Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-030-z Insulin glargin/Lixisenatid

Stand: April 2020

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

Insulin glargin/Lixisenatid
zur Behandlung des Diabetes mellitus Typ 2

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Sulfonylharnstoffe Biguanide DPP-4-Hemmer (Gliptine) Glinide Inkretinmimetika (Glutide) Alpha-Glukosidasehemmer SGLT-2-Inhibitoren (Gliflozine) 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 23.03.2012 und 21.02.2013 (erneute Nutzenbewertung) sowie Linagliptin (neues AWG) vom 16.05.2013 o Dapagliflozin vom 06.06.2013, Dapagliflozin/Metformin vom 07.08.2014 und Dapagliflozin sowie Dapagliflozin/Metformin (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) vom 21.06.2018 und vom 19.12.2019 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 04.12.2014 und vom 20.08.2015 sowie Insulin degludec (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) vom 16.05.2019 o Albiglutid vom 19.03.2015 o Dulaglutid vom 16. 07 2015

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

Insulin glargin/Lixisenatid
zur Behandlung des Diabetes mellitus Typ 2

Kriterien gemäß 5. Kapitel § 6 VerfO	
	o Insulin degludec/Liraglutid vom 15.10.2015 sowie Insulin degludec/Liraglutid (neues AWG) vom 04.02.2016 o Empagliflozin (erneute Nutzenbewertung) sowie Empagliflozin/Metformin vom 01.09.2016 o Sitagliptin, Sitagliptin/Metformin vom 15.12.2016 (erneute Nutzenbewertung nach Fristablauf) sowie Sitagliptin vom 22.3.2019 (erneute Nutzenbewertung nach Fristablauf) o Saxagliptin (neues AWG) vom 01.10.2013; Saxagliptin (neues AWG) vom 20.02.2014 sowie Saxagliptin (erneute Bewertung nach Fristablauf) o Saxagliptin/Metformin (neues AWG) vom 01.10.2013; Saxagliptin/Metformin vom 15.12.2016 (erneute Nutzenbewertung nach Fristablauf) sowie Saxagliptin/Metformin (neues AWG) vom 01.02.2018 o Insulin glargin/Lixisenatid vom 16.08.2018 o Ertugliflozin/Sitagliptin vom 01.11.2018 o Semaglutid vom 02.05.2019 – Bestehender Verordnungsausschluss (AM-RL, Anlage III): Glitazone – Bestehende Verordnungseinschränkungen (AM-RL, Anlage III): schnell wirkende/lang wirkende Insulinanaloga, Glinide, orale Antidiabetika, Harn- und Blutzuckerteststreifen – Richtlinie Methoden vertragsärztliche Versorgung (MVV-RL): Kontinuierliche interstitielle Glukosemessung mit Real-Time-Messgeräten (rtCGM) zur Therapiesteuerung bei insulinpflichtigem Diabetes mellitus – IQWiG- Rapid-Report zur LEADER Studie (Studie zu Liraglutid, Auftrag A17-09, Stand 23.08.2017)
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 glargin/Lixisenatid A10AE54 Suliqua®	Suliqua wird als Ergänzung zu Diät und Bewegung zusätzlich zu Metformin mit oder ohne 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) (EPAR Suliqua, Stand 03/2020)
Biguanide	
Metformin A10BA02 z.B. Metformin Heumann®	Therapie des Diabetes mellitus Typ II; insbesondere bei übergewichtigen Patienten, bei denen allein durch Diät und körperliche Betätigung keine ausreichende Einstellung des Blutzuckerspiegels erreicht wurde. - Bei Erwachsenen kann Metformin Heumann in Form einer Monotherapie oder in Kombination mit anderen oralen Antidiabetika bzw. Insulin angewendet werden. - Bei Kindern ab 10 Jahren und bei Jugendlichen kann Metformin Heumann in Form einer Monotherapie oder in Kombination mit Insulin angewendet werden. - Bei übergewichtigen erwachsenen Patienten mit Diabetes mellitus Typ II konnte nach Versagen diätetischer Maßnahmen eine Senkung der Häufigkeit von diabetesbedingten Komplikationen unter Behandlung mit Metforminhydrochlorid als Therapie der ersten Wahl nachgewiesen werden. (siehe Abschnitt 5.1) (FI Metformin, Stand 02/2017)
Sulfonylharnstoffe	
Glibenclamid A10BB01 z.B.Glibenclamid AbZ®	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, Stand 07/2018)
Glimepirid	Amaryl ist angezeigt zur Behandlung des Diabetes mellitus Typ 2, wenn eine Diät, körperliche Aktivität und Gewichtsreduktion allein

II. Zugelassene Arzneimittel im Anwendungsgebiet	
A10BB12 z.B. Amaryl®	nicht ausreichen. (FI Amaryl, Stand 04/2017)
Gliquidon A10BB08 z.B. Glurenorm®	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 Blutglucosespiegels geführt haben. Hinweise zu den Anwendungsgebieten - Das Arzneimittel kann als Monotherapie oder in Kombination mit Metformin verwendet werden. - In begründeten Fällen kann die zusätzliche Gabe von Glitazonen (Rosiglitazon, Pioglitazon) bei Patienten mit Metformin-Unverträglichkeit angezeigt sein. - Gliquidon kann auch mit nicht-insulinfreisetzenden oralen Antidiabetika (Guarmehl oder Acarbose) kombiniert werden. - Bei beginnendem Sekundärversagen kann eine Kombinationsbehandlung mit Insulin versucht werden. Kommt die körpereigene Insulinausschüttung vollständig zum Versiegen, ist eine Insulinmonotherapie angezeigt. (Lauer Taxe Glurenorm, Stand 10/2018)
Gliclazid A10BB09 z.B. DIAMICRON®	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 03/2016)
Alpha-Glucosidase-Inhibitoren	
Acarbose A10BF01 z.B. Acarbose – 1 A Pharma®	Acarbose - 1 A Pharma ist angezeigt zur Behandlung von Patienten mit nicht insulinabhängigem Diabetes mellitus (NIDDM, Diabetes mellitus Typ 2), wenn durch Diät und körperliche Betätigung keine ausreichende Blutzuckereinstellung erreicht wurde. Acarbose - 1 A Pharma kann in Kombination mit Metformin, einem Sulfonylharnstoff oder Insulin angewendet werden. (FI Acarbose, Stand 02/2014)
Miglitol A10BF02 z.B. Diastabol®1	Diastabol wird für die Behandlung von Patienten mit nicht insulinabhängigem Diabetes mellitus Typ 2 (NIDDM) in Verbindung mit Diät oder Diät und Sulfonylharnstoffen empfohlen, wenn durch Diät allein oder durch Diät und Sulfonylharnstoff-Therapie der Blutzucker nicht ausreichend eingestellt werden kann. (Lauer Taxe Diastabol, Stand 09/2017)
GLP-(Glucagon-like Peptide)-1-Rezeptor-Agonisten (Inkretinmimetika)	
Albiglutid A10BX13 Eperzan®1	Eperzan ist bei erwachsenen Patienten mit Typ 2 Diabetes zur Verbesserung der Blutzuckereinstellung indiziert als: <u>Monotherapie</u> Wenn Diät und Bewegung allein zur Blutzuckereinstellung nicht ausreichen bei Patienten, für die die Anwendung von Metformin

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	aufgrund von Kontraindikationen oder Unverträglichkeit als ungeeignet angesehen wird. Kombinationstherapie In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken (für verfügbare Daten zu den verschiedenen Kombinationen siehe Abschnitt 4.4, 5.1) (FI Eperzan, Stand 09/2017)
Exenatide A10BX04 z.B. 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 02/2019)
Liraglutid A10BX07 Victoza®	Victoza 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 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 untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. (FI Victoza, Stand 04/2019)
Insulin degludec/ Liraglutid[1] A10AE56 Xultophy®	Xultophy wird zur Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität in Ergänzung zu anderen oralen antidiabetisch wirksamen Arzneimitteln angewendet, um die glykämische Kontrolle zu verbessern. Für Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle sowie untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. (EPAR Product Information Xultophy, Stand 07/2018)

Lixisenatid[1] A10BX10 Lyxumia®	Lyxumia wird angewendet bei Erwachsenen zur Behandlung des Typ-2-Diabetes mellitus in Kombination mit oralen blutzuckersenkenden Arzneimitteln und/oder Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken (verfügbare Daten zu den verschiedenen Kombinationen, siehe Abschnitt 4.4 und 5.1). Warnhinweise: -Lixisenatid sollte bei Patienten mit Typ-1-Diabetes mellitus nicht angewendet werden, da keine therapeutischen Erfahrungen vorliegen. Lixisenatid darf nicht zur Behandlung der diabetischen Ketoazidose angewendet werden. (EPAR Product Information Lyxumia, Stand 10/2017)
Dulaglutid A10BX14 Trulicity®	Trulicity ist angezeigt zur Behandlung von Erwachsenen mit Typ 2 Diabetes mellitus, um eine verbesserte Blutzuckerkontrolle zu erreichen als: – Monotherapie: Sofern bei Patienten, für die die Einnahme von Metformin wegen Unverträglichkeitoder Kontraindikationen nicht angezeigt ist, durch Diät und Bewegung keine angemessene Blutzuckerkontrolle erreicht werden kann. – Kombinationstherapie: In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn durch diese zusammen mit Diät und Bewegung keine angemessene Blutzuckerkontrolle erreicht werden kann (siehe Abschnitt 5.1 bzgl. Daten zu verschiedenen Kombinationen). (FI Trulicity: Stand 02/2019)
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. (EPAR Product Information Ozempic, Stand 02/2019)
Gliptine (DPP (Dipeptidylpeptidase)-4 Hemmer)	
Linagliptin[1] A10BH05 Trajenta®	Trajenta wird angewendet bei Erwachsenen mit Typ-2-Diabetes mellitus als Ergänzung zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle als: Monotherapie - wenn Metformin wegen Unverträglichkeit ungeeignet oder aufgrund einer Nierenfunktionsstörung kontraindiziert ist. Kombinationstherapie - in Kombination mit anderen Arzneimitteln zur Behandlung von Diabetes einschließlich Insulin, wenn diese zur Blutzuckerkontrolle nicht ausreichen (siehe Abschnitte 4.4, 4.5 und 5.1 zu verfügbaren Daten zu verschiedenen Kombinationen). (EPAR Product Information Trajenta, Stand 07/2018)

[1] Marktrücknahme bei bestehender Zulassung

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 08/2018)
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 08/2018)
Sitagliptin A10BH01 z.B. Januvia®	Bei erwachsenen Patienten mit Typ-2-Diabetes mellitus ist Januvia indiziert zur Verbesserung der Blutzuckerkontrolle: <u>Als Monotherapie:</u> - 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. <u>Als orale Zweifachtherapie in Kombination mit:</u> - 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 08/2018)
Sitagliptin/Metformin A10BD07	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

z.B. Janumet®	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 06/2018)
Ertugliflozin/Sitagliptin A10BD24 Steglujan®	Bei Erwachsenen ab 18 Jahren mit Typ-2 Diabetes mellitus zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle: - bei Patienten, deren Blutzucker unter Metformin und/oder einem Sulfonylharnstoff und einem der in dem vorliegenden Arzneimittel enthaltenen Einzelwirkstoffe nicht ausreichend 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 04/2019)
Vildagliptin A10BH02 z.B. Jalra®	Vildagliptin ist angezeigt zur Behandlung von Diabetes mellitus Typ 2 bei Erwachsenen: <u>Monotherapie</u> - bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist. <u>In einer oralen Zweifach-Kombinationstherapie mit:</u> - Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist, - einem Sulfonylharnstoff bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen eines Sulfonylharnstoffs unzureichend eingestellt ist und bei denen Metformin wegen Kontraindikationen oder Unverträglichkeit ungeeignet ist, - einem Thiazolidindion bei Patienten mit ungenügender Blutzuckereinstellung, für die die Anwendung eines Thiazolidindions geeignet ist. <u>In orale Dreifach-Kombinationstherapie mit:</u> - einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung zusätzlich zu einer Zweifachtherapie mit diesen Arzneimitteln zu keiner adäquaten glykämischen Kontrolle führen. Vildagliptin ist auch für die Anwendung in Kombination mit Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung zusätzlich zu einer stabilen Insulindosis zu keiner adäquaten glykämischen Kontrolle führen.

	(FI Jalra: Stand 01/2019)
Vildagliptin/Metformin A10BD08 z.B. Eucreas®	Vildagliptin/Metformin ist für die Behandlung des Typ-2-Diabetes-mellitus indiziert: Vildagliptin/Metformin ist für die Behandlung von Erwachsenen indiziert, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine unzureichend eingestellt ist oder die bereits mit einer Kombination aus Vildagliptin und Metformin in separaten Tabletten behandelt werden. Vildagliptin/Metformin ist in Kombination mit einem Sulfonylharnstoff (d. h. Dreifachkombinationstherapie) zusätzlich zu Diät und Bewegung indiziert bei erwachsenen Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können. Vildagliptin/Metformin ist als Dreifachkombinationstherapie mit Insulin zusätzlich zu Diät und Bewegung indiziert, um die glykämische Kontrolle bei erwachsenen Patienten zu verbessern, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen. (FI Eucreas: Stand 04/2018)
Selektive Natrium-Glucose-Cotransport-Inhibitoren (SGLT-2-Inhibitoren)	
Canagliflozin A10BX11 Invokana®[1]	Invokana ist für die 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 als ungeeignet erachtet wird. - zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes mellitus Informationen zu Studienergebnissen in Bezug auf die Kombination von Therapien, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse und die untersuchten Populationen sind den Abschnitten 4.4, 4.5 und 5.1 zu entnehmen. (EPAR Product Information Invokana, Stand 10/2018)
Canagliflozin/Metformin A10BD16 Vokanamet®[1]	Vokanamet ist bei Erwachsenen mit Typ-2-Diabetes-mellitus als Ergänzung zu Diät und Bewegung angezeigt: - bei Patienten, bei denen Metformin in den maximal verträglichen Dosen allein den Blutzucker unzureichend kontrolliert, - in Kombination mit anderen Arzneimitteln zur Behandlung von Diabetes mellitus bei Patienten, die mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert werden, - bei Patienten, die bereits Canagliflozin und Metformin als separate Tabletten erhalten. Informationen zu Studienergebnissen in Bezug auf die Kombination von Therapien, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse und die untersuchten Populationen sind den Abschnitten 4.4, 4.5 und 5.1 zu entnehmen. (EPAR Product Information Vokanamet, Stand 10/2018)
Dapagliflozin A10BX09 z.B. Forxiga®	Forxiga ist bei erwachsenen Patienten indiziert zur Behandlung von unzureichend kontrolliertem - Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle in Ergänzung zu einer Diät und Bewegung: o <u>als Monotherapie</u> wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird o <u>Add-on-Kombinationstherapie</u> zusätzlich zu anderen Arzneimitteln zur Behandlung des Typ-2-Diabetes.

	[…] Zu Studienergebnissen im Hinblick auf die untersuchten Populationen, die Wirkung auf die Blutzuckerkontrolle und Kombinationen mit anderen Arzneimitteln siehe Abschnitte 4.4, 4.5 und 5.1 (FI Forxiga, Stand 03/2019)
Dapagliflozin/Metformin A10BD15 z.B. Xigduo®	Xigduo ist bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus indiziert, als Ergänzung zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle: - bei Patienten, bei denen der Blutzucker mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert wird - in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin bei Patienten, bei denen der Blutzucker mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert wird - bei Patienten, die bereits mit der Kombination aus Dapagliflozin und Metformin als separate Tabletten behandelt werden. (FI Xigdua, Stand 02/2019)
Empagliflozin A10BX12 Jardiance®	Jardiance wird zur Behandlung von Erwachsenen mit nicht ausreichend behandeltem Typ-2-Diabetes mellitus als Ergänzung zu Diät und Bewegung angewendet - als Monotherapie, wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird - zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes Zu Studienergebnissen im Hinblick auf Kombinationen, die Wirkung auf Blutzuckerkontrolle und kardiovaskuläre Ereignisse sowie die untersuchten Populationen siehe Abschnitte 4.4, 4.5 und 5.1. (FI Jardiance, Stand 02/2019)
Empagliflozin/Metformin[1] A10BD20 Synjardy®	Synjardy ist zur Behandlung von Erwachsenen mit Typ-2-Diabetes mellitus zusätzlich zu Diät und Bewegung angezeigt: - bei Patienten, die unter ihrer maximal verträglichen Dosis von Metformin allein nicht ausreichend eingestellt sind - in Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes, bei Patienten, die mit Metformin und diesen Arzneimitteln nicht ausreichend eingestellt sind - bei Patienten, die bereits mit der Kombination aus Empagliflozin und Metformin in Form getrennter Tabletten behandelt werden. Zu Studienergebnissen im Hinblick auf Kombinationen, die Wirkung auf Blutzuckerkontrolle und kardiovaskuläre Ereignisse sowie die untersuchten Populationen siehe Abschnitte 4.4, 4.5 und 5.1. (EPAR Product Information Synjardy, Stand 06/2018)
Glinide	*Verordnungseinschränkung Anlage III – AM-RL*
Nateglinid A10BX03 Starlix®	Kombinationstherapie mit Metformin bei Patienten mit Typ-2-Diabetes, die nicht ausreichend mit einer maximal tolerierbaren Metformin-Dosis eingestellt werden können. (FI Starlix, Stand 05/2018)
Repaglinid A10BX02 z.B. Repaglinid AL®	Repaglinid ist indiziert bei Patienten mit Typ 2 Diabetes (NIDDM, nicht insulinabhängiger Diabetes mellitus), wenn der Blutzuckerspiegel durch Diät, Gewichtsreduktion und körperliche Aktivität alleine nicht mehr ausreichend reguliert werden kann. Repaglinid kann bei Typ 2 Diabetes-Patienten 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 02/2016)
Glitazone	*Verordnungsausschluss Anlage III – AM-RL*
Humaninsuline	
Insulin human A10A C01 z.B. Berlinsulin H 30/70	Zur Behandlung von Patienten mit Diabetes mellitus, die Insulin für die Aufrechterhaltung einer normalen Glukosehomöostase benötigen. (FI Berlininsulin, Stand 03/2019)
Insulinanaloga	*Verordnungseinschränkung Anlage III – AM-RL*
Insuline schnell wirkend: Insulin lispro, Insulin aspart, Insulin glulisin A10AB01-06 z.B. NovoRapid 100 I.E./ml	NovoRapid wird angewendet zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr. (FI Novorapid, Stand 04/2018)
Insuline lang wirkend: Insulin detemir, Insulin glargin[1], Insulin degludec A10AE01-06 z.B. Lantus 100 I.E./ml z.B. Tresiba	Insulin glargin: Zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern im Alter von 2 Jahren und älter. .Insulin glargin ist nicht das Insulin der Wahl für die Behandlung der diabetischen Ketoazidose. In diesen Fällen wird die intravenöse Gabe eines Normalinsulins empfohlen. (EPAR Product Information Lantus, Stand 07/2018) Insulin degludec: Behandlung des Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr. (EPAR Product Information Tresiba, Stand 08/2018)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-030-z (Insulin glargin/Lixisenatid)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	5. November 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
A1C	glycated hemoglobin
AE	adverse event
AOD	oral antidiabetic drug
ASCVD	Atherosclerotic cardiovascular disease
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BB	Basal-Bolus
BMI	Body mass index
BP	Basa-Plus
CCO	Cancer Care Ontario
CI	confidence interval,
CKD	Chronic Kidney Disease
CrI	credible interval
CV	Cardiovascular
CVD	Cardiovascular disease
DAHTA	DAHTA-Datenbank
DBP	diastolic blood pressure
DPP-4	dipeptidyl peptidase-4
DRKS	Deutsches Register Klinischer Studien
eGFR	estimated glomerular filtration rate
EMPA	empagliflozin
ESMO	European Society for Medical Oncology
ESRD	End-Stage-Renal-Disease
FDC	fixed-dose combination
FPG	fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GLP-1	glucagon-like peptide 1

GTI	genital tract infection
GoR	Grade of Recommendations
HbA1c	Glycosylated hemoglobin A1c
HF	Heart Failure
HRQoL	health-related quality of life
HR	Hazard Ratio
ICTRP	International Clinical Trials Registry Platform
INS	Insulin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
KI	Konfidenzintervall
LoE	Level of Evidence
MACE	Major Adverse Cardiovascular Event
MET	metformin
MI	Myocardial infarction
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NMA	Netzwerk Metaanalyse
OAD	oral antidiabetic drug
OR	Odds Ratio
PPG	Post prandial plasma glucose
RCT	randomized controlled trial
RD	Risk Difference
RR	Relatives Risiko
SAE	serious adverse event
SBP	Systolic blood pressure

SGLT-2	sodium–glucose cotransporter-2
SIGN	Scottish Intercollegiate Guidelines Network
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TG	Triglycerides
TZD	Thiazolidinedione
UACR	Urinary albumin-to-creatinine-ratio
UTI	urinary tract infection
TRIP	Turn Research into Practice Database
WDAE	withdrawal due to adverse event
WHO	World Health Organization

1 Indikation

Anwendungsgebiet

Behandlung von Erwachsenen mit Typ 2 Diabetes mellitus

Indikation für die Synopse:

Diabetes mellitus Typ 2

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Diabetes Mellitus Typ 2 durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 13.02.2018 durchgeführt, die Folgerecherchen am 24.10.2018 und 07.10.2019. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherchen übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 2375 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 106 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [27].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Insulin degludec (Neubewertung aufgrund neuer Wissenschaftlicher Erkenntnisse).

Anwendungsgebiet

Behandlung des Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr.

„In der Mono- oder Kombinationstherapie

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin oder

- Humaninsulin + Empagliflozin[1] oder
- Humaninsulin + Liraglutid[1] oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit Insulin (mit oder ohne einem anderen blutzuckersenkenden Arzneimittel) den Blutzucker nicht ausreichend kontrollieren

Zweckmäßige Vergleichstherapie

Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Empagliflozin1 oder Liraglutid1)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, eines insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al.

G-BA, 2019 [26].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Insulin degludec (Änderung des Beschlusses vom 16. Mai 2019 / Aufhebung des Beschlusses vom 4. Dezember 2014 / Therapiekosten) vom 4. Juli 2019.

In Anlage XII werden die Angaben zu dem Wirkstoff „Insulin degludec“ in derFassung des Beschlusses vom 16. Oktober 2014 (BAnz AT 11.11.2014 B1) wie folgt geändert:

1.Die Angaben zu dem Wirkstoff „Insulin degludec“ in der Fassung des Beschlusses vom16.Mai 2019 werden wie folgt geändert:

Unter der Überschrift „Anwendungsgebiet (laut Fachinformation November 2018)“ wird am Ende des Satzes „Die nachfolgenden Angaben beziehen sich ausschließlich auf das Anwendungsgebiet zur Behandlung von Erwachsenen mit Diabetes mellitus.“ der Punkt aufgehoben und folgende Wörter angefügt: „einschließlich der Kombination mit GLP-1-RA bei Typ 2 Diabetes mellitus-Patienten.“

2.Die Angaben zu dem Wirkstoff „Insulin degludec“ in der Fassung des Beschlusses vom 4.Dezember 2014 (neues Anwendungsgebiet) (BAnz AT 26.01.2015 B2) werden aufgehoben.

G-BA, 2019 [51].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Mai 2019 / 4. Juli 2019 – Semaglutid.

Anwendungsgebiet

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.

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren, und für die die Anwendung von Metformin aufgrund einer Unverträglichkeit nicht geeignet ist

a1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

a2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren2

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit einem blutzuckersenkenden Arzneimittel (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

b1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder

- Metformin + Empagliflozin oder
- Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder kontraindiziert ist

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder

- Metformin + Empagliflozin oder
- Metformin + Liraglutid[3] oder
- Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder kontraindiziert ist

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen geringen Zusatznutzen.

Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

c1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin oder

nur Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam ist

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

Zweckmäßige Vergleichstherapie

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin3 oder
- Humaninsulin + Liraglutid3 oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen geringen Zusatznutzen.

d) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit Insulin (mit oder ohne einem anderen blutzuckersenkenden Arzneimittel) den Blutzucker nicht ausreichend kontrollieren

d1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Zweckmäßige Vergleichstherapie:

Die Optimierung des Humaninsulinregimes (ggf. + Metformin)

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

Zweckmäßige Vergleichstherapie:

• Die Optimierung des Humaninsulinregimes (ggf. + Metformin *oder* Empagliflozin[3] *oder* Liraglutid[3])

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen geringen Zusatznutzen.

1 manifeste kardiovaskuläre Erkrankung ist im vorliegenden Fall anhand der SUSTAIN 6-Studie (siehe Studienprotokoll, Marso et. al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016; 375:1834-1844. DOI: 10.1056/NEJMoa1607141) definiert und hier näherungsweise zusammengefasst als ≥ 50 Jahre mit mindestens einer kardiovaskulären Erkrankung (vorangegangener Herzinfarkt; Schlaganfall oder transitorische ischämische Attacke, Revaskularisation, > 50% Stenose, vorangegangene symptomatische koronare Herzerkrankung oder instabile Angina, asymptomatische kardiale Ischämie, chronisches Herzversagen (NYHA-Klasse II-III) oder chronisches Nierenversagen) oder ≥ 60 Jahre mit mindestens einem Risikofaktor für kardiovaskuläre Erkrankungen (Mikroalbuminurie oder Proteinurie, Bluthochdruck und linksventrikuläre Hypertrophie, linksventrikuläre systolische oder diastolische Dysfunktion oder Knöchel-Arm-Index < 0,9).
2 Insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker
3 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten

G-BA, 2019 [42].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 7. August 2014 / 21. Juni 2018 / 4. Juli 2019 - Dapagliflozin/Metformin

Anwendungsgebiet

Xigduo® ist bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus indiziert, als Ergänzung zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle:

- bei Patienten, bei denen der Blutzucker mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert wird

- in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin bei Patienten, bei denen der Blutzucker mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert wird

- bei Patienten, die bereits mit der Kombination aus Dapagliflozin und Metformin als separate Tabletten behandelt werden.

a) Zweifachkombination Dapagliflozin mit Metformin bei Patienten, bei denen der Blutzucker mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert wird:

Zweckmäßige Vergleichstherapie

Zweckmäßige Vergleichstherapie:

• Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder

• Metformin + Empagliflozin oder

• Metformin + Liraglutid1

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln außer Insulin, wenn der Blutzucker mit Metformin und diesen Arzneimitteln zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Kombinationstherapie mit Insulin, wenn der Blutzucker mit Metformin und Insulin zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Liraglutid in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker und nur für Patienten mit manifester kardiovaskulärer Erkrankung (zur Operationalisierung siehe Studienprotokoll: Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [31].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL): Anlage XII - (Frühe) Nutzenbewertung nach § 35a SGB V; Ertugliflozin/ Sitagliptin; Geltende Fassung zum Beschluss vom 1. November 2018 / 4. Juli 2019

Anwendungsgebiet

Steglujan ist bei Erwachsenen ab 18 Jahren mit Typ-2 Diabetes mellitus zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle angezeigt:

- bei Patienten, deren Blutzucker unter Metformin und/oder einem Sulfonylharnstoff und einem der in Steglujan enthaltenen Einzelwirkstoffe nicht ausreichend gesenkt werden kann.
- bei Patienten, die bereits mit der Kombination aus Ertugliflozin und Sitagliptin in Form von einzelnen Tabletten behandelt werden[1].

Vergleichstherapie

Erwachsene Patienten mit Diabetes mellitus Typ 2, die durch die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin, hier Metformin und/oder Sulfonylharnstoff und Ertugliflozin oder Sitagliptin) nicht ausreichend kontrolliert sind:

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[2] oder
- Humaninsulin + Liraglutid oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

Es liegen keine relevanten Daten im Vergleich zur zweckmäßigen Vergleichstherapie vor.

1 Ertugliflozin als Monopräparat ist derzeit in Deutschland nicht in Verkehr.
2 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [48].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. August 2018 / 4. Juli 2019 - Insulin glargin/Lixisenatid.

Anwendungsgebiet

Suliqua wird in Kombination mit Metformin zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen zur Verbesserung der Blutzuckerkontrolle angewendet, wenn Metformin allein oder Metformin in Kombination mit einem anderen oralen blutzuckersenkenden Arzneimittel oder mit Basalinsulin den Blutzuckerspiegel nicht ausreichend reguliert

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, die durch die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (ausschließlich orale, inklusive Metformin) nicht ausreichend kontrolliert sind

Zweckmäßige Vergleichstherapie:

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[1] oder
- Humaninsulin + Liraglutid[1] oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, die durch die Behandlung mit Insulin (mit einem anderen blutzuckersenkenden Arzneimittel, hier Metformin) nicht ausreichend kontrolliert sind

Zweckmäßige Vergleichstherapie:

- Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Empagliflozin1 oder Liraglutid)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1) Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827)..

G-BA, 2019 [41].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juni 2013 / 23. Januar 2014 / 21. Juni 2018 / 4. Juli 2019 – Dapagliflozin.

Anwendungsgebiet

Forxiga® ist bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle indiziert als:

Monotherapie

- Wenn Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren bei Patienten, bei denen die Anwendung von Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird.

Add-on-Kombinationstherapie

- In Kombination mit anderen Blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn diese den Blutzucker, zusammen mit einer Diät und Bewegung, nicht ausreichend kontrollieren

a) Monotherapie bei Patienten, bei denen Diät und Bewegung den Blutzucker nicht ausreichend kontrollieren und bei denen die Anwendung von Metformin aufgrund einer Unverträglichkeit als ungeeignet angesehen wird:

Vergleichstherapie:

Sulfonylharnstoff (Glibenclamid, Glimepirid)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sulfonylharnstoff (Glibenclamid, Glimepirid): Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin, hier Metformin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert:

Vergleichstherapie:

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin oder
- Metformin + Liraglutid[1]

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1) Liraglutid in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker und nur für Patienten mit manifester kardiovaskulärer Erkrankung (zur Operationalisierung siehe Studienprotokoll: Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [29].

Anlage III Übersicht über Verordnungseinschränkungen und –ausschlüsse in der Arzneimittelversorgung durch die Arzneimittel-Richtlinie und aufgrund anderer Vorschriften (§ 34 Absatz 1 Satz 6 und Absatz 3 SGB V), Hinweise zur wirtschaftlichen Verordnungsweise von nicht verschreibungspflichtigen Arzneimitteln für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr sowie

Verordnungseinschrän-kungen und –ausschlüsse von sonstigen Produkten; letzte Änderung in Kraft getreten am 13. September 2019

33. Insulinanaloga, schnell wirkende zur Behandlung des Diabetes mellitus Typ 2.

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

Hierzu zählen:

- Insulin Aspart
- Insulin Glulisin
- Insulin Lispro

Diese Wirkstoffe sind nicht verordnungsfähig, solange sie mit Mehrkosten im Vergleich zu schnell wirkendem Humaninsulin verbunden sind. Das angestrebte Behandlungsziel ist mit Humaninsulin ebenso zweckmäßig, aber kostengünstiger zu erreichen. Für die Bestimmung der Mehrkosten sind die der zuständigen Krankenkasse tatsächlich entstehenden Kosten maßgeblich.

Dies gilt nicht für Patienten

- mit Allergie gegen den Wirkstoff Humaninsulin
- bei denen trotz Intensivierung der Therapie eine stabile adäquate Stoffwechsellage mit Humaninsulin nicht erreichbar ist, dies aber mit schnell wirkenden Insulinanaloga nachweislich gelingt
- bei denen aufgrund unverhältnismäßig hoher Humaninsulindosen eine Therapie mit schnell wirkenden Insulinanaloga im Einzelfall wirtschaftlicher ist.

33a. Insulinanaloga, lang wirkende zur Behandlung des Diabetes mellitus Typ 2.

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

Hierzu zählen:

- Insulin glargin
- Insulin detemir

Diese Wirkstoffe sind nicht verordnungsfähig, solange sie - unter Berücksichtigung der notwendigen Dosierungen zur Erreichung des therapeutischen Zieles - mit Mehrkosten im Vergleich zu intermediär wirkendem Humaninsulin verbunden sind. Das angestrebte Behandlungsziel ist mit Humaninsulin ebenso zweckmäßig, aber kostengünstiger zu erreichen. Für die Bestimmung der Mehrkosten sind die der zuständigen Krankenkasse tatsächlich entstehenden Kosten maßgeblich.

Diese Regelungen gelten nicht für

- eine Behandlung mit Insulin glargin bei Patienten, bei denen im Rahmen einer intensivierten Insulintherapie auch nach individueller Therapiezielüberprüfung und individueller Anpassung des Ausmaßes der Blutzuckersenkung in Einzelfällen ein hohes Risiko für schwere Hypoglykämien bestehen bleibt,
- Patienten mit Allergie gegen intermediär wirkende Humaninsuline.

49. Glitazone zur Behandlung des Diabetes mellitus Typ 2.

Verordnungsausschluss verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [3]

Hierzu zählen:

- Pioglitazon
- Rosiglitazon

50. Glinide zur Behandlung des Diabetes mellitus Typ 2.

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

- Nateglinid
- Repaglinid

Ausgenommen ist die Behandlung von niereninsuffizienten Patienten mit einer Kreatinin-Clearance < 25 ml / min mit Repaglinid, soweit keine anderen oralen Antidiabetika in Frage kommen und eine Insulintherapie nicht angezeigt ist.

52. Harn- und Blutzuckerteststreifen bei Patienten mit Diabetes mellitus Typ 2, die nicht mit Insulin behandelt werden

Verordnungseinschränkung nach § 92 Absatz 1 Satz 1 Halbsatz 3 SGB V in Verbindung mit § 16 Absatz 1 AM-RL

ausgenommen bei instabiler Stoffwechsellage. Diese kann gegeben sein bei interkurrenten Erkrankungen, Ersteinstellung auf oder Therapieumstellung bei oralen Antidiabetika mit hohem Hypoglykämierisiko (grundsätzlich je Behandlungssituation bis zu 50 Teststreifen)

[3] Verordnungsausschluss nach dieser Richtlinie (§ 92 Abs. 1 Satz 1 Halbsatz 3 SGB V in Verbindung mit § 16 Abs. 1 und 2 AM-RL).
[4] Verordnungseinschränkung nach dieser Richtlinie (§ 92 Abs. 1 Satz 1 Halbsatz 3 SGB V in Verbindung mit § 16 Abs. 1 und 2 AM-RL).

G-BA, 2019 [28].

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Abs. 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) in der Fassung vom 20. März 2014, veröffentlicht im Bundesanzeiger (BAnz AT 2 6. Juni 2014 B3 AT 26. August 2014 B2), in Kraft getreten am 1. Juli 2014; zuletzt geändert am 17. Januar 2019, veröffentlicht im Bundesanzeiger (BAnz AT 22. März 2019 B5); Inkrafttreten: 1. April 2019

Anlage 1 Anforderungen an strukturierte Behandlungsprogramme für Diabetes mellitus Typ 2

1 Behandlung nach dem aktuellen Stand der medizinischen Wissenschaft unter Berücksichtigung von evidenzbasierten Leitlinien oder nach der jeweils besten, verfügbaren Evidenz sowie unter Berücksichtigung des jeweiligen Versorgungssektors (§ 137f Abs. 2 Satz 2 Nr. 1 des Fünften Buches Sozialgesetzbuch, SGB V)

…

1.3 Therapie des Diabetes mellitus Typ 2

1.3.1 TherapiezieleAnwendungsgebiet

- Die Therapie dient der Erhöhung der Lebenserwartung sowie der Erhaltung oder der Verbesserung der von einem Diabetes mellitus Typ 2 beeinträchtigten Lebensqualität. Dabei sind in Abhängigkeit z. B. von Alter und Begleiterkrankungen der Patientin oder des Patienten folgende individuelle Therapieziele anzustreben:

- Vermeidung von Symptomen der Erkrankung (z. B. Polyurie, Polydipsie, Abgeschlagenheit) einschließlich der Vermeidung neuropathischer Symptome, Vermeidung von Nebenwirkungen der Therapie (insbesondere schwere oder rezidivierende Hypoglykämien) sowie schwerer hyperglykämischer Stoffwechselentgleisungen,
- Reduktion des erhöhten Risikos für kardiale, zerebrovaskuläre und sonstige makroangiopathische Morbidität und Mortalität,
- Vermeidung der mikrovaskulären Folgeschäden (insbesondere Retinopathie mit schwerer Sehbehinderung oder Erblindung, Niereninsuffizienz mit der Notwendigkeit einer Nierenersatztherapie),
- Vermeidung des diabetischen Fußsyndroms mit neuro-, angio- und/oder osteoarthropathischen Läsionen und von Amputationen.

1.5.1 Grundsätze der Wirkstoffauswahl

Bei der Wirkstoffauswahl zur antidiabetischen Therapie sind neben der Beachtung von Zulassung, Verordnungsfähigkeit und Kontraindikationen prinzipiell folgende Kriterien zu berücksichtigen:

- Beleg der Wirksamkeit anhand klinisch relevanter mikro- und makrovaskulärer Endpunkte
- Eignung von Wirkungsmechanismus, Wirkungs- und Nebenwirkungsprofil (z. B. Risiko von Hypoglykämien und Gewichtszunahme), Arzneimittelinteraktionen und Pharmakokinetik für die individuelle Indikationsstellung
- individuelle Wirkung und Verträglichkeit
- Patientensicherheit
- individuelle Patientenbedürfnisse im Sinne eines „shared-decision-making“.

Kontrollierte Studien mit klinischen Endpunkten (Tod, Infarkt, Herzinsuffizienz, Niereninsuffizienz, Amputation etc.) sind das wichtigste Instrument zum Wirksamkeitsnachweis einer Therapie und daher auch wichtigste Grundlage aller Therapieentscheidungen.

Antidiabetika mit gesicherter günstiger Beeinflussung klinischer Endpunkte:

- Metformin
- Sulfonylharnstoffe (SH) Glibenclamid und Gliclazid
- Insulin.

Antidiabetika ohne gesicherte günstige Beeinflussung klinischer Endpunkte:

- Alpha-Glukosidasehemmer
- DPP-4-Inhibitoren (Dipeptidyl-Peptidase-4-Inhibitoren, Gliptine)
- SGLT2-Inhibitoren (Gliflozine), außer Empagliflozin in der unten genannten Indikation
- Glinide
- GLP-1-Rezeptoragonisten (Inkretinmimetika, GLP-1-Analoga)
- Andere Antidiabetika (z. B. Glimepirid).

Patientinnen und Patienten mit manifester kardiovaskulärer Erkrankung, die mit Medikamenten zur Behandlung kardiovaskulärer Risikofaktoren behandelt werden, können bei unzureichender Kontrolle des Diabetes mellitus / bei unzureichender Blutzuckerkontrolle von Empagliflozin in Kombination mit mindestens einem weiteren oralen Antidiabetikum und/oder mit Insulin profitieren.

1.5.2 Primärtherapie (Monotherapie)

Metformin ist bevorzugt zu verwenden. Sulfonylharnstoffe (Glibenclamid und Gliclazid) können als Alternative bei Unverträglichkeiten gegenüber Metformin eingesetzt werden. Eine Überlegenheit für Insulin als Ersttherapie gegenüber diesen oralen Antidiabetika in Monotherapie ist nicht belegt. Bei hohem Ausgangsblutzucker und HbA1c-Wert und erforderlicher starker Wirkung kann auch im Rahmen der Ersttherapie der Einsatz von Insulin notwendig sein.

1.5.3 Therapieeskalation/Kombinationstherapie

Reicht die primäre Monotherapie nicht aus, um das HbA1c-Ziel zu erreichen, kann eine Kombination mehrerer Antidiabetika helfen, den Blutzucker besser zu kontrollieren. Für solche Therapieregime liegen derzeit keine Langzeitstudien vor, die einen Nutzen in Bezug auf klinische Endpunkte bzw. die Langzeitsicherheit belegen. Umso sorgfältiger muss eine Nutzen-Schaden-Abwägung vorgenommen werden.

G-BA, 2019 [46].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 / 22. März 2019 / 4. Juli 2019 - Sitagliptin

Anwendungsgebiet

Bei erwachsenen Patienten mit Typ-2-Diabetes mellitus ist Januvia®/Xelevia® 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:

- Metformin, wenn Diät und Bewegung plus eine Metformin-Monotherapie den Blutzucker nicht ausreichend senken.
- einem Sulfonylharnstoff, wenn Diät und Bewegung plus eine Sulfonylharnstoff-Monotherapie in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senken und wenn Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist.
- 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.2

Als orale Dreifachtherapie in Kombination mit:

- 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.2

Januvia®/Xelevia® ist auch zusätzlich zu Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung sowie eine stabile Insulindosis den Blutzucker nicht ausreichend senken.

a) Für die Monotherapie bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend senken und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin, hier Metformin) den Blutzucker nicht ausreichend kontrollieren:

Zweckmäßige Vergleichstherapie:

- − Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- − Metformin + Empagliflozin oder
- − Metformin + Liraglutid3

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Anhaltspunkt für einen geringen Zusatznutzen.

c) In Kombination mit einem Sulfonylharnstoff, wenn Diät und Bewegung plus eine Sulfonylharnstoff-Monotherapie in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senken und wenn Metformin aufgrund von Gegenanzeigen/ Unverträglichkeit nicht geeignet ist:

Zweckmäßige Vergleichstherapie

Humaninsulin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: ggf. Therapie nur mit Humaninsulin)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

e) In Kombination mit Insulin (mit und ohne Metformin), wenn Diät und Bewegung sowie eine stabile Insulindosis den Blutzucker nicht ausreichend senken:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1 Zulassungen vom 29.07.2009 (a), 21.03.2007 (b), 19.12.2007 (c), 02.06.2009 (d), 09.11.2009 (e).
2 Aufgrund des Verordnungsausschlusses der Glitazone zur Behandlung des Diabetes mellitus Typ 2 (AM-Richtlinie, Anlage III) entfällt diese Wirkstoffkombination für die Nutzenbewertung von Sitagliptin nach § 35a SGB V.
3 Liraglutid in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker und nur für Patienten mit manifester kardiovaskulärer Erkrankung (zur Operationalisierung siehe Studienprotokoll: Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827)

G-BA, 2018 [30].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Februar 2018 - Saxagliptin/Metformin

Anwendungsgebiet

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.
- Bei Patienten, die bereits mit der Kombination von Saxagliptin und Metformin als separate Tabletten behandelt werden.

Hinweis: Der vorliegende Beschluss bezieht sich nur auf die Kombination von Saxagliptin/Metformin mit anderen Arzneimitteln außer Insulin oder Sulfonylharnstoffen zur Behandlung des Diabetes.

Zweckmäßige Vergleichstherapie

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin1 oder
- Humaninsulin + Liraglutid1 oder
- Humaninsulin, wenn Metformin und Empagliflozin[1] und Liraglutid[1] gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Empagliflozin und Liraglutid in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker und nur für Patienten mit manifester kardiovaskulärer Erkrankung (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI: 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827)

G-BA, 2016 [35].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 - Empagliflozin

Anwendungsgebiet

Jardiance® ist bei Erwachsenen mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle angezeigt als:

- Monotherapie: Wenn Diät und Bewegung allein zur Blutzuckerkontrolle nicht ausreichen, bei Patienten, bei denen die Anwendung von Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird.
- Add-on-Kombinationstherapie: In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn diese zusammen mit Diät und Bewegung zur Blutzuckerkontrolle nicht ausreichen (siehe Abschnitte 4.4, 4.5 und 5.1 für zurzeit vorliegende Daten zu verschiedenen Kombinationen).

a) In der Monotherapie, wenn Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit als ungeeignet erachtet wird

a1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie:

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

a2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

Vergleichstherapie:

Sulfonylharnstoff (Glibenclamid oder Glimepirid) in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert
b1) In der Zweifachkombination mit Metformin

b1.1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen geringen Zusatznutzen.

b1.2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2:

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b2) In der Zweifachkombination mit einem anderen blutzuckersenkenden Arzneimittel außer Metformin und Insulin

b2.1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

b2.2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

c) In Kombination mit mindestens zwei anderen blutzuckersenkenden Arzneimitteln, wenn diese den Blutzucker zusätzlich zu Diät und Bewegung nicht ausreichend kontrollieren

c1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie:

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

c2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

Vergleichstherapie:

Metformin + Humaninsulin in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

d) In Kombination mit Insulin (mit oder ohne orales Antidiabetikum)

d1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

d2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

Vergleichstherapie:

Metformin + Humaninsulin in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren2

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens

Anhaltspunkt für einen beträchtlichen Zusatznutzen

1 manifeste kardiovaskuläre Erkrankung ist im vorliegenden Fall anhand der EMPA-REG-Outcome-Studie (siehe Studienprotokoll, Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI: 10.1056/NEJMoa1504720) definiert und hier näherungsweise zusammengefasst als mind. eine der folgenden Bedingungen: bestätigter Myokardinfarkt, klinisch relevante koronare Eingefäßerkrankung mit ≥ 50% Stenose, koronare Mehrgefäßerkrankung, instabile Angina Pectoris mit angiografischem Nachweis einer koronaren Herzerkrankung, ischämischer oder hämorrhagischer Schlaganfall oder periphere arterielle Verschlusserkrankung mit klinischer relevanter Durchblutungsstörung.
2 Insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker

G-BA, 2016 [36].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 - Empagliflozin/Metformin

Anwendungsgebiet

Synjardy® ist bei Erwachsenen ab 18 Jahren mit Typ-2-Diabetes mellitus zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle angezeigt

- bei Patienten, die unter der maximal verträglichen Dosis von Metformin allein unzureichend eingestellt sind.
- bei Patienten, die mit Metformin in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin unzureichend eingestellt sind (siehe Abschnitte 4.5 und 5.1 für zurzeit vorliegende Daten zu verschiedenen Kombinationen).
- bei Patienten, die bereits mit der Kombination aus Empagliflozin und Metformin in Form getrennter Tabletten behandelt werden.

a) Zweifachkombination Empagliflozin mit Metformin bei Patienten, die unter der maximal verträglichen Dosis von Metformin zusätzlich zu Diät und Bewegung unzureichend eingestellt sind:

a1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

a2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren2

Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln (außer Insulin) bei Patienten, die mit Metformin in Kombination mit diesen anderen blutzuckersenkenden Arzneimitteln (außer Insulin) zusätzlich zu Diät und Bewegung unzureichend eingestellt sind:

b1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

Vergleichstherapie

Humaninsulin + Metformin in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

c) Kombinationstherapie mit Insulin bei Patienten, die mit Metformin in Kombination mit Insulin zusätzlich zu Diät und Bewegung unzureichend eingestellt sind:

c1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

c2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

Vergleichstherapie

Humaninsulin + Metformin in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1 manifeste kardiovaskuläre Erkrankung ist im vorliegenden Fall anhand der EMPA-REG-Outcome-Studie (siehe Studienprotokoll, Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI: 10.1056/NEJMoa1504720) definiert und hier näherungsweise zusammengefasst als mind. eine der

folgenden Bedingungen: bestätigter Myokardinfarkt, klinisch relevante koronare Eingefäßerkrankung mit ≥ 50% Stenose, koronare Mehrgefäßerkrankung, instabile Angina Pectoris mit angiografischem Nachweis einer koronaren Herzerkrankung, ischämischer oder hämorrhagischer Schlaganfall oder periphere arterielle Verschlusserkrankung mit klinischer relevanter Durchblutungsstörung.
2 Insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker

---

G-BA, 2016 [37].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 4. Februar 2016 - Insulin degludec/Liraglutid (neues Anwendungsgebiet: Diabetes mellitus Typ 2 in Kombination mit oralen Antidiabetika)

Anwendungsgebiet

Xultophy wird zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen angewendet, um in Kombination mit oralen blutzuckersenkenden Arzneimitteln die Blutzuckerkontrolle zu verbessern, wenn diese Mittel allein oder in Kombination mit einem GLP-1-Rezeptor-Agonisten oder Basalinsulin den Blutzuckerspiegel nicht ausreichend regulieren.

Vergleichstherapie

Metformin plus Humaninsulin

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [45].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 - Sitagliptin/Metformin

Anwendungsgebiet

Für erwachsene Patienten mit Typ-2-Diabetes mellitus:

Janumet®/Velmetia® 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®/Velmetia® 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®/Velmetia® 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.2

Janumet®/Velmetia® 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.

a) Zweifachkombination Sitagliptin/Metformin zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle bei Patienten, bei denen eine Monotherapie mit Metformin in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senkt:

Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Dreifachkombination Sitagliptin/Metformin mit Sulfonylharnstoff zusätzlich zu Diät und Bewegung bei Patienten, bei denen eine Kombination aus der jeweils höchsten vertragenen Dosis von Metformin und eines Sulfonylharnstoffs nicht ausreicht, um den Blutzucker zu senken:

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

c) Dreifachkombination Sitagliptin/Metformin mit Insulin als Ergänzung zu Diät und Bewegung bei Patienten, bei denen eine stabile Insulindosis und Metformin allein den Blutzucker nicht ausreichend senken:

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [43].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 – Saxagliptin

Anwendungsgebiet

Onglyza ist bei erwachsenen Patienten ab 18 Jahren mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle indiziert:

Als Monotherapie bei Patienten, die durch Diät und Bewegung allein nicht ausreichend kontrolliert sind und für die Metformin aufgrund von Kontraindikationen oder Unverträglichkeit ungeeignet ist.[2]

Als orale Zweifachtherapie in Kombination mit

- Metformin, wenn eine Metformin-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.
- einem Sulfonylharnstoff bei Patienten, für die die Anwendung von Metformin ungeeignet erscheint, wenn eine Sulfonylharnstoff-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.
- einem Thiazolidindion bei Patienten, für die die Anwendung eines Thiazolidindions geeignet erscheint, wenn eine Thiazolidindion-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.[3]

Als orale Dreifachtherapie

- in Kombination mit Metformin und einem Sulfonylharnstoff, wenn diese Behandlung allein, mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.

Als Kombinationstherapie mit Insulin (mit oder ohne Metformin), wenn diese Behandlung allein, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.

a) In Kombination mit Metformin, wenn eine Metformin-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem Sulfonylharnstoff bei Patienten, für die die Anwendung von Metformin ungeeignet erscheint, wenn eine Sulfonylharnstoff-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert:

Zweckmäßige Vergleichstherapie

Humaninsulin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: ggf. Therapie nur mit Humaninsulin)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Als orale Dreifachtherapie in Kombination mit Metformin und einem Sulfonylharnstoff, wenn diese Behandlung allein, mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit Insulin (mit oder ohne Metformin), wenn diese Behandlung allein, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

2 Die Monotherapie ist nicht Bestandteil des hier zugrunde liegenden, befristeten Beschlusses für die Nutzenbewertung nach § 35a SGB V von Saxagliptin.
3 Aufgrund des Verordnungsausschlusses der Glitazone zur Behandlung des Diabetes mellitus Typ 2 (AM-Richtlinie, Anlage III) entfällt diese Wirkstoffkombination für die Nutzenbewertung von Saxagliptin nach § 35a SGB V.

G-BA, 2016 [44].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 - Saxagliptin/Metformin

Anwendungsgebiet

Komboglyze® ist als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind, oder die bereits mit der Kombination von Saxagliptin und Metformin als separate Tabletten behandelt werden.

Komboglyze® ist auch in Kombination mit Insulin (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn Insulin und Metformin allein den Blutzucker nicht ausreichend kontrollieren.

Komboglyze® ist auch in Kombination mit einem Sulfonylharnstoff (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert.[2]

a) Zweifachkombinationstherapie Saxagliptin/Metformin bei erwachsenen Patienten im Alter von 18 Jahren und älter, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind:

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Dreifachkombination Saxagliptin/Metformin mit Insulin als Ergänzung zu Diät und Bewegung, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-

2-Diabetes mellitus zu verbessern, wenn Insulin und Metformin allein den Blutzucker nicht ausreichend kontrollieren:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

2 Die Kombination mit einem Sulfonylharnstoff ist nicht Bestandteil des hier zugrunde liegenden, befristeten Beschlusses für die Nutzenbewertung nach § 35a SGB V von Saxagliptin/Metformin.

G-BA, 2015 [49].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Juli 2015 – Dulaglutid

Anwendungsgebiet

Dulaglutid (Trulicity®) ist angezeigt zur Behandlung von Erwachsenen mit Typ 2 Diabetes mellitus, um eine verbesserte Blutzuckerkontrolle zu erreichen als:

Monotherapie

- Sofern bei Patienten, für die die Einnahme von Metformin wegen Unverträglichkeit oder Kontraindikationen nicht angezeigt ist, durch Diät und Bewegung keine angemessene Blutzuckerkontrolle erreicht werden kann.

Kombinationstherapie

- In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn durch diese zusammen mit Diät und Bewegung keine angemessene Blutzuckerkontrolle erreicht werden kann (siehe Abschnitt 5.1 bzgl. Daten zu verschiedenen Kombinationen).

a) In der Monotherapie, wenn Diät und Bewegung alleine nicht zu einer ausreichenden Blutzuckerkontrolle führen bei Patienten, bei denen Metformin wegen Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) In der Zweifachkombinationstherapie mit einem oralen Antidiabetikum, wenn dieses, zusammen mit Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert:

b1) In der Zweifachkombination mit Metformin:

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b2) In der Zweifachkombination mit einem anderen oralen blutzuckersenkenden Arzneimittel (außer Metformin):

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) In der Dreifachkombinationstherapie mit zwei oralen Antidiabetika, wenn diese, zusammen mit Diät und Bewegung, den Blutzucker nicht ausreichend kontrollieren:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit Insulin, mit oder ohne orales Antidiabetikum, wenn diese, zusammen mit Diät und Bewegung, den Blutzucker nicht ausreichend kontrollieren:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Anhaltspunkt für einen geringen Zusatznutzen

G-BA, 2015 [47].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Oktober 2015 - Insulin degludec/Liraglutid

Anwendungsgebiet

Xultophy® wird zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen angewendet, um in Kombination mit oralen blutzuckersenkenden Arzneimitteln die Blutzuckerkontrolle zu

verbessern, wenn diese Mittel allein oder in Kombination mit einem GLP-1-Rezeptor-Agonisten oder Basalinsulin den Blutzuckerspiegel nicht ausreichend regulieren

a) Insulin degludec/Liraglutid in Kombination mit oralen Antidiabetika zur Behandlung des Diabetes mellitus Typ 2, wenn eine orale antidiabetische Kombinationstherapie zur Blutzuckerkontrolle nicht ausreicht:

Vergleichstherapie

Metformin plus Humaninsulin

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet oder Metformin in Kombination mit Insulin nicht ausreichend wirksam ist, ist Humaninsulin als Therapieoption einzusetzen)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Insulin degludec/Liraglutid in Kombination mit oralen Antidiabetika zur Behandlung des Diabetes mellitus Typ 2, wenn diese oralen Antidiabetika in Kombination mit Basalinsulin zur Blutzuckerkontrolle nicht ausreichen:

b1) in der Kombination mit Metformin:

Vergleichstherapie

Humaninsulin plus ggf. Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt[1]:

b2) in Kombination mit oralen Antidiabetika (außer Metformin):

Vergleichstherapie

Humaninsulin plus ggf. Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Die vergleichende Bewertung erfolgt auf der Grundlage eines direkten Vergleichs von Insulin degludec/Liraglutid in Kombination mit Metformin gegenüber der Kombination aus einem langwirksamen Insulin-Analogon (Insulin glargin) mit Metformin.

G-BA, 2015 [52].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. März 2015/ 16. Juli 2015 - Albiglutid

Anwendungsgebiet

Albiglutid (Eperzan®) ist bei erwachsenen Patienten mit Typ 2 Diabetes zur Verbesserung der Blutzuckereinstellung indiziert als:

Monotherapie

- Wenn Diät und Bewegung allein zur Blutzuckereinstellung nicht ausreichen bei Patienten, für die die Anwendung von Metformin aufgrund von Kontraindikationen oder Unverträglichkeit als ungeeignet angesehen wird.

Kombinationstherapie

- In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken (für verfügbare Daten zu den verschiedenen Kombinationen siehe Abschnitt 4.4 und 5.1).

a) In der Monotherapie, wenn Diät und Bewegung allein zur Blutzuckereinstellung nicht ausreichen bei Patienten, für die die Anwendung von Metformin aufgrund von Kontraindikationen oder Unverträglichkeit als ungeeignet angesehen wird

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend senkt

b1) In der Zweifachkombination mit Metformin

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Hinweis für einen geringen Zusatznutzen

b2) In der Zweifachkombination mit einem anderen blutzuckersenkenden Arzneimittel außer Metformin und Insulin

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) In Kombination mit mindestens zwei anderen blutzuckersenkenden Arzneimitteln, wenn diese den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend senken

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit Insulin (mit oder ohne orale Antidiabetika)

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2015 [53].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. August 2015 - Insulin degludec (neues Anwendungsgebiet: Diabetes mellitus, Patienten ab 1 Jahr)

Anwendungsgebiet

Behandlung des Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr.

Der vorliegende Beschluss bezieht sich ausschließlich auf das neu zugelassene Anwendungsgebiet vom 30. Januar 2015 (größere Änderung des Typs 2 nach Anhang 2 Nummer 2 Buchstabe a der Verordnung (EG) Nr. 1234/2008 der Kommission vom 24. November 2008 über die Prüfung von Änderungen der Zulassungen von Human- und Tierarzneimitteln), d. h. auf die Behandlung des Diabetes mellitus bei Jugendlichen und Kindern ab dem Alter von 1 Jahr.

a) Behandlung des Diabetes mellitus Typ 1 bei Jugendlichen und Kindern ab 1 Jahr:

Zweckmäßige Vergleichstherapie

Humaninsulin

Ausmaß des Zusatznutzens[1]

Ein Zusatznutzen ist nicht belegt.

b) Behandlung des Diabetes mellitus Typ 2 bei Jugendlichen und Kindern ab 1 Jahr in der Monotherapie:

Zweckmäßige Vergleichstherapie

Humaninsulin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Behandlung des Diabetes mellitus Typ 2 bei Jugendlichen und Kindern ab 1 Jahr in Kombination mit anderen Antidiabetika:

Zweckmäßige Vergleichstherapie

Humaninsulin plus Metformin

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Die vergleichende Bewertung erfolgt auf der Grundlage eines direkten Vergleichs von Insulin degludec in Kombination mit einem kurzwirksamen Insulin-Analogon (Insulin aspart) gegenüber der Kombination aus einem langwirksamen Insulin-Analogon (Insulin detemir) mit einem kurzwirksamen Insulin-Analogon (Insulin aspart).

G-BA, 2015 [34].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 / 21. Mai 2015 – Vildagliptin

Anwendungsgebiet

Galvus®/Jalra® /Xiliarx® ist angezeigt zur Behandlung von Diabetes mellitus Typ 2

Als Monotherapie bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist.

In einer oralen Zweifach-Kombinationstherapie mit

- Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist,
- einem Sulfonylharnstoff bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen eines Sulfonylharnstoffs unzureichend eingestellt ist und bei denen Metformin wegen Kontraindikationen oder Unverträglichkeit ungeeignet ist,
- einem Thiazolidindion bei Patienten mit ungenügender Blutzuckereinstellung, für die die Anwendung eines Thiazolidindions geeignet ist.[1]

In einer oralen Dreifach-Kombinationstherapie mit einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung zusätzlich zu einer Zweifachtherapie mit diesen Arzneimitteln zu keiner adäquaten glykämischen Kontrolle führen.

Vildagliptin ist auch für die Anwendung in Kombination mit Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung zusätzlich zu einer stabilen Insulindosis zu keiner adäquaten glykämischen Kontrolle führen.

a) Monotherapie, bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Zweifachkombination Vildagliptin mit Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Aufgrund des Verordnungsausschlusses der Glitazone zur Behandlung des Diabetes mellitus Typ 2 (AM-Richtlinie, Anlage III) entfällt dieses Anwendungsgebiet für die Nutzenbewertung von Vildagliptin nach § 35a SGB V.

G-BA, 2015 [39].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 5. Februar 2015 - Canagliflozin/Metformin.

Anwendungsgebiet

Vokanamet wird angewendet bei Erwachsenen im Alter von 18 Jahren und älter mit Typ-2-Diabetes-mellitus zusätzlich zu Diät und Bewegung zur Blutzuckerkontrolle:

- bei Patienten, bei denen Metformin in den maximal verträglichen Dosen allein den Blutzucker nicht ausreichend kontrolliert,
- bei Patienten, bei denen Metformin in den maximal verträglichen Dosen zusammen mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin den Blutzucker nicht ausreichend kontrolliert (siehe Abschnitte 4.4, 4.5 und 5.1 für Daten zu verschiedenen Kombinationstherapien)
- bei Patienten, die bereits Canagliflozin und Metformin als separate Tabletten erhalten.

a) Kombinationstherapie mit Metformin, wenn Metformin in der maximal verträglichen Dosis den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln außer Insulin, wenn der Blutzucker mit Metformin und diesen Arzneimitteln zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Kombinationstherapie mit Insulin, wenn der Blutzucker mit Metformin und Insulin zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [40].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 5. September 2013 / 23. Januar 2014 – Lixisenatid.

Anwendungsgebiet

Lyxumia® wird angewendet bei Erwachsenen zur Behandlung des Typ-2-Diabetes mellitus in Kombination mit oralen blutzuckersenkenden Arzneimitteln und/oder Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken.

a) Add-on Kombinationstherapie mit Metformin, wenn Metformin den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend senkt:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Add-on Zweifach-Kombination mit einem oralen Antidiabetikum (außer Metformin), wenn dieses zusammen mit einer Diät und Bewegung den Blutzucker nicht ausreichend senkt:

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Add-on Dreifach-Kombination mit oralen Antidiabetika, wenn diese zusammen mit einer Diät und Bewegung den Blutzucker nicht ausreichend senken:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Ausmaß des Zusatznutzens

Ein Zusatznutzen gilt als nicht belegt.

d) Add-on Kombination mit einem Basalinsulin mit oder ohne Metformin, wenn Basalinsulin (mit oder ohne Metformin) zusammen mit einer Diät und Bewegung den Blutzucker nicht ausreichend senkt:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [54].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Februar 2013 / 23. Januar 2014 – Linagliptin

Anwendungsgebiet

Trajenta® ist bei erwachsenen Patienten mit Diabetes mellitus Typ 2 zur Verbesserung der Blutzuckerkontrolle indiziert:

als Monotherapie

- bei Patienten, wenn Diät und Bewegung allein zur Blutzuckerkontrolle nicht ausreichen und für die Metformin wegen Unverträglichkeit ungeeignet oder aufgrund einer Nierenfunktionsstörung kontraindiziert ist.

als Kombinationstherapie

- in Kombination mit Metformin, wenn Diät und Bewegung sowie eine Metformin-Monotherapie zur Blutzuckerkontrolle nicht ausreichen,
- in Kombination mit einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung sowie eine Zweifachtherapie mit diesen beiden Arzneimitteln zur Blutzuckerkontrolle nicht ausreichen.

a) Monotherapie

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid, Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen gilt als nicht belegt.

b) Zweifachkombinationstherapie: Linagliptin + Metformin

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid, Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [50].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Mai 2013 / 23. Januar 2014 - Linagliptin (neues Anwendungsgebiet: Diabetes mellitus Typ 2, Kombinationstherapie mit Insulin mit oder ohne Metformin)

Anwendungsgebiet

Trajenta® ist bei erwachsenen Patienten mit Diabetes mellitus Typ 2 zur Verbesserung der Blutzuckerkontrolle indiziert:

- in Kombination mit Insulin mit oder ohne Metformin, wenn diese Behandlung alleine mit Diät und Bewegung zur Blutzuckerkontrolle nicht ausreichen.

Dreifachkombination Saxagliptin/Metformin mit Sulfonylharnstoff, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Zweifachkombination von Metformin + Humaninsulin.

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist.)

Ausmaß des Zusatznutzens

Da die erforderlichen Nachweise nicht vollständig vorgelegt worden sind, gilt der Zusatz-nutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Abs. 1 Satz 5 SGB V).

G-BA, 2014 [33].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 - Vildagliptin/Metformin

Anwendungsgebiet

Eucreas®/ Icandra®/ Zomarist® ist für die Behandlung des Typ-2-Diabetes-mellitus indiziert:

- Eucreas®/ Icandra®/ Zomarist® ist für die Behandlung von Erwachsenen indiziert, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine

unzureichend eingestellt ist oder die bereits mit einer Kombination aus Vildagliptin und Metformin in separaten Tabletten behandelt werden.

- Eucreas®/ Icandra®/ Zomarist® ist in Kombination mit einem Sulfonylharnstoff (d. h. Dreifachkombinationstherapie) zusätzlich zu Diät und Bewegung indiziert bei Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können.
- Eucreas®/ Icandra®/ Zomarist® ist als Dreifachkombinationstherapie mit Insulin zusätzlich zu Diät und Bewegung indiziert, um die glykämische Kontrolle bei Patienten zu verbessern, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen.

a) Zweifachkombination Vildagliptin/Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine unzureichend eingestellt ist:

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Dreifachkombination Vildagliptin/Metformin mit Sulfonylharnstoff bei Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Kombination Vildagliptin/Metformin mit Insulin, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [38].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 4. September 2014 – Canagliflozin.

Anwendungsgebiet

Invokana® wird angewendet bei Erwachsenen im Alter von 18 Jahren und älter mit Typ-2-Diabetes-mellitus zur Blutzuckerkontrolle als:

Monotherapie

- Bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen als ungeeignet erachtet wird.

Kombinationstherapie

- Als Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn diese den Blutzucker, zusammen mit Diät und Bewegung, nicht ausreichend kontrollieren (siehe Abschnitte 4.4, 4.5 und 5.1 für verfügbare Daten zu den verschiedenen Kombinationstherapien).

a) In der Monotherapie, wenn Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen als ungeeignet erachtet wird

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert (Kombination mit Metformin)

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert (Kombination mit einem Sulfonylharnstoff)

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit mindestens zwei anderen blutzuckersenkenden Arzneimitteln, wenn diese den Blutzucker zusätzlich zu Diät und Bewegung nicht ausreichend kontrollieren

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

e) In Kombination mit Insulin (mit oder ohne orales Antidiabetikum)

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [32].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 - Saxagliptin/Metformin (neues Anwendungsgebiet: Diabetes mellitus, Kombination mit einem Sulfonylharnstoff).

Anwendungsgebiet

Komboglyze® ist auch in Kombination mit einem Sulfonylharnstoff (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert.

Dreifachkombination Saxagliptin/Metformin mit Sulfonylharnstoff, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt

IQWiG, 2017 [58].

Bewertung der Studie LEADER zu Liraglutid; Rapid Report; Auftrag A17-09

Fragestellung

Bewertung der Langzeitstudie LEADER im Anwendungsgebiet Diabetes mellitus Typ 2 hinsichtlich patientenrelevanter Endpunkte.

Methodik

Population: Erwachsene Patientinnen und Patienten mit Diabetes mellitus Typ 2 mit einem HbA1c-Wert von ≥ 7,0 % und einem Alter von mindestens 50 Jahren. Bei Patientinnen und Patienten ab 50 Jahren musste dabei zusätzlich eine kardiovaskuläre Erkrankung vorliegen, bei Patientinnen und Patienten ab 60 Jahren war das Vorliegen mindestens eines Risikofaktors für eine kardiovaskuläre Erkrankung ausreichend.

Intervention: Liraglutid + antidiabetischen Standardtherapie (blutzuckersenkende und kardiovaskuläre Therapie) OHNE GLP-1-Rezeptoragonisten, DPP-4-Inhibitoren oder Pramlintid

Komparator: Placebo + antidiabetischen Standardtherapie (blutzuckersenkende und kardiovaskuläre Therapie) OHNE GLP-1-Rezeptoragonisten, DPP-4-Inhibitoren oder Pramlintid

Endpunkte: Mortalität, Morbidität, gesundheitsbezogene Lebensqualität und Nebenwirkungen

Ergebnisse

Eingeschlossene Patienten: 9340

Qualität der Studie: Trotz des überwiegend niedrigen Verzerrungspotenzials auf Studien- und Endpunktebene ist die Aussagesicherheit der Studie niedrig, da im Verlauf der Studie bei einem Großteil der Patientinnen und Patienten die Studienvorgaben zur blutzucker- und blutdrucksenkenden Therapieeskalation nicht ausreichend umgesetzt wurden. Daher ist auch die Aussagesicherheit für jeden einzelnen patientenrelevanten Endpunkt der Studie LEADER niedrig.

Studienergebnisse:

- Gesamtmortalität: statistisch signifikanter Unterschied zugunsten von Liraglutid.
- Major Adverse Cardiovascular Event (MACE):
  - zusammengesetzt aus kardiovaskulärem Tod, nicht tödlichem Myokardinfarkt und nicht tödlichem Schlaganfall
  - statistisch signifikanter Unterschied zugunsten von Liraglutid. Dies gilt auch für die Einzelkomponente kardiovaskulärer Tod.
  - keine statistisch signifikanten Unterschiede für weitere Endpunkte
- SUE: unzureichend interpretierbar
- SUE oder nicht schwerwiegendes Medical Event of Special Interest (MESI): statistisch signifikanter Unterschied zuungunsten von Liraglutid für Erkrankungen des Gastrointestinaltrakts insgesamt sowie für die Einzelereignisse Diarrhö, Übelkeit und Erbrechen.
- Abbruch wegen SUE oder nicht schwerwiegendem MESI: statistisch signifikanter Unterschied zugunsten der Vergleichsbehandlung. Patientinnen und Patienten im Liraglutidarm brachen die Behandlung häufiger aufgrund eines SUE oder nicht schwerwiegenden MESI ab.

- Hypoglykämien:
  - Für den Endpunkt symptomatische Hypoglykämien mit einem Plasmaglukosewert < 56 mg/dl zeigte sich ein statistisch signifikanter Unterschied zugunsten von Liraglutid.
  - Für die Endpunkte symptomatische Hypoglykämien mit einem Plasmaglukosewert ≤ 70 mg/dl und schwere Hypoglykämien zeigten sich keine statistisch signifikanten Unterschiede zwischen den Behandlungsgruppen.

Die positiven und negativen Effekte von Liraglutid zusätzlich zu einer antidiabetischen Standardtherapie, die sich aus der Studie LEADER ergeben, unterscheiden sich je nach Ausprägung einer Nierenfunktionsstörung zu Studienbeginn

Patientengruppe mit einer eGFR < 60 ml/min/1,73 m2

Tabelle 1: Positive und negative Effekte von Liraglutid + antidiabetische Standardtherapie im Vergleich zu Placebo + antidiabetische Standardtherapie in der Studie LEADER (berechnet nach MDRD)

Positive Effekte	Negative Effekte
Mortalität ▪ Gesamtmortalität	
Morbidität ▪ MACE[a] ▪ nicht tödlicher Schlaganfall ▪ alle Schlaganfälle ▪ stationäre Behandlung aufgrund von Herzinsuffizienz[b]	
Nebenwirkungen ▪ symptomatische Hypoglykämien (Plasmaglukose < 56 mg/dl)	Nebenwirkungen ▪ SUE oder nicht schwerwiegendes MESI ▫ Erkrankung des Gastrointestinaltrakts (Diarrhö, Übelkeit, Erbrechen)
a: kombinierter Endpunkt, bestehend aus den Einzelkomponenten kardiovaskulärer Tod, nicht tödlicher Myokardinfarkt und nicht tödlicher Schlaganfall b: gilt nur für die Patientengruppe mit einer kardiovaskulären Erkrankung eGFR: geschätzte glomeruläre Filtrationsrate; MACE: Major Adverse Cardiovascular Event; MDRD: Modification of Diet in Renal Disease; MESI: Medical Event of Special Interest; SUE: schwerwiegendes unerwünschtes Ereignis	

Patientengruppe mit einer eGFR ≥ 60 ml/min/1,73 m2

Tabelle 2: Positive und negative Effekte von Liraglutid + antidiabetische Standardtherapie im Vergleich zu Placebo + antidiabetische Standardtherapie in der Studie LEADER (berechnet nach MDRD)

Positive Effekte	Negative Effekte
Mortalität ▪ Gesamtmortalität	
Morbidität ▪ stationäre Behandlung aufgrund von Herzinsuffizienz[a]	
Nebenwirkungen ▪ symptomatische Hypoglykämien (Plasmaglukose < 56 mg/dl)	Nebenwirkungen ▪ SUE oder nicht schwerwiegendes MESI ▫ Erkrankung des Gastrointestinaltrakts (Diarrhö, Übelkeit, Erbrechen) ▪ Abbruch wegen SUE oder nicht schwerwiegendem MESI
a: gilt nur für die Patientengruppe mit einer kardiovaskulären Erkrankung eGFR: geschätzte glomeruläre Filtrationsrate; MACE: Major Adverse Cardiovascular Event; MDRD: Modification of Diet in Renal Disease; MESI: Medical Event of Special Interest; SUE: schwerwiegendes unerwünschtes Ereignis	

Fazit

Insgesamt ist unklar, ob die in der Studie beobachteten Effekte zu den kardiovaskulären Endpunkten auf Liraglutid zurückzuführen sind oder auf die unterschiedliche Behandlungsqualität in den Behandlungsgruppen. Demgegenüber ist die Hypoglykämierate in der Interventionsgruppe trotz forcierter Titration von Liraglutid und insgesamt stärkerer Blutzuckersenkung geringer als in der Kontrollgruppe, sodass für diesen Endpunkt von einem substanzspezifischen Effekt von Liraglutid ausgegangen werden kann.

