National Institute for Health and Care Excellence

1

Draft for consultation

Type 2 diabetes in adults: management (medicines update)

[E1.1] Evidence reviews for initial pharmacological management of type 2 diabetes: review and appendices A to C

NICE guideline GID-NG10336

Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and recommendations for research in the NICE guideline

August 2025

Draft for Consultation

This evidence review was developed by NICE

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Contents

1. Initial pharmacological management

1.1. Review question

For different population subgroups, which individual and/or combinations of pharmacological therapies are most clinically and cost effective as initial treatment for the management of type 2 diabetes?

1.1.1. Introduction

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). The consequences of this include macrovascular complications (such as myocardial infarction, stroke and heart failure), microvascular complications (such as chronic kidney disease, retinopathy, neuropathy and sexual problems), acute complications (such as hyper- and hypoglycaemia, diabetic ketoacidosis and hyperosmolar hyperglycaemic state) and other complications (such as gum disease, increased risk of pancreatitis, cancer, polycystic ovary syndrome and other conditions). There are approximately 5.6 million people living with diabetes in the UK, 90% of those having type 2 diabetes and the incidence rises each year. The condition accounts for 10% of NHS annual budget with almost 80% of that being spent on managing the complications of type 2 diabetes.

The NICE guideline on Type 2 diabetes in adults: management was last updated in 2022 (NG28) where the focus was on cardiovascular impact. In this update we examine the holistic benefits of pharmacological therapy for type 2 diabetes to understand the effects of treatments on a range of factors including quality of life, cardiovascular and renal protection, weight management, other adverse effects (such as arrhythmias, falls and liver disease) and glycaemic control. This considers a wide range of trials and focusses on specific subpopulations of interest within the population with type 2 diabetes: people with type 2 diabetes and heart failure, people with type 2 diabetes and atherosclerotic cardiovascular disease, people with type 2 diabetes and chronic kidney disease and people with type 2 diabetes and different levels of risk of developing cardiovascular disease in the future. This will allow for clinical and cost-effectiveness evidence to be identified, considered and modelled to allow a comprehensive assessment of the effects of these treatments. The initial treatment review considers trials where people have not started any treatment before entering the trial or all other treatment has been discontinued for a set period before starting the trial medication.

1.1.2. Summary of the protocol

Table 1: PICO characteristics of review question

Population	Adults (age ≥18 years) with type 2 diabetes mellitus The population will be stratified into different groups for the analysis, these include: • People with type 2 diabetes mellitus and heart failure • People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease • People with type 2 diabetes mellitus and chronic kidney disease

	• People with type 2 diabetes mellitus and low cardiovascular risk with no other comorbidities • People with type 2 diabetes mellitus and high cardiovascular risk (or mixed/unclear cardiovascular risk) with no other comorbidities A stratum where all groups were analysed together was not included as the committee agreed this would not add any value. Exclusion: • Children and young people (age <18 years) with type 2 diabetes mellitus • Pregnant people with type 2 diabetes mellitus • People with type 1 diabetes mellitus • People with type 2 diabetes mellitus who are hyperglycaemic and require rescue treatment
Interventions	Pharmacological therapies for people with type 2 diabetes. • All therapies will be examined on an individual drug level (rather than a class level). • Typically in clinical practice, the aim is for people with type 2 diabetes to receive the maximally tolerated dose of antidiabetic medication rather than a specific dose. Therefore all doses will be pooled together. • Biguanides ○ Metformin hydrochloride standard release ○ Metformin hydrochloride slow release • DPP-4 inhibitors ○ Alogliptin (Vipidia) ○ Linagliptin (Trajenta) ○ Saxagliptin (Onglyza) ○ Sitagliptin (Januvia) ○ Vildagliptin (Galvus) • GLP-1 receptor agonist ○ Dulaglutide (Trulicity) ○ Exenatide (Byetta) ○ Liraglutide (Victoza) ○ Lixisenatide (Lyxumia) ○ Semaglutide (Rybelsus, Ozempic) • Dual GIP/GLP-1 receptor co-agonists ○ Tirzepatide (Mounjaro) • SGLT-2 inhibitors ○ Canagliflozin (Invokana) ○ Dapagliflozin (Forxiga) ○ Empagliflozin (Jardiance) ○ Ertugliflozin (Steglatro) • Sulfonylureas ○ Gliclazide ○ Glimepiride ○ Glipizide ○ Tolbutamide • Thiazolidinediones

	○ Pioglitazone • Combinations of therapies listed above (combinations may include medicines being given separately or combination products)
Comparisons	• Different pharmacological therapies listed in the intervention section to each other • An oral formulation compared with an injectable formulation of the same medication • Insulin (all types and doses pooled together in the same drug class) • Placebo
Outcomes	Outcomes will be extracted in this review for inclusion in the review. The final time point (end point of the trial) reported will be extracted and used in the analysis where possible. • Health-related quality of life (continuous outcomes): • All-cause mortality (time-to-event/dichotomous outcome) • Cardiovascular mortality (time-to-event/dichotomous outcome) • Major Cardiovascular Events (MACE) (where multiple MACE values are reported [for example: 3-item MACE and 4-item MACE], the highest number MACE value will be prioritised) (time-to-event/dichotomous outcome) ○ 3-item MACE ○ 4-item MACE ○ 5-item MACE • Events making up MACE (not previously stated) (time-to-event/dichotomous outcomes): ○ Non-fatal stroke ○ Non-fatal myocardial infarction ○ Unstable angina ○ Hospitalisation for heart failure • Renal events (time-to-event/dichotomous outcome): ○ Acute kidney injury ○ Persistent signs of worsening kidney disease (including doubling of serum creatinine) ○ Development of end stage kidney disease (including need for renal replacement therapy and transplant) ○ Death from renal cause • Serious adverse events (time-to-event/dichotomous outcome): ○ Cardiac arrhythmia (including atrial fibrillation) ○ Diabetic ketoacidosis ○ Falls requiring hospitalisation • Progression of liver disease (to non-alcoholic fatty liver disease, to fibrosis, to cirrhosis, to end stage liver disease) (time-to-event/dichotomous outcome) • Remission (time-to-event/dichotomous outcome) • Acute diabetic complications (time-to-event/dichotomous outcome): ○ Hypoglycaemia episodes

	○ At night hypoglycaemic episodes ○ Severe hypoglycaemic episodes • Continuous outcomes: ○ HbA1c change (absolute change scores prioritised over percentage change scores) ○ Weight change ○ BMI change
Study design	Systematic reviews of randomised controlled trials and randomised controlled trials Published network meta-analyses and individual patient data analyses were considered for inclusion.

For full details see the review protocol in Appendix A.

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

One hundred and twenty-five randomised controlled trial studies (one hundred and thirty-six papers) were included in the review;[1-84, 87-137] these are summarised in Table 2. All the available evidence was in people with type 2 diabetes and high, mixed or unclear cardiovascular risk and without the clear presence of heart failure, atherosclerotic cardiovascular disease or chronic kidney disease (and so analysed in model 5: people with type 2 diabetes mellitus and higher cardiovascular risk, see methods chapter). Studies were only included if they reported outcomes at follow-up times of 24 weeks or longer, and where multiple timepoints were reported, the longest timepoint was extracted. This review, the extracted timepoints ranged between 5.5 and 60 months. Evidence from these studies is summarised in the clinical evidence summary (sections 1.1.6 and 1.1.7).

No relevant clinical studies comparing the following population models were identified:

- Model 1: People with type 2 diabetes mellitus and heart failure
- Model 2: People with type 2 diabetes mellitus and atherosclerotic heart disease
- Model 3: People with type 2 diabetes mellitus and chronic kidney disease
- Model 4: People with type 2 diabetes mellitus and lower cardiovascular risk

No relevant clinical studies including the following drug interventions were identified:

- Lixisenatide
- Ertugliflozin

No relevant clinical studies reporting the following outcomes were identified:

- 3-item MACE
- 5-item MACE
- Falls requiring hospitalisation

See also the study selection flow chart in Appendix C and study evidence tables in Appendix D. The forest plots and GRADE tables can be found in report E2 (forest plots in Appendix E, GRADE tables in Appendix F).

1.1.4.2. Excluded studies

See the excluded studies list in report E2 appendix J.

1.1.5. Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Author	Population	Intervention and comparison	Outcomes	Comments
Aggarwal 2018	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic	Previous medication usage: 6) No response criteria N = 539 Metformin extended release (2000mg/d) (n=268) Metformin Immediate release (2000mg/d)	All-cause mortality, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: 148 sites in North America (USA, Canada, Puerto Rico), Europe (Germany, Hungary, Poland, Romania, UK) and South Africa Sources of

Author	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.05 (10.5008) years Time since type 2 diabetes diagnosis: 1.905 (2.7063) years	(n=271) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.		funding: Bristol-Myers Squibb
Arjona Ferreira 2013A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 59.5 (9.5116) years Time since type 2 diabetes diagnosis: Not stated/unclear	Previous medication usage: 7) Mixed population N = 129 Sitagliptin (n=64) Glipizide (n=65) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hospitalisation for heart failure, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12.4 months	Study location: Multinational Sources of funding: Sponsored by Merck Sharp & Dohme Corp.
Arjona Ferreira 2013B	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Mixed population T2DM and	Previous medication usage: 7) Mixed population N = 423 Sitagliptin (n=211) Glipizide (n=212) Concomitant therapy: None	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hospitalisation for heart failure, Development of end stage kidney disease, Diabetic ketoacidosis, Severe	Study location: Multinational Sources of funding: Sponsored by Merck Sharp & Dohme Corp

Author	Population	Intervention and comparison	Outcomes	Comments
	atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 64.55 (9.9231) years Time since type 2 diabetes diagnosis: 10.4 (7.6518) years	Antihyperglycaemic treatment received: No additional information available.	hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12.4 months	
Aroda 2019B PIONEER 1	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.5 (11) years Time since type 2 diabetes diagnosis: 3.5 (4.9021) years	Previous medication usage: 6) No response criteria N = 703 Semaglutide (n=525) Placebo (n=178) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Multicenter Sources of funding: The trial was funded by Novo Nordisk A/S. In addition, authors received consultancy fees, grants and research support from a range of pharmacological industries.
Aronoff 2000 drug naïve Pioglitazone 001	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Previous medication usage: 5) All treatment naïve N = 398 Placebo (n=79) Pioglitazone 7.5mg (n=79)	HbA1c change Follow up: 6 months	Study location: USA Sources of funding: Funded by Takeda America.

Author	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Pioglitazone 15mg (n=79) Pioglitazone 30mg (n=85) Pioglitazone 45mg (n=76) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.		
Aschner 2006 Sitagliptin 021	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 54.25 (9.9033) years Time since type 2 diabetes diagnosis: 4.45 (4.7661) years	Previous medication usage: 7) Mixed population N = 741 Sitagliptin (n=488) Placebo (n=253) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 5.5 months	Study location: Multinational Sources of funding: Sponsored by Merck
Aschner 2010 Sitagliptin 049	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Previous medication usage: 6) No response criteria N = 1050 Sitagliptin (n=528) Metformin (n=522)	All-cause mortality, Non-fatal myocardial infarction, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Multicenter Sources of funding: The study was funded by Merck & Co.,

Author	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 56 (10.503) years Time since type 2 diabetes diagnosis: 2.35 (3.7065) years	Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	change, Weight change Follow up: 6 months	Whitehouse Station, NJ, USA.
Bailey 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53 (10.5805) years Time since type 2 diabetes diagnosis: 1.4 (2.5232)	Previous medication usage: 7) Mixed population N = 282 Placebo once daily (n=68) dapagliflozin 1 mg (n=72) dapagliflozin 2.5 mg (n=74) dapagliflozin 5 mg (n=68) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: USA, Canada, Mexico, Russia, India, South Africa, Puerto Rico Sources of funding: Bristol-Myers Squibb and AstraZeneca
Banerji 1995	Model 5: People with type 2 diabetes at	Previous medication usage:	Remission, Severe hypoglycaemic	Study location: USA

Author	Population	Intervention and comparison	Outcomes	Comments
	higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	6) No response criteria Glipizide (n=10) Placebo (n=10) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	episodes, HbA1c change, BMI change Follow up: 36 months	Sources of funding: Supported by Pfizer
Barzilai 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 71.85 (6.0497) years Time since type 2 diabetes diagnosis: 7.1 (7.4017) years	Previous medication usage: 7) Mixed population N = 206 Sitagliptin (n=102) Placebo (n=104) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: USA Sources of funding: Sponsored by Merck & Co Inc.
Bi 2013	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Previous medication usage: 5) All treatment naïve N = 160 Glipizide (n=80)	HbA1c change, Weight change Follow up: 5.5 months	Study location: China. Sources of funding: Sponsored by grants from Pfizer

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 55.05 years Time since type 2 diabetes diagnosed: Not stated/unclear	Metformin (n=80) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.		Inc, the National Natural Science Foundation of China Grant Award (81270906, 81070636, 81000338), the China Postdoctoral Science Foundation (2012M521050), the Jiangsu Province's Key Discipline of Medicine (XK201105), Guangdong Natural Science Foundation (1015100890100 0033), Jiangsu Province's Key Provincial Talents Program (RC2011011) and the Key Project of Nanjing Medical Science and Technology Development Foundation (ZKX11017).
Birkeland 1994	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Mixed population	Previous medication usage: 5) All treatment naïve N = Glipizide (n=15) Placebo (n=16) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes Follow up: 15 months	Study location: Norway Sources of funding: Supported by Farmitalia Carlo Erba

Author	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 59 years Time since type 2 diabetes diagnosis: 3.5 years			
Bosi 2009	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 52.8667 (10.6789) years Time since type 2 diabetes diagnosis: 24.84 (36.9212) months	Previous medication usage: 6) No response criteria N = 1179 Vildagliptin + metformin (combination) (n=585) Vildagliptin (n=300) Metformin (n=294) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Non-fatal myocardial infarction, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: 250 centres in the USA, Canada, Europe, South America and India Sources of funding: Supported by Novartis Pharmaceutical Corporation.
Camerini-Davalos 1988	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Mixed population Mean age (SD): Not	Previous medication usage: 5) All treatment naïve N = 53 Glipizide (n=35) Placebo (n=18) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 24 months	Study location: USA Sources of funding: Supported by Pfizer, the Diabetes Research Fund and the Veterans Administration Research Fund

Author	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear			
Campbell 1994	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57 (9.5131) years Time since type 2 diabetes diagnosis: Not stated/unclear	Previous medication usage: 8) Not reported N = 48 Glipizide (n=24) Metformin (n=24) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: United Kingdom. Sources of funding: No additional information.
Chakrabor ty 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing	Previous medication usage: 6) No response criteria Metformin (n=110) Placebo (n=98) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, BMI change Follow up: 5.5 months	Study location: India. Sources of funding: Funding from the UGC-RFSMS programme for a fellowship for the first author and RSSDI for financial support. Instruments and funding provided by UGC-CAS (Phase-I) and DST-FIST.

