor allem SGLT-2-Inhibitoren und GLP1-Agonisten). Hierbei haben große RCT

gezeigt, dass vor allem Patienten mit einer manifesten kardiovaskulären oder renalen Erkrankung von den neuen Substanzklassen profitieren. Dies gilt speziell für die SGLT-2-Inhiboren Empagliflozin und Dapagliflozin und in geringerem Umfang auch das GLP1-Analogon Liraglutid. Der SGLT-2-Inhibitor Ertugliflozin konnte in einer großen RCT keinen Vorteil zeigen. Für die neueren GLP1-Agonisten Semaglutid und Dulaglutid liegen bisher zu wenige RCT bei Menschen mit einem Typ-2-Diabetes vor, um einen Nutzen hinsichtlich der Reduktion von kardiovaskulären Folgeschäden zu beurteilen.

Den unterschiedlichen Behandlungsentscheidungen liegen somit Kriterien zugrunde, die in den Begleiterkrankungen und der individuellen Risikoabschätzung jedes einzelnen Patienten zu suchen sind.

Insgesamt orientiert sich die Therapie an dem Algorithmus der NVL. Diese ist auch wissenschaftliche Grundlage des DMP Typ-2-Diabetes, das in Deutschland die Versorgung von Menschen mit einem Typ-2-Diabetes strukturiert.

Referenzliste:

1. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Typ-2-Diabetes – Langfassung. AWMF-Register-Nr. nvl-001; Version 3.0; 2023. Verfügbar unter: https://www.leitlinien.de/themen/diabetes.

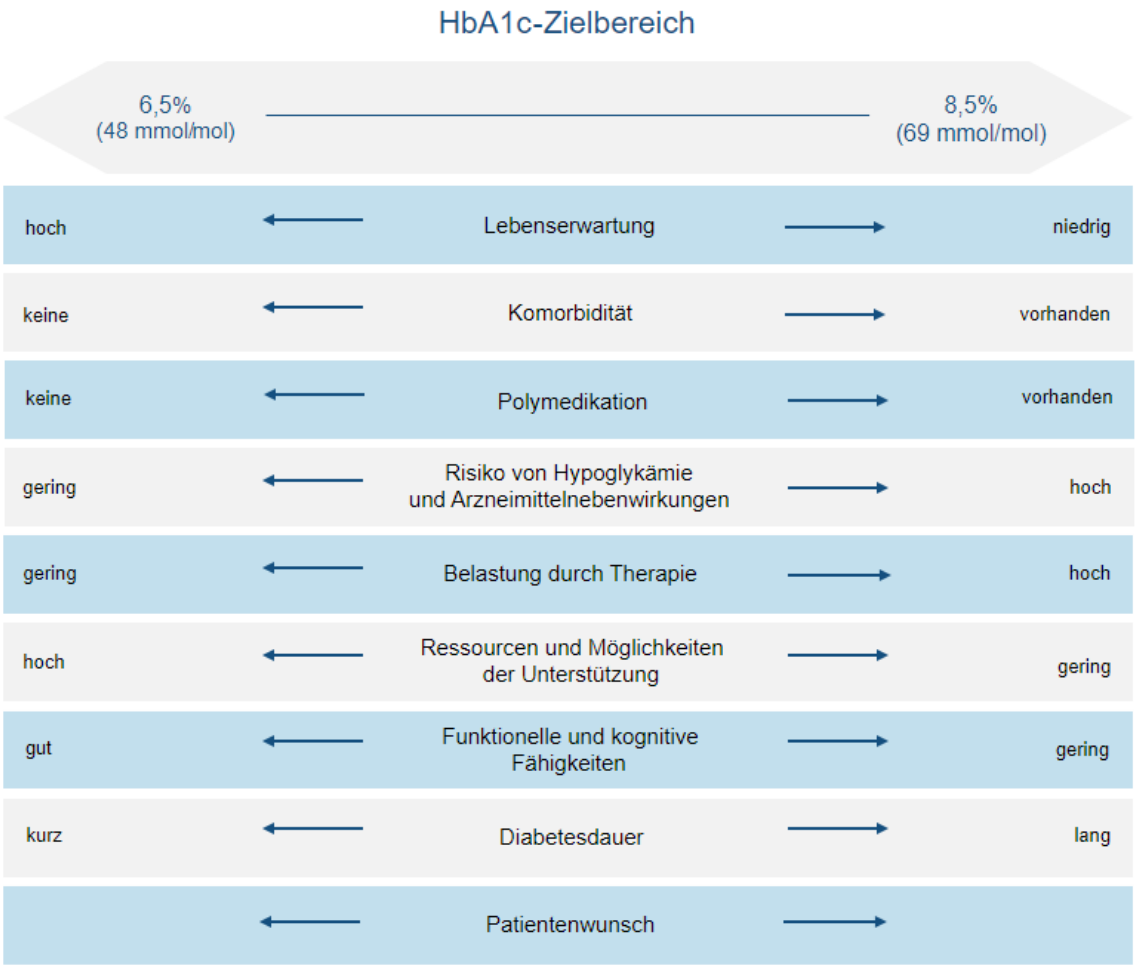
Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-098