3.2 Cochrane Reviews

Madsen KS et al., 2019 [69].

Metformin and second- or third-generation sulphonylurea combination therapy for adults with type 2 diabetes mellitus

Fragestellung

To assess the effects of metformin and sulphonylurea (second- or third-generation) combination therapy for adults with type 2 diabetes mellitus

Methodik

Population:

- T2DM

Intervention:

- Metformin plus second- or third-generation sulphonylurea (M +S) combination therapy

Komparator:

- Metformin plus another glucose-lowering intervention as a combination therapy (e.g. metformin plus dipeptidylpeptidase-4 inhibitor, metformin plus insulin)
- Metformin plus placebo
- Metformin monotherapy

Endpunkte:

- Primary endpoints: All-cause mortality, Health-related quality of life, Serious adverse events
- Secondary outcomes: Cardiovascular mortality, Non-fatal myocardial infarction, Heart failure, Non-fatal stroke, Amputation of lower extremity, Blindness or severe vision loss, End-stage renal disease, Non-serious adverse events, Hypoglycaemia, Socio-economic effects

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE, Embase, ClinicalTrials.gov and WHO ICTRP. The date of the last search was March 2018
- We included trials with a minimum duration of intervention of 52 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 32 RCTs randomising 28,746 people.

Charakteristika der Population:

- Two trials had both a placebo group and an active comparator group (Ahrén 2014; Nauck 2013), the rest of the included trials had an active comparator group.

- The mean age of the participants ranged from 52 years to 73 years.
- One trial only included participants aged 65 years and more (Schernthaner 2015).
- Mean HbA1c at baseline ranged from 7.3% to 9.3%.
- Metformin was administered in all intervention and comparator arms and was mostly given in doses of 500 mg/day to 3000 mg/day
- The included trials used different types of sulphonylureas; 16 trials administered a second-generation sulphonylurea and 16 trials administered a third-generation sulphonylurea.

Qualität der Studien:

- None of the 32 included trials in our review was classified as having low risk of bias in all 'Risk of bias' domains.
- The description of randomization and allocation in the included trials was insufficient in eight trials (Ahrén 2014; Del Prato 2014; Filozof 2010; Gerich 2005; Matthews 2010; NCT00367055; Petrica 2009; Petrica 2011).
- Eleven trials had insufficient reporting of one or more outcomes of relevance for our review and, therefore, we classified them as having high risk of bias for selective outcome reporting bias (Derosa 2005; Derosa 2009a; Derosa 2009b; Derosa 2010; Derosa 2011a; Derosa 2011b; Filozof 2010; Gerich 2005; Maffioli 2013; Petrica 2009; Petrica 2011). We were able to assess one or more of our predefined outcomes in all the included trials.
- For all the comparisons, we judged the certainty of the evidence to be low or very low mainly because of very limited data, various risk of bias and imprecision.
- Most trials received financial funding from the pharmaceutical industry. It is known that trials receiving funding or provision of free drugs or devices from a pharmaceutical company show more favourable results and conclusions compared to trials sponsored y other sources (Lundh 2017).

Studienergebnisse:

- All Cause Mortality

Outcomes	Metformin + antidiabetic drug	Metformin + sulphonylurea	Relative effect (95% CI)	No. of partic-ipants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality (N)						
M + GLP1-A Follow-up: 2-3 years	**7 per 1000**	**8 per 1000** (4 to 19)	**RR 1.15** (0.49 to 2.67)	2594 (3)	⊕⊕⊖⊖[a1] **Low**	
M + DPP4-I Follow-up: 1-3 years	**4 per 1000**	**5 per 1000** (3 to 9)	**RR 1.32** (0.76 to 2.28)	11,694 (9)	⊕⊕⊖⊖ **Low**[b1]	
M + thiazolidinedione Follow-up: 1-5.5 years	**34 per 1000**	**37 per 1000** (29 to 48)	**RR 1.09** (0.85 to 1.40)	6654 (6)	⊕⊕⊖⊖ **Low**[c1]	
M + nateglinide Follow-up: 1-2 years	See comment			874 (3)	⊕⊕⊖⊖ **Low**[d1]	1 participant died in each intervention group
M + SGLT2-I Follow-up: 2-4 years	**6 per 1000**	**6 per 1000** (3 to 13)	**RR 0.96** (0.44 to 2.09)	5134 (4)	⊕⊖⊖⊖ **Very low**[e1]	

Serious adverse events (N)						
M + GLP1-A Follow-up: 2-3 years	**126 per 1000**	**114 per 1000** (92 to 140)	**RR 0.90** (0.73 to 1.11)	2594 (3)	⊕⊖⊖⊖ **Very low**[a3]	
M + DPP4-I Follow-up: 1-3 years	**124 per 1000**	**132 per 1000** (120 to 146)	**RR 1.07** (0.97 to 1.18)	11,694 (9)	⊕⊖⊖⊖ **Very low**[b3]	
M + thiazolidinedione Follow-up: 1-5.5 years	**200 per 1000**	**202 per 1000** (186 to 222)	**RR 1.01** (0.93 to 1.11)	6654 (6)	⊕⊖⊖⊖ **Very low**[c3]	
M + nateglinide Follow-up:	**60 per 1000**	**101 per 1000** (32 to 313)	**RR 1.68** (0.54 to 5.21)	874 (3)	⊕⊕⊖⊖ **Low**[d3]	
M + SGLT2-I Follow-up: 2-4 years	**124 per 1000**	**126 per 1000** (94 to 170)	**RR 1.02** (0.76 to 1.37)	5134 (4)	⊕⊖⊖⊖ **Very low**[e3]	
Non-fatal stroke (N)						
M + GLP1-A	**Not reported**[a4]					
M + DPP4-I Follow-up: 1-2 years	**3 per 1000**	**6 per 1000** (2 to 18)	**RR 2.21** (0.74 to 6.58)	5093 (4)	⊕⊖⊖⊖ **Very low**[b4]	
M + thiazolidinedione Follow-up: 1-4.8 years	**10 per 1000**	**13 per 1000** (7 to 25)	**RR 1.29** (0.67 to 2.47)	3123 (2)	⊕⊖⊖⊖ **Very low**[c4]	
M + nateglinide Follow-up: 52 weeks	See comment			233 (1)	⊕⊖⊖⊖ **Very low**[d4]	No non-fatal stroke was reported
M + SGLT2-I Follow-up: 2 years	**4 per 1000**	**3 per 1000** (1 to 13)	**RR 0.87** (0.22 to 3.34)	2775 (2)	⊕⊖⊖⊖ **Very low**[e4]	
Non-fatal myocardial infarction (N)						
M + GLP1-A Follow-up: 2-3 years	**6 per 1000**	**3 per 1000** (1 to 16)	**RR 0.57** (0.12 to 2.82)	1575 (2)	⊕⊖⊖⊖ **Very low**[a5]	
M + DPP4-I Follow-up: 1-3 years	**3 per 1000**	**5 per 1000** (2 to 10)	**RR 1.45** (0.69 to 3.07)	6874 (6)	⊕⊖⊖⊖ **very low**[b5]	
M + thiazolidinedione Follow-up: 1-4.8 years	**11 per 1000**	**14 per 1000** (8 to 24)	**RR 1.21** (0.68 to 2.14)	3718 (3)	⊕⊖⊖⊖ **Very low**[c5]	
M + nateglinide Follow-up: 1 year	See comment			446 (2)	⊕⊕⊖⊖ **Low**[d5]	In 1 trial 2/101 (2%) participants had a non-fatal myocardial infarction in the M +S group compared with 0/112 partici-pant in the metformin plus nateglinide group
M + SGLT2-I Follow-up: 2-4 years	**6 per 1000**	**8 per 1000** (3 to 24)	**RR 1.43** (0.49 to 4.18)	2264 (2)	⊕⊖⊖⊖ **Very low**[e5]	

Anmerkung/Fazit der Autoren

There is no firm evidence whether metformin plus sulphonylurea combination compared with metformin plus another glucose-lowering agent or metformin monotherapy increases benefit or harm for most patient-important outcomes (all-cause mortality, serious adverse events, macrovascular complications (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke) and microvascular complications (amputation of lower extremity, blindness or severe vision loss, end-stage renal disease)).

There were more reported hypoglycaemic episodes with metformin plus sulphonylurea combination in comparison to all other metformin-antidiabetic agent combinations. The risk of hypoglycaemia increases with low glucose level targets which may not apply to the majority of elderly people with diabetes.

Vos RC et al., 2016 [89].

Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control

Fragestellung

To assess the effects of insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin monotherapy for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control.

Methodik

Population:

- type 2 diabetes mellitus (according to the appropriate diagnostic criteria at the time) already on insulin therapy and inadequate glycaemic control

Intervention:

- insulin monotherapy

Komparator:

- combinations of insulin with one or more oral glucose-lowering agent

Endpunkte:

- All-cause mortality, Diabetes-related morbidity, Adverse events, Health-related quality of life, Patient satisfaction, Glycosylated HbA1c, Fasting glucose, Lipids, Insulin dose

Recherche/Suchzeitraum:

- To November 2015

Qualitätsbewertung der Studien:

- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 37 trials with 40 treatment comparisons involving 3 227 participants
- insulin monotherapy: once-daily long-acting, once-daily intermediate-acting, twice daily premixed insulin, basal-bolus regimens (multiple injections) compared to
- insulin in combination with
    - sulphonylureas (17 comparisons: glibenclamide = 11, glipizide = 2, tolazamide = 2, gliclazide = 1, glimepiride = 1), metformin (11 comparisons),
    - pioglitazone (four comparisons),

  - alpha-glucosidase inhibitors (four comparisons: acarbose = 3, miglitol = 1),
  - dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) (three comparisons: vildagliptin = 1, sitagliptin = 1, saxagliptin = 1) and
  - the combination of metformin and glimepiride (one comparison)
- duration of the interventions ranged from 2 to 12 months for parallel trials and two to four months for cross-over trials

Qualität der Studien:

- The majority of trials had an unclear risk of bias in several risk of bias domains. Fourteen trials showed a high risk of bias, mainly for performance and detection bias.

Studienergebnisse:

- No trials assessed **all-cause mortality, diabetes-related morbidity or health-related quality of life**
- **hypoglycaemic events**
  - no meta-analysis because of different definitions
  - in most trials insulin-sulphonylurea combination resulted in a higher number of mild episodes of hypoglycaemia, compared to the IM group (range: 2.2 to 6.1 episodes per participant in CT versus 2.0 to 2.6 episodes per participant in IM; low-quality evidence)
  - pioglitazone CT resulted in more mild to moderate hypoglycaemic episodes compared with IM (range 15 to 90 episodes versus 9 to 75 episodes, respectively; low-quality evidence
  - in the other combinations comparable numbers of mild to moderate hypoglycaemic events (low-quality evidence)
- **additional weight gain**
  - addition of sulphonylureas resulted in an additional weight gain of 0.4 kg to 1.9 kg versus -0.8 kg to 2.1 kg in the IM group (220 participants; 7 trials; low-quality evidence)
  - pioglitazone CT caused more weight gain compared to IM: MD 3.8 kg (95% CI 3.0 to 4.6); P < 0.01; 288 participants; 2 trials; low-quality evidence
  - metformin CT associated with weight loss: MD -2.1 kg (95% CI -3.2 to -1.1), P < 0.01; 615 participants; 7 trials; low-quality evidence)
  - DPP-4 inhibitors CT showed weight gain of -0.7 to 1.3 kg versus 0.6 to 1.1 kg in the IM group (362 participants; 2 trials; low-quality evidence)
  - alpha-glucosidase CT compared to IM showed a MD of -0.5 kg (95% CI -1.2 to 0.3); P = 0.26; 241 participants; 2 trials; low-quality evidence
- Users of metformin CT (range 7% to 67% versus 5% to 16%), and alpha-glucosidase inhibitors CT (14% to 75% versus 4% to 35%) experienced more **gastro-intestinal adverse effects** compared to participants on IM.
- Two trials reported a higher frequency of **oedema** with the use of pioglitazone CT (range: 16% to 18% versus 4% to 7% IM).

Anmerkung/Fazit der Autoren

The addition of all oral glucose-lowering agents in people with type 2 diabetes and inadequate glycaemic control who are on insulin therapy has positive effects on glycaemic control and

insulin requirements. The addition of sulphonylureas results in more hypoglycaemic events. Additional weight gain can only be avoided by adding metformin to insulin. Other well-known adverse effects of oral glucose lowering agents have to be taken into account when prescribing oral glucose-lowering agents in addition to insulin therapy.

3.3 Systematische Reviews

Neue systematische Reviews für das Update 2019

Alfayez OM et al., 2019 [1].

Update on Cardiovascular Safety of Incretin-Based Therapy in Adults With Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcome Trials.

Fragestellung

we conducted a systematic review and meta-analysis of GLP-1 receptor agonists and DPP-4 inhibitors in CV outcome trials to assess their CV safety in patients with type 2 diabetes.

Methodik

Population:

- adults with type 2 diabetes

Intervention:

- GLP-1 receptor agonists
- DPP-4 inhibitors

Komparator:

- K.A.

Endpunkte:

- major adverse CV events (MACE), defined as the composite endpoint of death from CV causes, nonfatal myocardial infarction (MI) and nonfatal stroke.
- death from any cause and hospitalization for heart failure (HF).

Recherche/Suchzeitraum:

- literature search in the Embase and MEDLINE databases from January to October 2018

Qualitätsbewertung der Studien:

- Cochrane collaboration tool for assessing risk of bias in randomized trials

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCT

Charakteristika der Studien:

Table 1
Comparison of glucagon like peptide-1 receptor agonist and dipeptidyl peptidase IV inhibitor cardiovascular outcome trials

Study	Design	Medications	Sample size, N	Male sex, N (%)	Age, years, mean (SD)	Median follow up, years	Duration of diabetes, years, mean (SD)	A1C, %, mean (SD)	Existence of CVD at enrollment, N (%)
Glucagon-like peptide-1 receptor agonist									
ELIXA	Randomized, double-blind, placebo-controlled trial	Lixisenatide once daily vs placebo	6,068	4,207 (69)	59.9 (9.7)*	2.1	9.2 (8.2)*	7.7 (1.3)*	6068 (100)
LEADER	Randomized, double-blind, placebo-controlled trial	Liraglutide once daily vs placebo	9,340	6,003 (64)	64.2 (7.2)*	3.8	12.8 (8.0)*	8.7 (1.6)*	7598 (81)
SUSTAIN-6	Randomized, double-blind, placebo-controlled trial	Semaglutide once weekly vs placebo	3,297	2,002 (61)	64.6 (7.4)	2.1	13.9 (8.1)	8.7 (1.5)	2735 (83)
EXSCEL	Randomized, double-blind, placebo-controlled trial	Exenatide once weekly vs placebo	14,752	9,149 (62)	61.9 (9.4)	3.2	13.1 (8.3)	8.1 (1.0)	10 782 (73)
HARMONY	Randomized, double-blind, placebo-controlled trial	Albiglutide once weekly vs placebo	9,463	6,569 (69)	64.1 (8.7)	1.6	14.1 (8.6)*	8.7 (1.5)	6,678 (71)
Dipeptidyl peptidase IV inhibitor									
EXAMINE	Randomized, double-blind, placebo-controlled trial	Alogliptin once daily vs placebo	5,380	3,651 (68)	61 (median)	1.5	7.3* (median)	8.0 (1.1)*	5,366 (100)
TECOS	Randomized, double-blind, placebo-controlled trial	Sitagliptin once daily vs placebo	14,671	10,374 (71)	65.5 (8)	3	11.6 (8.1)	7.2 (0.5)	10,863 (74.)
SAVOR/TIMI 53	Randomized, double-blind, placebo-controlled trial	Saxagliptin once daily vs placebo	16,492	11,037 (70)	65.1 (8.6)*	2.1	10.3 (median)	8.0 (1.4)	12,959 (79)
CARMELINA	Randomized, double-blind, placebo-controlled trial	Linagliptin once daily vs placebo	6,980	4,390 (63)	65.8 (9.1)	2.2	14.7 (9.5)	7.9 (1.0)	6,258 (90)

A1C, glycated hemoglobin level; *CARMELINA*, cardiovascular safety and renal microvascular outcome study with linagliptin; *CVD*, cardiovascular disease; *ELIXA*, the evaluation of lixisenatide in acute coronary syndrome trial; *EXAMINE*, an examination of cardiovascular outcomes with alogliptin vs standard-of-care trial; *EXSCEL*, the exenatide study of cardiovascular event lowering; *HARMONY*, a long-term, randomized, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood-glucose-lowering therapies, on major cardiovascular events in patients with type 2 diabetes mellitus; *LEADER*, the liraglutide effect and action in diabetes evaluation of cardiovascular outcome results trial; *SAVOR-TIMI 53*, saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus thrombolysis in myocardial infarction trial; *SD*, standard deviation; *SUSTAIN-6*, the preapproval trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes; *TECOS*, trial evaluating cardiovascular outcomes with sitagliptin.
* Data for the treatment arm.

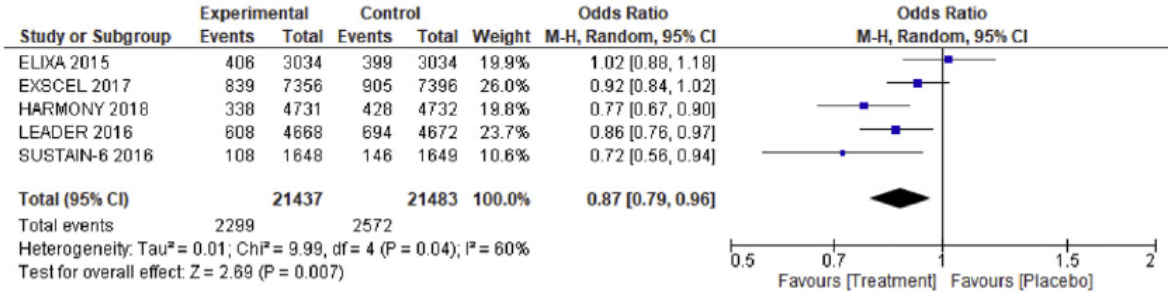
Qualität der Studien:

- All studies with low risk of selection bias, performance bias, detection bias, attrition bias and reporting bias und unclear risk of other bias

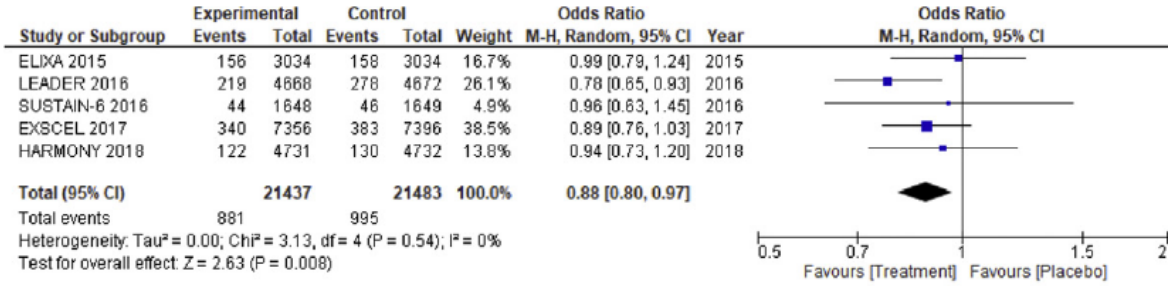
Studienergebnisse:

GLP-1 receptor agonists vs. control: stat. sign. differences in MACE, CV death, stroke, death from any cause:

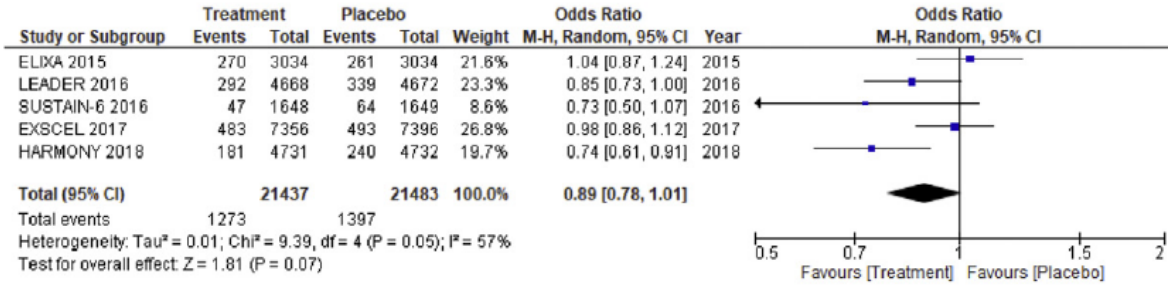
1- MACE



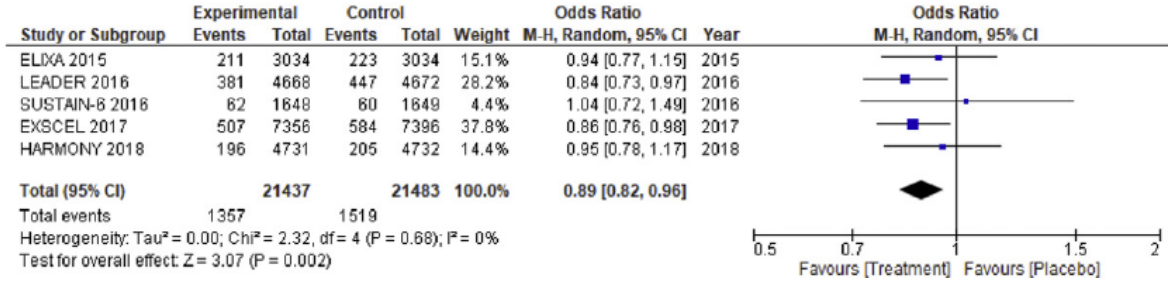
2- CV death



3- MI



5- Death from any cause



6- Hospitalization for HF

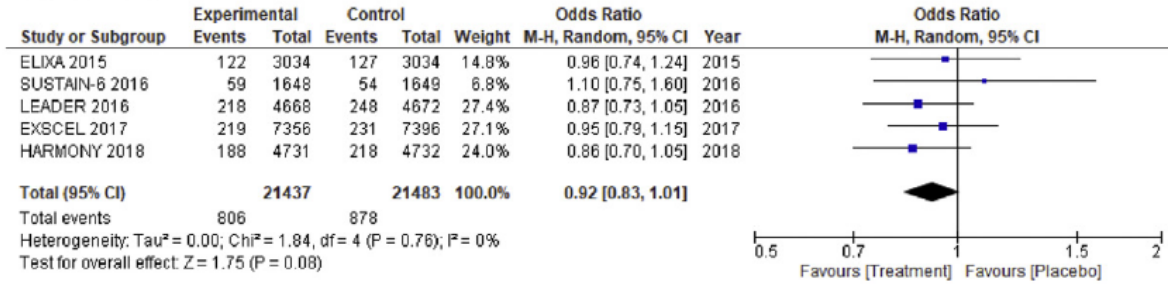
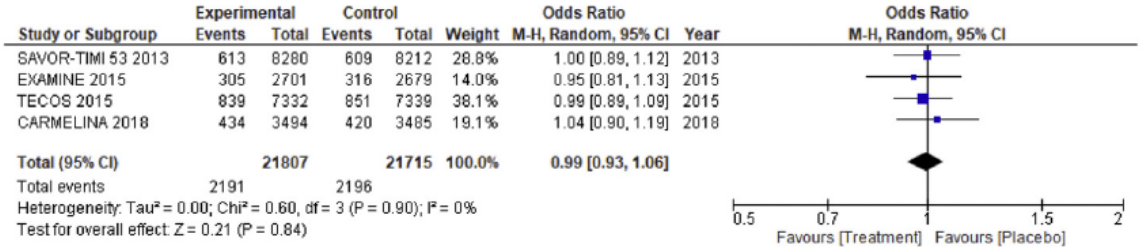


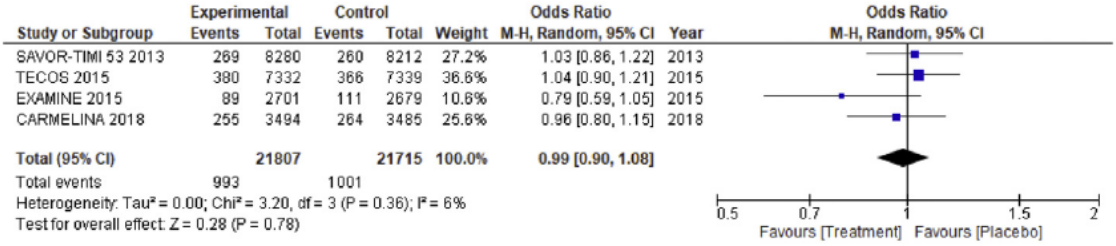
Figure 1. Meta-analysis results of GLP-1 receptor agonists cardiovascular outcome trials. CV, cardiovascular; ELIXA, the evaluation of lixisenatide in acute coronary syndrome trial; EXSCEL, the exenatide study of cardiovascular event lowering; GLP-1, glucagon-like peptide-1; HARMONY, a long-term, randomized, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood-glucose-lowering therapies, on major cardiovascular events in patients with type 2 diabetes mellitus; HF, heart failure; LEADER, the liraglutide effect and action in diabetes evaluation of cardiovascular outcome results trial; MACE, major adverse CV events; MI, myocardial infarction; SUSTAIN-6, the preapproval trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes

DPP-4 inhibitors: no stat. significant differences in the CV outcomes:

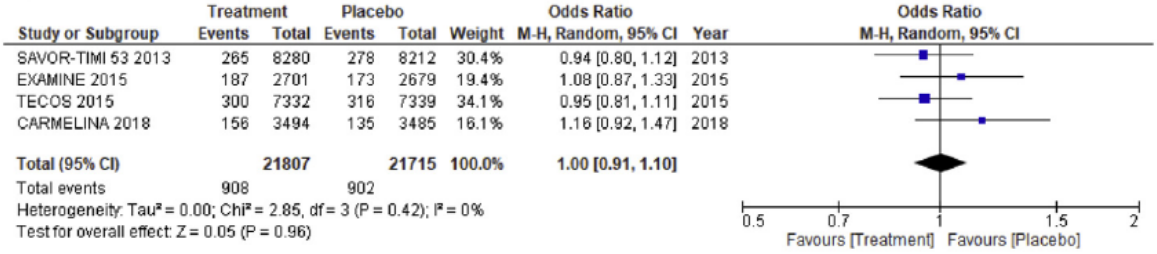
1. Major adverse cardiovascular events



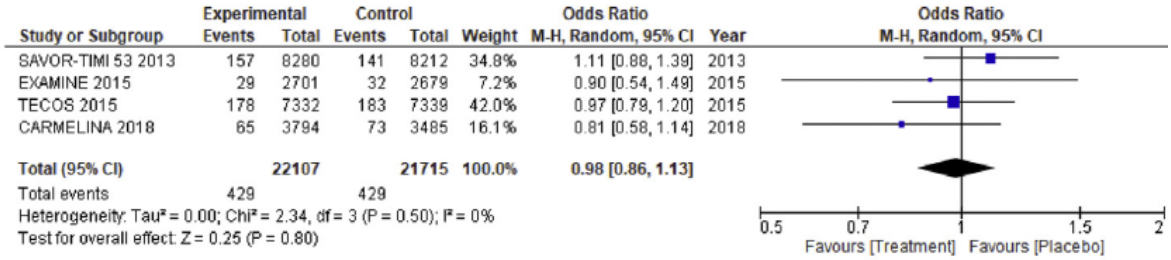
2. Cardiovascular death



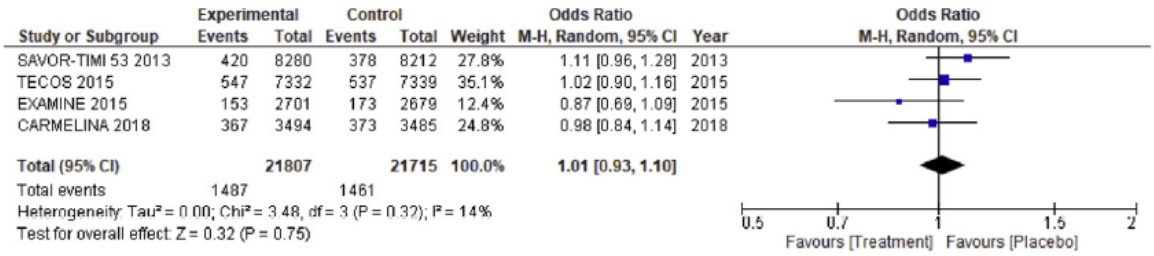
3. Myocardial infarction



4. Stroke



5. Death from any cause



6. Hospitalization for heart failure

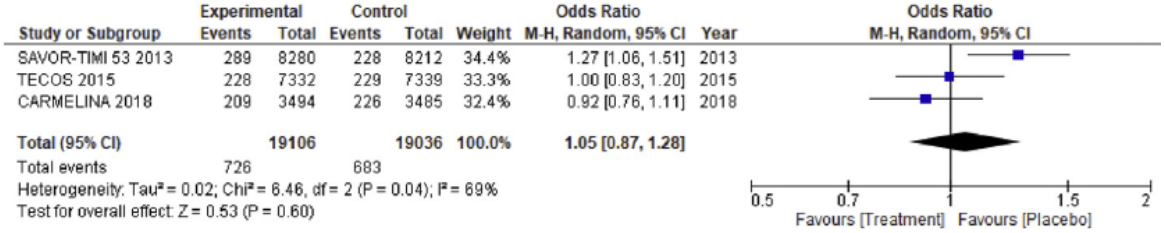


Figure 2. Metanalysis results of dipeptidyl peptidase-4 inhibitors cardiovascular outcome trials. CARMELINA, cardiovascular safety and renal microvascular outcome study with linagliptin; EXAMINE, an examination of cardiovascular outcomes with alogliptin vs standard-of-care trial; SAVOR-TIMI 53, saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus thrombolysis in myocardial infarction trial; TECOS, trial evaluating cardiovascular outcomes with sitagliptin

Anmerkung/Fazit der Autoren

This meta-analysis demonstrated that GLP-1RAs were associated with a significant reduction in major adverse CV events, CV death, stroke and death from any cause, while DPP-4 inhibitors were comparable to placebo for all CV outcomes, including hospitalizations for heart failure.

Avgerinos I et al., 2019 [4].

Glucagon-like peptide-1 receptor agonists and microvascular outcomes in type 2 diabetes: A systematic review and metaanalysis.

Fragestellung

We conducted a systematic review and meta-analysis of RCTs to clarify the effect of GLP-1 RAs on renal and diabetic retinopathy-related outcomes in adults with T2DM.

Methodik

Population:

- in adults with T2DM

Intervention:

- GLP-1 RA

Komparator:

- placebo or another antidiabetic agent

Endpunkte:

- primary outcomes: change from baseline in urinary albumin-to-creatinine ratio (UACR, mg/g) and incidence of diabetic retinopathy.
- Secondary outcomes: change from baseline in estimated glomerular filtration rate (eGFR, mL/min/1.73 m2) and in glycated haemoglobin (HbA1c, %), and incidence of macular oedema, retinal detachment, retinal haemorrhage, or vitreous haemorrhage

Recherche/Suchzeitraum:

- MEDLINE, Embase and the Cochrane Library up to June 11, 2018,
- RCTs with treatment duration of at least 12 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 60 RCTs (60 077 participants)

Charakteristika der Population:

- Twenty-six trials assessed liraglutide, while exenatide, lixisenatide, dulaglutide and semaglutide were assessed in 9, 7, 10 and 8 trials, respectively.

- Study duration ranged from 12 weeks to 3.8 years, and was ≥52 weeks in 26 trials, while HbA1c levels at baseline ranged from 7.1% to 10.3%.

Qualität der Studien:

- Overall risk of bias was high in most studies assessing change from baseline in UACR or incidence of diabetic retinopathy, mainly because of the high discontinuation rate, missing data, or the need for imputation of mean and standard deviation values

Studienergebnisse:

Outcome	Comparison	Studies included, *n*	Number of participants analysed, n		Effect estimate WMD/ OR[a] (95% CI)	I^2, %
			GLP-1 RA	Comparator		
Mean change in UACR from baseline (mg/g)	GLP-1 RAs vs. placebo	19	11 923	9643	−2.55 (−4.37, −0.73)	45
	GLP-1 RAs vs. active comparator	17	4454	2850	−5.52 (−10.89, −0.16)	41
Mean change in eGFR from baseline (ml/min/1.73 m^2)	GLP-1 RAs vs. placebo	14	9329	7861	−0.97 (−1.84, −0.11)	69
	GLP-1 RAs vs. active comparator	10	3790	1897	0.03 (−0.70, 0.76)	25
Diabetic retinopathy	GLP-1 RAs vs. placebo	15	16 525	15 099	1.01 (0.89, 1.16)	0
	GLP-1 RAs vs. active comparator	18	6960	4233	0.95 (0.67, 1.35)	0
Macular oedema	GLP-1 RAs vs. placebo	9	8339	7252	0.84 (0.44, 1.57)	0
	GLP-1 RAs vs. active comparator	6	1940	1817	1.14 (0.34, 3.84)	0
Retinal detachment	GLP-1 RAs vs. placebo	8	10 588	10 143	1.20 (0.52, 2.80)	0
	GLP-1 RAs vs. active comparator	8	3528	2190	0.67 (0.26, 1.74)	0
Retinal haemorrhage	GLP-1 RAs vs. placebo	8	8170	7126	0.93 (0.42, 2.08)	0
	GLP-1 RAs vs. active comparator	10	3682	2185	0.79 (0.34, 1.88)	0
Vitreous haemorrhage	GLP-1 RAs vs. placebo	6	10 748	9964	1.93 (1.09, 3.42)	0
Mean change in HbA1c from baseline (%)	GLP-1 RAs vs. placebo	28	14 489	12 336	−0.88 (−1.01, −0.74)	93
	GLP-1 RAs vs. active comparator	30	9426	6024	−0.37 (−0.51, −0.24)	94

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; NE, not estimable; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio; WMD, weighted mean difference.
[a] For change in UACR, eGFR and HbA1c, the effect estimate is weighted mean difference, while for diabetic retinopathy, macular oedema, retinal detachment, retinal haemorrhage and vitreous haemorrhage, the effect estimate is odds ratio, along with 95% confidence interval.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis provides some reassurance that GLP-1 RAs are safe in terms of their effect on diabetic retinopathy and albuminuria or change in eGFR. Caution may be warranted for incidence of vitreous haemorrhage.

Bae 2019 JH et al., 2019 [5].

Effects of Dipeptidyl Peptidase-4 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Fragestellung

In the present study, we performed a systematic review and meta-analysis of RCTs to investigate the effects of DPP-4 inhibitors on individual renal outcomes including ESRD compared with placebo or other antidiabetic agents in patients with type 2 diabetes.

Methodik

Population:

- type 2 diabetes

Intervention:

- DPP-4 inhibitors

Komparator:

- placebo or other antidiabetic agents

Endpunkte:

- renal outcomes including changes in UACR or eGFR, and the development of microalbuminuria, macroalbuminuria, doubling of serum creatinine levels, renal failure, end-stage renal disease (ESRD), renal replacement therapy (RRT), dialysis, or kidney transplantation

Recherche/Suchzeitraum:

- MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials to Sep 2017
- eligible studies were at least 12 weeks of study duration

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

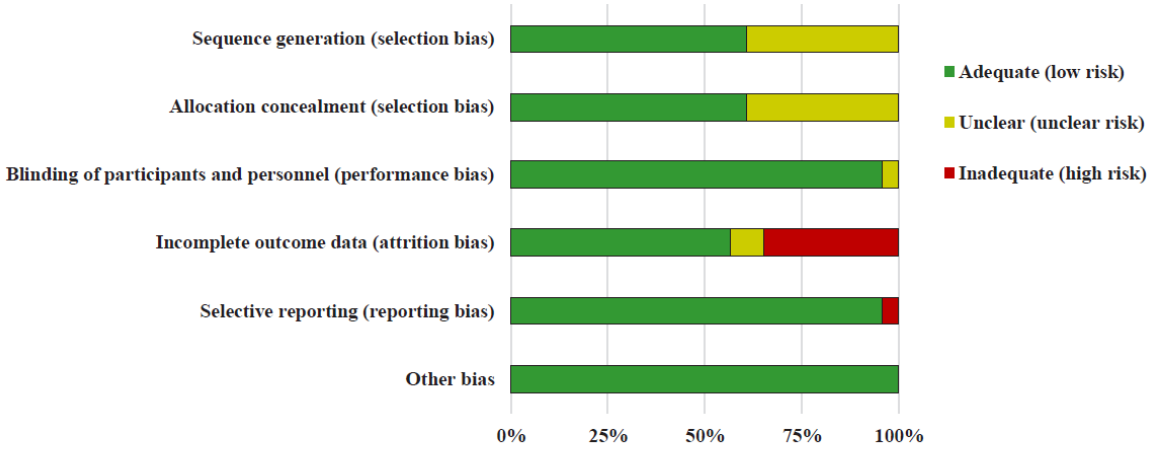
Anzahl eingeschlossener Studien:

- 23 RCTs in 19 publications (n=41359)

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:



Supplemental Fig. S1. Study quality and risk of bias assessment.

Studienergebnisse:

eGFR

- 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).

Development, progression, and regression of albuminuria

- 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

In conclusion, our systematic review and meta-analysis demonstrated that DPP-4 inhibitors had renoprotective effects by reducing the risk of development or progression of albuminuria without affecting the risk of ESRD in patients with type 2 diabetes compared with placebo or other antidiabetic agents.

Bae JH et al., 2019 [6] + Feng C et al., 2019 [24].

Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

+

Feng C et al, 2019. Effect of SGLT2 inhibitor on renal function in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

In this regard, we conducted this systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effects of SGLT2 inhibitors on individual renal outcomes compared with placebo or other antidiabetic drugs in patients with type 2 diabetes.

Methodik

Population:

- Patients with Type 2 Diabetes

Intervention:

- SGLT2 inhibitors

Komparator:

- placebo or other antidiabetic drugs

Endpunkte:

- renal outcomes: changes in urine albumin-to-creatinine ratio (UACR) or eGFR, and incident microalbuminuria, macroalbuminuria, doubling of serum creatinine, renal failure, end-stage renal disease (ESRD), RRT, dialysis, or kidney transplantation

Recherche/Suchzeitraum:

- MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to September 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

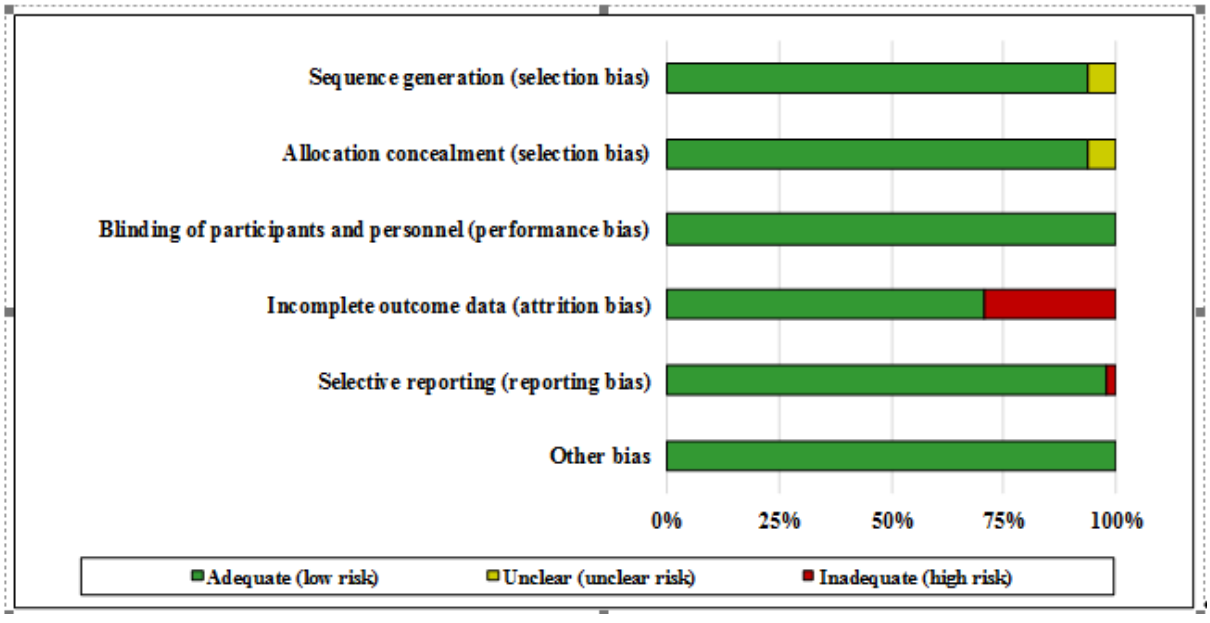
Anzahl eingeschlossener Studien:

- 48 RCTs (n= 58,165 (n=34,661 in the SGLT2 inhibitor group and n=23,504 in the control group).

Charakteristika der Population:

- The number of participants in each study ranged from 114 to 10,142. Three studies had a duration of 187 to 296 weeks6,9,22, whereas the remaining studies had a duration ranging from 12 to 104 weeks.
- The baseline eGFR of the participants was ≥55 (or 60) mL/min/1.73 m2 in 24 studies4,8,38–59, ≥30 mL/min/1.73 m2 in 14 studies6,7,9,15,20,22,30,32–34,60–63, ≥20 mL/ min/1.73 m2 and in 1 study21. In one study, 74 of 741 participants had an eGFR of ≥15 and <30 mL/min/1.73 m2 at baseline35.

Qualität der Studien:



Studienergebnisse:

eGFR

- The changes in eGFR were not significantly different between SGLT2 inhibitors and controls (WMD, 0.19 mL/min/1.73 m2; 95% CI, −0.44 to 0.82; P = 0.552) (Fig. 4A,B). The test for heterogeneity for this showed substantial heterogeneity across the studies (I2 = 79.6%; P < 0.001). There was a large discrepancy noted in estimated treatment effects between fixed effect and random effects models, depending on weights given to two large trials20,22.
- SGLT2 inhibitors significantly slowed the decline in eGFR in patients with >52 weeks of treatment duration compared with controls.
- In the meta-regression, the decline in eGFR were slower in patients with a higher baseline eGFR (P = 0.116) and a longer duration of follow-up (P = 0.038)

ESRD

- SGLT2 inhibitors significantly reduced the risk of ESRD compared with controls (RR, 0.70; 95% CI, 0.57 to 0.87; P = 0.001) (Fig. 5D).
- The number of events was 151 of 15,212 and 194 of 10,694 participants in the SGLT2 inhibitor and control groups, respectively.
- Heterogeneity was regarded as not significant across the studies (I2 = 0.1%; P = 0.433).

Anmerkung/Fazit der Autoren

Our meta-analysis demonstrated that SGLT2 inhibitors had beneficial effects on the kidney by lowering the risk of albuminuria development or progression and reducing the risk of ESRD compared with placebo or other antidiabetic drugs in patients with type 2 diabetes. In addition, the renoprotective effects of SGLT2 inhibitors were greater in patients with a higher UACR and GFR, and a long duration of treatment.

Chen Q et al., 2019 [11].

Risk of Fractures Associated with Dipeptidyl Peptidase 4 Inhibitor Treatment: A Systematic Review and Meta Analysis of Randomized Controlled Trials

Fragestellung

The aim of this research is to obtain a meta-analysis and systematic review to ascertain the treatment of DPP-4 inhibitors is related to the occurrence of fracture in T2DM patients or not.

Methodik

Population:

- T2DM

Intervention:

- DDP-4 inhibitors as interventions, including sitagliptin, saxagliptin, vildagliptin, alogliptin, linagliptin, trelagliptin, and anagliptin;

Komparator:

- comparators or placebo

Endpunkte:

- data on fracture occurrence

Recherche/Suchzeitraum:

- Medline, Embase, and Cochrane Central Register of Controlled Trials RCTs up to 2 December 2018
- RCTs with duration of with a duration greater than or equal to 12 weeks;

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 87 RCTs (n= 93,772 participants)

Charakteristika der Population:

- The DDP-4 inhibitors included in all 87 trials were as follows: sitagliptin in 45, saxagliptin in 15, linagliptin in 15, alogliptin in seven, and vildagliptin in five.
- A total of 28 studies and 44 studies, including 22,082 patients and 63,135 patients, were used to compare DPP-4 inhibitors with active comparators and placebo, respectively, while 15 trials including 8555 patients compared DPP-4 inhibitors with active comparators and placebo simultaneously
- The main population in the study was middle-aged and elderly people; the average age of the study population was 49.7–- 78.3 years.
- Follow-up time of the study ranged from 12 to 206 weeks. We used 52 weeks as the cutoff point for the duration of treatment; 44 RCTs lasted less than it and 43 RCTs lasted longer.

Qualität der Studien:

- nine studies did not mention the method used for randomization.
- The methods used to describe assignment and blinding method for outcome assessment were unclear in 19 and 44 studies, respectively.
- Almost all the studies described the method for handling incomplete outcome data, blinding of participants and personnel, and selective reporting.
- Overall, the bias risk in research was considered relatively low.

Studienergebnisse:

- Fracture risk - According to Control Regimen
- A total of 30,637 participants in trials were compared using active comparators, the MH-OR was 1.04 (95% CI 0.74–1.46, P = 0.81) in trials vs. active comparators, and fractures occurred in 72 cases and 68 cases in the DDP-4 inhibitor treatment group and the control group, respectively.
- The I2 value obtained was equal to 0.0% and heterogeneity was not observed.
- Through the GRADE system, we believe that the quality of evidence was moderate.

Anmerkung/Fazit der Autoren

Although the results of our study indicate that DPP-4 inhibitors show no significant anti-fracture capabilities, this study is still of value to physicians when choosing these drugs as a treatment option. In addition, treatment of diabetic patients with DDP-4 inhibitors, which is thus usually independent of the risk of fractures can be considered as an advantage worth mentioning compared with drugs such as thiazolidinedione or exenatide, which are known to increase the risk of fracture

---

Chen Z et al., 2019 [12].

Sodium-Glucose Co-Transporter 2 Inhibitors Compared with Sulfonylureas in Patients with Type 2 Diabetes Inadequately Controlled on Metformin: A Meta-Analysis of Randomized Controlled Trials

Fragestellung

we therefore conducted a meta-analysis of randomized controlled trials (RCTs) to collectively compare the efficacy, safety, and durability of SGLT2 inhibitors with Sulfunylureas (SUs) as second-line therapy in patients with T2DM with inadequate glycemic control on metformin.

Methodik

Population:

- T2DM

Intervention/Komparator:

- SGLT2 inhibitors vs. SUs addon to Metformin

Endpunkte:

- Primary outcomes: HbA1c and weight between baseline and end of intervention, and number of participants with any hypoglycemic episodes. Hypoglycemic events include documented hypoglycemia (episodes with a capillary or plasma glucose level ≤ 3.9 mmol/L with or without symptoms), and symptomatic hypoglycemia (episodes with clinical symptoms reported by the investigator as hypoglycemia, biochemical documentation not required).
- Secondary outcomes were as follows: changes from baseline in fasting plasma glucose (FGP), systolic and diastolic blood pressures (SBP and DBP); and incidence of genital tract infection, urinary tract infection, and serious adverse events at the end of intervention.

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Central Register of Controlled Trials published up to 10 January 2018
- RCTs had at least 8-week follow-up periods

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

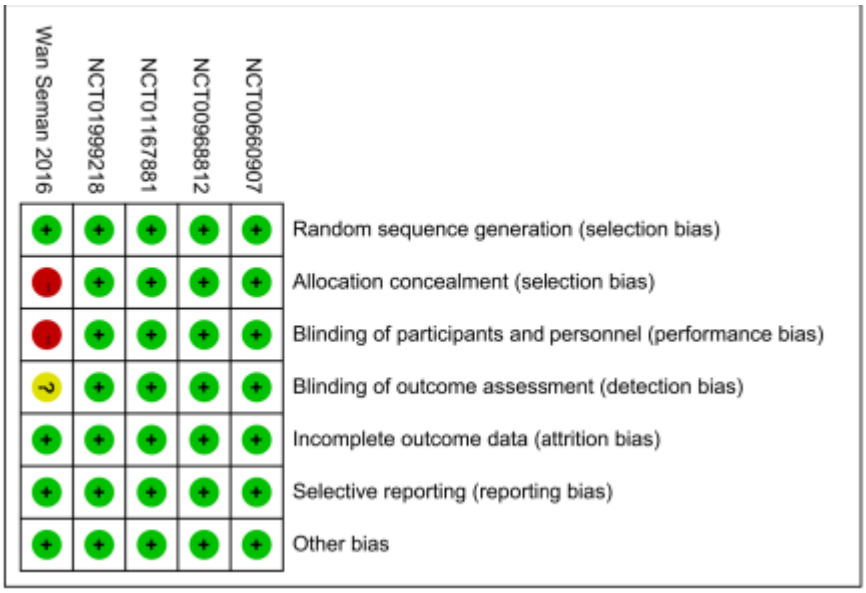
Anzahl eingeschlossener Studien:

- 5 RCTs (n=4300)

Charakteristika der Population:

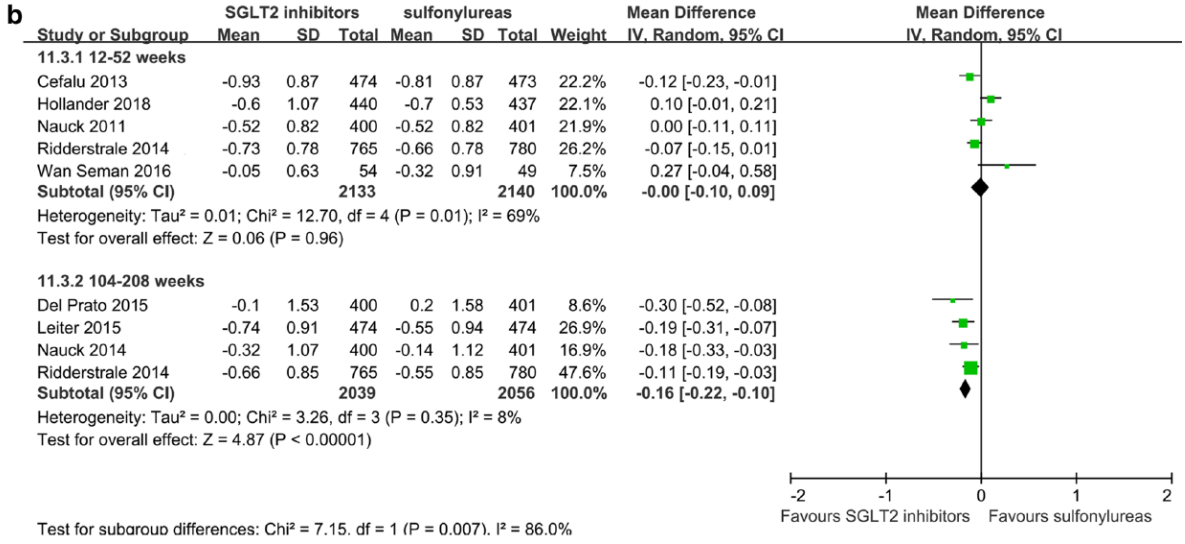
- Mean duration of the five trials was 96 weeks (range 12–208 weeks). Patients had a mean baseline HbA1c of 7.78% (range 7.65–7.92), mean baseline body mass index (BMI) of 30.8 kg/m2 (29.8–31.5), and mean duration of diabetes of 6.5 years (5.5–7.5).
- Two trials (NCT00660907, Wan [21]) compared dapagliflozin with SUs, one trial (NCT00968812) compared canagliflozin with a SU, one trial (NCT01167881) compared empagliflozin with a SU, and one study (NCT01999218) compared ertugliflozin with a SU.
- Outcomes of three trials (NCT00660907, NCT00968812, NCT01167881) were assessed at different durations of follow-up, and two trials (NCT00968812, NCT01999218) used two doses of SGLT2 inhibitors

Qualität der Studien:

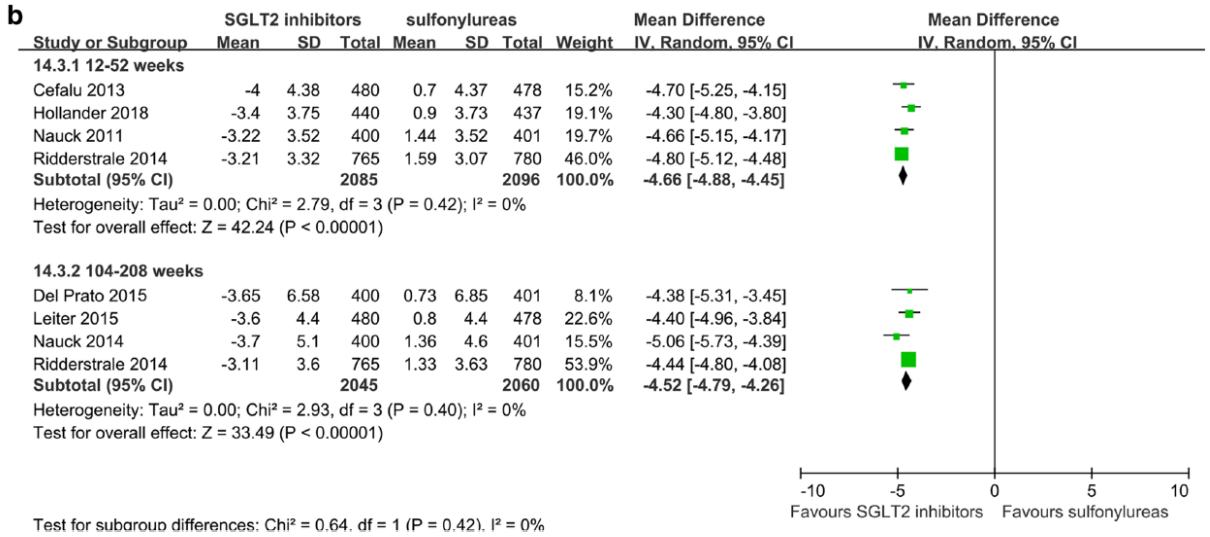


Studienergebnisse:

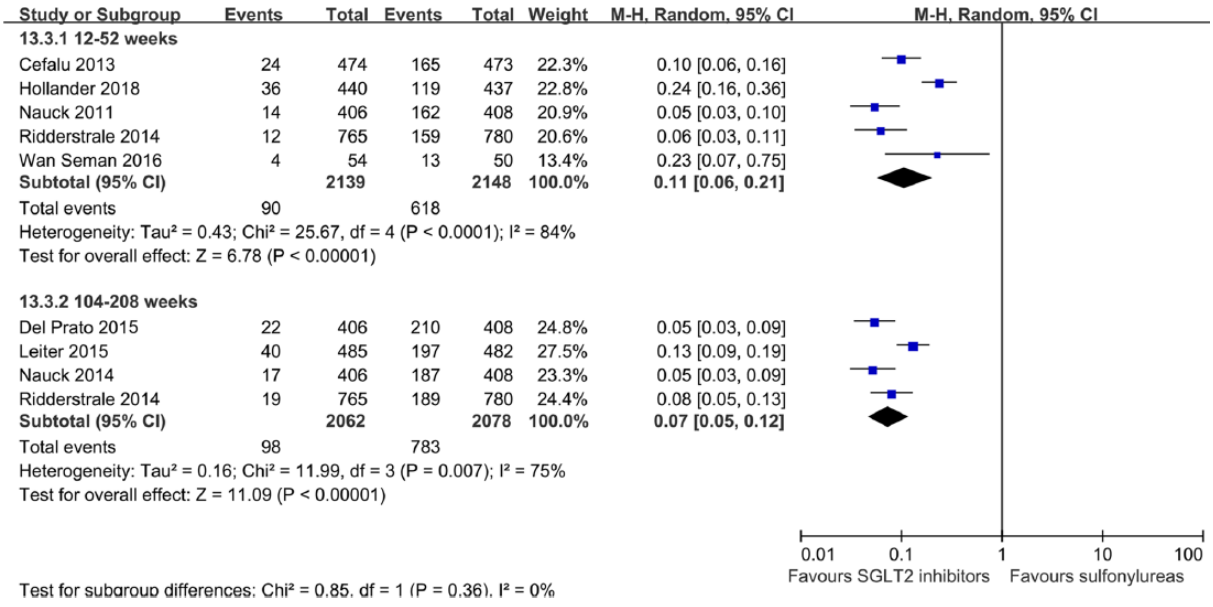
HbA1c



Weight



Hypoglycemia



Safety

- SGLT2 inhibitors led to greater reductions in FGP (MD − 0.53 [− 0.75, − 0.32] mmol/L, p < 0.00001), SBP (MD − 5.00 [− 5.77, − 4.22] mmHg, p < 0.00001), and DBP (MD − 2.19 [− 2.91, − 1.46] mmHg, p < 0.00001; Table 2), whereas the incidence of genital tract infection (OR 5.54 [3.63, 8.45], p < 0.00001) was significantly higher after SGLT2 inhibitor treatment compared with SUs (Table 3).
- There was no significant difference in the incidence of urinary tract infection (OR 1.17 [0.96, 1.43], p = 0.12) and serious adverse events (OR 1.02 [0.69, 1.52], p = 0.92) between the two groups

12. Nauck MA, Del PS, Duran-Garcia S, Rohwedder K, Langkild AM, Sugg J, et al. Durability of glycaemic efficacy over 2 yea with dapagliflozin versus glipizide as add-on therapies in patient whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes Obes Metab. 2014;16(11):1111–20.
17. Leiter LA, Yoon KH, Arias P, Langslet G, Xie J, Balis DA, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015;38(3):355–64.
18. Del PS, Nauck M, Duran-Garcia S, Maffei L, Rohwedder K, Theuerkauf A, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes Obes Metab. 2015;17(6):581–90.
19. Hollander P, Liu J, Hill J, Johnson J, Jiang ZW, Golm G, et al. Ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: the VERTIS SU randomized study. Diabetes Ther. 2018;9(1):193–207.
20. Ridderstrale M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride a add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2(9):691–700.
21. Wan SWJ, Kori N, Rajoo S, Othman H, Mohd NN, Wahab NA, et al. Switching from sulphonylurea to a sodium-glucose cotransporter2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia. Diabetes Obes Metab. 2016;18(6):628–32.
27. Nauck MA, Del PS, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double- blind, active-controlled noninferiority trial. Diabetes Care. 2011;34(9):2015–22.

Anmerkung/Fazit der Autoren

Despite similar glycemic efficacy over a relatively short term, SGLT2 inhibitors are more effective over a longer term than SUs as add-on treatment to metformin. In addition, SGLT2 inhibitors produce less hypoglycemic events and lead to greater reductions in weight and blood pressure compared with SUs. Finally, SGLT2 inhibitors appear to be well tolerated apart from genital tract infection, which is frequent but usually mild. Therefore, SGLT2 inhibitors might be effective and well tolerated second-line agents for patients with T2DM who have not achieved good glycemic control on metformin alone.

Dai D et al., 2019 [18].

Efficacy and hypoglycemic risk of sitagliptin in obese/overweight patients with type 2 diabetes compared with GLP-1 receptor agonists.

Fragestellung

To assess the efficacy and hypoglycemic risk of sitagliptin versus that of GLP-1 receptor agonists in the management of obese/overweight patients with T2DM.

Methodik

Population:

T2DM patients

Intervention/Komparator:

Sitagliptin vs. GLP-1 receptor agonists

Endpunkte:

Decreases in hemoglobin A1c (HbA1C) levels, the percentage of patients achieving an HbA1C goal of <7%, weight loss, decreases in fasting plasma glucose (FPG) and postprandial plasma glucose (PPG), and decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP); incidence of hypoglycemia

Recherche/Suchzeitraum:

EMBASE, PubMed, Cochrane Library, and ClinicalTrials.gov until March 2018

Qualitätsbewertung der Studien:

Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 studies

Charakteristika der Population:

- Seven RCTs were parallel studies, and 1 was a crossover study.
- Patients had been treated with a stable metformin regimen in 7 trials and metformin or thiazolidinedione in 1 trial.

- The mean BMI at baseline ranged from 31kg/m2 to 36.8kg/m2 in the sitagliptin group and 31kg/m2 to 36.8kg/m2 in the GLP-1 receptor agonist group.
- The mean values of HbA1C at baseline ranged from 8.1% to 8.5% in the sitagliptin group and 8.1% to 8.6% in the GLP-1 receptor agonist group.
- 1240 patients were included in the sitagliptin group, and 75.8% were White, 7.2% were Black, 7.7% were Asian (a study by Charbonnel et al did not report this value) and 9.3% were other races
- 1378 patients were included in the GLP-1 receptor agonist group, and 76.2% were White, 6.1% were Black, 6.4% were Asian (a study by Charbonnel et al did not report this value), and 11.3% were other races.

Qualität der Studien:

The participants of all 8 trials were randomly allocated, 5 studies adequately described the methods of randomization and others did not mention it. There were no differences in the baseline characteristics between the sitagliptin group and the GLP-1 receptor agonist group. Studies by Charbonel et al and Gadde et al were not blinded to the participants. All 8 studies clearly reported participants withdrawing from the trial and accounted for it.

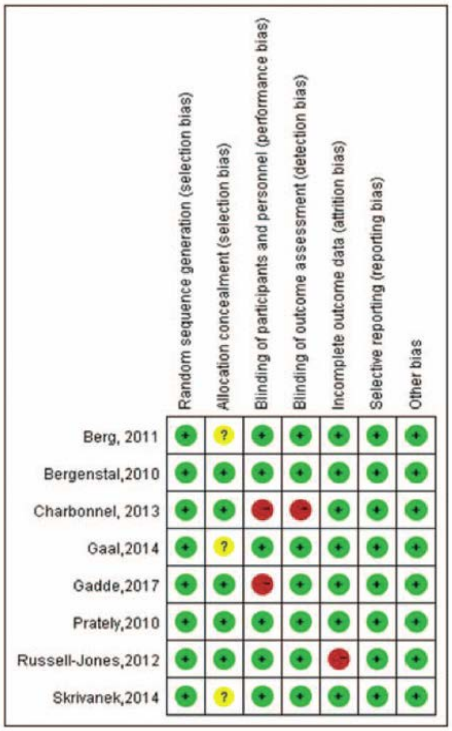


Figure 3. Risk of bias for the included studies.

Studienergebnisse:

- Compared with GLP-1 receptor agonists, sitagliptin was less effective at reducing HbA1c (0.42 [0.27, 0.56]), FPG (0.78 [0.36, 1.19]), PPG (2.61 [1.35, 3.87]), and body weight (1.42 [0.71, 2.14]).
- Conversely, there were no significant differences in SBP reduction (0.38 [-1.14, 1.89]), DBP reduction (-0.30 [-1.00, 0.39]), and hypoglycemic risk (1.09 [0.50, 2.35]).

Summary of meta-analyses for outcome measures from included studies.

Outcome	No. of studies contributing data	Risk Ratio (95% CI), sitagliptin vs GLP-1 receptor agonists	Mean Difference (95% CI), sitagliptin vs GLP-1 receptor agonists	No. of participants of experimental group	No. of participants of control group	I^2 heterogeneity, %	P
Decrease in HbA_{1C}	7		0.42 [0.27, 0.56]	1376	1473	68	<.00001
participants achieving HbA_{1C} goal of <7.0%	7	0.70 [0.58, 0.83]		1391	1493	80	<.0001
Decrease in FPG	8		0.78 [0.36, 1.19]	1418	1514	86	.0003
Decrease in PPG	3		2.61 [1.35, 3.87]	238	242	75	<.00001
Decrease in body weigh	6		1.42 [0.71, 2.14]	1115	1226	85	<.00001
Decrease in SBP	5		0.38 [−1.14, 1.89]	954	1073	50	.63
Decrease in DBP	5		−0.30 [−1.00, 0.39]	954	1073	5	.4
Participants experiencing hypoglycemia	8	1.09 [0.50, 2.35]		1543	1666	77	.84

DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA_{1C} = hemoglobin A_{1C}, PPG = postprandial plasma glucose, SBP = systolic blood pressure.

Subgroup analysis:

Factor	Studies, n	Mean Difference (95% CI), sitagliptin vs GLP-1 receptor agonists	Risk Ratio (95% CI), sitagliptin vs GLP-1 receptor agonists	I^2 (%)	P
Subgroup analyses for decrease in HbA1c (%)					
Type of GLP-1 receptor agonists					
Exenatide	3	0.48 [0.33, 0.63]		2	< .00001
liraglutide	2	0.37 [0.24, 0.50]		0	< .00001
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	0.54 [0.42, 0.66]		19	< .00001
Short-acting GLP-1 receptor agonists	3	0.27 [0.06, 0.48]		66	.01
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3	0.42 [0.06, 0.79]		87	.02
Studies including the potential confounding factor	4	0.39 [0.28, 0.49]		0	< .00001
Subgroup analyses for the percentage of patients achieving HbA1c goal of <7.0%					
Type of GLP-1 receptor agonists					
Exenatide	3			50	<.00001
liraglutide	2		0.68[0.39, 1.18]	92	.17
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4		0.64 [0.56, 0.73]	29	<.00001
Short-acting GLP-1 receptor agonists	3		0.77 [0.55, 1.07]	85	.12
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3		0.68[0.49, 0.94]	83	.02
Studies including the potential confounding factor	4		0.71[0.56, 0.89]	78	.003
Subgroup analyses for decrease in FPG (mmol/l)					
Type of GLP-1 receptor agonists					
Exenatide	4	0.66 [0.09, 1.22]		80	.02
liraglutide	2	1.13 [0.85, 1.41]		0	<.00001
Formulation of long-acting GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	1.08 [0.72, 1.44]		56	<.00001
Short-acting GLP-1 receptor agonists	4	0.52 [−0.16, 1.21]		90	.13
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	4	0.52 [−0.30, 1.35]		93	.21
Studies including the potential confounding factor	4	1.08 [0.85, 1.31]		7	<.00001
Subgroup analyses for weight loss (kg)					
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	1.33 [0.31, 2.36]		90	.01
Short-acting GLP-1 receptor agonists	2	1.65 [1.09, 2.20]		0	<.00001
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3	1.82 [1.24, 2.41]		49	<.00001
Studies including the potential confounding factor	3	1.01 [−0.16, 2.19]		89	.09

Anmerkung/Fazit der Autoren

In conclusion, for obese/overweight patients, sitagliptin might exert a less potent effect regarding HbA1C, FPG, PPG, and weight reduction than GLP-1 receptor agonists; however, there was no

difference in hypoglycemic risk. Meanwhile, long-acting GLP-1 receptor agonists seemed more effective in reducing FPG.

Dicembrini I et al., 2019 [21].

Peripheral artery disease and amputations with Sodium-Glucose co-Transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials

Fragestellung

Aim of the present metanalysis is the assessment of the effect of SGLT-2 inhibitors on peripheral artery disease and lower limb amputations in randomized controlled trials performed in patients with type 2 diabetes.

Methodik

Population:

- Type 2 diabetes

Intervention:

- SGLT-2 inhibitors (i.e., canagliflozin 100/300 mg, dapagliflozin 5/10 mg, empagliflozin 10/25 mg, ertugliflozin 5/15 mg, ipragliflozin 25/50 mg, luseogliflozin 2.5/5 mg, and tofogliflozin 20 mg)
  - Treatment duration at least 52 weeks

Komparator:

- Placebo or active comparator

Endpunkte:

- Incidence of peripheral artery disease, as reported by investigators as serious adverse event.
  - A further outcome was amputation of lower limbs, specified as serious adverse event.

Recherche/Suchzeitraum:

  - Medline, clinicaltrials.gov, FDA till December 1st, 2018.

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

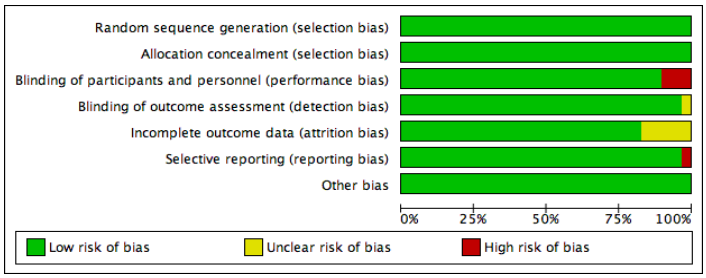
Anzahl eingeschlossener Studien:

- 27 RCTs (29,404 and 21,556 patients in SGLT-2 inhibitor and comparator groups)

Charakteristika der Population:

- Mean duration of treatment of 84.0 weeks. The mean age, duration of diabetes, baseline HbA1c, and BMI of enrolled patients at baseline were 59.0 years, 8.3 years, 8.0%, and 30.9 Kg/m2, respectively

Qualität der Studien:



Studienergebnisse:

Peripheral artery disease

- Cases of peripheral artery disease were reported in 14 trials (3, 6, and 5 with dapagliflozin, canagliflozin, and empagliflozin, respectively), with 301 cases in SGLT-2 inhibitors and 177 cases in control groups.
- The overall incidence of peripheral artery disease was increased with SGLT-2 inhibitors (MH-OR 1.26 [1.04–1.52].

Amputations

- Risk of amputations for SGLT-2 inhibitors versus different comparators: Odds ratio: 0,83 [0,55; 1,25], p=0,38; I2: 52%
- Only with canagliflozin a significant risk was observed: MH-Odds Ratio 1,80 [1,28; 2,54}]; p=0,0008; I2: 0%, 6 RCTs

Anmerkung/Fazit der Autoren

At present, there is no reason to believe that empagliflozin or dapagliflozin increase the risk of either peripheral artery disease of lower limb amputations. Canagliflozin could be associated with a specific risk, which needs to be further investigated.

Dicembrini I et al., 2019 [20]. + Cosentino C et al., 2019 [15].

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and cancer: A meta-analysis of randomized controlled trials

+

Cosentino C et al., 2019 [15]. Nephrolithiasis and sodium-glucose co-transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials

(Zusätzliche Analysen auf Grundlage des Reviews von Dicembrini et al., 2019)

Fragestellung

The aim of the present meta-analysis was to assess the effects of SGLT-2 inhibitors on the overall incidence of malignancies and on different types of cancer, summarizing the results of trials with a duration of at least 1 year.

Methodik

Population:

- Type 2 diabetes

Intervention:

- SGLT-2 inhibitors (ie, canagliflozin 100/300 mg, dapagliflozin 5/10 mg, empagliflozin 10/25 mg, ertugliflozin 5/15 mg, ipragliflozin 25/50 mg, luseogliflozin 2.5/5 mg and tofogliflozin 20 mg)

Komparator:

- Placebo or active control other than SGLT-2 inhibitors. Sergliflozin and remogliflozin were discontinued

Endpunkte:

- All types of cancer and several site-specific cancers (ie breast, pulmonary, gastrointestinal, hepatic, pancreatic, skin, prostate and bladder)
- Nephrolithiasis

Recherche/Suchzeitraum:

- Medline up to 1 December 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

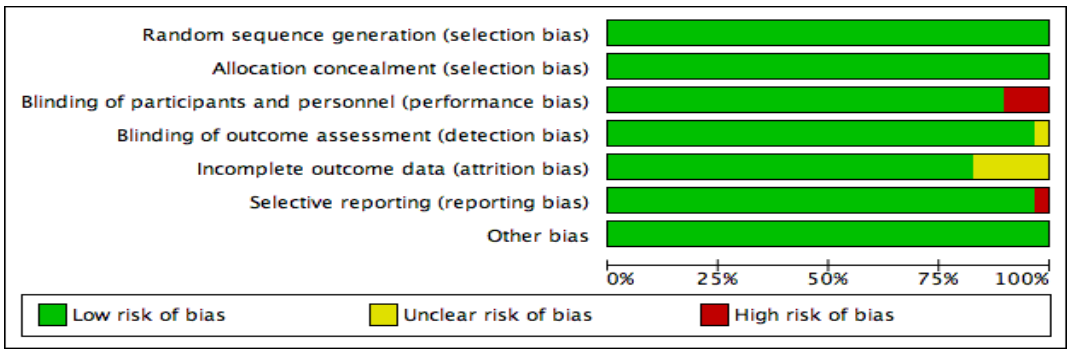
Anzahl eingeschlossener Studien:

- 27 trials (n=27744)

Charakteristika der Population:

- Mean duration of treatment of 84 weeks.
- Mean age, duration of diabetes, baseline HbA1c and BMI of enrolled patients at baseline were 59.0, 8.3 years, 8.0% and 30.9 Kg/m2, respectively.