Author	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease			
Charbonnel 2005	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 5) All treatment naïve Pioglitazone (n=635) Gliclazide (n=635) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change Follow up: 12 months	Study location: Multicenter Sources of funding: Funded by Takeda Euro R&D and Eli Lilly, Indianapolis, IN, USA.
Chen 2015	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 54.35 (9.8432) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 7) Mixed population N = 299 Linagliptin (n=200) Placebo (n=99) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Non-fatal myocardial infarction, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: China, Malaysia and the Philippines Sources of funding: Supported by Boehringer Ingelheim, Pharma GmbH & Co
Chen 2018B AWARD-CHN1	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Previous medication usage: 7) Mixed population N = 737	All-cause mortality, Cardiovascular mortality, Non-fatal stroke,	Study location: International (48 centres in China, South Korea and

Author	Population	Intervention and comparison	Outcomes	Comments
	disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 52.8333 (10.3002) years Time since type 2 diabetes diagnosis: 3.7667 (4.1993) years	Dulaglutide 1.5 mg once weekly (n=244) Glimepiride 1-3 mg once daily (n=245) Dulaglutide 0.75 mg once weekly (n=248) Concomitant therapy: Placebo Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Taiwan) Sources of funding: Funded by Eli Lilly & Co.
Chen 2022 SUCCESS	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 50.7 (11.204) years Time since type 2 diabetes diagnosis: 11.35 (28.2) months	Previous medication usage: 5) All treatment naïve N = 432 Saxagliptin + Gliclazide (n=216) Saxagliptin + Metformin (n=216) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, BMI change Follow up: 5.5 months	Study location: China. Sources of funding: AstraZeneca.

Author	Population	Intervention and comparison	Outcomes	Comments
Chiasson 2001	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57.8 (9.2728) years Time since type 2 diabetes diagnosis: 6.3 (6.2757) years	Previous medication usage: 7) Mixed population N = 166 Metformin (n=83) Placebo (n=83) Concomitant therapy: None Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 24.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 45.8%	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 8.3 months	Study location: Multicenter (location unclear). Sources of funding: An unrestricted research grant from Bayer Canada, Inc. and additional financial support from Sanofi-Synthelabo.
Chou 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 5) All treatment naïve Placebo (n=137) Rivoglitazone 1.0 mg (n=274) Rivoglitazone 1.5mg (n=750) Pioglitazone 45mg (n=751) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Hypoglycaemia episodes, HbA1c change Follow up: 6 months	Study location: USA, Europe, India, South America, South Africa Sources of funding: This study was funded by Daiichi Sankyo, Inc.
de Boer 2017 RELEASE	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Previous medication usage: 5) All treatment naïve N = 44	HbA1c change, Weight change Follow up: 6 months	Study location: The Netherlands Sources of funding: Supported by

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Linagliptin (n=22) Placebo (n=22) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.		Boehringer Ingelheim BV
DeFronzo 1995	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53 years	Previous medication usage: 5) All treatment naïve N = 289 Metformin (n=143) Placebo (n=146) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6.7 months	Study location: Multicenter study in the United States of America. Sources of funding: A grant from Lipha Pharmaceuticals, Inc.

Author	Population	Intervention and comparison	Outcomes	Comments
	Time since type 2 diabetes diagnosis: 6 years			
DeFronzo 2008 Alogliptin Study 010	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 53.4 years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 328 Alogliptin (n=264) Placebo (n=64) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: No additional information Sources of funding: Supported by Takeda Global Research and Development
Dejager 2007	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53.1 (10.8258) years	Previous medication usage: 7) Mixed population N = 378 Vildagliptin (n=284) Placebo (n=94) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 5.5 months	Study location: USA, Russia and Tunisia Sources of funding: Funded by Novartis Pharmaceuticals Corporation

Author	Population	Intervention and comparison	Outcomes	Comments
	Time since type 2 diabetes diagnosis: 1.9 (3.4424) years			
del Prato 2003	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 56 (9) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 7) Mixed population N = 428 Metformin (n=284) Placebo (n=144) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: International, multicenter trial (316 centers in France, Italy and the Netherlands). Sources of funding: Funded by IRIS (Institut de Recherches Internationales Servier Courbevoie Cedex, France).
del Prato 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 503 Linagliptin 5 mg (n=336) Placebo (n=167) Concomitant therapy: Rescue treatment with metformin only. Antihyperglycaemic treatment received: None.	Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter trial. Sources of funding: Boehringer Ingelheim.

Author	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 56.4 (10.1) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Derosa 2004	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57 (9.507) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 8) Not reported N = 164 Glimepiride (n=81) Metformin (n=83) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, BMI change Follow up: 12 months	Study location: Italy. Sources of funding: No additional information.
Derosa 2009	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease:	Previous medication usage: 5) All treatment naïve N = 271 Pioglitazone (n=69) Metformin (n=67) Pioglitazone and metformin (n=69) Glimepiride and metformin (n=66) Concomitant therapy: None Antihyperglycaemic treatment received: No additional	Hypoglycaemia episodes, HbA1c change, BMI change Follow up: 15 months	Study location: Italy. Sources of funding: No funding declared.

Author	Population	Intervention and comparison	Outcomes	Comments
	People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 55.925 (6.3053) years Time since type 2 diabetes diagnosed: Not stated/unclear	information available.		
Dou 2018 START	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 50.1333 (10.7673) years Time since type 2 diabetes diagnosis: 0.8067 (1.9361) years	Previous medication usage: 7) Mixed population N = 640 Saxagliptin + metformin (n=216) Saxagliptin (n=214) Metformin (n=210) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Non-fatal myocardial infarction, Non-fatal stroke, Persistent signs of worsening kidney disease, Progression of liver disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: 25 centres in China. Sources of funding: Funding from AstraZeneca.
Erem 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic	Previous medication usage: 5) All treatment naïve N = 60 Pioglitazone (n=20) Gliclazide (n=20) Metformin (n=20) Concomitant therapy: None	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight	Study location: Turkey. Sources of funding: Supported by a research grant from the Karadeniz Technical University

Author	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53.2333 (8.4258) years Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: No additional information available.	change, BMI change Follow up: 12 months	(Project No. 2008.114.003.1).
Esposito 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.55 (6.3549) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 110 Pioglitazone (n=55) Metformin (n=55) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Italy. Sources of funding: Supported by the Secondary University of Naples and by an unconditional research grant from Takeda Italia Farmaceutici S. p. A.
Feng 2017 Subsidiary paper:	Model 2: People with type 2 diabetes and chronic kidney disease Model 3: People with type 2 diabetes and chronic kidney	Previous medication usage: 6) No response criteria N = 93 Liraglutide (n=30)	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change	Study location: China. Sources of funding: Grants from the National Natural Science

Author	Population	Intervention and comparison	Outcomes	Comments
Feng 2019	disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 47.1 years Time since type 2 diabetes diagnosis: months	Metformin (n=31) Gliclazide (n=32) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	Foundation of China (81570737, 81570736, 81370947); Project of National Key Clinical Division, Jiangsu Province's Key Discipline of Medicine (XK201105); Medical and Health Research Projects of Nanjing Health Bureau in Jiangsu Province of China (YKK14055); Nanjing Outstanding Youth Fund Projects in Jiangsu Province of China (JQX13010); Nanjing Science and Technology Development projects in Jiangsu province of China (2013ZD005); Project of Standardized Diagnosis and Treatment of Key Diseases in Jiangsu province of China (2015604); China Diabetes Young Scientific Talent Research Project (2017-N-05); and Nanjing University Central University Basic Scientific Research (14380296).
Ferrannini 2010	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Previous medication usage: 5) All treatment naïve N = 559 Placebo once daily	All-cause mortality, Hypoglycaemia episodes, HbA1c change, Weight change	Study location: US, Canada, Mexico, Russia Sources of funding: Bristol-

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 52.2425 (10.8247) years Time since type 2 diabetes diagnosed: Not stated/unclear	(n=75) Dapagliflozin 2.5 mg daily (n=132) Dapagliflozin 5 mg daily (n=167) Dapagliflozin 10 mg daily (n=185) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	Myers Squibb and AstraZeneca.
Foley 2009	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 54.75 (10.5005) years Time since type 2 diabetes diagnosis: 2.15 (3.7483) years	Previous medication usage: 7) Mixed population N = 1092 Vildagliptin (n=546) Gliclazide (n=546) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, HbA1c change, Weight change Follow up: 24 months	Study location: Multinational - Europe, Latin America and South Africa Sources of funding: Authored by Novartis

Author	Population	Intervention and comparison	Outcomes	Comments
Foley 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57.2 (8.139) years Time since type 2 diabetes diagnosis: 1 (2.1135) years	Previous medication usage: 5) All treatment naïve N = 59 Vildagliptin (n=29) Placebo (n=30) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 12 months	Study location: The Netherlands Sources of funding: Sponsored by the Novartis Pharmaceutical Cooperation
Frederich 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.2 (10.36) years Time since type 2	Previous medication usage: 7) Mixed population N = 365 Saxagliptin (n=291) Placebo (n=74) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, HbA1c change, Weight change Follow up: 5.5 months	Study location: 72 sites in the United States, Russia, India and Taiwan. Sources of funding: Funding was provided by Bristol-Myers Squibb and AstraZeneca.

Author	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosis: 1.7 (3.2057) years			
Gantz 2017D Omariglipt in Protocol 020	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 60.5 (9) years Time since type 2 diabetes diagnosis: 8 (5.2342) years	Previous medication usage: 7) Mixed population N = 248 Sitagliptin (n=165) Placebo (n=83) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Japan Sources of funding: Funding for this study was provided by MSD K.K., a subsidiary of Merck & Co
Garber 2009 LEAD-3	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease	Previous medication usage: 5) All treatment naïve N = 746 1.2 mg Liraglutide (n=251) 1.8 mg Liraglutide (n=247) Glimepiride (n=248) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 12 months	Study location: USA and Mexico Sources of funding: Funded by Novo Nordisk

Author	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 53.0333 (10.9008) years Time since type 2 diabetes diagnosis: 5.3667 (5.238) years			
Goldner 1971	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 53 years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 8) Not reported N = Tolbutamide (n=204) Insulin (n=414) Placebo (n=205) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Persistent signs of worsening kidney disease, Cardiac arrhythmia Follow up: 60 months	Study location: United States of America. Sources of funding: No additional information.
Goldstein 2007 Sitagliptin 036	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular	Previous medication usage: 7) Mixed population N = 1091 Sitagliptin + Metformin (n=372) Metformin (n=364) Sitagliptin (n=179) Placebo (n=176) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter trial. Sources of funding: Funded by Merck & Company, Whitehouse Station, New Jersey.

Author	Population	Intervention and comparison	Outcomes	Comments
	disease Mean age (SD): 53.475 (9.932) years Time since type 2 diabetes diagnosis: 4.5 (4.487) years			
Grant 1996	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 8) Not reported Metformin (n=52) Placebo (n=23) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 6 months	Study location: United Kingdom. Sources of funding: Supported by Lipha Pharmaceuticals, West Drayton, Middlesex, U.K.
Guo 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54 (7.3) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 5) all treatment naïve N = 58 Metformin (n=29) Placebo (n=29) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 5.5 months	Study location: China Sources of funding: 'This study was supported, in part, by a grant for diabetes research from Peking University, Program for Scientific Research Innovation Team in Colleges and Universities of Shandong Province and Taishan Scholars Construction Engineering.'

Author	Population	Intervention and comparison	Outcomes	Comments
Haak 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.5 (10.8183) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 7) Mixed population N = 791 Linagliptin + metformin (n=286) Linagliptin (n=142) Metformin (n=291) Placebo (n=72) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Funded by Boehringer Ingelheim.
Hadjadj 2016	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease	Previous medication usage: 8) Not reported N = 1360 Empagliflozin + metformin (n=680) Empagliflozin (n=339) Metformin (n=341) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Authors were employees of Boehringer Ingelheim Pharma GmbH & Co. Authors received funding from other companies including AstraZeneca, Bristol-Myers Squibb, Abbott, Eli Lilly, Janssen, Lexicon, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier and Takeda.

Author	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 52.6667 (10.9515) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Hällsten 2002 Subsidiary study: Koffert 2017	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57.75 years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 27 Metformin (n=13) Placebo (n=14) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 6 months	Study location: Finland. Sources of funding: Grants from the Academy of Finland, the Novo Nordisk Foundation, the Finnish Diabetes Research Society and GlaxoSmithKline.
Hartley 2015	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not	Previous medication usage: 7) Mixed population N = 480 Sitagliptin (n=241) Glimepiride (n=239) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Study location: Multinational trial (85 sites) - locations not specified Sources of funding: Merck & Co.

Author	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 70.7 (4.85) years Time since type 2 diabetes diagnosis: 8.7 (6.5022) years			
Henry 2012A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.9333 (9.7805) years Time since type 2 diabetes diagnosis: 1.6 (2.7209) years	Previous medication usage: 6) No response criteria N = 598 Dapagliflozin + metformin (study 1) (n=194) Dapagliflozin (study 1) (n=203) Metformin (study 1) (n=201) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter trial (North America, Latin America, Europe and Asia). Sources of funding: Funded by Bristol-Myers Squibb and AstraZeneca. This study and Henry 2012B are both reported in the same paper.
Henry 2012B	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other	Previous medication usage: 6) No response criteria N = 638 Dapagliflozin + metformin (study 2) (n=211) Dapagliflozin (study 2) (n=219) Metformin (study 2) (n=208) Concomitant	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter trial (North America, Latin America, Europe and Asia). Sources of funding: Funded by Bristol-Myers Squibb and AstraZeneca.