Verfasser	
Name der Institution	Deutsche Diabetes Gesellschaft (DDG) Deutsche Gesellschaft für Endokrinologie (DGE) Deutsche Gesellschaft für Allgemeinmedizin (DEGAM) Deutsche Gesellschaft für Kardiologie (DGK)
Datum der Erstellung	19. April 2024

Indikation
Behandlung von erwachsenen Patienten mit Typ 2 Diabetes mellitus.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Der Behandlungsstandard für die Therapie des Typ-2-Diabetes (T2D) ist in der Version 3.0 (2023) der entsprechenden Nationalen VersorgungsLeitlinie (NVL) dargelegt (1) und entspricht weitestgehend den internationalen Empfehlungen der amerikanischen- und europäischen Diabetesgesellschaften (ADA und EASD) und der Europäischen Gesellschaft für Kardiologie (ESC) sowie den Praxisempfehlungen der Deutschen Diabetes Gesellschaft (DDG) und der Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM - DEGAM-Anwenderversion als Addendum zur Nationalen VersorgungsLeitlinie (NVL)) (1-6). Zum Behandlungsstandard weisen wir auch auf die entsprechenden Stellungnahmen der Fachgesellschaften im Rahmen der "Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kap. § 7 Abs. 6" B-129, -132, -224, 306 (jeweils 2021), B-142 (2022) sowie B-190 (2023) hin, sowie auf die im Juni 2022 vom Gemeinsamen Bundesausschuss beschlossene Änderung der Anlage 1 (DMP Diabetes mellitus Typ 2) (https://www.g-ba.de/downloads/40-268-8621/2022-06-16_DMP-A-RL_Aenderung-Anlage-1-2-8-Diabetes-mellitus_Servicedokument.pdf). Die NVL Diabetes hat neue Evidenz zu kardiovaskulärer und kardiorenaler Sicherheit verschiedener medikamentöser Therapien berücksichtigt. Es wurden entsprechend der Datenlage unterschiedliche Patientenkollektive mit T2D in Abhängigkeit ihres kardiovaskulären- und kardiorenalen Risikos skizziert, für die unterschiedliche Therapiealgorithmen (s.u.) nach der Einleitung einer Standardtherapie mit Metformin empfohlen werden (1). Übergreifend und als wesentlicher Grundgedanke ist in der NVL die partizipative Entscheidungsfindung (PEF) zur Erreichung individueller Behandlungsziele in allen Therapiestadien in den Vordergrund gestellt. Die Versorgungslage hat sich auch bei T2D verbessert und die diabetesbezogene Sterblichkeit hat in den letzten Jahrzehnten abgenommen (7). Trotzdem ist das Sterblichkeitsrisiko bei Diabetes ca. 2-3-fach erhöht und die Lebenserwartung im Vergleich