Qualität der Studien:



Studienergebnisse:

- Among the 1659 cases of cancer (938 and 721 in patients treated with SGLT2-is and comparators, respectively), 197 (11.9%) were prostate cancers, 121 (7.3%) were skin cancers,

107 (6.5%) were breast cancers, 126 (7.6%) were gastrointestinal tract cancers, 106 (6.4%) were bladder cancers, 88 (5.3%) were respiratory airways cancers, 36 (2.2%) were kidney cancers, 29 (1.7%) were pancreas cancers, 23 were female genital tract cancers (1.4%) and 17 (1.0%) were liver cancers.

- No difference was observed in the overall incidence of malignancies between patients allocated to SGLT-2is and those allocated to comparators (MH-OR 0.98 [0.77–1.24]), with no evidence of heterogeneity. No significant difference in the effect on overall malignancies was observed when trials with different comparators, (Figure 1) or with different SGLT- 2 inhibitors (Figure 2), were analysed separately
- No association of SGLT-2 inhibitors with nephrolithiasis was observed (MH-OR 0.85 [0.57–1.26). I2 statistics did not suggest any relevant heterogeneity.
- In subgroup analyses, risk of nephrolithiasis was 1.04 [0.51–2.13], 0.70 [0.35–1.41], 0.82 [0.43–1.60], and 1.48 [0.06–36.34], all p > 0.50, for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, respectively.
- When comparing SGLT-2 inhibitors with different comparators, the risk of nephrolithiasis was 0.69 [0.17–2.79], 0.87 [0.57–1.33], and 1.17 [0.06–24.66] (all p > 0.050) versus insulin secretagogues, placebo, and metformin, respectively.
- Similarly, non between-group difference was detected in the risk of renal colic (MH-OR 0.70 [0.24–2.01]), hydronephrosis (MH-OR 1.06 [0.41–2.72]), and urinary retention (MH-OR 1.29 [0.63–2.64];

Anmerkung/Fazit der Autoren

In conclusion, available data from randomized trials do not suggest a detrimental effect of SGLT-2 inhibitors on the incidence of malignancies in general, or on the incidence of bladder cancer in particular. Further data should be collected from observational databases for a longer-term assessment.

In conclusion, based on the results of available randomized controlled trials, treatment with SGLT-2 inhibitors appears to be neither beneficial nor detrimental with respect to nephrolithiasis. The possible effects of SGLT-2 inhibitors on urinary concentrations and solubility of urate and oxalate are not sufficient to determine relevant differences in clinical outcomes.

Dorsey-Trevino, EG et al., 2019 [22].

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors and microvascular outcomes in patients with type 2 diabetes: systematic review and meta-analysis

Fragestellung

We conducted a systematic review of randomized trials to estimate the effectiveness of SGLT-2 inhibitors on patient important outcomes—that patients perceive and value—and surrogate outcomes—laboratory parameters that are oblivious to patient's perception—of microvascular complications in adult patients with type 2 diabetes.

Methodik

Population:

- adult patients with type 2 diabetes

Intervention:

- SGLT-2 inhibitors

Komparator:

- Active treatment or placebo

Endpunkte:

- end-stage renal disease (ESRD) defined as the need for continuous renal replacement therapy or renal transplant, chronic renal disease stage > II, and renal death
- diabetes-related blindness, vitreous hemorrhage, retinal detachment, severe macular edema, and retinal artery occlusion
- pain, numbness, sensory loss (touch or vibration), and quality of life, wound healing, ulcers, or limb amputation

Recherche/Suchzeitraum:

- Ovid, EMBASE, Web of Science, Scopus from each database's inception to May 05, 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

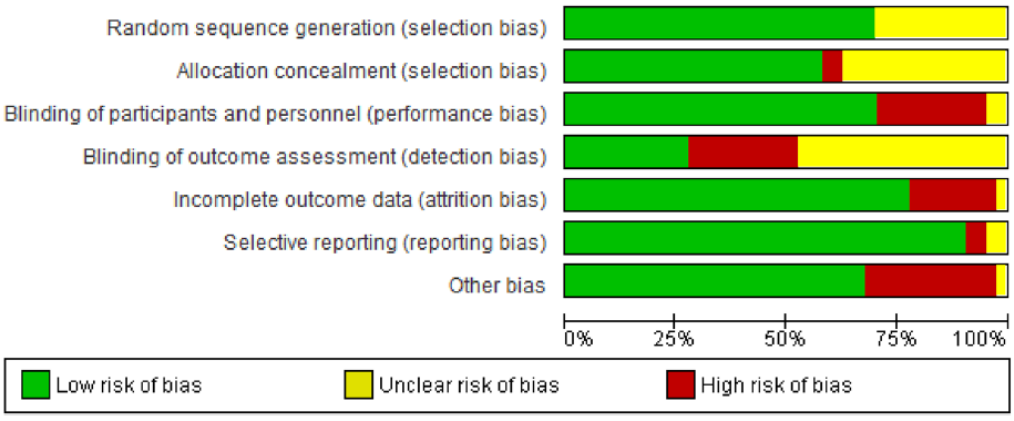
Anzahl eingeschlossener Studien:

- 40 RCTs

Charakteristika der Population:

- n=57560
- duration between 8 and 208 weeks

Qualität der Studien:



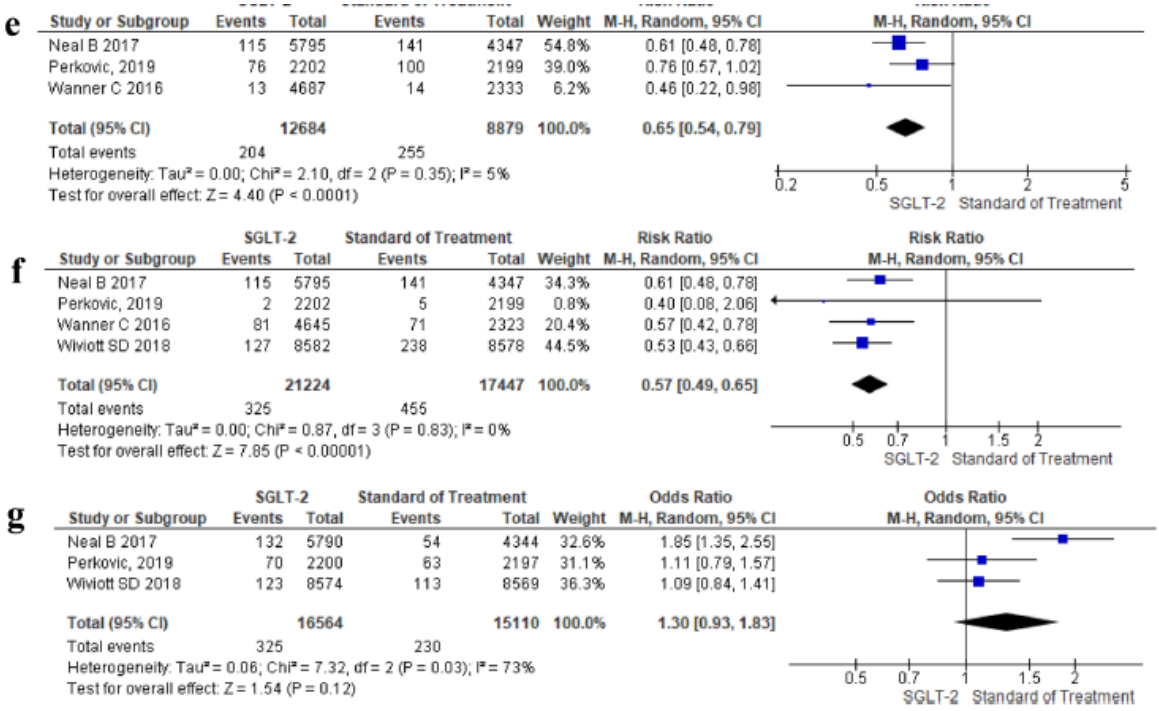
Studienergebnisse:

Renal microvascular outcomes

- a 35% reduction in the risk of renal replacement therapy (0.65, 95% CI 0.54–0.79 I2 = 5% 3 RCTs)

- a 43% reduction of death from renal causes (0.57, 95% CI 0.49–0.65 I2 = 0% 4 RCTs)

Pooled analysis of (e) Renal-Replacement Therapy, (f) Renal Death, (g) Amputation



Anmerkung/Fazit der Autoren

Based on limited evidence dominated by four high-quality RCTs, SGLT-2 inhibitors may reduce the risk of patient important renal outcomes. This inference is weakened by the inconsistent effect of treatment on known precursors of these outcomes, the lack of blind independent adjudication of these endpoints, and the difficulty of attributing these effects to the use of these drugs. Their effects on other microvascular outcomes remain uncertain.

Giugliano D et al., 2019 [55].

Type 2 diabetes and risk of heart failure: a systematic review and meta-analysis from cardiovascular outcome trials

Fragestellung

We performed a meta-analysis of randomized controlled trials (RCTs) that evaluated the effect of dipeptidyl peptidase- 4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium glucose co-transporter-2 inhibitors (SGLT-2i) on heart failure (HF) risk in patients with type 2 diabetes (T2D).

Methodik

Population:

- T2D

Intervention/Komparator:

- add-on therapy with any DPP-4i, GLP-1RA, or SGLT-2i with placebo

Endpunkte:

- hospitalization for HF, MACE (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke)

Recherche/Suchzeitraum:

- PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials. Gov on 10 November 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

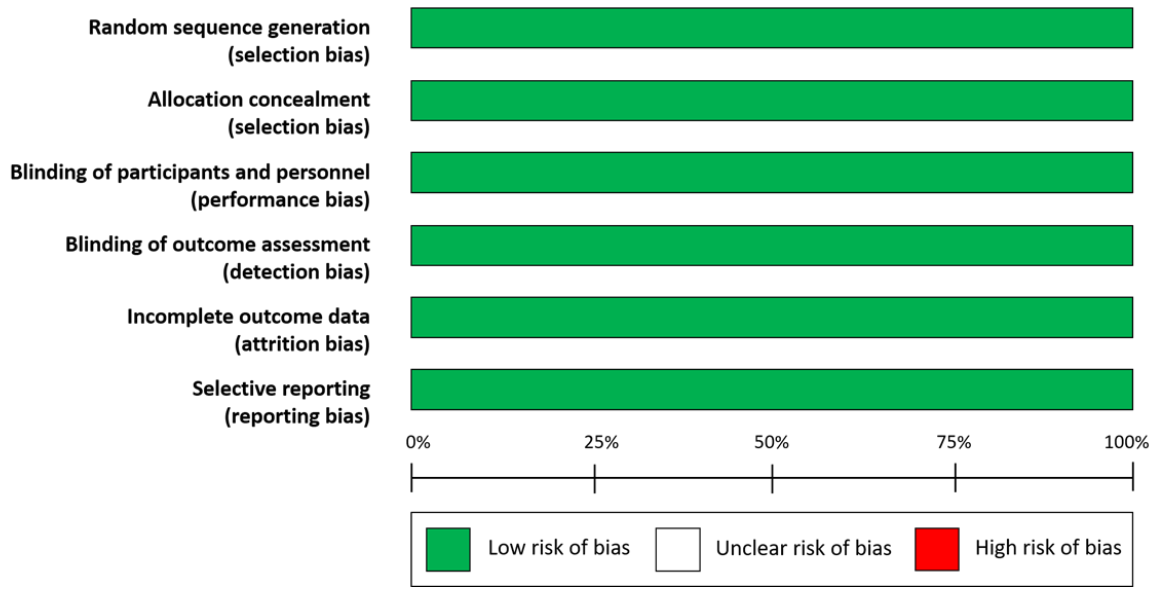
Anzahl eingeschlossener Studien:

- 12 RCTs (n=120765)

Charakteristika der Population:

- The participants were all patients with T2D (>18 years old).
- All trials were multinational and sponsored by industry. The trials have been published between 2013 and 2018, with 3 studies published in 2018. All trials were of parallel-group double-blind design, and their mean duration ranged from 1.5 to 4.2 years.
- The baseline HbA1c level ranged from 7.3% to 8.7%, but was almost identical between groups (drug vs placebo) within the same trial.
- The populations studied ranged in size from 3297 (SUSTAIN-6) to 17,160 (DECLARE) and were of similar age (range: 60–66 years).

Qualität der Studien:



Studienergebnisse:

Outcome	Trials (*n*)	Estimate (HR)	95% CI	*P* value	I^2 (%)	*P* value *Q* test
HF						
All	12	0.90	0.80–1.01	0.068	69.2	<0.001
DPP-4i	4	1.05	0.90–1.24	0.531	60.0	0.058
GLP-1 RAs	5	0.91	0.83–1.00	0.058	0	0.717
SGLT-2i	3	0.69	0.61–0.79	<0.001	0	0.741
MACE						
All	12	0.92	0.87–0.96	0.001	45.8	0.041
DPP-4i	4	0.99	0.94–1.05	0.798	0	0.948
GLP-1 RAs	5	0.88	0.80–0.96	0.005	58.8	0.045
SGLT-2i	3	0.89	0.83–0.96	0.001	0	0.550
CV mortality						
All	12	0.90	0.83–0.97	0.009	48.3	0.031
DPP-4i	4	0.98	0.89–1.08	0.655	2.6	0.379
GLP-1 RAs	5	0.88	0.80–0.96	0.004	0	0.518
SGLT-2i	3	0.81	0.63–1.05	0.116	79.9	0.007
Non-fatal MI						
All	12	0.93	0.87–0.99	0.018	27.6	0.174
DPP-4i	4	1.00	0.92–1.10	0.928	0	0.445
GLP-1 RAs	5	0.90	0.80–1.01	0.063	50.9	0.087
SGLT-2i	3	0.88	0.79–0.97	0.011	0	0.935
Non-fatal stroke						
All	12	0.95	0.88–1.03	0.203	8.6	0.361
DPP-4i	4	1.00	0.87–1.14	0.949	0	0.664
GLP-1 RAs	5	0.87	0.77–0.99	0.028	6.0	0.373
SGLT-2i	3	1.02	0.87–1.19	0.803	25.7	0.260
All-cause mortality						
All	12	0.92	0.86–0.98	0.013	55.4	0.010
DPP-4i	4	1.01	0.93–1.09	0.792	14.1	0.322
GLP-1 RAs	5	0.89	0.83–0.95	0.001	0	0.663
SGLT-2i	3	0.83	0.70–0.99	0.013	75.2	0.018

15.
B.M. Scirica, D.L. Bhatt, E. Braunwald, P.G. Steg, J. Davidson, B. Hirshberg, P. Ohman, R. Frederich, S.D. Wiviott, E.B. Hoffman, M.A. Cavender, J.A. Udell, N.R. Desai, O. Mosenzon, D.K. McGuire, K.K. Ray, L.A. Leiter, I. Raz; SAVOR-TIMI 53 Steering Committee and Investigators, Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N. Engl. J. Med. 369, 1317–1326 (2013)CrossRefPubMedGoogle Scholar
16.
W.B. White, C.P. Cannon, S.R. Heller, S.E. Nissen, R.M. Bergenstal, G.L. Bakris, A.T. Perez, P.R. Fleck, C.R. Mehta, S. Kupfer, C. Wilson, W.C. Cushman, F. Zannad; EXAMINE Investigators, Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N. Engl. J. Med. 369, 1327–1335 (2013)CrossRefPubMedGoogle Scholar
17.
J.B. Green, M.A. Bethel, P.W. Armstrong, J.B. Buse, S.S. Engel, J. Garg, R. Josse, K.D. Kaufman, J. Koglin, S. Korn, J.M. Lachin, D.K. McGuire, M.J. Pencina, E. Standl, P.P. Stein, S. Suryawanshi, F. Van de Werf, E.D. Peterson, R.R. Holman; TECOS Study Group, Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 373, 232–242 (2015)CrossRefPubMedGoogle Scholar
18.
J. Rosenstock, V. Perkovic, O.E. Johansen, M.E. Cooper, S.E. Kahn, N. Marx, J.H. Alexander, M. Pencina, R.D. Toto, C. Wanner, B. Zinman, H.J. Woerle, D. Baanstra, E. Pfarr, S. Schnaidt, T. Meinicke, J.T. George, M. von Eynatten, D.K. McGuire; CARMELINA Investigators, Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk. The CARMELINA randomized clinical trial. J. Am. Med. Assoc. 321, 69–79 (2019)Google Scholar
19.
M.A. Pfeffer, B. Claggett, R. Diaz, K. Dickstein, H.C. Gerstein, L.V. Køber, F.C. Lawson, L. Ping, X. Wei, E.F. Lewis, A.P. Maggioni, J.J. McMurray, J.L. Probstfield, M.C. Riddle, S.D. Solomon, J.C. Tardif; ELIXA Investigators, Lixisenatide in

patients with type 2 diabetes and acute coronary syndrome. N. Engl. J. Med. 373, 2247–2257 (2015)CrossRefPubMedGoogle Scholar
20.
S.P. Marso, G.H. Daniels, K. Brown-Frandsen, P. Kristensen, J.F. Mann, M.A. Nauck, S.E. Nissen, S. Pocock, N.R. Poulter, L.S. Ravn, W.M. Steinberg, M. Stockner, B. Zinman, R.M. Bergenstal, J.B. Buse; LEADER Steering Committee; LEADER Trial Investigators, Liraglutide and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 375, 311–322 (2016)CrossRefPubMedPubMedCentralGoogle Scholar
21.
S.P. Marso, S.C. Bain, A. Consoli, F.G. Eliaschewitz, E. Jódar, L.A. Leiter, I. Lingvay, J. Rosenstock, J. Seufert, M.L. Warren, V. Woo, O. Hansen, A.G. Holst, J. Pettersson, T. Vilsbøll; SUSTAIN-6 Investigators, Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N. Engl. J. Med. 375, 1834–1844 (2016)CrossRefPubMedPubMedCentralGoogle Scholar
22.
R.R. Holman, M.A. Bethel, R.J. Mentz, V.P. Thompson, Y. Lokhnygina, J.B. Buse, J.C. Chan, J. Choi, S.M. Gustavson, N. Iqbal, A.P. Maggioni, S.P. Marso, P. Öhman, N.J. Pagidipati, N. Poulter, A. Ramachandran, B. Zinman, A.F. Hernandez; EXSCEL Study Group, Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 377, 1228–1239 (2017)CrossRefPubMedGoogle Scholar
23.
A.F. Hernandez, J.B. Green, S. Janmohamed, R.B. D'Agostino Sr, C.B. Granger, N.P. Jones, L.A. Leiter, A.E. Rosenberg, K.N. Sigmon, M.C. Somerville, K.M. Thorpe, J.J.V. McMurray, S. Del Prato; Harmony Outcomes committees and investigators, Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 392, 1519–1529 (2018)CrossRefPubMedGoogle Scholar
24.
B. Zinman, C. Wanner, J.M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, M. Mattheus, T. Devins, O.E. Johansen, H.J. Woerle, U.C. Broedl, S.E. Inzucchi; EMPA-REG OUTCOME Investigators, Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N. Engl. J. Med. 373, 2117–2128 (2015)CrossRefPubMedGoogle Scholar
25.
B. Neal, V. Perkovic, K.W. Mahaffey, D. de Zeeuw, G. Fulcher, N. Erondu, W. Shaw, G. Law, M. Desai, D.R. Matthews; CANVAS Program Collaborative Group, Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med. 377, 644–657 (2017)CrossRefPubMedGoogle Scholar
26.
S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, M.S. Sabatine; DECLARE–TIMI 58 Investigators, Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 380, 347–357 (2019)

Anmerkung/Fazit der Autoren

In conclusion, the findings of this meta-analysis suggest that SGLT-2i are useful in the prevention and treatment of HF in T2D patients. Future CV outcome trials of glucoselowering therapies should enroll a proportion of patients with baseline HF similar to the prevalence of HF in the general population with T2D.

Jingfan Z et al., 2019 [59].

Efficacy and safety of sodium glucose cotransporter-2 inhibitor in type 2 diabetes mellitus wit inadequate glycemic control a metformin: a meta-analysis

Fragestellung

We conducted the present meta-analysis to update and synthesize the efficacy and safety of SGLT2-i, as addon to metformin in T2DM patients with inadequate glycemic control in metformin alone.

Methodik

Population:

- adult patients of T2DM with inadequate glycemic control on metformin

Intervention:

- SGLT2-i as add-on to metformin

Komparator:

- Placebo combined with metformin

Endpunkte:

- change of fasting plasma glucose (FPG), the change of HbA1C, the change of body weight, the change of systolic blood pressure (SBP) and diastolic blood pressure (DBP),
- special interest adverse events (AEs) of SGLT2-i included hypoglycemia AEs, AEs suggestive of urinary tract infection (UTI), AEs suggestive of genital infection (GI), and volume related AEs-hypotension/dehydration/ hypovolemia.

Recherche/Suchzeitraum:

- MEDLINE (1978 to November 2017), Embase (1974 to November 2017) and Cochrane Collaborative database

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 studies (11-19) with total 2509 patients

Charakteristika der Population:

Table 1. Basic characteristics of included studies

Study (year)	Age (years) Mean ± SD		Male (%)		Study duration (weeks)	Number of patients		Dosage		Revised Jadad score
	SGLT2-i plus MET	PBO plus MET	SGLT2-i plus MET	PBO plus MET		SGLT2-i plus MET	PBO plus MET	SGLT2-i	MET	
Lu CH (11) (2016)	53.9 ± 11.3	53.4 ± 11.3	50.6	39.8	24	87	83	IPRA 50 mg/d	≥ 1500 mg/d (or ≥ 1000 mg/d if safety concerns prohibited higher doses)	7
Bailey CJ (12) (2013)	54.4 ± 9.4	53.7 ± 10.3	50	55	102	137	137	DAPA 5 mg/d	≥ 1500 mg/d	7
Lavalle-González FJ (13) (2013)	55.5 ± 9.4	55.3 ± 9.8	47.3	51.4	26	368	183	CANA 100 mg/d	≥ 2000 mg/d (or ≥ 1500 mg/d if unable to tolerate higher dose)	6
Wilding JP (14) (2012)	58.6 ± 7.6	57.3 ± 8.6	47.1	54.5	12	68	66	IPRA 50 mg/d	≥ 1500 mg/d	3
Rosenstock J (15) (2013)	59 ± 9.0	60 ± 8.5	47	47	12	71	71	EMPA 10 mg/d	≥ 1500 mg/d or maximum tolerated dose	5
Merker L (16) (2015)	55.5 ± 9.9	56 ± 9.7	57.6	56	76	217	207	EMPA 10 mg/d	≥ 1500 mg/d or maximum dose according to the local label	5
Schumm-Draeger PM (17) (2015)	58.3 ± 9.0	58.5 ± 9.4	37	46.5	16	100	101	DAPA 5 mg/d	≥ 1500 mg/d	7
Ross S (18) (2015)	58.5 ± 10.8	57.9 ± 11.2	50.5	51.4	16	214	107	EMPA 10 mg/d	≥ 1500 mg/d	3
Yang W (19) (2016)	53.1 ± 9.1	53.5 ± 9.2	45.6	59.3	24	147	145	DAPA 5 mg/d	≥ 1500 mg/d	6

SGLT2-i: sodium-glucose co-transporter 2 inhibitors; MET: metformin; PBO: placebo; IPRA: ipragliflozin; DAPA: dapagliflozin; CANA: canagliflozin; EMPA: empagliflozin.

Qualität der Studien:

- The mean revised Jadad's score of 9 included RCTs was 5.4, and seven of nine studies had a score ≥ 5, which demonstrated the adequate methodologic quality of the enrolled studies

Studienergebnisse:

- The efficacy results of our meta-analysis showed that the SGLT2-i combined with metformin had
  - higher reduction level in HbA1C (%) [MD = -0.50, 95% CI (-0.62, -0.38), p 0.00001], however, with a great quantity of heterogeneity (I^2 = 68%);
  - higher reduction in body weight (kg) [MD = -1.72, 95% CI (-2.05, -1.39), p < 0.00001], with heterogeneity (I^2 = 52%) compared with metformin monotherapy
- No significant difference between the SGLT2-i plus metformin group and the metformin monotherapy
  - in the incidence risk of hypoglycemia [RR = 1.44, 95%CI (0.89, 2.32), p = 0.13],
  - or the risk of AEs of UTI [RR = 1.19, 95% CI (0.89, 1.58), p = 0.25],
  - nor the risk of volume related AEs [RR = 1.86, 95% CI (0.59, 5.90), p = 0.29].
- SGLT2-i plus metformin group presented higher risk of AEs of GI [RR = 3.98, 95% CI (2.38, 6.67), p < 0.00001], compared with the group of placebo plus metformin

12. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebocontrolled 102-week trial. BMC Med. 2013;11:43.
13. FJ Lavalle-Gonzalez, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013; 56: 2582-2592.
14. Wilding JP, Ferrannini E, Fonseca VA, Wilpshaar W, Dhanjal P, Houzer A. Efficacy and safety of ipragliflozin in patients with typ 2 diabetes inadequately controlled on metformin: a dose-finding study. Diabetes Obes Metab. 2013;15(5):403-9.
15. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab. 2013;15(12):1154-60.
16. Merker L, Häring HU, Christiansen AV, Roux F, Salsali A, Kim G, et al.; EMPA-REG EXTEND MET investigators. Empagliflozin as add-on to metformin in people with Type 2 diabetes. Diabet Med. 2015;32(12):1555-67.
17. Schumm-Draeger PM, Burgess L, Korányi L, Hruba V, Hamer-Maansson JE, de Bruin TW. Twice-daily dapagliflozin coadministere with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. Diabetes Obes Metab. 2015;17(1):42-51.
18. Ross S, Thamer C, Cescutti J, Meinicke T, Woerle HJ, Broedl UC. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2015;17(7):699-702.
19. Yang W, Han P, Min KW, Wang B, Mansfield T, T'Joen C, et al Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: A randomized controlled trial. J Diabetes. 2016;8(6):796-808.

Anmerkung/Fazit der Autoren

Overall, the present meta-analysis evaluated the effectiveness and safety of SGLT2-i plus metformin treatment, compared with metformin monotherapy in the T2DM patients with inadequate glycemic control on metformin alone. In conclusion, although the risk of genital infection may increase, SGLT2-i plus metformin may provide an attractive treatment option to those T2DM patients who are unable to achieve glycemic control with metformin alone, on account of its effects on glycemic control, reducing body weight and lowering blood pressure.

Kanters S et al., 2019 [60].

Comparative efficacy of once-weekly semaglutide versus SGLT-2 inhibitors in patients inadequately controlled with one to two oral antidiabetic drugs: a systematic literature review and network meta-analysis

Fragestellung

We sought to conduct an SLR and NMA to determine the efficacy of once-weekly semaglutide relative to SGLT-2is licensed in both Europe and North America among patients (aged ≥18 years) with T2D with inadequate glycaemic control using 1–2 OADs. A separate study has evaluated the comparative efficacy and safety of once-weekly semaglutide and SGLT-2i in T2D patients inadequately controlled with metformin.12

Methodik

Population:

- adults aged 18 years or older with T2D inadequately controlled with 1–2 prior OADs;

Intervention:

- 1.0 or 0.5 mg doses of once-weekly semaglutide, or any approved doses of SGLT-2is that are licensed in Europe and North America

Komparator:

- SGLT-2is: Empagliflozin 10 mg and 25 mg once daily, Canagliflozin 100 mg and 300 mg once daily, Dapagliflozin 5 mg and 10 mg once daily
- Other treatments that are connected with once-weekly once-weekly semaglutide and/or a SGLT-2i

Endpunkte:

- change from baseline HbA1c, weight, body mass index (BMI), and systolic blood pressure (SBP), postprandial blood glucose (PPG), fasting plasma glucose (FPG), proportion of patients achieving <7% or ≤6.5% HbA1c, proportion of patients achieving ≥5 or 10% wt loss,
- safety outcomes and triple composite outcome (based on reaching <7.0% HbA1c, having no hypoglycaemic events and no weight gain)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and CENTRAL through Ovid from January 1994 to 5 April 2016, with updates on 3 October 2016 and 16 August 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 trials

Charakteristika der Population:

- A majority of the trials were multicentre, phase III, double-blind trials. The only open-label trials were SUSTAIN 326 and SUSTAIN 7.27
- Duration of follow-up was reported in all 21 trials, ranging from 24 to 104 weeks; mean age ranged from 53.5 to 61.0 years25 28; mean weight at baseline ranged from 76.9 to 96.0 kg26 29; mean SBP ranged from 126 to 135 mm Hg21 30 and mean baseline HbA1c ranged from 7.2% to 9.3%.31 32

Qualität der Studien:

- The trials were considered to have low-risk of bias based on the assessment using Cochrane Risk of Bias Assessment tool.[14]
- The only source of high-risk bias came from the lack of blinding and selective reporting in few included trials.

Studienergebnisse:

- Grafik zur Netzwerksymmetrie siehe Anhang.

Relative efficacy with 95% credible intervals comparing HbA1c (%) in once-weekly semaglutide versus SGLT-2is

Table 4 Relative efficacy with 95% credible intervals comparing HbA_{1c} (%) in once-weekly semaglutid

	Mean difference for HbA_{1c} (%) random-effect NMA		
	Placebo	Once-weekly semaglutide 0.5 mg	Once-weekly semaglutide 1.0 mg
Placebo	–	–1.12 (–1.35 to –0.89)	–1.38 (–1.59 to –1.16)
Once-weekly semaglutide 0.5 mg	1.12 (0.89 to 1.35)	–	–0.26 (–0.38 to –0.13)
Once-weekly semaglutide 1.0 mg	1.38 (1.16 to 1.59)	0.26 (0.13 to 0.38)	–
Canagliflozin 100 mg once daily	0.67 (0.55 to 0.80)	–0.45 (–0.68 to –0.21)	–0.71 (–0.92 to –0.48)
Canagliflozin 300 mg once daily	0.82 (0.69 to 0.95)	–0.30 (–0.52 to –0.07)	–0.56 (–0.76 to –0.33)
Dapagliflozin 5 mg once daily	0.43 (0.29 to 0.57)	–0.70 (–0.96 to –0.43)	–0.95 (–1.20 to –0.69)
Dapagliflozin 10 mg once daily	0.58 (0.48 to 0.68)	–0.55 (–0.78 to –0.29)	–0.80 (–1.02 to –0.57)
Empagliflozin 10 mg once daily	0.59 (0.45 to 0.71)	–0.53 (–0.80 to –0.27)	–0.79 (–1.04 to –0.53)
Empagliflozin 25 mg once daily	0.61 (0.48 to 0.74)	–0.51 (–0.78 to –0.25)	–0.77 (–1.02 to –0.51)

Each cell represents the comparison (mean difference and 95% CrI) of the column treatment versus the row treatment. All bolded values are statistically meaningful at the 0.05 significance level.

Mean differences of change from baseline with 95% credible intervals comparing the relative efficacy of once-weekly semaglutide versus SGLT-2is using fixedeffect NMA

	Mean difference for weight (kg)		
	Placebo	Once-weekly semaglutide 0.5 mg	Once-weekly semaglutide 1.0 mg
Placebo	–	–2.62 (–3.21 to –2.03)	–3.98 (–4.54 to –3.43)
Once-weekly semaglutide 0.5 mg	2.62 (2.03 to 3.21)	–	–1.36 (–1.71 to –1.02)
Once-weekly semaglutide 1.0 mg	3.98 (3.43 to 4.54)	1.36 (1.02 to 1.71)	–
Canagliflozin 100 mg once daily	2.00 (1.66 to 2.34)	–0.62 (–1.22 to –0.01)	–1.98 (–2.56 to –1.40)
Canagliflozin 300 mg once daily	2.64 (2.26 to 3.01)	0.02 (–0.54 to 0.58)	–1.35 (–1.89 to –0.79)
Dapagliflozin 5 mg once daily	1.51 (1.14 to 1.87)	–1.11 (–1.79 to –0.43)	–2.48 (–3.13 to –1.82)
Dapagliflozin 10 mg once daily	1.82 (1.54 to 2.09)	–0.80 (–1.42 to –0.18)	–2.17 (–2.75 to –1.57)
Empagliflozin 10 mg once daily	1.74 (1.47 to 2.02)	–0.88 (–1.53 to –0.23)	–2.24 (–2.86 to –1.61)
Empagliflozin 25 mg once daily	1.98 (1.71 to 2.26)	–0.63 (–1.29 to 0.01)	–2.00 (–2.62 to –1.38)

Each cell represents the comparison (mean difference and 95% CrI) of the column treatment versus the row treatment. All bolded values are statistically meaningful at the 0.05 significance level.

Limitation

- while the population of interest was patients with inadequate glycaemic control using 1–2 OADs, a large number of studies only included patients on OAD monotherapy while others only included patients on dual therapy, which may have affected the homogeneity of the population. The pooling of such populations was required to ensure network connectivity, and models

adjusting for these differences through metaregression suggest minimal impact from these differences.

Anmerkung/Fazit der Autoren

Using an SLR and NMA, this study provided evidence in support of improved efficacy using once-weekly semaglutide relative to SGLT-2is licensed in Europe and North America for the treatment of patients with inadequate glycaemic control using 1–2 OADs.

Results of the NMA demonstrated that across most efficacy outcomes (HbA1c, target HbA1c<7%, weight loss and FPG), once-weekly semaglutide had the highest estimated efficacy. There was very strong evidence that once-weekly semaglutide led to larger decreases in both HbA1c and weight. Specifically, the magnitude of the differences was large and clinically meaningful.

Li X et al., 2019 [64]. + Cheng L et al., 2019 [13].

Effects of SGLT2 inhibitors on fractures and bone mineral density in type 2 diabetes: An updated meta-analysis

+

Cheng L et al., 2019 [13]. Risk of bone fracture associated with sodium-glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials

Fragestellung

The aim of the study is to update and determine the effects of sodium glucose cotransporter 2 (SGLT2) inhibitor therapy on fracture and bone mineral density (BMD) in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- patients with T2DM

Intervention:

- SGLT2 inhibitor therapy

Komparator:

- Placebo + background therapy

Endpunkte:

- incidence of bone fractures or a change in the bone mineral density (BMD) from baseline

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases and ClinicalTrials.gov
- randomized controlled trials (RCTs) extending at least 24 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

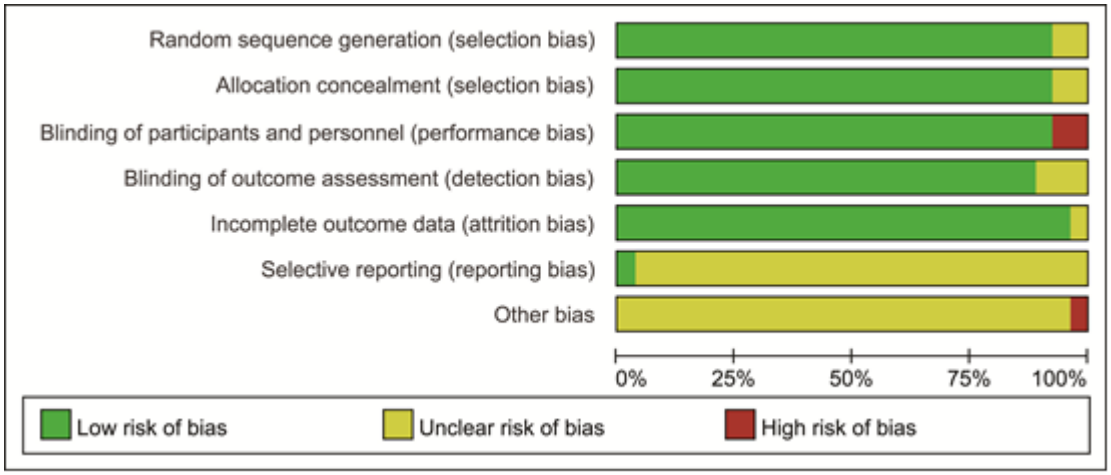
Anzahl eingeschlossener Studien:

- 27 trials that enrolled 20 895 patients

Charakteristika der Population:

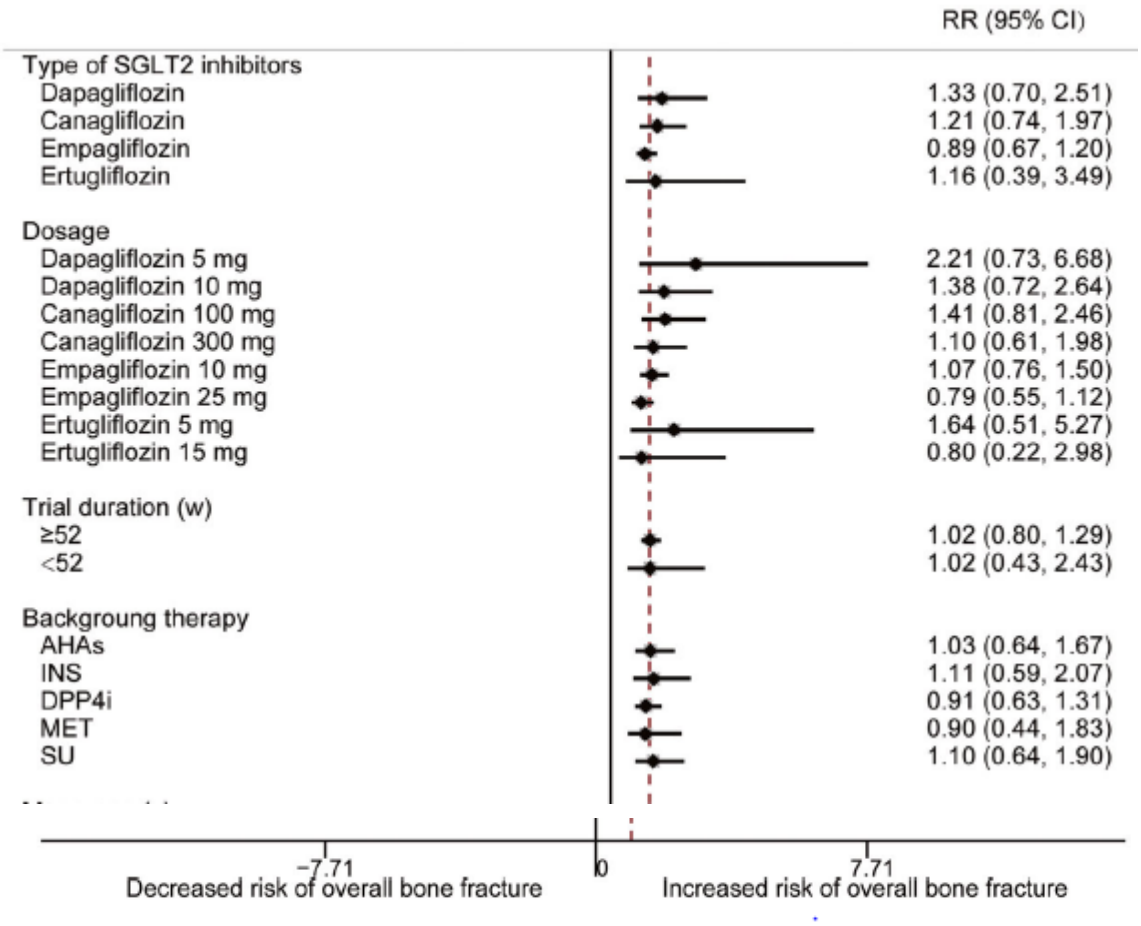
- The types of SGLT2 inhibitors used in these trials were as follows: dapagliflozin (eight studies, 29.63%), canagliflozin (seven studies, 25.93%), ertugliflozin (four studies, 14.81%), empagliflozin (seven studies, 25.93%), and ipragliflozin (one study, 3.70%).
- Fracture events occurred in 211 (1.55%) participants in the SGLT2 inhibitor groups (13581 in total) and 108 (1.48%) participants in the placebo groups (7314 in total).
- The trial durations ranged from 24 to 206 weeks, with an average of 64.22 weeks. A total of 19 (70.37%) trials had a duration greater than or equal to 52 weeks, and 8 (29.63%) trials had a duration less than 52 weeks
- In the 27 included trials, the mean age was greater than or equal to 60 years in 11 (40.74%) trials and less than 60 years in 16 (59.26%) trials, and the HbA1c was greater than or equal to 8% in 20 (74.08%) trials, less than 8% in 6 (22.22%) trials, and 1 (3.70%) trial lacked mean HbA1c data.

Qualität der Studien:



Studienergebnisse:

- Effect of SGLT2 inhibitors on fractures
- SGLT2 inhibitor therapy did not increase the risk of bone fracture (overall RR = 1.02, 95% CI [0.81, 1.28]), as shown in Figure 1. The pooled RR analysis presented low heterogeneity (I2 = 0.0%), and a fixed-effect model was conducted.
- The pooled RRs for dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin were 1.33 (95% CI [0.70, 2.51]), 1.21 (95% CI [0.74, 1.97]), 0.89 (95% CI [0.67, 1.20]), and 1.16 (95% CI [0.39, 3.49]), respectively.



Anmerkung/Fazit der Autoren

However, given that bone health damage is a relatively long-term process and may be affected by several external factors, SGLT2 inhibitors may not have adverse effects on bone health, but more long-term detailed data are needed to validate this conclusion.

Liao HW et al., 2019 [66].

Sodium-glucose cotransporter 2 inhibitor plus pioglitazone vs pioglitazone alone in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials.

Fragestellung

To evaluate the efficacy and safety of combined therapy with sodium-glucose cotransporter 2 (SGLT-2) inhibitors plus pioglitazone versus pioglitazone alone in type 2 diabetic patients.

Methodik

Population:

- Patients had a history of type 2 diabetes mellitus

Intervention/Komparator:

- SGLT-2 inhibitor plus pioglitazone vs. pioglitazone

Endpunkte:

- HbA1c, fasting glucose, body weight, hypoglycaemia, death, heart failure, urinary tract infection, genital tract infection

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov from 1966 to September 2018

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

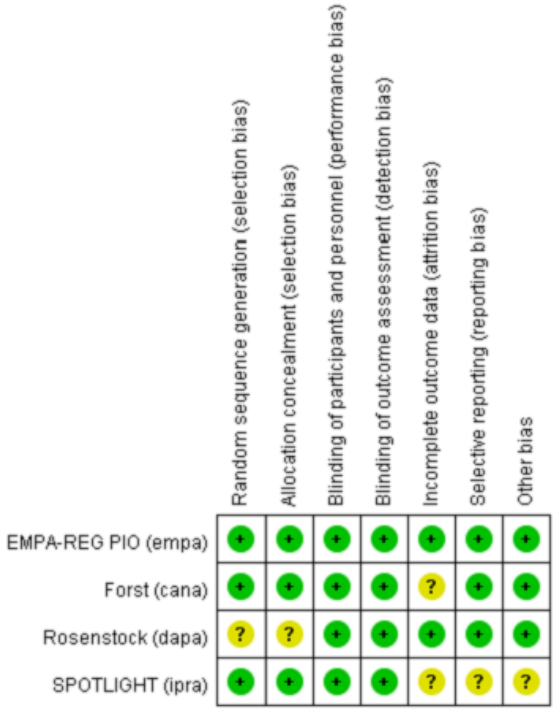
- Four randomized controlled trials with 1411 diabetic patients

Charakteristika der Population:

- About 938 participants were randomly assigned to the active group which received SGLT-2 inhibitor and background treatment with pioglitazone with or without metformin while 473 were randomly assigned to control group which received pioglitazone with or without metformin.

Qualität der Studien:

- The quality of a body of evidence was found to be low to moderate in most end-points.



Studienergebnisse:

- Pooling data from included trials showed that HbA1c change was significantly larger in both low-dose SGLT-2 inhibitors (MD: −0.59%, 95% CI: −0.77 to −0.41%; P < 0.001) and high dose SGLT-2 inhibitors (MD: −0.65%, 95% CI: −0.78 to −0.53%; P < 0.001) plus pioglitazone than pioglitazone alone in 24-26 weeks.

- Favourable outcomes were also found in achieving HbA1c <7% in SGLT-2 inhibitor plus pioglitazone (OR: 3.21, 95% CI: 1.99 to 5.16; P < 0.001).
- Pooling data from included trials showed fasting glucose reduction was larger in both low-dose SGLT-2 inhibitor plus pioglitazone (mean difference: −28.23 mg/dL, 95% CI: −36.57 to −19.89 mg/dL, P < 0.001) and high-dose SGLT-2 inhibitor plus pioglitazone (mean difference: −29.46 mg/dL, 95% CI: −35.58 to −23.34 mg/ dL, P < 0.001) than pioglitazone alone.
- Low-dose and high-dose SGLT-2 inhibitors plus pioglitazone were associated with larger weight change than pioglitazone alone (low-dose: mean difference: −2.22 kg, 95% CI −2.67 to −1.77 kg, P < 0.001; high-dose: mean difference: −2.27 kg, 95% CI −3.36 to −1.17 kg, P < 0.001).
- Both low-dose (mean difference: −4.04 mm Hg, 95% CI: −5.57 to −2.51 mm Hg, P < 0.001) and high-dose (mean difference: −3.72 mm Hg, 95% CI: −5.30 to −2.14 mm Hg, P < 0.001) SGLT-2 inhibitors combined with pioglitazone had a better systolic blood pressure control than pioglitazone at the end of core period.
- Pooling data from included trials showed that both low-dose (mean difference: −3.00 mm Hg, 95% CI: −4.47 to −1.54 mm Hg, P < 0.001) and high-dose (mean difference: −2.34 mm Hg, 95% CI: −3.34 to −1.35 mm Hg, P < 0.001) SGLT-2 inhibitors combined with pioglitazone had a better diastolic blood pressure control than pioglitazone at the end of core period.
- The risks of death, heart failure, hypoglycaemia and urinary tract infection were not different between active and control groups although genital tract infection was more frequently seen in SGLT-2 inhibitor group (OR: 4.04, 95% CI: 2.09 to 7.81, P < 0.001).

16. Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab.2014;16:147-158.
17. Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab. 2014;16:467-477.
18. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 Inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35:1473-1478.
19. Kashiwagi A, Shiga T, Akiyama N, et al. Efficacy and safety of ipragliflozin as an add-on to pioglitazone in Japanese patients with inadequately controlled type 2 diabetes: a randomized, doubleblind, placebo-controlled study (the SPOTLIGHT study). Diabetol Int. 2015;6:104-116.
20. Kovacs CS, Seshiah V, Merker L, et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. Clin Ther. 2015;37:1773-1788.

Anmerkung/Fazit der Autoren

In conclusion, in this meta-analysis of randomized controlled trials comparing an SGLT-2 inhibitor plus pioglitazone vs pioglitazone, we found that an SGLT-2 inhibitor plus pioglitazone was associated with better glycaemic control, and reduced body weight and blood pressure, without any increase in hypoglycaemia, death or urinary tract infection. However, genital tract infection increased with combination therapy. Large randomized controlled trials might be warranted to evaluate whether such combination therapy is beneficial for cardiovascular outcomes in diabetic patients with high cardiovascular risks.

Maiorino MI et al., 2019 [71].

The good companions: insulin and glucagon-like peptide-1 receptor agonist in type 2 diabetes. systematic review and meta-analysis o randomized controlled trials

Fragestellung

We provided an updated systematic review with meta-analysis of randomized controlled trials (RCTs) assessing the metabolic effects of combination therapy of insulin and GLP- 1RA (combo) in comparison with other injectable therapy

Methodik

Population:

- type 2 diabetic patients

Intervention/Komparator:

- compared both free or fixed combo of short- and long-acting GLP-1RAs and insulin with other injectable treatment strategy, had at least duration of 8 weeks,

Endpunkte:

- HbA1c and weight change, safety (hypoglycemia)

Recherche/Suchzeitraum:

- MEDLINE (via Pubmed), Cochrane Central Register of Controlled Trials, Google Scholar, and ClinicalTrials.gov to March 21, 2019.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

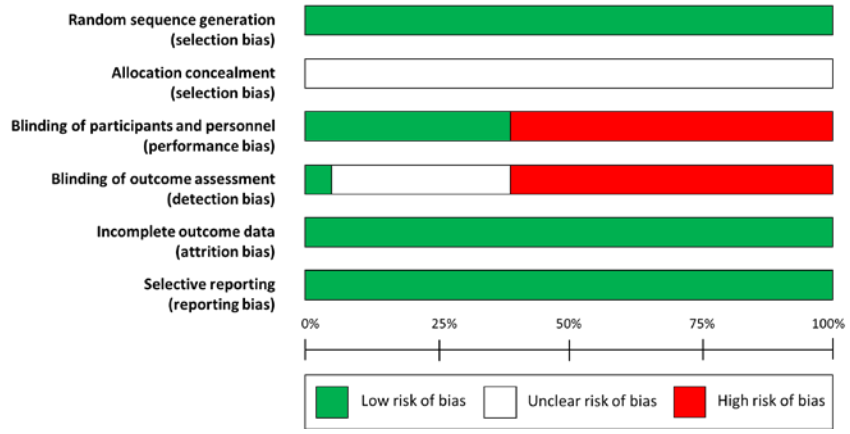
Anzahl eingeschlossener Studien:

- 36 RCTs (n=14636)

Charakteristika der Population:

- Most RCTs were multinational and received industry funding [19–27,29–45,47–52]; six studies [21,22,36,46,53,54] focused on Asian population.
- All trials were of parallel-group design, 14 were double-blind [19,22–25,29–31,36–37,39–42] and the remaining utilised an open-label design. The trials had a duration ranging from 8 to 52 weeks.
- The participants in all trials were adults (>18 years old) with type 2 diabetes; only one study [51] included patients with moderate-severe kidney disease. Mean patients' age ranged from 42 to 66 years, and mean baseline HbA1c levels ranged from 6.9% to 9.0%, with a median of 8.3% (IQR 7.8–8.5%) in the intervention groups and 8.2% (IQR 7.7–8.5%) in the comparator groups.

Qualität der Studien:



Outcome measure	N of studies	Limitations	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
HbA1c change	36	no serious limitations	no serious	very serious	no serious	no serious	undetected	moderate
HbA1c <7%	31	no serious limitations	no serious	very serious	no serious	some imprecision	suspected	low
Risk of hypoglycemia	30	no serious limitations	no serious	very serious	no serious	some imprecision	suspected	low
Weight change	35	no serious limitations	no serious	very serious	no serious	no serious	suspected	low

Studienergebnisse:

Table 2 – Pre-planned subgroup analysis

Parameter	Comparisons	Patients	Controls	Estimate (95% CI)	p-value	I^2	p-value of Q test
HbA1c (%)				**WMD**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	27	5196	4965	−0.71 (−0.82, −0.59)	<0.001	91.4	<0.001
Vs Basal-plus/Basal-bolus	15	2328	2147	−0.08 (−0.15, −0.01)	0.038	58.7	0.002
Combo with short-acting GLP-1RA	16	2786	3147	−0.29 (−0.44, −0.14)	<0.001	93.7	<0.001
Combo with long-acting GLP-1RA	26	4738	3965	−0.63 (−0.78, −0.47)	<0.001	93.3	<0.001
All trials	42	7524	7112	−0.49 (−0.61, −0.38)	<0.001	94.2	<0.001
HbA1c < 7%				**RR**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	27	5196	4965	2.23 (1.88, 2.65)	<0.001	93.5	<0.001
Vs Basal-plus/Basal-bolus	10	2205	2022	1.07 (0.99, 1.15)	0.077	15.3	0.302
Combo with short-acting GLP-1RA	12	2676	3034	1.57 (1.28, 1.93)	<0.001	92.4	<0.001
Combo with long-acting GLP-1RA	25	4725	3953	1.91 (1.61, 2.27)	<0.001	92.1	<0.001
All trials	37	7401	6987	1.77 (1.56, 2.01)	<0.001	92.1	<0.001
Hypoglycemia				**RR**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	25	5111	4889	1.26 (1.06, 1.49)	0.008	82.2	<0.001
Vs Basal-plus/Basal-bolus	10	1628	1735	0.64 (0.52, 0.79)	<0.001	82.0	<0.001
Combo with short-acting GLP-1RA	15	2775	3132	1.02 (0.81, 1.28)	0.866	84.8	<0.001
Combo with long-acting GLP-1RA	20	3964	3492	1.04 (0.85, 1.27)	0.733	87.6	<0.001
All trials	35	6739	6624	1.03 (0.88, 1.19)	0.728	86.4	<0.001
Weight (Kg)				**WMD**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	26	5022	4793	−1.8 (−2.6, −1.1)	<0.001	97.1	<0.001
Vs Basal-plus/Basal-bolus	15	2328	2147	−3.6 (−4.5, −2.7)	<0.001	92.5	<0.001
Combo with short-acting GLP-1RA	16	2786	3147	−2.2 (−3.1, −1.4)	<0.001	96.0	<0.001
Combo with long-acting GLP-1RA	25	4564	3793	−2.7 (−3.6, −1.7)	<0.001	97.2	<0.001
All trials	41	7350	6940	−2.5 (−3.1, −1.8)	<0.001	96.8	<0.001

RR, relative risk; WMD, weighted mean difference.

Anmerkung/Fazit der Autoren

Combination therapy of GLP-1RA and insulin could represent a valuable treatment strategy to improve metabolic control in the management of type 2 diabetes. This combination presents a higher efficacy associated with a slight increase of hypoglycemia and weight loss when compared with other injectable therapy (insulin up-titration or GLP-1RA alone), and similar efficacy when compared with insulin regimens (basal-plus or basal-bolus), with low risk of hypoglycemicevents and more weight loss.

Men P et al., 2019 [75].

Comparison of lixisenatide in combination with basal insulin versus other insulin regimens for the treatment of patients with type 2 diabetes mellitus inadequately controlled by basal insulin: systematic review, network meta-analysis and cost-effectiveness analysis.

Fragestellung

To evaluate the comparative efficacy and safety of lixisenatide combined with basal insulin (BI) versus intensive premix insulin (premix), BI plus prandial insulin with the main meal (basal-plus) or progressively covering all meals (basal-bolus) in patients with type 2 diabetes mellitus (T2DM) inadequately controlled by BI

Methodik

Protocol of this SLR and NMA has been registered on PROSPERO

Population:

- Adult T2DM patients inadequately controlled on basal insulin

Intervention:

- Lixisenatide in combination with basal insulin
- Premix insulin regimen (twice daily or third daily)
- Basal-bolus regimen (basal insulin + prandial insulin covering all meals (3 shots)
- Basal-plus regimen (basal insulin + prandial insulin with the main meal (1 shot))

Komparator:

- Any insulin intervention of interest in an approved dose

Endpunkte:

- Mean changes in the HbA1c from baseline
- Mean changes in the FPG from baseline
- Mean change in body weight from baseline
- Incidence and event per patient of systematic hypoglycemia

Recherche/Suchzeitraum:

- Syst. search in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI) and Wanfang databases from January 1998 to January 2018

Qualitätsbewertung der Studien:

- Using Cochrane Collaborations Risk of Bias tool

- GRADE assessment for rating the quality of treatment effect estimates from NMA

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCT

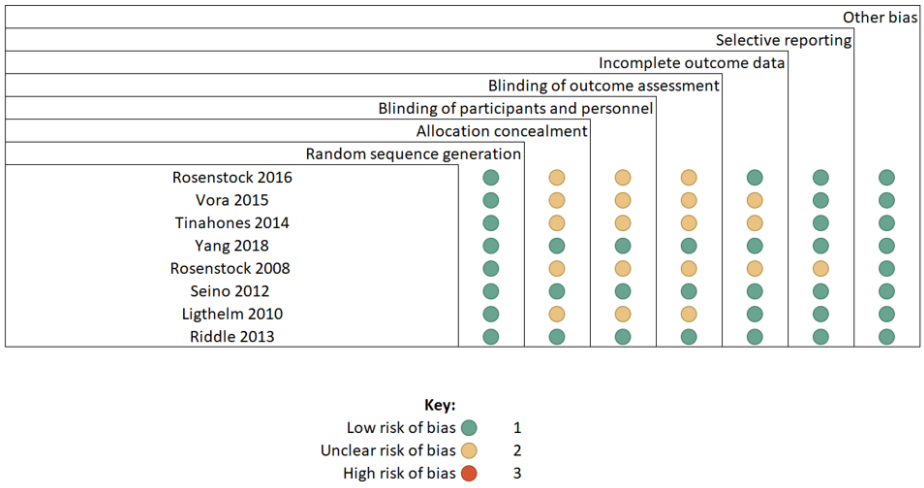
Studiencharakteristika:

- The baseline characteristics, including age, gender, BMI, HbA1c, treatment duration and diabetes duration, were similar across the studies
- Patients in the included trials had a mean age of 57.3 years, a BMI of 30.9 kg/m2, a baseline HbA1c of 8.6%, and a diabetes duration of 12.0 years.
- All but one of the treatment durations was 24 weeks.
- Besides the insulin treatments (with or without lixisenatide), most of the patients were allowed to receive background OAD therapy (metformin for most).

Qualität der Studien:

- The majority of included studies possessed low and/or moderate risk of bias.
  - Random sequence generation was adequate in all of the eight trials.
  - We did not identify any studies with definite high risk of bias

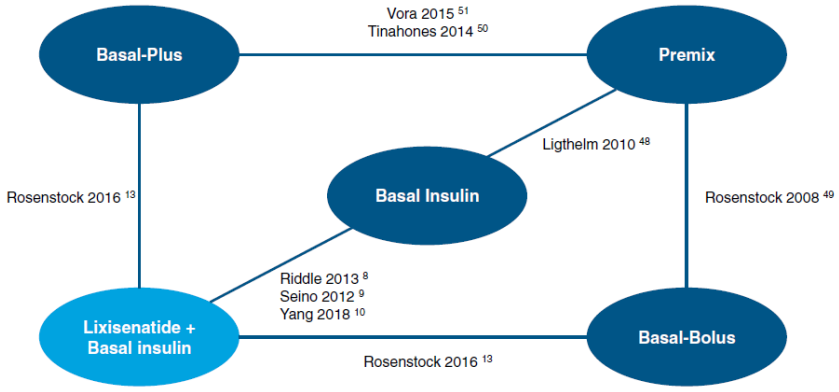
Appendix S9 Quality assessment for included trials



Studienergebnisse:

NMA

Netzwerkgeometrie



Parameter	Direct evidence		Indirect evidence		Network meta-analysis	
	MD (95% CI)	Quality of evidence	MD (95% CI)	Quality of evidence	MD (95% CI)	Quality of evidence
Changes in the HbA1c from baseline (%)						
Lixi + BI vs. Premix	--	--	-0.654 (-1.406,0.098)	low	-0.124 (-0.498, 0.250)	low
Lixi + BI vs. Basal-Plus	0.000 (-0.374,0.374)	high	-0.623 (-1.119,-0.127)	moderate	-0.229 (-0.607, 0.150)	high
Lixi + BI vs. Basal-Bolus	0.200 (-0.298,0.698)	high	0.180 (-0.594,0.954)	moderate	0.090 (-0.310, 0.490)	high
Changes in the body weight from baseline (kg)						
Lixi + BI vs. Premix	--	--	-1.181 (-2.71,0.348)	low	-2.276 (-2.909, -1.643)	low
Lixi + BI vs. Basal-Plus	-0.400 (-1.252,0.452)	high	-0.913 (-1.958,0.132)	moderate	-1.732 (-2.375, -1.089)	high
Lixi + BI vs. Basal-Bolus	-2.000 (-2.832,-1.168)	high	-3.213 (-4.508,-1.918)	moderate	-2.354 (-3.054, -1.654)	high
Incidence of symptomatic hypoglycemia						
Lixi + BI vs. Premix	--	--	0.568 (0.098,3.281)	moderate	0.654 (0.458, 0.933)	moderate
Lixi + BI vs. Basal-Plus	0.770 (0.500,1.188)	high	0.310 (0.022,4.317)	moderate	0.754 (0.548, 1.038)	high
Lixi + BI vs. Basal-Bolus	0.601 (0.257,1.404)	high	0.230 (0.005,10.568)	low	0.599 (0.430, 0.834)	high
Event per patient of symptomatic hypoglycemia						
Lixi + BI vs. Premix	--	--	0.698 (0.517,0.941)	moderate	0.589 (0.353, 0.995)	moderate

Lixi + BI vs. Basal-Plus	0.835 (0.731,0.953)	high	0.756 (0.575,0.993)	moderate	0.805 (0.475, 1.376)	high
Lixi + BI vs. Basal-Bolus	0.501 (0.327,0.767)	high	1.049 (1.098,1.002)	moderate	0.624 (0.360, 1.103)	high

Results for direct evidence, indirect evidence and mixed treatment effect

Abbreviations: basal-plus: basal insulin plus prandial insulin with the main meal; basal-bolus: basal insulin plus prandial insulin covering all meal; BI: basal insulin; CI: confidence interval; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; MD: mean difference; premix: intensive premixed insulin; RR: risk ratio

Anmerkung/Fazit der Autoren

In conclusion, lixisenatide combined with BI is shown to have a comparable glycaemic control ability, but is superior to premix, basal-plus and basal-bolus in terms of weight control and hypoglycaemia risk.

Kommentare zum Review

- Limitation: Keine Angaben zur Untersuchung der Transitivitätsannahme; jedoch Festlegung enger Einschlusskriterien der Studien; Studien hinsichtlich der Baselinecharakteristika Alter, BMI, HbA1c, Krankheitsdauer ähnlich
- Überprüfung der Konstistenz zw. direkter und indirekter Evidenz

---

Milder TY et al., 2019 [76].

Combination Therapy with an SGLT2 Inhibitor as Initial Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis.

Fragestellung

To compare the efficacy and safety of (i) sodium-glucose cotransporter 2 (SGLT2) inhibitor combination therapy in treatment-naïve type 2 diabetes adults; (ii) initial high and low dose SGLT2 inhibitor combination therapy.

Methodik

Population:

- Treatment-naïve (defined as no pharmacotherapy for at least 12 weeks prior to randomisation) adults with type 2 diabetes

Intervention/Komparator:

- All dosing regimens of combination therapy that included an SGLT2 inhibitor that were compared to monotherapy (each agent in the combination)

Endpunkte:

- HbA1c, change in body weight, blood pressure (BP), adverse events including hypoglycaemia, genital and urinary tract infections (UTIs)

Recherche/Suchzeitraum:

- PubMed, Embase and Cochrane Library were searched from inception through to April 2018

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Four studies (n = 3749 subjects) compared initial combination SGLT2 inhibitor and metformin therapy, to either metformin monotherapy or SGLT2 inhibitor monotherapy.
- Studies evaluated the combination of metformin and empagliflozin, dapagliflozin or canagliflozin.

Charakteristika der Population:

- Participants in these four studies had a mean baseline HbA1c which ranged from 8.7%–9.1% and a mean body weight which ranged from 83–91 kg.
- One study (n = 667 subjects) compared combination therapy with an SGLT2 inhibitor (empagliflozin) and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor to monotherapy with each agent in the combination. Participants in this study had a mean baseline HbA1c of 8.0% and mean body weight of 88 kg.

Qualität der Studien:

- In general, the majority of the domains for the five studies were considered to have a low risk of bias.

Studienergebnisse:

- In 4 RCTs (n = 3749) there was moderate quality evidence that SGLT2 inhibitor/metformin combination therapy resulted in a greater reduction in HbA1c (MD (95% CI); -0.55% (-0.67, -0.43)) and weight (-2.00 kg (-2.34, -1.66)) compared with metformin monotherapy, and a greater reduction in HbA1c (-0.59% (-0.72, -0.46)) and weight (-0.57 kg (-0.89, -0.25)) compared with SGLT2 inhibitor monotherapy.
- The high dose SGLT2 inhibitor/metformin combination resulted in a similar HbA1c but greater weight reduction; -0.47 kg (-0.88, -0.06) than the low dose combination therapy.
- The RR of genital infection with combination therapy was 2.22 (95% CI 1.33, 3.72) and 0.69 (95% CI 0.50, 0.96) compared with metformin and SGLT2 inhibitor monotherapy, respectively.
- The RR of diarrhoea was 2.23 (95% CI 1.46, 3.40) with combination therapy compared with SGLT2 inhibitor monotherapy.

Anmerkung/Fazit der Autoren

Initial SGLT2 inhibitor/metformin combination therapy has glycaemic and weight benefits compared with either agent alone and appears relatively safe. High dose SGLT2 inhibitor/metformin combination therapy appears to have modest weight, but no glycaemic benefits compared with the low dose combination therapy.

Toyama T et al., 2019 [88].

Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis

Fragestellung

We undertook a systematic review and meta-analysis of randomized controlled trials to better understand the role of this nclass of agent for cardio-renal protection in individuals with T2DM and CKD, defined as eGFR <60 mL/min/1.73 m2.

Methodik

Population:

- adult humans with T2DM when studies reported data for participants with CKD, defined as eGFR <60 mL/min/1.73m2

Intervention:

- SGLT2 inhibitor

Komparator:

- Placebo or active control

Endpunkte:

- Biomarkers
- Cardiovascular (composite of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke.) Other cardiovascular outcomes were cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, as well as hospitalized or fatal heart failure. All-cause mortality was also reported
- renal (annual mean difference in kidney function between treatment and control (eGFR slope) and a composite of doubling of serum creatinine, end-stage kidney disease or renal death.
- safety (urinary tract infection, genital infection, hypovolaemia, hypoglycaemia, amputation, bone fracture, ketoacidosis, renal-related adverse events, acute kidneyinjury and hyperkalaemia)

Recherche/Suchzeitraum:

- MEDLINE via Ovid (from 1 January 1946), EMBASE (from 1 January 1947) and the Cochrane Central Register of Controlled Trials (without date restriction

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

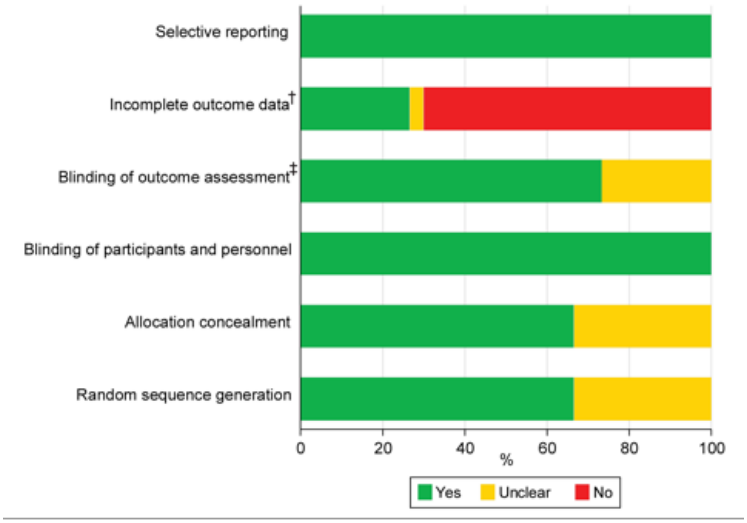
- 27 eligible studies (18 individual trials, 8 pooled analyses, 1 regulatory report)
- N=6376 for analyses of cardiovascular outcomes, 7363 for analyses of all-cause mortality, 5863 for analyses of renal outcomes and 6160 for analyses of safety outcomes

- 19 assessed the effects of empagliflozin, 19 assessed effects of dapagliflozin, seven assessed effects of ertugliflozin, six assessed effects of ipragliflozin and five assessed effects of canagliflozin, while luseogliflozin, sotagliflozin and tofogliflozin were assessed in one trial each.

Charakteristika der Population:

- SGLT2 inhibitors were compared to placebo in all cases, with the exception of one regulatory report for ertugliflozin, which pooled data on all-cause mortality across seven trials (n = 566), two of which were against active control.
- Study duration ranged from 7 days to a median of 4.2 years, with mean participant age between 63.5 and 68.5 years.
- Mean eGFR ranged from 38.0 to 53.5 mL/min/1.73 m2

Qualität der Studien:



Studienergebnisse:

Cardiovascular outcomes

- SGLT2 inhibitors reduced the risk of the composite cardiovascular outcome (RR, 0.81; 95% CI, 0.70-0.94), hospitalised or fatal heart failure (RR, 0.61; 95% CI, 0.48-0.78) and myocardial infarction (RR, 0.77; 95% CI, 0.60-0.99), with no clear effect on stroke or cardiovascular death.
- While the point estimate favoured SGLT2 inhibitors for all-cause mortality, the confidence interval spanned unity (RR, 0.86; 95% CI, 0.73-1.01).

Renal outcomes

- Based on two trials, SGLT2 inhibitors slowed the annual decline in eGFR slope, with a placebo-subtracted difference of 1.35 mL/min/1.73 m2 per year (95% CI, 0.78-1.93) and a moderate likelihood of differences beyond chance between canagliflozin and empagliflozin (I2 = 62%; P-heterogeneity = 0.11).
- SGLT2 inhibitors also reduced the risk of the composite renal outcome of doubling of serum creatinine, end-stage kidney disease or renal death (RR, 0.71 9;5% CI, 0.53-0.95), with no evidence of heterogeneity by individual agents (I2 = 0%; P-heterogeneity = 0.93).

Safety outcomes

- There was an overall increased risk of genital infections with SGLT2 inhibition (RR, 2.86; 95% CI, 2.00-4.10).
- While there was no overall increased risk of other safety outcomes, including amputations and fractures, there was at least a moderate likelihood of difference between agents arising beyond chance for a number of outcomes, including hypoglycaemia, hypovolaemia and amputation (all I2 ≥ 57%; all P-heterogeneity ≤0.04). In each case, empagliflozin was associated with a lesser risk compared to the other agents.
- SGLT2 inhibitors did not increase the risk of renal-related adverse events, acute kidney injury or hyperkalaemia

Anmerkung/Fazit der Autoren

Currently available data suggest that SGLT2 inhibitors reduce the risk of cardiovascular and renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns; however, the robustness of these findings requires confirmation in upcoming dedicated CKD outcome trials.

Wang A et al., 2019 [90].

Effects of sodium-glucose cotransporter 2 inhibitors on risk of venous thromboembolism in patients with type 2 diabetes: A systematic review and meta-analysis

Fragestellung

Therefore, we performed this meta-analysis of published and unpublished randomized controlled trials (RCTs) to evaluate the effects of SGLT2 inhibitors on risk of VTE in patients with T2D.

Methodik

Population:

- adult patients with T2D

Intervention:

- SGLT2 inhibitors

Komparator:

- placebo or other active antidiabetic drugs regardless of background treatments

Endpunkte:

- venous thromboembolism

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 2018 + Update April 2019
- RCTs with duration of follow-up of at least 12 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

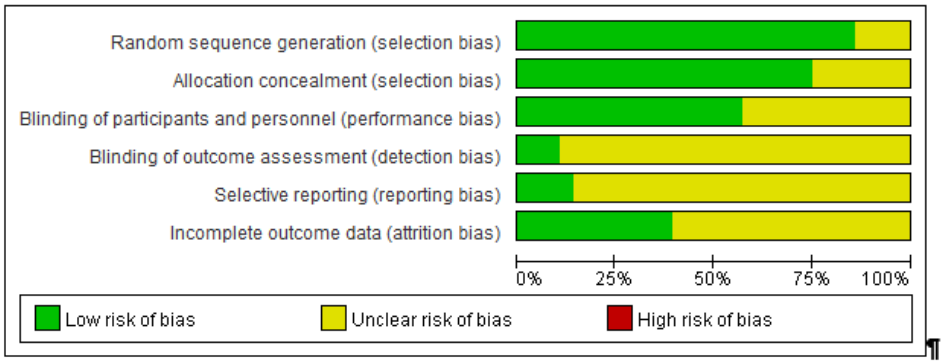
- 29 eligible RCTs (n=56035)

Charakteristika der Population:

- The duration of follow-up ranged from 24 to 218 weeks; mean age of study population ranged from 51.6 to 68.5 years; and the mean HbA1c values among all participants ranged from 7.7% to 8.9%.