Author	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.6 (10.6956) years Time since type 2 diabetes diagnosis: 2.0667 (3.7114) years	therapy: None Antihyperglycaemic treatment received: No additional information available.		This study and Henry 2012A are both reported in the same paper.
Henry 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 7) Mixed population N = 1332 Pioglitazone (n=565) Sitagliptin (n=186) Pioglitazone + Sitagliptin (n=581) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: No additional information Sources of funding: Sponsored by Merck & Co.
Horton 2000	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear	Previous medication usage: 6) No response criteria N = 350 Metformin (n=178) Placebo (n=172) Concomitant	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes Follow up: 5.5 months	Study location: United States of America. Sources of funding: Financial support from Novartis.

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 58.2 (10.9) years Time since type 2 diabetes diagnosis: 4.55 (5.1225) years	therapy: None Antihyperglycaemic treatment received: No additional information available.		
Inagaki 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Mixed population T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58 (10.8386) years Time since type 2 diabetes diagnosis: 58 (10.8386) years	Previous medication usage: 7) Mixed population N = 272 Placebo once daily (n=93) Canagliflozin 100 mg once daily (n=90) Canagliflozin 200 mg once daily (n=89) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Japan Sources of funding: This study was funded by Mitsubishi Tanabe Pharma Corp.
Inagaki 2015	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Previous medication usage: 7) Mixed population N = 142 Alogliptin (n=92)	Hypoglycaemia episodes, HbA1c change	Study location: Japan Sources of funding: Sponsored by

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Placebo (n=50) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	Takeda Pharmaceuticals
Inagaki 2022 SURPASS J-mono	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.625 (10.3282) years Time since type 2 diabetes diagnosis: Not stated/unclear	Previous medication usage: 7) Mixed population N = 636 Tirzepatide 15 mg once weekly (n=160) Tirzepatide 10 mg once weekly (n=158) Tirzepatide 5 mg once weekly (n=159) Dulaglutide 0.75 mg once weekly (n=159) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Unstable angina, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Japan Sources of funding: Funded by Eli Lilly & Co.
Ji 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Previous medication usage: 7) Mixed population N = 393	All-cause mortality, Cardiovascular mortality, Persistent signs of worsening kidney disease,	Study location: China, Korea, Tai wan, India Sources of

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 51.3667 (10.616) years Time since type 2 diabetes diagnosis: 1.3733 (2.3916)	Placebo (n=132) Dapagliflozin 5 mg once daily (n=128) Dapagliflozin 10 mg once daily (n=133) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	funding: Bristol-Myers Squibb and AstraZeneca.
Ji 2016A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 52.65 (10.0498) years Time since type 2	Previous medication usage: 7) Mixed population N = 744 Sitagliptin + metformin (n=247) Metformin (n=250) Sitagliptin (n=120) Placebo (n=127) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: China. Sources of funding: Funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Author	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosis: 1.1 (0.238) years			
Ji 2017	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 53.65 (10.0424) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 647 Alogliptin + metformin (n=159) Alogliptin (n=163) Metformin (n=162) Placebo (n=163) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: China, Malaysia, the Republic of Korea (South Korea) and Taiwan. Sources of funding: Funded by Takeda Pharmaceutical Company Limited. Some authors received grants from this organisation.
Jiang 2021	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.81 (8.3638) years Time since type 2	Previous medication usage: 5) All treatment naïve N = 29 Placebo once daily (n=10) Dapagliflozin 10 mg once daily (n=19) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	No outcomes relevant to the review protocol (outcomes relevant to the extended outcome set that are not included in the review)	Study location: China Sources of funding: Jiangsu Natural Science Foundation and the Nanjing Medical Science and Technique Development Foundation.

Author	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: Not stated/unclear			
Kahl 2019	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.1 (8.6313) years Time since type 2 diabetes diagnosis: 38 (27) months	Previous medication usage: 7) Mixed population N = 84 Empagliflozin (n=42) Placebo (n=42) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 5.5 months	Study location: Germany (five centers). Sources of funding: Funded by the German Federal Ministry of Health and the Ministry of Innovation, Science and Research to the German Center for Diabetes Research.
Kaku 2014	Model 1: People with type 2 diabetes and heart failure Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: People with heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease	Previous medication usage: 3) Selection of specific population N = 261 Dapagliflozin 5 mg once daily (n=86) Dapagliflozin 10 mg once daily (n=88) Placebo (n=87) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Persistent signs of worsening kidney disease, HbA1c change, Weight change Follow up: 5.5 months	Study location: Japan Sources of funding: Funded by AstraZeneca and Bristol-Myers Squibb.

Author	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 58.8333 (9.8063) years Time since type 2 diabetes diagnosis: 4.9367 (5.4556) years			
Kaku 2018A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57.15 (9.6061) years Time since type 2 diabetes diagnosis: 8 (5.3071) years	Previous medication usage: 1) Including only responders N = 215 Empagliflozin + linagliptin (n=107) Empagliflozin (n=108) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Japan Sources of funding: Funded by Boehringer Ingelheim Kaku 2018A and Kaku 2018B are a part of the same paper and represent two parts of the trial that are reflected as two different studies in this analysis.
Kaku 2018B	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular	Previous medication usage: 1) Including only responders N = 232 Empagliflozin + linagliptin (n=116) Empagliflozin (n=116) Concomitant therapy: None Antihyperglycaemic treatment received:	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: Japan Sources of funding: Funded by Boehringer Ingelheim Kaku 2018A and Kaku 2018B are a part of the same paper and represent two parts of the trial that are reflected

Author	Population	Intervention and comparison	Outcomes	Comments
	diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57.6 (9.9247) years Time since type 2 diabetes diagnosis: 8.4 (5.6009) years	No additional information available.		as two different studies in this analysis.
Kashyap 2020	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 6) No response criteria N = 16 Canagliflozin (n=11) Placebo (n=5) Concomitant therapy: None Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 10% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: NR Sources of funding: Investigator initiated study to S.R.K. by Janssen Scientific Affairs, LLC.
Kikuchi 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure	Previous medication usage: 5) All treatment naïve Placebo (n=54) Rosiglitazone (n=159) Pioglitazone (n=159)	Non-fatal myocardial infarction, HbA1c change, Weight change Follow up: 6.5 months	Study location: Japan Sources of funding: sponsored by GlaxoSmithKline

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.		
Kim 2017	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Mixed population Mean age (SD): 53.95 (8.8545) years Time since type 2 diabetes diagnosis: 4.25 (4.1774) years	Previous medication usage: 7) Mixed population N = 292 Sitagliptin + Metformin (n=147) Glimepiride (n=145) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Study location: South Korea Sources of funding: Funded by MSD Korea
Kondo 2016	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear	Previous medication usage: 6) No response criteria N = 171 Glimepiride (n=85) Sitagliptin (n=86) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Persistent signs of worsening kidney disease, Progression of liver disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, BMI change Follow up: 12 months	Study location: Japan in 18 centers. Sources of funding: The trial was supported by the Japan Diabetes Foundation.

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 63.5 (8.5176) years Time since type 2 diabetes diagnosis: 6.1 (5.5709)			
Kumar 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 48.7 (9.2068) years Time since type 2 diabetes diagnosis: 0.9 (1.3034) years	Previous medication usage: 6) No response criteria N = 213 Saxagliptin (n=107) Placebo (n=106) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: India (12 centers). Sources of funding: Funded by Bristol-Myers Squibb and AstraZeneca.
Lambadiari 2018	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney	Previous medication usage: 5) All treatment naïve N = 60 Liraglutide (n=30) Metformin (n=30) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Greece. Sources of funding: No funding.

Author	Population	Intervention and comparison	Outcomes	Comments
	disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 50.5 (11.0454) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Lee 2013A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 5) All treatment naïve Pioglitazone (n=25) Placebo (n=25) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke Follow up: 6 months	Study location: Korea Sources of funding: Grant from Korean Society of Hypertension.
Lewin 2015	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD):	Previous medication usage: 3) Selection of specific population N = 667 Empagliflozin 25 mg once daily (n=133) Empagliflozin 10 mg once daily (n=132) Linagliptin 5 mg once daily (n=133) Empagliflozin 25mg/linagliptin 5mg (n=134) Empagliflozin 10mg/linagliptin 5mg (n=135) Concomitant therapy: None	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: US Sources of funding: Boehringer Ingelheim and Eli Lilly and Company.

Author	Population	Intervention and comparison	Outcomes	Comments
	54.475 (9.2409) years Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: No additional information available.		
Li 2019A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 47.7667 (8.8594) years Time since type 2 diabetes diagnosis: 10.3667 (6.6184) years	Previous medication usage: 5) All treatment naïve N = 95 Saxagliptin 5 mg once daily (n=31) Glimepiride 2 mg once daily (n=33) Glimepiride 2 mg once daily + Polyene phosphatidylcholine 456 mg thrice daily (n=31) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, BMI change Follow up: 5.5 months	Study location: Shandong, China Sources of funding: Not reported
Liu 2020	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD):	Previous medication usage: 5) All treatment naïve N = 76 Exenatide 10 mcg twice daily (n=38) Insulin glargine 0.1-0.3IU/kg once daily (n=38) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: China Sources of funding: Funded by: 3SBio Inc; AstraZeneca China; National Key R&D Program of China, Grant/Award Numbers: 2017YFC1309800,2017YFC1309801, 2017YFC1309804.

Author	Population	Intervention and comparison	Outcomes	Comments
	49.095 (10.9906) years Time since type 2 diabetes diagnosis: 0.42 (1.0456)			
Mari 2008 Subsidiary study: Scherbaum 2008	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 63.05 (10.5997) years Time since type 2 diabetes diagnosis: 2.6 (3.0507) years	Previous medication usage: 7) Mixed population N = 306 Vildagliptin 50 mg once daily (n=156) Placebo (n=150) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: International (69 sites in Finland, France, Germany, Romania, Spain and Sweden) Sources of funding: Funded by Novartis Pharmaceuticals Corporation
Mita 2019	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: No information T2DM and atherosclerotic cardiovascular disease: No information T2DM and chronic kidney disease: No information T2DM and higher cardiovascular risk: No information Mean age (SD): 59.7 (11.5959) years	Previous medication usage: 5) All treatment naïve N = 43 Linagliptin 5 mg once daily (n=21) Metformin 2250 mg daily (n=22) Concomitant therapy: None or insulin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, BMI change Follow up: 5.5 months	Study location: Japan Sources of funding: Nippon Boehringer Ingelheim Co., Ltd. and Eli Lilly and Company.

Author	Population	Intervention and comparison	Outcomes	Comments
	Time since type 2 diabetes diagnosis: 3.35 (5.0587)			
Miyagawa 2015 Subsidiary paper: Odawara 2016 Suzuki 2017	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.6 (9.6443) years Time since type 2 diabetes diagnosis: 6.4667 (5.6415) years	Previous medication usage: 7) Mixed population N = 501 Dulaglutide 0.75 mg once weekly (n=281) Liraglutide 0.9 mg once daily (n=141) Placebo once weekly for 26 weeks then dulaglutide 0.75 mg once weekly for 26 weeks (n=79) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: Japan (33 sites in 14 cities) Sources of funding: Eli Lilly Japan K.K., Kobe, Japan.
Miyazaki 2002	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54 years Time since type 2	Previous medication usage: 3) Selection of specific population N = Pioglitazone 7.5mg/day (n=13) Pioglitazone 15mg/day (n=12) Pioglitazone 30mg/day (n=11) Pioglitazone 45mg/day (n=11) Placebo (n=11) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: NR Sources of funding: Support for the multicenter trial was provided by Takeda

Author	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: Not stated/unclear			
Moretto 2008	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54 (9.6767) years Time since type 2 diabetes diagnosis: 1.6667 (2.7067) years	Previous medication usage: 5) All treatment naïve N = 233 Exenatide 10 mcg twice daily (n=78) Exenatide 5 mcg twice daily (n=77) Placebo (n=78) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: International (23 centres in India, Puerto Rico, Romania, Russia, USA) Sources of funding: Funded by Amylin Pharmaceuticals, Inc, San Diego, CA, USA and Eli Lilly and Co. Indiana, IN, USA. Publication funded by Eli Lilly and Co.
Mu 2017	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk:	Previous medication usage: 7) Mixed population N = 730 Linagliptin + metformin (study A) (n=294) Metformin (study A) (n=289) Linagliptin (study A) (n=147) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	4-point MACE, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter. China, Malaysia, Philippines and Vietnam. Sources of funding: Supported by Boehringer Ingelheim and Eli Lilly and Company.

Author	Population	Intervention and comparison	Outcomes	Comments
	Not stated/unclear Mean age (SD): 51.2333 (10.0231) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Nauck 2016	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.4 (8.2253) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 7) Mixed population N = 805 Pioglitazone 45 mg + Linagliptin 5 mg SPC once daily (n=133) Pioglitazone 30 mg + Linagliptin 5 mg SPC once daily (n=133) Pioglitazone 15 mg + Linagliptin 5 mg SPC once daily (n=126) Linagliptin 5 mg once daily (n=135) Pioglitazone 45 mg once daily (n=138) Pioglitazone 30 mg once daily (n=140) Pioglitazone 15 mg once daily (n=131) Concomitant therapy: Placebo Antihyperglycaemic treatment received: No additional information available.	4-point MACE, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Study location: International (132 sites in Estonia, Germany, Latvia, Spain, UK and USA) Sources of funding: Funded by Boehringer Ingelheim and Eli Lilly and Co.
Pan 2012A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular	Previous medication usage: 7) Mixed population N = 568 Saxagliptin 5 mg once daily (n=284) Placebo (n=284) Concomitant therapy: None Antihyperglycaemic treatment received: No additional	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: International (40 sites in China, India, Philippines, and South Korea) Sources of funding: Funded by Astra-Zeneca and Bristol-Myers Squibb.