zur altersadjustierten nicht an Diabetes erkrankten Bevölkerung um ca. 4-6 Jahre verkürzt (8).
Allerdings sinkt diese Übersterblichkeit in den industrialisierten Ländern kontinuierlich. Die Übersterblichkeit an Diabetes ist in höherem Alter >70 Jahre allerdings nicht mehr vorhanden, jedoch höher, wenn mehrere Risikofaktoren (jeweils erhöhte Glykämieparameter, Lipide, Bluthochdruck oder Rauchen) vorliegen. Bei allen Todesfällen in Deutschland sind 16 Prozent direkt oder indirekt mit einem Typ-2-Diabetes assoziiert, Folge- und Begleiterkrankungen, vor allem diabetesbedingte kardiovaskuläre Erkrankungen, sind hierfür die Ursache (8-12). Hieraus ergibt sich bei über 75-Jährigen in den meisten Fällen bei der Diabetes-Therapie eine Orientierung an Symptomfreiheit und nicht eine prognostische Intention der Behandlung.
Im DMP Nordrhein (13) hatten über 40% der über 75-Jährigen ein HbA1c <6,5% - hatten also entweder keinen Diabetes (14) oder erhielten möglicherweise unnötig eine antihyperglykämische Medikation.
Nach wie vor ist die kontinuierliche Lebensstilintervention mit Kontrolle des Körpergewichts, günstiger Ernährung, Intensivierung der körperlichen Aktivität und der Nikotinkarenz als nichtmedikamentöse Basistherapie in der NVL implementiert.
Die NVL Typ-2-Diabetes empfiehlt einen Ziel-Korridor für das HbA1c von 6,5-8,5%.



Zu Limitationen der Aussagekraft des HbA1c-Wertes siehe auch Kapitel 4.1.2.2 Diagnosekriterien.

Für diesen Korridor sind u.a. Lebenserwartung, Komorbidität, Diabetes-Dauer etc. berücksichtigt.
Für eine medikamentöse Senkung des HbA1c unter 7,0% existiert keine ausreichende Evidenz (15- 20).
Die Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM) empfiehlt darum in Übereinstimmung mit dem American College of Physicians (21) in ihrer Anwenderversion zur Nationalen VersorgungsLeitlinie Diabetes (6) einen Korridor für die medikamentöse Senkung des HbA1c von 7,0-7,5%, bei über 70-Jährigen sollte das HbA1c einen Wert von 8,5% nicht dauerhaft überschreiten – ein Typ-2-Diabetes führt in der Regel ab einem HbA1c von 9% zu Symptomen (22).
Nichtmedikamentöse Maßnahmen (Patientenschulung, Ernährungs- und Lebensstilintervention, Bewegung) sind der nichtmedikamentöse Rahmen der Therapie, der bei Erstdiagnose eines Typ-2-Diabetes im Disease Management Programm (DMP) für Typ-2-Diabetes vorgesehen ist. Diese Lebensstilintervention soll nach den Leitlinien kontinuierlich beibehalten und ggf. modifiziert werden. Bei der medikamentösen Therapie ist trotz der schwachen Evidenzbasis, die das aktuelle Cochrane-Review zu dem Thema darstellt (23) Metformin das empfohlene initiale Präparat, dies gilt vor allem für Menschen mit Typ-2-Diabetes ohne erhöhtes kardiovaskuläres Risiko oder bereits manifestierte kardiovaskuläre oder kardiorenale Erkrankung. Ca. 75% der Menschen mit T2D sind in das DMP für Typ-2-Diabetes eingeschrieben und erhalten im Rahmen dieses Programms Metformin sowie die vorgesehenen Kontrolluntersuchungen. Für die glykämischen Behandlungsziele ist ein individueller Zielkorridor für den HbA1c-Wert in der NVL beschrieben.
Für Personen ohne kardiovaskuläre Vorerkrankungen, deren individuelles HbA1c-Ziel nicht erreicht werden kann, bleibt die NVL allgemein und spricht nur von einer Kombination von Metformin mit einem "zweiten Medikament". Die DEGAM empfiehlt in ihrer Anwenderversion zur NVL als nächstes Medikament Glibenclamid. Die lange diskutierte kardiovaskuläre Toxizität von Sulfonylharnstoffen kann seit den Studien ADOPT (24) und CAROLINA (25) als widerlegt gelten. Anders als für Glimepirid konnte in der UKPDS 33 (15) ein Nutzen hinsichtlich mikrovaskulärer Endpunkte belegt werden. Glibenclamid ist ein starker Senker des HbA1c – sein Einsatz führt wesentlich seltener als Sitagliptin zu einem Sekundärversagen (26).
Wegen des Hypoglykämie-Risikos empfiehlt die DEGAM unter Sulfonylharnstoffen wie unter Insulin, eine HbA1c-Senkung unter 7,5% nach Möglichkeit zu vermeiden.
Lässt sich bei Personen ohne kardiovaskuläre Vorerkrankungen das HbA1c mit Hilfe von Metformin+Glibenclamid nicht auf den individuell vereinbarten Wert senken, empfiehlt die DEGAM den Einsatz von Empagliflozin und (wegen einer geringeren Wirksamkeit) nachrangig den von Liraglutid (27).