Qualität der Studien:

Figure S1. Risk of bias assessment results with risk of each bias presented as percentages across all included trials.



Studienergebnisse:

TABLE 2 Subgroup analyses of the effects of SGLT2 inhibitors on risk of venous thromboembolism in patients with type 2 diabetes

Subgroup Analyses	No. of Trials	SGLT2 Inhibitors (n/N)	Controls (n/N)	Risk Ratio (95% CI)	Heterogeneity (I^2, %)	Difference Between Subgroups (P Value)
Subgroup by type of SGLT2 inhibitor						
Empagliflozin	10	35/8450	23/4934	0.78 (0.47-1.31)	0	0.73
Dapagliflozin	8	29/11 571	25/10 516	1.02 (0.59-1.75)	0	
Canagliflozin	8	61/10 799	42/7938	1.11 (0.75-1.64)	0	
Ertugliflozin	3	3/1218	2/609	0.70 (0.12-4.18)	20	
Subgroup by type of control[a]						
Placebo	20	122/27 440	86/21 024	1.00 (0.76-1.32)	0	0.56
Other active drugs	10	6/5046	6/2973	0.71 (0.23-2.15)	0	
Subgroup by mode of therapy						
Monotherapy	5	6/2033	2/1108	0.83 (0.18-3.82)	0	0.83
Add-on therapy	24	122/30 005	90/22 889	1.00 (0.75-1.33)	0	

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis found no association between SGLT2 inhibitors on risk of VTE among patients with T2D. Further prospective studies are required to confirm our findings.

Zelniker TA et al., 2019 [100] + Singh AK et al., 2019 [86] + Yamani N et al., 2019 [95].

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

+

Singh AK et al.,, 2019. Heart failure hospitalization with SGLT-2 inhibitors: a systematic review and meta-analysis of randomized controlled and observational studies

+

Yamani N et al., 2019. Sodium-glucose co-transporter 2 inhibitors for the prevention of heart failure in type 2 diabetes: A systematic review and meta-analysis

Fragestellung

The goal of the present meta-analysis was to combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2i to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups.

Methodik

Population:

- Patients were stratified into those with established ASCVD versus patients with multiple risk factors (MRFs) for ASCVD

Intervention:

- SGLT2 inhibitors

Komparator:

- placebo

Endpunkte:

- Major adverse cardiovascular events (the composite of myocardial infarction, stroke, or cardiovascular death); the composite of cardiovascular death or hospitalization for heart failure, their individual components
- A standardised composite of renal outcomes including worsening eGFR, end-stage renal disease, or renal death
- Safety endpoints: non-traumatic lower limb amputations, fractures, and diabetic ketoacidosis

Recherche/Suchzeitraum:

- PubMed and Embase up to Sept 24, 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 trials1–3 (n=34322)

Charakteristika der Population:

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

Qualität der Studien:

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (Mortality)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
EMPA-REG Outcome	Low	Low	Low	Low	Low	Low	Low	Low
CANVAS Program	Low	Low	Low	Low	Low	Low	Low	Low
DECLARE-TIMI 58	Low	Low	Low	Low	Low	Low	Low	Low

Studienergebnisse:

Major adverse cardiac event (myocardial infarction, stroke, cardiovascular death)

- In total, 3342 (9·7%) of 34 322 patients had a major adverse cardiac event in the trials. Of those events, 2588 (77·4%) occurred in the group with established atherosclerotic cardiovascular disease.
- Overall, SGLT2i reduced the risk of a major adverse cardiac event by 11% (HR 0·89 [95% CI 0·83–0·96], p=0·0014).
- However, this effect was entirely restricted to a 14% reduction in patients with atherosclerotic cardiovascular disease (HR 0·86 [0·80 to 0·93]), whereas no treatment effect was found in patients with multiple risk factors (1·00 [0·87–1·16], p for interaction=0·0501)

Myocardial infarction

- 1604 (4·7%) patients had a myocardial infarction (80·5% of which occurred in patients with atherosclerotic cardiovascular disease), SGLT2i reduced the risk of myocardial infarction by 11% (HR 0·89 [95% CI 0·80–0·98], p=0·0177)

- SGLT2i reduced myocardial infarction (HR 0·85 [0·76–0·95]) in patients with atherosclerotic cardiovascular disease

Stroke

- 1060 (3·1%) had a stroke (73·1% of which occurred in patients with atherosclerotic cardiovascular disease), SGLT2i had no effect on stroke (HR 0·97 [0·86–1·10], p=0·64

Cardiovascular death

- 1256 (3·7%) had cardiovascular death (78·6% of which occurred in patients with the disease). SGLT2i reduced the risk of cardiovascular death by 16% (HR 0·84 [0·75–0·94], p=0·0023, but with high heterogeneity [I^2=79·9%])
- SGLT2i reduced cardiovascular death (HR 0·80 [0·71–0·91]) in patients with atherosclerotic cardiovascular disease

All cause death

- SGLT2i significantly reduced the risk for allcause death by 15% (HR 0·85 [95% CI 0·78–0·93], p=0·0002), but with high heterogeneity (I^2=75·2%;).
- In patients with atherosclerotic cardiovascular disease the HR was 0·83 (0·75–0·92) and in those with multiple risk factors it was 0·90 (0·77–1·05, p for interaction=0·69;).
- Similarly, in patients with history of heart failure the HR was 0·80 (0·67–0·95) and in those without a history of heart failure it was 0·88 (0·80–0·97, p for interaction=0·63).

Composite of cardiovascular death or hospitalisation for heart failure

- SGLT2i significantly reduced the risk for the composite of cardiovascular death or hospitalisation for heart failure by 23% (HR 0·77 [95% CI 0·71–0·84], p<0·0001), and hospitalisation for heart failure by 31% (0·69 [0·61–0·79], p<0·0001)
- The effect on hospitalization for heart failure alone was robust, with an approximately 30% reduction in relative risk in both subgroups

Composite of worsening of renal function, end-stage renal disease, renal death

- SGLT2i were renoprotective and reduced the composite of worsening of renal function, end-stage renal disease, or renal death by 45% (HR 0·55 [95% CI 0·48–0·64], p<0·0001).
- This effect was similarly robust both in patients with atherosclerotic cardiovascular disease (HR 0·56 [95% CI 0·47– 0·67]) and those with multiple risk factors, (0·54 [0·42–0·71], p for interaction=0,71)

Safety outcomes

- Diabetic ketoacidosis showed a consistent increased risk of almost two times higher in patients given SGLT2i than those given placebo (2·20 [1·25–3·87], p=0·0060), but the event rates were low (<one per 1000 patient-years)

1 Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. mN Engl J Med 2015; 373: 2117–28.
2 Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377: 644–57.
3 Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2018; published online Nov 10. DOI:10.1056/NEJMoa1812389.

Anmerkung/Fazit der Autoren

In conclusion, SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that appear confined to patients with established atherosclerotic cardiovascular disease. However, robust reductions in hospitalisation for heart failure and progression of renal disease are seen regardless of baseline atherosclerotic risk category or a history of heart failure.

Zelniker T et al., 2019 [101].

Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus - Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials

Fragestellung

the present meta-analysis of cardiovascular outcomes trials was designed to compare and contrast the clinical benefit of GLP1-RA and SGLT2i in patients with and without established atherosclerotic cardiovascular disease (ASCVD).

Methodik

Population:

- Patients were stratified into those with established ASCVD versus patients with multiple risk factors (MRFs) for ASCVD

Intervention/Komparator:

- GLP1-RA and SGLT2i

Endpunkte:

- MACE (and its individual components), HHF, and progression of kidney disease (new onset of macroalbuminuria, worsening of estimated glomerular filtration rate (eGFR), end-stage kidney disease, or death attributable to renal causes and a narrower kidney outcome excluding macroalbuminuria

Recherche/Suchzeitraum:

- PubMed and EMBASE until November 11, 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 trials (n=77242), 5 GLP1-RA [3–5,25,26] trials (n=42920) and 3 SGLT2i [6,7,21] trials (n=34322)

Charakteristika der Population:

- The mean age of patients (range, 60–65 years) and the proportion of women (range, 28% to 40%) were similar across the trials.

- A total of 56,473 patients (73.1%) had established ASCVD, but this proportion ranged from 41% to 100% across the trials. A total of 12,568 patients (16.3%) had a history of heart failure, and this proportion ranged from 10% to 24% across the trials.
- The proportion of patients with eGFR <60 mL·min−1·1.73·m−2 ranged from 20% to 29% across the trials, with the exception of DECLARE-TIMI58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), which had a substantially smaller proportion (7.4%).

Qualität der Studien:

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (Mortality)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
EMPA-REG Outcome	Low	Low	Low	Low	Low	Low	Low	Low
CANVAS Program	Low	Low	Low	Low	Low	Low	Low	Low
DECLARE-TIMI 58	Low	Low	Low	Low	Low	Low	Low	Low
ELIXA	Low	Low	Low	Low	Low	Low	Low	Low
LEADER	Low	Low	Low	Low	Low	Low	Low	Low
SUSTAIN-6	Low	Low	Low	Low	Low	Low	Low	Low
EXSCEL	Low	Low	Low	Low	Low	Low	Low	Low
HARMONY	Low	Low	Low	Low	Low	Low	Low	Low

Studienergebnisse:

MACE

- In total, 8213 of 77 242 patients (10.6%) experienced a MACE event (4871 patients in the GLP1-RA trials and 3342 patients in the SGLT2i trials).
- Overall, both drug classes reduced MACE by a similar magnitude, with GLP1-RA reducing the relative risk by 12% (HR, 0.88; 95% CI, 0.84–0.94; P<0.001) and SGLT2i by 11% (HR, 0.89; 95% CI, 0.83–0.96; P=0.001; P for heterogeneity, 0.86).

Treatment Effect on the Individual Components of MACE

- There were 4274 patients who experienced a myocardial infarction (2670 patients in GLP1-RA trials and 1604 patients in SGLT2i trials), 2237 who experienced a stroke (1177 patients in GLP1-RA trials and 1060 patients in SGLT2i trials), and 3132 who experienced a cardiovascular death (1876 in GLP1-RA trials and 1256 patients in SGLT2i trials).
- Both GLP1-RA and SGLT2i reduced the relative risk of myocardial infarction: by 9% with GLP1-RA (HR, 0.91; 95% CI, 0.84–0.98; P=0.012) and by 11% with SGLT2i (HR, 0.89; 95% CI, 0.80–0.98; P=0.018; P for heterogeneity, 0.87;
- GLP1-RA reduced the relative risk of stroke significantly by 14% (HR, 0.86; 95% CI, 0.77–0.97; P=0.012), whereas SGLT2i had no effect (HR, 0.97; 95% CI, 0.86–1.10; P for heterogeneity, 0.25).
- Both drug classes significantly reduced the relative risk of cardiovascular death: by 12% with GLP1-RA (HR, 0.88; 95% CI, 0.80–0.96; P=0.004) and by 16% with SGLT2i (HR, 0.84; 95% CI, 0.75–0.94; P=0.002; P for heterogeneity, 0.51;

Treatment effects on Kidney Function

- GLP1-RA reduced the relative risk of broad composite kidney outcome significantly by 18% (HR, 0.82; 95% CI, 0.75–0.89; P<0.001), whereas there was a 38% reduction with SGLT2i (HR, 0.62; 95% CI, 0.58–0.67; P<0.001; P for heterogeneity, 0.010
- hospitalization for a broad kidney end point (new-onset macroalbuminuria sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause) stratified by drug class. The P value for subgroup differences was 0.010. For GLP1-RA: Q statistic=3.60, P=0.31, I2=16.6%; and for SGLT2i: Q statistic=2.99, P=0.22, I2=33.2%.
- kidney outcome excluding macroalbuminuria: The P value for subgroup differences was <0.001. For GLP1-RA: Q statistic= 2.18, P=0.54, I2=0%; and for SGLT2i: Q statistic=0.59, P=0.74. I2=0%.

3. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–322. doi: 10.1056/NEJMoa1603827
4. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–1844. doi: 10.1056/NEJMoa1607141
5. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, Thorpe KM, McMurray JJV, Del Prato S; Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392:1519–1529. doi: 10.1016/S0140-6736(18)32261-X
6. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117– 2128. doi: 10.1056/NEJMoa1504720
7. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–657. doi: 10.1056/NEJMoa1611925
21. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–357. doi: 10.1056/NEJMoa1812389
25. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Stud Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377:1228–1239. doi: 10.1056/NEJMoa1612917
26. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373:2247–2257. doi: 10.1056/NEJMoa1509225

Anmerkung/Fazit der Autoren

In conclusion, GLP1-RA and SGLT-2i reduce the risk of MACE to a similar degree in patients with established ASCVD but have no effect in patients without established ASCVD over a short-term follow-up ranging from 2 to 4 years. The prevention of heart failure and progression of kidney disease by SGLT2i should be considered in the decision-making process when treating patients with type 2 diabetes mellitus

---

Zhou W et al., 2019 [105].

Insulin Degludec, a Novel Ultra-Long-Acting Basal Insulin versus Insulin Glargine for the Management of Type 2 Diabetes: A Systematic Review and Meta- Analysis

Fragestellung

Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to establish the effect of insulin degludec versus insulin glargine on key outcomes in the treatment of patients with T2DM, including glycemic control, hypoglycamia, body weight gain, and SAEs.

Methodik

Population:

- Patients with T2DM

Intervention:

- insulin degludec

Komparator:

- insulin glargine

Endpunkte:

- changes in glycated hemoglobin (HbA1c), changes in laboratory-measured fasting plasma, glucose (FPG) or proportion of participants with, HbA1c ≤ 7.0% OR proportion of participants experiencing ≥ 1 hypoglycemic event or changes in body weight or proportion of participants with major adverse cardiovascular events (MACEs), or proportion of participants with SAEs

Recherche/Suchzeitraum:

- PubMed, Embase, Web of Science, and Cochrane Library databases published prior to 13 August 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

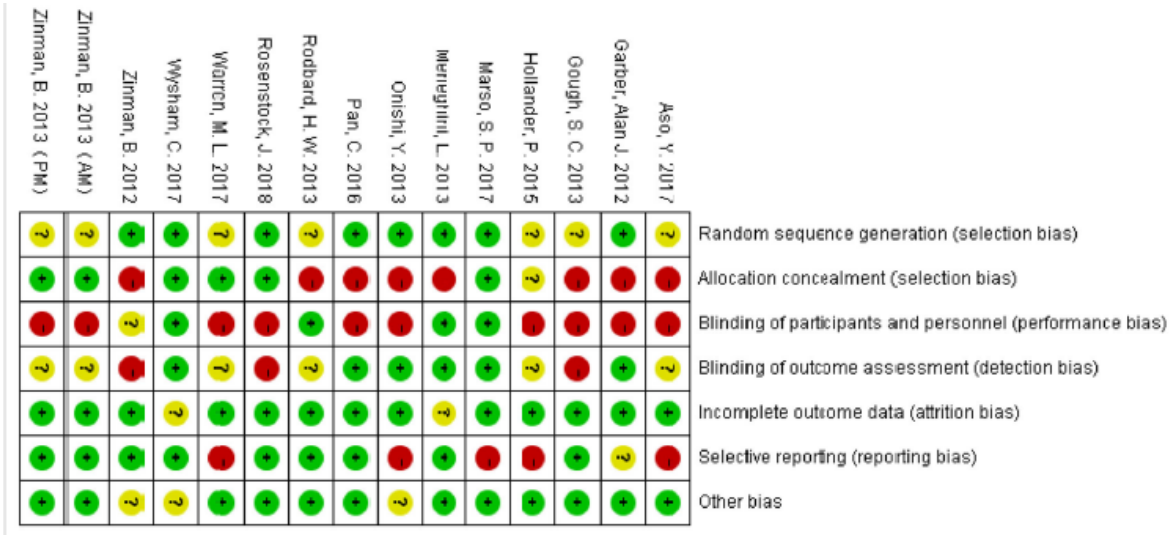
Anzahl eingeschlossener Studien:

- 15 RCTs (with data for 16,694 participants)

Charakteristika der Population:

- Mean trial duration was 43.3 (range 24–104) weeks.
- Patients had a mean baseline HbA1c of 8.31% (range 7.6–8.86%), mean baseline FPG of 165.7 (range 137–186) mg/dL, mean baseline BMI of 30.9 (range 24.6–36.2) kg/ m2, and mean duration of diabetes of 11.1 (range 8–16.4) years.
- Of the 15 RCTs, 12 were carried out in multiple countries [13–21, 24, 25], two in the USA [22, 23], and one in Japan [12]. In the two crossover trials, participants were switched directly to the other intervention without a washout period [22, 23].
- In 13 trials used Insulin degludec was administered once daily in 13 trials [12–23, 25] and three times per week in only two trials [24].

Qualität der Studien:



Studienergebnisse:

Glycemic Control

- Ten studies (containing 11 trials) that included 7719 patients in the insulin degludec group and 6279 patients in the insulin glargine group reported the change in HbA1c between baseline and the end of the intervention.
- A random-effects model was used for this analysis (I2 = 66.5%). A pooled analysis of all 11 trials revealed that insulin glargine led to a greater mean reduction in HbA1c than did insulin degludec (WMD 0.07, 95% CI 0.01, 0.13, P = 0.019), with statistically significant between-study heterogeneity (P\0.1, I2 [50%).
- Subgroup analysis (P = 0.204, I2 = 27%) based on the background treatment (insulin-naı¨ve vs. insulin) was also performed to demonstrate that there was no statistically significant difference between the two treatment groups regarding changes in the HbA1c level (WMD 0.03, 95% CI 0.00, 0.07, P = 0.08;

Hypoglycemic Events

- Pooled analysis of the 12 studies (8903 participants; I2 = 43.5%) that assessed the proportion of participants experiencing ≥ 1 hypoglycemic event showed a lower incidence of all confirmed hypoglycemic episodes when participants were treated with insulin degludec, as compared to treatment insulin glargine, but the difference was not statistically significant
- RR 0.98, 95% CI 0.93, 1.03, P = 0.43

Body weight Control

- Six studies that included 6713 patients in the insulin degludec group and 5431 patients in the insulin glargine group reported changes in body weight.
- A random-effect model was applied for this analysis (P = I2 = 79%). Pooling the data of these studies showed that insulin degludec led to a greater mean weight gain than did insulin glargine, but the difference was not statistically significant (WMD 0.23, 95% CI - 0.14, 0.61, P = 0.22;

Serious Adverse Events

- Thirteen studies that included 9961 patients in the insulin degludec group and 7310 patients in the insulin glargine group reported the proportion of participants with SAEs
- Insulin degludec was associated with a lower ratio of participants with SAEs as compared to insulin glargine, but the difference was not statistically significant (RR 0.97, 95% CI 0.92, 1.02, P = 0.20)

12.Aso Y, Suzuki K, Chiba Y, et al. Effect of insulin degludec versus insulin glargine on glycemic control and daily fasting blood glucose variability in insulin-naive Japanese patients with type 2 diabetes: I'D GOT trial. Diabetes Res Clin Pract. 2017;130:237–43.CrossRefGoogle Scholar
13.Garber AJ, King AB, Prato SD, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012;379(9825):1498–507.CrossRefGoogle Scholar
14.Gough SC, Bhargava A, Jain R, et al. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. Diabetes Care. 2013;36(9):2536–42.CrossRefGoogle Scholar
15.Hollander P, King AB, Del Prato S, et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. Diabetes Obes Metab. 2015;17(2):202–6.CrossRefGoogle Scholar
16.Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med. 2017;377(8):723–32.CrossRefGoogle Scholar
17.Meneghini L, Atkin SL, Gough SC, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care. 2013;36(4):858–64.CrossRefGoogle Scholar
18.Onishi Y, Iwamoto Y, Yoo SJ, et al. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. J Diabetes Investig. 2013;4(6):605–12.CrossRefGoogle Scholar
19.Pan C, Gross JL, Yang W, et al. A multinational, randomized, open-label, treat-to-target trial comparing insulin degludec and insulin glargine in insulin-naive patients with type 2 diabetes mellitus. Drugs R D. 2016;16(2):239–49.CrossRefGoogle Scholar
20.Rodbard HW, Cariou B, Zinman B, et al. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. Diabet Med. 2013;30(11):1298–304.CrossRefGoogle Scholar
21.Rosenstock J, Cheng A, Ritzel R, et al. More similarities than differences testing insulin glargine 300 Units/mL versus insulin degludec 100 Units/mL in insulin-naive type 2 diabetes: the randomized head-to-head BRIGHT trial. Diabetes Care. 2018;41(10):2147–54.CrossRefGoogle Scholar
22.Warren ML, Chaykin LB, Jabbour S, et al. Insulin degludec 200 units/mL Is associated with lower injection frequency and improved patient-reported outcomes compared with insulin glargine 100 Units/mL in patients with type 2 diabetes requiring high-dose insulin. Clin Diabetes. 2017;35(2):90–5.CrossRefGoogle Scholar
23.Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA. 2017;318(1):45–56.CrossRefGoogle Scholar
24.Zinman B, DeVries JH, Bode B, et al. Efficacy and safety of insulin degludec three times a week versus insulin glargine once a day in insulin-naive patients with type 2 diabetes: results of two phase 3, 26 week, randomised, open-label, treat-to-target, non-inferiority trials. Lancet Diabetes Endocrinol. 2013;1(2):123–31.CrossRefGoogle Scholar
25. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012;35(12):2464–71.CrossRefGoogle Scholar

Anmerkung/Fazit der Autoren

Findings from our meta-analysis show that insulin degludec has an overall beneficial effect on the management of type 2 diabetes as compared to insulin glargine, mainly manifesting in the lower risks of severe and nocturnal hypoglycemia.

2018

Andreadis P et al., 2018 [3].

Semaglutide for type 2 diabetes mellitus: A systematic review and meta-analysis

Fragestellung

We conducted a systematic review and meta-analysis of RCTs comparing semaglutide with placebo or other antidiabetic agents in patients with T2DM to summarize all available evidence concerning the efficacy and safety of semaglutide.

Methodik

Population:

- Adult patients with T2DM

Intervention:

- Subcutaneous semaglutide

Komparator:

- placebo or with another antidiabetic agent

Endpunkte:

- Our primary outcome was change from baseline in HbA1c.
- Secondary efficacy outcomes included change in body weight, systolic and diastolic blood pressure and heart rate
- Safety: nausea, vomiting, diarrhoea, any hypoglycaemia and severe hypoglycaemia acute pancreatitis and diabetic retinopathy because of the association of semaglutide

Recherche/Suchzeitraum:

- Medline (via PubMed), Embase (via Ovid) and the Cochrane Library. in January 2018
- RCTs with treatment duration of at least 12 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 12 studies, with 9501 patients

Charakteristika der Population:

- Subcutaneous semaglutide was compared with placebo or with another antidiabetic agent in 6 studies3,4,9,20,21,24 and 7 studies,5–8,21–23 respectively, while 1 trial compared both subcutaneous and oral semaglutide with placebo.3
- The antidiabetic agents used in control arms included sitagliptin,5,22 insulin glargine,7 liraglutide,21 exenatide extended-release (ER)6 or dulaglutide8 while, in 1 study, control

treatment was chosen by trial clinicians from among dipeptidyl peptidase-4 inhibitors, metformin, sulphonylureas, glinides, α-glucosidase inhibitors and thiazolidinediones.23

- Two studies enrolled treatment-naïve patients,4,22 whereas the remaining trials recruited patients receiving single3,8,20,21,23 or dual5–7,9,24 antidiabetic therapy.
- Duration of intervention in most trials ranged from 12 to 56 weeks, with the exception of the SUSTAIN-6 trial, a dedicated cardiovascular outcomes study,9 that had a duration of 104 weeks.
- Participants' mean age and mean baseline HbA1c ranged from 52.7 to 64.7 years and from 7.3% to 8.7%, respectively.

Qualität der Studien:

- Risk of bias within studies was deemed low for 8 studies4–9,22,23 and high for 2 studies,3,21 mainly because of missing outcome data. Furthermore, there were some concerns about 1 study because of lack of information concerning the randomization process,8 and we did not assess risk of bias for 1 study20 because it did not provide data for our primary outcome.20

Study ID	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Ahmann 2016	Low	Low	Low	Low	Low	Low
Ahren 2017	Low	Low	Low	Low	Low	Low
Aroda 2017	Low	Low	Low	Low	Low	Low
Davies 2017	Low	High	High	Low	Low	High
Kaku 2018	Low	Low	Low	Low	Low	Low
Marso 2017	Low	Low	Low	Low	Low	Low
Nauck 2016	Low	Low	High	Low	Low	High
Pratley 2018	Low	Low	Low	Low	Low	Low
Rodbard 2016	Some concerns	Low	Low	Low	Low	Some concerns
Seino 2017	Low	Low	Low	Low	Low	Low
Sorli 2017	Low	Low	Low	Low	Low	Low

Studienergebnisse:

Heart rate

- In comparisons against other antidiabetic agents (WMD, 1.53, 95% CI, 0.89-2.17; I2 = 58% and WMD, 2.03, 95% CI, 1.47-2.60; I2 = 65% for semaglutide 0.5 and 1 mg, respectively).

Hypoglycaemia

- Results were similar for semaglutide 1 mg when compared to antidiabetic agents (OR, 0.72, 95% CI, 0.51-1.03; I2 = 37%).
- Results for semaglutide 0.5 mg, showing a decrease in the incidence of any hypoglycaemia compared to any other agent (OR, 0.52, 95% CI, 0.31-0.87; I2 = 47%)

Adverse events

- Nausea; any other comparator: n=7 OR: 2.60 (95% KI: 2.18-3.10), I^2: 84%
- Vomiting: any other comparator; n=6 OR 2.06 (1.61-2.63),; I^2: 51%
- Diarrhea: any other comparator; n=7; OR 1.84 (1.52-2.23), I^2: 74%

3. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. JAMA. 2017;318:1460-1470.

4. Sorli C, Harashima S-I, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5:251-260.
5. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5:341-354.
6. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41:258-266.
7. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin(with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017;5:355-366.
8. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6: 275-286.
9. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375: 1834-1844.
20. Kapitza C, Dahl K, Jacobsen JB, Axelsen MB, Flint A. Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial. Diabetologia. 2017;60:1390-1399.
21. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label Liraglutide in patients with type 2 diabetes. Diabetes Care. 2016;39:231.
22. Seino Y, Terauchi Y, Osonoi T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. Diabetes Obes Metab. 2018;20:378-388.
23. Kaku K, Yamada Y, Watada H, et al. Safety and efficacy of once-weekly semaglutide versus additional oral antidiabetic drugs, in Japanese subjects with inadequately controlled T2D: a randomized trial. Diabetes Obes Metab. 2018;20:1202-1212.
24. Rodbard HL, Reed J, de la Rose R, et al. Efficacy and safety of semaglutide once-weekly vs placebo as add-on to basal insulin alone or in combination with metformin in subjects with type 2 diabetes (SUSTAIN 5). Paper presented at: EASD 2016; Munich, Germany.

Anmerkung/Fazit der Autoren

In conclusion, a once weekly subcutaneous dose of semaglutide In efficacious in lowering HbA1c, body weight and systolic blood pressure, compared to both placebo and other antidiabetic agents, including several other GLP-1 RAs. However, it is associated with an increased incidence of gastrointestinal adverse events and its relationship with diabetic retinopathy-related outcomes requires further examination through post-approval pharmacovigilance studies.

Kommentare zum Review

- Studien mit vorbehandelten und nicht vorbehandelten Patienten in Meta-Analyse gepoolt
- Autoren erhielten Förderungen seitens pharmazeutischer Unternehmer

---

Fadini GP et al., 2018 [23].

Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors

Fragestellung

In the present study, we evaluated whether combination therapy with an SGLT2 inhibitor and a dipeptidyl peptidase-4 (DPP-4) inhibitor is associated with a lower risk of GUTI than the SGLT2 inhibitor therapy alone.

Methodik

Population:

- D2T

Intervention:

- DPP-4 inhibitor/SGLT2 inhibitor combination therapy

Komparator:

- treatment with an SGLT2 inhibitor alone

Endpunkte:

- frequency of genital tract infection (GTIs), and of urinary tract infection (UTIs) separately and combined (GUTIs

Recherche/Suchzeitraum:

- PubMed and then in ISI Web of Science, Scopus, www.clinicalttrials.gov, and Cochrane Central Register of Controlled Trials
- AERSmine query strings

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

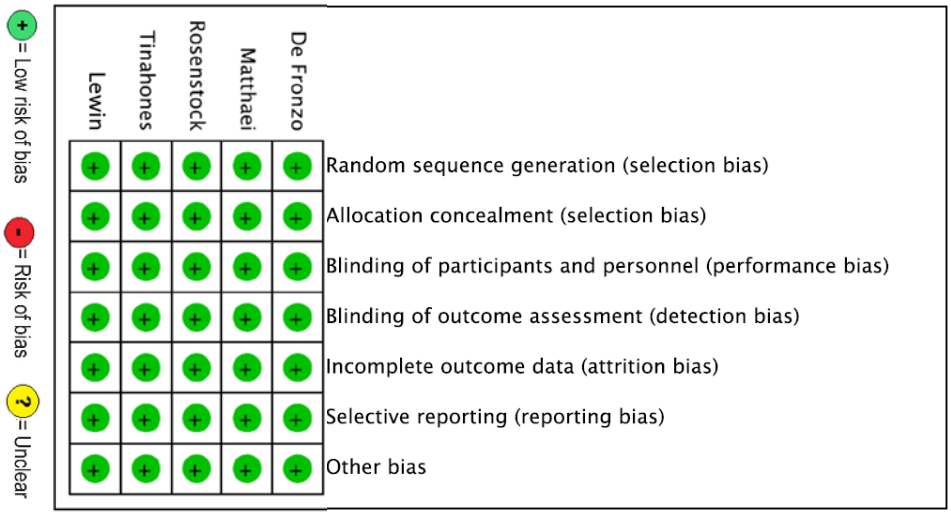
Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Population:

- The five trials reported the results of adding the DPP-4 inhibitors saxagliptin or linagliptin vs placebo to a baseline therapy composed of the SGLT2 inhibitor dapagliflozin or empagliflozin, respectively, for 24 weeks,7,8 or the dual add-on of a combination therapy with saxagliptin/ dapagliflozin or linagliptin/empagliflozin vs the single add-on of dapagliflozin or empagliflozin, respectively, for 24 or 52 weeks.9–11

Qualität der Studien:



Studienergebnisse:

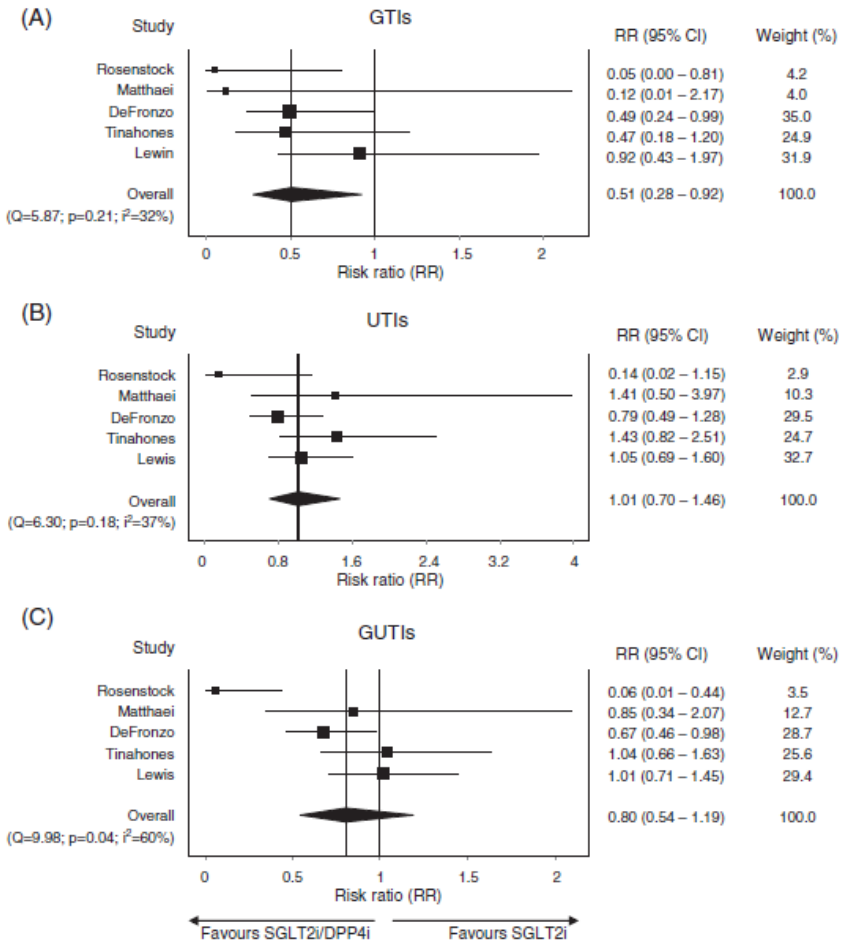


FIGURE 1 Meta-analysis forest plots. The forest plots are shown for UTIs (A), GTIs (B) and combined GUTIs (C). RRs with 95% CIs in each study and in the pooled estimate are given in the tables on the right. The random effects model was used

For GTIs, the RR was 0.51 (95% confidence interval [CI] 0.28-0.92) in favour of the DPP-4 inhibitor/SGLT2 inhibitor combination, with no heterogeneity (Figure 1A). For UTIs, the overall RR was 1.01 (95% CI 0.70-1.46; Figure 1B), and for combined GUTIs the RR was 0.80 (95% CI 0.43-1.19; Figure 1C), with significant heterogeneity. In

Anmerkung/Fazit der Autoren

Our meta-analysis of five high-quality RCTs indicates a 49% lower GTI risk in patients who received a DPP-4 inhibitor in combination with an SGLT2 inhibitor as compared with patients who received an SGLT2 inhibitor alone. A lower rate was not observed in the frequency of UTIs. This is not surprising as, in RCTs, SGLT2 inhibitors typically increase the risk of GTIs, but not that of UTIs.

Gomes GKA et al., 2018 [56].

Linagliptin safety profile: A systematic review

Fragestellung

To describe the safety profile of linagliptin.

Methodik

Population:

- DM2

Intervention:

- linagliptin

Komparator:

- control group was composed of conventional (non placebo) pharmacotherapy.

Endpunkte:

- AE

Recherche/Suchzeitraum:

- PubMed/MEDLINE, BVS and Web of Science published till 07/07/2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

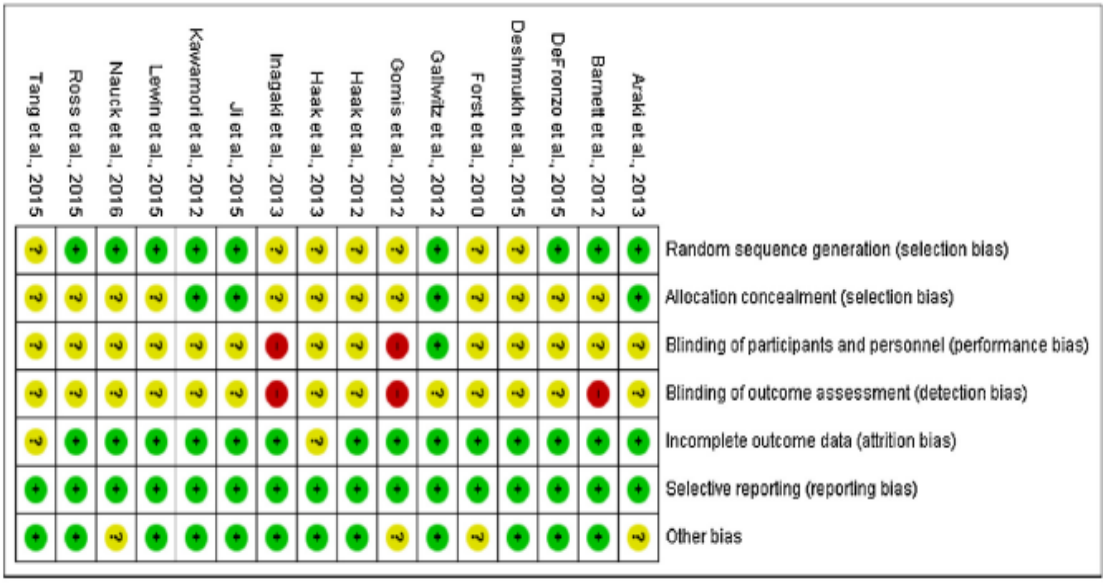
Anzahl eingeschlossener Studien:

- 16 RCTs

Charakteristika der Population:

- Most studies (87.5%) were conducted in Asia. The followup time ranged from 12 to 104 weeks. Among the studies thatreported the clinical phase, the majority (62.5%) were phaseIII.
- The mean age of participants ranged from 48 to 63 years.
- The sample size in each group ranged from 40 to 700individuals, with a total sample ranging from 227 to 2121participants between the studies. Most of the studies (93.8%) reported financing by the pharmaceutical industry.

Qualität der Studien:



Studienergebnisse:

There was a discrepancy in the classification of these AEs. Some arti-cles generalized AEs per system (e.g., gastrointestinal AEs), while others evaluated each manifested AE separately, suchas diarrhea and constipation. No article reported the useof an algorithm to assess the causality of AE. Only 56.25%of the articles evaluated cardiovascular [22,24,26–30,37,41]events and 56.25% evaluated the occurrence of pancreatitis[13,24,26,28–30,36,37,41].

EAs most prevalent in linagliptin in monotherapy

- Among the AEs evaluated, the most frequent occurrence was nasopharyngitis using linagliptin at 5 mg and 10 mg, with a frequency of 31.6% and 29.6%, respec-tively [30].
- Nine deaths occurred in participants who used linagliptinin monotherapy during the study, all in groups usinglinagliptin at 5 mg.
- Hyperglycemia events were more frequent compared tohypoglycemia in studies that used the two AEs as outcomesto be measured, except in the study by Gallwitz et al. [24], where the frequency of hypoglycemia was 1.4 times higherthan hyperglycemia
- The frequency of gastrointestinal AEs was high among thegroups that evaluated it as an outcome (>20.0%), except inthe studies by Tang et al. and Ross et al. [23,29].

AEs most prevalent in linagliptin in combination

- The most frequent AEs were gastrointesti-nal, with a frequency greater than 10.0% in the groups thatused this AE as the outcome to be evaluated [20,29]. Allevaluated groups that presented this AE as outcome usedlinagliptin associated with metformin.
- The incidence of hypoglycemia was considerably low (<4.0%)in the other studies that used this AE as one of the outcomes[20].
- Two deaths were identified during the studies conductedin the groups using linagliptin at 5 mg and empagliflozin at10 mg [13,36] and three deaths in the groups using linagliptinat 2.5 mg and metformin [37],
- Some studies emphasize the importance of pancreatic reac-tions such as pancreatic cancer and pancreatitis, such as thoseperformed by Hohl et al. [34] and Scheen [38], but in the

studiesevaluated, the frequency of pancreatic events was consid-erably low (<1%), among those that evaluated the event incombination.

Anmerkung/Fazit der Autoren

ConclusionThe use of linagliptin whether in monotherapy or not, isassociated with important AEs, and their occurrence andfrequency are varied, being of mild to moderate intensity.The most frequent AEs were nasopharyngitis with linagliptinin monotherapy and gastrointestinal AEs with linagliptinin combination. Therefore, further studies, especially post-marketing, are needed to elucidate the most clinically relevantAEs associated with linagliptin in the real world and withoutpotential conflict of interest.

Li X et al., 2018 [65].

The safety and efficacy of once-weekly glucagon-like peptide-1 receptor agonist semaglutide in patients with type 2 diabetes mellitus: a systemic review and meta-analysis.

Fragestellung

To investigate the safety and efficacy of once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide as monotherapy or add-on to other antihyperglycaemic agents (AHAs) in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- T2DM patients

Intervention/Komparator:

- semaglutide with placebo or other antihyperglycaemic agents (AHAs)

Endpunkte:

- reduction in HbA1c, reduction in SMPG, reduction in FPG, number of participants achieving HbA1c <7.0%, weight loss, AEs, SAEs and hypoglycaemic events (severe or BG-confirmed symptomatic)

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane library and ClinicalTrials.gov were searched from the inception to January 18, 2018

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

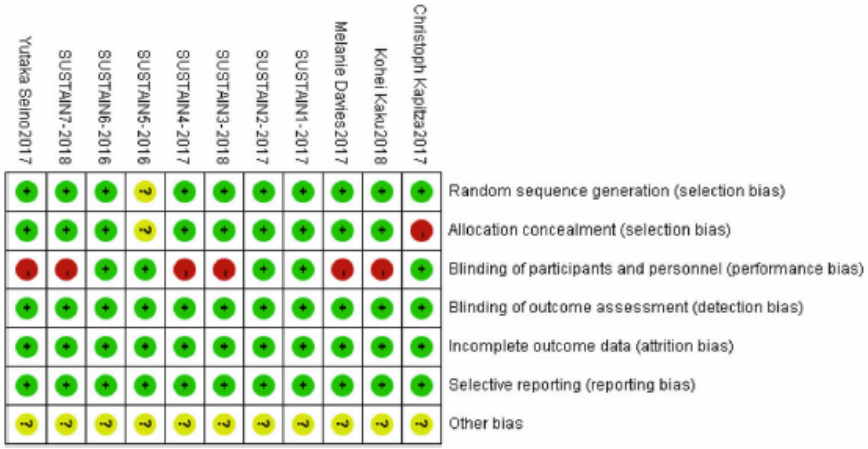
Anzahl eingeschlossener Studien:

- A total of 11 studies with 9519 patients
- Among 11 trials, 5 trials compared the efficacy and safety of semaglutide with placebo and 6 trials compared the efficacy and safety of semaglutide with other AHAs. In the included studies,

the diabetes duration ranged from 3.62 to 14.3 years and the treatment duration ranged from 12 to 104 weeks.

Qualität der Studien:

Fig. 2 Risk of bias graph and summary for included studies



Studienergebnisse:

- The results revealed that compared with placebo or other AHAs, semaglutide had further reduced
  - the level of haemoglobin A1c (HbA1c) [MD 1.03%, 95% CI (0.85%, 1.22%), p < 0.00001],
  - weight [MD 3.61 kg, 95% CI (3.05 kg, 4.17 kg), p < 0.00001]
  - and significantly increased participants who achieved HbA1c < 7.0% [RR 2.26, 95% CI (1.89, 2.70), p < 0.00001] in T2DM patients.
- Semaglutide had a significant increase in
  - the incidence of adverse events (AEs) [RR 1.06, 95% CI (1.02, 1.11), p < 0.0001] and
  - an analogous incidence in serious adverse events (SAEs) [RR 0.94, 95% CI (0.86, 1.02), p = 0.11] and
  - hypoglycaemic events (severe or blood glucose (BG)-confirmed symptomatic) [RR 0.93, 95% CI (0.74, 1.16), p = 0.50] compared with the control group.

Anmerkung/Fazit der Autoren

In conclusion, semaglutide had a favourable efficacy and safety as monotherapy or add-on to other AHAs in the treatment of T2DM patients. It may be a superior choice for T2DM patients with obesity or T2DM patients who have a poor adherence to daily AHAs. Semaglutide is generally well tolerated and has obviously better efficacy than either placebo or other AHAs in treating T2DM.

Wang B et al., 2018 [91].

Comparison of dipeptidyl peptidase-4 inhibitors and pioglitazone combination therapy versus pioglitazone monotherapy in type 2 diabetes

Fragestellung

This is the first meta-analysis to comparison the effects of dipeptidyl peptidase-4 inhibitors and pioglitazone combination therapy versus pioglitazone monotherapy in type 2 diabetes based on RCTs.

Methodik

Population:

- T2DM with HbA1c levels >7%,

Intervention:

- pioglitazone and DPP-4 inhibitor therapy

Komparator:

- monotherapy (placebo)

Endpunkte:

- changes in HbA1c and fasting plasma glucose (FPG)

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases through May 2016
- double-blind RCTs with duration ≥12 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs

Charakteristika der Population:

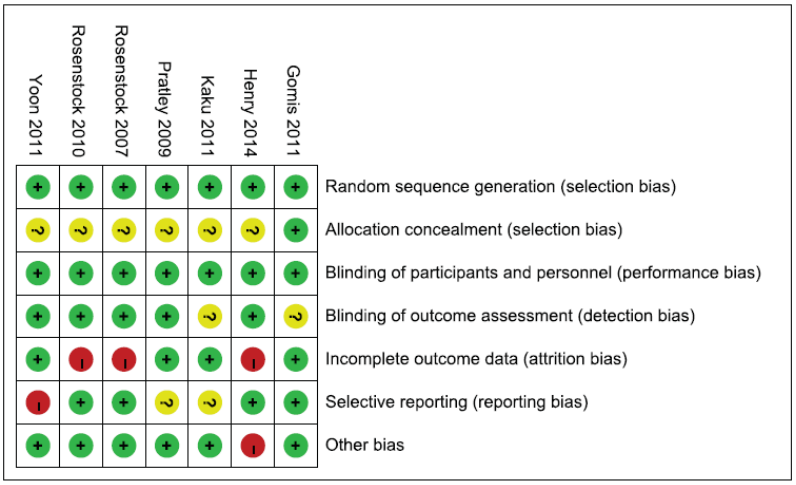
Characteristics of RCTs included in the meta-analysis.

Study	Location	Study size	Study duration, weeks	Study type	Tpye of DDP-4 inhibitor	Mean age	Men (%)	Baseline HbA1c level	Body weight	BMI	Drug navie
Rosenstock 2007[17] NCT00722371	multiregional	607	24	Double-blinded placebo-controlled, RCT	Vildagliptin 100 mg qd	51.5	61.1	DP: 8.8 P: 8.7	NA	DP: 29.6 P: 28.9	Yes
Rosenstock et al[19]	multiregional	655	26	Double-blind, placebo-controlled, RCT	Alogliptin 25 mg qd	NA	NA	DP: 8.8 P: 8.76	NA	~31	Yes
Pratley et al 2009[15]	multiregional	493	26	Double-blind, placebo-controlled, RCT	Alogliptin 25 mg qd	55.4	58.2	DP: 8.0 P: 8.0	NA	DP: 33.1 P: 33.2	No
Gomis et al[13] NCT00641043	multiregional	389	24	Double-blind, placebo-controlled, RCT	Linagliptin 5 mg qd	57.5	60.9	DP: 8.60 P: 8.58	DP: 78.0 P: 82.7	DP: 28.7 P: 29.7	No
Kaku et al[16]	multiregional	339	12	Double-blinded placebo-controlled open-label RCT	Alogliptin 25 mg qd	60.1	62.8	DP: 7.89 P: 7.92	DP: 68.07 P: 69.0	DP: 26.06 P: 26.4	No
Yoon et al[18] NCT00397631	multiregional	520	24	Double-blinded placebo-controlled, RCT	Sitagliptin 100 mg qd	51	54.2	DP: 9.5 P: 9.5	DP: 80.1 P: 80.4	DP: 29.7 P: 29.6	Yes
Henry et al[14] NCT 722371	multiregional	1332	54	Double-blinded placebo-controlled, RCT	Sitagliptin 100 mg qd	51.8	57	DP: 8.7 P: 8.9	NA	NA	No

Data are expressed as mean.

BMI = body mass index, DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor, DP = Dpp-4 inhibitor and pioglitazone combination group, FPG = fasting plasma glucose, NA = not applicable, P = pioglitazone group.

Qualität der Studien:



Studienergebnisse:

- All 7 studies assessed change in HbA1c levels at baseline and the end of the study. Six of them, including a total of 1081 patients had valid data. A greater reduction in HbA1c levels was observed in combination therapy groups, with heterogeneity (MD -0.64;-0.73,-0.55, I2=59%, P=.03).
- There were also no differences in reported hypoglycaemia between these studies (relative risk [RR] 0.80, 95% CI 0.43–1.50).
  - Combination therapy with DPP-4 inhibitors and pioglitazone were generally well tolerated over the 12 to 54 week treatment period. There were no differences in AEs between combination therapy with DPP-4 inhibitors and pioglitazone and pioglitazone in any of the 7 RCTs

[13]. Gomis R, Espadero R-M, Jone R, et al. Efficacy and safety of initial combination therapy with linagliptin and piogltazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind placebo-controlled study. Diabetes Obes Metab 2011;13:653–61.
[14]. Henry RR, Staels B, Fonseca VA, et al. Efficacy and safety of initial combination treatment with sitagliptin and pioglitazone—a factorial study. Diabetes Obesity Metab 2014;16:223–30.
[15]. Pratley RE, Reusch JE, Fleck PR, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin 2009;25:2361–71.
[16]. Kaku K, Itayasu T, Hiroi S, et al. Efficacy and safety of alogliptin added to pioglitazone in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label long-term extension study. Diabetes Obes Metab 2011;13:1028–35.
[17]. Rosenstock J, Kim SW, Baron MA, et al. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with componentmonotherapy in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:175–85.
[18]. Yoon KH, Steinberg H, Teng R, et al. Efficacy and safety of initial combination therapy with sitagliptin and pioglitazone in patients with type 2 diabetes: a 54-week study. Diabetes Obes Metab 2012;14:745–52.
[19]. Rosenstock J, Inzucchi SE, Seufert J, et al. Combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes. Diabetes Care 2010;33:2406–8.

Anmerkung/Fazit der Autoren

DPP-4 inhibitor and pioglitazone combination therapy provided better glycemic control, both according to HbA1c and FPG levels, than pioglitazone monotherapy. Safety analysis showed well tolerance of combination therapy, even in hypoglycemic and edema AEs.

Wei ZG et al., 2018 [93].

PRISMA—efficacy and safety of lixisenatid for type 2 diabetes mellitus A meta-analysis of randomized controlled trials

Fragestellung

The objective of this metaanalysis was to systematically evaluate the efficacy and safety of lixisenatide in patients with T2DM.

Methodik

Population:

- patients ages>18 years, with inadequately controlled type 2 diabetes and a glycated hemoglobin (HbA1c) level of 7–10%

Intervention/Komparator:

lixisenatide or placebo was administered subcutaneously, with or without oral antidiabetic agents (OADs)/insulin

Endpunkte:

- HbA1c, FPG, body weight, and rescue therapy, safety

Recherche/Suchzeitraum:

MEDLINE, EMBASE, Cochrane library, ClinicalTrials.gov, Google, Web of Science, and the Chinese Science Citation Database were searched up to March 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

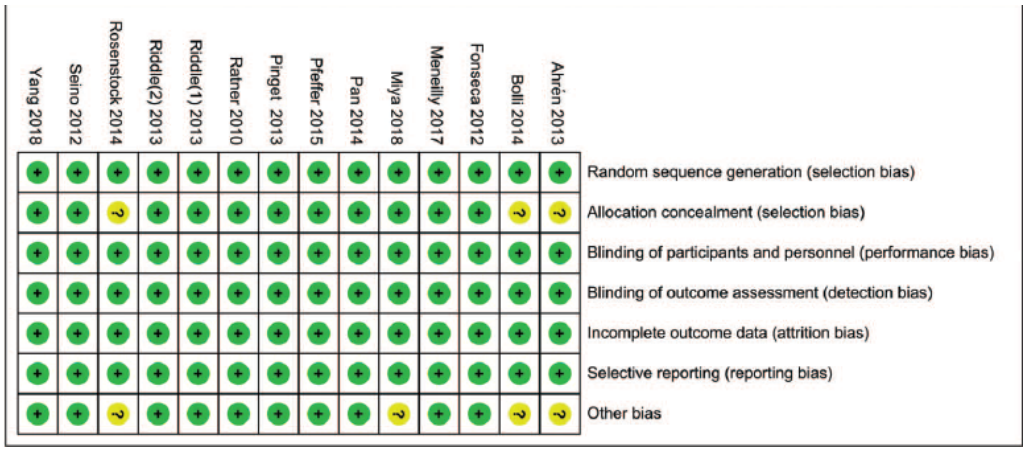
Anzahl eingeschlossener Studien:

- Fourteen eligible multicenterRCTs[5,6,14,18–28] were included finally, with a total sample size of 11,947

Charakteristika der Population:

- The baseline HbA1c level was 7 to 10% in all studies, and the follow-up durations were 24 weeks,[6,18–24,26,28] 13 weeks,[5] 12 weeks,[14,27] and 25 months.[25]
- Lixisenatide 20mg once daily was subcutaneously administered in most of the included studies. Metformin, [5,18–25,28] sulfonylurea, [6,18–21,25] thiazolidinedione, [24,25] pioglitazone,[22] and insulin [6,23–25,28] were used in different studies for glycemic control.

Qualität der Studien:



Studienergebnisse:

Outcomes	Study	I^2%	Random effects model WMD/RR (95% CI)	P
Efficacy				
HbA1c	7	66	−0.48 (−0.60, −0.36)	<.00001
HbA1c<7.0%	11	58	1.94 (1.73–2.16)	<.00001
HbA1c<6.5%	10	43	3.03 (2.54–3.63)	<.00001
Fasting plasma glucose	7	28	−0.43 (−0.62, −0.25)	<.00001
Body weight	6	0	−1.34 (−2.67,−0.02)	0.05
Rescue therapy	9	0	0.39 (0.30–0.51)	<.00001
Glucose excursion	5	93#	−3.91 (−4.72, −3.10)	<.00001
2-hour PPG	5	92&	−4.31 (−5.50, −3.12)	<.00001
Safety				
Any adverse events (AE)	12	46	1.14 (1.08–1.19)	<.00001
Discontinuation due to AE	14	0	1.79 (1.57–2.05)	<0.00001
Serious adverse events	13	0	0.94 (0.86–1.04)	.49
Death*	6	0	0.64 (0.18, 2.32)	.49
Gastrointestinal disorders	13	74	2.23 (1.86–2.68)	<.00001
Nausea	12	30	4.09 (3.38–4.95)	<.00001
Vomiting	12	18	5.57 (3.88–7.98)	<.00001
Diarrhea	10	7	1.28 (1.05–1.55)	.01
Symptomatic hypoglycemia	14	0	1.59 (1.35–1.89)	<.0001
Severe hypoglycemia	5	0	0.74 (0.40–1.36)	.33
Injection-site reactions	9	0	2.05 (1.43–2.95)	.0001
Allergic reaction	6	0	2.11 (0.68–6.54)	.20

Anmerkung/Fazit der Autoren

Compared to placebo, lixisenatide could significantly reduce the levels of HbA1c, FPG, and PPG, and higher proportion of lixisenatide-treated patients achieved the HbA1c targets of<7.0% and<6.5% in lixisenatide-treatment group. It increased the incidence of mild-to-moderate gastrointestinal AEs and symptomatic hypoglycemia, but it was not associated with serious AEs, death, or severe hypoglycemia. In conclusion, lixisenatide was effective and relatively well tolerated in patients with inadequately controlled T2DM.

Zhang YJ et al., 2018 [102].

Efficacy and safety of empagliflozin for type 2 diabetes mellitus Meta-analysis of randomized controlled trials

Fragestellung

We carried out this meta-analysis to assess the efficiency and safety of EMPA (10 and 25mg once daily) compared with placebo both as monotherapy and as addon therapy to OAD in patients with T2DM.

Methodik

Population:

- T2DM

Intervention:

- EMPA

Komparator:

- Placebo, placebo as add-on to other antidiabetes therapy

Endpunkte:

- change from baseline in hemoglobin A1c (HbA1c), proportion of patients with HbA1c ≥7.0% at baseline who reached HbA1c <7.0% at last follow-up; changes from baseline in fasting plasma glucose (PFG); changes from baseline in body weight, proportion of patients with >5.0% reduction in body weight; change from baseline in systolic and diastolic blood pressures

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL), Web of Knowledge, and Pubmed up to May 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

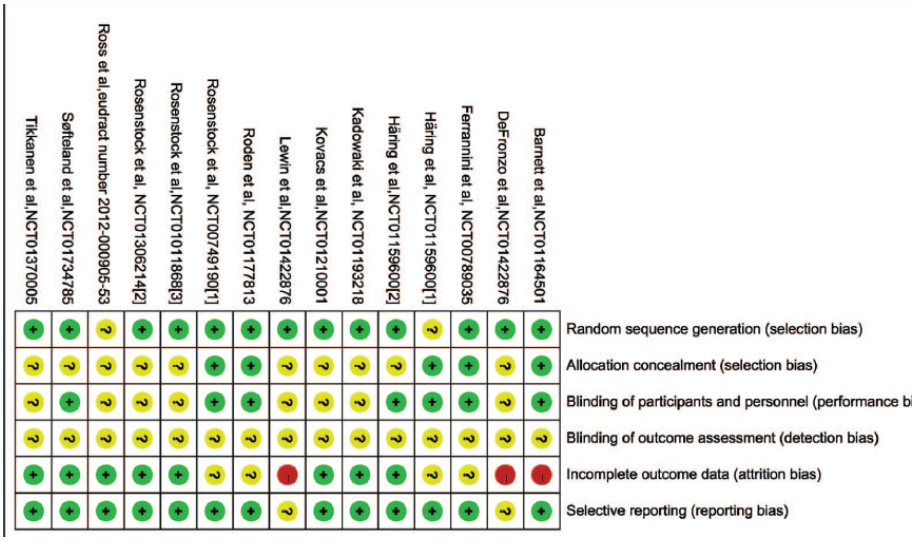
Anzahl eingeschlossener Studien:

- 15 studies (n=7891)

Charakteristika der Population:

- There were 3 trials comparing EMPA vs placebo as monotherapy[13,17,18]; 3 trials comparing EMPA vs placebo as add-on to metformin[4,15,20]; 1 trial comparing EMPA vs placebo as add-on to metformin plus sulfonylurea[16]; 2 trial comparing EMPA vs placebo as add-on to metformin plus linagliptin[6,23]; 1 trial comparing EMPA vs placebo as add-on to pioglitazone or pioglitazone plus metformin[21]; 2 trials comparing EMPA vs placebo as add-on to insulin with or without OADs[3,19]; 1 trial comparing EMPA vs placebo as add-on to linagliptin[2]; 2 trials comparing EMPA vs placebo with other OADs unclear.[5,22]

Qualität der Studien:



Studienergebnisse:

Subgroup analysis of efficacy effect sizes (e.g., change from baseline in HbA1c, proportion of patient with HbA1c >7% who had HbA1c <7% and change from baseline in FPG) according to concomitant therapy of EMPA on type 2 diabetes mellitus.

	Change from baseline in HbA1c (%)			Proportion of patient with HbA1c>7% who had HbA1c<7%			change from baseline in FPG		
	No. of study	No. of participants	WMD (95% CI) Heterogeneity	No. of study	No. of participants	RR (95% CI) heterogeneity	No. of study	No. of participants	WMD (95% CI) heterogeneity
EMPA monotherapy	3	1335	−0.74 (−0.84, −0.64) $P=.54$, $I^2=0\%$	2	1019	4.63 (1.64, 13.09) $P=.07$, $I^2=69\%$	3	1335	−2.01 (−2.52, −1.49) $P=.004$, $I^2=82\%$
EMPA add-on to metformin	3	1351	−0.58 (−0.71, −0.46) $P=.12$, $I^2=53\%$	2	1054	1.90 (1.33, 2.71) $P=.27$, $I^2=17\%$	3	1707	−1.48 (−1.67, −1.29) $P=.41$, $I^2=0\%$
EMPA add-on to metformin plus sulfonylurea	1	666	−0.63 (−0.75, −0.51) not applicable	1	627	3.18 (2.04, 4.95) not applicable	1	666	−1.60 (−1.86, −1.34) not applicable
EMPA add-on to metformin plus linagliptin	2	715	−0.68 (−0.78, −0.58) $P=.39$, $I^2=0\%$	2	677	1.85 (1.42, 2.39) $P=.51$, $I^2=0\%$	2	721	−1.64 (−2.21, −1.07) $P=.06$, $I^2=71\%$
EMPA add-on to pioglitazone or pioglitazone plus metformin	1	501	−0.54 (−0.71, −0.38) not applicable	1	466	3.49 (1.97, 6.19) not applicable	1	496	−1.44 (−1.80, −1.08) not applicable
EMPA add-on to insulin with or without OAD	2	701	−0.47 (−0.62, −0.32) $P=.40$, $I^2=0\%$	2	1045	1.81 (1.37, 2.39) $P=.52$, $I^2=0\%$	2	840	−0.92 (−1.25, −0.59) $P=.88$, $I^2=0\%$
EMPA add-on to linagliptin	1	402	−0.73 (−0.94, −0.53) not applicable	1	370	1.82 (1.39, 2.39) not applicable	1	402	−1.52 (−1.91, −1.13) not applicable
EMPA with background OAD therapy unclear	2	1547	−0.56 (−0.73, −0.40) $P=.04$, $I^2=76\%$	1	290	3.09 (1.35, 7.04) not applicable	2	1561	−1.28 (−1.76, −0.80) $P=.04$, $I^2=76\%$
Overall effect	15	7218	−0.62 (−0.67, −0.57) $P=.03$, $I^2=45\%$	13	6122	2.20 (1.68, 2.87) $P<.00001$, $I^2=82\%$	15	7728	−1.52 (−1.72, −1.32) $P<.00001$, $I^2=79\%$

95% CI = 95% confidence interval, EMPA = empagliflozin, HbA1c = hemoglobin A1c, No = number, OAD = other oral antidiabetic agent, PFG = fasting plasma glucose, RR = relative risk, WMD = weight mean difference.

	Change from baseline in body weight		
	No. of study	No. of participants	WMD (95% CI) heterogeneity
EMPA monotherapy	3	1335	−1.87 (−2.19, −1.54) P=.28, I^2=22%
EMPA add-on to metformin	3	1814	−1.81 (−2.11, −1.52) P=.56, I^2=0%
EMPA add-on to metformin plus sulfonylurea	1	666	−1.88 (−2.25, −1.52) not applicable
EMPA add-on to metformin plus linagliptin	2	725	−2.49 (−2.90, −2.08) P=.75, I^2=0%
EMPA add-on to pioglitazone or pioglitazone plus metformin	1	498	−1.88 (−2.36, −1.41) not applicable
EMPA add-on to insulin with or without OAD	2	846	−2.56 (−3.26, −1.86) P=.62, I^2=0%
EMPA add-on to linagliptin	1	402	−1.50 (−2.45, −0.54) not applicable
EMPA with backgroud OAD therapy unclear	2	1561	−1.68 (−1.93, −1.43) P=.49, I^2=0%
Overall effect	15	7847	−1.91 (−2.07, −1.75) P=.13, I^2=30%

Anmerkung/Fazit der Autoren

In summary, it is demonstrated that EMPA therapy can improve glycemia, weight and blood pressure control, and was well tolerated except for increased genital infections in patients with T2DM. We recommend that EMPA should be offered to patients with T2DM, especially to patient who are overweight or at risk for body weight gain. As for combination therapy, we recommend EMPA firstly added to metformin, metformin plus sulfonylurea, metformin plus linagliptin, pioglitazone or pioglitazone plus metformin, insulin with or without OAD and linagliptin.

Systematische Reviews vor dem Update 2019

Castellana M et al., 2018 [10].

GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: A systematic review and meta-analysis

Fragestellung

We conducted a systematic review and meta-analysis to compare the effects of GLP-1RA/insulin combinations versus BP/BB.

Methodik

Population:

- patients with type 2 diabetes

Intervention:

- short-acting GLP-1RA added to basal insulin (1)
- long-acting GLP-1RA added to basal insulin (2)
- long-acting GLP-1RA added to prandial insulin (3)
- fixed-ratio combinations of GLP-1RA and basal insulin (4)

Komparator:

- basal-plus (BP) or basal-bolus (BB) insulin

Endpunkte:

- Primary: HbA1c change
- Secondary: body weight change, total daily insulin dose, incidence of hypoglycaemic events discontinued patients due to lack of efficacy

Recherche/Suchzeitraum:

- on 15 July 2018 in PubMed, Scopus, CENTRAL, and ClinicalTrials.gov

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 trials with 5308 adult patients
  - 3 studies exenatide, 3 lixisenatide, 2 albiglutide, 2 dulaglutide, 2 liraglutide, and 1 IDegLira
  - 3 studies 3 armed

Charakteristika der Population:

- type 2 diabetes mellitus, with HbA1c of 6% to 11%
- Prescreening therapy: 96% of basal insulin, 27% on prandial insulin, 82% on metformin

Qualität der Studien:

- Random sequence generation and allocation concealment adequate in 8 trials; 4 not reported
- risk of performance and detection bias: high risk, all 13 trials were open label
- Discontiuation rate between 0-30%; significant betweens arms in 2 studies
- No selective reporting bias
- Industry sponsored: 9 trials

Studienergebnisse:

- Subgroups: Interventions 1-4
- Change in HbA1c (Baseline to last available follow-up): not significant I2 = 52%
  - Subgroup long-acting GLP-1RA added to prandial insulin: -0.16%; 95% CI, -0.29 to -0.04; p=0.01
- body weight change: reduction with GLP-1RA -3.72 kg; CI, -4.49 to -2.95; p<0.001; I2 =89%
  - consistent in all subgroups
  - high heterogeneity in all analysis (total and subgroup)
- total daily insulin dose: GLP-1RA added to insulin was associated with a reduction -30.3 IU/day; 95% CI, -41.2 to -19.3; p<0.001; I2 = 94%
  - consistent in all subgroups
  - high heterogeneity in all analysis
- hypoglycaemic events: GLP-1RA added to insulin showed to be superior to BP/BB insulin (RR = 0.46; 95% CI, 0.38-0.55; p< 0.001; I2 = 99%)
  - consistent in all subgroups
  - high heterogeneity in all analysis
- discontinuation due to lack of efficacy: no difference

Anmerkung/Fazit der Autoren

In patients with type 2 diabetes mellitus, a combination therapy with GLP-1RA and insulin proved to be as effective as BP/BB insulin on HbA1c, while leading to a significant weight loss, reduced risk of hypoglycaemia, and use of less insulin dose. Since the addition of GLP-1RA could exert the same glucose-lowering effects of up to 60 IU/day of insulin, a significant number of patients on BP/BB could be potentially shifted to GLP-1RA/insulin regimens.

Kommentare zum Review

Es ist zu beachten, dass alle Studien open-label waren. Zudem bestand eine starke Heterogenität. Die Autoren führen dazu aus: This could be due to (1) characteristics of GLP-1RA in each subgroup (ie, exenatide versus lixisenatide), (2) trial design, and (3) patients characteristics other than the extracted ones. HbA1c at baseline was between 6% and 11%,

---

Cho YK et al., 2018 [14]; Li D et al., 2018 [62]; Min SH et al., 2018 [77]

Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: A systematic review and meta-analysis

Fragestellung

Comparing the efficacy of SGLT2i/DPP4i vs. that of either a DPP4i or a SGLT2i.

Methodik

Population:

- Patients with T2DM

Intervention:

- SGLT2i/DPP4i as combined treatment

Komparator:

- DPP4i + placebo or SGLT2i + placebo

Endpunkte:

- HbA1c; Secondary outcomes: fasting plasma glucose (FPG), body weight, proportion of subjects achieving the therapeutic goal of an HbA1c < 7.0%, risk of hypoglycaemia

Recherche/Suchzeitraum:

- Bis 31 Mai 2017 in PuMed, Embase and Cochrane Library

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs (1 Study included 2 separate RCTs)
  - 8 RCT SGLT2i/DPP4i vs.DPP4i with 2220 Patients
  - 5 RCT SGLT2i/DPP4i vs.SGLT2i with 1681 Patients
  - 3 RCTs included in both meta-analyses as they included both comparisons

Charakteristika der Population:

- Metformin as background therapy: 9 RCTs
- Simultaneaous combination treatment 3 RCTs
- Additional efficacy and safety of SGLT2i or DPP4i in 10 trials (placebo added)

Author (year)	Background therapy	Interventions	Duration (weeks)	Patients (*n*)	Age (years)	Male (%)	BMI (kg/m^2)	HbA_{1c} (%)	HbA_{1c} (mmol/mol)	FPG (mg/dL)
Defronzo (2015) [20]	Metformin	Empagliflozin 25 mg	24	134	57.1	53.7	30.6	7.9	62.8	154.6
		+linagliptin 5 mg		140	55.5	46.4	31.8	8.0	64.2	159.9
		Empagliflozin 25 mg		128	56.2	50.0	30.6	8.0	64.2	156.3
		Linagliptin 5 mg								
Lewin (2015) [19]	None	Empagliflozin 25 mg	24	134	54.2	52.2	31.8	8.0	63.8	156.1
		+linagliptin 5 mg		133	56.0	57.9	31.2	8.0	63.8	152.8
		Empagliflozin 25 mg		133	53.8	56.4	31.9	8.1	64.5	156.0
		Linagliptin 5 mg								
Rosenstock (2015) [18]	Metformin	Dapagliflozin 10 mg	24	179	53	47	31.8	8.9	74.0	180.0
		+saxagliptin 5 mg		179	54	53	31.8	9.0	75.2	192.0
		Dapagliflozin 10 mg		176	55	50	31.5	8.9	73.4	185.0
		Saxagliptin 5 mg								
Jabbour (2014) [24]	Metformin + sitagliptin 100 mg	Dapagliflozin 10 mg	24	223	54.8	57.0	NA	7.9	62.8	162.2
		Placebo		224	55.0	52.7	NA	8.0	63.9	163.0
Mathieu (2015) [26]	Metformin + saxagliptin 5 mg	Dapagliflozin 10 mg	24	160	55.2	43.7	31.2	8.2	66.6	179.0
		Placebo		160	55.0	47.5	32.2	8.2	65.8	177.0
Rodbard (2016) [27]	Metformin + sitagliptin 100 mg	Canagliflozin 100 mg	26	107	57.4	61.7	32.3	8.5	69.4	185.5
		or 300 mg		106	57.5	51.9	31.7	8.4	68.3	180.4
		Placebo[b]								
Kadowaki (2017) [25]	Teneligliptin 20 mg	Canagliflozin 100 mg	24	70	58.4	77.1	25.5	8.2	65.9	173.9
		Placebo		68	56.0	77.9	26.4	7.9	62.5	166.3
Søfteland (2017) [28]	Metformin + linagliptin 5 mg	Empagliflozin 25 mg	24	110	55.4	64.5	29.9	8.0	63.6	169.2
		Placebo		108	55.9	55.6	29.6	8.0	63.6	163.8
Matthaei (2015) [29]	Metformin + dapagliflozin 10 mg	Saxagliptin 5 mg	24	153	54.7	47.7	31.4	8.0	63.6	164.0
		Placebo		162	54.5	46.9	31.4	7.9	62.4	158.0
Tinahones (a)[a] (2017) [22]	Metformin + empagliflozin 10 mg	Linagliptin 5 mg	24	122	56.6	56.6	31.3	8.0	64.4	159.5
		Placebo		125	56.8	56.0	30.8	8.0	64.3	157.1
Tinahones (b)[a] (2017) [22]	Metformin + empagliflozin 25 mg	Linagliptin 5 mg	24	110	56.6	47.3	30.8	7.8	61.9	152.1
		Placebo		110	56.1	57.3	32.0	7.9	62.6	155.4

Data are means (continuous variables) or percentages (dichotomous variables) unless otherwise indicated. BMI: body mass index; FPG: fasting plasma glucose; HbA_{1c}: haemoglobin A_{1c}; NA: not available.