Author	Population	Intervention and comparison	Outcomes	Comments
	diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.4 (10.1511) years Time since type 2 diabetes diagnosis: 1 (2.0881) years	information available.		
Pavo 2003	Model 1: People with type 2 diabetes and heart failure T2DM and heart failure: People with heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55 (8.7656) years Time since type 2 diabetes diagnosis: 5.95 (3.8491) months	Previous medication usage: 5) All treatment naïve N = 205 Pioglitazone (n=105) Metformin (n=100) Concomitant therapy: NA Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 7.5 months	Study location: Russia and Hungary Sources of funding: NR
Perez 2009 Subsidiary study: Perez 2010	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease:	Previous medication usage: 2) Excluding non-responders N = 600 Pioglitazone + Metformin (n=201) Pioglitazone (n=189) Metformin (n=210) Concomitant therapy: None Antihyperglycaemic treatment received: No additional	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Funded by Takeda Global Research & Development Center, Inc.

Author	Population	Intervention and comparison	Outcomes	Comments
	People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 54.1333 (12.0988) years Time since type 2 diabetes diagnosed: Not stated/unclear	information available.		
Pfützner 2011A CV181-039 Subsidiary study: Jadzinsky 2009	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 52 (10.7247) years Time since type 2 diabetes diagnosis: 1.7 (3.0259) years	Previous medication usage: 7) Mixed population N = 1306 Saxagliptin + Metformin (n=643) Saxagliptin (n=335) Metformin (n=328) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 18 months	Study location: Multicenter trial. Sources of funding: Funded, designed and supervised by Bristol-Myers Squibb and AstraZeneca.
Pistrosch 2013	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Previous medication usage: 5) All treatment naïve N = 75 Metformin (n=36)	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change	Study location: Multicenter trial. Sources of funding: Funded by Sanofi-

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 61.015 (9.3481) years Time since type 2 diabetes diagnosis: 2.7 (1.4992) years	Insulin (n=39) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Follow up: 8.4 months	Aventis, Germany.
Pi-Sunyer 2007	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.2 (11.7181) year years Time since type 2 diabetes diagnosis: 2.2 (3.1517) years	Previous medication usage: 7) Mixed population N = 354 Vildagliptin 100 mg once daily (n=91) Vildagliptin 50 mg twice daily (n=83) Vildagliptin 50 mg once daily (n=88) Placebo (n=92) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 5.5 months	Study location: International (98 centres in US, India, and Slovakia) Sources of funding: Funded by Novartis Pharmaceuticals Corporation.
Pratley 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Previous medication usage: 7) Mixed population N = 784	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial	Study location: Multisite trial (198 sites worldwide).

Author	Population	Intervention and comparison	Outcomes	Comments
	disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53.5 (10.3669) years Time since type 2 diabetes diagnosis: 3.95 (4.4681) years	Alogliptin + Metformin (n=225) Metformin (n=225) Alogliptin (n=225) Placebo (n=109) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	infarction, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Sources of funding: Sponsored by Takeda Development Center Americas, Inc., Deerfield, IL, USA, and Takeda Development Centre Europe Ltd., London, UK.
Roden 2005 1.1	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.25 (9.0338) years Time since type 2 diabetes diagnosis: 5.15 (4.6515) years	Previous medication usage: 5) All treatment naïve N = 1830 Pioglitazone (n=597) Metformin (n=597) Pioglitazone (background sulfonylurea) (n=316) Metformin (background sulfonylurea) (n=320) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Weight change Follow up: 52 months	Study location: Europe (study A and B) and Canada (study B only). Sources of funding: Sponsored by Eli Lilly and Company and Takeda Europe R & D.

Author	Population	Intervention and comparison	Outcomes	Comments
Roden 2015 EMPA-REG MONO EXTEND	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55 (11.0227) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 7) Mixed population N = 899 Empagliflozin 25 mg once daily (n=224) Empagliflozin 10 mg once daily (n=224) Sitagliptin 100 mg once daily (n=223) Placebo (n=228) Concomitant therapy: Placebo Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 17.5 months	Study location: Multicenter Sources of funding: Funded by Boehringer Ingelheim and Eli Lilly & Co.
Rosenstock 2007A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.45 (10.8429) years Time since type 2	Previous medication usage: 7) Mixed population N = 607 Pioglitazone 30 mg once daily (n=161) Pioglitazone 15 mg + Vildagliptin 50 mg once daily (n=144) Pioglitazone 30 mg + Vildagliptin 100 mg once daily (n=148) Vildagliptin 100 mg once daily (n=154) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Funded by Novartis Pharmaceuticals Corporation.

Author	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosis: 2.025 (3.1779) years			
Rosenstock 2009A CV181-011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53.455 (5.4702) years Time since type 2 diabetes diagnosis: 2.45 (3.1689) years	Previous medication usage: 6) No response criteria N = 401 Saxagliptin (n=306) Placebo (n=95) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes Follow up: 5.5 months	Study location: International Sources of funding: Funded by Bristol Myers-Squibb and AstraZeneca
Rosenstock 2010	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 5) All treatment naïve Alogliptin (n=164) Pioglitazone (n=163) Alogliptin 12.5 mg + Pioglitazone 30 mg (n=163) Alogliptin 25 mg + Pioglitazone 30 mg (n=164) Concomitant therapy: NA Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 6 months	Study location: NR Sources of funding: Three authors are employees of Takeda Global Research and Development. , Other authors declare honoraria and funding from multiple pharmaceutical companies
Rosenstock 2016	Model 5: People with type 2 diabetes at	Previous medication usage:	All-cause mortality, Cardiovascular	Study location: Multicenter

Author	Population	Intervention and comparison	Outcomes	Comments
	higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 54.9667 (9.923) years Time since type 2 diabetes diagnosis: 3.2667 (4.1205) years	7) Mixed population N = 1186 Canagliflozin + metformin (n=474) Canagliflozin (n=475) Metformin (n=237) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	mortality, Non-fatal stroke, Unstable angina, Persistent signs of worsening kidney disease, Cardiac arrhythmia, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Sources of funding: Supported by Janssen Research & Development LLC. Researchers received grants from multiple pharmacological companies.
Ross 2015	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing	Previous medication usage: 6) No response criteria N = 316 Linagliptin + Metformin (n=159) Linagliptin (n=157) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter trial (Canada, India, Israel, Malaysia, Mexico, the Philippines, Russia, Sri Lanka, Thailand, Ukraine and the USA). Sources of funding: Sponsored by Boehringer Ingelheim.

Author	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease Mean age (SD): 48.8 (11.0501) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Russell-Jones 2012 DURATION-4	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53.75 (11) years Time since type 2 diabetes diagnosis: 2.675 (3.5251) years	Previous medication usage: 6) No response criteria N = 820 Exenatide (n=248) Metformin (n=246) Pioglitazone (n=163) Sitagliptin (n=163) Concomitant therapy: Placebo Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter trial (including Argentina, Belgium, Brazil, Canada, France, Germany, Hungary, India, Israel, Italy, South Korea, Mexico, Poland, Romania, the Russian Federation, Slovakia, South Africa, Spain, Taiwan, Turkey, the United Kingdom and the United States). Sources of funding: Funded by Amylin Pharmaceuticals and Eli Lilly. Authors received grants from various pharmaceutical companies.
Scherbaum 2002	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher	Previous medication usage: 2) Excluding non-responders Placebo + diet (n=84) Placebo 15mg / day + diet (n=89) Placebo 30mg / day + diet (n=78) Concomitant therapy: None Antihyperglycaemic treatment received: No additional	HbA1c change, Weight change Follow up: 6 months	Study location: Germany Sources of funding: This study was supported by Takeda Pharmaceuticals, Europe

Author	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular risk: Not stated/unclear	information available.		
Scherntha ner 2004 QUARTE T	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 56.5 (9.3501) years Time since type 2 diabetes diagnosis: 3.25 (4.0577) years	Previous medication usage: 5) All treatment naïve N = 1194 Pioglitazone (n=597) Metformin (n=597) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality Follow up: 12 months	Study location: Multicenter Sources of funding: No additional information.
Schwartz 2006	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 7) Mixed population ER metformin 1500mg /day (n=178) ER metformin 1500mg (AM/PM) (n=182) ER metformin 2000 mg / day (n=172) 1500 mg immediate-release metformin (n=174) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 5.5 months	Study location: USA Sources of funding: Financial support for this study was provided by Depomed
Schweizer 2007	Model 5: People with type 2 diabetes at	Previous medication usage:	All-cause mortality, Cardiovascular	Study location: Multicenter trial.

Author	Population	Intervention and comparison	Outcomes	Comments
Subsidiary paper: Goke 2008	higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 53.2 (11.2342) years Time since type 2 diabetes diagnosis: Not stated/unclear	6) No response criteria N = 780 Vildagliptin (n=526) Metformin (n=254) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	mortality, Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Sources of funding: Funded by Novartis Pharmaceutical Corporation.
Schweizer 2009	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: Mixed population T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease	Previous medication usage: 6) No response criteria N = 780 Vildagliptin (n=169) Metformin (n=166) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter trial. Sources of funding: Funded by Novartis Pharmaceutical Corporation.

Author	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 71 (5.1) years Mean time since type 2 diabetes diagnosis (SD): 2.9 (4.5) years			
Seino 2018	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.3(10.7) years Time since type 2 diabetes diagnosis: 8.0 (6.3) years	Previous medication usage: 7) Mixed population N = 308 Semaglutide 0.5 mg once weekly (n=103) Semaglutide 1.0 mg once weekly (n=102) Sitagliptin 100mg once daily (n=103) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Severe hypoglycaemic episodes, HbA1c change, weight change, BMI change Follow up: 8 months	Study location: Japan Sources of funding: Novo Nordisk The findings from this study are included in the pairwise analysis but not the NMA analysis due to this study being identified during quality checks. It was agreed that this was unlikely to change the results of the analysis.
Shihara 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear	Previous medication usage: 8) Not reported N = 191 Glimepiride (n=95) Pioglitazone (n=96) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Weight change, BMI change Follow up: 6 months	Study location: Japan Sources of funding: Funded by Sanofi Aventis

Author	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 57.25 (10.3499) years Time since type 2 diabetes diagnosis: 5.05 (6.5373) years			
Sorli 2017 SUSTAIN 1	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 53.7333 (11.342) years Time since type 2 diabetes diagnosis: 4.1633 (5.5077) years	Previous medication usage: 7) Mixed population N = 388 Semaglutide 1 mg once weekly (n=130) Semaglutide 0.5 mg once weekly (n=129) Placebo once weekly (n=129) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: International (72 sites in Canada, Italy, Japan, Mexico, Russia, South Africa, UK and USA) Sources of funding: Funded directly by Novo Nordisk A/S, Denmark.
Stenlöf 2013 CANTATA -M	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Mixed population T2DM and higher cardiovascular risk:	Previous medication usage: 7) Mixed population N = 584 Placebo once daily (n=192) Canagliflozin 100 mg (n=195) Canagliflozin 300 mg (n=197) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Janssen Global Services, LLC. Canagliflozin is being developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.

Author	Population	Intervention and comparison	Outcomes	Comments
	People at higher risk of developing cardiovascular disease Mean age (SD): 55.3667 (10.635) years Time since type 2 diabetes diagnosis: 4.3333 (4.4094)			
Suzuki 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.35 (15.6659) years Time since type 2 diabetes diagnosis: 2.15 (2.6141)	Previous medication usage: 5) All treatment naïve N = 40 Liraglutide (n=24) Sitagliptin (n=16) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 6 months	Study location: Japan Sources of funding: None
Tan 2005 GLAL	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 567 Gliclazide (n=297) Pioglitazone (n=270) Concomitant therapy: None Antihyperglycaemic treatment received: No additional	HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter trial. Sources of funding: Funded by Takeda Europe Research and Development Centre.

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.5 (9.8525) years Time since type 2 diabetes diagnosis: 2.8 (3.6602) years	information available.		
Tao 2018	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 29 (4.4347) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 8) Not reported N = 75 Saxagliptin + Metformin (n=25) Saxagliptin (n=25) Metformin (n=25) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: China. Sources of funding: Supported by the National Natural Science Foundation of China (grant number 81200628), the Chinese Medical Association Clinical Research and Special Funds - Squibb Endocrinology Diabetes Research projects [2012]; the Natural Science Foundation of Shanghai, China [grant number 12ZR1417800]l and the Shanghai Science and Technology Development Fund [grant number 08411953000].
Terauchi 2017 START-J	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not	Previous medication usage: 7) Mixed population N = 305 Sitagliptin (n=153) Glimepiride (n=152) Concomitant therapy: None Antihyperglycaemic treatment received: No additional	All-cause mortality, Progression of liver disease, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Japan. Sources of funding: Funded by MSD K.K., a subsidiary of Merck & Co.