Als weitere evidenzbasierte Empfehlung der NVL und der anderen oben zitierten Leitlinien sollen Menschen mit klinisch relevanter kardiovaskulärer- oder kardiorenaler Vorerkrankung zusätzlich zur Metformintherapie (bei Kontraindikationen oder Unverträglichkeit von Metformin auch ohne Metformin als Monotherapie) entweder einen SGLT-2-inhibitor (SGLT-2i) oder einen GLP-1-Rezeptoragonisten (GLP-1RA) erhalten, die beide in mehreren RCT einen entsprechenden Vorteile für kardiovaskuläre Endpunkte gezeigt hatten (1-5,28-35).
Die ESC empfielt für dieses Patientenkollektiv vorrangig einen SGLT-2i und/oder einen GLP-1RA als Erstlinientherapie (4). Bei Vorliegen einer Herzinsuffizienz oder einer chronischen

Nierenerkrankung (CKD) soll eher ein SGLT-2i eingesetzt werden, bei einer atherosklerotischen makrovaskulären Erkrankung eher ein GLP-1RA (2-4).
Die DEGAM empfiehlt den Einsatz von Empagliflozin bzw. nachrangig Liraglutid erst dann, wenn das individuelle HbA1c-Ziel nicht erreicht werden konnte – und nicht sofort mit Diagnose eines Diabetes bzw. eines akuten Koronarsyndroms – in den genannten Studien waren die Teilnehmenden bereits über Jahre antihyperglykämisch vorbehandelt worden – und in keiner der Studien zu SGLT-2-Hemmern bzw. GLP-1-Analoga lag das Baseline-HbA1c unter 7,0%.