[a] Tinahones et al. [22] comprised two separate trials of linagliptin 5 mg/empagliflozin 10 mg or placebo/empagliflozin 10 mg plus metformin (Tinahones [a]) or linagliptin 5 mg/empagliflozin 25 mg or placebo/empagliflozin 25 mg plus metformin (Tinahones [b])

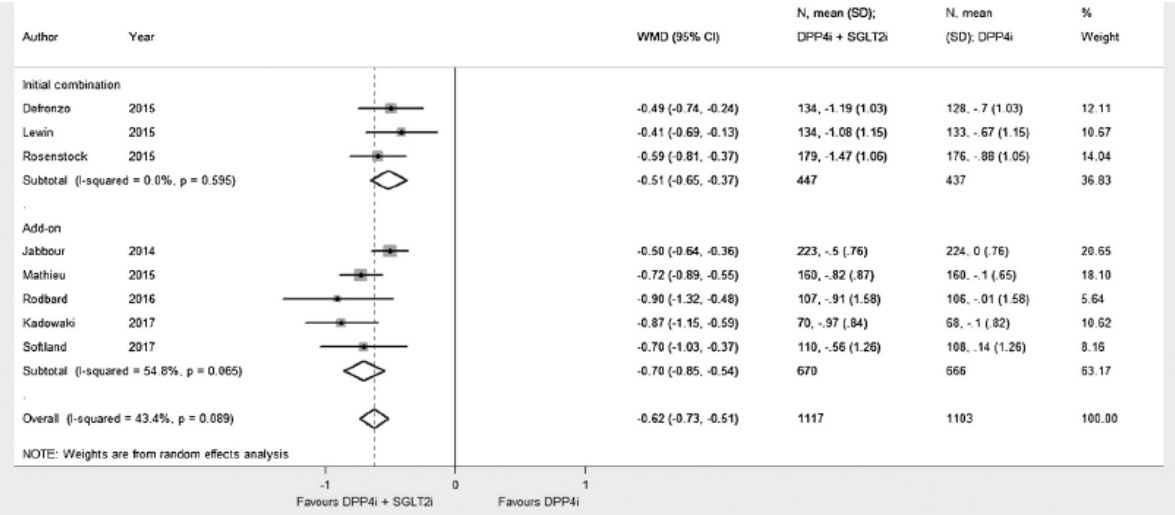
[b] 6 weeks after starting canagliflozin 100 mg, the dose was increased to 300 mg (or from placebo to matching placebo) if all of the following criteria were met: baseline estimated glomerular filtration rate ≥ 70 mL/min/1.73 m^2; fasting self-monitored blood glucose ≥ 5.6 mmol/L (≥ 100 mg/dL); no volume-depletion-related adverse events within 2 weeks of dose increase.

<u>Qualität der Studien:</u>

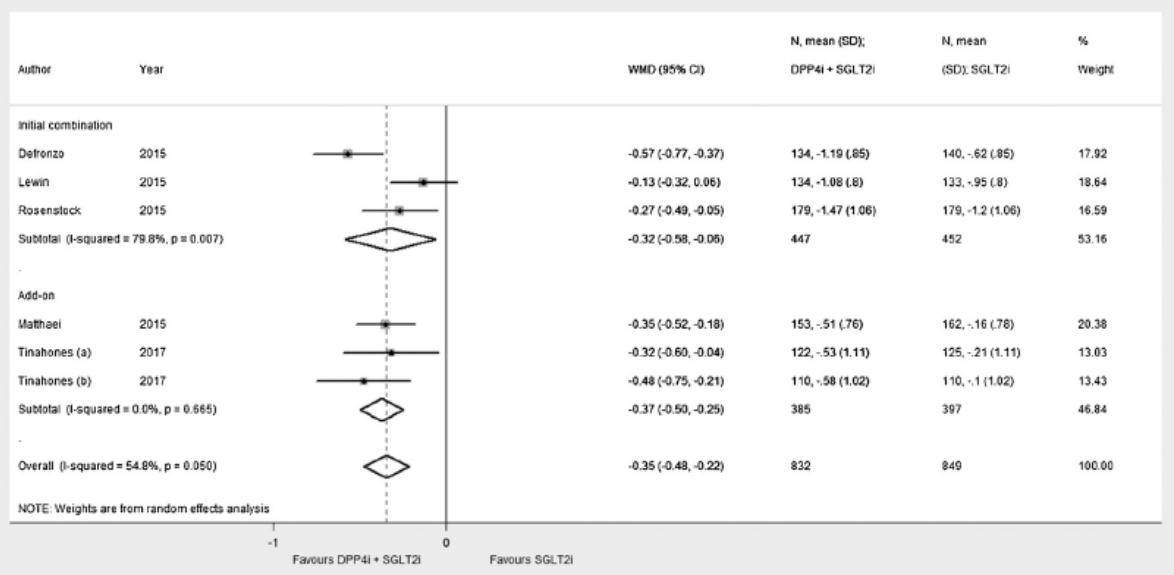
- funnel plots and Egger's regression test (HbA1c), no obvious asymmetrical distribution or small-study effect was detected

<u>Studienergebnisse:</u>

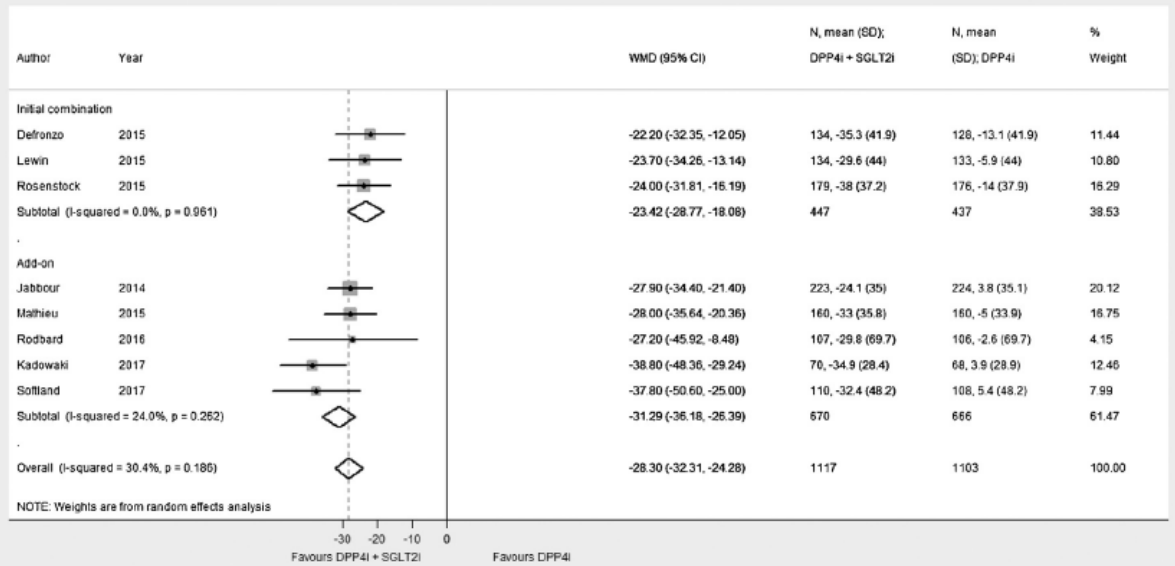
- HbA1c reduction
  - SGLT2i/DPP4i vs DPP4i:



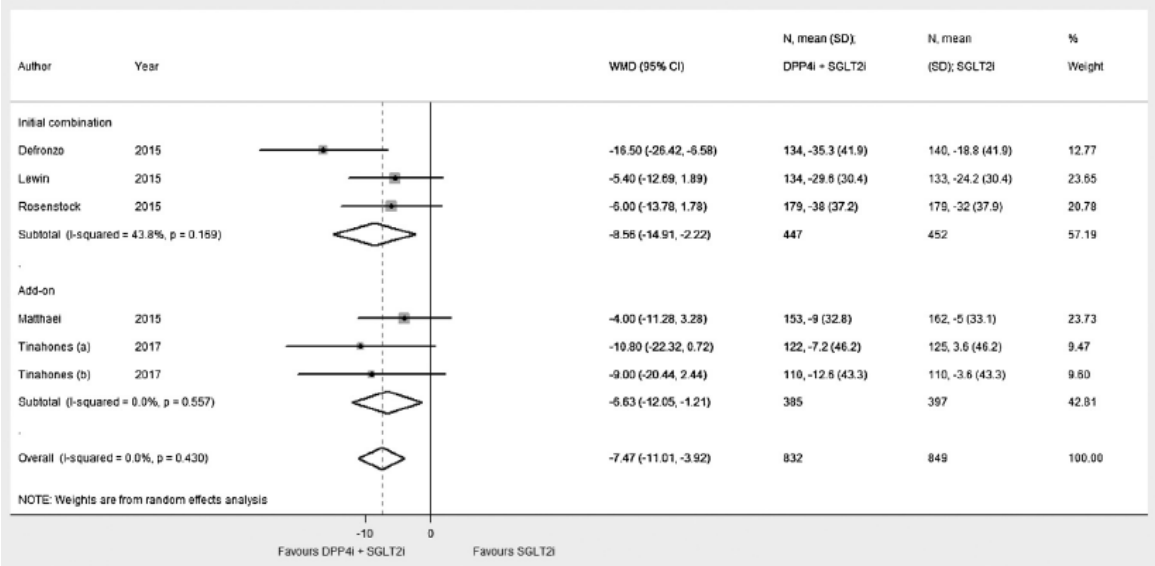
  - SGLT2i/DPP4i vs SGLT2i:



- Changes in FPG
  - SGLT2i/DPP4i vs DPP4i:



  - SGLT2i/DPP4i vs SGLT2i:



- proportion of participants attaining the HbA1c target of < 7.0%
  - SGLT2i/DPP4i vs DPP4i: RR: 2.03, 95% CI: 1.73–2.39; P < 0.001
  - SGLT2i/DPP4i vs. SGLT2i: RR: 1.74, 95% CI: 1.46–2.08; P < 0.001
  - The difference was significant regardless of the manner of combination
- Change of body weight from baseline
  - SGLT2i/DPP4i vs DPP4i: WMD: -1.75 kg, 95% CI: -2.02 to -1.49 kg; P < 0.001
  - SGLT2i/DPP4i vs. SGLT2i: WMD: 0.29 kg, 95% CI: -0.14 to 0.71 kg; P = 0.191
  - No significant differences observed vs. SGLT2i; result similar regardless of combination
- Change of SBP from Baseline
  - SGLT2i/DPP4i vs DPP4i: WMD: -2.50 mmHg, 95% CI: -3.77 to -1.24 mmHg; P < 0.001
  - SGLT2i/DPP4i vs. SGLT2i: not significant
- Hypoglycaemia: risk of hypoglycaemia was low and similar between treatment groups
- genital infections
  - SGLT2i/DPP4i vs DPP4i: higher risk (RR: 2.94, 95% CI: 1.23 to 7.00; P = 0.015)
  - SGLT2i/DPP4i vs SGLT2i: lower risk (RR: 0.42, 95% CI: 0.18 to 0.99; P = 0.046)

Anmerkung/Fazit der Autoren

Combined therapy with SGLT2i/DPP4i is effective and safe. However, interestingly, a marked additional glucose-lowering effect is evident when SGLT2i is combined with or added to DPP4i, but not vice versa. In addition, baseline HbA1c levels significantly influence the glucose-lowering effects of SGLT2i in combination with DPP4i and, thus, further studies are needed to elucidate the underlying mechanism of this effect.

Kommentare zum Review

- *Li D et al., 2018 [62] führten eine Meta-Analyse mit einer fast identischen Fragestellung durch. Obwohl dieser Review 3 zusätzliche Studien einschloss (jeweils asiatische Patienten und SGLT2i in unterschiedlichen Dosierungen) war die Schlussfolgerung vergleichbar:*

- *„In conclusion, compared with monotherapy, SGLT2 inhibitor/ DPP-4 inhibitor combination therapy was efficacious in treatment naïve patients or metformin-treated patients. However, this combination therapy might be associated with a higher risk of genital infections and increased levels of TC, HDL-C and LDL-C than those associated with a DPP-4 inhibitor. Low doses of an SGLT2 inhibitor might be prioritised when combination therapy is required.“*
- *Min SH et al., 2018 [77] führten ebenfalls einen SR inklusive Metaanalyse zur Kombinationstherapie von SGLT2i/DPP4i durch, jedoch nur im Vergleich zu DPP4i. Die 7 eingeschlossenen RCTs waren mit einer Ausnahme (Insuline und weitere OADs waren als Begleittherapie erlaubt) ebenfalls in der Metaanalyse von Cho YK et al., 2018 [14] enthalten. Die Ergebnisse und Schlussfolgerungen waren vergleichbar:*
- *„In conclusion, the SGLT2 inhibitor and DPP4 inhibitor combination therapy improves glycemic control and reduces body weight without increasing the risk of hypoglycemia and UTI in patients with inadequately controlled type 2 diabetes.“*

Keshavarz K et al., 2017 [61].

Linagliptin versus sitagliptin in patients with type 2 diabetes mellitus: a network meta-analysis of randomized clinical trials

Fragestellung

The aim of this study was also to compare the clinical efficiency of linagliptin and sitagliptin in patients with type 2 diabetes

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- Linagliptin (5mg) ± Metformin

Komparator:

- Sitagliptin (100mg) ± Metformin

Endpunkte:

- HbA1c change, patients achieving HbA1c <7%, hypoglycemic events, body weight change

Recherche/Suchzeitraum:

- To end of 2015 in Scopus, PubMed, and Web of Science

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 32 RCTs

- o Linagliptin vs Placebo (n=8); Sitagliptin vs Placebo (n=13)
- o Linagliptin + Met vs Placebo + Met (n=4); Sitagliptin + Met vs Placebo + Met (n=7)

Qualität der Studien:

- the selected studies obtained a score equal to or more than three

Studienergebnisse:

Table 3 Network meta-analysis for comparison HbA1c changes from baseline, Body weight change from baseline, Percentage of patients achieving HbA1c <7 and Percentage of patients experiencing hypoglycemic events between 2 groups (If in Table 2 pairs (1 similar 3) & (2 similar 4))

Comparison	Drug1	Drug2	HbA1c change from baseline			Body weight change from baseline			Percentage of patients achieving HbA1c <7%			Percentage of patients experiencing hypoglycemic events		
			Freq	Mean difference (SE)	*p*-value	Freq	Mean difference (SE)	*p*-value	Freq	Ln(OR) (SE)	*p*-value	Freq	Ln(OR) (SE)	*p*-value
Direct (7)	Linagliptin 5 mg	placebo	12	−.495(.119)	0	7	−0.211(.701)	0.764	9	0.711 (.257)	0.006	10	−1.250 (.271)	0
Direct (8)	Sitagliptin 100 mg	placebo	20	−.375(.072)	0	11	−0.664 (.553)	0.229	13	0.514 (.209)	0.014	19	−0.753 (.228)	0.001
Indirect (9)	Linagliptin 5 mg	Sitagliptin 100 mg	–	−0.12(.139)	>.05	–	0.454 (.893)	>0.05	–	0.197 (.332)	>.05	4	−0.497(.354)	>0.05

Anmerkung/Fazit der Autoren

The results showed no significant difference between linagliptin and sitagliptin in terms of clinical efficacy and they had the same effect.

Kommentare zum Review

Die Publikation wurde von der Shafayab Gostar Company, Tehran, Iran finanziell unterstützt.

Li D et al., 2018 [63].

Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials

Fragestellung

to evaluate the association between SGLT2i and risk of DFS and amputation in patients with T2D, and to clarify whether the increased risk of amputations is a drug-specific effect or a class effect.

Methodik

Population:

- patients with type 2 diabetes

Intervention:

- SGLT2i

Komparator:

- placebo or other OADs

Endpunkte:

- Diabetic foot syndrome and amputation were identified using pre-specified lists from the Medical Dictionary for Regulatory Activities (MedDRA)

Recherche/Suchzeitraum:

- To June 2017 PubMed, Embase and CENTRAL

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- fourteen RCTs consisting of 26,167 participants

Charakteristika der Population:

- Different Background therapies in the trials

Qualität der Studien:

- Thirteen RCTs were judged low risk of bias because they reported adequate random sequence generation and allocation concealment. Eight RCTs were low risk of performance bias, and six RCTs were low risk of detection bias. However, twelve RCTs reported the occurrence of events of interest online but not in the published paper, and judged unclear risk of reporting bias. All RCTs were judged low risk of attrition bias owing to the clear elaboration of discontinuation situation.

Studienergebnisse:

- Diabetic foot syndrome risk: only nine studies reported at least one case with **no significant** differences between SGLT2i and comparators
- Amputation risk: only four RCTs reported at least one case; No RCT was available to evaluate the amputation risk of dapagliflozin. SGLT2i as a class were **not significantly** associated with increased risk of amputation as compared with comparators
  - Subgroupmeta-analysis showed that canagliflozin (OR 1.89, 95% CI 1.37–2.60), but not empagliflozin (OR 0.71, 95% CI: 0.71–1.48), was significantly associated with an increase in amputation risk.

Anmerkung/Fazit der Autoren

Current evidence from available RCTs suggests that SGLT2i, as a class, are not significantly associated with increased risk of DFS. However, canagliflozin, but not empagliflozin, may increase the risk of amputations. Although the underlying mechanism remains uncertain, SGLT2i, especially canagliflozin, should be used with caution in patients who are at high risk of amputation.

Liu W et al., 2018 [68].

Efficacy and Safety of Insulin Degludec versus Insulin Glargine: A Systematic Review and Meta-Analysis of Fifteen Clinical Trials

Fragestellung

This study aimed to assess the effects and safety of IDeg versus IGlar.

Methodik

Population:

- patients diagnosed with type 1DM(T1DM) or type 2DM

Intervention:

- Insulin Degludec once a day

Komparator:

- Insulin Glargine

Endpunkte:

- change in the HbA1c and (FPG); proportion of patients who achieved HbA1c levels of <7%.
- The safety assessments considered adverse events, hypoglycemia, and body weight.

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library electronic databases up to July 15, 2017

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 studies with 16,328 patients
  - ten studies enrolled patients withT2DM

Qualität der Studien:

- all the studies had Jadad scores of 3 points or more. Therefore, all the included studies were of high quality

Studienergebnisse:

Population Items	N2	T2DM: pooled effect size IDeg : IGlar (95% confidence interval)
Change of HbA1c	13,986	MD = 0.04% (0.00, 0.07%)#
Change of FPG	12,544	MD = −0.34 (−0.45, −0.23)#
Change of body weight	13,986	MD = 0.05 (−0.11, 0.22)
Participants achieved HbA1c levels of <7%	4754	RR = 0.96, (0.90, 1.03)
Overall hypoglycemia	6349	RR = 0.82 (0.73, 0.92)#
Nocturnal hypoglycemia	6349	RR = 0.74 (0.66, 0.82)#
Adverse events	13,590	OR = 0.94 (0.87, 1.01)
Serious adverse events	13,590	OR = 0.95, (0.87, 1.03)
Adverse events possibly/probably related to the trial product	5496	OR = 1.05 (0.86, 1.29)

Anmerkung/Fazit der Autoren

In conclusion, this systematic review and meta-analysis of 15 RCTs demonstrate that IDeg exhibits a similar reduction of HbA1c to that of IGlar but a lower FPG value. The rates of nocturnal hypoglycemia were significantly decreased in the IDeg group for both T1DM and T2DM patients, while the overall hypoglycemia was only reduced in patients with T2DM. These findings indicate that IDeg might be a safer option to patients with diabetes mellitus who need basal insulin therapy.

Kommentare zum Review

In den Review waren auch Studien mit T1DM eingeschlossen. Die Ergebnisse wurden nicht dargestellt.

Maiorino MI, et al. 2018 [70].

Free and fixed-ratio combinations of basal insulin and GLP-1 receptor agonists versus basal insulin intensification in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials

Fragestellung

What is the effect of GLP-1RA and insulin combination, as compared with insulin intensification, on glycaemic control in type 2 diabetes?

Methodik

Population:

- Patients with T2DM

Intervention:

- free or fixed combo basal insulin and GLP-1

Komparator:

- up-titration of basal insulin

Endpunkte:

- decrease of HbA1c; secondary endpoints: proportion of patients at the HbA1c target <7% (53 mmol/ mol), the incidence of hypoglycaemic events, and change in body weight

Recherche/Suchzeitraum:

- 23.February 2018 in PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and ClinicalTrials.gov

Qualitätsbewertung der Studien:

- Cochrane Collaboration Risk-of-Bias tool
- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs with 6176 patients

Charakteristika der Population:

- Heterogene Hintergrundtherapie:
  - 6x Metformin, 2x Metformin x Glitazon, 2x Metfomin ± SU/Glinide, 1x Metformin ± OAD
  - Insulin: 3x None, 8x Basal Insulin at different UI/daily

Qualität der Studien:

- Cochrane risk of bias tool: three common biases blinding of participants (5x high), blinding of outcome assessment (2x high and 4x unclear), and allocation concealment (all unclear)
- median score of methodologic quality: 4.0; 6 studies had a score ≥4, indicating high quality

Studienergebnisse:

Parameter	Comparisons (n)	Intervention/control (n)	Estimate (95% CI)	*P* value	I^2	*P* value Q Test
HbA1c change (%)			WMD			
All	11	3386/2790	−0.53 (−0.66, −0.40)	<0.001	87.6	<0.001
Free combo	5	1070/893	−0.57 (−0.77, −0.38)	<0.001	80.7	<0.001
Fixed combo	6	2316/1897	−0.50 (−0.67, −0.33)	<0.001	91.0	<0.001
HbA1c < 7%			RR			
All	11	3386/2790	1.69 (1.42, 2.00)	<0.001	91.6	<0.001
Free combo	5	1070/893	2.08 (1.53, 2.84)	<0.001	80.7	<0.001
Fixed combo	6	2316/1897	1.48 (1.23, 1.77)	<0.001	92.3	<0.001
Hypoglycaemia			RR			
All	11	3386/2790	0.97 (0.84, 1.12)	0.684	71.6	<0.001
Free combo	5	1070/893	1.13 (0.95, 1.36)	0.166	35.3	0.186
Fixed combo	6	2316/1897	0.87 (0.72, 1.04)	0.114	72.9	0.002
Weight change (kg)			WMD			
All	11	3386/2790	−1.9 (−2.3, −1.4)	<0.001	83.4	<0.001
Free combo	5	1070/893	−1.7 (−2.3, −1.1)	<0.001	76.4	0.002
Fixed combo	6	2316/1897	−2.0 (−2.6, −1.4)	<0.001	86.0	<0.001

- Decrease of HbA1c:

  - significantly greater than insulin up-titration (-0.53%, 95% CI −0.66, -0.40%, P < 0.001)
  - high heterogeneity (I^2=87.6%, p<0.001) and evidence of publication bias (Egger test, p=0.043)
  - free and fixed combos reduced HbA1c in a similar way (-0.57% and -0.50% respectively)
- HbA1c target of <7%
  - likelihood of achieving the HbA1c target was 69% higher in favour of the combination
  - high heterogeneity (I2 = 91.6%, p<0.001), and evidence of publication bias (P < 0.001)
  - likelyhood for both subroups was significantly higher than in insulin intensification groups
- risk of any hypoglycaemia: not significantly different
- body weight decrease
  - grater in the combo therapy (-1.9 kg, 95% CI -2.3, -1.4, p<.001), evident in both subgroups
  - high heterogeneity (I2 = 83.4%)

Anmerkung/Fazit der Autoren

In conclusion, combo strategies, either free or fixed, represent a good option to intensify basal insulin therapy in patients with type 2 diabetes who need amelioration of glycaemic control. On the other hand, long-term effectiveness is still uncertain, owing to the limited duration of the trials published to date.

Kommentare zum Review

Hohe Heterogenität zwischen den Studien, sowie Hinweise auf einen Publikationsbias limitieren die Aussagekraft der Ergebnisse. Zur Heterogenität tragen neben den verschiedenen Vortherapien auch die unterschiedlichen GLP-1RA und zusätzliche eingenommene OADs bei.

Men P et al., 2018 [74].

Efficacy and safety of saxagliptin in patients with type 2 diabetes: A systematic review and meta-analysis

Fragestellung

This systematic review synthesized currently available evidence to provide a better understanding of the comparative efficacy and safety of saxagliptin in treating type 2 diabetes.

Methodik

Population:

- patients over 18 years of age with type 2 diabetes

Intervention:

- saxagliptin (as monotherapy or in dual or triple therapy)

Komparator:

- placebo or other active antidiabetic interventions (as monotherapy or in dual or triple therapy)

Endpunkte:

- HbA1c, proportion of patients achieving HbA1c targets of <7%, fasting plasma glucose (FPG) concentration, overall and serious adverse events, body weight, confirmed hypoglycemia, heart failure, pancreatitis, arthralgia, and other adverse events

Recherche/Suchzeitraum:

- To March 2018 in PubMed, Embase, the Cochrane Library, Web of Science, and 2 Chinese databases

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 30 trials involving 29,938 participants

Charakteristika der Population:

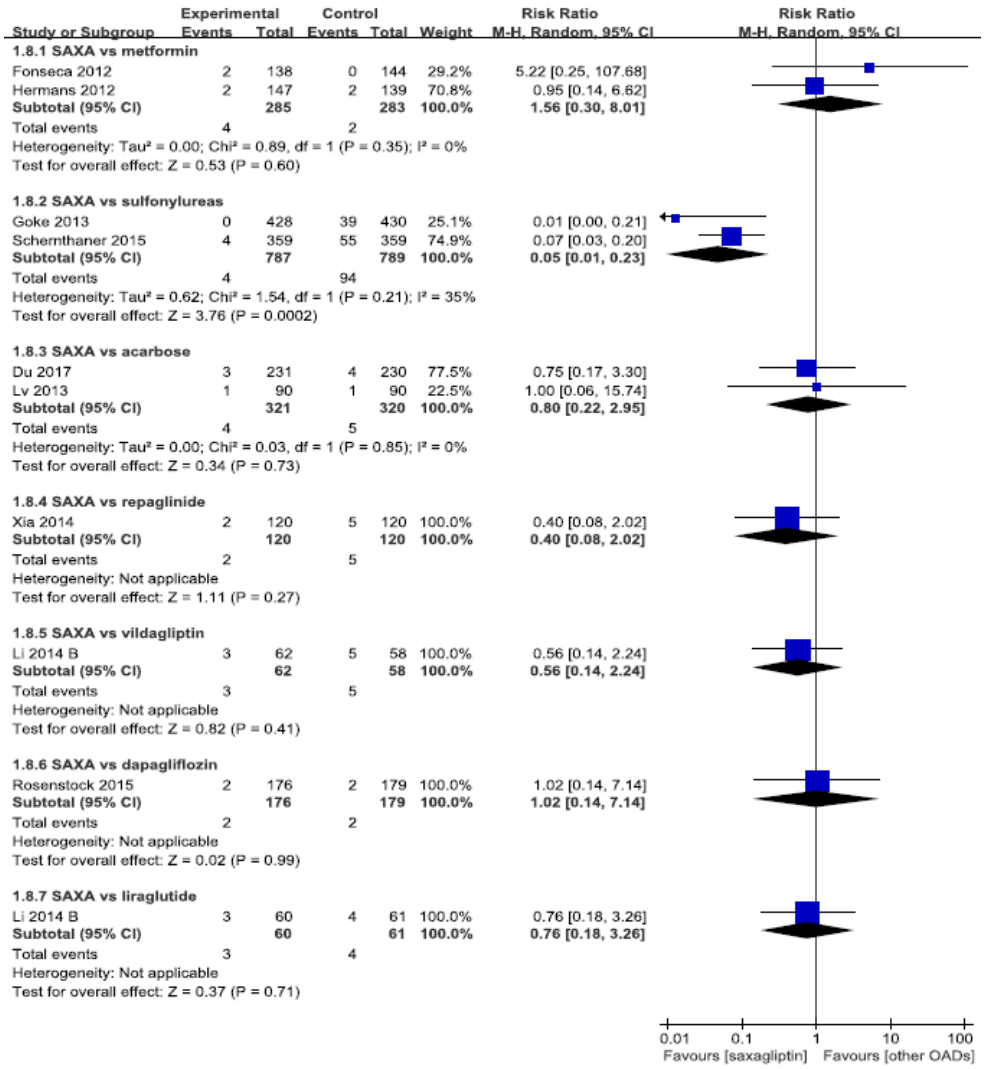
- Only RCTs involving >150 patients.
- demographics of the patient populations were comparable
  - mean age of 42.0 to 72.6 years
  - mean duration of type 2 diabetes ranged from 0.4 to 16.7 years
  - mean baseline HbA1c levels between 7.6% and 10.7%.

Qualität der Studien:

- Random sequence generation adequate in 25 trials, and allocation concealment adequately described in 16 trials. Two trials were considered to be at high risk of performance and detection bias. All studies were judged to be at low risk of attrition, reporting and other bias.

Studienergebnisse:

- HbA1c of <7%: Proportin significantly greater with saxagliptin as add-on (RR 1.67, 95% CI 1.55 to 1.81; p < 0.00001) or compared to metformin (RR 1.30, 95% CI 1.04 to 1.63; p = 0.02) and acarbose (RR 2.38, 95% CI 1.17 to 4.83; p = 0.02). However, no significant differences were observed in comparisons comparisons of saxagliptin with other active comparators
- FPG: significantly greater reductions of saxagliptin as add-on therapy to other andtidiabetic agents: (WMD −14,08 mg/dL, 95% CI −15.82 to −12.34; p < 0.00001); added to metformin, saxagliptin produced a significantly smaller reduction in FPG compared with sulfonylureas (WMD 9.05 mg/dL, 95% CI 6.18 to 11.93; p < 0.00001), liraglutide (WMD 7.60 mg/dL, 95% CI 1.76 to 13.44; p = 0.01) and dapagliflozin (WMD 18.00 mg/ dL, 95% CI 10.10 to 25.90; p < 0.00001). However, no significant differences were observed when saxagliptin was compared with other active comparators
- Hypoglycemia: Compared with sulfonylureas, saxaglitpin significantly reduced the risk of hypoglycemia by 95% (see figure). No significant differences were observed in comparison with other active comparators, including other DPP-4 inhibitors.



- Body weight: Saxagliptin was inferior to liraglutide (WMD 5.10 kg, 95% CI 1.66 to 8.54; p = 0.004) and dapagliflozin (WMD 2.40 kg, 95% CI 1.69 to 3.11; p < 0.00001). However, treatment with saxagliptin was associated with significantly less effect on body weight than sulfonylureas (WMD −2.34 kg, 95% CI −3.31 to −1.36; p < 0.00001). In comparison with other DPP-4 inhibitors, changes in body weight were similar.
- Overall and serious adverse events: Reduction in AE vs acarbose (RR 0.71, 95% CI 0.57 to 0.89; p = 0.03) and liraglutide (RR 0.41, 95% CI 0.24 to 0.71; p = 0.001) when added to metformin, no other significant differences.
- Other adverse events:
  - Pancreatitis and heart failure: no significant difference vs placebo and SU
  - Arthralgia: saxagliptin could significantly reduced the risk of arthralgia vs sitagliptin (RR 0.20, 95% CI 0.04 to 0.90; p = 0.04), but not compared with other active treatments.
  - saxagliptin was not associated with any increased risks of upper respiratory tract infection, urinary tract infection and nasopharyngitis compared with both placebo and active comparators

Anmerkung/Fazit der Autoren

In conclusion, Generally, saxagliptin has similar efficacy compared with most oral antidiabetic drugs, while may be more effective than acarbose. Saxagliptin is safe in the treatment of T2D, especially having a better safety profile than acarbose and sulfonylureas.

Kommentare zum Review

Die Ergebnisse der Studien mit Placebo als Komparator wurden nicht dargestellt, genau wie die Ergebnisse zu Sagagliptin 2,5 mg.

Mishriky BM et al., 2018 [78].

Comparing once-weekly semaglutide to incretin-based therapies in patients with type 2 diabetes: a systematic review and meta-analysis

Fragestellung

to compare once-weekly semaglutide to incretin-based therapies – defined as either dipeptidyl peptidase-4 inhibitors (DPP-4i) or other glucagon-like peptide-1 receptor agonist (GLP- 1RA) – in patients with type 2 diabetes.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- once-weekly subcutaneous semaglutide

Komparator:

- incretin-based therapy (i.e., any other DPP-4i or GLP-1RA)

Endpunkte:

- primary: change in HbA1c
- Secondary: change in body weight, change in FPG, change in blood pressure, number of patients achieving goal haemoglobin A1c < 7.0% and ≤ 6.5%, number of patients achieving goal haemoglobin A1c < 7.0% without hypoglycaemia or weight gain, numbers of patients with body weight loss ≥ 5% and ≥10%, number of patients requiring rescue medications, and incidence of side effects.

Recherche/Suchzeitraum:

- Up to March 14th, 2018 in MEDLINE the Cochrane Central Register of Controlled trials, EMBASE, Web of Science and CINAHL

Qualitätsbewertung der Studien:

- Cochrane risk of bias and the 7-point modified Oxford Score

Ergebnisse

Anzahl eingeschlossener Studien:

- Five trials with 3769 patients
  - 3 vs another GLP-1RA
  - 2 vs DPP-4i (Sitagliptin)

Charakteristika der Population:

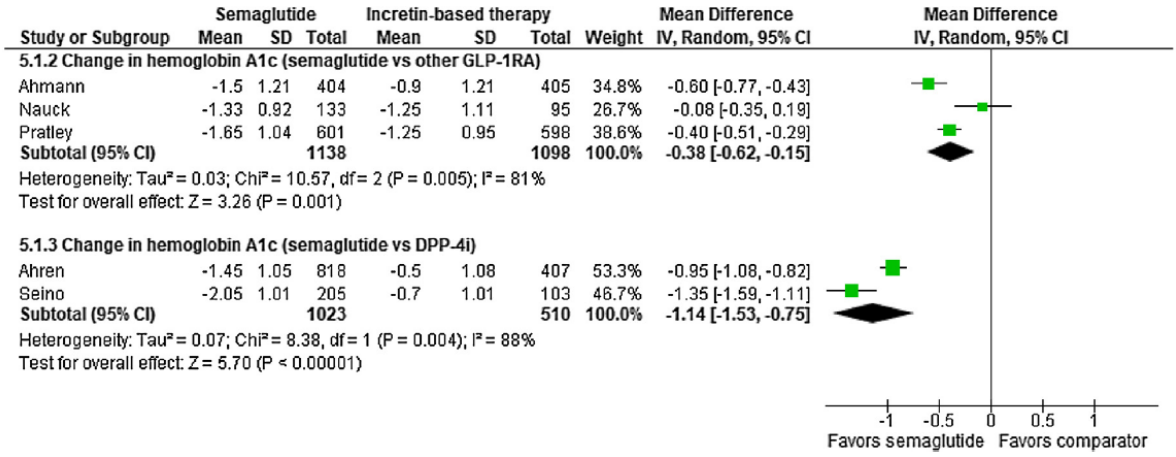
- Three trials investigated semaglutide as add-on therapy, one as added to either diet/exercise or metformin, and one as monotherapy.
- The primary outcome for four trials was the change in haemoglobin A1c over time, and one was the treatment-emergent adverse events.

Qualität der Studien:

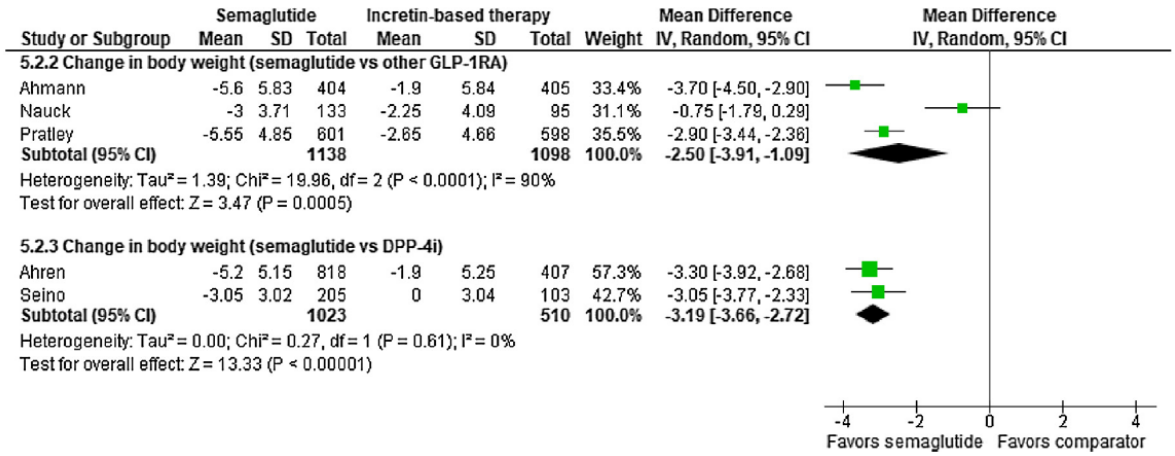
- Just mentioned in the supplement online

Studienergebnisse:

- Change in HbA1c



- HbA1c < 7.0%, ≤ 6.5% and composite outcome:
  - GLP-1RA: Pooled results favoured semaglutide [RR (95% CI) = 1.33 (1.06, 1.68), I2 = 88%, 1.52 (1.09, 2.12), I2 = 87% and 1.63 (1.10, 2.43), I2 = 93%, respectively]
  - DPP-4i: pooled favoured semaglutide [RR (95% CI) = 2.22 (1.77, 2.77), I2 = 58%, 3.70 (2.14, 6.39), I2 = 80%, and 3.17 (1.94, 5.19), I2 = 80%, respectively]
- Change in body weight



- Patients with body weight loss ≥ 5% and ≥10%: significantly higher vs both comparators

- Adverse effects:
  - GLP-1RA Semaglutide-treated patients had a significantly higher incidence of adverse effects leading to discontinuation of study drug, nausea, and vomiting
  - DPP-4i Semaglutide-treated patients had a significantly higher incidence of adverse effects leading to discontinuation of study drug, vomiting, and diarrhoea

Anmerkung/Fazit der Autoren

The present systematic review and meta-analysis suggests that once-weekly semaglutideproduces greaterreductions in haemoglobin A1c, weight, and blood pressure when compared to other GLP-1RA or DPP-4i while requiring less need for rescue medications. In addition, the number of patients achieving glycaemic goals was higher in semaglutide-treated patients compared to either other GLP-1RAor DPP-4i.Furthermore, the number of patients achieving weight loss was higher in semaglutide-treated patients compared to other GLP-1RA or DPP-4i. However, while semaglutide seems more potent compared to other incretin-based therapies, it was associated with an increased risk for nausea, vomiting, diarrhoea and adverse effects leading to discontin- uation of the medication.

Kommentare zum Review

Signifikante Heterogenität zwischen den Studien, da verschiedene GLP-1RA Komperatoren gepoolt wurden und sowohl Monotherapien als auch add-on einbezogen wurden.

Monami M et al., 2017 [81]; Bethel MA et al., 2018 [7]

Effects of glucagon-like peptide-1 receptor agonists on mortality and cardiovascular events: A comprehensive meta-analysis of randomized controlled trials

Fragestellung

The aim of the present metaanalysis is to collect and synthetize all available evidence on the effect of GLP-1 receptor agonists on cardiovascular events and mortality.

Methodik

Population:

- patients with type 2 diabetes

Intervention:

- GLP-1 receptor agonist

Komparator:

- placebo or any other non-GLP-1RA, provided that concurrent treatment was the same for all treatment arms

Endpunkte:

- all-cause and cardiovascular mortality, overall (fatal plus nonfatal) myocardial infarction, stroke, and heart failure (HF).
  - For the latter outcome, hospitalization for HF was considered whenever available; when that information was not reported, heart failure reported as serious treatment-emergent adverse event was considered.

Recherche/Suchzeitraum:

- to September 15th. 2016 in Medline/Embase and clinicaltrials.gov

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 113 trials with 33,167 and 26,683 patients in GLP-1 receptor agonist and comparator arms

Charakteristika der Population:

- RCTs with a duration of treatment of at least 12 weeks

Qualität der Studien:

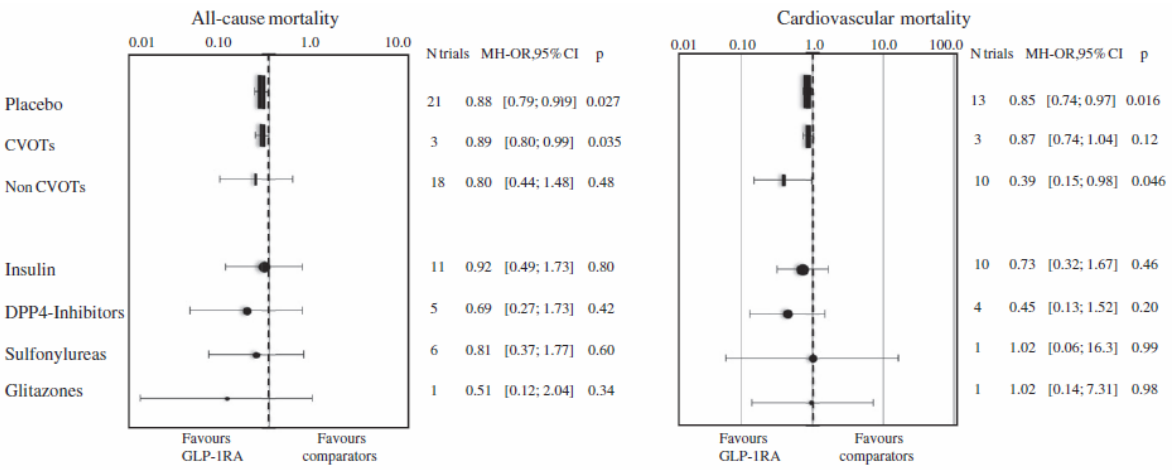
- The quality of trials (all with intention-to-treat analysis) was generally good

Studienergebnisse:

- All-cause mortality: available 32 trials, enrolling 20,280 and 16,939 patients
  - significantly lower than in comparators (MH-OR [95% CI] 0.88 [0.79–0.97]. p = 0.015
  - When trials with different molecules were analysed separately, the difference in mortality versus comparators was significant only with dulaglutide and liraglutide
  - different comparators: significant reduction of all-cause mortality only in placebo-controlled trials, driven by the cardiovascular outcome studies (Figure 1)
  - When trials with a duration of treatment ≥52 weeks (n=20) were analysed separately, MH-OR was 0.88[0.79–0.98], p=0.023
- Cardiovascular mortality: available in 25 trials, enrolling 16,656 and 15,175 patients
  - significantly reduced by GLP-1RA (MH-OR [95% CI] 0.84 [0.74–0.96]. p=0.009

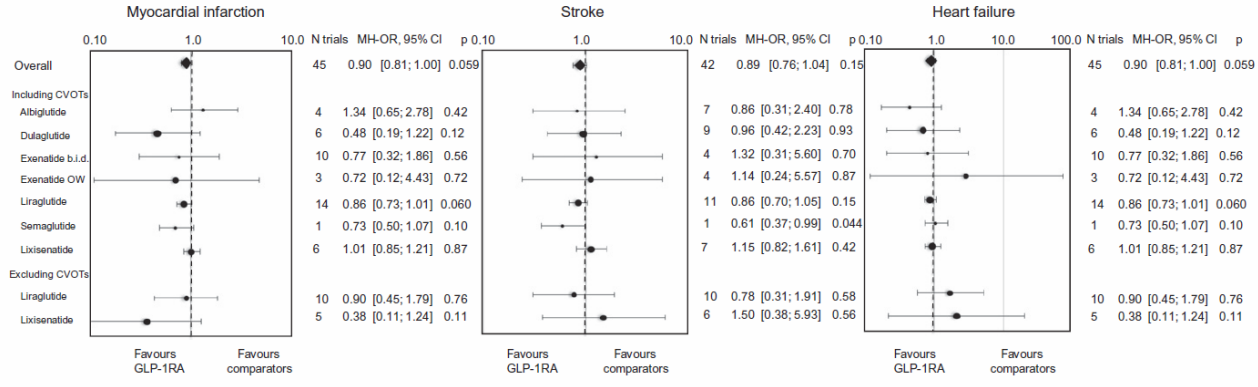
- In separate analyses for different GLP-1RA, none of them reached a statistically significant effect;
- Differences from any class of active comparators did not reach statistical significance, but the difference was significant in placebo-controlled trials (Figure 2)
- When trials with a duration of treatment ≥52 weeks (n=14) were analysed separately, MH-OR was 0.85[0.74–0.97], p = 0.017

Fig. 1. MH-OR with 95% CI for all-cause and cardiovascular mortality for GLP-1 receptor agonists versus placebo or other active comparators.



- Myocardial infarction: 48 RCTs with at least one event (22,990 and 19,412 patients)
  - effect of GLP-1RA reached a marginal statistical significance (MH-OR 0.90 [0.80–1.00], p = 0.050
  - No significant effect in different GLP-1RA and different controls (Figure 2)
  - trials with a duration of treatment ≥52 weeks: not significant

Fig. 2. MH-OR with 95% CI for acute myocardial infarction, stroke, and heart failure with different molecules, considering all RCTs with and without cardiovascular endpoints.



- Stroke: No significant differences (Figure 2)
- Heart failure: No significant differences (Figure 2)

Anmerkung/Fazit der Autoren

Overall, the agents of this class appear to reduce all-cause and cardiovascular mortality, and the incidence of myocardial infarction at mid-termfollowup. Available data suggest differences

acrossmolecules of the class, but they are insufficient to verifywhether those differences are due to kinetics or other features of individual drugs. The possibility that patientswith a higher degree of obesity have greater cardiovascular benefits with GLP-1 receptor agonists deserves further investigation.

Kommentare zum Review

- *it should be considered that the majority of events was observed in cardiovascular outcome trials, in which a large proportion of the patients enrolled was already treated with other drugs for cardiovascular protection, such as statins, antiplatelet agents, beta blockers, and ACE inhibitors or angiotensin receptor blockers. the protective effect of GLP-1 receptor agonists appears to be additive to that of current cardiovascular treatments*
- *In einer weiteren Meta-Analyse zur kardivaskulären Effektivität von Lixisenatid, Liraglutid, Semaglutide und Exenatide untersuchten Bethel MA et al., [7] eine vergleichbare Fragestellung. Insbesondere aufgrund des Einschlusskriteriums „kardiovaskulärer Endpunkt" als Teil des primären Endpunktes wurden jedoch nur 4 RCTs mit 33.457 Teilnehmern in diese Meta-Analyse eingeschlossen, wovon 3 ebenfalls wesentlicher Teil der Untersuchung von Monami M et al., 2017 [81] waren. Die Diskrepanz der einen Studie (n=14.752) erklärt sich durch Abschluss der Recherche vor Publikation der Studie. Trotz leicht des unterschiedlichen Studienpools zeigten auch in dieser Meta-Analyse GLP-1RA eine Risikoreduktion bei der Gesamtmortalität und der kardiovaskulären Mortalität, sowie bei dem zusammengesetzten Endpunkt MACE bei nicht signifikanten UE (Hypoglykämien, Pankreatitis, Pankreaskarzinom oder Schilddrüsenkarzinom) im Vergleich zu Placebo. Die Publikation wurde von einem Pharmaunternehmen finanziert.*

Qian D et al., 2018 [84].

Comparison of antidiabetic drugs added to sulfonylurea monotherapy in patients with type 2 diabetes mellitus: A network meta-analysis

Fragestellung

This study aimed to investigate the efficacy and safety of dual therapy comprising sulfonylurea (SU) plus antidiabetic drugs for the treatment of type 2 diabetes mellitus (T2DM).

Methodik

Population:

- patients with T2DM and inadequate glycemic control with sulfonylurea monotherapy

Intervention/Komparator

- drugs in the SGLT-2i, DPP-4i, GLP-1RA, TZD, AGI, metformin, and insulin classes

Endpunkte:

- (HbA1c), fasting plasma glucose (FPG), body weight, hypoglycemia, serious adverse events (SAEs)

Recherche/Suchzeitraum:

- PubMed (from January 1, 1946 to December 28, 2017), Embase (from January 1, 1974 to December 28, 2017), and Cochrane library databases

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Assessment

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 RCTs with 10,032 patients

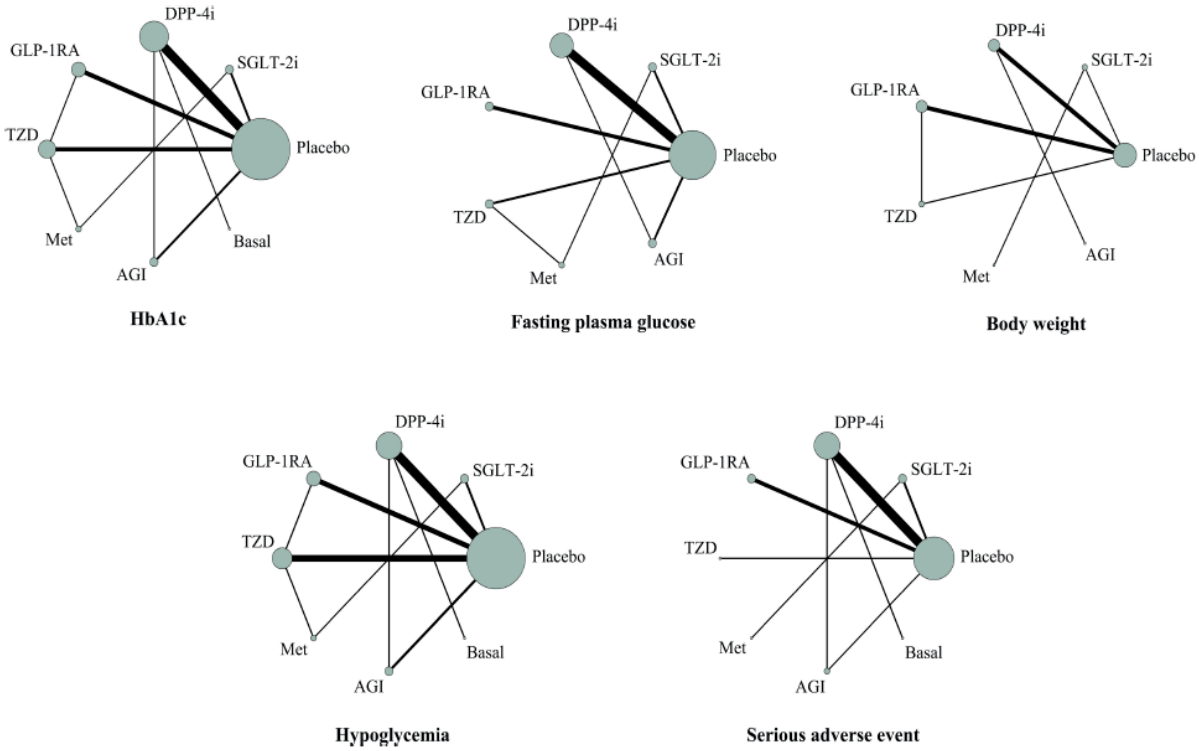


Fig 2. Network maps for efficacy and safety outcomes. Note: Connecting lines represent direct comparisons between the pairs of treatments, and the line widths represent the numbers of trials. The node sizes represent the overall sample sizes of the interventions. HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; TZD, thiazolidinedione; Met, metformin; AGI, α-glucosidase inhibitor; Basal, basal (long-acting) insulin.

Charakteristika der Population:

- The baseline characteristics of participants in these studies were deemed sufficiently similar in terms of age, sex, HbA1c, body weight, and body mass index (BMI) to permit network comparison.

Qualität der Studien:

All studies were randomized and double blinded, and the risks of bias for random sequence generation, concealment of treatment allocation, and blinding of participants and personnel were low or unclear. Three studies had a high risk of reporting bias, of which 1 presented a high risk of detection bias. One study had incomplete outcome data.

Studienergebnisse:

- Hypoglycemia: The analysis included data from 23 RCTs including 9486 participants
  - Excluding placebo, AGI and SGLT-2i most strongly reduced the risk of hypoglycemia, with SUCRA values of 79% and 71.7%, respectively. The lowest SUCRA value was calculated for GLP-1RA (5.2%)

Table 2. Effect of glucose-lowering agents in patients with type 2 diabetes.

Hypoglycemia (OR, 95% CI)							
PLA	1.35 (0.81, 2.25)	**1.51 (1.05, 2.15)**	**4.75 (2.61, 8.62)**	**2.04 (1.25, 3.33)**	**2.76 (1.55, 4.92)**	1.16 (0.55, 2.44)	**3.61 (1.48, 8.77)**
0.74 (0.44, 1.24)	**SGLT-2i**	1.12 (0.60, 2.08)	**3.52 (1.65, 7.54)**	1.52 (0.78, 2.93)	**2.05 (1.05, 4.02)**	0.86 (0.35, 2.10)	2.68 (0.96, 7.45)
0.66 (0.46, 0.95)	0.89 (0.48, 1.66)	**DPP-4i**	**3.15 (1.63, 6.11)**	1.36 (0.78, 2.36)	1.83 (0.95, 3.54)	0.77 (0.35, 1.68)	2.40 (1.06, 5.40)
0.21 (0.12, 0.38)	**0.28 (0.13, 0.61)**	**0.32 (0.16, 0.62)**	**GLP-1RA**	**0.43 (0.25, 0.74)**	0.58 (0.29, 1.18)	**0.24 (0.10, 0.59)**	0.76 (0.27, 2.17)
0.49 (0.30, 0.80)	0.66 (0.34, 1.28)	0.74 (0.42, 1.29)	**2.33 (1.35, 4.01)**	**TZD**	1.35 (0.81, 2.25)	0.57 (0.26, 1.24)	1.77 (0.66, 4.73)
0.36 (0.20, 0.65)	**0.49 (0.25, 0.96)**	0.55 (0.28, 1.05)	1.72 (0.84, 3.50)	0.74 (0.45, 1.23)	**Met**	0.42 (0.17, 1.03)	1.31 (0.46, 3.72)
0.86 (0.41, 1.83)	1.16 (0.48, 2.85)	1.30 (0.60, 2.84)	**4.10 (1.70, 9.88)**	1.77 (0.81, 3.86)	2.39 (0.98, 5.84)	**AGI**	**3.12 (1.01, 9.63)**
0.28 (0.11, 0.67)	0.37 (0.13, 1.04)	0.42 (0.19, 0.94)	1.32 (0.46, 3.75)	0.57 (0.21, 1.52)	0.77 (0.27, 2.18)	**0.32 (0.10, 0.99)**	**Basal**

- HbA1c: available from 8930 patients in 23 RCTs
  - Notably, GLP-1RA and basal insulin yielded the greatest reductions in HbA1c, with SUCRA values of 94% and 75%, respectively

HbA1c, % (MD, 95% CI)							
PLA	**-0.65 (-0.96, -0.35)**	**-0.67 (-0.83, -0.51)**	**-1.12 (-1.36, -0.89)**	**-0.85 (-1.07, -0.63)**	**-0.82 (-1.20, -0.44)**	**-0.59 (-0.89, -0.29)**	**-0.97 (-1.48, -0.46)**
0.65 (0.35, 0.96)	**SGLT-2i**	-0.02 (-0.36, 0.32)	**-0.47 (-0.85, -0.09)**	-0.19 (-0.54, 0.15)	-0.17 (-0.53, 0.19)	0.06 (-0.36, 0.49)	-0.32 (-0.91, 0.27)
0.67 (0.51, 0.83)	0.02 (-0.32, 0.36)	**DPP-4i**	**-0.45 (-0.73, -0.16)**	-0.17 (-0.45, 0.10)	-0.15 (-0.56, 0.26)	0.08 (-0.23, 0.39)	-0.30 (-0.78, 0.18)
1.12 (0.89, 1.36)	**0.47 (0.09, 0.85)**	**0.45 (0.16, 0.73)**	**GLP-1RA**	0.27 (-0.02, 0.56)	0.30 (-0.13, 0.73)	**0.53 (0.15, 0.91)**	0.15 (-0.41, 0.71)
0.85 (0.63, 1.07)	0.19 (-0.15, 0.54)	0.17 (-0.10, 0.45)	-0.27 (-0.56, 0.02)	**TZD**	0.02 (-0.34, 0.39)	0.26 (-0.12, 0.63)	-0.13 (-0.68, 0.43)
0.82 (0.44, 1.20)	0.17 (-0.19, 0.53)	0.15 (-0.26, 0.56)	-0.30 (-0.73, 0.13)	-0.02 (-0.39, 0.34)	**Met**	0.23 (-0.25, 0.72)	-0.15 (-0.79, 0.49)
0.59 (0.29, 0.89)	-0.06 (-0.49, 0.36)	-0.08 (-0.39, 0.23)	**-0.53 (-0.91, -0.15)**	-0.26 (-0.63, 0.12)	-0.23 (-0.72, 0.25)	**AGI**	-0.39 (-0.97, 0.18)
0.97 (0.46, 1.48)	0.32 (-0.27, 0.91)	0.30 (-0.18, 0.78)	-0.15 (-0.71, 0.41)	0.13 (-0.43, 0.68)	0.15 (-0.49, 0.79)	0.38 (-0.19, 0.96)	**Basal**

- Body weight: available for 4516 participants in 11 RCTs
  - SGLT-2i and GLP-1RA yielded the greatest reductions in body weight, with respective SUCRA values of 95.7% and 81.8%

Body weight, kg (MD, 95% CI)							
PLA	**-1.00 (-1.73, -0.27)**	**1.00 (0.90, 1.11)**	**-0.56 (-1.10, -0.02)**	**1.91 (0.92, 2.91)**	**1.45 (0.47, 2.43)**	-0.30 (-0.98, 0.39)	-
1.00 (0.27, 1.73)	**SGLT-2i**	**2.00 (1.27, 2.74)**	0.44 (-0.47, 1.35)	**2.91 (1.68, 4.15)**	**2.45 (1.80, 3.10)**	0.70 (-0.30, 1.71)	-
-1.00 (-1.11, -0.90)	**-2.00 (-2.74, -1.27)**	**DPP-4i**	**-1.56 (-2.11, -1.02)**	0.91 (-0.09, 1.91)	0.45 (-0.54, 1.43)	**-1.30 (-1.98, -0.62)**	-
0.56 (0.02, 1.10)	-0.44 (-1.35, 0.47)	**1.56 (1.02, 2.11)**	**GLP-1RA**	**2.47 (1.61, 3.34)**	**2.01 (0.89, 3.12)**	0.26 (-0.61, 1.14)	-
-1.91 (-2.91, -0.92)	**-2.91 (-4.15, -1.68)**	-0.91 (-1.91, 0.09)	**-2.47 (-3.34, -1.61)**	**TZD**	-0.46 (-1.86, 0.93)	**-2.21 (-3.42, -1.00)**	-
-1.45 (-2.43, -0.47)	**-2.45 (-3.10, -1.80)**	-0.45 (-1.43, 0.54)	**-2.01 (-3.12, -0.89)**	0.46 (-0.93, 1.86)	**Met**	**-1.75 (-2.94, -0.55)**	-
0.30 (-0.39, 0.98)	-0.70 (-1.71, 0.30)	**1.30 (0.62, 1.98)**	-0.26 (-1.14, 0.61)	**2.21 (1.00, 3.42)**	**1.75 (0.55, 2.94)**	**AGI**	-

- Serious adverse events: SAE data were available for 6335 participants in 17 RCTs. The NMA indicated no significant differences in the ORs of SAE for any agent when added to SU. Excluding placebo basal insulin and AGI received the highest (76.8%) and lowest (36.2%) SUCRA values, respectively

Anmerkung/Fazit der Autoren

In conclusion, all classes of antidiabetic drugs improved glucose control when added to SU. However, SGLT-2i exhibited superior effects in terms of weight loss and did not increase the risk of hypoglycemia, suggesting that it might be the best option. Clinicians should particularly consider the risk of hypoglycemia when selecting antidiabetic drugs for administration together with SU.

Wang K et al., 2018 [92].

SGLT-2 Inhibitors and DPP-4 Inhibitors as Second-Line Drugs in Patients with Type 2 Diabetes: A Meta-Analysis of Randomized Clinical Trials

Fragestellung

To directly compare the efficacy and safety of SGLT-2 inhibitors to those of DPP-4 inhibitors and provide a basis for the selection of second-line drugs in patients with T2DM.

Methodik

Population:

- Patientes with T2DM

Intervention:

- SGLT-2 inhibitors, mono or combined with other drugs

Komparator:

- DPP-4 inhibitors, mono or combined with other drugs

Endpunkte:

- HbA1c, fasting plasma glucose (FPG) levels, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides (TG) and adverse events

Recherche/Suchzeitraum:

- To July 2018 in PubMed, MEDLINE, the Cochrane Library, EMBASE, Web of Science, CNKI, and Biomedical database

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool
- Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Ergebnisse

Anzahl eingeschlossener Studien:

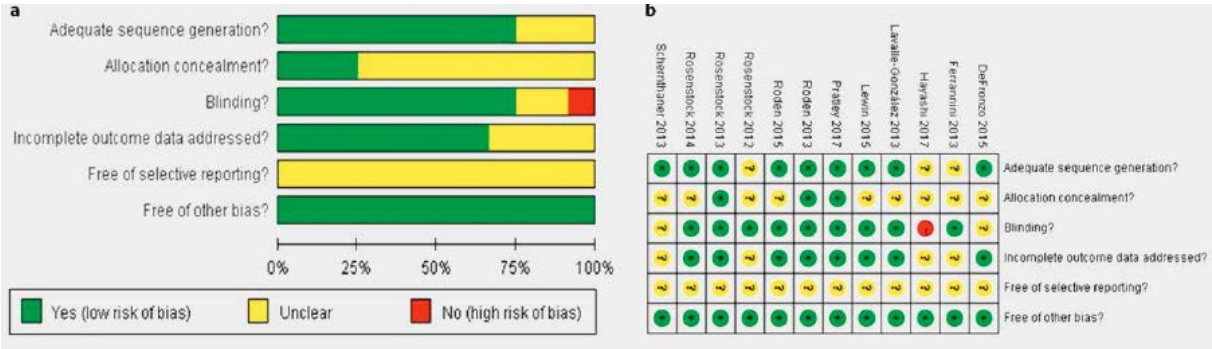
- 12 RCTs including 4342 patients

Charakteristika der Population:

- Background therapy
  - metformin (6 RCTs); None (3 RCTs); metformin + SU (1 RCT); SU, Metformin or α-Glucosidase inhibitor (1 RCT); glimepiride or insulin glargine (1 RCT)
- no significant differences in baseline characteristics

Qualität der Studien:

- Risk of bias of the included studies was low to unclear.



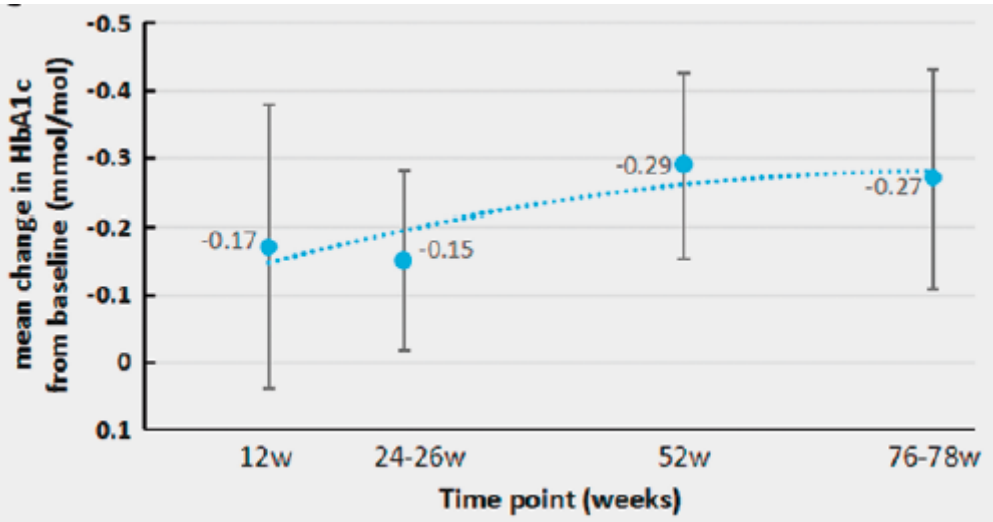
Studienergebnisse:

- The following talble showes the study results. Significant outcomes are highlighted yellow. Outcomes at different timepoints from one study are pooled together (eg. Week 26 and 52)

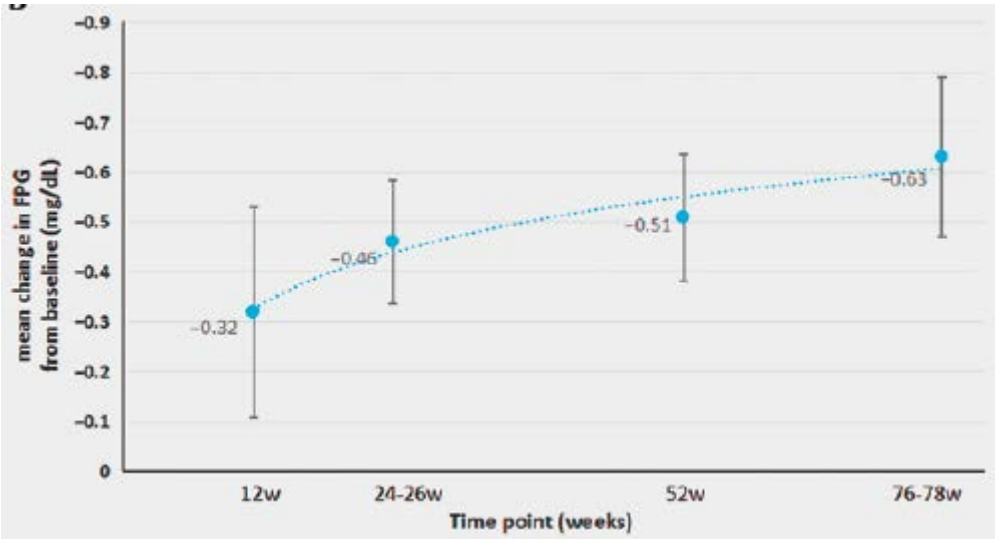
Outcomes	No. of participants (Studies)	Relative effect (95 % CI)	Quality of the evidence
HbA1c	4261(12)	SMD −0.22 (−0.30 to −0.14)	MODERATE[abg]
FPG	4261(12)	SMD −0.48 (−0.56 to −0.41)	MODERATE[abg]
Body weight	4269(12)	SMD −0.72 (−0.81 to −0.63)	LOW[abcg]
Systolic blood pressure	3796(10)	SMD −0.30 (−0.35 to −0.25)	MODERATE[acg]
Diastolic blood pressure	3301(9)	SMD −0.26 (−0.33 to −0.20)	LOW[ac]
Total cholesterol	1997(6)	SMD 0.12 (0.03 to 0.21)	LOW[ac]
HDL-cholesterol	2677(7)	SMD 0.48 (0.39 to 0.57)	LOW[abcg]
LDL-cholesterol	2671(7)	SMD 0.13 (0.05 to 0.20)	VERY LOW[acd]
Triglycerides	1961(6)	SMD 0.03 (−0.06 to 0.12)	VERY LOW[acd]
ADR	4260(11)	OR 1.01 (0.95 to 1.07)	LOW[acdg]
Urinary tract infection	4260(11)	OR 0.96 (0.77 to 1.21)	LOW[acdg]
Genital infection	3722(9)	OR 4.49 (2.96 to 6.83)	MODERATE[acefg]
Hypoglycaemia	2234(7)	OR 0.77 (0.40 to 1.46)	VERY LOW[acd]
Headache	938(5)	OR 0.64 (0.35 to 1.15)	VERY LOW[acd]
Pollakiuria	1758(4)	OR 2.24 (1.05 to 4.79)	MODERATE[acefg]
Nasopharyngitis	1430(4)	OR 0.75 (0.52 to 1.08)	VERY LOW[acd]
Back pain	1125(4)	OR 0.60 (0.34 to 1.05)	MODERATE[acg]
Hypertension	855(3)	OR 0.28 (0.12 to 0.66)	MODERATE[acg]
Hyperglycaemia	1572(5)	OR 0.43 (0.28 to 0.67)	LOW[ac]
Diarrhoea	843(3)	OR 1.17 (0.52 to 2.66)	VERY LOW[acde]
Upper respiratory tract infection	984(3)	OR 0.96 (0.61 to 1.52)	VERY LOW[bcd]
Event consistent with volume depletion	984(3)	OR 0.55 (0.16 to 1.86)	LOW[cd]

[a]Limitations in study design or execution (risk of bias), [b]Inconsistency in results, [c]Indirectness of evidence, [d]Imprecision of results, [e]Publication bias, [f]Magnitude of the effect, [g]Dose-response gradient.

- changes in HbA1c between SGLT-2 inhibitors and DPP-4 inhibitors by week



- changes in FPG between SGLT-2 inhibitors and DPP-4 inhibitors by week



- Sensitivity analysis showed no differences

Anmerkung/Fazit der Autoren

In this meta-analysis of 12 randomized controlled trials directly comparing the efficacy and safety between SGLT-2 and DPP-4 inhibitors, SGLT-2 inhibitors were found to be superior to DPP-4 inhibitors for treating type 2 diabetes. The results indicate that these two novel second-line antidiabetic agents both have advantages and disadvantages and thus should be chosen with caution to best suit each individual patient, especially as an add-on therapy after the failure of metformin or another anti-diabetic drug.

Kommentare zum Review

- *Es ist zu beachten, dass die Ergebnisse der Studien zu verschiedenen Zeitpunkten (z.B. Woche 24 und 52) miteinander gepoolt wurden, sodass Studien mit drei Erhebungszeitpunkten dreifach in die Metaanalyse eingeflossen sind. Mögliche Verzerrungen hierdurch können nicht ausgeschlossen werden. Ausgenommen sind die Endpunkte HbA1c und FPG, für die auch separate Schätzer berechnet wurden.*
- *Weiterhin ist die heterogene Vor- bzw. Hintergrundtherapie zu beachten wobei diese in 6 Studien aus Metformin bestand. Diese Studien wurden auch von einem weiteren SR von Mishriky BM et al., 2018 [80] (insgesamt 7 Studien), der SGLT-2 Inhibitoren mit DPP-4 Inhibitoren als add-on Therapie zu Metformin verglich, eingeschlossen. Auch hier zeigten sich vergleichbare Ergebnisse, mit signifikant niedrigeren HbA1c Werte und reduziertem Körpergewicht, bei vermehrten Genitalinfektionen bei SGLT-2 Inhibitoren.*

Yoon JH et al., 2018 [98].

Comparison of non-insulin antidiabetic agents as an add-on drug to insulin therapy in type 2 diabetes: a network meta-analysis

Fragestellung

we performed a systematic review with a network meta-analysis to evaluate the comparative efficacy and safety of DPP4i, GLP-1RA, SGLT2i, and TZD as an adjunctive treatment in patients with poorly controlled T2DM on insulin therapy.

Methodik

Population:

- patients with T2DM

Intervention/Komparator:

- DPP4i, GLP-1RA, SGLT2i, or TZD as an add-on drug to pre-existing insulin therapy
- concurrent use of other anti-diabetic agents was allowed

Endpunkte:

- primary outcome, the change in HbA1c from baseline
- secondary outcomes, the change in FPG levels, body weight, insulin dose and the proportion of patients achieving HbA1c goals; and as a safety outcome, the risk of hypoglycemia

Recherche/Suchzeitraum:

- To April 2016 in Medline, Embase, CENTRAL, and ClinicalTrials.gov

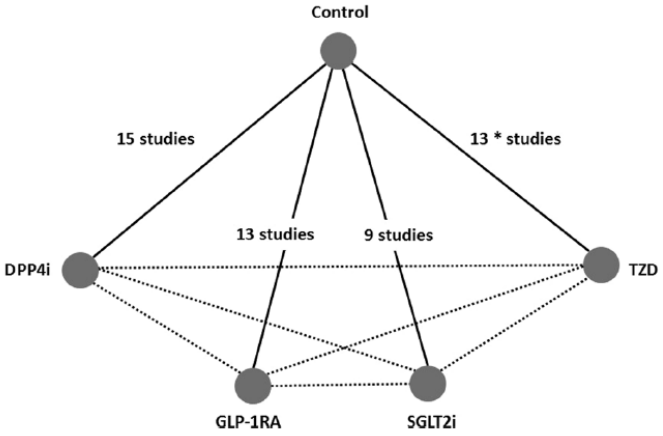
Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

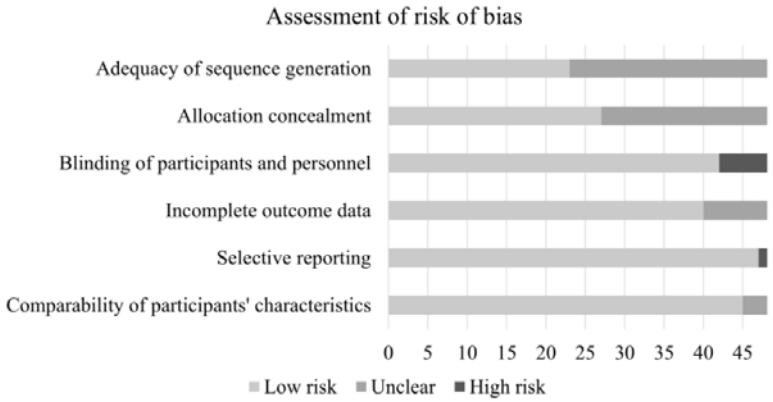
- 50 RCTs with 15,494 randomized participants
- No study with head-to-head comparisons between the non-insulin agents was found
- Structure of the network formed by interventions and both direct and indirect comparisons for primary outcomes.