Author	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 70.5 (5.4501) years Time since type 2 diabetes diagnosis: months	information available.		
Umpierrez 2014 AWARD-3 Subsidiary study: Mari 2016	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.6667 (10.3453) years Time since type 2 diabetes diagnosis: 3 (2) years	Previous medication usage: 7) Mixed population N = 807 Dulaglutide 1.5 mg (n=269) Dulaglutide 0.75 mg (n=270) Metformin (n=268) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter trial. Sources of funding: Sponsored by Eli Lilly and Company.
Wainstein 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic	Previous medication usage: 6) No response criteria N = 517 Sitagliptin + Metformin (n=261) Pioglitazone (n=256) Concomitant therapy: None Antihyperglycaemic treatment received:	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 7.4 months	Study location: Multicenter trial. Sources of funding: All authors except one were employees of Merck Sharp and Dohme Corporation, with the other author receiving honoraria for

Author	Population	Intervention and comparison	Outcomes	Comments
	kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 52.3 (10.8496) years Time since type 2 diabetes diagnosis: 3.25 (3.7607) years	No additional information available.		lecturing with the organisation.
Wang 2013	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 54.945 (10.4005) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 60 Gliclazide (n=30) Metformin (n=30) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 6 months	Study location: China. Sources of funding: Supported by a Young Medical Talents Training Program Grant of Pudong Health Bureau of Shanghai (No. PWRq2012-08) and the Key Disciplines Group Construction Project of Pudong Health Bureau of Shanghai (No. PWZxkq2010-04).
Wang 2016A Subsidiary study: Li 2016	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular	Previous medication usage: 5) All treatment naïve N = 28 Dapagliflozin (n=18) Placebo (n=10) Concomitant therapy: None	HbA1c change Follow up: 5.5 months	Study location: China Sources of funding: Grants from the National Natural Science Foundation of China, Jiangsu Planned Projects of Postdoctoral Research Funds, the Peak of Six

Author	Population	Intervention and comparison	Outcomes	Comments
	disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60 (9.7333) years Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: No additional information available.		Personnel in Jiangsu, and the Nanjing Medical Science and Technique Development Foundation.
Wang 2022A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 54.86 (8.8833) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 8) Not reported N = 54 Sitagliptin + Metformin (n=20) Sitagliptin (n=17) Metformin (n=17) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	HbA1c change, BMI change Follow up: 5.5 months	Study location: China. Sources of funding: Supported by the Climbing Talent Program of Shanghai Tenth People's Hospital (2021SYPDRC047) and National Nature Science Foundation of China (NO.81900781).
Wolever 2000	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Previous medication usage: 6) No response criteria N = 107 Metformin (n=62) Placebo (n=45)	HbA1c change Follow up: 9 months	Study location: Canada. Sources of funding: Supported by Bayer Canada Inc which also provided the

Author	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 58.6 years Time since type 2 diabetes diagnosis: 5.9 (0.7883) years	Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.		study medications.
Wu 2015	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.85 (9.0637) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 57 Linagliptin 5 mg once daily (n=34) Placebo (n=23) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Zhejiang, China Sources of funding: Supported by the National Science Foundation for Young Scholars of China (Grant No.81000356)
Xu 2015 CONFIDENCE Subsidiary	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Previous medication usage: 5) All treatment naïve N = 416 Exenatide 10 mcg	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: China (25 university-affiliated hospitals in 13 provinces) Sources of

Author	Population	Intervention and comparison	Outcomes	Comments
study: Li 2015	T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 50.3333 (0.8) years Time since type 2 diabetes diagnosed: Not stated/unclear	twice daily (n=142) Biphasic insulin lispro 25%/insulin lispro protamine 75% twice daily (n=138) Pioglitazone 45 mg once daily (n=136) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	change, Weight change, BMI change Follow up: 11.1 months	funding: Funded by Key Projects of Clinical Disciplines of Hospitals Affiliated to Ministry of Health from Ministry of Health of the People's Republic of China, the National Science Fund for Distinguished Young Scholars (81025005), investigator-initiated trial research funds from Eli Lilly and Co. and Amylin Pharmaceuticals, Inc., and the 5010 Project of Sun Yat-sen University.
Yamada 2020 PIONEER 9	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.5 (8.4821) years Time since type 2 diabetes diagnosis: 7.35 (4.9534) years	Previous medication usage: 7) Mixed population N = 243 Semaglutide 14 mg once daily (n=48) Semaglutide 7 mg once daily (n=49) Semaglutide 3 mg once daily (n=49) Liraglutide 0.9 mg once daily (n=48) Placebo (n=49) Concomitant therapy: None Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 4% Biguanides: 14.8% DPP-4 inhibitors: 10.20% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 6%	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Acute kidney injury, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Japan (16 sites) Sources of funding: Funded by Novo Nordisk.

Author	Population	Intervention and comparison	Outcomes	Comments
		Sulfonylureas: 0.8%		
Yamanouchi 2005	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 55.1667 (9.4415) years Time since type 2 diabetes diagnosis: 3.1667 (2.4087) months	Previous medication usage: 5) All treatment naïve N = 114 Pioglitazone (n=38) Metformin (n=39) Glimepiride (n=37) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, BMI change Follow up: 12 months	Study location: Japan. Sources of funding: No additional information.
Yoon 2011A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease	Previous medication usage: 5) All treatment naïve N = 232 Glimepiride (n=118) Metformin (n=114) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change Follow up: 11 months	Study location: South Korea. Sources of funding: Grants from the Korean Diabetes Association. The investigators received drugs from Handok Pharmaceuticals Co. Ltd., GlaxoSmithKline Ltd. Korea, and Merck Ltd. Korea.

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.3 (8.7058) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Yoon 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.85 (10.7732) years Time since type 2 diabetes diagnosis: 2.1 (3.8535) years	Previous medication usage: 7) Mixed population N = 520 Pioglitazone 30 mg + Sitagliptin 100 mg once daily (n=261) Pioglitazone 30 mg once daily (n=259) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12.5 months	Study location: Multicenter Sources of funding: Funded by Merck Sharp & Dohme LLC
Yuan 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without other cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear	Previous medication usage: 5) All treatment naïve N = 59 Exenatide (n=33) Metformin (n=26) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: China. Sources of funding: No additional information.

Author	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57.65 (9.4028) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Zhang 2020A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 50.85 (11.8038) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 6) No response criteria N = 60 Liraglutide 1.2 mg once daily (n=30) Pioglitazone 30 mg once daily (n=30) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Shandong, China Sources of funding: Funded by Yantai Affiliated Hospital of Binzhou Medical University
Zhou 2021	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease:	Previous medication usage: 5) All treatment naïve N = 25 Canagliflozin + Metformin (n=12) Glimepiride + Metformin (n=13) Concomitant therapy: NA Antihyperglycaemic treatment received: No additional	Weight change Follow up: 5.5 months	Study location: China Sources of funding: 'This work was supported by Bethune-Merck Diabetes Research Fund (no.G-X-2019-056), the financial support from the National Natural Science Foundation of China

Author	Population	Intervention and comparison	Outcomes	Comments
	People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 39.35 (7.4933) years Time since type 2 diabetes diagnosed: Not stated/unclear	information available.		(no.81600643, no.91746205), Tianjin Science and Technology Support Project (no.17JCYBJC27000), Science and Technology Foundation of Tianjin Health Commission (no. ZC20128), Sammy China Diabetes Research Fund (Z-2017-26-1902).'
Zhou 2022	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 47.705 (5.2901) years Time since type 2 diabetes diagnosed: Not stated/unclear	Previous medication usage: 8) Not reported N = 150 Dapagliflozin + Metformin (n=75) Metformin (n=75) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, BMI change Follow up: 5.5 months	Study location: China. Sources of funding: No additional information.
Zougrafou 2015	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular	Previous medication usage: 5) All treatment naïve N = 64 Vildagliptin + Metformin (n=32) Metformin (n=32) Concomitant therapy: None	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Greece. Sources of funding: None declared.

Author	Population	Intervention and comparison	Outcomes	Comments
	disease: People without other cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54 (10.8556) years Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: No additional information available.		

1 See report E1.2, appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence (network meta-analysis)

Table 3: Summary of effectiveness evidence (network meta-analysis)

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
HbA1c change at 8 months	106	RCT	58160	See report E3	Very serious[a]	No serious	No serious	Not serious	**Low**
Weight change at 7 months	68	RCT	37816	See report E3	Very serious[a]	No serious	No serious	Serious[b]	**Very low**

Footnotes:
a) Downgraded by 2 increments as greater than 33.3% of the studies in the meta-analysis were at high risk of bias.
b) Downgraded by 1 increment as a significant proportion of inputs or measures produced by the network meta-analysis showed imprecision that had a moderate impact on the ability of the committee to draw conclusions from the results of the analysis.

1.1.7. Summary of the effectiveness evidence (pairwise meta-analysis)

1.1.7.1. Model 5: People with type 2 diabetes at high cardiovascular risk with no other comorbidities

1.1.7.1.1. Monotherapy compared to placebo

Table 4: A summary matrix showing the outcomes for individual drugs (GLP-1 receptor agonists and SGLT-2 inhibitors) compared to placebo for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
Health-related quality of life	1 study (n=350), Very low	No outcomes identified	No outcomes identified	1 study (n=191), Low quality:	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
	quality: PAM-D21-J convenience/flexibility subscale: MD 6.73 higher (0.34 higher to 13.12 higher) PAM-D21-J perceived effectiveness subscale: MD 50.79 higher (20.8 higher to 80.78 higher) PAM-D21-J emotional effects subscale: MD 3.71 higher (0.4 higher to 7.02 higher) IDMQ-J satisfaction subscale: MD 32.05 higher (13.12 higher to 50.98 higher) IDMQ-J ease of use subscale:			SF-36v2 acute version – physical component subscale: MD 0.76 lower (1.72 lower to 0.21 higher) Very low quality: SF-36v2 acute version – mental component subscale, MD 1.73 higher (0.31 higher to 3.15 higher), DTR QoL – overall, MD 4.55 higher (1.61 higher to 7.48 higher)			

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
	MD 12.94 higher (5.3 higher to 20.58 higher) IDMQ-J lifestyle impact subscale: MD 10.12 higher (4.14 higher to 16.1 higher) IDMQ-J blood glucose control subscale: MD 34.43 higher (14.11 higher to 54.75 higher) Low quality: PAM-D21-J physical effects subscale: MD 0.95 lower (2.71 lower to 0.81 higher)						
All-cause mortality	1 study (n=350), Low quality, 0 fewer per 1,000 (from 20	1 study (n=232), Low quality, 0 fewer per 1,000 (from 20 fewer to 20 more)	2 studies (n=304), Very low quality, 0 fewer per 1,000 (from 20	3 studies (n=1286), Very low quality, 1 more per 1,000 (from 7 fewer to 8 more)	1 study (n=584), Low quality, 3 fewer per 1000 (5 fewer to 35 more)	3 studies (n=1160), Very low quality, 1 more per 1,000 (from 9 fewer to 10 more)	1 study (n=676), Very low quality, 2 fewer per 1,000 (from 4 fewer to 31 more)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
	fewer to 20 more)		fewer to 20 more)				
Cardiovascular mortality	1 study (n=350), Low quality, 0 fewer per 1,000 (from 20 fewer to 20 more)	1 study (n=232), Low quality, 0 fewer per 1,000 (from 20 fewer to 20 more)	2 studies (n=304), Low quality, 0 fewer per 1,000 (from 20 fewer to 20 more)	3 studies (n=1286), Very low quality, 1 more per 1,000 (from 7 fewer to 8 more)	1 study, (n=584), Low quality, 5 fewer per 1000 (from 15 fewer to 5 more)	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	1 study (n=97), Very low quality, 0 fewer per 1,000 (from 39 fewer to 39 more)	3 studies (n=1285), Very low quality, 5 fewer per 1,000 (from 16 fewer to 7 more)	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	1 study (n=97), Very low quality, 0 fewer per	3 studies (n=1285), Very low quality, 2 more	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
			1,000 (from 39 fewer to 39 more)	per 1,000 (from 6 fewer to 10 more)			
Unstable angina	No outcomes identified	No outcomes identified	1 study (n=97), Very low quality, 0 fewer per 1,000 (from 39 fewer to 39 more)	1 study (n=195), Very low quality, 0 fewer per 1,000 (from 29 fewer to 29 more)	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=703), High quality, 0 fewer per 1,000 (from 8 fewer to 8 more)	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	1 study (n=97), Very low quality, 0 fewer per 1,000 (from 39 fewer to 39 more)	2 studies (n=898), Very low quality, 3 fewer per 1,000 (from 14 fewer to 8 more)	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n=654), Low quality,	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
						2 more per 1,000 (14 fewer to 49 more)	
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	1 study (n=97), Very low quality, 0 fewer per 1,000 (from 39 fewer to 39 more)	1 study (n=195), Very low quality, 0 fewer per 1,000 (from 29 fewer to 29 more)	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
Hypoglycaemia episodes	1 study (n=350), Very low quality, 7 more per 1,000 (from 12 fewer to 161 more)	1 study (n=232), Very low quality, 32 more per 1,000 (from 7 fewer to 348 more)	2 studies (n=304), Very low quality, 24 more per 1,000 (from 12 fewer to 153 more)	3 studies (n=1,285), Very low quality, 4 fewer per 1,000 (from 9 fewer to 17 more)	2 studies (n=288), Very low quality, 35 more per 1000 (10 fewer to 174 more)	3 studies (n=1,134), Very low quality, 5 fewer per 1,000 (11 fewer to 15 more)	1 study (n=676), Very low quality, 0 fewer per 1,000 (from 7 fewer to 40 more)
At night hypoglycaemic episodes	1 study (n=350), Very low quality, 7 more per 1,000 (from 3 fewer to 17 more)	No outcomes identified	1 study (n=207), Low quality, 0 fewer per 1,000 (from 22 fewer to 22 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=350), Low quality, 0 fewer per 1,000 (from 20 fewer to 20 more)	1 study (n=232), Low quality, 0 more per 1,000 (from 20 fewer to 20 more)	2 studies (n=304), Low quality, 0 fewer per 1,000 (from 20 fewer to 20 more)	3 studies (n=1285), Very low quality, 4 fewer per 1,000 (from 15 fewer to 6 more)	No outcomes identified	No outcomes identified	1 study (n=676), Very low quality, 2 more per 1,000 (from 2 fewer to 7 more)
HbA1c change	1 study (n=351), Moderate quality, MD 1.57%	1 study (n=232), Low quality, MD 0.6% lower	2 studies (n=305), Low quality, MD 1.29 % lower (1.65	3 studies (n=1,376), Very low quality, MD 1.07 % lower	3 studies (n=861), Moderate quality, MD 1.02% lower	5 studies (n=1,423), Very low quality, MD 0.73% lower	2 studies (n=760), Very low quality, MD 0.52% lower (1.16 lower to 0.11 higher)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin
	lower (1.79 lower to 1.35 lower)	(0.84 lower to 0.36 lower)	lower to 0.93 lower)	(1.31 lower to 0.83 lower)	(1.14 lower to 0.90 lower)	(1.02 lower to 0.44 lower)	
Weight change	No outcomes identified	1 study (n=232), Moderate quality, MD 1.55 kg lower (2.27 lower to 0.83 lower)	1 study (n=94), Low quality, MD 0.6 kg higher (0.25 lower to 1.45 higher)	3 studies (n=1,376), Very low quality, MD 1.17 kg lower (2.14 lower to 0.20 lower)	3 studies (n=863), Very low quality, MD 3.15 kg lower (4.19 lower to 2.11 lower)	2 studies (n=720), Very low quality, MD 0.47 kg lower (2.13 lower to 1.18 higher)	2 studies (n=760), Low quality, MD 2.04 kg lower (2.49 lower to 1.6 lower)
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	3 studies (n=1285), Very low quality, MD 0.45 kg/m^2 lower (0.79 lower to 0.1 lower)	1 study (n=16), Low quality, MD 2.89 kg/m^2 lower (4.54 lower to 1.24 lower)	No outcomes identified	No outcomes identified