Durch diese Empfehlung in der NVL tritt der frühere Stellenwert der Insulintherapie in vorangegangenen Leitlinien und Empfehlungen bei T2D mehr in den Hintergrund, da die oben beschriebene Risikogruppe als Zweitlinien-therapie einen GLP-1RA oder einen SGLT-2i erhalten sollte. Die Indikationen zu einer Insulintherapie und deren Platzierung im Therapiealgorithmus sind in der NVL in Kap. 2.5.6 dargelegt (1). Zusammengefasst soll die Indikation zu einer Insulintherapie bei defizienter endogener Insulinsekretion in den folgenden Situationen geprüft werden: 1. Bei Nichterreichen der Therapieziele bei schon bestehender sonst ausgeschöpfter Therapie, 2. bei Stoffwechselentgleisungen (auch bei solchen bei Erstdiagnose und unklarer Diabetesklassifikation) oder in Akutsituationen bei anderen schweren Erkrankungen, 3. periinterventionell sowie 4. bei Therapie mit diabetogenen Medikamenten oder bei stark eingeschränkter Nierenfunktion. Erstmals sind in der NVL im Kapitel 2.5.6. zur Insulintherapie auch Rahmenbedingungen für die Deeskalation einer Insulintherapie genannt (1). Hier ist neben eventuell nicht mehr gegebenen Indikationen das Auftreten von Hypoglykämien ein wichtiger Grund zur Deeskalation einer Insulintherapie, insbesondere der intensivierten Insulintherapie (1).
Die zunächst empfohlene Form der Insulintherapie in der NVL und auch in den anderen Leitlinien ist eine Basalinsulintherapie (BOT, s.a. Abb. 7 in der NVL) (1), die gegenüber anderen Therapieformen einfacherer und sicherer ist, vgl. Abschnitt "Formen der Insulintherapie" S. 57 ff und Tabelle 11 S. 58 der NVL (1). Langwirksame Insulinanaloga sind hierbei gegenüber NPH-Insulin aus Sicht der DDG und der DGE deutlich von Vorteil, da sie individueller eingesetzt werden können und weniger Hypoglykämien verursachen, während die DEGAM auf den Vorteil des tags nicht wirksamen Einsatzes von NPH Insulin als Bedtime-Insulin hinweist, s. Abschnitt "Langwirksame Insuline" S. 59 der NVL (1).
Erst wenn mit einer Kombination aus Metformin+Glibenclamid+Empagliflozin, ggf. alternativ GLP-1RA das individuelle HbA1c-Ziel nicht erreicht werden kann, empfiehlt die DEGAM den Einsatz von Humaninsulin – vorzugsweise zur Nacht. Eine intensivierte Insulintherapie geht mit dem höchsten Hypoglykämie-Risiko einher (36).
Glibenclamid soll beim Einsatz von Insulin wegen des ähnlichen Wirkprinzips beendet werden, die Kombination mit Metformin dagegen hilft Insulin einzusparen und damit eine Gewichtszunahme zu verhindern (37).
Insulin-Analoga haben nach Einschätzung der DEGAM nahezu keinen Stellenwert in der Behandlung des Typ-2-Diabetes – ein Einsatz erscheint allenfalls überlegenswert, wenn die Betroffenen den Insulin-Pen nicht zu schwenken in der Lage sind. Eine Umstellung von Glargin oder anderen lang wirksamen Analoga auf NPH-Insulin ist problemlos und ohne Erhöhung des Hypoglykämie-Risikos möglich (38,39).
Auch die Tatsache, dass dort, wo in Deutschland im ambulanten Bereich die meisten Insulinanaloga eingesetzt werden, die meisten Hypoglykämien auftreten, unterstützt die Empfehlung der DEGAM, Analoga nur noch in besonderen Situationen zu nutzen (36).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Zunächst ist zu entscheiden, ob die Insulintherapie als Monotherapie oder als Kombinationstherapie mit oralen Antidiabetika und/oder s.c. zu verabreichenden GLP-1-RA durchgeführt werden soll. Die Kombinationstherapie hat gegenüber der Monotherapie den Vorteil, dass das Stoffwechselziel häufig zunächst mit einer einmal täglichen Basalinsulindosis bzw. einem relativ einfachen Insulinschema erreicht wird. Insbesondere bei Patienten, die initial eine Kombinationstherapie aus Metformin und einem SGLT2-Inhibitor oder einem GLP-1-RA erhalten wird gemäß NVL empfohlen, diese Therapie in Kombination mit Insulin fortzusetzen, solange sie gut vertragen wird (NVL, S. 55, ff, (1)). Verschiedene Formen der Insulintherapie stehen zur Verfügung (vgl. Tab. 11, S. 57 der NVL Diabetes (1)): Mischinsuline als fixe Wirkstoffkombination aus einem Basalinsulin und einem schnellwirkenden Insulin können im Rahmen einer sogenannten "Konventionellen Insulintherapie (CT)" eingesetzt werden. Die Therapie ist mit Metformin und prinzipiell auch mit anderen oralen Antidiabetika (OAD) ohne intrinsisches Hypoglykämierisiko kombinierbar. Die Kombination mit Metformin hilft auch bei Mischinsulinen, Insulin einzusparen. Eine Kombination mit Sulfonylharnstoffen ist wegen deren Wirkmechanismus nicht sinnvoll (1). Bei der CT wird ein Mischinsulin zunächst einmal, ist dies nicht ausreichend zweimal täglich subkutan gegeben. Die Insulingabe erfolgt bei einmaliger Gabe morgens vor dem Frühstück, bei zweimaliger Gabe vor dem Frühstück und vor dem Abendessen. Dies ist eine seit Jahrzehnten gebräuchliche Therapie, die jedoch in den letzten Jahren zunehmend von einer reinen Basalinsulintherapie in Kombination mit oralen Antidiabetika aus Praktikabilitätsgründen, aber auch aufgrund eines geringeren Hypoglykämiersikos abgelöst wird. Entscheidend für das Erreichen der Therapieziele und die Vermeidung von Hypoglykämien unter einer CT ist eine verbindliche und feste Abstimmung der Insulindosen als auch der Abfolge und Größe der Mahlzeiten (feste Kohlehydratportionen) mit festem Kostplan und auch einer festen Tagesablaufstruktur. Ggf kann aber die Dosisfindung bei einer CT auch durch Blutzuckerselbstmessungen durch die Patienten variabel angepasst werden. In einer direkten Vergleichsstudie, die die üblichen Formen der Insulintherapie bei T2D miteinander verglichen hat (Basalinsulin plus OAD, CT, supplementäre Insulintherapie [SIT] mit mahlzeitengebundenen Gaben von kurzwirksamem Insulin, intensivierter Insulintherapie [ICT] mit getrennter Gabe von Basalinsulin und flexibler Gabe von schnellwirkendem Insulin zu den Mahlzeiten und zur Korrektur) war die CT einfacher für die Patientinnen und Patienten oder die Pflegenden durchführbar, ging jedoch mit mehr Hypoglykämien als bei einer Basalinsulintherapie einher. Die Hypoglykämierate war jedoch niedriger als bei den Insulintherapieformen SIT und ICT (22). Der Schulungsaufwand für eine CT ist höher als für eine Basalinsulintherapie, jedoch weniger hoch als für eine SIT oder ICT. In der NVL ist die CT als Therapieeskalation einer Basalinsulintherapie in Abb. 7 in der Abbildung des Therapiealgorithmus platziert (1). Insbesondere in der basal unterstützten oralen Therapie (BOT) werden verschiedene langwirksame Insuline eingesetzt. NPH-Insulin und langwirksame Insulinanaloga zeigen Unterschiede in Anflutung und Wirkungsmaximum, die in der individuellen patientenzentrierten Therapieoptimierung genutzt werden können. Ein systematischer Review zum Vergleich der Insulinanaloga Glargin 100 E/ml bzw. Detemir mit NPH-Insulin bei Menschen mit Typ-2-Diabetes fand zwar keine Unterschiede in der metabolischen Kontrolle,