Charakteristika der Population:

- insulin regimens classified into 2 categories: a stable insulin dose group (n=26) and an insulin dose titration group (n=19); 5 studies could not be classified

Qualität der Studien:



Studienergebnisse:

- Table: Pairwise results of comparisons between antidiabetic agents as an add-on to pre-existing insulin therapy from network meta-analyses adjusted by study-level covariates.

Difference in mean change of HbA1c from baseline (95% credible interval), %				
Control	−0.54(−0.68, −0.39)	−0.84(−1.00,−0.69)	−0.66(−0.84,−0.48)	−0.73(−0.93,−0.52)
—	DPP4i	−0.30(−0.52,−0.09)	−0.11(−0.36, 0.12)	−0.18(−0.44, 0.07)
—	—	GLP-1RA	0.19(−0.06, 0.43)	0.11(−0.16, 0.40)
—	—	—	SGLT2i	−0.07(−0.33, 0.20)
—	—	—	—	TZD
Difference in mean change of FPG from baseline (95% credible interval), mg/dL [mmol/L]				
Control	−11.42(−15.47, −7.36) [−0.63(−0.86, −0.41)]	−9.96(−14.55, −5.38) [−0.55(−0.81, −0.30)]	−24.14(−29.64, −18.54) [−1.34(−1.65, −1.03)]	−19.57(−24.78, −14.25) [−1.09(−1.38, −0.79)]
—	DPP4i	1.48(−4.58, 7.42) [0.08(−0.25, 0.41)]	−12.72(−19.53, −5.82) [−0.71(−1.08, −0.32)]	−8.12(−14.79, −1.37) [−0.45(−0.82, −0.08)]
—	—	GLP-1RA	−14.17(−21.69, −6.73) [−0.79(−1.20, −0.37)]	−9.61(−16.65, 2.38) [−0.53(−0.92, 0.13)]
—	—	—	SGLT2i	4.61(−2.93, 12.11) [0.26(−0.16, 0.67)]
—	—	—	—	TZD
Difference in mean change of body weight from baseline (95% credible interval), kg				
Control	−0.10(−0.83, 0.64)	−2.20(−2.87, −1.57)	−1.75(−2.65, −0.85)	2.58(1.63, 3.48)
—	DPP4i	−2.11(−3.11, −1.15)	−1.65(−2.81, −0.47)	2.67(1.46, 3.82)
—	—	GLP-1RA	0.46(−0.64, 1.58)	4.78(3.63, 5.90)
—	—	—	SGLT2i	4.32(2.98, 5.60)
—	—	—	—	TZD
Relative proportion of participants attaining HbA1c levels of <7% (95% credible interval)				
Control	2.68(1.80, 3.81)	3.70(2.89, 4.67)	1.83(0.64, 3.90)	2.18(1.12, 3.58)
—	DPP4i	1.43(0.93, 2.15)	0.72(0.21, 1.69)	0.84(0.39, 1.51)
—	—	GLP-1RA	0.50(0.16, 1.11)	0.60(0.29, 1.02)
—	—	—	SGLT2i	1.48(0.42, 3.81)
—	—	—	—	TZD
Difference in mean change of daily insulin dose from baseline (95% credible interval), IU/day				
Control	−3.87(−7.70, −0.10)	−8.61(−12.34, −5.00)	−4.64(−9.62, 0.32)	−11.97(−15.48, −8.41)
—	DPP4i	−4.76(−9.68, 0.16)	−0.79(−6.99, 5.51)	−8.09(−13.26, −2.88)
—	—	GLP-1RA	3.94(−2.23, 10.14)	−3.36(−8.33, 1.74)
—	—	—	SGLT2i	−7.29(−13.45, −1.12)
—	—	—	—	TZD
Relative risk of hypoglycemia (95% credible interval)				
Control	1.06(0.85, 1.32)	1.37(1.08, 1.71)	1.22(0.88, 1.67)	1.94(1.39, 2.62)
—	DPP4i	1.30(0.94, 1.77)	1.15(0.78, 1.70)	1.83(1.23, 2.65)
—	—	GLP-1RA	0.89(0.60,1.32)	1.41(0.95, 2.06)
—	—	—	SGLT2i	1.59(1.01, 2.49)
—	—	—	—	TZD

- weighted mean changes in HbA1c: large extent of within-group heterogeneity (I2 = 94.5% DPP4i, 97.9% GLP-1RA, 94.7%SGLT2i, and 80.5% TZD). Considerable between-group heterogeneity was also observed (P < 0.0001).
- Table: Probabilities (%) of being the highest-ranked group for each study outcome

	DPP4i	GLP-1RA	SGLT2i	TZD
Reduction of HbA1c from baseline	0.13	77.14	4.21	18.52
Reduction of FPG from baseline	0.00	0.00	88.94	11.06
Reduction of body weight from baseline	0.00	79.64	20.36	0.00
Proportion of HbA1c <7%	4.64	88.76	4.14	2.46
Reduction of insulin dose from baseline	0.00	9.55	0.79	89.61
Risk of hypoglycemia	0.00	3.82	1.88	94.24

Anmerkung/Fazit der Autoren

The principal findings of our study are as follows: (1) GLP-1RA showed the greatest effect on HbA1c reduction, followed by TZD, SGLT2i, and DPP4i; (2) the reduction in FPG was higher with SGLT2i than with DPP4i and GLP1-RA; (3) GLP-1RA and SGLT2i were associated with body weight reduction, whereas TZD increased body weight; (4) TZD and GLP-1RA reduced total daily insulin requirements; (5) the risk of hypoglycemia was increased with TZD and GLP-1RA.

Kommentare zum Review

Die Endpunke sind zum Teil Laborparameter. Weiterhin war die Studiendauer bei einigen Studien mit 12 oder 16 Wochen relativ kurz.

The studies included in our analysis had different baseline characteristics and showed significant within-group and between-group heterogeneity.

patients in the studies included in this study used various baseline insulin regimens, but we could not isolate the effects of the studied medications on top of the basal insulin therapy regimen, which is the most common practice of insulin therapy at present.

Zheng SL et al., 2018 [103].

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis

Fragestellung

The purpose of this network meta-analysis was to compare the efficacy of SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists in reducing mortality and cardiovascular outcomes in participants with type 2 diabetes and their relative safety profiles

Methodik

Population:

- Patients with T2DM

Intervention/Komparator:

- SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors at market-approved doses with each other or with a control group (defined as placebo or no treatment)

Endpunkte:

- primary outcome: all-cause mortality.
- Secondary outcomes: cardiovascular mortality, heart failure events,myocardial infarction (MI) (all and nonfatal), unstable angina, and stroke (all and nonfatal).
- Safety end points: adverse events (any, serious, and leading to study withdrawal), and hypoglycemia (minor and major)
- Cardiovascular outcome trials:
  - composite cardiovascular outcome (cardiovascular mortality, nonfatal MI, nonfatal stroke)
  - Additional drug class–specific safety end points (UTI, GI, acute pancreatitis, retinopathy)

Recherche/Suchzeitraum:

- Up to October 11, 2017 MEDLINE, EMBASE, and CENTRAL

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias tool
- Egger test to identify asymmetry

Ergebnisse

Anzahl eingeschlossener Studien:

- 236 RCTs with 176 310 participants (Network plot Anhang 1)

Included studies on each comparator

Drug Type	No. of Trials	Total No. Randomized
DPP-4 inhibitor vs control	83	67 958
GLP-1 agonist vs control	65	55 740
SGLT-2 inhibitor vs control	65	40 009
DPP-4 inhibitor vs GLP-1 agonist	14	8024
DPP-4 inhibitor vs SGLT-2 inhibitor	8	4121
GLP-1 agonist vs SGLT-2 inhibitor	1	458

- cardiovascular outcome trials: 9 with 87 162 participants

Charakteristika der Population:

- The baseline characteristics of studies were deemed sufficiently similar based on sex, age, body mass index (BMI), and hemoglobin A1c (HbA1c) levels to permit network comparison. Baseline cardiovascular disease and background medical therapy for participants in cardiovascular outcome trials were deemed similar, although 2 studies enrolled participants after being diagnosed with acute coronary syndrome.

Qualität der Studien:

- 104 (44.1%)were lowrisk of bias across all domains. Three (1.3%) were high risk of bias for allocation concealment, 16 (6.8%) for blinding, and 58 (24.6%) for attrition bias. No studies were high risk of bias for sequence allocation or detection.
- There was no evidence of publication bias (Egger test, 0.10; P = .27)

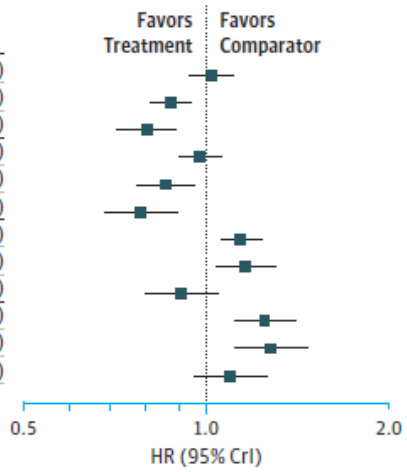
Studienergebnisse:

- Mortality

A Primary outcome: all-cause mortality, 97 trials; $I^2 = 12\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.1 (-0.3 to 0.6)	1.02 (0.94 to 1.11)
GLP-1 agonist		-0.6 (-1.0 to -0.3)	0.88 (0.81 to 0.94)
SGLT-2 inhibitor		-1.0 (-1.5 to -0.6)	0.80 (0.71 to 0.89)
Control	vs DPP-4 inhibitor	-0.1 (-0.4 to 0.2)	0.98 (0.90 to 1.06)
GLP-1 agonist		-0.5 (-0.9 to -0.2)	0.86 (0.77 to 0.96)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.4)	0.78 (0.68 to 0.90)
Control	vs GLP-1 agonist	0.6 (0.3 to 1.0)	1.14 (1.06 to 1.23)
DPP-4 inhibitor		0.7 (0.2 to 1.3)	1.17 (1.04 to 1.30)
SGLT-2 inhibitor		-0.4 (-0.9 to 0.2)	0.91 (0.79 to 1.04)
Control	vs SGLT-2 inhibitor	0.9 (0.4 to 1.5)	1.25 (1.12 to 1.40)
DPP-4 inhibitor		1.0 (0.4 to 1.7)	1.28 (1.11 to 1.47)
GLP-1 agonist		0.4 (-0.1 to 0.9)	1.10 (0.96 to 1.26)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	88	2955 (5.2)	57022
DPP-4 inhibitor	49	1171 (3.9)	30178
GLP-1 agonist	32	1195 (4.4)	27373
SGLT-2 inhibitor	29	714 (3.6)	19587

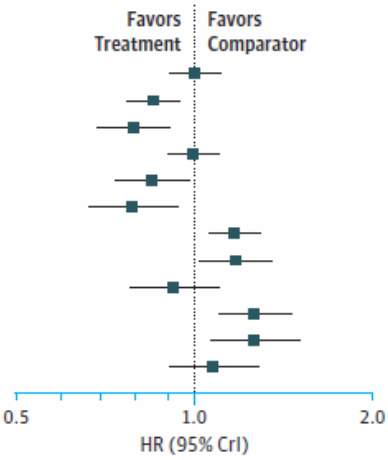


- Cardiovascular mortality

B Cardiovascular mortality, 56 trials; $I^2 = 19\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (-0.3 to 0.4)	1.00 (0.91 to 1.11)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.85 (0.77 to 0.94)
SGLT-2 inhibitor		-0.8 (-1.1 to -0.3)	0.79 (0.69 to 0.91)
Control	vs DPP-4 inhibitor	0.0 (-0.3 to 0.3)	1.00 (0.90 to 1.10)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.85 (0.74 to 0.98)
SGLT-2 inhibitor		-0.7 (-1.1 to -0.2)	0.79 (0.66 to 0.94)
Control	vs GLP-1 agonist	0.5 (0.2 to 0.9)	1.17 (1.06 to 1.30)
DPP-4 inhibitor		0.5 (0.1 to 1.1)	1.18 (1.02 to 1.36)
SGLT-2 inhibitor		-0.2 (-0.7 to 0.3)	0.93 (0.78 to 1.10)
Control	vs SGLT-2 inhibitor	0.8 (0.3 to 1.3)	1.27 (1.10 to 1.46)
DPP-4 inhibitor		0.8 (0.2 to 1.5)	1.27 (1.07 to 1.51)
GLP-1 agonist		0.2 (-0.3 to 0.8)	1.08 (0.91 to 1.29)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	50	1833 (3.6)	50869
DPP-4 inhibitor	27	763 (3.1)	24519
GLP-1 agonist	19	704 (3.0)	23554
SGLT-2 inhibitor	19	468 (2.5)	18407

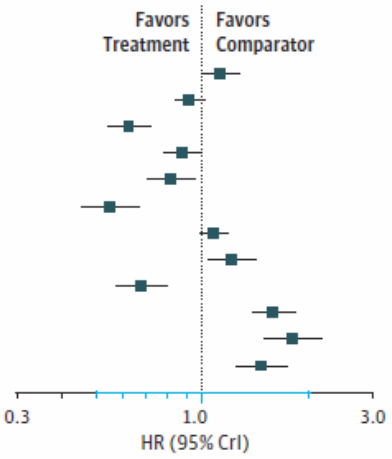


- Heart failure

C Heart failure events, 58 trials; $I^2 = 19\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.4 (0.0 to 0.8)	1.13 (1.00 to 1.28)
GLP-1 agonist		-0.2 (-0.5 to 0.1)	0.93 (0.84 to 1.02)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.62 (0.54 to 0.72)
Control	vs DPP-4 inhibitor	-0.3 (-0.5 to 0.0)	0.88 (0.78 to 1.00)
GLP-1 agonist		-0.4 (-0.7 to -0.1)	0.82 (0.70 to 0.95)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.55 (0.46 to 0.67)
Control	vs GLP-1 agonist	0.2 (-0.1 to 0.5)	1.08 (0.98 to 1.18)
DPP-4 inhibitor		0.6 (0.1 to 1.1)	1.22 (1.05 to 1.42)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.5)	0.67 (0.57 to 0.80)
Control	vs SGLT-2 inhibitor	1.0 (0.6 to 1.4)	1.60 (1.39 to 1.84)
DPP-4 inhibitor		1.3 (0.8 to 2.0)	1.81 (1.50 to 2.18)
GLP-1 agonist		0.8 (0.4 to 1.3)	1.48 (1.25 to 1.76)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	55	1370 (2.8)	48362
DPP-4 inhibitor	24	544 (2.4)	22327
GLP-1 agonist	21	638 (2.7)	23363
SGLT-2 inhibitor	19	266 (1.7)	15989

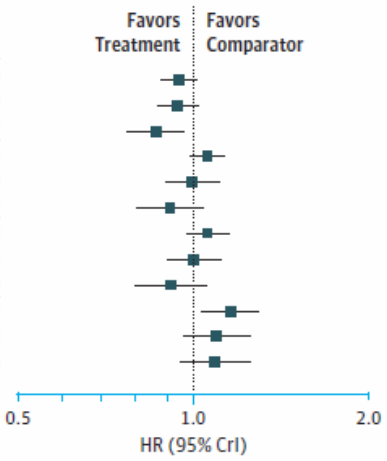


- Unstable Angina:
  - o There was no significant difference between drug classes. No drug class was associated with reduction in unstable angina
- Myocardial infarction:
  - o SGLT-2 inhibitors: nonfatal MIs (HR, 0.84 [95% CrI, 0.72 to 0.98]; absolute RD, -0.8% [95% CrI, -1.4% to -0.1%]) compared with the control groups.

A All myocardial infarction, 97 trials; $I^2 = 15\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	-0.2 (-0.5 to 0.0)	0.94 (0.88 to 1.01)
GLP-1 agonist		-0.2 (-0.5 to 0.1)	0.94 (0.87 to 1.02)
SGLT-2 inhibitor		-0.6 (-0.9 to -0.1)	0.86 (0.77 to 0.97)
Control	vs DPP-4 inhibitor	0.1 (0.0 to 0.3)	1.06 (0.99 to 1.13)
GLP-1 agonist		0.0 (-0.2 to 0.2)	1.00 (0.90 to 1.11)
SGLT-2 inhibitor		-0.2 (-0.4 to 0.1)	0.91 (0.80 to 1.04)
Control	vs GLP-1 agonist	0.3 (-0.1 to 0.6)	1.06 (0.98 to 1.15)
DPP-4 inhibitor		0.0 (-0.4 to 0.5)	1.00 (0.90 to 1.12)
SGLT-2 inhibitor		-0.3 (-0.9 to 0.2)	0.92 (0.80 to 1.05)
Control	vs SGLT-2 inhibitor	0.4 (0.1 to 0.8)	1.16 (1.04 to 1.30)
DPP-4 inhibitor		0.3 (-0.1 to 0.6)	1.10 (0.96 to 1.25)
GLP-1 agonist		0.2 (-0.1 to 0.6)	1.09 (0.95 to 1.25)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	87	2133 (4.0)	53099
DPP-4 inhibitor	50	616 (2.2)	27462
GLP-1 agonist	30	1140 (4.3)	26400
SGLT-2 inhibitor	32	505 (2.5)	19958



- Stroke:
  - o No drug class was associated with reduction in all stroke compared with the control groups; however, GLP-1 agonists were associated with reduction in nonfatal stroke compared with the control groups (HR,0.87 [95%CrI,0.76 to 0.99]; absolute RD -0.3% [95%CrI, -0.5%to -0.02%]).
  - o There was no associated difference between drug classes for nonfatal stroke.

Safety Endpoints

- any hypoglycemia:
  - DPP-4 inhibitors (HR, 1.29 [95% CrI, 1.12 to 1.50]); GLP-1 agonists (HR, 1.44 [95% CrI, 1.25 to 1.66]), and SGLT-2 inhibitors (HR, 1.24 [95% CrI, 1.06 to 1.45]) were all associated with increased risk compared with the control groups
  - no significant differences for major hypoglycaemia
  - no difference between drug classes for any or major hypoglycemia.
- Serious adverse events: SGLT-2 inhibitors associated with a reduction compared with the control groups (HR, 0.90 [95%CrI, 0.85 to 0.96]), DPP-4 inhibitor (HR,0.91 [95% CrI, 0.84 to 0.98], and GLP-1 agonist (HR,0.92 [95%CrI,0.85 to 0.99]).
- adverse events leading to trial withdrawal: GLP-1 agonists increased risk compared with the control groups (HR, 2.00 [95%CrI, 1.70 to 2.37]), SGLT-2 inhibitors (HR, 1.80 [95% CrI, 1.44 to 2.25]), and DPP-4 inhibitors (HR, 1.93 [95%CrI, 1.59 to 2.35]).

Cardiovascular Outcome Trials:

- composite cardiovascular outcome: only SGLT-2 inhibitors (HR, 0.88 [95%CrI, 0.79 to 0.97]) and GLP-1 agonists (HR, 0.91 [95%CrI, 0.85 to 0.96]) with reduction compared to placebo; UTI and lower limb ampuatation not significant.
- Genital infections: SGLT-2 inhibitors with an increased risk (RR, 4.19 [95% CI, 3.45 to 5.09])
- Acute pancreatitis DPP4 inhibitors with an increased risk (RR, 1.58 [95% CI, 1.04 to 2.39]); GLP1 not significant

<u>Individual Drug Types:</u>

- For 16 individual drug types compared with the control groups, all-cause mortality was reduced only with 1 SGLT-2 inhibitor: empagliflozin (HR, 0.68 [95% CrI, 0.57 to 0.82]), and 2 GLP-1 agonists: liraglutide (HR, 0.85 [95% CrI, 0.75 to 0.98]) and exenatide (HR, 0.86 [95% CrI, 0.77 to 0.97]).
- No DPP-4 inhibitor individually reduced all-cause mortality.

<u>Drug Class Rankings:</u>

- For all-cause and cardiovascular mortality, SGLT-2 inhibitors were most likely to rank best, GLP-1 agonists second best, and DPP-4 inhibitors worst.
- The SGLT-2 inhibitors were most likely to rank best for heart failure and MI outcomes
- GLP-1 agonists were most likely to rank best for stroke outcomes.

<u>Frequentist Meta-analysis:</u>

- Frequentist network meta-analysis findings were similar to those using the Bayesian approach

Fazit der Autoren

In this network meta-analysis, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

Kommentare zum Review

The British Heart Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication

---

Zhuang XD, et al., 2018 [106].

Comparative cardiovascular outcomes in the era of novel anti-diabetic agents: a comprehensive network meta-analysis of 166,371 participants from 170 randomized controlled trials

Fragestellung

to evaluate whether differences in CV outcomes exist between novel anti-diabetic medications, including dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP1ra), and sodium-glucose co-transporter 2 inhibitors (SGLT2i), and the more traditional classes of drugs, including insulin (INS), metformin (MET), sulfonylureas (SU) and thiazolidinedione (TZD).

Methodik

Population:

- Patients with T2DM

Intervention:

- DPP4i, GLP1ra and SGLT2i

Komparator:

- Placebo, MET, SU, TZD, Insulin and another novel anti-diabetic drug mentioned above

Endpunkte:

- Major adverse cardiovascular events (MACE), consisting of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and unstable angina or hospitalization for unstable angina
- Mortality
- Severe hypoglycemia (hypoglycemia episode requiring the assistance of another person or medical assistance)

Recherche/Suchzeitraum:

- Between Jan 1, 1980, and June 30, 2016 in MEDLINE, EMBASE, and the Cochrane Library Central Register of Controlled Trials

Qualitätsbewertung der Studien:

- Cochrane collaboration handbook, tool with 7 Items

Ergebnisse

Anzahl eingeschlossener Studien:

- 170 RCTs including 166,371 adults
- Seven drug classes were compared with PLA or each other: DPP4i, GLP1ra, SGLT2i, MET, SU, TZD and INS
- For individual comparison, 18 treatment groups were analyzed

Charakteristika der Population:

- Treatment duration ranged from 24 to 208 weeks.
- Ten studies enrolled subjects with high CV risk (65,650 patients),
- 9 studies were exclusively of patients with renal impairment (1349 patients).

Qualität der Studien:

- Overall quality of studies was good; some studies without details about randomization and allocation concealment; only few RCTs at low risk of bias in every question-based entry

Studienergebnisse:

- MET not presented in the ranking as it was used as background treatment in most trials.
- MACE and mortality of anti-diabetic agents compared with sulfonylurea (categorized and individual agents)

SGLT2i	0.84 (0.67,1.04)	**0.72 (0.57,0.91)**	**0.72 (0.60,0.87)**	0.69 (0.43,1.11)	**0.64 (0.42,0.97)**	**0.58 (0.41,0.83)**
0.99 (0.85,1.15)	INS	0.86 (0.73,1.00)	**0.87 (0.77,0.97)**	0.83 (0.53,1.30)	0.77 (0.52,1.13)	**0.70 (0.50,0.97)**
0.93 (0.81,1.07)	0.94 (0.85,1.05)	GLP1ra	1.01 (0.91,1.13)	0.97 (0.62,1.50)	0.90 (0.62,1.30)	0.81 (0.60,1.12)
0.91 (0.80,1.03)	0.92 (0.85,1.01)	0.98 (0.92,1.05)	DPP4i	0.95 (0.61,1.48)	0.89 (0.61,1.28)	0.81 (0.59,1.10)
0.80 (0.56,1.15)	0.81 (0.57,1.16)	0.86 (0.61,1.22)	0.88 (0.62,1.25)	PLA	0.93 (0.64,1.36)	0.84 (0.59,1.22)
0.72 (0.54,0.97)	**0.73 (0.56,0.97)**	0.78 (0.59,1.02)	0.79 (0.61,1.04)	0.90 (0.66,1.24)	TZD	0.91 (0.72,1.15)
0.70 (0.55,0.90)	**0.71 (0.57,0.90)**	**0.76 (0.61,0.94)**	**0.77 (0.62,0.96)**	0.88 (0.65,1.19)	0.97 (0.80,1.18)	SU

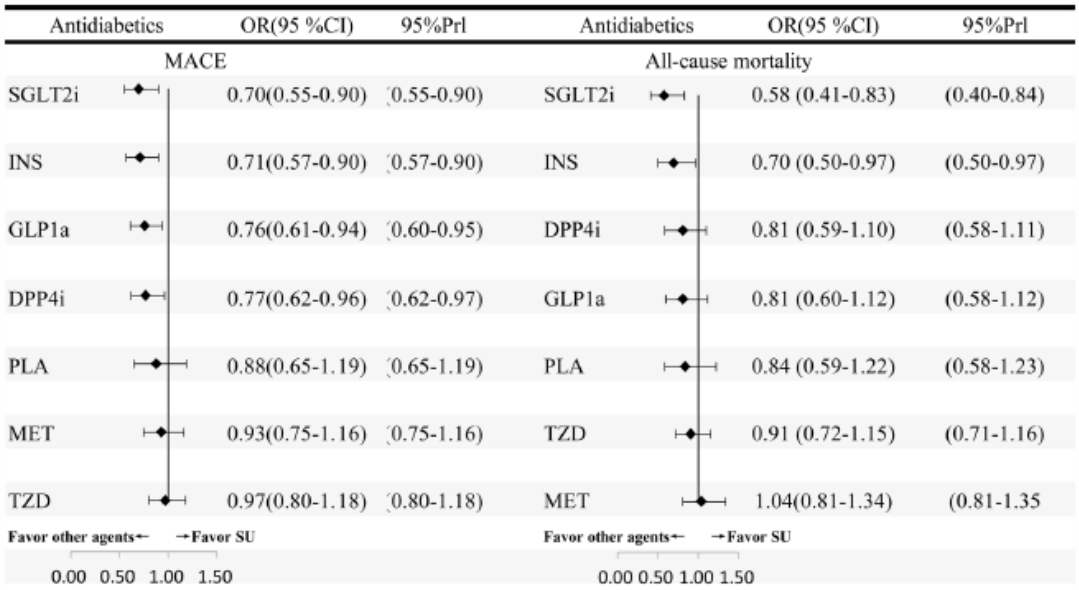
MACE (OR with 95%CI)

All-cause mortality (OR with 95%CI)

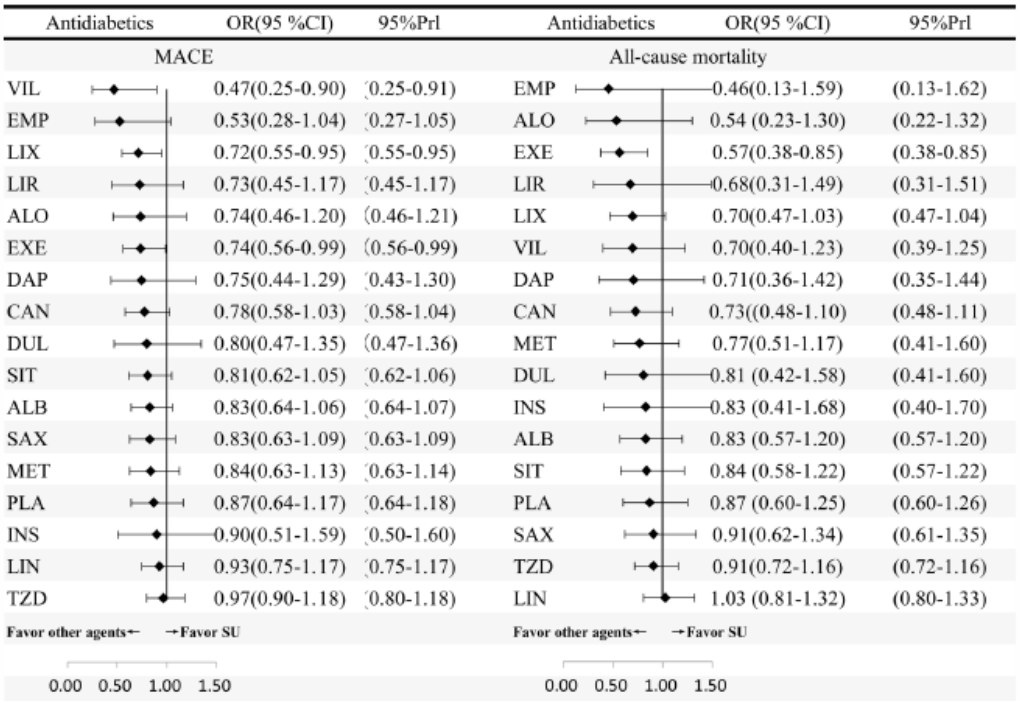
- Comparisons of the drugs on MACE and all-cause mortality

VIL	1.54 (0.40,5.94)	1.01 (0.54,1.89)	1.24 (0.66,2.33)	1.03 (0.40,2.60)	1.29 (0.47,3.55)	0.96 (0.51,1.84)	0.98 (0.42,2.31)	0.86 (0.38,1.98)	0.84 (0.45,1.55)	0.85 (0.46,1.56)	0.77 (0.41,1.44)	0.81 (0.43,1.53)	0.85 (0.35,2.06)	0.68 (0.37,1.25)	0.77 (0.42,1.40)	0.70 (0.40,1.23)
0.88 (0.35,2.20)	EMP	0.66 (0.19,2.31)	0.81 (0.23,2.85)	0.67 (0.16,2.81)	0.84 (0.19,3.72)	0.63 (0.18,2.23)	0.64 (0.16,2.56)	0.56 (0.14,2.22)	0.55 (0.16,1.91)	0.55 (0.16,1.92)	0.50 (0.14,1.77)	0.53 (0.15,1.91)	0.55 (0.14,2.16)	0.44 (0.13,1.53)	0.50 (0.14,1.77)	0.46 (0.13,1.59)
0.65 (0.33,1.28)	0.74 (0.38,1.46)	LIX	1.23 (0.97,1.55)	1.02 (0.48,2.17)	1.28 (0.54,3.03)	0.96 (0.74,1.24)	0.98 (0.52,1.84)	0.86 (0.46,1.58)	**0.83 (0.69,1.00)**	**0.84 (0.73,0.97)**	**0.77 (0.63,0.94)**	0.80 (0.49,1.31)	0.84 (0.40,1.78)	0.67 (0.43,1.06)	0.76 (0.49,1.18)	0.70 (0.47,1.03)
0.63 (0.32,1.25)	0.72 (0.36,1.42)	0.97 (0.82,1.15)	EXE	0.83 (0.39,1.77)	1.04 (0.44,2.49)	0.78 (0.58,1.04)	0.79 (0.42,1.52)	0.70 (0.37,1.30)	**0.68 (0.54,0.84)**	**0.68 (0.57,0.82)**	**0.62 (0.49,0.79)**	0.65 (0.39,1.08)	0.68 (0.32,1.46)	**0.55 (0.35,0.87)**	**0.62 (0.40,0.97)**	**0.57 (0.38,0.85)**
0.65 (0.30,1.43)	0.74 (0.33,1.63)	1.00 (0.62,1.60)	1.03 (0.64,1.66)	LIR	1.26 (0.41,3.85)	0.94 (0.43,2.04)	0.96 (0.37,2.51)	0.84 (0.33,2.17)	0.82 (0.39,1.74)	0.83 (0.39,1.74)	0.75 (0.35,1.61)	0.79 (0.34,1.82)	0.83 (0.30,2.30)	0.66 (0.29,1.49)	0.75 (0.34,1.68)	0.68 (0.31,1.49)
0.64 (0.29,1.40)	0.72 (0.33,1.58)	0.98 (0.60,1.58)	1.00 (0.62,1.64)	0.98 (0.51,1.86)	ALO	0.75 (0.31,1.80)	0.76 (0.27,2.17)	0.67 (0.24,1.87)	0.65 (0.28,1.52)	0.66 (0.28,1.54)	0.60 (0.25,1.42)	0.63 (0.25,1.58)	0.66 (0.22,1.96)	0.53 (0.22,1.27)	0.60 (0.25,1.45)	0.54 (0.23,1.30)
0.61 (0.31,1.20)	0.69 (0.35,1.37)	0.93 (0.77,1.13)	0.96 (0.78,1.18)	0.94 (0.58,1.52)	0.96 (0.58,1.57)	CAN	1.02 (0.53,1.97)	0.89 (0.47,1.69)	0.87 (0.68,1.12)	0.88 (0.70,1.09)	0.80 (0.62,1.04)	0.84 (0.50,1.40)	0.88 (0.41,1.89)	0.70 (0.44,1.13)	0.80 (0.51,1.26)	0.73 (0.48,1.10)
0.63 (0.27,1.44)	0.71 (0.31,1.64)	0.96 (0.57,1.64)	0.99 (0.58,1.70)	0.97 (0.49,1.92)	0.99 (0.50,1.97)	1.03 (0.60,1.78)	DAP	0.88 (0.37,2.06)	0.85 (0.45,1.60)	0.86 (0.46,1.60)	0.79 (0.42,1.48)	0.82 (0.38,1.75)	0.86 (0.33,2.23)	0.69 (0.33,1.43)	0.78 (0.38,1.61)	0.71 (0.36,1.42)
0.59 (0.26,1.33)	0.67 (0.30,1.51)	0.90 (0.56,1.47)	0.93 (0.57,1.52)	0.91 (0.47,1.75)	0.93 (0.48,1.80)	0.97 (0.59,1.60)	0.94 (0.47,1.89)	DUL	0.97 (0.53,1.78)	0.98 (0.54,1.78)	0.90 (0.49,1.65)	0.94 (0.46,1.93)	0.98 (0.39,2.49)	0.79 (0.39,1.59)	0.89 (0.45,1.78)	0.81 (0.42,1.58)
0.58 (0.30,1.14)	0.66 (0.34,1.29)	0.89 (0.77,1.03)	0.92 (0.78,1.08)	0.90 (0.56,1.44)	0.91 (0.57,1.47)	0.96 (0.80,1.15)	0.93 (0.55,1.57)	0.99 (0.61,1.60)	SIT	1.01 (0.89,1.14)	0.92 (0.77,1.11)	0.96 (0.60,1.56)	1.01 (0.48,2.12)	0.81 (0.52,1.25)	0.92 (0.60,1.40)	0.84 (0.58,1.22)
0.57 (0.29,1.11)	0.65 (0.33,1.27)	**0.88 (0.79,0.98)**	0.90 (0.79,1.03)	0.88 (0.55,1.40)	0.90 (0.56,1.44)	0.94 (0.81,1.10)	0.91 (0.54,1.53)	0.97 (0.60,1.56)	0.98 (0.89,1.08)	ALB	0.91 (0.79,1.05)	0.95 (0.59,1.53)	1.00 (0.48,2.09)	0.80 (0.52,1.23)	0.91 (0.60,1.37)	0.83 (0.57,1.20)
0.57 (0.29,1.11)	0.64 (0.33,1.27)	0.87 (0.75,1.01)	0.90 (0.75,1.06)	0.87 (0.54,1.40)	0.89 (0.55,1.44)	0.93 (0.77,1.12)	0.90 (0.53,1.54)	0.96 (0.59,1.56)	0.97 (0.84,1.13)	0.99 (0.89,1.10)	SAX	1.05 (0.64,1.71)	1.10 (0.52,2.32)	0.88 (0.56,1.38)	1.00 (0.65,1.53)	0.91 (0.62,1.34)
0.54 (0.27,1.08)	0.62 (0.30,1.26)	0.83 (0.57,1.22)	0.86 (0.58,1.27)	0.84 (0.49,1.44)	0.86 (0.49,1.49)	0.89 (0.60,1.33)	0.87 (0.47,1.59)	0.92 (0.51,1.65)	0.94 (0.64,1.36)	0.95 (0.66,1.38)	0.96 (0.65,1.41)	PLA	1.05 (0.48,2.29)	0.84 (0.54,1.30)	0.95 (0.65,1.39)	0.87 (0.60,1.25)
0.53 (0.22,1.23)	0.60 (0.26,1.37)	0.81 (0.45,1.46)	0.83 (0.46,1.51)	0.81 (0.39,1.67)	0.83 (0.40,1.69)	0.86 (0.47,1.58)	0.84 (0.39,1.80)	0.89 (0.42,1.88)	0.90 (0.50,1.63)	0.92 (0.51,1.65)	0.93 (0.51,1.68)	0.97 (0.51,1.82)	INS	0.80 (0.39,1.65)	0.91 (0.43,1.90)	0.83 (0.41,1.68)
0.51 (0.26,1.00)	0.57 (0.30,1.10)	0.77 (0.56,1.07)	0.80 (0.57,1.11)	0.78 (0.46,1.30)	0.79 (0.49,1.30)	0.83 (0.59,1.17)	0.80 (0.45,1.43)	0.86 (0.49,1.49)	0.87 (0.63,1.19)	0.88 (0.65,1.21)	0.89 (0.64,1.23)	0.93 (0.64,1.34)	0.96 (0.54,1.70)	LIN	1.13 (0.81,1.60)	1.03 (0.81,1.32)
0.49 (0.25,0.94)	0.55 (0.28,1.09)	0.74 (0.54,1.02)	0.77 (0.56,1.06)	0.75 (0.45,1.23)	0.76 (0.46,1.26)	0.80 (0.58,1.10)	0.77 (0.44,1.36)	0.82 (0.48,1.42)	0.83 (0.61,1.13)	0.85 (0.63,1.14)	0.86 (0.63,1.17)	0.89 (0.65,1.23)	0.92 (0.51,1.67)	0.96 (0.72,1.28)	TZD	0.91 (0.72,1.16)
0.47 (0.25,0.90)	0.53 (0.28,1.04)	**0.72 (0.55,0.95)**	**0.74 (0.56,0.99)**	0.73 (0.45,1.17)	0.74 (0.46,1.20)	0.78 (0.58,1.03)	0.75 (0.44,1.29)	0.80 (0.47,1.35)	0.81 (0.62,1.05)	0.83 (0.64,1.06)	0.83 (0.63,1.09)	0.87 (0.64,1.17)	0.90 (0.51,1.59)	0.93 (0.75,1.17)	0.97 (0.80,1.18)	SU

- MACE and mortality of anti-diabetic agents compared with sulfonylurea (categorized agents) Treatments are ranked by surface under the cumulative ranking (SUCRA) values.



- MACE and mortality of anti-diabetic agents compared with sulfonylurea (individual agents) Treatments are ranked by surface under the cumulative ranking (SUCRA) values.



Anmerkung/Fazit der Autoren

First, among anti-diabetic agents included in the network, SGLT2i in class comparisons, and vildagliptin in individual comparisons, respectively ranked first in terms of MACE. Furthermore, when compared with other individual or classes of drugs, SU are associated with the highest risks of MACE and all-cause mortality. Finally, the ranking of CV risk was linearly correlated with the ranking of severe hypoglycemia risk by individual comparisons, with SU displaying the highest risks in both endpoints.

Canadian Agency for Drugs and Technologies in Health (CADTH), 2017 [9].

New drugs for type 2 diabetes: second-line therapy – science report

Fragestellung

1. For adults with type 2 diabetes on metformin monotherapy with inadequate glycemic control, what is the comparative efficacy and safety of using a drug from one of the following classes as a second-line drug?

a. Sulfonylurea

b. Insulin

c. DPP-4 inhibitor

d. GLP-1 analogue

e. SGLT-2 inhibitor.

2. For adults with type 2 diabetes, what are the comparative cardiovascular effects of drugs belonging to one of the following classes?

a. Insulin

b. DPP-4 inhibitor

c. GLP-1 analogue

d. SGLT-2 inhibitor.

Methodik

Table 3: Population, Intervention, Comparator, Outcome, and Study Designs of Interest

Population	For research question 1: Adults with type 2 diabetes on pharmacotherapy with inadequate glycemic control[a] For research question 2: Adults with type 2 diabetes	
Interventions[b]	**SGLT-2 inhibitors**	canagliflozin, dapagliflozin, empagliflozin
	GLP-1 analogues	dulaglutide, exenatide, liraglutide, albiglutide
	DPP-4 inhibitors	alogliptin, linagliptin, saxagliptin, sitagliptin
Comparators[b]	**SGLT-2 inhibitors**	canagliflozin, dapagliflozin, empagliflozin
	GLP-1 analogues	dulaglutide, exenatide, liraglutide
	DPP-4 inhibitors	alogliptin, linagliptin, saxagliptin, sitagliptin
	Sulfonylureas	chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide
	Insulin, insulin analogues, and insulin analogue biosimilars	Regular insulin, pork insulin, insulin aspart, insulin lispro, insulin glulisine, insulin NPH, insulin detemir, insulin glargine, mixed regular insulin/insulin NPH, mixed insulin lispro/lispro protamine and mixed insulin aspart/aspart protamine (see Table 2)
	Metformin	
	Placebo	
Outcomes	**Clinical benefits[c]**	Reduction in: • composite of death from cardiovascular causes/nonfatal myocardial infarction/nonfatal stroke • death from cardiovascular causes • all-cause mortality • fatal and nonfatal myocardial infarction • fatal and nonfatal stroke • unstable angina • hospitalization for unstable angina • heart failure • hospitalization for heart failure • transient ischemic attack • coronary revascularization procedure • blood pressure • body weight • body mass index • hemoglobin A1C Discontinuation of: • blood pressure medication
	Clinical harms	• total adverse events • serious adverse events • withdrawals due to adverse events
	Other notable harms	• hypoglycemia • urogenital adverse events • renal adverse events • lipids • ketoacidosis • bone fractures • bladder cancer • pancreatitis • pancreatic cancer

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; SGLT-2 = sodium-glucose cotransporter-2.
[a] In the previous CADTH reviews, inadequate control was defined as hemoglobin A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L.
[b] Interventions may include regimens combining the above drugs with metformin, a sulfonylurea, insulin product and/or other drug (e.g., pioglitazone) as indicated in the Health Canada product monographs. Other drugs (including meglitinides, alpha-glucosidase inhibitors, thiazolidinediones or insulin degludec) may also be included as comparators in the network meta-analysis.
[c] Based on a reduction in events, or a change in clinical measurement signifying improvement or clinical benefit.
[d] A decrease in weight will be considered a clinical benefit, while an increase in weight will be considered a harm.

<u>Recherche/Suchzeitraum:</u>

- up to March, 2016

<u>Qualitätsbewertung der Studien:</u>

- Cochrane Collaboration’s Risk of Bias (ROB) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 Reports included, Presenting data from 3 unique studies
- Results research question 1
  - systematic review identified 175 unique RCTs
  - evidence available for sulfonylureas, SGLT-2 inhibitors, DPP-4 inhibitors, thiazolidinediones (TZDs), GLP-1 analogues, basal insulin, alpha-glucosidase inhibitors, meglitinides, and biphasic insulin
  - No studies of bolus insulin reported outcomes of interest.
- Results Research Question 2
  - systematic review identified 17 unique RCTs
  - 11 reported outcomes of interest
  - evidence available for SGLT-2 inhibitors, DPP-4 inhibitors, TZDs, and GLP-1 analogues

Charakteristika der Population:

Table 5: Summary of Trial Characteristics

Trial Characteristics	Categories	Number of Included Studies
Publication status	Unique RCTs	175
	Unique RCTs reporting outcomes of interest	166
Country	Multinational	83
	Single country	73
	Not reported	10
Study design	Parallel RCTs	164
	Crossover RCTs	2
Sponsors	Industry	119
	Public funding	9
	Not reported	36
Intervention comparison	Placebo control	48
	Active control	87
	Both	31
Duration of stable background therapy		Range: ≥ 4 weeks to ≥ 12 weeks
Publication year		Range: 1997 to 2016
Randomized sample size		Range: 21 to 2,789
Duration of study treatment		Range: 4 to 156 weeks

RCT = randomized controlled trial.

Qualität der Studien:

- RCTs generally had a moderate risk of bias (ROB)
- commonly failed to adequately report their methods for random sequence generation and allocation concealment
- At least 20% of the studies were assessed to be at high ROB related to incomplete reporting of efficacy or safety outcomes.
- Limitations
  - For populations inadequately controlled with first-line metformin monotherapy who required a second-line drug, most identified trials included patients using varied and unspecified anti-diabetes drugs at baseline which limited their inclusion in this review.
  - This specifically impacted the inclusion of results from emerging trials reporting clinically important outcomes (e.g., EMPA-REG OUTCOME and LEADER) in the analyses for research question 1. Outcomes from these studies could not be considered in the

economic evaluation, as only NMA results from research question 1 informed the analyses.

- For populations inadequately controlled on metformin, there was little evidence for the effect of second-line drugs on long-term diabetes-related complications.
- Low events rates limited the ability to perform NMA for many outcomes. When feasible and appropriate, the best possible alternative synthesis approach was used (meta-analysis, narrative).
- Statistical approaches to Bayesian NMA rely on a number of key assumptions, including transitivity, consistency, and homogeneity. The NMA analyses presented in this report for research questions 1 and 2 were generally assessed to be valid; however, we were unable to statistically assess the consistency assumption for some outcomes reported due to the limited number of studies informing the evidence network.
- The varied baseline characteristics of the participants included in research question 2 may also have produced some heterogeneity, which was difficult to investigate comprehensively due to the limited number of studies reporting outcomes of interest.

Studienergebnisse:

Results research question 1: Selected NMA results found the following:

- Nonsevere hypoglycemia:
  - Compared with metformin monotherapy, the odds of nonsevere hypoglycemia were higher with sulfonylurea and basal and biphasic insulin.
  - When the classes were compared, all classes except biphasic insulin significantly reduced odds of nonsevere hypoglycemia relative to sulfonylurea (67 RCTs).
- Body weight:
  - Relative to metformin monotherapy, sulfonylurea and basal insulin increased mean body weight (range 2.1 kg to 2.8 kg) with no significant differences between these classes. SGLT-2 inhibitors and GLP-1 agonists were associated with significant reductions in mean body weight relative to metformin monotherapy (range –1.4 kg to –2.2 kg). All noninsulin treatments added to metformin resulted in significant reductions in mean body weight relative to sulfonylurea (range –1.9 kg to –4.3 kg).
  - SGLT-2 inhibitors and GLP-1 agonists also resulted in significant reductions in mean body weight relative to DPP-4 inhibitors (70 RCTs).
- Total adverse events:
  - Compared with metformin monotherapy, GLP-1 agonists and basal or biphasic insulin significantly increased the total number of adverse events.
  - When the classes were compared, basal and biphasic insulin significantly increased total adverse events when compared with all other classes.
  - GLP-1 agonists significantly increased total adverse events when compared with DPP-4 and SGLT-2 inhibitors (57 RCTs).
- There were limited data for mortality and clinically important long-term complications of diabetes.

Results Research Question 2: Select NMA results found the following:

- Major adverse cardiovascular events (6 RCTs), cardiovascular mortality (5 RCTs), hospitalizations for heart failure (5 RCTs), total adverse events (3 RCTs):

- When compared with placebo, SGLT-2, DPP-4 inhibitors, and GLP-agonists did not significantly increase or decrease the relative risk of events.
- Severe hypoglycemia: There was a significantly lower risk of severe hypoglycemia with GLP-1 agonists relative to DPP-4 inhibitors and placebo (8 RCTs).
- All-cause mortality: Compared with placebo and DPP-4 inhibitors, SGLT-2 inhibitors reduced the risk of all-cause mortality. None of the other treatments reduced the risk of all-cause mortality (8 RCTs).

Anmerkung/Fazit der Autoren

Results from the systematic review align with other class-level systematic reviews and meta-analyses that have assessed the comparative efficacy of anti-diabetes drugs in patients with inadequate glycemic control on metformin monotherapy, although this review includes significantly more RCTs and examines many more clinical outcomes and adverse events.

Results also support current clinical practice guidelines for this patient population by Diabetes Canada. Similar to the previous CADTH review and other systematic reviews on oral anti-diabetes drugs, there remained a lack of conclusive evidence regarding the effects of various therapies on the long-term complications of diabetes.

There are clear correlations between type 2 diabetes and the long-term health impacts related to heart disease, premature death, and cardiovascular complications. Many of the large cardiovascular outcome RCTs were powered for cardiovascular safety outcomes yet limited in the reporting of many other efficacy outcomes. As a result, it is difficult to place the noted cardiovascular benefits in context with other outcomes related to glycemic control.

Although it was not possible to consider the data from the recent large clinical trials (e.g., EMPA-REG OUTCOME and LEADER) in the NMA for research question 1, results show benefit in the high-risk populations studied. Treatment options for patients at high risk for cardiovascular disease should consider these study results in context with the results from the NMA.

Kommentare zum Review

- *CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.*
- *Funding: For this project, CADTH worked in partnership with the Methods and Applications Group for indirect Comparisons (MAGIC), funded by the Canadian Institutes of Health Research (CIHR) through the Drug Safety and Effectiveness Network (DSEN) initiative.*

Singh S et al., 2017 [87].

Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis

Fragestellung

This systematic review and metaanalysis assessed the clinical efficacy and safety of GLP-1 RAs compared with basal insulins.

Methodik

Population:

- adults with type 2 diabetes inadequately controlled with oral antihyperglycemic drugs

Intervention:

- GLP-1 RAs

Komparator:

- basal insulins

Endpunkte:

- change from baseline to 26 weeks (10 weeks) of treatment in haemoglobin A1c (HbA1c) and weight, proportion of patients experiencing hypoglycaemia

Recherche/Suchzeitraum:

- from database inception to September 9, 2016

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs meta-analysed

Charakteristika der Population:

-

Qualität der Studien:

- selection bias assessed as unclear in
  - 7 trials for random sequence generation and in
  - 4 trials for allocation concealment
- all trials open label
- attrition bias (see incomplete outcome data) was assessed to be low in
  - 12 trials (percentage of patients lost to follow-up reported as 0%-3% in all arms) and
  - unclear in 3 trials

Studienergebnisse:

- Body weight
  - mean difference in bodyweight for insulin glargine vs. …
  - exenatide 10 µg: −4.31 kg (95% CI, −4.71, −3.90; I2 = 76%),
  - exenatide 2 mg LAR: −2.85 kg (95% CI, −3.20, −2.49; I2 = 96.5%),
  - liraglutide 1.8 mg: −4.65 kg (95% CI, −5.08, −4.22; I2 = 89.1%), and
  - dulaglutide 0.75 mg: −1.98 kg (95% CI, −2.32, −1.64, I2 = 91%)
  - mean weight reduction was seen with all GLP-1 RAs

- Hypoglycaemia
  - interpretation of analysis limited by inconsistent definitions and reporting
- Gastrointestinal events
  - meta-analyses not conducted as reporting across studies was insufficient to allow meaningful analyses

Anmerkung/Fazit der Autoren

Although weight reduction is seen with all GLP-1 RA's, only the once-weekly agents, exenatide LAR and dulaglutide, demonstrate significant HbA1c reductions when compared to basal insulins.

Yang Y et al., 2017 [97].

Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes: Systematic review and meta-analysis of randomized controlled trials Titel des Reviews

Fragestellung

We aimed to assess the safety and efficiency of the novel sodium glucose co-transporter 2 (SGLT2) inhibitor in combinations with insulin for type 1 and type 2 diabetes mellitus (T1DM and T2DM).

Methodik

Population:

- more than 18 years old, HbA1c between 7% and 12%, treated by insulin who were diabetes mellitus diagnosed by WHO diagnostic criteria

Intervention:

- SGLT2 inhibitors plus insulin versus placebo plus insulin or only insulin no matter the dose and kind of SGLT2 inhibitor and insulin

Komparator:

- placebo combined with insulin or only insulin in which the insulin method was same to experimental group

Endpunkte:

- adverse reactions including hypoglycemia, UTI, and GTI, the effective indicators including HbA1c and fasting plasma glucose (FPG)

Recherche/Suchzeitraum:

- from January 2010 to December 2016

Qualitätsbewertung der Studien:

- Cochrance System Evaluate Method

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 with 3069 Patients

Charakteristika der Population:

- 8 of 9 studies double-blinded, randomized, placebo controlled trials,
- 1 study randomized no placebo control trail,
- 2 studies IIa pilot trials;
- 1 study single-center,
- 6 studies multicentre
- experimental group in 9 studies SGLT2 inhibitor combined with insulin,
  - SGLT2 inhibitors were respectively dapagliflozin (3 studies), empagliflozin (3 studies), sapagniflozin (1 study), canagliflozin (1 study), and tofogliflozin (1 study),
  - control group were placebo with insulin or insulin itself
- Insulin therapy was not limited as long as the insulin therapy was the same in both 2 groups
- Intervention duration ranged from 2 to 78 weeks

Qualität der Studien:

- studies had low risk of bias

Studienergebnisse:

- Body weight
  - reduction was 2.53kg with SGLT2 inhibitors as add-on treatment in DM2 compared with placebo
  - n=696, MD -2,53 kg, 95%CI [-3,50 to -1,56], P<.00001
- Risk of GTI
  - events of GTI higher in SGLT2 inhibitors group compared with control group (OR 4,28, 95%CI [2,00-9,16], P=.0002)
- Risk of hypoglycemia and UTI
  - no statistical difference in the incidence of hypoglycemia (but a tendency to increase) and urinary infection

Anmerkung/Fazit der Autoren

SGLT2 inhibitors have improved the HbA1c, FPG, and body weight when combined with insulin and decreased the dose of insulin without increasing the risk of hypoglycemia. However, SGLT2 inhibitor was proved to be related to the events of GTI, despite SGLT2 inhibitors appeared to be well tolerated. We suggest that more monitoring should be done to prevent the events of GTI, and more randomized controlled trials should be planned next step

Kommentare zum Review

- *The authors have no funding and conflicts of interest to disclose.*

Zaccardi F et al., 2017 [99].

Comparison of glucose-lowering agents after dual therapy failure in type 2 diabetes: A systematic review and network meta-analysis of randomized controlled trial.

Fragestellung

To assess the evidence supporting the choice of third-line agents in adults with inadequately controlled type 2 diabetes.

Methodik

Population:

- adult patients with type 2 diabetes with sub-optimal glucose control on dual therapy with metformin and a second-line agent (“dual therapy failure”)

Intervention/Komparator:

- third-line glucose-lowering agents added to metformin-based dual treatments

Endpunkte:

- cardiometabolic outcomes (HbA1c, fasting plasma glucose [FPG], body weight, systolic and diastolic blood pressure, total cholesterol, LDL and HDL cholesterol, and triglycerides) and hypoglycaemia

Recherche/Suchzeitraum:

- between January 2000 and July 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 43 with 16 590 participants
- metformin combined with: sulphonylureas (SUs) in 20 RCTs; thiazolidinediones (TZDs) in 10; basal or rapid-acting insulin in 6; dipeptidyl peptidase-4 (DPP-4) inhibitors in 3; glucagon-like peptide-1 receptor agonists (GLP-1RAs) in 2; and sodium-glucose co-transporter-2 (SGLT-2) inhibitors in 2

Qualität der Studien:

- overall risk of bias: low, high and unclear in 31 (63.3%), 3 (6.1%) and 15 (30.6%) studies, respectively
- high or unclear domain-specific bias was lowest for selective reporting (20.4%) and highest for incomplete outcome data (34.7%)
- almost all studies were supported by one or more pharmaceutical companies (other bias)

Studienergebnisse:

- Direct pairwise comparisons for HbA1c, fasting plasma glucose, and body weight, by outcome, background therapy, and RCTs duration

Outcome	Drug A	Drug B	Metformin + Sulphonylurea (24-36 weeks)			
			No. of		Mean Difference (95% CI)	I^2 (p-value)
			RCT	Part.		
HbA1c (%)	DPP-4i	Placebo	5	2146	-0.65 (-0.78, -0.52)	59.5 (0.042)
	Basal	GLP-1RA	4	2191	0.21 (-0.03, 0.45)	86.9 (0.000)
	SGLT-2i	Placebo	3	959	-0.73 (-0.92, -0.54)	69.9 (0.036)
FPG (mmol/l)	DPP-4i	Placebo	4	1678	-0.76 (-0.99, -0.53)	10.5 (0.341)
	SGLT-2i	Placebo	3	959	-1.71 (-1.95, -1.47)	0.0 (0.512)
Body weight (kg)	Basal	GLP-1RA	4	2141	3.50 (2.93, 4.07)	69.5 (0.020)
	SGLT-2i	Placebo	3	961	-1.96 (-2.29, -1.62)	0.0 (0.747)
	GLP-1RA	Placebo	2	832	-0.91 (-1.52, -0.29)	26.3 (0.244)
	Basal	Placebo	2	557	2.74 (1.39, 4.09)	77.0 (0.037)
	DPP-4i	Placebo	2	1190	0.52 (0.07, 0.98)	51.8 (0.150)

Outcome	Drug A	Drug B	Metformin + Thiazolidinedione (24-36 weeks)			
			No. of		Mean Difference (95% CI)	I^2 (p-value)
			RCT	Part.		
HbA1c (%)	GLP-1RA	Placebo	4	1337	-0.88 (-1.14, -0.61)	81.1 (0.001)
	SGLT-2i	Placebo	2	477	-0.68 (-0.86, -0.51)	35.3 (0.214)
	DPP-4i	Placebo	2	573	-0.70 (-0.87, -0.53)	0.0 (0.366)
FPG (mmol/l)	GLP-1RA	Placebo	3	982	-1.57 (-2.26, -0.88)	85.6 (0.001)
	DPP-4i	Placebo	2	572	-0.77 (-1.15, -0.38)	10.5 (0.291)
Body weight (kg)	GLP-1RA	Placebo	4	1284	-2.40 (-2.86, -1.95)	5.5 (0.365)

- Direct pairwise comparisons for hypoglycaemia, by outcome, background therapy, and RCTs duration

Drug A	Drug B	Metformin + Sulphonylurea (24-36 weeks)				
		No. of			Odds Ratio (95% CI)	I^2 (p-value)
		RCT	Part.	Hypo*		
DPP-4i	Placebo	5	2280	293	3.06 (1.52, 6.14)	54.0 (0.069)
Basal	GLP-1RA	3	1684	523	1.58 (0.86, 2.90)	84.1 (0.002)
SGLT-2i	Placebo	3	972	77	1.77 (1.02, 3.07)	14.9 (0.309)
Basal	Placebo	2	557	166	2.76 (1.49, 5.11)	55.6 (0.134)
GLP-1RA	Placebo	2	832	180	2.33 (1.62, 3.35)	0.0 (0.351)

Drug A	Drug B	Metformin + Thiazolidinedione (24-36 weeks)				
		No. of			Odds Ratio (95% CI)	I^2 (p-value)
		RCT	Part.	Hypo*		
GLP-1RA	Placebo	4	1408	122	2.85 (1.71, 4.74)	8.6 (0.350)
DPP-4i	Placebo	3	847	40	1.38 (0.69, 2.76)	0.0 (0.514)

Drug A	Drug B	Metformin + Sulphonylurea (52-54 weeks)				
		No. of			Odds Ratio (95% CI)	I^2 (p-value)
		RCT	Part.	Hypo*		
SGLT-2i	Placebo	2	530	46	1.62 (0.87, 3.02)	0.0 (0.428)

*Hypo: Participants with hypoglycaemia event(s), Comparisons with only one study are not shown. CI: Confidence interval; Part.: = Participants; Basal: Basal (long-acting) insulin; DPP-4i: Dipeptidyl peptidase-4 inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; SGLT-2i: Sodiumglucose cotransporter-2 inhibitor.

Anmerkung/Fazit der Autoren

Moderate-quality evidence supports the choice of a third-line agent only in patients on metformin combined with a SU or a TZD, with SGLT-2 inhibitors performing generally better than other

drugs. In suggesting third-line agents, future guidelines should recognize the widely differing evidence on the various dual therapy failures.

Kommentare zum Review

- *Funding information: F.Z. is a Clinical Research Fellow funded with an unrestricted Educational Grant from Sanofi-Aventis to the University of Leicester. The funding source had no involvement in this study.*

Andersen SE and Christensen M, 2016 [2].

Hypoglycaemia when adding sulphonylurea to metformin: a systematic review and network meta-analysis

Fragestellung

The risk of hypoglycaemia may differ among sulphonylureas (SUs), but evidence from head-to-head comparisons is sparse. Performing a network meta-analysis to use indirect evidence from randomized controlled trials (RCTs), we compared the relative risk of hypoglycaemia with newer generation SUs when added to metformin.

Methodik

Population:

- patients with T2DM aged 18 or older, who had received metformin monotherapy ≥1000 mg for at least 4 weeks and required add-on therapy with another oral antihyperglycaemic agent due to inadequate control (HbA1C > 6.5% (47.5 mmol/mol))

Intervention:

- glimepiride, gliclazide, glibenclamide (glyburide), glipizide

Komparator:

- placebo or an oral non-SU agent

Endpunkte:

- overall hypoglycaemia of any severity, severe hypoglycaemia, mean change in HbA1C and change in body weight

Recherche/Suchzeitraum:

- (Aktualität der Recherche): inception until 8 January 2016

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl eingeschlossener Studien:

- 27 RCTs (n = 16.260)

Charakteristika der Population:

Study	Group[a]	No.	Mean age (y)	Female (%)	Known duration of diabetes (y)	HbA_{1c} (%)	HbA_{1c} (mmol/mol)	Fasting plasma glycose, (mmol l^{-1})
Fonseca *et al.* [47]	Rosiglitazone	I	58.3 (8.8)	32	8.3 (6.3)	8.9 (1.3)	73.8	12.2 (3.1)
	Placebo	116	58.8 (9.2)	26	7.3 (5.7)	8.6 (1.3)	70.5	11.9 (2.9)
Charpentier *et al.* [43]	**Glimepiride**	147	Median 56.8	42	Median 5.6	6.4 (1.1)	46.4	10.4 (1.8)
	Placebo	75	Median 56.7	40	Median 7.0	7.8 (1.2)	61.7	10.6 (1.8)
Marre *et al.* [52]	**Glibenclamide**	101	58.0 (13.0)	51	5.9 (5.4)	7.9 (1.6)	62.8	10.7 (3.0)
	Placebo	104	57.5 (11.5)	40	5.4 (4.9)	8.1 (1.8)	65.0	11.0 (3.2)
Marre *et al.* [53]	Nateglinide	160	57.3 (10.5)	39	6.8 (5.5)	8.2 (NR)	66.1	9.9 (2.5)[b]
	Placebo	152	56.4 (10.3)	45	6.5 (6.5)	8.3 (NR)	67.2	10.1 (2.5)[b]
Schernthaner *et al.* [22]	**Gliclazide**	405	60.5 (9.9)	49	5.6 (5.9)	8.4 (1.1)	68.3	10.2 (2.6)
	Glimepiride	440	60.6 (10.5)	48	5.8 (5.8)	8.2 (1.0)	66.1	10.1 (2.6)
Feinglos *et al.* [45]	**Glipizide**	61	57.7 (10.7)	54	6.5 (NR)	7.5 (NR)	58.5	8.6 (1.5)[b]
	Placebo	61	58.8 (10.0)	59	4.6 (NR)	7.6 (NR)	59.6	8.7 (1.5)[b]
Matthews *et al.* [54]	Pioglitazone	317	56 (9.2)	49	5.8 (5.1)	8.7 (1.1)	49.7	11.8 (3.1)
	Gliclazide	313	57 (9.0)	51	5.5 (5.1)	8.5 (0.9)	69.4	11.3 (2.6)
Charbonnel *et al.* [42]	Sitagliptin	464	54.4 (10.4)	44	6.0 (5.0)	8.0 (0.8)	63.9	9.4 (2.3)
	Placebo	237	54.7 (9.7)	41	6.6 (5.5)	8.0 (0.8)	63.9	9.7 (2.3)
Garber *et al.* [48]	**Glibenclamide**	160	56 (NR)	44	5 (4)	8.5 (1.2)	69.4	10.6 (2.9)
	Rosiglitazone	158	56 (NR)	35	6 (5)	8.4 (1.1)	68.3	10.4 (2.7)
Ristic *et al.* [59]	Nateglinide	133	62.0 (11.0)	46	7.2 (6.3)	7.7 (0.6)	60.7	9.0 (1.5)
	Gliclazide	129	61.6 (10.1)	50	6.7 (5.6)	7.6 (0.6)	59.6	8.7 (1.5)
Nauck *et al.* [55]	Sitagliptin	588	56.8 (9.3)	43	6.5 (6.1)	7.7 (0.9)	60.7	8.8 (1.9)
	Glipizide	584	56.6 (9.8)	39	6.2 (5.4)	7.6 (0.9)	59.6	8.8 (2.1)
Bolli *et al.* [39]	Vildagliptin	295	56.3 (9.3)	38	6.4 (4.9)	8.4 (1.0)	68.3	10.9 (2.6)
	Pioglitazone	281	57.0 (9.7)	36	6.4 (5.2)	8.4 (0.9)	68.3	11.0 (2.7)
Bosi *et al.* [40]	Vildagliptin	185	53.9 (9.5)	39	5.8 (4.7)	8.4 (1.0)	68.3	9.9 (2.6)
	Placebo	182	54.5 (10.3)	47	6.2 (5.3)	8.3 (0.9)	67.2	10.1 (2.4)
Raz *et al.* [58]	Sitagliptin	96	53.6 (9.5)	49	8.4 (6.5)	9.3 (0.9)	78.1	11.2 (2.6)
	Placebo	94	56.1 (9.5)	59	7.3 (5.3)	9.1 (0.8)	76.0	11.0 (2.4)
Scott *et al.* [63]	Sitagliptin	94	55.2 (9.8)	45	4.9 (3.5)	7.8 (1.0)	61.7	8.7 (1.7)
	Rosiglitazone	87	54.8 (10.5)	37	4.6 (4.0)	7.7 (0.8)	60.7	8.7 (1.8)
	Placebo	92	55.3 (9.3)	41	5.4 (3.7)	7.7 (0.9)	60.7	8.9 (2.1)
DeFronzo *et al.* [44]	Saxagliptin	191	54.7 (9.6)	46	6.4 (4.7)	8.1 (0.8)	65.0	10.0 (2.6)
	Placebo	179	54.8 (10.2)	46	6.7 (5.6)	8.1 (1.0)	65.0	9.7 (2.4)
Ferrannini *et al.* [46]	Vildagliptin	1396	57.5 (9.1)	47	5.7 (5.2)	7.3 (0.6)	56.3	9.2 (2.3)
	Glimepiride	1393	57.5 (9.3)	46	5.8 (5.0)	7.3 (0.7)	56.3	9.2 (2.2)

Study	Group[a]	No.	Mean age (y)	Female (%)	Known duration of diabetes (y)	HbA_{1c} (%)	HbA_{1c} (mmol/mol)	Fasting plasma glycose, (mmol l^{-1})
Goodman *et al.* [50]	Vildagliptin	248	54.9 (10.8)	47	NR	8.5 (1.0)	69.4	10.8 (2.8)
	Placebo	122	54.5 (9.7)	33	NR	8.7 (1.0)	71.6	11.1 (2.8)
Bailey *et al.* [38]	Dapagliflozin	135	52.7 (9.9)	43	6.1 (5.4)	7.9 (0.8)	62.8	8.7 (2.2)
	Placebo	137	53.7 (10.3)	45	5.8 (5.1)	8.1 (1.0)	65.0	9.2 (2.6)
Göke *et al.* [49]	Saxagliptin	428	57.5 (10.3)	51	5.5 (4.5)	7.7 (0.9)	60.7	9.0 (2.3)
	Glipizide	430	57.6 (10.4)	46	5.4 (4.7)	7.7 (0.9)	60.7	8.9 (2.2)
Scheen *et al.* [61]	Saxagliptin	403	58.8 (10.1)	53	6.3 (5.0)	7.7 (1.0)	60.7	8.9 (2.5)
	Sitagliptin	398	58.1 (10.5)	49	6.3 (4.7)	7.7 (0.9)	60.7	8.9 (2.4)
Arechavaleta *et al.* [37]	Sitagliptin	516	56.3 (9.7)	45	6.8 (4.6)	7.5 (0.7)	58.5	8.0 (1.8)
	Glimepiride	519	56.2 (10.1)	46	6.7 (4.8)	7.5 (0.8)	58.5	8.1 (1.9)
Nauck *et al.* [56]	Dapagliflozin	406	58 (9)	45	6 (5)	7.7 (0.9)	60.7	9.0 (2.1)
	Glipizide	408	59 (10)	45	7 (6)	7.7 (0.9)	60.7	9.1 (2.3)
Pan *et al.* [57]	Vildagliptin	145	54.2 (9.6)	50	4.9 (4.8)	8.1 (0.9)	65.0	8.8 (2.0)
	Placebo	144	54.5 (9.7)	54	5.2 (4.6)	8.0 (0.8)	63.9	8.8 (2.1)
Cefalu *et al.* [41]	**Glimepiride**	482	56.3 (9.0)	45	6.6 (5.0)	7.8 (0.8)	61.7	9.2 (2.1)
	Canagliflozin	485	55.8 (9.2)	50	6.7 (5.5)	7.8 (0.8)	61.7	9.1 (2.0)
Lavalle-González *et al.* [51]	Placebo	183	55.3 (9.8)	49	6.8 (5.3)	8.0 (0.9)	63.9	9.1 (2.1)
	Canagliflozin	367	55.3 (9.2)	55	7.1 (5.4)	7.9 (0.9)	62.8	9.6 (2.5)
	Sitagliptin	366	55.5 (9.6)	53	6.8 (5.2)	7.9 (0.9)	62.8	9.4 (2.3)
Rosenstock *et al.* [60]	Saxagliptin	176	55 (10)	47	8.2 (5.5)	9.0 (1.1)	74.9	10.7 (2.5)
	Dapagliflozin	179	54 (10)	50	7.4 (5.4)	8.9 (1.2)	73.8	10.3 (2.7)

Data are presented as mean with standard deviation (SD) unless stated otherwise. NR, not reported; HbA1c, glycosylated haemoglobin
[a]Only study arms included in the meta-analysis are shown
[b]SD calculated from standard error of mean (SE)

Qualität der Studien:

- Jadad score was 4 out of 5, most often due to missing information about the randomization (15 trails) or blinding (12 trials). No definition of hypoglycaemia was mentioned in 1 out of 11 trials rated 5 out of 5 and in 2 out of 5 trials rated 4 out of 5 in Jadad. Nine trials provided no definition of severe hypoglycaemia, one of which rated 5 out of 5 and two of which rated 4 out of 5 in Jadad.
- Visual inspection of comparison-adjusted funnel plots did not suggest any small study effects or publication bias.

Studienergebnisse:

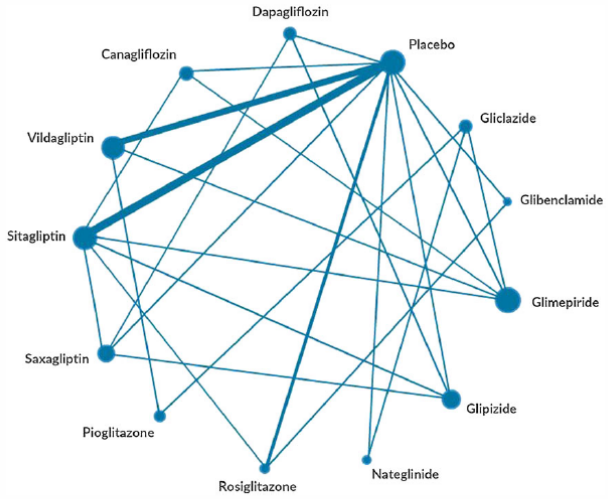


Figure 2
The evidence network of eligible comparisons for hypoglycaemia. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the area of each node is proportional to the number of randomized participants (sample size)

- comparative risk of hypoglycaemia of any severity with the four SUs + metformin.
  - Among the SUs, the risk of hypoglycaemia was lowest with gliclazide. Only the risk associated with glipizide, however, was statistically higher than the risk with gliclazide (OR 4.60, CrI: 1.04, 19.48).
- comparative risk of hypoglycaemia when comparing all the individual oral anti-glycaemic agents using placebo as reference
  - A significantly higher risk of hypoglycaemia than with placebo was noted for nateglinide, glimepiride, glipizide, and glibenclamide, but not for gliclazide (OR 2.91, CrI: 0.87–9.93). Moreover, the risk with gliclazide was not statistically different from that of the other non-SU agents included in the present analysis with the exception of pioglitazone (OR 9.75, CrI: 2.40–42.38)
- Severe hypoglycaemia (22 studies)
  - rare for all drug classes. Most trials reported zero events. Severe hypoglycaemia affected none of the patients enrolled for glibenclamide or gliclazide compared to 0–2.1% of the patients enrolled for glimepiride and 0–2.6% of the patients enrolled for glipizide.

Anmerkung/Fazit der Autoren

In this systematic review, we examined the risk of hypoglycaemia associated with four SUs and eight non-SU antihyperglycaemic drugs by compiling direct and indirect evidence from 27 RCTs in patients with T2DM inadequately controlled by metformin monotherapy. Indicating that the risk of hypoglycaemia may differ among the SUs with gliclazide having the lowest of the four, our results are consistent with direct evidence from the only sufficiently powered head-to-head trial, the GUIDE study, which demonstrated fewer hypoglycaemic episodes with gliclazide than with glimepiride. Although our analysis suggests a relevant difference between the SU agents, the credibility intervals are wide, reflecting considerable clinical uncertainty.