1

Table 5: A summary matrix showing the outcomes for individual drugs (biguanides, DPP-4 inhibitors, sulfonylureas, thiazolidinediones) compared to placebo for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glipizide	Tolbutamide	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	6 studies (n=2522), Very low quality, 0 fewer per 1,000 (6 fewer to 6 more)	2 studies (n=662), Low quality, 0 fewer per 1,000 (12 fewer to 12 more)	1 study (n=214), Very low quality, 0 fewer per 1,000 (21 fewer to 21 more)	4 studies (n=1,547), Very low quality, 2 more per 1,000 (5 fewer to 9 more)	4 studies (n=1,301), Very low quality, 0 fewer per 1,000 (from 9 fewer to 6 more)	1 study (n=306), Very low quality, 7 fewer per 1,000 (20 fewer to 6 more)	No outcomes identified	1 study (n=409), Very low quality, 45 more per 1,000 (15 fewer to 146 more)	2 studies (n=926), Very low quality, 2 more per 1,000 (from 10 fewer to 15 more)
Cardiovascular mortality	6 studies (n=2252), Very low quality, 0 fewer per 1,000 (6 fewer to 6 more)	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	1 study (n=214), Very low quality, 0 fewer per 1,000 (21 fewer to 21 more)	3 studies (n=979), Low quality, 0 fewer per 1,000 (10 fewer to 10 more)	2 studies (n=601), Very low quality, 3 fewer per 1,000 (from 15 fewer to 8 more)	No outcomes identified	No outcomes identified	1 study (n=409), Low quality, 79 more per 1,000 (14 fewer to 209 more)	1 study (n=876), Very low quality, 1 fewer per 1,000 (from 1 fewer to 4 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glipizide	Tolbutamide	Pioglitazone
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n=926), Very low quality, 2 more per 1,000 (from 10 fewer to 15 more)
Non-fatal myocardial infarction	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	1 study (n=334), Very low quality, 4 more per 1,000 (4 fewer to 13 more)	1 study (n=299), Very low quality, 10 fewer per 1,000 (30 fewer to 10 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	3 studies (n=1139), Very low quality, 2 fewer per 1,000 (from 15 fewer to 11 more)
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glipizide	Tolbutamide	Pioglitazone
Hospitalisation for heart failure	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=876), Very low quality, 3 more per 1,000 (from 1 fewer to 6 more)
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=372), Very low quality, 7 fewer per 1,000 (39 fewer to 64 more)	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glipizide	Tolbutamide	Pioglitazone
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=386), Very low quality, 57 fewer per 1,000 (94 fewer to 8 more)	No outcomes identified
Diabetic ketoacidosis	1 study (n=540), Very low quality, 6 fewer per 1,000 (17 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=355), Very low quality, 6 fewer per 1,000 (from 17 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=20), Very low	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glipizide	Tolbutamide	Pioglitazone
							quality, 0 fewer per 1,000 (263 fewer to 770 more)		
Hypoglycaemia episodes	7 studies (n= 2,385), Very low quality, 19 more per 1,000 (3 more to 48 more)	3 studies (n=796), Very low quality, 17 more per 1,000 (1more to 33 more)	3 studies (n=7,74), Very low quality, 4 fewer 1,000 (16 fewer to 8 more)	3 studies (n=1,182), Very low quality, 3 more 1,000 (7 fewer to 13 more)	5 studies (n=1,507), Very low quality, 3 more per 1,000 (from 8 fewer to 14 more)	1 study (n= 302), Very low quality, 7 fewer 1,000 (20 fewer to 6 more)	1 study (n=30), Very low quality, 267 fewer per 1,000 (491 fewer to 43 fewer)	No outcomes identified	2 studies (n=1,284), Very low quality, 7 fewer per 1,000 (from 24 fewer to 9 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	4 studies (n=1418), Very low quality, 1 more per 1,000 (6 fewer to 8 more)	2 studies (n=659), Low quality, 0 fewer per 1,000 (12 fewer to 12 more)	2 studies (n=513), Very low quality, 3 more per 1,000 (11 fewer to 17 more)	1 study (n=568), Low quality, 0 fewer per 1,000 (7 fewer to 7 more)	3 studies (n=946), Moderate quality, 0 fewer per 1,000 (from 8 fewer to 8 more)	1 study (n=302), Very low quality, 0 fewer 1,000 (13 fewer to 13 more)	1 study (n=20), Very low quality, 0 fewer per 1,000 (174 fewer to 174 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glipizide	Tolbutamide	Pioglitazone
HbA1c change	13 studies (n=3,163), Very low quality, MD 1.22 % lower (1.48 lower to 0.95 lower)	3 studies (n=775), High quality, MD 0.68% lower (0.82 lower to 0.55 lower)	5 studies (n=1,092), Very low quality, MD 0.58% lower (0.73 lower to 0.42 lower)	3 studies (n=1,103), Very low quality, MD 0.45% lower (0.62 lower to 0.28 lower)	6 studies (n=2,191), Low quality, MD 0.73% lower (0.84 lower to 0.62 lower)	4 studies (n=1,081), Very low quality, MD 0.5% lower (0.64 lower to 0.37 higher)	2 studies (n=70), Very low quality, MD 1.89% lower (5.65 lower to 1.86 higher)	No outcomes identified	5 studies (n=1,675), Moderate quality, MD 0.81 % lower (0.92 lower to 0.7 lower)
Weight change	7 studies (n= 1,927), Low quality, MD 0.09 kg higher (0.23 lower to 0.40 higher)	2 studies (n=662), Very low quality, MD 0.31 kg higher (0.93 lower to 1.56 higher)	4 studies (n=554), Moderate quality, MD 0.64 kg higher (0.11 higher to 1.17 higher)	3 studies (n=1,122), Low quality, MD 0.88 kg higher (0.47 higher to 1.29 higher)	5 studies (n=1,888), Moderate, MD 0.81 kg higher (0.5 higher to 1.13 higher)	3 studies (n=989), Very low quality, MD 0.4 kg higher (0.43 lower to 1.22 higher)	No outcomes identified	No outcomes identified	4 studies (n=911), Very low quality, MD 2.55 kg higher (1.22 higher to 3.88 higher)
BMI change	2 studies (n=625), Very low quality, MD 1.8 kg/m^2 lower (5.13 lower to 1.53 higher)	No outcomes identified	No outcomes identified	1 study (n=211), Moderate quality, MD 0.4 kg/m^2 higher (0.16 higher to 0.64 higher)	No outcomes identified	No outcomes identified	1 study (n=20), Very low quality, MD 2.52 kg/m^2 lower (8.35 lower to 3.31 higher)	No outcomes identified	1 study (n=58), Very low quality, MD 0.77 kg/m^2 higher (0.45 higher to 1.1 higher)

1

1.1.7.1.2. Combination therapy compared to placebo

Table 6: A summary matrix showing the outcomes for combination therapy compared to placebo for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to placebo	Alogliptin + Metformin	Linagliptin + Metformin	Sitagliptin + Metformin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	1 study (n=358), Low quality, 0 fewer per 1,000 (20 fewer to 20 more)	2 studies (n=921), Very low quality, 2 fewer per 1,000 (12 fewer to 7 more)
Cardiovascular mortality	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	1 study (n=358), Low quality, 0 fewer per 1,000 (20 fewer to 20 more)	2 studies (n=921), Very low quality, 2 fewer per 1,000 (12 fewer to 7 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=334), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Alogliptin + Metformin	Linagliptin + Metformin	Sitagliptin + Metformin
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	1 study (n=548), Very low quality, 6 fewer per 1,000 (17 fewer to 5 more)
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	2 studies (n=648), Very low quality, 29 more per 1,000 (1 more to 149 more)	1 study (n=358), Very low quality, 4 more per 1000 (from 12 fewer to 133 more)	2 studies (n=921), Moderate quality, 42 more per 1,000 (from 7 more to 130 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=329), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)	1 study (n=358), Low quality, 0 fewer per 1,000 (20 fewer to 20 more)	1 study (n=373), Moderate quality, 0 fewer per 1,000 (from 12 fewer to 12 more)

Outcomes for drugs compared to placebo	Alogliptin + Metformin	Linagliptin + Metformin	Sitagliptin + Metformin
HbA1c change	1 study (n=315), Low quality, MD 1.26 % lower (1.48 lower to 1.04 lower)	1 study (n=342), Low quality, MD 1.5 % lower (1.74 lower to 1.26 lower)	2 studies (n=854), Very low quality, MD 0.97% lower (1.31 lower to 0.64 lower)
Weight change	1 study (n=334), Low quality, MD 0.00 kg lower (0.68 lower to 0.68 higher)	1 study (n=296), Low quality, MD 0.24 kg higher (0.64 lower to 1.12 higher)	1 study (n=371), Moderate quality, MD 1.4 kg higher (0.46 higher to 2.34 higher)
BMI change	No outcomes identified	No outcomes identified	No outcomes identified

1.1.7.1.3. Metformin slow release compared to metformin standard release

Table 7: A summary matrix showing the outcomes for metformin slow release compared to metformin standard release for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to Metformin standard release	Metformin slow release
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=568), Very low quality, 4 fewer per 1,000 (3 fewer to 10 more)
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified

Outcomes for drugs compared to Metformin standard release	Metformin slow release
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n= 568), Very low quality, 11 fewer per 1,000 (22 fewer to 1 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	2 studies (n=1,274), Low quality, MD 0% lower (0.12 lower to 0.12 higher)
Weight change	1 study (n= 471), Low quality, MD 0.15 kg higher (0.53 lower to 0.83 higher)
BMI change	No outcomes identified

1.1.7.1.4. Monotherapy compared to metformin

Table 8: A summary matrix showing the outcomes for individual drugs (GLP-1 receptor agonists and SGLT-2 inhibitors) compared to metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to metformin	Dulaglutide	Exenatide	Liraglutide	Canagliflozin	Dapagliflozin	Empagliflozin
Health-related quality of life	No outcomes identified	1 study (n=459), High quality, EQ-5D score: MD 0 (0.03 lower to 0.03 higher)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=807), Moderate quality, 0 fewer per 1000 (6 fewer to 6 more)	1 study (n=494), Low quality, 4 fewer per 1,000 (from 12 fewer to 4 more)	No outcomes identified	1 study (n=712), Very low quality, 4 fewer per 1,000 (12 fewer to 4 more)	2 studies (n=831), Very low quality, 0 fewer per 1,000 (7 fewer to 7 more)	1 study (n=680), High quality, 0 fewer per 1,000 (6 fewer to 6 more)
Cardiovascular mortality	1 study (n=807), Moderate quality, 0 fewer per 1000 (6 fewer to 6 more)	1 study (n=494), High quality, 0 fewer per 1,000 (from 8 fewer to 8 more)	No outcomes identified	1 study (n=712), Very low quality, 4 fewer per 1,000 (12 fewer to 4 more)	2 studies (n=831), Very low quality, 0 fewer per 1,000 (7 fewer to 7 more)	1 study (n=680), High quality, 0 fewer per 1,000 (6 fewer to 6 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Dulaglutide	Exenatide	Liraglutide	Canagliflozin	Dapagliflozin	Empagliflozin
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=712), Very low quality, 2 fewer per 1,000 (2 fewer to 6 more)	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=712), Low quality, 0 fewer per 1,000 (7 fewer to 7 more)	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Dulaglutide	Exenatide	Liraglutide	Canagliflozin	Dapagliflozin	Empagliflozin
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=712), Very low quality, 2 more per 1,000 (2 fewer to 6 more)	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=712), Very low quality, 2 more per 1,000 (2 fewer to 6 more)	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=807), Very low quality, 10 fewer per 1000 (48 fewer to 46 more)	2 studies (n=553), Low quality, 19 more per 1,000 (from 12 fewer to 85 more)	1 study (n=61), Very low, 51 fewer per 1,000 (from 64 fewer to 202 more)	1 study (n=712), Very low quality, 13 fewer per 1,000 (31 fewer to 25 more)	2 studies (n=831), Very low quality, 8 fewer per 1,000 (38 fewer to 22 more)	1 study (n=680), Low quality, 0 fewer per 1,000 (5 fewer to 36 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Dulaglutide	Exenatide	Liraglutide	Canagliflozin	Dapagliflozin	Empagliflozin
Severe hypoglycaemic episodes	1 study (n=808), Moderate quality, 0 fewer per 1000 (6 fewer to 6 more)	1 study (n=59), Very low quality, 0 fewer per 1,000 (from 65 fewer to 65 more)	No outcomes identified	1 study (n=712), Very low quality, 4 fewer per 1,000 (12 fewer to 4 more)	2 studies (n=831), High quality, 0 fewer per 1,000 (7 fewer to 7 more)	No outcomes identified
HbA1c change	1 study (n=807), Moderate quality, MD 0.18% lower (0.33 lower to 0.04 lower)	2 studies (n=495), High quality, MD 0.07 % lower (0.26 lower to 0.12 higher)	2 studies (n=121), Very low quality, MD 0.5 % lower (1 lower to 0)	1 study (n=694), Low quality, MD 0.1 % lower (0.27 lower to 0.07 higher)	2 studies (n=810), High quality, MD 0.06 % (0.1 lower to 0.22 higher)	1 study (n=554), High quality, MD 0.15 % higher (0.02 lower to 0.32 higher)
Weight change	1 study (n=807), Moderate quality, MD 0.40 kg higher (0.18 lower to 0.97 higher)	2 studies (n=553), Very low quality, MD 0.98 kg lower (2.93 lower to 0.97 lower)	2 studies (n=118), Very low quality, MD 8.69 kg higher (3.82 higher to 13.57 higher)	1 study (n=709), Very low quality, MD 1.35 kg lower (2.07 lower to 0.63 lower)	2 studies (n=831), High quality, MD 1.34 kg lower (1.81 lower to 0.88 lower)	No outcomes identified
BMI change	No outcomes identified	1 study (n=59, Low quality, MD 1.41 kg/m^2 lower (1.81 lower to 1.01 lower)	2 studies (n=118), Very low quality, MD 2.0 kg/m^2 higher (0.69 higher to 3.31 higher)	No outcomes identified	No outcomes identified	No outcomes identified