aber eine signifikant geringere Rate an (v.a. nächtlichen) Hypoglykämien bei Therapie mit Insulinanaloga. Nachteil könnte die Notwendigkeit einer zusätzlichen Nahrungsaufnahme bei Tag sein. Weitere Vorteile ist die einfachere Anwendbarkeit (z.T. unabhängig von der Tageszeit) und die sicherere Anwendung durch Vermeidung von Mischfehlern. Allerdings wurden die neueren langwirksamen Analoginsuline bzw. Formulierungen (z.B. Degludec und Glargin 300 E/ml) in den neueren Studien nicht mehr gegen NPH-Insulin, sondern meist gegen Insulin Glargin 100 E/ml getestet (40-42)(Weitere Einzelheiten in der NVL Diabetes S. 59 ff. (1)). Bei der Gabe von dem konzentrierten Insulin Glargin 300 E/ml ist auf eine ggf. 10 bis zu 18% geringere Wirkung bei Austausch des Präparates von Insulin Glargin 100E/ml nach initialer Titrierung zu achten (43). Für die Insulin-Analoga Insulin Glargin und Insulin Degludec konnte in 2 großen randomisierten kontrollierten Outcome-Studien kardiovaskuläre Sicherheit bewiesen werden (44,45). Diese Evidenz liegt z.B. für kurzwirksame Insuline nicht vor. Daher empfiehlt die aktuelle ESC-Leitlinie (4) im Falle einer nötigen zusätzlichen Blutzuckersenkung Insulin Glargin und Insulin Degludec anderen Insulinen (wie z.B. kurzwirksamen Insulinen) vorzuziehen.
Nach Einschätzung der DEGAM dagegen haben Insulin-Analoga in der Behandlung des Typ-2-Diabetes keinen relevanten klinischen Vorteil.

Die folgende Tabelle gibt eine Zusammenstellung langwirksamer Insuline und Insulinanaloge sowie einiger Festkombinationen (modifiziert nach und entnommen aus der S3-Leitlinie Typ-1-Diabetes (24); dort auch Literatur).

Wirkung/ Insulin	Eintritt	Maximum	Dauer	Übliche Anwendung
Humaninsuline				
NPH-Insulin	1-2 h	6-7 h	14 h	zweimal täglich
Mischinsulin NPH (70)/ Normal (30)	30-60 min	3-3,5 h	14 h	vor Frühstück und Abendessen
Insulin-Analoga				
Degludec	1-2 h	8-14 h Geringes Maximum	> 42 h	Einmal täglich
Detemir	1 h	7-9 h	19-26 h	Ein- oder zweimal täglich
Glargin U100	1 h	8-12 h	20-27 h	Ein- oder zweimal täglich
Glargin U300	1-6 h	12-16 h Geringes Maximum	30-32 h	Einmal täglich
Mischinsulin protamin. Aspart (70)/ Aspart (30); protamin. Lispro (70), Lispro (30)	20-25 min	2-3 h	10-14 h	0-15 min vor Frühstück und Abendessen
Kombinationsinsulin Degludec (70)/ Aspart (30)	20-25 min	2-3 h	> 30 h	0-15 min vor einer oder vor zwei Hauptmahlzeiten

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