The risk of hypoglycaemia does not seem to pertain to SUs as a drug class as such. We conclude that when added tometformin, gliclazide confers the lowest risk of hypoglycaemia between the newer generation SU agents.

Bolen S et al., 2016 [8].

Diabetes medications for adults with type 2 diabetes: an update

Fragestellung

This review updates the 2011 review on oral diabetes medications for adults with type 2 diabetes. We are focusing on priority head-to-head drug class comparisons identified, a priori,as clinically relevant comparisons for which there are evidence gaps.

Methodik

Population:

- adults ages 18 or older with type 2 diabetes mellitus

Intervention/Komparator:

- monotherapy (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] agonists, and sodium glucose cotransporter-2 [SGLT-2] inhibitors) or
- metformin-based combination therapy (metformin plus one of these monotherapy drugs or insulin) comparisons

Endpunkte:

- Hemoglobin A1c, weight, systolic blood pressure, heart rate. All-cause mortality, Cardiovascular and cerebrovascular morbidity and mortality, Retinopathy, Nephropathy, Neuropathy, safety

Recherche/Suchzeitraum:

- April 2009 through April 2015. We updated the MEDLINE search to identify randomized controlled trials indexed through December 31, 2015

Qualitätsbewertung der Studien:

- Jadad criteria, GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 216 Studies. Nicht nur RCTs, auch Beobachtungsstudien

Qualität der Studien:

- Siehe Studienergebnisse

Studienergebnisse: (hier nur patientenrelevante Endpunkte dargestellt)

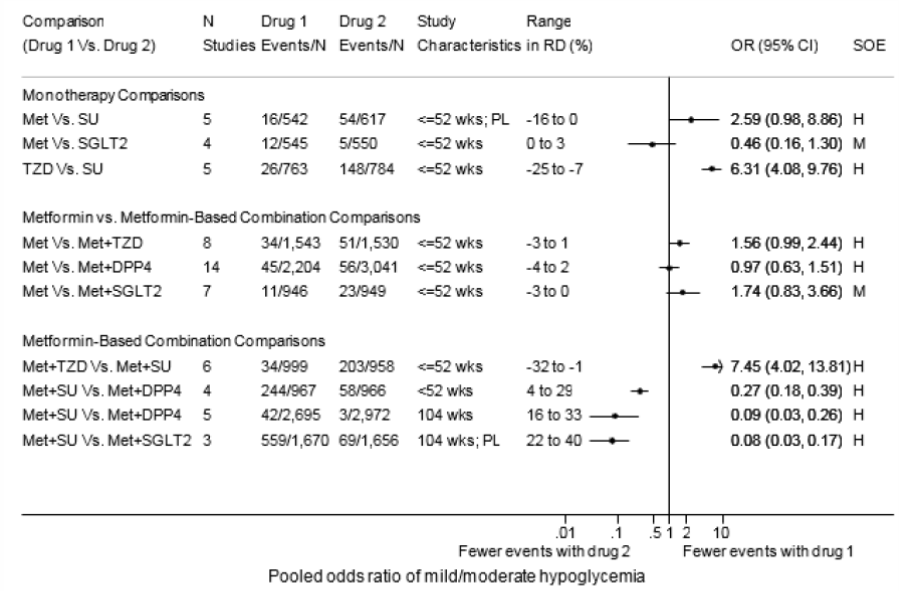
- All-Cause Mortality and Macrovascular and Microvascular Outcomes (118 studies, 96 were RCTs and 21 were observational (mainly retrospective cohort) studies)
  - Only one comparison had moderate strength of evidence for any of these outcomes. The rest of the outcomes were rated as low strength of evidence or insufficient. We found moderate strength of evidence that sulfonylurea monotherapy was associated with a 50-percent to 70-percent higher relative risk (absolute risk difference, 0.1% to 2.9% in RCTs;

number needed to treat, 20 to 1,000) of cardiovascular mortality compared with metformin monotherapy

- Our findings on all cause-mortality and cardiovascular morbidity, drawn from the same RCTs plus additional observational studies, also favored metformin over sulfonylureas; however, the strength of evidence was low for these outcomes because of less consistency in results across studies.

- Safety
  - Sulfonylureas alone and in combination with metformin had a higher risk of mild, moderate, or total hypoglycemia than any other monotherapies and metformin-based combinations for which we identified evidence.

Figure D. Pooled odds ratios of mild/moderate hypoglycemia and strength of evidence for monotherapy and metformin-based combination comparisons



CI = confidence interval; DPP4 = dipeptidyl peptidase-4 inhibitors; H = high; M = moderate; Met = metformin; OR = odds ratio; PL = profile likelihood estimate; RD = absolute risk difference; SGLT2 = sodium-glucose cotransporter-2 inhibitors; SOE = strength of evidence; SU = sulfonylurea; TZD = thiazolidinediones.
The width of the horizontal lines represents the 95% confidence intervals for each pooled analysis. Drug 1 is the reference group.

- Metformin and GLP-1 receptor agonists were associated with more gastrointestinal side effects (typically nausea, vomiting, or diarrhea) than any other medications with sufficient studies for comparison, regardless of whether they were used as monotherapy or in combination
- We found low strength of evidence that the risk of congestive heart failure was 1.2 to 1.6 times as great with thiazolidinediones as with sulfonylureas (pooled OR, 1.6; 95% CI, 0.96 to 2.8; range in RD, 0% to 2%) or metformin (2 RCTs lasting less than a year with no events; 1 4-year RCT with an RD of 3%; and range in hazard ratio of 1.2 to 1.5 in 2 observational studies).

Anmerkung/Fazit der Autoren

Combination therapy with metformin generally reduced HbA1c by 0.7 to 1 absolute percentage points compared with metformin monotherapy. While we found moderate strength of evidence that some combination comparisons were more effective than others, most between-group differences were small (<0.3 percentage points), with questionable clinical relevance. Only one combination comparison with moderate strength of evidence was favored by greater than 0.3

percentage points over any other combination comparison: the combination of metformin plus a GLP-1 receptor agonist reduced HbA1c more than metformin plus a DPP-4 inhibitor by 0.65 percentage points.

The “best” second-line therapy after metformin is still unclear. We evaluated non–metformin-based monotherapy comparisons in this report and demonstrated that the other monotherapies, with the exception of DPP-4 inhibitors, which are not as effective in reducing HbA1c as metformin, generally decrease HbA1c to a similar extent (and comparably to metformin). These other monotherapies’ effects on body weight vary, as do their risks, such as congestive heart failure (increased risk for thiazolidinediones), hypoglycemia (highest risk with sulfonylureas, including for severe hypoglycemia for many comparisons), gastrointestinal side effects (nausea and vomiting with GLP-1 receptor agonists), and genital mycotic infections (increased risk for SGLT-2 inhibitors). Most importantly, we do not have conclusive evidence on the relative long-term effects of non–metformin-based monotherapy comparisons on all-cause mortality or cardiovascular outcomes, microvascular outcomes, and rare serious adverse events (e.g., pancreatitis risk with GLP-1 receptor agonists).

The evidence supports metformin as a firstline therapy, given its beneficial effects on HbA1c, weight, cardiovascular mortality (vs. sulfonylureas), and relative safety profile. The comparative long-term benefits and harms of other diabetes medications remain unclear.

Kommentare zum Review

Aus öffentlichen Mitteln finanziert

Crowley MJ et al., 2016 [17].

Metformin Use in Patients with Contraindications or Precautions

Fragestellung

KQ 1. For patients with type 2 diabetes and an apparent contraindication or precaution to metformin use (eg, renal insufficiency, congestive heart failure, chronic liver disease, or older age):

- a. What is the rate of lactic acidosis in patients taking metformin?
- b. How does the rate of lactic acidosis in patients taking metformin compare with the rate in patients taking other hypoglycemics?

KQ 2. For patients with type 2 diabetes and an apparent contraindication or precaution to metformin use, what are the potential benefits and harms (other than lactic acidosis) of continued treatment with metformin?

Methodik

Population:

- patients with type 2 diabetes and an apparent contraindication or precaution to metformin

Intervention:

- Metformin use alone or in combination with other glucose-lowering treatment.

Komparator:

- Non-metformin oral or injectable hypoglycemic medication(s)

Endpunkte:

- mortality and major adverse cardiovascular event (MACE) outcomes

Recherche/Suchzeitraum:

- up to November 2015

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias (ROB) tool for RCTs and the key quality criteria described in the Agency for Healthcare Research and Quality's (AHRQ's) Methods Guide for Effectiveness and Comparative Effectiveness Reviews, adapted to this specific topic and customized to observational studies, Strength of evidence (SOE) was assessed using the approach described in the Agency for Healthcare Research and Quality (AHRQ)'s Methods Guide

Ergebnisse

Anzahl eingeschlossener Studien:

- overall 37 (29 observational studies and 8 RCTs) included
  - 9 studies addressed KQ 1 and
  - 32 studies addressed KQ 2

Charakteristika der Population:

- studies reported data relevant to older adults (n = 16), patients with CHF (n = 11), patients with CKD (n = 9), and patients with CLD (n = 3)

Since a 2010 Cochrane review (16), there are limited new data examining the rate of LA with metformin use; however, we found 9 contemporary observational studies reporting on this outcome in individuals with an identified precaution or contraindication to metformin use.

16. Salpeter SR, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010(4):CD002967.

KQ 1a

Qualität der Studien:

- The risk of bias for these studies was judged to be high.

Studienergebnisse:

- Limited data (2 studies, no RCTs) suggest the incidence of LA in metformin users who have CKD is slightly higher than the upper bounds (4.3/100,000) reported in the Cochrane review.
- The limited data (2 studies, no RCTs) on incidence rates of LA among older adults are inconclusive.
- No studies reported incidence rates for individuals with CHF or CLD.

KQ 1b

Qualität der Studien:

- The risk of bias for these studies was judged to be low (n = 2) or moderate (n = 3).

Studienergebnisse:

- Five studies (no RCTs) comparing rates of LA with metformin use versus non-metformin diabetes treatment do not suggest a higher rate of LA with metformin use among individuals with CKD, CHF, or CLD.
- No study reported this outcome for older adults without one of these comorbid conditions.
- Based on our synthesis of observational evidence, the risk of LA with metformin use among individuals with a contraindication or precaution appears to be low (ie, not higher than the risk of LA with other hypoglycemic medications).

KQ 2

Qualität der Studien:

- Studies included for KQ 2 were mostly rated as moderate ROB, with some rated low ROB

Studienergebnisse:

- Five studies (no RCTs) comparing rates of LA with metformin use versus non-metformin diabetes treatment do not suggest a higher rate of LA with metformin use among individuals with CKD, CHF, or CLD.
- Among patients with T2D and CKD, metformin use is associated with a significantly lower risk of all-cause mortality (n = 5); limited evidence was identified for major adverse cardiovascular events (MACE, n = 2).
- Among patients with T2D and CHF, metformin use is also associated with a significantly lower risk of all-cause mortality (n = 11) and heart failure readmission (n = 4), but risk of cardiovascular mortality did not differ (n = 3).
- Among patients with T2D and CLD, limited evidence suggests a lower risk of all-cause mortality (n = 3) may be associated with metformin use.
- There was no evidence identified for MACE in relation to CLD.
- Among patients with T2D and older age (generally age ≥65 years), limited evidence suggests that metformin is not associated with a higher risk of all-cause mortality (n = 4), MACE (n = 1), or hypoglycemia (n = 6).
- These results are all in comparison to non-metformin treatment.
- While limited evidence suggests that progressively lower estimated glomerular filtration rate (eGFR) may diminish the mortality benefit associated with metformin use, the impact of CHF severity, CLD severity, and increasing older age on the effects of metformin is unclear. No evidence was identified regarding the effects of metformin on glycemic control, lipid control, weight, hypoglycemia, or vitamin B12 deficiency among patients with medically treated T2D and CKD, CHF, or CLD.
- Based on our quantitative syntheses of observational evidence, metformin use is associated with a lower risk of all-cause mortality when compared with non-metformin treatment among patients with medically treated T2D and CKD or CHF. Limited evidence is available regarding all-cause mortality in CLD, but qualitative synthesis of available

evidence suggests that metformin may be beneficial in this population. Data on the effects of metformin in older adults are limited, but does not indicate increased harm from the use of metformin compared to non use.

Anmerkung/Fazit der Autoren

Based on limited evidence, the rate of LA associated with metformin use among patients with historical contraindications or precautions does not appear higher than that of other diabetes medications. Metformin appears to be associated with reduced all-cause mortality in patients with CKD and patients with CHF, and appears to be associated with reduced CHF readmission. Though data are otherwise limited, other risks of metformin use do not appear higher than those associated with other diabetes medications among patients with historical contraindications or precautions. Despite this review's limitations, our findings support recent FDA labeling changes, may inform clinical practice, and point toward important areas for future research.

Kommentare zum Review

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Durham VA Medical Center, Durham, NC, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative.

Foroutan N et al., 2016 [25].

Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs sulfonylurea in metformin-based combination therapy for type 2 diabetes mellitus: Systematic review and meta-analysis

Fragestellung

The purpose of this study was to compare the safety and efficacy of DPP-4 inhibitors versus sulfonylurea as adjunctive second-line therapy in patients with type 2 diabetes mellitus, inadequately controlled with metformin mono-therapy.

Methodik

Population:

- all adults with T2DM requiring an OHA to be added to MET because of inadequate glycemic control (HbA1c > 6.5%, FPG > 7 mmol/L or 2-hour postprandial glucose > 10 mmol/L)

Intervention:

- DPP-4 inhibitors

Komparator:

- sulfonylurea

Endpunkte:

- cardiovascular events, HbA1c % change from baseline, body weight, hypoglycemic event rate

Recherche/Suchzeitraum:

- from 1980 to June 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 RCTs: 10 139, 9 187 and 10 616 participants included for HbA1c%, body weight and hypoglycemia, respectively

Qualität der Studien:

- studies were of "low risk of bias"
- incomplete outcome data (missing data) was quite high in four studies
- concerns about risk of bias in four studies
- ultimate quality of evidence per outcome according to GRADE was "moderate

Studienergebnisse:

- Cardiovascular events (CVE): no studies measured CVE
- Safety assessment: significant decrease in the rate of hypoglycemic events in favor of DPP-4 inhibitors (RR= 0.12; P<0.00001) involving 10 616 patients, with at least one hypoglycemic event during the follow-up period (12-104 weeks)
- Body weight: decreased by 2.2 kg (95% CI 1.7-2.7) with DPP-4 inhibitors, compared with sulfonylureas

Anmerkung/Fazit der Autoren

Conclusion: The review shows that, in terms of clinical efficacy, there is no significant difference between DPP4-inhibitors and sulfonylurea when either is added to metformin mono-therapy. In contrast, the safety assessment analysis showed a significant decrease in the risk of hypoglycemic events in patients using DPP4-inhibitors.

Gu J et al., 2016 [57].

The efficacy and safety of liraglutide added to metformin in patients with diabetes: a meta-analysis of randomized controlled trials

Fragestellung

In this study we conducted a meta-analysis to compare the efficacy and safety of liraglutide plus metformin with other drugs in patients with T2DM

Methodik

Population:

- adult patients with T2DM [HbA1c between either 6.5 or 7.0 and either 10.0 or 11.0%, depending on previous treatment]

Intervention:

- Liraglutide plus metformin

Komparator:

- antidiabetic therapy or placebo

Endpunkte:

- HbA1c, bodyweight, fasting plasma glucose (FPG), postprandial plasma glucose(PPG), systolic blood pressure (SBP), and diastolic blood pressure (DBP)

Recherche/Suchzeitraum:

- bis Feb. 2016

Qualitätsbewertung der Studien:

- Jadad scale
- I2 statistic of < 25%, ~50%, ~75%, ~100% are considered to have no, low, moderate, and high degree of heterogeneity

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs (N= 4,657)

Study	Year	Intervention
Nauck M[19]	2009	0.6 mg liraglutide
		1.2 mgliraglutide
		1.8 mg liraglutide
		4 mg glimepiride
		Placebo
Russell-Jones D[20]	2009	1.8 mg liraglutide
		Placebo
		24 IU insulin glargine
Dungan KM[41]	2014	1.8 mg liraglutide
		1.5 mg dulaglutide
Ma ZJ[42]	2015	1.8 mg liraglutide
		NPH
Davies M[43]	2011	1.2 mg liraglutide
		1.8 mg liraglutide
		100 mg sitagliptin
Brady EM[44]	2014	1.2 mg liraglutide
		4 mg glimepiride
Yang W[45]	2011	0.6 mg liraglutide
		1.2 mg liraglutide
		1.8 mg liraglutide
		4 mg glimepiride
Charbonnel B[46]	2013	1.2 mgliraglutide
		100 mg sitagliptin
Pratley R[40]	2011	1.2 mgliraglutide
		1.8 mg liraglutide
		100 mg sitagliptin

Qualität der Studien:

- 5 Studien = Jaded Score 3; 4 Studien = Jaded Score 4 (Any study with a score ≥ 3 is considered to be of high quality)

Studienergebnisse:

- Seven studies reported the data in bodyweight. As an add-on to metformin, liraglutide lowered bodyweight more than control (placebo, sitagliptin, glimepiride, dulaglutide, insulin glargine, and NPH) (WMD = − 2.13 kg, 95%CI: − 2.87, − 1.38; P < 0.001).
- When used combination with metformin, 1.2 mg/day liraglutide notably decreased bodyweight compared with sitagliptin (WMD = − 2.01 kg, 95%CI: − 2.78, − 1.25; P < 0.001), and glimepiride (WMD = − 2.42 kg, 95%CI: − 2.73, − 2.12; P < 0.001).

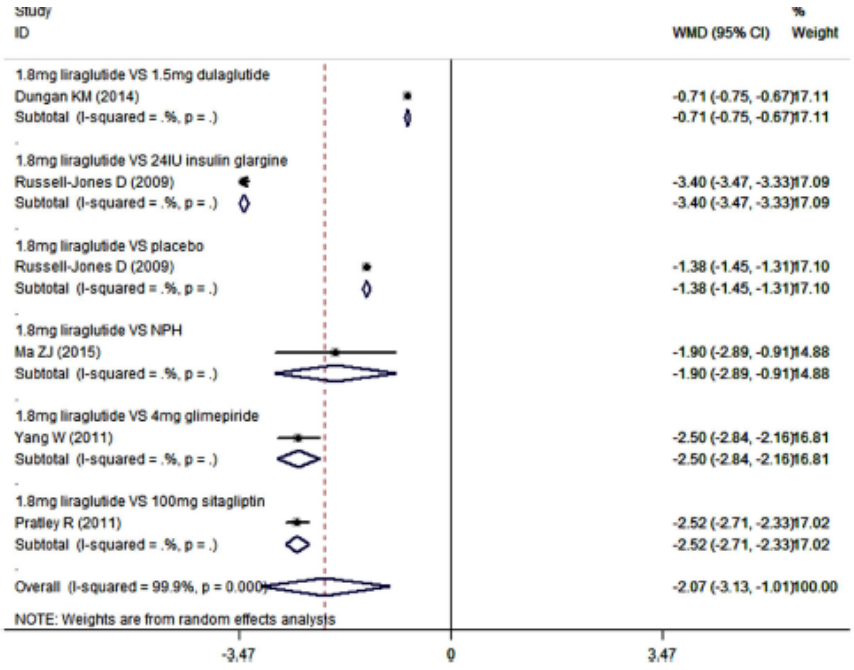


Figure 4. Bodyweight: 1.8 mg liraglutide add-on to metformin VS. control.

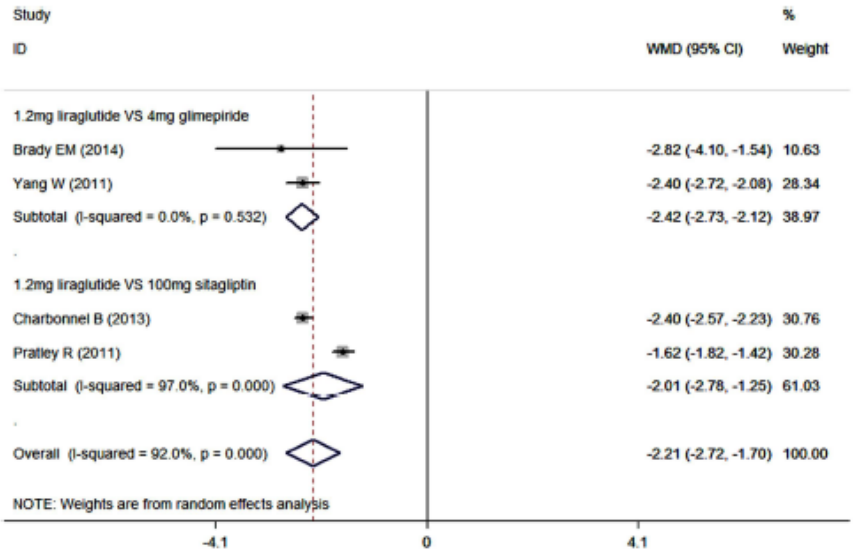


Figure 5. Bodyweight: 1.2mg liraglutide add-on to metformin VS. control.

Anmerkung/Fazit der Autoren

This meta-analysis investigated the efficacy and safety of liraglutide in combination with metformin, compared to other therapies for patients with T2DM. Overall, the results of our study suggest that compared with other therapies, liraglutide in combination with metformin showed greater reduction in terms of HbA1c levels, body weight, FPG, and PPG, and similar changes in SBP and DBP. In addition, when used as add-on therapy to metformin, liraglutide did not increase the risk of hypoglycemia, but induced a higher incidence of gastrointestinal disorders. However, considering the potential limitations in this study, more large-scale, well-conducted RCTs are needed to identify our findings.

Kommentare zum Review

- *This study was supported by the Science and Technology projects of Liaoning Province and the Science and Technology projects of Shenyang City*
- *The authors declare no competing financial interests.*

Liu FP et al., 2015 [67].

Glucagon-like peptide 1 receptor agonist therapy is more efficacious than insulin glargine for poorly controlled type 2 diabetes: A systematic review and meta-analysis

Fragestellung

The aim of the present study was to compare the reported efficacy and safety of glucagon-like peptide-l receptor agonist (GLP-1RA) and insulin glargine (IGlar) for poorly controlled type 2 diabetes.

Methodik

Population:

- adult patients (≥18 years of age) with type 2 diabetes inadequately controlled by OADs

Intervention:

- exenatide or liraglutide as the supplemental therapy

Komparator:

- IGlar as the supplemental therapy

Endpunkte:

- HbA1c, body weight, blood lipids (total cholesterol [TC], triglyceride [TG], low-density lipoprotein [LDL], and high-density lipoprotein [HDL]), blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), safety outcomes (AE, SAE, hypoglycemic event, nasopharyngitis, headache, nausea, vomiting, diarrhea)

Recherche/Suchzeitraum:

- K.A.

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7/1 587 (IGlar) and 1 606 (exenatide or liraglutide)
- 5 studies compared IGlar to exenatide, 2 compared to liraglutide

Qualität der Studien:

- no substantial difference in intention-to-treat (patients randomized) or modified intention-to-treat (randomized patients received at least one dose) analyses
- withdrawal rates: 8% to 15% for all trials, main reason: AE
- no risk of bias assessment of unpublished NCT0111735023 study
- none of the other six trials adopted blinding methods
- NCT0036033418 did not provide a detailed description of random sequence generation and allocation concealment
- no publication bias found

Studienergebnisse:

- Body weight
  - GLP-1RA showed significant advantage in decreasing body weight compared to IGlar (WMD, −4.08; 95% CI, −5.09 to −3.07) with a significant heterogeneity of I2 = 94%
  - sensitivity analysis without studies NCT00360334, NCT00935532,21 and NCT0111735023 (considerable difference in BMI and dosage of IGlar with the other studies might be the reasons for heterogeneity)
  - significantly greater decline in body weight with GLP-1RA (WMD, −3.97; 95% CI, −4.32 to −3.62; I2 = 0%)
- Safety
  - SAE uncommon and not significantly different
  - more gastrointestinal complications with GLP-1RA: nausea, diarrhea, vomiting
  - no difference in nasopharyngitis and headache
- Hypoglycemia events
  - severe hypoglycaemia events were rare
  - minor hypoglycemia less common for GLP-1RA

Anmerkung/Fazit der Autoren

GLP-1RA showed greater efficacy compared to IGlar for type 2 diabetes, and it may also prove beneficial for other diabetes-associated characteristics, including obesity, hypertension, and hyperlipidemia.

Mearns ES et al., 2015 [72].

Efficacy and safety of antihyperglycaemic drug regimens added to metformin and sulphonylurea therapy in Type 2 diabetes: a network meta-analysis

Fragestellung

we performed a network meta-analysis (NMA) to assess the comparative efficacy and safety of third-line adjunctive AHAs in people with Type 2 diabetes not adequately controlled on a stable, optimized combination of metformin and SU.

Methodik

Population:

- adult subjects with Type 2 diabetes (include only who showed inadequate response [defined as a having an HbA1c concentration > 53 mmol/mol (7%)] to stable, optimum metformin and SU combination therapy at randomization (at least 3 weeks)

Intervention:

- non-insulin and longacting, once-daily basal insulin agents (as a single or combination therapy)

Komparator:

- placebo/control (in addition to metformin and an SU

Endpunkte:

- HbA1c (p.E.); body weight, systolic blood pressure (SBP), proportion of participants experiencing confirmed hypoglycaemia, urinary tract infections (UTIs) and genital tract infections (GTIs) (s.E.)

Recherche/Suchzeitraum:

- bis Mai 2014 (in Medline & Cochrane CENTRAL bibliographic databases)

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- Heterogenität: A random-effects model assuming common heterogeneity across all comparisons was implemented. We assessed inconsistency in our network metaanalysis using a ‘loop-specific’ approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 20 RCTs

Qualität der Studien:

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting	Other bias
Moses 2014	?	?	+	?	+	-	-
Lukashevich 2014	?	?	?	?	+	-	+
NCT01392677	?	?	+	?	+	-	-
NCT01076075	?	?	?	?	+	+	-
Liu 2013	?	+	-	?	?	+	-
Haring 2013	?	+	?	?	+	+	+
Wilding 2013	+	+	+	+	+	+	-
Schernthaner 2013	+	+	+	+	-	+	-
Owens 2011	?	?	?	?	+	+	-
Kadoglou 2010	+	+	-	?	-	-	+
Russell-Jones 2009	?	+	-	+	-	+	-
Charpentier 2009	?	?	?	?	-	-	+
Kadoglou 2008	?	?	-	?	?	-	+
Hermansen 2007	?	+	?	?	+	-	-
Triplitt 2006	?	?	-	?	?	+	?
Rosenstock 2006	?	?	-	?	+	+	-
Heine 2005	?	+	-	?	-	-	+
Kendall 2005	?	?	?	?	-	-	+
Dailey 2004	?	?	?	?	-	+	-
Lam 1998	?	?	?	?	-	-	+

Supplemental Figure 1. Risk of Bias Assessment of Randomized Controlled Trials
Legend: +=low risk of bias, ?=unclear risk of bias, –=high risk of bias

Studienergebnisse:

- All AHAs assessed in the NMA significantly lowered HbA1c from baseline but by different magnitudes [ranging from 7 mmol/mol (0.6%) for acarbose and linagliptin to 13 mmol/mol (1.20%) for liraglutide] when compared with placebo/control.
- Canagliflozin, GLP-1 analogues, insulin glargine and TZDs all reduced HbA1c by ~11 mmol/mol (1%) [11–13 mmol/mol (0.98–1.2%)]; whereas acarbose, dapagliflozin, empagliflozin and DPP-4 inhibitors reduced HbA1c by 7–8 mmol/mol (0.60–0.76%) when compared with placebo/control.
- When comparing active drugs, liraglutide, insulin glargine and TZDs significantly reduced HbA1c compared with empagliflozin and DPP-4 inhibitors (with the exception of vildagliptin; Fig. S2).
- Among the SGLT2 inhibitors, canagliflozin was the only therapy for which statistically significant reductions in HbA1c were observed when compared with other active therapies, while dapagliflozin was inferior to liraglutide and rosiglitazone.

ACA	0.47 (-1.47, 2.41)	1.11 (-1.06, 3.28)	0.92 (-1.15, 2.99)	1.09 (-1.67, 3.85)	**-2.98 (-5.34, -0.62)**	-1.29 (-3.36, 0.78)	0.42 (-1.85, 2.69)	**-4.58 (-6.55, -2.62)**	-0.96 (-2.52, 0.6)	**-3.39 (-6.18, -0.59)**	-1.76 (-3.87, 0.35)	**-2.44 (-4.34, -0.55)**
-0.47 (-2.41, 1.47)	CANA	0.64 (-1.25, 2.53)	0.45 (-1.34, 2.24)	0.62 (-1.93, 3.17)	**-3.45 (-5.56, -1.34)**	-1.76 (-3.54, 0.02)	-0.05 (-2.06, 1.96)	**-5.06 (-6.54, -3.57)**	**-1.43 (-2.58, -0.28)**	**-3.86 (-6.45, -1.27)**	**-2.23 (-4.06, -0.4)**	**-2.91 (-4.06, -1.77)**
-1.11 (-3.28, 1.06)	-0.64 (-2.53, 1.25)	DAPA	-0.19 (-2.22, 1.84)	-0.02 (-2.75, 2.71)	**-4.09 (-6.41, -1.77)**	**-2.4 (-4.43, -0.37)**	-0.69 (-2.92, 1.54)	**-5.69 (-7.61, -3.78)**	**-2.07 (-3.57, -0.57)**	**-4.5 (-7.26, -1.74)**	**-2.87 (-4.93, -0.81)**	**-3.55 (-5.4, -1.71)**
-0.92 (-2.99, 1.15)	-0.45 (-2.24, 1.34)	0.19 (-1.84, 2.22)	EMPA	0.17 (-2.49, 2.83)	**-3.9 (-6.13, -1.67)**	**-2.21 (-4.14, -0.28)**	-0.5 (-2.64, 1.64)	**-5.5 (-7.32, -3.69)**	**-1.88 (-3.25, -0.51)**	**-4.31 (-7.0, -1.62)**	**-2.68 (-4.65, -0.71)**	**-3.36 (-5.1, -1.63)**
-1.09 (-3.85, 1.67)	-0.62 (-3.17, 1.93)	0.02 (-2.71, 2.75)	-0.17 (-2.83, 2.49)	EXEN	**-4.07 (-5.51, -2.63)**	-2.38 (-5.03, 0.27)	-0.67 (-2.87, 1.53)	**-5.67 (-8.25, -3.1)**	-2.05 (-4.33, 0.23)	**-4.48 (-6.56, -2.4)**	**-2.85 (-5.53, -0.17)**	**-3.53 (-6.05, -1.02)**
2.98 (0.62, 5.34)	**3.45 (1.34, 5.56)**	**4.09 (1.77, 6.41)**	**3.9 (1.67, 6.13)**	**4.07 (2.63, 5.51)**	GLAR	1.69 (-0.54, 3.92)	**3.4 (1.74, 5.06)**	-1.6 (-3.73, 0.52)	**2.02 (0.26, 3.78)**	-0.41 (-1.91, 1.09)	1.22 (-1.04, 3.48)	0.54 (-1.53, 2.6)
1.29 (-0.78, 3.36)	1.76 (-0.02, 3.54)	**2.4 (0.37, 4.43)**	**2.21 (0.28, 4.14)**	2.38 (-0.27, 5.03)	-1.69 (-3.92, 0.54)	LINA	1.71 (-0.43, 3.85)	**-3.29 (-5.1, -1.49)**	0.33 (-1.03, 1.69)	-2.1 (-4.79, 0.59)	-0.47 (-2.43, 1.49)	-1.15 (-2.89, 0.58)
-0.42 (-2.69, 1.85)	0.05 (-1.96, 2.06)	0.69 (-1.54, 2.92)	0.5 (-1.64, 2.64)	0.67 (-1.53, 2.87)	**-3.4 (-5.06, -1.74)**	-1.71 (-3.85, 0.43)	LIRA	**-5.0 (-7.04, -2.97)**	-1.38 (-3.03, 0.27)	**-3.81 (-6.05, -1.57)**	-2.18 (-4.36, 0)	**-2.86 (-4.83, -0.89)**
4.58 (2.62, 6.55)	**5.06 (3.57, 6.54)**	**5.69 (3.78, 7.61)**	**5.5 (3.69, 7.32)**	**5.67 (3.1, 8.25)**	1.6 (-0.52, 3.73)	**3.29 (1.49, 5.1)**	**5.0 (2.97, 7.04)**	PIO	**3.62 (2.43, 4.82)**	1.2 (-1.41, 3.8)	**2.82 (0.97, 4.68)**	**2.14 (0.92, 3.36)**
0.96 (-0.6, 2.52)	**1.43 (0.28, 2.58)**	**2.07 (0.57, 3.57)**	**1.88 (0.51, 3.25)**	2.05 (-0.23, 4.33)	**-2.02 (-3.78, -0.26)**	-0.33 (-1.69, 1.03)	1.38 (-0.27, 3.03)	**-3.62 (-4.82, -2.43)**	PLC	**-2.43 (-4.74, -0.11)**	-0.8 (-2.22, 0.62)	**-1.48 (-2.56, -0.41)**
3.39 (0.59, 6.18)	**3.86 (1.27, 6.45)**	**4.5 (1.74, 7.26)**	**4.31 (1.62, 7.0)**	**4.48 (2.4, 6.56)**	0.41 (-1.09, 1.91)	2.1 (-0.59, 4.79)	**3.81 (1.57, 6.05)**	-1.2 (-3.8, 1.41)	**2.43 (0.11, 4.74)**	ROSI	1.63 (-1.09, 4.34)	0.94 (-1.61, 3.5)
1.76 (-0.35, 3.87)	**2.23 (0.4, 4.06)**	**2.87 (0.81, 4.93)**	**2.68 (0.71, 4.65)**	**2.85 (0.17, 5.53)**	-1.22 (-3.48, 1.04)	0.47 (-1.49, 2.43)	2.18 (0, 4.36)	**-2.82 (-4.68, -0.97)**	0.8 (-0.62, 2.22)	-1.63 (-4.34, 1.09)	SAXA	-0.68 (-2.46, 1.09)
2.44 (0.55, 4.34)	**2.91 (1.77, 4.06)**	**3.55 (1.71, 5.4)**	**3.36 (1.63, 5.1)**	**3.53 (1.02, 6.05)**	-0.54 (-2.6, 1.53)	1.15 (-0.58, 2.89)	**2.86 (0.89, 4.83)**	**-2.14 (-3.36, -0.92)**	**1.48 (0.41, 2.56)**	-0.94 (-3.5, 1.61)	0.68 (-1.09, 2.46)	SITA

Supplemental Figure 3. Network Meta-Analysis Results of the Effect of Antihyperglycemic Agents on Change in Body Weight From Baseline
Therapies are reported in alphabetical order. Results are reported in WMD, kg (95% CI). Results for changes in weight on the top portion of the matrix represent changes in the row-defining treatment vs. those in the column-defining treatment (referent). For changes in weight, negative values favor the first agent in alphabetical order. Statistically significant results are bolded. The results on the upper portion of the matrix represent the reciprocal of the bottom portion.
ACA=acarbose; CANA=canagliflozin; DAPA=dapagliflozin; EMPA=empagliflozin; EXEN=exenatide; GLAR=glargine; LINA=linagliptin; LIRA=liraglutide; PIO=pioglitazone; PLC=placebo; ROSI=rosiglitazone; SAXA=saxagliptin; SITA=sitagliptin

Anmerkung/Fazit der Autoren

In our NMA of 20 RCTs conducted from the earliest date up to May 2014, we found all AHAs significantly reduced HbA1c as compared with placebo/control when added to metformin and SU therapy.

Kommentare zum Review

Many of AHAs were only compared in one or two trials and certain endpoints were sparsely reported (UTI and GTI), which makes it difficult to draw concrete conclusions (potential for type 2 error).

At the same time, we either directly and/or indirectly compared

13 AHAs plus placebo/control on six different endpoints; thus there is the possibility of erred conclusions of statistical differences between therapies (type 1 error) because of multiple hypothesis testing. Thirdly, most trials only followed patients for 24 weeks, which is not sufficient to assess the long-term urability of medications. Next, we saw little evidence of incoherence in our network (as evidenced by finding only two out of 36 possible direct vs. indirect evidence comparisons statistically significant). While, we cannot entirely exclude the presence of incoherence in our network, the two statistically significant findings stemming from 36 statistical tests are consistent with what would be expected due to chance (the probability of observing one significant result just due to chance in our analysis = 1- (1 - 0.05)3^6 or 84%).

- *Funding sources: This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc.*

- *Competing interests: C.I.C. has received grant funding from Boehringer Ingelheim Pharmaceuticals and Janssen Pharmaceuticals. The remaining authors have no competing interests to report.*

Mearns ES et al., 2015 [73].

Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis

Fragestellung

We performed a NMA (Network meta-analysis) to assess the comparative efficacy and safety of adjunctive antidiabetic medication therapies in patients with Type 2 DM not adequately controlled on stable and optimized metformin monotherapy.

Methodik

Population:

- adults (18 years) with Type 2 DM; only patients who showed inadequate response to stable, optimized metformin monotherapy at randomization

Intervention/Komparator:

- non-insulin and long-acting, once-daily basal insulin agents (as a single or combination adjunctive therapy) to another antidiabetic therapy or placebo (in addition to metformin)

Endpunkte:

- Change in HbA1c; Body Weight; Urinary (UTI) and Genital Tract Infection (GTI); Systolic Blood Pressure; Confirmed Hypoglycemia

Recherche/Suchzeitraum:

- Systematische Literaturrecherche bis Mai 2014; Datenbanken: MEDLINE and Cochrane CENTRAL

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 62 RCTs (n = 32,185 participants)

Charakteristika der Population:

Qualität der Studien:

- The overall quality of RCTs was rated as good to unclear with the majority of studies having few domains with a high risk of bias

Studienergebnisse:

Body Weight

- SGLT2 Inhibitors
  - All SGLT2 inhibitors were associated with significant weight loss when compared to placebo (range: 2.08–2.17 kg)
  - SGLT2 inhibitors were associated with statistically greater weight loss compared to allother agents analyzed except GLP-1 analogs, empagliflozin/ linagliptin and miglitol.
- Combination Agents
  - empagliflozin/linagliptin was associated with significant weight loss compared to all other agents except SGLT-2 inhibitors, and GLP-1 analogs.
  - In terms of clinically superior weight gain, (lower bound of the 95%CI depicted a decrease in weight less than 2.3 kg), alogliptin/pioglitazone was associated with clinically superior weight gain compared to SGLT2 inhibitors, empagliflozin/linagliptin, GLP-1 analogs, and miglitol (range: 3.54–4.65 kg).
- All Other Agents
  - GLP-1 analogs and miglitol were associated with significant weight loss (range: 1.15–2.26 kg) but there was no weight change with acarbose, any DPP-4 inhibitor, colesevelam and nateglinide when compared to placebo.
  - When comparing active agents, GLP-1 analogs were associated with statistically greater weight loss when compared to all other agents except SGLT2 inhibitors and miglitol. While several agents exhibited statistically significant weight loss, no agent demonstrated clinically superior weight loss compared to placebo (lower bound of the 95%CI depicted a decrease in weight less than 2.3 kg).
  - When comparing the clinical superiority of single active agents, TZDs were associated with clinically superior weight gain when compared to GLP-1A (range:3.22-4.41 kg)

Confirmed Hypoglycemia

- SGLT2 Inhibitors
  - Upon NMA, the SGLT2 inhibitors were not associated with an increased risk of confirmed hypoglycemia compared with placebo. In the active drug comparisons, insulin glargine, nateglinide and all SUs were associated with significantly higher rates of confirmed hypoglycemia compared to any SGLT2 inhibitor (RR range, 4.14–22.93).
- Combination Agents
  - Empagliflozin/linagliptin was not associated with increased risk of hypoglycemia compared with placebo in the NMA (0.38, 95% CI: 0.06–2.34). In the active drug comparisons, insulin glargine, nateglinide, both meglitinides and all SUs were associated with significantly higher rates of confirmed hypoglycemia compared to empagliflozin/linagliptin (RR range, 10.54–49.88). There were no data to evaluate alogliptin/pioglitazone for this endpoint.
- All Other Agents
  - All GLP-1 analogs, DPP-4 inhibitors, TZDs, repaglinide and acarbose were not associated with an increased risk of confirmed hypoglycemia compared with placebo.
  - In the active drug comparisons, insulin glargine and all SUs were associated with significantly higher rates of confirmed hypoglycemia compared to any SGLT2 or DPP-4 inhibitor (RR range, 4.32–71.29). There were no data to evaluate glibenclamide, colesevelam and miglitol for this endpoint.

Urinary and Genital Tract Infection

- NMA suggested canagliflozin and empagliflozin were associated with an increased risk of GTI when compared with placebo; with dapagliflozin (RR 2.16, 95% CI 0.97–4.82) trending towards an increased risk versus placebo. However, only 10 identified RCTs evaluating 8 of 25 agents reported GTI data

Anmerkung/Fazit der Autoren

- Our HbA1c results showed both statistical differences and clinical superiority between antidiabetic therapies.
- All therapies significantly reduced HbA1c, but to differing degrees when compared to placebo. Combination therapies (empagliflozin/linagliptin and alogliptin/pioglitazone) and insulin glargine were statistically and clinically superior in reducing HbA1c compared to a majority of other antidiabetic agents.
- As a class, the SGLT2 inhibitors were similar in efficacy to other non-insulin monotherapies recommended by the ADA as add-ons to metformin, which warrants an update to clinical practice guidelines to include them as a treatment option.
- The newest class of antidiabetic agents, the SGLT2 inhibitors, was found to provide similar HbA1c efficacy to other non-insulin monotherapies (albeit not oral combination therapies) with the added benefits of weight loss, reduced SBP and a low risk of hypoglycemia; but at a cost of an increased risk of GTI.
- Combination therapies resulted in some of the largest reductions in HbA1c and may be appropriate for patients requiring profound (>1%) HbA1c reductions after failing optimized metformin.

Kommentare zum Review

- *This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICJME) and were fully responsible for all content and editorial decisions, and were involved in all stages of manuscript development. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*
- *Competing Interests: CIC has received grant funding from Boehringer Ingelheim Pharmaceuticals and Janssen Pharmaceuticals. No other authors have any conflicts germane to this manuscript to report. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.*

Mishriky BM et al., 2015 [79].

The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with Type 2 diabetes: A systematic review and meta-analysis

Fragestellung

This meta-analysis was performed to determine the efficacy and safety of Dipeptidyl peptidase-4 inhibitors (DPP4-I) compared to sulfonylurea (SU) as add-on therapy to metformin in inadequately controlled T2D patients.

Methodik

Population:

- patients with T2D who were inadequately controlled on metformin monotherapy

Intervention:

- DPP4-I as add-on therapy to metformin

Komparator:

- SU as add-on therapy to metformin

Endpunkte:

- HbA1c, FPG, weight, hypoglycaemia, side effects

Recherche/Suchzeitraum:

- up to November 26th, 2014

Qualitätsbewertung der Studien:

- risk of bias tables suggested by the Cochrane Collaboration

Ergebnisse

Anzahl eingeschlossener Studien:

- 16 RCTs 15.176 patients (8.047 received DPP4-I and 7.129 SU)

Studienergebnisse:

- Change in body weight from baseline
  - from baseline to 12 weeks: eight studies, MD [95% CI] = -1.57 kg [-1.85,-1.28]; I2 = 74%
  - from baseline to 52 weeks: five studies, MD [95% CI] = -2.11 kg [-2.49, -1.72]; I2 = 82%
  - from baseline to 104 weeks: six studies, MD [95% CI] = -2.13 kg [-2.58, -1.68]; I2 = 82%
  - all studies independently reporting a significantly greater weight reduction with DPP4-I compared to weight gain with SU
  - pooled weight reduction at 12, 52, and 104 weeks of 0.8, 0.9, and 1.1 kg respectively in patients who received DPP4-I compared to a pooled mean weight gain of 0.8, 1.2, and 1.1 kg respectively in patients who received SU
- Proportion of patients with one or more episodes of hypoglycemia
  - incidence at 12 weeks: two studies, significantly greater with SU (20%) compared to DPP4-I (6%)
  - incidence at 52 weeks: three studies, significantly greater with SU (24%) compared to DPP4-I (3%)
  - incidence at 104 weeks: six studies, significantly greater with SU (27%) compared to DPP4-I (4%)
  - proportion of patients with HbA1c < 7%(53 mmol/mol) without hypoglycemia significantly higher at 52 and 104 weeks among patients on DPP4-I (RR[95% CI] = 1.20 [1.05, 1.37] and 1.53 [1.16, 2.02] respectively)
- Other side effects

- o no significant difference between the two groups

Anmerkung/Fazit der Autoren

While both SU and DPP4-I can be considered as options for add-on therapy to metformin in inadequately controlled T2D, SU results in a significantly increased risk of hypoglycemia and weight gain. By contrast, DPP4-I produce 0.4–0.6% (4–7 mmol/mol) reduction in HbA1c, lower risk of hypoglycemia, and weight loss.

Kommentare zum Review

BM and DC have no conflict of interest; RT is on the speakers' bureau for Boehringer Ingelheim.

Yang T et al., 2015 [96].

Titel des Reviews

Fragestellung

The aim of this study is to assess the efficacy and tolerability of canagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, added on to metformin in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- T2DM patients aged over 18 years who had inadequate glycemic control (HbA1c > 7.0 %) on metformin monotherapy or combined with another OAD with both agents at maximum or nearmaximum effective doses

Intervention:

- canagliflozin in combination with metformin

Komparator:

- placebo in combination with metformin

Endpunkte:

- changes in HbA1c, the number of patients who achieved HbA1c <7.0 %, changes in FPG, percent changes in body weight, changes in β cell function

Recherche/Suchzeitraum:

- up to April 2015

Qualitätsbewertung der Studien:

- method referred to the Cochrane Handbook

Ergebnisse

Anzahl eingeschlossener Studien:

- 6RCTs with n=3.658

Qualität der Studien:

- 3 studies with low risk of bias
- 3 RCTs with unclear selection bias, performance bias, detection bias
- low-level publication bias evident from the visual examination of the funnel plots

Studienergebnisse:

- body weight improvement
  - o Canagliflozin demonstrated significant superiority compared with placebo (−2.09 % [−2.43 %, −1.75 %], P < 0.00001 (100 mg/day); −2.66 % [−3.18 %, −2.14 %], P < 0.00001 (300 mg/day))
- Safety and tolerability

Table 2 Meta-analyses for safety outcomes

Adverse events (AEs)	Studies, N	Canagliflozin		Placebo		Effect estimate (95 % CI)	*P*	I^2 (%)
		Events	Total	Events	Total			
AEs	6	735	2039	337	838	1.00 [0.091, 1.10]	1.00	0
Serious AEs	6	58	2039	28	838	0.86 [0.54, 1.34]	0.50	0
Urinary tract infection	6	90	2039	39	838	0.98 [0.67, 1.42]	0.90	10
Genital mycotic infection/male	3	14	484	2	247	2.85 [0.74, 10.95]	0.13	0
Genital mycotic infection/female	3	40	465	8	228	2.54 [1.22, 5.29]	0.01	0
Pollakiuria	3	48	1090	3	363	5.59 [1.71, 18.29]	0.004	0
Hypoglycemia	4	69	1118	21	562	1.65 [1.02, 2.65]	0.04	0
Headache	4	51	1403	23	519	0.83 [0.52, 1.33]	0.45	41
Nasopharyngitis	4	61	1403	31	519	0.76 [0.50, 1.15]	0.19	38
Diarrhea	3	57	1275	24	454	0.85 [0.53, 1.34]	0.68	53

CI confidence intervals

Anmerkung/Fazit der Autoren

Canagliflozin is a potential option as an add-on to metformin based on its improvement in HbA1c, FPG, body weight, and β cell function, but further studies are demanded to strengthen this evidence. Common adverse events (AEs) like genital mycotic infection/female and pollakiuria were identified.

Zhong X et al., 2015 [104].

Effects of three injectable antidiabetic agents on glycaemic control, weight change and drop-out in type 2 diabetes suboptimally controlled with metformin and/or a sulfonylurea: A network meta-analysis

Fragestellung

The objective of this review was to assess glucagon-like peptide-1 receptor agonists (GLP-1 RAs), basal insulin, and premixed insulin among participants with type 2 diabetes inadequately controlled with metformin and/or a sulfonylurea.

Methodik

Population:

- adults aged ≥18 years with T2DM and a baseline HbA1c level >7.0% while receiving metformin and/or a sulfonylurea for at least 3 months before the screening visit

Intervention/Komparator:

- two or more of the three injectables (GLP-1 RAs, basal insulin, premixed insulin) and placebo

Endpunkte:

- mean change in HbA1c, body weight with standard; number of participants who achieved an HbA1c <7% at the endpoint, number of participants who dropped out from the study, reported number of severe hypoglycemic episodes, severe hypoglycemic events defined as those requiring third-party assistance or blood glucose levels ≤1.9 mmol/L (35 mg/dL)

Recherche/Suchzeitraum:

- up to June 2014

Qualitätsbewertung der Studien:

- according to PRISMA recommendations

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 distinct randomized controlled trials (5.874 adult individuals)

Qualität der Studien:

- 15 RCTs reported concealment of the randomization or the use of central randomization;
- no trial stopped early
- 7 RCTs used a double-blinded design and 8 RCTs used an open-label design
- no trial clearly specified whether data collectors and outcome assessors were blinded to the study data
- overall quality of included RCTs was good

Studienergebnisse:

- Changes in body weight
  - use of GLP-1 RAs resulted in significant body weight loss:
  - −3.73 kg, 95% CI, −4.52 to −2.95 kg vs. basal insulin and
  - -5.27 kg, 95% CI,-6.17 to -4.36kg vs. premixed insulin (higher drop-out rate of participants)
- Risk of severe hypoglycemia
  - no meta-analysis due to lack of event data
  - 3 premixed insulin arms (18 episodes among 975 participants) and
  - 3 basal insulin arms (10 episodes among 1 272 participants) were at higher risk of severe hypoglycaemia episodes when compared to the
  - 4 GLP-1 RAs arms (12 episodes among 2 527 participants) and

- 1 placebo arm (one episode among 1 100 participants).

Anmerkung/Fazit der Autoren

The three injectables had similar impact on glycemic control but other differentiating features relevant to the management of type 2 diabetes with GLP-1 RAs having the most favorable profile.

Kommentare zum Review

This study was funded by 2 National ‘‘Eleven Five’’ ‘‘Significant New Drugs Creation’’ Special Science and Technology Major a grant from the Leading Talents of Science in Shanghai 2010 (022), and the Key Discipline Construction of Evidence-based Public Health in Shanghai.

3.4 Leitlinien

Neue Leitlinien für das Update 2019

NICE, 2015/2019 [82].

National Institute for Health and Care Excellence

Type 2 diabetes in adults: management - Clinical Guideline Update

Leitlinienorganisation/Fragestellung

4.5.1 Pharmacological management of blood glucose levels

- Which pharmacological blood glucose-lowering therapies should be used as monotherapy to control blood glucose levels in people with type 2 diabetes?
- Which pharmacological blood glucose-lowering therapies should be used as part of dual therapy to control blood glucose levels in people with type 2 diabetes?
- Which pharmacological blood glucose-lowering therapies should be used as part of triple therapy to control blood glucose levels in people with type 2 diabetes?
- What are the long-term effects of pharmacological interventions to control blood glucose levels in people with type 2 diabetes, including adverse events and impact on development of microvascular and macrovascular complications?

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- searches undertaken between July 2012 and June 2013, re-run searches in June 2014

Sonstige methodische Hinweise

- Die Empfehlungen zur Therapie eines Diabetes Typ 2 wurden nicht aktualisiert und sind aus dem Jahr 2015:
  - „Update August 2019: The section on blood pressure therapy was updated and replaced by the NICE guideline on hypertension in adults."

Empfehlungen

Alglorithmus siehe Anhang

Initial drug treatment (2015)

- 1.6.19 Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. [new 2015]
- 1.6.20 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. [new 2015]
- 1.6.21 If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. [new 2015]
- 1.6.22 In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m2:

  Stop metformin if the eGFR is below 30 ml/minute/1.73m2.

  Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m2. [2015]
- 1.6.23 In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment [3] with:
  - a dipeptidyl peptidase-4 (DPP-4) inhibitor or
  - pioglitazone [4]or
  - a sulfonylurea. [new 2015]
- 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone [4] if they have any of the following:
  - heart failure or history of heart failure
  - hepatic impairment
  - diabetic ketoacidosis
  - current, or a history of, bladder cancer
  - uninvestigated macroscopic haematuria. [new 2015]

  Treatment with sodium–glucose cotransporter 2 (SGLT-2) inhibitors [5],[6] may be appropriate for some adults with type 2 diabetes if metformin is contraindicated or not tolerated (see NICE's guidance on canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes).

First intensification of drug treatment (2015)

- 1.6.25 In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with:
  - metformin and a DPP-4 inhibitor or
  - metformin and pioglitazone [4]or
  - metformin and a sulfonylurea. [new 2015]
- 1.6.26 In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy [7] with:

- a DPP-4 inhibitor and pioglitazone[4]or
- a DPP-4 inhibitor and a sulfonylurea or
- pioglitazone [4]and a sulfonylurea. [new 2015]

Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors [5],[6] may be appropriate for some people with type 2 diabetes; see the NICE guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes.

Second intensification of drug treatment (2015)

- 1.6.27 In adults with type 2 diabetes, if dual therapy with metformin and another oral drug (see recommendation 1.6.25) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either:
  - triple therapy with:
    - metformin, a DPP-4 inhibitor and a sulfonylurea or
    - metformin, pioglitazone[4]and a sulfonylurea or
    - starting insulin-based treatment (see recommendations 1.6.32–1.6.34). [new 2015]
- 1.6.28 If triple therapy with metformin and 2 other oral drugs (see recommendation 1.6.27) is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who:
  - have a 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/m2and:
  - for whom insulin therapy would have significant occupational implications or
  - weight loss would benefit other significant obesity-related comorbidities. [new 2015]
- 1.6.29 Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months). [2015]
- 1.6.30 In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with 2 oral drugs (see recommendation 1.6.26) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider insulin-based treatment (see recommendations 1.6.32–1.6.34). [new 2015]
- 1.6.31 In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team [8]. [new 2015]

  Treatment with combinations of medicines including SGLT-2 inhibitors [5],[6] may be appropriate for some people with type 2 diabetes; see the NICE guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in triple therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes.

Insulin-based treatments (2015)

- 1.6.32 When starting insulin therapy in adults with type 2 diabetes, use a structured programme employing 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 understanding
    - DVLA guidance (At a glance guide to the current medical standards of fitness to drive)
    - management of hypoglycaemia
    - management of acute changes in plasma glucose control
    - support from an appropriately trained and experienced healthcare professional. [2015]
- 1.6.33 When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies [9]. [new 2015]
- 1.6.34 Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens:
    - Offer 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[10] if:
    - the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine[10] 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:
        - a person prefers injecting insulin immediately before a meal or
        - hypoglycaemia is a problem or
        - blood glucose levels rise markedly after meals. [2015]
- 1.6.35 Consider switching to insulin detemir or insulin glargine [10] 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 who 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]
- 1.6.36 Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine [10]) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). [2015]
- 1.6.37 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[10], if blood glucose control remains inadequate. [2015]

  Treatment with combinations of medicines including SGLT-2 inhibitors[5],[6] may be appropriate for some people with type 2 diabetes; see the NICE guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes.

Cosentino F et al., 2019 [16].

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.

Leitlinienorganisation/Fragestellung

The emphasis in these Guidelines is to provide information on the current state of the art in how to prevent and manage the effects of DM on the heart and vasculature.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Gegenüber älteren Leitlinien in der Evidenzsynopse (z.B. SIGN 2017, CADTH 2018), weist die ESC-Leitlinie folgende methodische Limitation auf: Es wird nur im allgemeinem Methodikhandbuch auf eine systematische Literaturrecherche verwiesen, konkrete Angaben zu Datenbanken, Suchzeitraum und Suchstrategie fehlen jedoch. Die Beurteilung des „Level of Evidence" bezieht sich nur auf die Anzahl an RCTs bzw. systematischen Reviews. Eine Qualitätsbeurteilung der Studien konnte nicht identifiziert werden.

Die ESC-LL ist eine Leitlinie aus dem Jahr 2019, die vor dem Hintergrund einer aktuell in Überarbeitung befindlichen deutschen NVL-Leitlinie, dem aktuellen europäischen Versorgungskontext entspricht. Trotz der genannten methodischen Einschränkungen hat die Leitlinie auf Grund der Aktualität für den europäischen Versorgungskontext einen gesonderten Stellenwert und wird daher ergänzend dargestellt.

<u>Grundlage der Leitlinie</u>

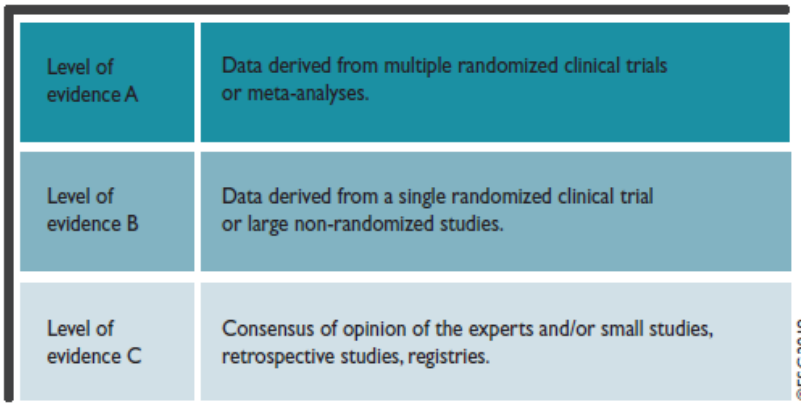
- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz für die Leitlinie nicht explizit dargelegt

- Formale Konsensusprozesse und externes Begutachtungsverfahren für die Leitlinie nicht explizit dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

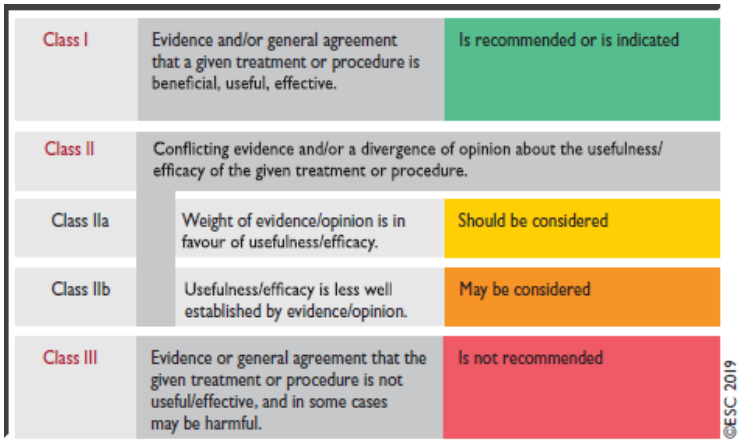
Recherche/Suchzeitraum:

- Keine Angaben

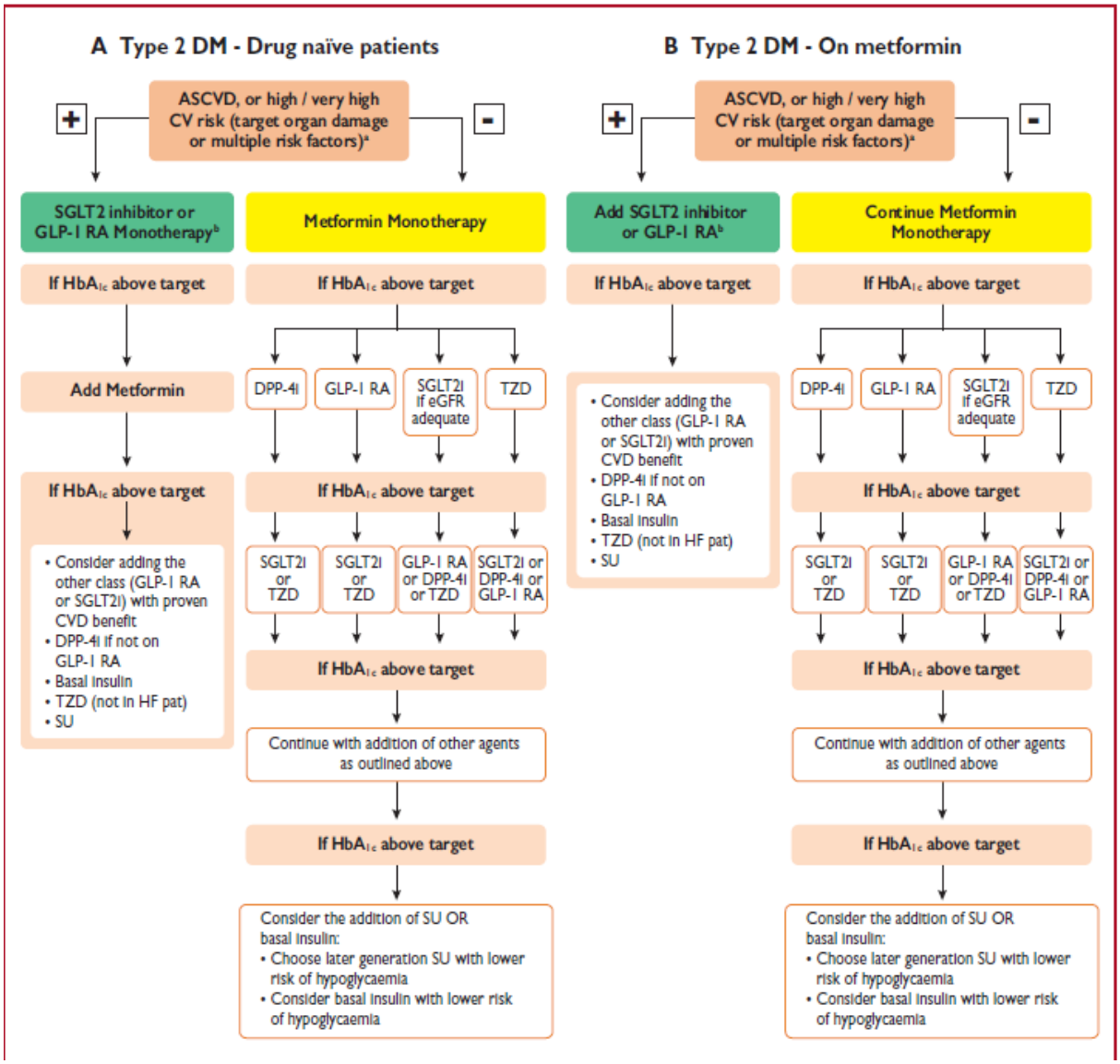
LoE



GoR



Empfehlungen



Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

ACS = acute coronary syndromes; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase-4; GLP1-RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

See Table 7

For the first time in the history of DM, we have data from several CVOTs that indicate CV benefits from the use of glucose-lowering drugs in patients with CVD or at very high/high CV risk. The results obtained from these trials, using both GLP1-RAs (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER 6) and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARETIMI 58, and CREDENCE), strongly suggest that these drugs should be recommended in patients with T2DM with prevalent CVD or very high/high CV risk, such as those with target-organ damage or several CVRFs, whether they are treatment naı¨ve or already on metformin.

In addition, based on the mortality benefits seen in LEADER and EMPA-REG OUTCOME, liraglutide is recommended in patients with prevalent CVD or very high/high CV risk, and empagliflozin is recommended in patients with prevalent CVD, to reduce the risk of death. The recommendation for empagliflozin is supported by a recent meta-analysis which found high heterogeneity between CVOTs in mortality reduction.312

The benefits seen with GLP1-RAs are most likely derived through the reduction of arteriosclerosis-related events, whereas SGLT2 inhibitors seem to reduce HF-related endpoints.

Thus, SGLT2 inhibitors are potentially of particular benefit in patients who exhibit a high risk for HF. In subjects with newly diagnosed T2DM without CVD and at moderate risk, the results of UKPDS suggest a beneficial effect of metformin in primary prevention.

Although the trial-based evidence for metformin monotherapy from UKPDS is not as strong as with the novel drugs tested in recent CVOTs, it is supported by extensive observations from everyday clinical practice. In the recent CVOTs, a majority of patients received metformin before and concurrently with the newer drug under test. However, because metformin was similarly present in the active and placebo groups, it is unlikely to explain the beneficial effects of the newer drugs under test. Thus, the choice of drug to reduce CV events in patients with T2DM should be prioritized based on the presence of CVD and CV risk

World Health Organization (WHO), 2018 [94].

Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus

Leitlinienorganisation/Fragestellung

- To consider the use of DPP-4 inhibitors, SGLT-2 inhibitors, and TZDs as second- and third-line treatment after metformin and sulfonylurea for controlling hyperglycaemia in type 2 diabetes in non-pregnant adults, including whether these oral agents are preferable to insulin.
- To provide guidance regarding the use of insulin analogues for type 1 and type 2 diabetes.
- The scope has been limited to agents for glycaemic control because that field is a dynamic one and has seen more change in evidence and practice in recent years than have other aspects of diabetes management
- Evidence-based protocols for managing diabetes in primary health care, including managing CVD risk and screening for complications, are available in the WHO PEN 2013 and are not repeated in this guideline.

Methodik

Grundlage der Leitlinie

- Update of the WHO PEN recommendations on the choice of second- and third-line treatment for type 2 diabetes based
- WHO established three groups: WHO Guideline Steering Group, Guidelines Development Group and external Peer Review Group
- developed in accordance with the WHO Handbook for Guideline Development. In brief, the WHO Steering Group, in collaboration with the Guideline Development Group developed key questions and rated outcomes to identify those critical for the guideline development
- SR of the evidence were used to build Summary of Findings tables according GRADE
- Outcome rating for recommendations: development of outcome lists, then rating oft he Guideline Group if ist critical (rated 7-9), important (rated 4-6) or not important (rated 1-3)
- SR identified in Literatur search assessment with AMSTAR
- Deciding upon recommendations at Guideline Group met in Geneva in March 2017 on basis of evidence-to-decision tables incorporating Systematic reviews and GRADE tables

Recherche/Suchzeitraum:

- In Pubmed from 2006.
- Es existiert nur ein Datum für den Beginn des Suchzeitraums. Das Ende ist ausschließlich mit „current“ angegeben. Aus den eingeschlossenen Dokumenten kann auf das Jahr 2016 geschlossen werden.

LoE

The following levels of assessment of the evidence were used in the GRADE profiles:

Evidence level	Rationale
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate ⊕⊕⊕O	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low ⊕⊕OO	Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate.
Very low ⊕OOO	Any estimate of effect is very uncertain.

GoR

The recommendations in these guidelines were graded into two categories:

- **A strong recommendation** is one for which the Guideline Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.
- **A weak** or **conditional recommendation** is one for which the Guideline Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects, but the Guideline Group was not confident about these trade-offs.

Empfehlungen:

Hypoglycaemic agents for second-line treatment in type 2 diabetes

- Give a sulfonylurea to patients with type 2 diabetes who do not achieve glycaemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence)
- Remarks: Glibenclamide should be avoided in patients aged 60 years and older. Sulfonylureas with a better safety record for hypoglycaemia (e.g. gliclazide) are preferred in patients for whom hypoglycaemia is a concern (people who are at risk of falls, people who have impaired awareness of hypoglycaemia, people who live alone, people who drive or operate machinery as part of their job).
- The WHO PEN protocol recommends a target fasting blood glucose of <7 mmol/L (126 mg/dl). However, an individualized approach is encouraged in setting the patient's target level for glycaemic control, taking into account their comorbidities, risks from medication side-effects and their likely benefit from tight glycaemic control in view of life expectancy.

The evidence summary for second-line treatment intensification (adding medicines to metformin) was obtained from the systematic review and network meta-analysis carried out by the Methods and Applications Group for Indirect Treatment Comparisons (MAGIC) for the Canadian Agency for Drugs and Technologies in Health (CADTH) (6). The systematic review included 166 Randomized Controlled Trials (RCTs) that reported at least one of the outcomes of interest. The network meta-analysis included sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, TZDs and basal insulins, as well as bolus insulins, biphasic insulins, meglitinides, alpha-glucosidase inhibitors, and glucagon-like peptide-1 (GLP-1) agonists (which were not of interest to the guidelines).

All evaluated hypoglycaemic agents added to metformin performed similarly in lowering HbA1c compared to placebo. DPP-4 inhibitors performed less well compared to sulfonylurea (mean difference 0.12%, 95% CI: 0.01, 0.24) and TZD (mean difference 0.19%, 95% CI: 0.05, 0.33). There was lower risk of severe hypoglycaemia with DPP-4 inhibitors (OR 0.14, 95% CI: 0.07, 0.26) and SGLT-2 inhibitors (OR 0.09, 95% CI: 0.02, 0.44) compared to sulfonylurea. DPP-4 inhibitors and SGLT-2

inhibitors were associated with weight loss, while TZDs and basal insulin were associated with weight gain. Evidence on quality of life and microvascular complications was not available. There were no significant differences for CVD incidence (myocardial infarction (MI) or stroke) or CVD mortality, but the network meta-analysis (NMA) model was not robust (very few events and a large number of trials with no events). In a separate analysis of patients at high risk of CVD, there was no significant difference in CVD mortality.

Hypoglycaemic agents for third-line treatment in type 2 diabetes

- Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence)
- If insulin is unsuitable, a DPP-4 inhibitor, SGLT-2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence)

  Remark: Insulin treatment could be unsuitable when circumstances make its use difficult (e.g. persons who live alone and are dependent on others to inject them with insulin).

  The evidence summary for third line treatment (medicines added to metformin and sulfonylurea) was obtained from a systematic review and network meta-analysis that was published in 2016 (12). Five trials evaluated triple therapy. The network meta-analysis included DPP-4 inhibitors, SGLT-2 inhibitors, TZDs, basal insulin (medicines of interest to this guideline) as well as meglitinides, alpha-glucosidase inhibitors, GLP-1 agonists, and basal-bolus insulin (medicines not of interest for these guidelines).

  All drug classes lowered HbA1c to a similar extent. TZDs (mean difference: -0.86%, 95% CI: -0.25, -1.48) and basal insulin (mean difference: -0.86%, 95% CI: -0.18, -1.55) were the only two medicines that performed significantly better than placebo in lowering HbA1c. DPP-4 inhibitors (mean difference: -0.23kg, 95% CI: -0.46, 0.00) and SGLT-2 inhibitors (mean difference: -0.33kg, 95% CI: -0.59, -0.07) were associated with a lower body weight compared to TZDs. There were very few events of CVD mortality and no significant differences between treatments. Insufficient observations were available to generate evidence networks for CVD incidence. There were no data for the critical outcomes severe hypoglycaemia and quality of life.

Insulin

- Use human insulin to control blood glucose levels in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence)

  Remark: Recommendation 4 covers both short-acting (regular human insulin – RHI) and intermediate-acting human insulin (NPH insulin). The recommendation is strong because evidence of better effectiveness of insulin analogues is lacking and human insulin has a better resource-use profile.
- Consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycaemia)

  Remark: Recommendation 5 is a weak recommendation reflecting the lack of, or very low-quality, evidence for any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin.

  Summary of the evidence:

  […] The third systematic review evaluated long-acting insulin analogues versus NPH insulin for type 2 diabetes (42)

6. New drugs for type 2 diabetes: second-line therapy – science report. CADTH Therapeutic Review. 2017;4:1b (https://cadth.ca/sites/default/files/pdf/TR0012_T2D_Science_Report.pdf, accessed 5 December 2017).
11. Tricco C, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. British Medical Journal. 2014;349:g5459.
12. Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with Type 2 Diabetes. A meta-analysis. JAMA. 2016;316(3):313–324.
13. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. Cochrane Database of Systematic Reviews. 2016;(6):CD012161.

42. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews. 2007;(2):CD005613.

Diabetes Canada, 2018 [19].

2018 Full guidelines.

Leitlinienorganisation/Fragestellung

The Diabetes Canada Clinical Practice Guidelines are intended to guide practice; inform general patterns of care; enhance diabetes prevention efforts in Canada; and reduce the burden of diabetes complications.