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Table 9: A summary matrix showing the outcomes for individual drugs (DPP-4 inhibitors, sulfonylureas and thiazolidinediones) compared to metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Gliclazide	Glimepiride	Glipizide	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=376), Moderate quality, EQ-5D score: MD 0.01 lower (0.04 lower to 0.02 higher)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=373), Moderate quality, Overall – EQ5D: MD 0.04 lower (0.07 lower to 0.01 lower)
All-cause mortality	1 study (n=450), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=433), Very low quality, 3 fewer per 1,000 (10 fewer to 3 more)	2 studies (n=1087), Very low quality, 0 fewer per 1,000 (14 fewer to 6 more)	4 studies (n=2372), Very low quality, 0 fewer per 1,000 (from 4 fewer to 4 more)	3 studies (n=1697), Very low quality, 0 fewer per 1,000 (6 fewer to 6 more)	No outcomes identified	No outcomes identified	No outcomes identified	5 studies (n = 1552), Very low quality, 0 fewer per 1,000 (from 7 fewer to 6 more)
Cardiovascular mortality	1 study (n=450), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=433), Very low quality, 3 fewer per 1,000 (10	1 study (n=663), Very low quality, 6 fewer per 1,000 (11	3 studies (n=1,322), Low quality, 0 fewer per 1,000 (from 6 fewer to 6 more)	1 study (n=332), Very low quality, 6 more per 1,000 (6	1 study (n=40), Very low quality, 0 fewer per 1,000 (92	No outcomes identified	No outcomes identified	4 studies (n = 958), Very low quality, 1 fewer per 1,000 (from 9 fewer to 6 more)

Outcomes for drugs compared to metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Gliclazide	Glimepiride	Glipizide	Pioglitazone
		fewer to 3 more)	fewer to 20 more)		fewer to 18 more)	fewer to 92 more)			
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	1 study (n=436), Very low quality, 3 fewer per 1,000 (10 fewer to 3 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	1 study (n=424), Very low quality, 0 fewer per 1,000 (4 fewer to 69 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Gliclazide	Glimepiride	Glipizide	Pioglitazone
Non-fatal myocardial infarction	1 study (n=450), Very low quality, 4 more per 1,000 (4 fewer to 13 more)	No outcomes identified	1 study (n=424), Very low quality, 5 fewer per 1,000 (14 fewer to 5 more)	1 study (n=1,050), Very low quality, 2 fewer per 1,000 (from 6 fewer to 2 more)	3 studies (n=1,706), Moderate quality, 7 fewer per 1,000 (13 fewer to 1 fewer)	1 study (n=40), Very low quality, 0 fewer per 1,000 (92 fewer to 92 more)	No outcomes identified	No outcomes identified	2 studies (n = 439), Very low quality, 5 fewer per 1,000 (from 9 fewer to 19 more)
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=450), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=436), Low quality, 0 fewer per 1,000 (10 fewer to 10 more)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=40), Very low quality, 0 fewer per 1,000 (92 fewer to 92 more)	No outcomes identified	No outcomes identified	2 studies (n = 150), Moderate quality, 0 fewer per 1,000 (from 37 fewer to 37 more)
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening	No outcomes identified	No outcomes identified	1 study (n=424), Very low	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Gliclazide	Glimepiride	Glipizide	Pioglitazone
kidney disease			quality, 5 fewer per 1,000 (14 fewer to 5 more)						
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1,050), Very low quality, 2 fewer per 1,000 (from 6 fewer to 2 more)	1 study (n=332), Very low quality, 0 fewer per 1,000 (17 fewer to 17 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=543), Moderate quality, 0 fewer per	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Gliclazide	Glimepiride	Glipizide	Pioglitazone
				1,000 (from 9 fewer to 9 more)					
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	1 study (n=424), Very low quality, 5 fewer per 1,000 (14 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	2 studies (n=765), Very low quality, 26 fewer per 1,000 (44 fewer to 51 more)	2 studies (n= 869), Very low quality, 12 fewer per 1,000 (16 fewer to 10 more)	2 studies (n=1,087), Very low quality, 26 fewer per 1,000 (36 fewer to 7 fewer)	4 studies (n=2,372), Low quality, 10 fewer per 1,000 (from 18 fewer to 4 more)	2 studies (n=1,112), Very low quality, 3 fewer per 1,000 (12 fewer to 7 more)	2 studies (n=103), Very low quality, 1 fewer per 1,000 (74 fewer to 72 more)	3 studies (n=472), Very low quality, 61 more per 1,000 (109 fewer to 230 more)	1 study (n=48), Very low quality, 0 fewer per 1,000 (80 fewer to 80 more)	5 studies (n=1061),Very low quality, 5 fewer per 1,000 (from 19 fewer to 9 more)

Outcomes for drugs compared to metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Gliclazide	Glimepiride	Glipizide	Pioglitazone
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=442), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	2 studies (n=869), Very low quality, 1 fewer per 1,000 (9 fewer to 7 more)	2 studies (n=1,087), Very low quality, 3 fewer per 1,000 (10 fewer to 4 more)	2 studies (n=1,420), Very low quality, 3 fewer per 1,000 (from 3 fewer to 9 more)	3 studies (n=1,706), Very low quality, 1 fewer per 1,000 (5 fewer to 4 more)	1 study (n=40), Very low quality, 0 fewer per 1,000 (92 fewer to 92 more)	1 study (n=164), Very low quality, 0 fewer per 1,000 (24 fewer to 24 more)	1 study (n=48), Very low quality, 0 fewer per 1,000 (80 fewer to 80 more)	1 study (n = 40), Very low quality, 0 fewer per 1,000 (from 92 fewer to 92 more)
HbA1c change	2 studies (n=742), Very low quality, MD 0.36 % higher (0.18 higher to 0.54 higher)	3 studies (n=872), Very low quality, MD 0.36% higher (0.09 higher to 0.63 higher)	, 1 study (n=723), Very low quality, MD 0.32 % higher (0.09 lower to 0.72 higher)	5 studies (n=2,164), Very low quality, MD 0.05% higher (0.26 lower to 0.36 higher)	3 studies (n=1,674), Moderate quality, MD 0.25 % higher (0.14 higher to 0.37 higher)	3 studies (n=161), Very low quality, MD 0.36 % higher (0.05 higher to 0.77 higher)	3 studies (n=472), Low quality, MD 0.0 % lower (0.2 lower to 2 higher)	2 studies (n=186), Very low quality, MD 0.34% higher (1.01 lower to 1.69 higher)	6 studies (n = 1071),Moderate quality, MD 0.07% lower (0.08 lower to 0.23 higher)
Weight change	1 study (n=450), Very low quality, MD 1.08 kg higher (0.53	2 studies (n=687), Low quality, MD 0.72 kg higher (0.28	2 study (n=462), Low quality, MD 1.57 kg higher (1.13	3 studies (n=1683), Moderate quality, MD 1.31 kg higher (1.01	3 studies (n=1,689), Very low quality, MD 1.32 kg higher (0.52	3 studies (n=154), Very low quality, MD 4.59 kg higher (0.31	No outcomes identified	2 studies (n=186), Very low quality, MD 1.81 kg higher (2.41	5 studies (n = 1,956), Very low quality, MD 2.9 kg higher (1.16

Outcomes for drugs compared to metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Gliclazide	Glimepiride	Glipizide	Pioglitazone
	higher to 1.63 higher)	higher to 1.17 higher)	higher to 2.0 higher)	higher to 1.61 higher)	higher to 2.12 higher)	higher to 8.88 higher)		lower to 6.03 higher)	higher to 4.64 higher)
BMI change	No outcomes identified	No outcomes identified	2 study (n=462), Very low quality, MD 0.02 kg/m^2 higher (1.07 lower to 1.04 higher)	1 study (n=34),Very low quality, MD 1.36 kg/m^2 lower (3.58 lower to 0.86 higher)	No outcomes identified	2 studies (n=94),Very low quality, MD 1.08 kg/m^2 higher (0.87 higher to 3.02 higher)	2 studies (n=240), Very low quality, MD 0.1 kg/m^2 lower (1.06 lower to 0.86 higher)	No outcomes identified	4 studies (n=361), Very low quality, MD 0.24 kg/m^2 lower (1.73 lower to 1.24 higher)

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1.1.7.1.5. Combination therapy compared to metformin

Table 10: A summary matrix showing the outcomes for combinations of drugs compared to metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to metformin	Alogliptin + Metformin	Linagliptin + Metformin	Saxagliptin + Metformin	Sitagliptin + Metformin	Vildagliptin + Metformin	Canagliflozin + Metformin	Empagliflozin + Metformin	Glimepiride + Metformin	Pioglitazone + Metformin	Dapagliflozin + Metformin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=450), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=577), Very low quality, 3 fewer per 1,000 (10 fewer to 3 more)	2 studies (n=1,396), Very low quality, 4 fewer per 1,000 (18 fewer to 9 more)	2 studies (n=1,233), Low quality, 0 fewer per 1,000 (4 fewer to 4 more)	1 study (n=879), Very low quality, 2 fewer per 1,000 (2 fewer to 5 more)	1 study (n=711), Very low quality, 0 fewer per 1,000 (12 fewer to 4 more)	1 study (n=1,021), High quality, 0 fewer per 1,000 (5 fewer to 5 more)	No outcomes identified	1 study (n=410), Low quality, 0 fewer per 1,000 (10 fewer to 10 more)	2 studies (n = 814), Very low quality, **no**, 2 fewer per 1,000 (11 fewer to 6 more)
Cardiovascular mortality	1 study (n=450), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=577), Very low quality, 3 fewer per 1,000 (10 fewer to 3 more)	1 study (n=971), Very low quality, 9 fewer per 1,000 (12 fewer to 5 more)	2 studies (n=1,233), Low quality, 0 fewer per 1,000 (4 fewer to 4 more)	No outcomes identified	1 study (n=711), Very low quality, 4 fewer per 1,000 (12 fewer to 4 more)	1 study (n=1,021), High quality, 0 fewer per 1,000 (5 fewer to 5 more)	No outcomes identified	1 study (n=410), Low quality, 0 fewer per 1,000 (10 fewer to 10 more)	2 studies (n = 814), Very low quality, 2 fewer per 1,000 (11 fewer to 6 more)

Outcomes for drugs compared to metformin	Alogliptin + Metformin	Linagliptin + Metformin	Saxagliptin + Metformin	Sitagliptin + Metformin	Vildagliptin + Metformin	Canagliflozin + Metformin	Empagliflozin + Metformin	Glimepiride + Metformin	Pioglitazone + Metformin	Dapagliflozin + Metformin
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	1 study (n=583), Very low quality, 3 fewer per 1,000 (10 fewer to 3 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	1 study (n=425) Very low quality, 5 fewer per 1,000 (from 14 fewer to 5 more)	No outcomes identified	No outcomes identified	1 study (n=711) Very low quality, 2 more per 1,000 (2 fewer to 6 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Alogliptin + Metformin	Linagliptin + Metformin	Saxagliptin + Metformin	Sitagliptin + Metformin	Vildagliptin + Metformin	Canagliflozin + Metformin	Empagliflozin + Metformin	Glimepiride + Metformin	Pioglitazone + Metformin	Dapagliflozin + Metformin
Non-fatal myocardial infarction	1 study (n=450) Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	No outcomes identified	1 study (n=425) Very low quality, 5 fewer per 1,000 (14 fewer to 5 more)	No outcomes identified	1 study (n=879) Low quality, 7 fewer per 1,000 (16 fewer to 3 more)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=410) Low quality, 0 fewer per 1,000 (10 fewer to 10 more)	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=711) Very low quality, 2 more per 1,000 (2 fewer to 6 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=450), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=583), Low quality, 0 fewer per 1,000 (7 fewer to 7 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Alogliptin + Metformin	Linagliptin + Metformin	Saxagliptin + Metformin	Sitagliptin + Metformin	Vildagliptin + Metformin	Canagliflozin + Metformin	Empagliflozin + Metformin	Glimepiride + Metformin	Pioglitazone + Metformin	Dapagliflozin + Metformin
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	1 study (n=425), Very low quality, 5 fewer per 1,000 (14 fewer to 5 more)	No outcomes identified	No outcomes identified	1 study (n=711), Very low quality, 8 more per 1,000 (0 more to 17 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=711), Very low quality, 0 fewer per 1,000 (7	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Alogliptin + Metformin	Linagliptin + Metformin	Saxagliptin + Metformin	Sitagliptin + Metformin	Vildagliptin + Metformin	Canagliflozin + Metformin	Empagliflozin + Metformin	Glimepiride + Metformin	Pioglitazone + Metformin	Dapagliflozin + Metformin
						fewer to 7 more)				
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=736), Low quality, 0 fewer per 1,000 (5 fewer to 5 more)	No outcomes identified	1 study (n=711), Very low quality, 0 fewer per 1,000 (7 fewer to 7 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	1 study (n=425), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Alogliptin + Metformin	Linagliptin + Metformin	Saxagliptin + Metformin	Sitagliptin + Metformin	Vildagliptin + Metformin	Canagliflozin + Metformin	Empagliflozin + Metformin	Glimepiride + Metformin	Pioglitazone + Metformin	Dapagliflozin + Metformin
Hypoglycaemia episodes	2 studies (n=759), Very low quality, 13 fewer per 1,000 (31 fewer to 23 more)	2 studies (n=1,160), Very low quality, 0 fewer per 1,000 (10 fewer to 25 more)	2 studies (n=1,396), Very low quality, 7 fewer per 1,000 (from 22 fewer to 18 more)	2 studies (n=1,233), Moderate quality, 33 more per 1,000 (7 more to 79 more)	No outcomes identified	1 study (n=711), Very low quality, 2 more per 1,000 (22 fewer to 52 more)	1 study (n=1,021), Low quality, 4 more per 1,000 (4 fewer to 43 more)	1 study (n=133), Very low quality, 46 more per 1,000 (5 fewer to 96 more)	2 studies (n=546), Very low quality, 3 more per 1,000 (7 fewer to 47 more)	3 studies (n = 964), Low quality, 13 more per 1,000 (3 fewer to 52 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=440), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=1,160), Very low quality, 1 fewer per 1,000 (7 fewer to 4 more)	2 studies (n=1,396), Very low quality, 1 fewer per 1,000 (7 fewer to 6 more)	1 study (n=497), Moderate quality, 0 fewer per 1,000 (8 fewer to 8 more)	1 study (n=879), Very low quality, 3 fewer per 1,000 (10 fewer to 3 more)	1 study (n=711), Very low quality, 4 fewer per 1,000 (12 fewer to 4 more)	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n = 814), High quality, 0 fewer per 1,000 (7 fewer to 7 more)
HbA1c change	2 study (n=743), Very low quality, MD 0.48	2 studies (n=1,016), Very low quality, MD 0.45	3 studies (n=967), Very low quality, MD 0.32%	3 studies (n=1,218), Very Low quality, MD 0.76	2 studies (n=943), Moderate quality, MD 0.32%	1 study (n=701), Very low quality, MD 0.47	1 study (n=838), Moderate quality, MD 0.54	1 study (n=133), High quality, MD 0.8%	2 studies (n=517), Low quality, MD 1.13	3 studies (n = 935), Very low quality,