- Pharmacologic Glycemic Management of Type 2 Diabetes in Adults

Methodik

Grundlage der Leitlinie

- Update of the 2013 Clinical Practice Guidelines
- Expert Committee members evaluated the relevant literature. The studies used to develop and support each recommendation are cited beside the level of evidence.
- Executive Committee, Steering Committee and Expert Committee
- Each recommendation was reviewed by an Independent Methods Review member and had to be approved by the Steering Committee and Executive Committee, with 100% consensus.
- Only medications with Health Canada Notice of Compliance granted by September 15, 2017 were included in the recommendations
- After formulating new recommendations or modifying existing ones based on new evidence, each recommendation was assigned a grade from A through D
- Independent Methodological Review and External Peer Review

Recherche/Suchzeitraum:

- Literatur searches included literature published in September 2013 or later. For new topics, the search time frame included the literature published since 1990 or earlier where relevant.
- Es wird kein finales Datum der Suche genannt

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

Treatment of Newly Diagnosed People with Type 2 Diabetes

- 1. Healthy behaviour interventions should be initiated at diagnosis [Grade B, Level 2 (2)]. Metformin may be used at the time of diagnosis, in conjunction with healthy behaviour interventions [Grade D, Consensus].

2. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489– 96.

- 2. If glycemic targets are not achieved using healthy behaviour interventions alone within 3 months, antihyperglycemic therapy should be added to reduce the risk of microvascular complications [Grade A, Level 1A (3)]. Metformin should be chosen over other agents due to its low risk of hypoglycemia and weight gain [Grade A, Level 1A (19)], and long-term experience [Grade D, Consensus].

3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–53.
19. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2016;164:740–51.

- 3. If A1C values are ≥1.5% above target at diagnosis, initiating metformin in combination with a second antihyperglycemic agent should be considered to increase the likelihood of reaching target [Grade B, Level 2 (7–9)].

7. Phung OJ, Sobieraj DM, Engel SS, et al. Early combination therapy for the treatment of type 2 diabetes mellitus: Systematic review and meta-analysis. Diabetes Obes Metab 2014;16:410–17.
8. Rosenstock J, Chuck L, Gonzalez-Ortiz M, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drugnaive type 2 diabetes. Diabetes Care 2016;39:353–62.
9. Gao W, Dong J, Liu J, et al. Efficacy and safety of initial combination of DPP-IV inhibitors and metformin versus metformin monotherapy in type 2 diabetes: A systematic review of randomized controlled trials. Diabetes Obes Metab 2014;16:179-85.

- 4. Individuals with metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss) should receive insulin with or without metformin to correct the relative insulin deficiency [Grade D, Consensus].

Treatment Advancement in People with T2DM in Whom Glycemic Targets are Not Achieved with Existing Antihyperglycemic Medication

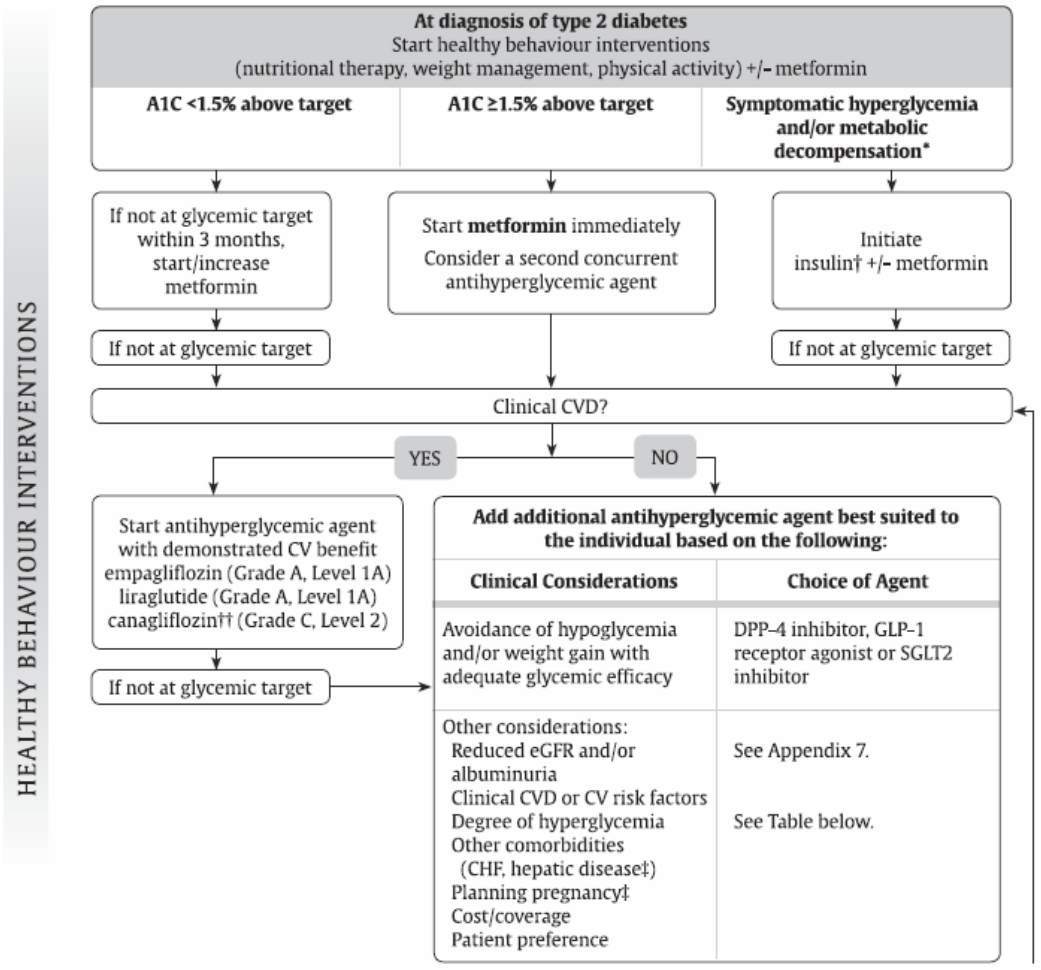
- 5. Dose adjustments to and/or addition of antihyperglycemic medications should be made in order to attain target A1C within 3 to 6 months [Grade D, Consensus].
- 6. If glycemic targets are not achieved with existing antihyperglycemic medication(s), other classes of agents should be added to improve glycemic control. The choice should be individualized taking into account the information in Figure 1 [Grade B, Level 2 (19)].

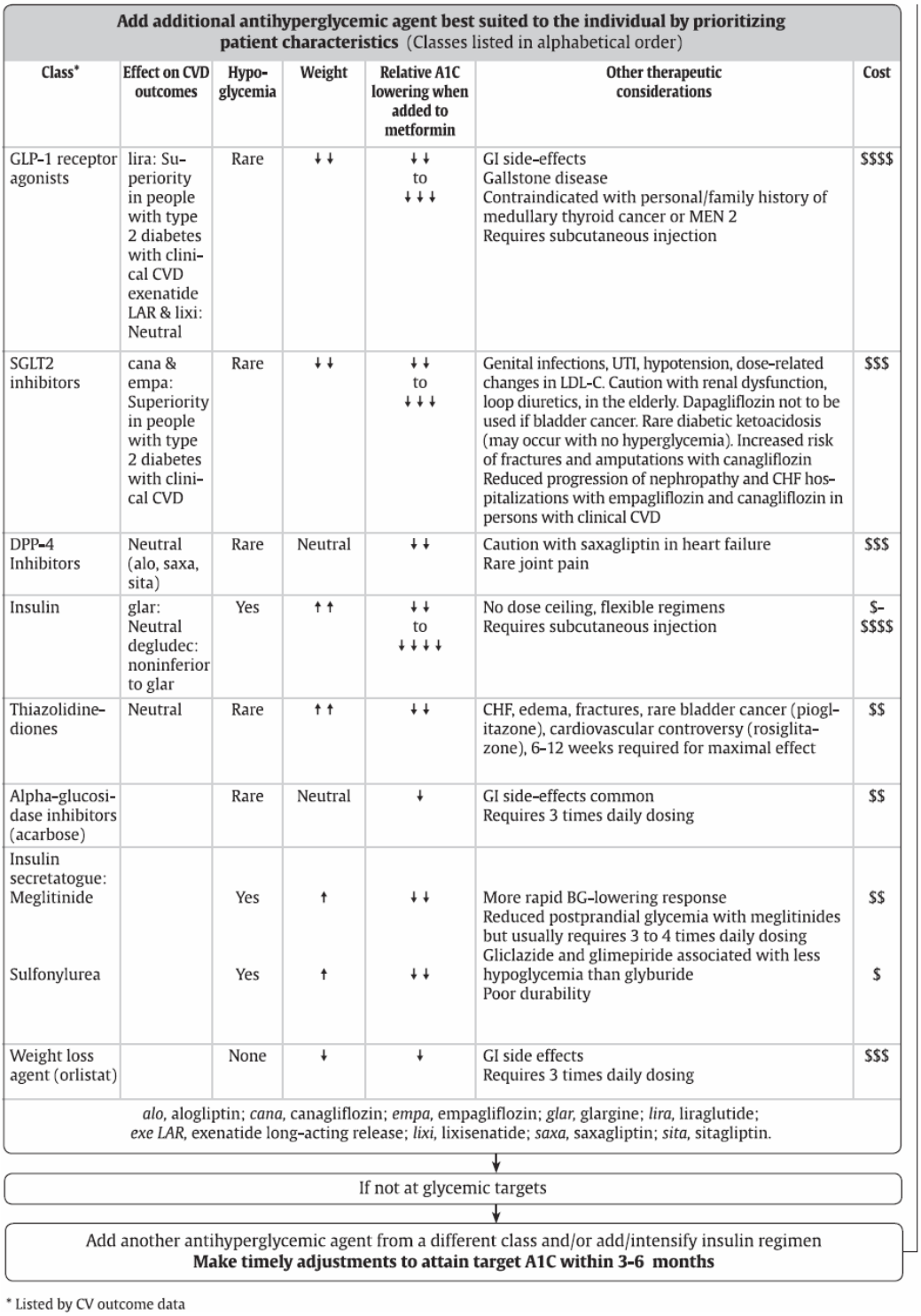
19. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2016;164:740–51

- 7. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR > 30 mL/min/1.73m^2, an anti-hyperglycemic agent with demonstrated CV outcome benefit should be added to reduce risk of:
    - a. Major CV events [Grade A, Level 1A (53) for empagliflozin; Grade A, Level 1A (55) for liraglutide; Grade C, Level 2 (54) for canagliflozin]
    - b. Heart failure hospitalization [Grade B, Level 2 (53) for empagliflozin; Grade C, Level 2 (54) for canagliflozin]
    - c. Progression of nephropathy [Grade B, Level 2 (141) for empagliflozin; Grade C, Level 3 (54) for canagliflozin].

53. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
54. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;
55. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.
56. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.
114. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes. The SWITCH 2 Randomized Clinical Trial. JAMA 2017;318(1):45–56.

Figure 1: Management of hyperglycemia in type 2 diabetes.





Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (Classes listed in alphabetical order)

Class*	Effect on CVD outcomes	Hypo-glycemia	Weight	Relative A1C lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1 receptor agonists	lira: Superiority in people with type 2 diabetes with clinical CVD exenatide LAR & lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects Gallstone disease Contraindicated with personal/family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	cana & empa: Superiority in people with type 2 diabetes with clinical CVD	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures and amputations with canagliflozin Reduced progression of nephropathy and CHF hospitalizations with empagliflozin and canagliflozin in persons with clinical CVD	$$$
DPP-4 Inhibitors	Neutral (alo, saxa, sita)	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑↑	↓↓ to ↓↓↓↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$-$$$$
Thiazolidinediones	Neutral	Rare	↑↑	↓↓	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Alpha-glucosidase inhibitors (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretatogue: Meglitinide		Yes	↑	↓↓	More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing	$$
Sulfonylurea		Yes	↑	↓↓	Gliclazide and glimepiride associated with less hypoglycemia than glyburide Poor durability	$
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

alo, alogliptin; *cana*, canagliflozin; *empa*, empagliflozin; *glar*, glargine; *lira*, liraglutide; *exe LAR*, exenatide long-acting release; *lixi*, lixisenatide; *saxa*, saxagliptin; *sita*, sitagliptin.

* Listed by CV outcome data

- 8. In adults with type 2 diabetes without clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s), incretin agents (DPP-4 inhibitors or GLP-1 receptor agonists) and/or SGLT2 inhibitors should be considered as add-on medication over insulin secretagogues, insulin and TZDs to improve glycemic control if lower risk of hypoglycemia and/or weight gain are priorities [Grade A, Level 1A (19,23,26,62,63,74)].

19. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2016;164:740–51.

23. Liu SC, Tu YK, Chien MN, et al. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: A network meta-analysis. Diabetes Obes Metab 2012;14:810– 20.
26. Zhou JB, Bai L, Wang Y, et al. The benefits and risks of DPP4-inhibitors vs. sulfonylureas for patients with type 2 diabetes: Accumulated evidence from randomised controlled trial. Int J Clin Pract 2016;70:132–41.
62. Mishriky BM, Cummings DM, Tanenberg RJ. The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy tometformin in patients with Type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2015;109:378–88.
63. Foroutan N, Muratov S, Levine M. Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs sulfonylurea in metformin-based combination therapy for type 2 diabetes mellitus systematic review and meta-analysis. ClinInvestMed2016;39:E48-62

74. McIntosh B, Cameron C, Singh SR, et al. Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: A systematic review and mixed-treatment comparison meta-analysis. Open Med 2012;6:e62–74.

- 9. For adults with type 2 diabetes with metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss), insulin should be used [Grade D, Consensus].
- 10. Insulin may be used at any time in the course of type 2 diabetes [Grade D, Consensus]. In people not achieving glycemic targets on existing noninsulin antihyperglycemic medication(s), the addition of a once-daily basal insulin regimen should be considered over premixed insulin or bolus only regimens, if lower risk of hypoglycemia and/or weight gain are priorities [Grade B, Level 2 (101)].

101. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009;361:1736–47

- 12. In adults with type 2 diabetes receiving insulin, doses should be adjusted and/or additional antihyperglycemic medication(s) (noninsulin and/or bolus insulin) should be added if glycemic targets are not achieved [Grade D, Consensus].
    - a. A GLP-1 receptor agonist should be considered as add-on therapy [Grade A, Level 1A (87,97)], before initiating bolus insulin or intensifying insulin to improve glycemic control with weight loss and a lower hypoglycemia risk compared to single or multiple bolus insulin injections [Grade A, Level 1A (25,98,99)].
    - b. An SGLT2 inhibitor should be considered as add-on therapy to improve glycemic control with weight loss and lower hypoglycemic risk compared to additional insulin [Grade A, Level 1A (27,93,94)].
    - c. A DPP-4 inhibitor may be considered as add-on therapy to improve glycemic control without weight gain or increased hypoglycemia risk compared to additional insulin [Grade B, Level 2 (27,91)].

25. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes Obes Metab 2014;16:636– 44.
27. Min SH, Yoon JH, Hahn S, et al. Comparison between SGLT2 inhibitors and DPP4 inhibitors added to insulin therapy in type 2 diabetes: A systematic review with indirect comparison meta-analysis. Diabetes Metab Res Rev 2016;33:
87. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: A randomized, controlled trial. Ann Intern Med 2011;154:103–12.
91. Zinman B, Ahren B, Neubacher D, et al. Efficacy and cardiovascular safety of linagliptin as an add-on to insulin in type 2 diabetes: A pooled comprehensive post hoc analysis. Can J Diabetes 2016;40:50–7.
93. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014;37:1815–23.
94. Wilding JP, Woo V, Rohwedder K, et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: Efficacy and safety over 2 years. Diabetes Obes Metab 2014;16:124–36.
97. Ahmann A, Rodbard HW, Rosenstock J, et al. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: A randomized, placebo-controlled trial. Diabetes Obes Metab 2015;17:1056–64.
98. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin glargine therapy: Testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 Trial. Diabetes Care 2016;39:1318–28.
99. Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: A systematic review and meta-analysis. Lancet 2014;384:2228– 34.

Scottish Intercollegiate Guidelines Network (SIGN), 2017 [85].

Pharmacological management of glycaemic control in people with type 2 diabetes

Leitlinienorganisation/Fragestellung

In adults with type 2 diabetes what is the evidence that

- metformin or sulphonylureas,
- alpha-glucosidase inhibitors or thiazolidinediones,
- DPP-4 inhibitors or GLP-1 receptor agonists,
- SGLT2 inhibitors or
- insulin

affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?

Methodik

Grundlage der Leitlinie

- rapid systematic literature review based on a series of structured key questions
- AHRQ reviews plus NICE guidelines plus systematic review of primary literature
- SIGN methodological checklists used for critical appraisal, specialist review, public consultation
- members declare all financial interests, whether direct or indirect

Recherche/Suchzeitraum:

- 2011-2016

LoE/GoR

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
RECOMMENDATIONS	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.	
R	For **'strong'** recommendations on interventions that **'should'** be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For **'strong'** recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.
R	For **'conditional'** recommendations on interventions that should be **'considered'**, the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
GOOD-PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group.

Sonstige methodische Hinweise

- no process of consensus described

4 Metformin

- R: Metformin should be considered as the first-line oral treatment option for people with type 2 diabetes. (GoR conditional)

5 Sulphonylureas

- R: Sulphonylureas should be considered as first-line oral agents in people who are intolerant of, or have contraindications to metformin. (GoR conditional)
- R: Sulphonylureas should be considered as add-on second-line treatment to other oral therapies and may be useful in triple oral therapy. (GoR conditional)
- Sulphonylurea therapy is associated with hypoglycaemia (caution should be taken in the elderly) and weight gain.

6 Thiazolidinediones

6.1 PIOGLITAZONE

- R: Pioglitazone should be considered, usually as dual or triple therapy, for lowering HbA1c. (GoR conditional)
- R: Pioglitazone should not be used in patients with heart failure. (GoR strong)
- R: The risk of fracture should be considered during long-term use of pioglitazone. (GoR conditional)
- Patients prescribed pioglitazone should be made aware of the increased risk of peripheral oedema, heart failure, weight gain, bladder cancer and fractures.

6.2 ROSIGLITAZONE

In September 2010 the European Medicines Agency (EMA) completed a review of rosiglitazone containing medicines at the request of the European Commission, following reports of an increase in the risk of cardiovascular problems with rosiglitazone. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of rosiglitazone did not outweigh its risks, and that the marketing authorisation for all rosiglitazone-containing medicines should be suspended across the European Union (EU). The marketing authorisation for Avandia (rosiglitazone) in the EU was suspended on 11 July 2015 when the holder of the MA decided not to apply for a renewal. Further information can be found on the EMA website (www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2016/06/WC500208350.pdf).

In February 2011 the U.S. Food and Drug Administration (FDA) notified the public that information on the cardiovascular risks of rosiglitazone has been added to the physician labelling and patient Medication Guide. Following re-evaluation of contemporary evidence on the cardiovascular safety of rosiglitazone, restrictions on its use were reduced in 2013 and, ultimately, removed in 2015. From December 2015, distribution of rosiglitazone-containing medicines is no longer restricted in the USA. Further details are available on the FDA website (www.fda.gov/Drugs/DrugSafety/ucm376389.htm).

7 Dipeptidyl peptidase-4 inhibitors

- R: DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c. (GoR conditional)

8 Sodium glucose co-transporter 2 inhibitors

- R: SGLT2 inhibitors should be considered as an add-on therapy to metformin in people with type 2 diabetes. (GoR conditional)
- R: In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit (currently empagliflozin and canagliflozin) should be considered. (GoR conditional)

9 Glucagon-like peptide-1 receptor agonists

- R: GLP-1 receptor agonist therapy should be considered in people with a body mass index of ≥30 kg/m2 (or ethnicity-adjusted equivalent) in combination with oral glucose-lowering drugs or basal insulin (or both) as third- or fourth-line treatment, when adequate glycaemic control has not been achieved with these drugs.

- R: GLP-1 receptor agonist therapy should be considered as an alternative to insulin in people for whom treatment with combinations of oral glucose-lowering drugs has been inadequate. (GoR conditional)
- R: For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide) should be considered. (GoR conditional)

10 Insulin

10.1 CONTINUING ORAL AGENTS WHEN INITIATING BASAL INSULIN

- R: Oral metformin therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control. (GoR strong)

  Consider stopping or reducing sulphonylurea therapy when insulin therapy is initiated. The benefits and risks of continuing other glucose-lowering agents should also be reviewed at this time on an individualised basis.

10.2 CHOOSING BASAL INSULIN

- R: Once-daily bedtime NPH insulin should be used when adding insulin to metformin. (GoR strong) Basal insulin analogues should be considered according to hypoglycaemia risk, for example in those who suffer from recurrent episodes of hypoglycaemia or require assistance with insulin injections. (GoR conditional)

  Careful clinical judgement must be applied to ensure insulin therapy is not delayed inappropriately.

10.3 INSULIN INITIATION AND INTENSIFICATION

- R: When commencing insulin therapy, bedtime basal insulin should be initiated and the dose titrated against morning (fasting) glucose. (GoR strong) If the HbA1c level does not reach target then addition of prandial insulin should be considered. (GoR conditional)

  10.3.1 INTENSIFYING WITH PREMIXED PREPARATIONS

  Aim to optimise insulin dose and regimen to achieve target glycaemia while minimising the risk of hypoglycaemia and weight gain.

  10.3.2 INTENSIFYING WITH RAPID-ACTING INSULIN ANALOGUES VERSUS HUMAN INSULIN
- R: Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycaemic control. (GoR conditional)

Qaseem A et al., 2017 [83].

Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians

Leitlinienorganisation/Fragestellung

The purpose of this ACP guideline is to present the updated evidence regarding the oral pharmacologic treatment of (all adults with) type 2 diabetes; it replaces the 2012 ACP guideline on the same topic.

Methodik

Grundlage der Leitlinie

- Systematic AHRQ literature review (5) based on a series of key questions, systematic review of primary literature
- Jadad and Downs and Black methodological checklists used for critical appraisal
- Meta-analysis conducted if feasible, peer review, public consultation, all financial interests of the members discussed and managed

5. Bolen S, et al. Diabetes Medications for Adults with Type 2 Diabetes: An Update. Comparative Effectiveness Review no. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under contract no. 290-2012-00007-I.) Rockville: Agency for Healthcare Research and Quality; 2016.

Recherche/Suchzeitraum:

- April 2009 through March 2015 and updated through December 2015

LoE/GoR

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

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

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

Sonstige methodische Hinweise

- no process of consensus described

Recommendation 1:

ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)

Recommendation 2:

ACP recommends that clinicians consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.

Table 1 contain further details about the comparative effectiveness and safety evidence.

Appendix Table 1. Summary of Clinical Outcomes for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention*, by Outcome	Strength of Evidence	Studies, n	Summary†
All-cause mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	5	Neither treatment favored for short-term mortality
Metformin vs. rosiglitazone	Low	4	Metformin favored
Metformin vs. SU (shorter-duration studies)	Low	4	Neither favored for short-term mortality
Metformin vs. SU (longer-duration studies)	Low	9	Metformin favored for long-term mortality
Metformin vs. DPP-4 inhibitors	Low	6	Neither treatment favored for short-term mortality
Metformin vs. SGLT-2 inhibitors	Low	4	Neither treatment favored
Pioglitazone vs. DPP-4 inhibitors	Low	2	Neither treatment favored
SU vs. DPP-4 inhibitors	Low	1	DPP-4 inhibitors favored for short-term mortality
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	6	Metformin monotherapy favored; OR, 2.51 (95% CI, 0.66–9.52) ‡
Metformin vs. metformin + SU	Low	5	Neither treatment favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitors (<2 y)	Low	14	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (shorter duration)	Low	6	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (long-duration studies)	Low	2	Neither treatment favored
Combination vs. combination			
Metformin + rosiglitazone vs. metformin + SU	Low	3	Neither treatment favored for short-term mortality
Metformin + SU vs. metformin + DPP-4 inhibitors (longer duration)	Low	6	Metformin + DPP-4 inhibitors favored for long-term mortality; OR, 0.64 (CI, 0.27–1.52) ‡
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	Low	3	Neither treatment favored for long-term mortality
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Low	2	Neither favored for short-term mortality
Cardiovascular mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	2	Neither treatment favored
Metformin vs. rosiglitazone	Low	1	Neither treatment favored
Metformin vs. SU (longer-duration studies)	Moderate§	5	Metformin favored; range in RR from RCTs, 0.6–0.7; adjusted HR from observational studies, 0.6–0.9
Metformin vs. DPP-4 inhibitors	Low	3	DPP-4 inhibitors favored for short-term mortality
Rosiglitazone vs. SU (longer-duration studies)	Low	1	Rosiglitazone favored
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	5	Metformin favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitor	Low	7	Metformin + DPP-4 inhibitors favored for short-term mortality
Combination vs. combination			
Metformin + SU vs. metformin + DPP-4 inhibitors (104 wk follow-up)	Low	5	Metformin + DPP-4 inhibitors favored for long-term CVD mortality
Metformin + SU vs. metformin + SGLT-2 inhibitor (longer-duration studies)	Low	2	Metformin + SGLT-2 inhibitors favored
Cardiovascular morbidity			
Monotherapy vs. monotherapy			
Metformin vs. rosiglitazone	Low	5	Metformin favored for long-term CVD morbidity
Metformin vs. pioglitazone	Low	5	Neither treatment favored
Metformin vs. SU	Low	7	Metformin favored for long-term CVD morbidity; range in RR from RCTs, 0.7–1.6; adjusted HR from observational studies, 0.3–0.9
Rosiglitazone vs. SU	Low	4	SU favored for long-term CVD morbidity
Pioglitazone vs. SU	Low	3	Pioglitazone favored for short-term CVD morbidity
SU vs. DPP-4 inhibitors	Low	2	DPP-4 inhibitor favored for short-term CVD morbidity
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone (shorter duration)	Low	6	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SU (shorter duration)	Low	1	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SGLT-2 inhibitor (shorter duration)	Low	1	Metformin favored for short-term CVD
Combination vs. combination			
Metformin + pioglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + DPP-4 inhibitor favored for short-term cardiovascular morbidity
Metformin + rosiglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + rosiglitazone favored for short-term CVD morbidity
Metformin + SU vs. metformin + DPP-4 inhibitor (long-term nonfatal MI)	Low	2	Metformin + DPP-4 inhibitor favored for long-term nonfatal MI
Metformin + SU vs. metformin + SGLT-2 inhibitor (long-term)	Low	1	Neither favored

(Continued on following page)

Appendix Table 1–Continued

Intervention*, by Outcome	Strength of Evidence	Studies, *n*	Summary†
Nephropathy			
Monotherapy vs. monotherapy			
Metformin vs. SU (shorter-duration studies)	Low	4	Metformin favored
TZD vs. SU (mainly shorter-duration studies)	Low	7	TZD favored for short-term nephropathy outcomes
SU vs. DPP-4 inhibitors (shorter-duration study)	Low	1	Neither treatment favored
Metformin vs. metformin combination			
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	2	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 (shorter-duration study)	Low	1	Neither treatment favored
Neuropathy			
Metformin vs. metformin + DPP-4 inhibitor (shorter-duration study)	Low	1	Metformin favored
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	1	Neither treatment favored

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Only comparisons that were evaluated by at least 1 randomized controlled trial are listed. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short term (1 y or shorter), because few longer-duration studies evaluated this outcome.
† Unless otherwise specified, the estimates are the pooled mean between-group differences (95% CIs).
‡ Effect is not statistically significant.
§ Grade given by the evidence reviewers. The Clinical Guidelines Committee reviewed the individual studies and found the 2 trials to be under-powered, with no significant reductions in cardiovascular mortality with metformin versus sulfonylureas, and therefore considered the quality of evidence to be low.

Harms

- Metformin: increased risk for gastrointestinal side effects
- Sulfonylureas: increased risk for hypoglycemia compared with other drugs
- Thiazolidinediones: increased risk for heart failure
- SGLT-2 inhibitors: increased genital mycotic infections

Clinical Considerations

- Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss.
- Management of type 2 diabetes often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors.
- Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss or lifestyle modification fails.
- Metformin monotherapy effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight.
- Although combination therapy reduces HbA1c levels more effectively than monotherapy, it is associated with more adverse events.
- The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease.
- Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m2).

COMPARATIVE BENEFITS OF ORAL MEDICATIONS FOR TYPE 2 DIABETES

Evidence from new studies (52 randomized, controlled trials and 13 observational studies, mostly 1 year or less in duration) was either low quality or insufficient for evaluating clinical outcomes, such as mortality, cardiovascular mortality and morbidity, retinopathy, nephropathy, and neuropathy.

- All-Cause Mortality

8. Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, et al; SPREADDIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013;36:1304-11.
9. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355: 2427-43.
10. Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jørgensen CH, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010;53:2546-53.
11. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011;32:1900-8.
12. Wheeler S, Moore K, Forsberg CW, Riley K, Floyd JS, Smith NL, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia. 2013;56:1934-43.
13. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012;14: 803-9.
14. Corrao G, Romio SA, Zambon A, Merlino L, Bosi E, Scavini M. Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol. 2011;67:289-99.
15. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009;46:145-54.
16. Wang CP, Lorenzo C, Espinoza SE. Frailty attenuates the impact of metformin on reducing mortality in older adults with type 2 diabetes. J Endocrinol Diabetes Obes. 2014;2:1031.

- Cardiovascular Mortality

8 – 11 und 16 (siehe oben)
17. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. Diabet Med. 2005;22:497-502.

- Cardiovascular and Cerebrovascular Morbidity

8 – 16 (siehe oben)

- Retinopathy, Nephropathy, and Neuropathy

All randomized, controlled trials were short term, and evidence for all comparisons was insufficient or low quality, thus inconclusive for these outcomes.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2019) am 07.10.2019

#	Suchfrage
#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#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 Between Oct 2014 and Oct 2019

Systematic Reviews in Medline (PubMed) am 07.10.2019

#	Suchfrage
1	"diabetes mellitus, type 2"[MeSH Terms]
2	(T2DM[Title/Abstract] OR DMT2[Title/Abstract] OR NIDDM[Title/Abstract] OR MODY[Title/Abstract])
3	(Diabetes[Title/Abstract] OR dm[Title/Abstract])
4	"adult onset"[Title/Abstract] OR "maturity onset"[Title/Abstract] OR (non insulin dependan*[Title/Abstract]) OR noninsulin dependan*[Title/Abstract] OR "slow onset"[Title/Abstract] OR ketosis resistan*[Title/Abstract] OR "type 2"[Title/Abstract] OR "type II"[Title/Abstract] OR "T 2"[Title/Abstract] OR T2[Title/Abstract] OR TII[Title/Abstract] OR "T II"[Title/Abstract]
5	(#3 AND #4)
6	(#1 OR #2 OR #5)
7	(metformin[MeSH Terms]) OR metformin[Title/Abstract] OR Dimethylbiguanidine[Title/Abstract] OR Dimethylguanylguanidine [Title/Abstract] OR Glucophage[Title/Abstract]
8	((Dipeptidyl-Peptidase IV Inhibitors[MeSH Terms]) OR gliptin*[Title/Abstract]) OR dpp4 inhibitor*[Title/Abstract]
9	((("Dipeptidyl Peptidase"[Title/Abstract] OR Dipeptidylpeptidase[Title/Abstract] OR dpp[Title/Abstract])) AND (4[Title/Abstract] OR IV[Title/Abstract])) AND inhibitor*[Title/Abstract]
10	("Sodium-Glucose Transporter 2"[MeSH Terms]) OR "Sodium-Glucose Transporter 2 Inhibitors"[MeSH Terms] OR Gliflozin*[Title/Abstract] OR sglt2 inhibitor*[Title/Abstract]
11	((((sodium[Title/Abstract] AND glucose[Title/Abstract])) AND (2[Title/Abstract] OR II[Title/Abstract])) AND (transporter[Title/Abstract] OR cotransporter[Title/Abstract] OR co-transporter[Title/Abstract])) AND inhibitor*[Title/Abstract]
12	((sglt[Title/Abstract]) AND (2[Title/Abstract] OR II[Title/Abstract])) AND inhibitor*[Title/Abstract]
13	(Sulfonylurea Compounds[MeSH Terms]) OR (Sulfonylurea*[Title/Abstract] OR Sulphonylurea*[Title/Abstract])

14	(Glycoside Hydrolase Inhibitors[MeSH Terms]) OR Glycoside Hydrolase Inhibitor*[Title/Abstract]
15	((alpha[Title/Abstract]) AND (Amylase[Title/Abstract] OR Glucosidase[Title/Abstract])) AND inhibitor*[Title/Abstract]
16	insulins[MeSH Terms] OR insulin*[Title]
17	Incretins[MeSH Terms] OR incretin*[Title/Abstract]
18	Hypoglycemic Agents[MeSH Terms] OR glinid*[Title/Abstract] OR Antidiabetics[Title] OR Antihyperglycemics[Title] OR Antihyperglycaemics[Title] OR Hypoglycemics[Title] OR Hypoglycaemics[Title]
19	(Antidiabetic*[Title] OR Antihyperglycemic*[Title] OR Antihyperglycaemic*[Title] OR Hypoglycemic*[Title] OR Hypoglycaemic*[Title]) AND (Agent*[Title] OR drug*[Title])
20	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21	#6 AND #20
22	(#21) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
23	(#22) AND ("2014/10/01"[PDAT] : "3000"[PDAT])
24	(#23) NOT "The Cochrane database of systematic reviews"[Journal]
25	(#24) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 07.10.2019

#	Suchfrage
1	"diabetes mellitus, type 2"[MeSH Terms]
2	(T2DM[Title/Abstract] OR DMT2[Title/Abstract] OR NIDDM[Title/Abstract] OR MODY[Title/Abstract])
3	(Diabetes[Title/Abstract] OR dm[Title/Abstract])
4	"adult onset"[Title/Abstract] OR "maturity onset"[Title/Abstract] OR (non insulin dependan*[Title/Abstract]) OR noninsulin dependan*[Title/Abstract] OR "slow onset"[Title/Abstract] OR ketosis resistan*[Title/Abstract] OR "type 2"[Title/Abstract] OR "type II"[Title/Abstract] OR "T 2"[Title/Abstract] OR T2[Title/Abstract] OR TII[Title/Abstract] OR "T II"[Title/Abstract]
5	(#3 AND #4)
6	(#1 OR #2 OR #5)
7	(metformin[MeSH Terms]) OR metformin[Title/Abstract] OR Dimethylbiguanidine[Title/Abstract] OR Dimethylguanylguanidine [Title/Abstract] OR Glucophage[Title/Abstract]
8	((Dipeptidyl-Peptidase IV Inhibitors[MeSH Terms]) OR gliptin*[Title/Abstract]) OR dpp4 inhibitor*[Title/Abstract]
9	((("Dipeptidyl Peptidase"[Title/Abstract] OR Dipeptidylpeptidase[Title/Abstract] OR dpp[Title/Abstract])) AND (4[Title/Abstract] OR IV[Title/Abstract])) AND inhibitor*[Title/Abstract]
10	("Sodium-Glucose Transporter 2"[MeSH Terms]) OR "Sodium-Glucose Transporter 2 Inhibitors"[MeSH Terms] OR Gliflozin*[Title/Abstract] OR sglt2 inhibitor*[Title/Abstract]
11	((((sodium[Title/Abstract] AND glucose[Title/Abstract])) AND (2[Title/Abstract] OR II[Title/Abstract])) AND (transporter[Title/Abstract] OR cotransporter[Title/Abstract] OR co-transporter[Title/Abstract])) AND inhibitor*[Title/Abstract]
12	((sglt[Title/Abstract]) AND (2[Title/Abstract] OR II[Title/Abstract])) AND inhibitor*[Title/Abstract]
13	(Sulfonylurea Compounds[MeSH Terms]) OR (Sulfonylurea*[Title/Abstract] OR Sulphonylurea*[Title/Abstract])
14	(Glycoside Hydrolase Inhibitors[MeSH Terms]) OR Glycoside Hydrolase Inhibitor*[Title/Abstract]
15	((alpha[Title/Abstract]) AND (Amylase[Title/Abstract] OR Glucosidase[Title/Abstract])) AND inhibitor*[Title/Abstract]
16	insulins[MeSH Terms] OR insulin*[Title]
17	Incretins[MeSH Terms] OR incretin*[Title/Abstract]
18	Hypoglycemic Agents[MeSH Terms] OR glinid*[Title/Abstract] OR Antidiabetics[Title] OR Antihyperglycemics[Title] OR Antihyperglycaemics[Title] OR Hypoglycemics[Title] OR Hypoglycaemics[Title]
19	(Antidiabetic*[Title] OR Antihyperglycemic*[Title] OR Antihyperglycaemic*[Title] OR Hypoglycemic*[Title] OR Hypoglycaemic*[Title]) AND (Agent*[Title] OR drug*[Title])
20	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21	#6 AND #20
22	(#21) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
23	(#22) AND ("2014/10/01"[PDAT] : "3000"[PDAT])
24	(#23) NOT retracted publication[ptyp]

Referenzen

1. **Alfayez OM, Almutairi AR, Aldosari A, Al Yami MS.** Update on Cardiovascular Safety of Incretin-Based Therapy in Adults With Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcome Trials. Can J Diabetes 2019;43(7):538-545 e532.

2. **Andersen SE, Christensen M.** Hypoglycaemia when adding sulphonylurea to metformin: a systematic review and network meta-analysis. Br J Clin Pharmacol 2016;82(5):1291-1302.

3. **Andreadis P, Karagiannis T, Malandris K, Avgerinos I, Liakos A, Manolopoulos A, et al.** Semaglutide for type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Obes Metab 2018;20(9):2255-2263.

4. **Avgerinos I, Karagiannis T, Malandris K, Liakos A, Mainou M, Bekiari E, et al.** Glucagon-like peptide-1 receptor agonists and microvascular outcomes in type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2019;21(1):188-193.

5. **Bae JH, Kim S, Park EG, Kim SG, Hahn S, Kim NH.** Effects of Dipeptidyl Peptidase-4 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Endocrinol Metab (Seoul) 2019;34(1):80-92.

6. **Bae JH, Park EG, Kim S, Kim SG, Hahn S, Kim NH.** Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Sci Rep 2019;9(1):13009.

7. **Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, et al.** Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol 2018;6(2):105-113.

8. **Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, et al.** Diabetes medications for adults with type 2 diabetes: An update [online]. Rockville (USA): Agency for Healthcare Research and Quality; 2016. [Zugriff: 23.10.2018]. URL: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/diabetes-update-2015_research.pdf.

9. **Canadian Agency for Drugs and Technologies in Health (CADTH).** New drugs for type 2 diabetes: Second-line therapy; Science report [online]. Ottawa (CAN): CADTH; 2017. [Zugriff: 23.10.2018]. (CADTH Therapeutic Review; Band 4 No. 1b). URL: https://www.cadth.ca/sites/default/files/pdf/TR0012_T2D_Science_Report.pdf.

10. **Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F.** GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab Res Rev 2019;35(1):e3082.

11. **Chen Q, Liu T, Zhou H, Peng H, Yan C.** Risk of Fractures Associated with Dipeptidyl Peptidase-4 Inhibitor Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Diabetes Ther 2019;10(5):1879-1892.

12. **Chen Z, Li G.** Sodium-Glucose Co-Transporter 2 Inhibitors Compared with Sulfonylureas in Patients with Type 2 Diabetes Inadequately Controlled on Metformin: A Meta-Analysis of Randomized Controlled Trials. Clin Drug Investig 2019;39(6):521-531.

13. **Cheng L, Li YY, Hu W, Bai F, Hao HR, Yu WN, et al.** Risk of bone fracture associated with sodium-glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials. Diabetes Metab 2019;45(5):436-445.

14. **Cho YK, Kang YM, Lee SE, Lee J, Park JY, Lee WJ, et al.** Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab 2018;44(5):393-401.

15. **Cosentino C, Dicembrini I, Nreu B, Mannucci E, Monami M.** Nephrolithiasis and sodium-glucose co-transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2019;155:107808.

16. **Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al.** 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019.

17. **Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron B, Stanifer J, Mock CK, et al.** Metformin use in patients with contraindications or precautions [online]. Washington (USA): Department of Veterans Affairs; 2016. [Zugriff: 23.10.2018]. URL: https://www.hsrd.research.va.gov/publications/esp/metformin.pdf.

18. **Dai D, Mao Y, Jin H, Zhang W.** Efficacy and hypoglycemic risk of sitagliptin in obese/overweight patients with type 2 diabetes compared with GLP-1 receptor agonists: A meta-analysis. Medicine (Baltimore) 2019;98(36):e17081.

19. **Diabetes Canada.** 2018 Full guidelines. Canadian Journal of Diabetes 2018;42(Suppl 1).

20. **Dicembrini I, Nreu B, Mannucci E, Monami M.** Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and cancer: A meta-analysis of randomized controlled trials. Diabetes Obes Metab 2019;21(8):1871-1877.

21. **Dicembrini I, Tomberli B, Nreu B, Baldereschi GI, Fanelli F, Mannucci E, et al.** Peripheral artery disease and amputations with Sodium-Glucose co-Transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2019;153:138-144.

22. **Dorsey-Trevino EG, Gonzalez-Gonzalez JG, Alvarez-Villalobos N, Gonzalez-Nava V, Contreras-Garza BM, Diaz Gonzalez-Colmenero A, et al.** Sodium-glucose cotransporter 2 (SGLT-2) inhibitors and microvascular outcomes in patients with type 2 diabetes: systematic review and meta-analysis. J Endocrinol Invest 2019.

23. **Fadini GP, Bonora BM, Mayur S, Rigato M, Avogaro A.** Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors. Diabetes Obes Metab 2018;20(3):740-744.

24. **Feng C, Wu M, Chen Z, Yu X, Nie Z, Zhao Y, et al.** Effect of SGLT2 inhibitor on renal function in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Int Urol Nephrol 2019;51(4):655-669.

25. **Foroutan N, Muratov S, Levine M.** Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs sulfonylurea in metformin-based combination therapy for type 2 diabetes mellitus: Systematic review and meta-analysis. Clin Invest Med 2016;39(2):E48-62.

26. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Insulin degludec (Änderung des Beschlusses vom 16. Mai 2019 / Aufhebung des Beschlusses vom 4. Dezember 2014 / Therapiekosten) vom 4. Juli 2019 [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/39-261-3866/2019-07-04_AM-RL-XII_Insulin-degludec_D-405_BAnz.pdf.

27. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Insulin degludec (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) vom 16. Mai 2019 [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/39-261-3786/2019-05-16_AM-RL-XII_Insulin-degludec_D-405_BAnz.pdf.

28. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Abs. 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL), zuletzt geändert am 17. Januar 2019 [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/62-492-1788/DMP-A-RL_2019-01-17_iK-2019-04-01.pdf.

29. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage III: Übersicht über Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung durch die Arzneimittel-Richtlinie und aufgrund anderer Vorschriften (§ 34 Absatz 1 Satz 6 und Absatz 3 SGB V), Hinweise zur wirtschaftlichen Verordnungsweise von nicht verschreibungspflichtigen Arzneimitteln für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr sowie Verordnungseinschränkungen und -ausschlüsse von sonstigen Produkten; zuletzt geändert am 13. September 2019 [online]. Berlin (GER): G-BA; 2019. [Zugriff: 07.10.2019]. URL: https://www.g-ba.de/downloads/83-691-566/AM-RL-III-Verordnungeinschr%C3%A4nkungen_2019-09-13.pdf.

30. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Februar 2018 - Saxagliptin/Metformin [online]. Berlin (GER): G-BA; 2018. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-302/2018-02-01_Geltende-Fassung_Saxagliptin_Metformin_D-306.pdf.

31. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. November 2018 / 4. Juli 2019 - Ertugliflozin/Sitagliptin [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/91-1385-364/2019-07-04_Geltende-Fassung_Ertuglifozin-Sitagliptin_D-361.pdf.

32. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 - Saxagliptin/Metformin (neues Anwendungsgebiet: Diabetes mellitus, Kombination mit einem Sulfonylharnstoff) [online]. Berlin (GER): G-BA; 2014. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-66/2014-01-23_Geltende-Fassung_Saxagliptin-Metformin_D-063.pdf.

33. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 - Vildagliptin/Metformin [online]. Berlin (GER): G-BA; 2014. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-53/2014-01-23_Geltende-Fassung_Vildagliptin-Metformin_D-048.pdf.

34. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach §

35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 / 21. Mai 2015 - Vildagliptin [online]. Berlin (GER): G-BA; 2015. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-151/2015-05-21_Geltende-Fassung_Vildagliptin_D-049_D-145.pdf.

35. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 - Empagliflozin [online]. Berlin (GER): G-BA; 2016. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-220/2016-09-01_Geltende-Fassung_Empagliflozin_D-214.pdf.

36. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 - Empagliflozin/Metformin [online]. Berlin (GER): G-BA; 2016. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-221/2016-09-01_Geltende-Fassung_Empagliflozin-Metformin_D-215.pdf.

37. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 4. Februar 2016 - Insulin degludec/Liraglutid (neues Anwendungsgebiet: Diabetes mellitus Typ 2 in Kombination mit oralen Antidiabetika) [online]. Berlin (GER): G-BA; 2016. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-182/2016-02-04_Geltende-Fassung_Insulin-degludec-Liraglutid_nAWG_D-179.pdf.

38. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 4. September 2014 - Canagliflozin [online]. Berlin (GER): G-BA; 2014. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-105/2014-09-04_Geltende-Fassung_Canagliflozin_D-101.pdf.

39. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 5. Februar 2015 - Canagliflozin/Metformin [online]. Berlin (GER): G-BA; 2015. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-129/2015-02-05_Geltende-Fassung_CanagliflozinMetformin_D-124.pdf.

40. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 5. September 2013 / 23. Januar 2014 - Lixisenatid [online]. Berlin (GER): G-BA; 2014. [Zugriff: 23.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-63/2014-01-23_Geltende-Fassung_Lixisenatid_D-061.pdf.

41. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juni 2013 / 23. Januar 2014 / 21. Juni 2018 / 4. Juli 2019 - Dapagliflozin [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/91-1385-338/2019-07-04_Geltende-Fassung_Dapagliflozin_D-045_D-335.pdf.

42. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 7. August 2014 / 21. Juni 2018 / 4. Juli 2019 - Dapagliflozin/Metformin [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL:

https://www.g-ba.de/downloads/91-1385-337/2019-07-04_Geltende-Fassung_Dapagliflozin-Metformin_D-097_D-336.pdf.

43. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 - Saxagliptin [online]. Berlin (GER): G-BA; 2016. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-245/2016-12-15_Geltende-assung_Saxagliptin_D-243.pdf.

44. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 - Saxagliptin/Metformin [online]. Berlin (GER): G-BA; 2016. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-246/2016-12-15_Geltende-Fassung_Saxagliptin-Metformin_nAWG_D-244.pdf.

45. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 - Sitagliptin/Metformin [online]. Berlin (GER): G-BA; 2016. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-247/2016-12-15_Geltende-Fassung_Sitagliptin_Metformin_D-246.pdf.

46. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 / 22. März 2019 / 4. Juli 2019 - Sitagliptin [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/91-1385-250/2019-07-04_Geltende-Fassung_Sitagliptin_D-245_D-393.pdf.

47. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Oktober 2015 - Insulin degludec/Liraglutid [online]. Berlin (GER): G-BA; 2015. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-168/2015-10-15_Geltende-Fassung_Insulin-degludec_Liraglutid_D-165.pdf.

48. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. August 2018 / 4. Juli 2019 Insulin glargin/Lixisenatid [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/91-1385-353/2019-07-04_Geltende-Fassung_Insulin-glargin-Lixisenatid_D-346.pdf.

49. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Juli 2015 - Dulaglutid [online]. Berlin (GER): G-BA; 2015. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-157/2015-07-16_Geltende-Fassung_Dulaglutid_D-154.pdf.

50. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Mai 2013 / 23. Januar 2014 - Linagliptin (neues Anwendungsgebiet: Diabetes mellitus Typ 2, Kombinationstherapie mit Insulin mit oder ohne Metformin) [online]. Berlin (GER): G-BA; 2014. [Zugriff: 29.11.2018]. URL: https://www.g-ba.de/downloads/91-1385-49/2014-01-23_Geltende-Fassung_Linagliptin_nAWG_D-047.pdf.

51. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Mai 2019 / 4. Juli 2019 - Semaglutid [online]. Berlin (GER): G-BA; 2019. [Zugriff: 04.10.2019]. URL: https://www.g-ba.de/downloads/91-1385-412/2019-07-04_Geltende-Fassung_Semaglutid_D-404.pdf.

52. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. März 2015 / 16. Juli 2015 - Albiglutid [online]. Berlin (GER): G-BA; 2015. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-140/2015-03-19_Geltende-Fassung_Albiglutid_D-132.pdf.

53. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. August 2015 - Insulin degludec (neues Anwendungsgebiet: Diabetes mellitus, Patienten ab 1 Jahr) [online]. Berlin (GER): G-BA; 2015. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-162/2015-08-20_Geltende-Fassung_Insulin-degludec_nAWG_D-158.pdf.

54. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Februar 2013 / 23. Januar 2014 - Linagliptin [online]. Berlin (GER): G-BA; 2014. [Zugriff: 18.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-37/2014-01-23_Geltende-Fassung_Linagliptin_D-035.pdf.

55. **Giugliano D, Maiorino MI, Longo M, Bellastella G, Chiodini P, Esposito K.** Type 2 diabetes and risk of heart failure: a systematic review and meta-analysis from cardiovascular outcome trials. Endocrine 2019;65(1):15-24.

56. **Gomes GKA, De Camargos Ramos AI, De Sousa CT, Sanches C, Pereira ML, Baldoni AO.** Linagliptin safety profile: A systematic review. Prim Care Diabetes 2018;12(6):477-490.

57. **Gu J, Meng X, Guo Y, Wang L, Zheng H, Liu Y, et al.** The efficacy and safety of liraglutide added to metformin in patients with diabetes: a meta-analysis of randomized controlled trials. Sci Rep 2016;6:32714.

58. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Bewertung der Studie LEADER zu Liraglutid; Rapid Report; Auftrag A17-09 [online]. Köln (GER): IQWiG; 2017. [Zugriff: 24.10.2018]. (IQWiG-Berichte; Band 530). URL: https://www.iqwig.de/download/A17-09_Bewertung-der-Studie-LEADER-zu-Liraglutid_Rapid-Report_V1-0.pdf.

59. **Jingfan Z, Ling L, Cong L, Ping L, Yu C.** Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus with inadequate glycemic control on metformin: a meta-analysis. Arch Endocrinol Metab 2019.

60. **Kanters S, Wilkinson L, Vrazic H, Sharma R, Lopes S, Popoff E, et al.** Comparative efficacy of once-weekly semaglutide versus SGLT-2 inhibitors in patients inadequately controlled with one to two oral antidiabetic drugs: a systematic literature review and network meta-analysis. BMJ Open 2019;9(7):e023458.

61. **Keshavarz K, Lotfi F, Sanati E, Salesi M, Hashemi-Meshkini A, Jafari M, et al.** Linagliptin versus sitagliptin in patients with type 2 diabetes mellitus: a network meta-analysis of randomized clinical trials. Daru 2017;25(1):23.

62. **Li D, Shi W, Wang T, Tang H.** SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2018;20(8):1972-1976.

63. **Li D, Yang JY, Wang T, Shen S, Tang H.** Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials. Diabetes Metab 2018;44(5):410-414.

64. **Li X, Li T, Cheng Y, Lu Y, Xue M, Xu L, et al.** Effects of SGLT2 inhibitors on fractures and bone mineral density in type 2 diabetes: An updated meta-analysis. Diabetes Metab Res Rev 2019:e3170.

65. **Li X, Qie S, Wang X, Zheng Y, Liu Y, Liu G.** The safety and efficacy of once-weekly glucagon-like peptide-1 receptor agonist semaglutide in patients with type 2 diabetes mellitus: a systemic review and meta-analysis. Endocrine 2018;62(3):535-545.

66. **Liao HW, Wu YL, Sue YM, Lee M, Ovbiagele B.** Sodium-glucose cotransporter 2 inhibitor plus pioglitazone vs pioglitazone alone in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Endocrinol Diabetes Metab 2019;2(1):e00050.

67. **Liu FP, Dong JJ, Yang Q, Xue XZ, Ren ZF, Gan YZ, et al.** Glucagon-like peptide 1 receptor agonist therapy is more efficacious than insulin glargine for poorly controlled type 2 diabetes: A systematic review and meta-analysis. J Diabetes 2015;7(3):322-328.

68. **Liu W, Yang X, Huang J.** Efficacy and Safety of Insulin Degludec versus Insulin Glargine: A Systematic Review and Meta-Analysis of Fifteen Clinical Trials. Int J Endocrinol 2018;2018:8726046.

69. **Madsen KS, Kähler P, Kähler LKA, Madsbad S, Gnesin F, Metzendorf MI, et al.** Metformin and second- or third-generation sulphonylurea combination therapy for adults with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews [online]. 2019(4):Cd012368. URL: http://dx.doi.org/10.1002/14651858.CD012368.pub2.

70. **Maiorino MI, Chiodini P, Bellastella G, Scappaticcio L, Longo M, Esposito K, et al.** Free and fixed-ratio combinations of basal insulin and GLP-1 receptor agonists versus basal insulin intensification in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab 2018;20(9):2309-2313.

71. **Maiorino MI, Chiodini P, Bellastella G, Scappaticcio L, Longo M, Giugliano D, et al.** The good companions: insulin and glucagon-like peptide-1 receptor agonist in type 2 diabetes. A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2019;154:101-115.

72. **Mearns ES, Saulsberry WJ, White CM, Kohn CG, Lemieux S, Sihabout A, et al.** Efficacy and safety of antihyperglycaemic drug regimens added to metformin and sulphonylurea therapy in Type 2 diabetes: a network meta-analysis. Diabet Med 2015;32(12):1530-1540.

73. **Mearns ES, Sobieraj DM, White CM, Saulsberry WJ, Kohn CG, Doleh Y, et al.** Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. PLoS One 2015;10(4):e0125879.

74. **Men P, Li XT, Tang HL, Zhai SD.** Efficacy and safety of saxagliptin in patients with type 2 diabetes: A systematic review and meta-analysis. PLoS One 2018;13(5):e0197321.

75. **Men P, Qu S, Luo W, Li C, Zhai S.** Comparison of lixisenatide in combination with basal insulin vs other insulin regimens for the treatment of patients with type 2 diabetes inadequately controlled by basal insulin: Systematic review, network meta-analysis and cost-effectiveness analysis. Diabetes Obes Metab 2019 [Epub ahead of print].

76. **Milder TY, Stocker SL, Abdel Shaheed C, McGrath-Cadell L, Samocha-Bonet D, Greenfield JR, et al.** Combination Therapy with an SGLT2 Inhibitor as Initial Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis. J Clin Med 2019;8(1).

77. **Min SH, Yoon JH, Moon SJ, Hahn S, Cho YM.** Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. Sci Rep 2018;8(1):4466.

78. **Mishriky BM, Cummings DM, Powell JR, Sewell KA, Tanenberg RJ.** Comparing once-weekly semaglutide to incretin-based therapies in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Metab 2019;45(2):102-109.

79. **Mishriky BM, Cummings DM, Tanenberg RJ.** The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with Type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2015;109(2):378-388.

80. **Mishriky BM, Tanenberg RJ, Sewell KA, Cummings DM.** Comparing SGLT-2 inhibitors to DPP-4 inhibitors as an add-on therapy to metformin in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab 2018;44(2):112-120.

81. **Monami M, Zannoni S, Pala L, Silverii A, Andreozzi F, Sesti G, et al.** Effects of glucagon-like peptide-1 receptor agonists on mortality and cardiovascular events: A comprehensive meta-analysis of randomized controlled trials. Int J Cardiol 2017;240:414-421.

82. **National Institute for Health and Care Excellence (NICE).** Type 2 diabetes in adults: management (last updated August 2019) [online]. London (GBR): 2019. [Zugriff: 04.10.2019]. (NICE guidelines; Band 28). URL: https://www.nice.org.uk/guidance/ng28/evidence/full-guideline-pdf-78671532569.

83. **Qaseem A, Barry MJ, Humphrey LL, Forciea MA, Clinical Guidelines Committee of the American College of Physicians.** Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med 2017;166(4):279-290.

84. **Qian D, Zhang T, Tan X, Zheng P, Liang Z, Xie J, et al.** Comparison of antidiabetic drugs added to sulfonylurea monotherapy in patients with type 2 diabetes mellitus: A network meta-analysis. PLoS One 2018;13(8):e0202563.

85. **Scottish Intercollegiate Guidelines Network (SIGN).** Pharmacological management of glycaemic control in people with type 2 diabetes [online]. Edinburgh (GBR): SIGN; 2017. [Zugriff: 23.10.2018]. (SIGN publication; Band 154). URL: http://www.sign.ac.uk/assets/sign154.pdf.

86. **Singh AK, Singh R.** Heart failure hospitalization with SGLT-2 inhibitors: a systematic review and meta-analysis of randomized controlled and observational studies. Expert Rev Clin Pharmacol 2019;12(4):299-308.

87. **Singh S, Wright E. Jr., Kwan AY, Thompson JC, Syed IA, Korol EE, et al.** Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2017;19(2):228-238.

88. **Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, et al.** Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. Diabetes Obes Metab 2019;21(5):1237-1250.

89. **Vos RC, Van Avendonk MJ, Jansen H, Goudswaard AN, Van den Donk M, Gorter K, et al.** Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. Cochrane Database of Systematic Reviews [online]. 2016(9):Cd006992. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006992.pub2/abstract.

90. **Wang A, Yang K, Wang T, Zhang N, Tang H, Feng X.** Effects of sodium-glucose cotransporter 2 inhibitors on risk of venous thromboembolism in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab Res Rev 2019:e3174.

91. **Wang B, Sun Y, Sang Y, Liu X, Liang J.** Comparison of dipeptidyl peptidase-4 inhibitors and pioglitazone combination therapy versus pioglitazone monotherapy in type 2 diabetes: A system review and meta-analysis. Medicine (Baltimore) 2018;97(46):e12633.

92. **Wang K, Zhang Y, Zhao C, Jiang M.** SGLT-2 Inhibitors and DPP-4 Inhibitors as Second-Line Drugs in Patients with Type 2 Diabetes: A Meta-Analysis of Randomized Clinical Trials. Horm Metab Res 2018;50(10):768-777.

93. **Wei ZG, Wang MC, Zhang HH, Wang ZY, Wang GN, Wei FX, et al.** PRISMA-efficacy and safety of lixisenatide for type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97(51):e13710.

94. **World Health Organizatin (WHO).** Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus [online]. WHO; 2018. [Zugriff: 24.10.2018]. URL: https://www.who.int/diabetes/publications/guidelines-diabetes-medicines/en/.

95. **Yamani N, Usman MS, Akhtar T, Fatima K, Asmi N, Khan MS.** Sodium-glucose co-transporter 2 inhibitors for the prevention of heart failure in type 2 diabetes: A systematic review and meta-analysis. Eur J Prev Cardiol 2019:2047487319841936.

96. **Yang T, Lu M, Ma L, Zhou Y, Cui Y.** Efficacy and tolerability of canagliflozin as add-on to metformin in the treatment of type 2 diabetes mellitus: a meta-analysis. Eur J Clin Pharmacol 2015;71(11):1325-1332.

97. **Yang Y, Chen S, Pan H, Zou Y, Wang B, Wang G, et al.** Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes: Systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96(21):e6944.

98. **Yoon JH, Min SH, Ahn CH, Cho YM, Hahn S.** Comparison of non-insulin antidiabetic agents as an add-on drug to insulin therapy in type 2 diabetes: a network meta-analysis. Sci Rep 2018;8(1):4095.

99. **Zaccardi F, Dhalwani NN, Dales J, Mani H, Khunti K, Davies MJ, et al.** Comparison of glucose-lowering agents after dual therapy failure in type 2 diabetes: A systematic review and network meta-analysis of randomized controlled trials. Diabetes Obes Metab 2018;20(4):985-997.

100. **Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al.** SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393(10166):31-39.

101. **Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al.** Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. Circulation 2019;139(17):2022-2031.

102. **Zhang YJ, Han SL, Sun XF, Wang SX, Wang HY, Liu X, et al.** Efficacy and safety of empagliflozin for type 2 diabetes mellitus: Meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018;97(43):e12843.

103. **Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, et al.** Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA 2018;319(15):1580-1591.

104. **Zhong X, Zhang T, Liu Y, Wei X, Zhang X, Qin Y, et al.** Effects of three injectable antidiabetic agents on glycaemic control, weight change and drop-out in type 2 diabetes suboptimally controlled with metformin and/or a sulfonylurea: A network meta-analysis. Diabetes Res Clin Pract 2015;109(3):451-460.

105. **Zhou W, Tao J, Zhou X, Chen H.** Insulin Degludec, a Novel Ultra-Long-Acting Basal Insulin versus Insulin Glargine for the Management of Type 2 Diabetes: A Systematic Review and Meta-Analysis. Diabetes Ther 2019;10(3):835-852.

106. **Zhuang XD, He X, Yang DY, Guo Y, He JG, Xiao HP, et al.** Comparative cardiovascular outcomes in the era of novel anti-diabetic agents: a comprehensive network meta-analysis of 166,371 participants from 170 randomized controlled trials. Cardiovasc Diabetol 2018;17(1):79.

Anhang

Abbildung 1: Overall network of evidence of semaglutide, SGLT-2is and other treatments for type II diabetes that is uncontrolled using 1-2 oral antidiabetics. Kanters et al., 2019 [60].

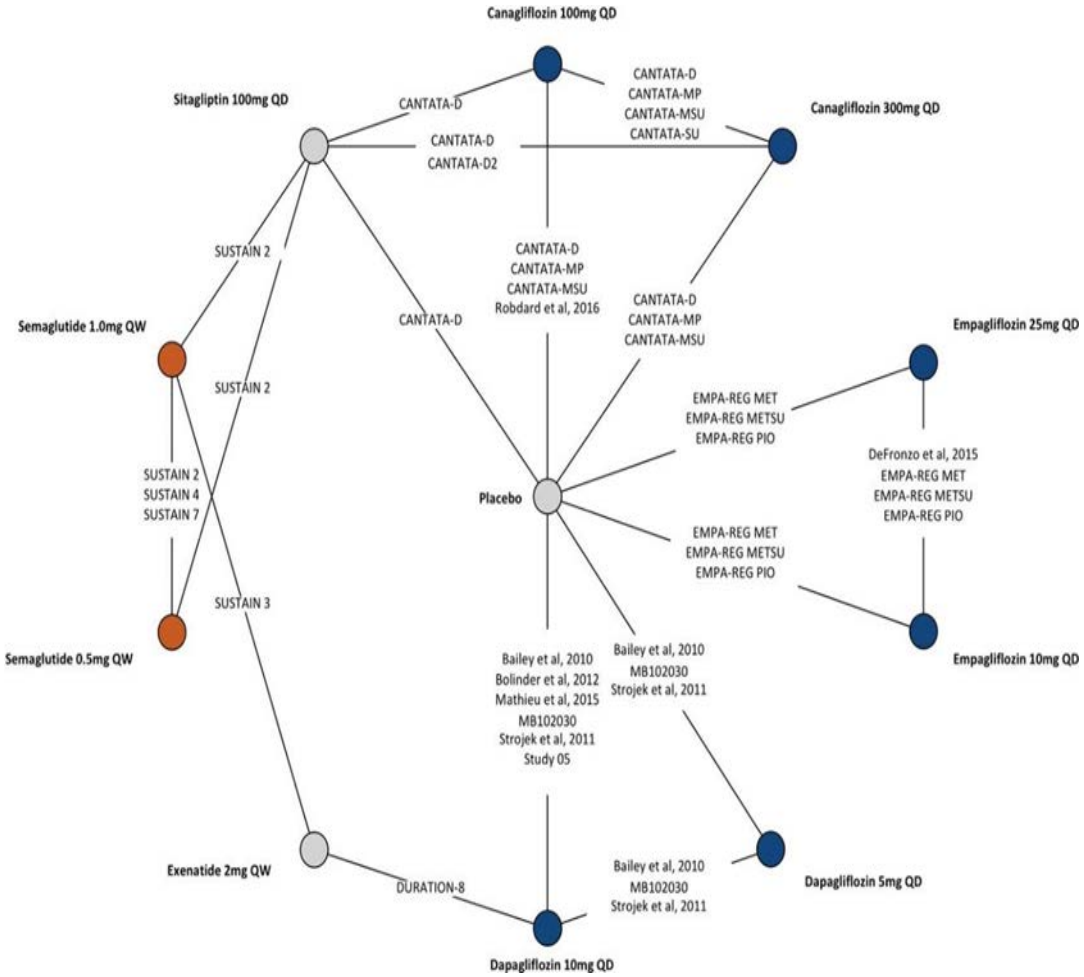


Abbildung 2: Network plot for all studies Zhuang XD et al., [106]

Figure 2. Network Plot for All Studies

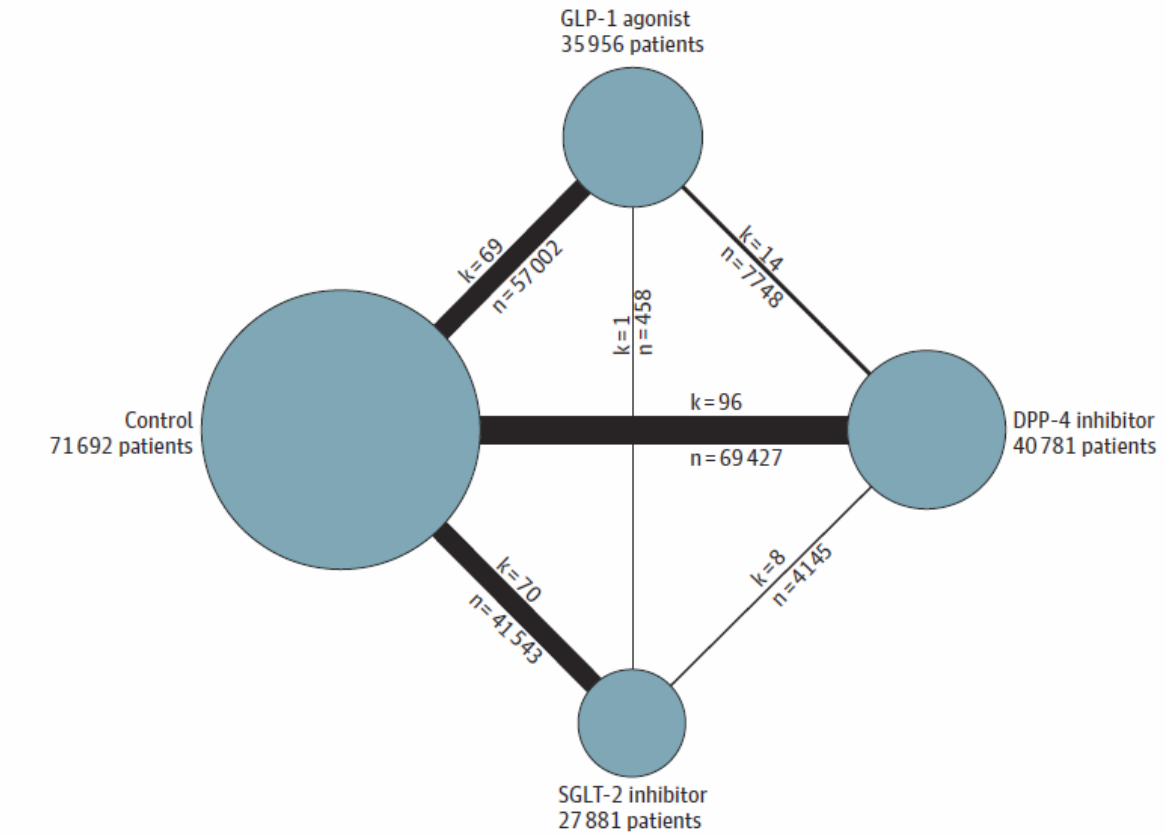


Abbildung 2: Network plot of treatment comparisons Zhuang XD et al., [106]

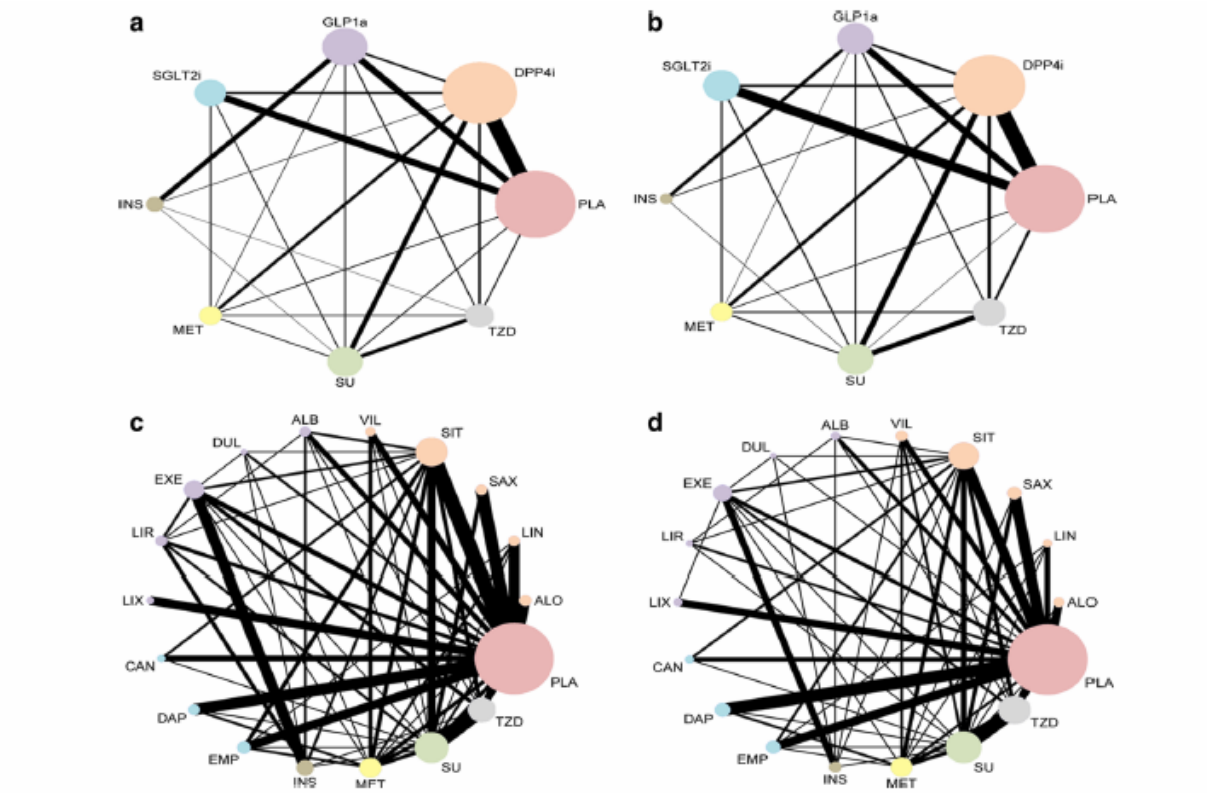


Fig. 1 Network plot of treatment comparisons for major adverse cardiovascular events (MACE) and all-cause mortality. **a** Categorized drugs comparisons for MACE; **b** Categorized drugs comparisons for all-cause mortality; **c** Individual drugs comparisons for MACE; **d** Individual drugs comparisons for all-cause mortality. The size of the nodes represents the number of trials that study the treatments. Direct comparison of treatments is linked with a line, the thickness of which represents the number of trials that assess the comparison. *SGLT2i* sodium-glucose co-transporter 2 inhibitor(s), *GLP1ra* glucagon-like peptide-1 receptor agonist(s), *DPP4i* dipeptidyl peptidase 4 inhibitor(s), *TZD* thiazolidinedione, *MET* metformin, *SU* sulfonylurea, *INS* insulin, *PLA* placebo, *VIL* vildagliptin, *EMP* empagliflozin, *LIX* lixisenatide, *ALO* alogliptin, *EXE* exenatide, *LIR* liraglutide, *CAN* canagliflozin, *DAP* dapagliflozin, *DUL* dulaglutide, *SIT* sitagliptin, *LIN* linagliptin, *ALB* albiglutide, *SAX* saxagliptin

NICE 2015/2019: Type 2 diabetes in adults: management (last updated August 2019)

Algorithm for blood glucose lowering therapy