Outcomes for drugs compared to metformin	Alogliptin + Metformin	Linagliptin + Metformin	Saxagliptin + Metformin	Sitagliptin + Metformin	Vildagliptin + Metformin	Canagliflozin + Metformin	Empagliflozin + Metformin	Glimepiride + Metformin	Pioglitazone + Metformin	Dapagliflozin + Metformin
	% lower (0.65 lower to 0.31 lower)	% lower (0.58 lower to 0.32 lower)	lower (0.54 lower to 0.09 lower)	% lower (1.22 lower to 0.3 lower)	lower (0.45 lower to 0.18 lower)	% lower (0.64 lower to 0.3 lower)	% lower (0.69 lower to 0.39 lower)	lower (1.04 lower to 0.56 lower)	% lower (1.68 lower to 0.59 lower)	MD 0.82 % lower (1.26 lower to 0.39 lower)
Weight change	1 study (n=450), Low quality, MD 0.15 kg lower (0.4 lower to 0.69 higher)	2 studies (n=965), Low quality, MD 0.29 kg higher (0.11 lower to 0.68 higher)	2 studies (n=459), Low quality, MD 0.42 kg higher (0.12 lower to 0.96 higher)	1 study (n=497) Moderate quality, MD 1.15 kg higher (0.4 higher to 1.9 higher)	2 studies (n=943) Moderate quality, MD 0.44 kg higher (0.07 lower to 0.94 higher)	1 study (n=709) Very low quality, MD 1.75 kg lower (2.47 lower to 1.03 lower)	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n = 809) High quality, MD 1.68 kg lower (2.15 lower to 1.21 lower)
BMI change	No outcomes identified	No outcomes identified	2 studies (n=459), Very low quality, MD 0.1 kg/m2 lower (0.65 lower to 0.45 higher)	1 study (n=37), Very low quality, MD 0.22 kg/m2 lower (2.36 lower to 1.92 higher)	1 study (n=64), Very low quality, MD 0.2 kg/m^2 (0.35 lower to 0.75 higher)	No outcomes identified	No outcomes identified	1 study (n = 133), moderate quality, MD 0.3 kg/m^2 higher (0.41 lower to 1.01 higher)	1 study (n=136), moderate quality, MD 1.2 kg/m^2 lower (1.77 lower to 0.63 lower)	1 study (n = 150), Low quality, MD 0.91 kg/m^2 lower (1.27 lower to 0.55 lower)

1.1.7.1.6. Monotherapy and combination therapy compared to alogliptin

Table 11: A summary matrix showing the outcomes for individual drugs and drug combinations compared to alogliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to alogliptin	Alogliptin + metformin	Pioglitazone + alogliptin
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=450), Low quality**,** 0 fewer per 1,000 (9 fewer to 9 more)	No outcomes identified
Cardiovascular mortality	1 study (n=450), Low quality**,** 0 fewer per 1,000 (9 fewer to 9 more)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	1 study (n=450), Very low quality, 4 fewer per 1,000 (13 fewer to 4 more)	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=450), Low quality**,** 0 fewer per 1,000 (9 fewer to 9 more)	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified

Outcomes for drugs compared to alogliptin	Alogliptin + metformin	Pioglitazone + alogliptin
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	2 studies (n=762), Very low quality, 11 more per 1,000 (9 fewer to 56 more)	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=442), Low quality**,** 0 fewer per 1,000 (9 fewer to 9 more)	No outcomes identified

Outcomes for drugs compared to alogliptin	Alogliptin + metformin	Pioglitazone + alogliptin
HbA1c change	2 studies (n=741), Low quality, MD 0.83% lower (1 lower to 0.66 lower)	1 study (n=491), Low quality, MD 0.68% lower (0.88 lower to 0.48 lower)
Weight change	1 study (n=450), Low quality, MD 0.93 lower (1.48 lower to 0.38 lower)	1 study (n=491), Moderate quality, MD 3.12 kg higher (2.42 higher to 3.82 higher)
BMI change	No outcomes identified	No outcomes identified

1.1.7.1.7. Monotherapy and combination therapy compared to linagliptin

Table 12: A summary matrix showing the outcomes for individual drugs and drug combinations compared to linagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to linagliptin	Linagliptin + metformin	Pioglitazone + linagliptin	Empagliflozin + linagliptin	Empagliflozin	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	2 studies (n=744), Low quality, 0 fewer per 1,000 (8 fewer to 8 more)	No outcomes identified	1 study (n=407), Very low quality, 4 more per 1000 (4 fewer to 11 more)	1 study (n=405), Very low quality, 11 more per 1,000 (1 fewer to 24 more)	No outcomes identified
Cardiovascular mortality	2 studies (n=744), Low quality, 0 fewer	No outcomes identified	1 study (n=407), Very low quality, 4	1 study (n=405), Very low quality, 4 more per 1,000 (4 fewer to 11 more)	No outcomes identified

Outcomes for drugs compared to linagliptin	Linagliptin + metformin	Pioglitazone + linagliptin	Empagliflozin + linagliptin	Empagliflozin	Pioglitazone
	per 1,000 (8 fewer to 8 more)		more per 1000 (4 fewer to 11 more)		
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	1 study (n=441), Low quality, 0 fewer per 1,000 (10 fewer to 10 more)	1 study (n=527),Very low quality, 10 fewer per 1000 (14 fewer to 21 more)	No outcomes identified	No outcomes identified	1 study (n=544), Very low quality, 10 fewer per 1000 (31 fewer to 12 more)
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	2 studies (n=757), Low quality, 0 fewer per 1,000 (8 fewer to 8 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to linagliptin	Linagliptin + metformin	Pioglitazone + linagliptin	Empagliflozin + linagliptin	Empagliflozin	Pioglitazone
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	3 studies (n=1,185), low quality, 6 more per 1,000 (6 fewer to 39 more)	1 study (n=527), Very low quality, 10 more per 1,000 (0 fewer to 20 more)	1 study (n=407), Very low quality, 6 fewer per 1000 (7 fewer to 23 more)	1 study (n=405), Very low quality, 11 more per 1,000 (5 fewer to 150 more)	1 study (n=544), Very low quality, 12 more per 1,000 (from 2 more to 23 more)

Outcomes for drugs compared to linagliptin	Linagliptin + metformin	Pioglitazone + linagliptin	Empagliflozin + linagliptin	Empagliflozin	Pioglitazone
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	3 studies (n=1,185), Low quality, 0 fewer per 1,000 (10 fewer to 10 more)	1 study (n=527), Very low quality, 3 more per 1000 (2 fewer to 8 more)	1 study (n=407), Low quality, 0 fewer per 1000 (11 fewer to 11 more)	1 study (n=405), Low quality, 0 fewer per 1,000 (11 fewer to 11 more)	1 study (n=544), Moderate quality, 0 fewer per 1,000 (from 11 fewer to 11 more)
HbA1c change	3 studies (n=1,039), Low quality, MD 0.92% lower (1.06 lower to 0.77 lower)	1 study (n=501), Low quality, MD 0.67% lower (0.86 lower to 0.48 lower)	1 study (n=357), Very low quality, MD 0.48% lower (0.64 lower to 0.31 lower)	1 study (n=398), Moderate quality, MD 0.23 % lower (0.39 lower to 0.07 lower)	No outcomes identified
Weight change	3 studies (n=1,099), Low quality, MD 0.62 kg lower (1 lower to 0.23 lower)	1 study (n=353), Moderate quality, MD 1.63 kg higher (0.1 higher to 3.16 higher)	No outcomes identified	1 study (n=399), Moderate quality, MD 1.4 kg lower (4.82 lower to 2.02 higher)	No outcomes identified
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

1

1.1.7.1.8. Monotherapy and combination therapy compared to saxagliptin

Table 13: A summary matrix showing the outcomes for individual drugs and drug combinations compared to saxagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to saxagliptin	Glimepiride	Saxagliptin + metformin
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	2 studies (n=1,407), Very low quality, 2 fewer per 1,000 (9 fewer to 5 more)
Cardiovascular mortality	No outcomes identified	1 study (n=978), Very low quality, 3 fewer per 1,000 (6 fewer to 16 more)
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	1 study (n=429), Very low quality, 5 fewer per 1,000 (14 fewer to 4 more)
Non-fatal myocardial infarction	No outcomes identified	1 study (n=429), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	1 study (n=429), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)

Outcomes for drugs compared to saxagliptin	Glimepiride	Saxagliptin + metformin
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	1 study (n=429), Very low quality, 5 fewer per 1,000 (14 fewer to 4 more)
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	2 studies (n=1,407), Very low quality, 5 more per 1,000 (15 fewer to 152 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	2 studies (n=1,407), Very low quality, 3 more per 1,000 (3 fewer to 8 more)
HbA1c change	1 study (n=63), Low quality, MD 0.01% higher (0.25 lower to 0.27 higher)	3 studies (n=940), Very low quality, MD 0.63% lower (1.02 lower to 0.23 lower)
Weight change	No outcomes identified	2 studies (n=465), Very low quality, MD 0.54 kg lower (2.06 lower to 0.98 higher)
BMI change	1 study (n=63), Very low quality, MD 1.04kg/m2 lower (2.85 lower to 0.77 higher)	2 studies (n=465), Very low quality, MD 0.1 kg/m2 lower (0.61 lower to 0.41 higher)

1

1.1.7.1.9. Monotherapy and combination therapy compared to sitagliptin

Table 14: A summary matrix showing the outcomes for individual drugs and drug combinations compared to sitagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to sitagliptin	Exenatide	Semaglutide	Empagliflozin	Glimepiride	Glipizide	Liraglutide	Pioglitazone	Sitagliptin + metformin
Health-related quality of life	1 study (n=381), High quality, EQ-5D, MD 0.01 higher (0.02 lower to 0.04 higher)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=395), Moderate quality, EQ-5D, MD 0.03 lower (0.06 lower to 0)	No outcomes identified
All-cause mortality	1 study (n=411), High quality, 0 fewer per 1,000 (from 10 fewer to 10 more)	No outcomes identified	1 study (n=670), Very low quality, 2 fewer per 1,000 (4 fewer to 31 more)	2 studies (n=782), Very low quality, 3 more per 1000 (6 fewer to 11 more)	2 studies (n=551), Very low quality, 21 more per 1,000 (from 6 fewer to 89 more)	No outcomes identified	2 studies (n=1,077), Very low quality, 2 fewer per 1,000 (from 10 fewer to 6 more)	2 studies (n=918), Moderate quality, 0 fewer per 1,000 (from 7 fewer to 7 more)
Cardiovascular mortality	1 study (n=411), High quality, 0 fewer per	No outcomes identified	No outcomes identified	1 study (n=477), High quality, 0 fewer per	1 study (n=422), Very low quality, 5 more per	No outcomes identified	2 studies (n=1,077), Low quality, 0 fewer per	2 studies (n=918), Moderate quality, 0 fewer per

Outcomes for drugs compared to sitagliptin	Exenatide	Semaglutide	Empagliflozin	Glimepiride	Glipizide	Liraglutide	Pioglitazone	Sitagliptin + metformin
	1,000 (from 10 fewer to 10 more)			1000 (8 fewer to 8 more)	1,000 (from 7 fewer to 74 more)		1,000 (7 fewer to 7 more)	1,000 (from 7 fewer to 7 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=422), Very low quality, 5 fewer per 1,000 (from 9 fewer to 42 more)	No outcomes identified	1 study (n=754), Very low quality, 2 fewer per 1,000 (5 fewer to 33 more)	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=754), Low quality, 11 fewer per	No outcomes identified

Outcomes for drugs compared to sitagliptin	Exenatide	Semaglutide	Empagliflozin	Glimepiride	Glipizide	Liraglutide	Pioglitazone	Sitagliptin + metformin
							1,000 (26 fewer to 4 more)	
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n= 552), Very low quality, 11 more per 1,000 (from 8 fewer to 29 more)	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=133), Very low quality, 46 fewer per 1000 (97 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Exenatide	Semaglutide	Empagliflozin	Glimepiride	Glipizide	Liraglutide	Pioglitazone	Sitagliptin + metformin
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=422), Very low quality, 5 fewer per 1,000 (from 9 fewer to 43 more)	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=422), Very low quality, 5 fewer per 1,000 (from 14 fewer to 5 more)	No outcomes identified	No outcomes identified	1 study (n=551), Moderate quality, 0 fewer per 1,000 (from 9 fewer to 9 more)

Outcomes for drugs compared to sitagliptin	Exenatide	Semaglutide	Empagliflozin	Glimepiride	Glipizide	Liraglutide	Pioglitazone	Sitagliptin + metformin
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n=438),Very low quality, 5 fewer per 1000 (15 fewer to 36 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=411), Low quality, 22 more per 1,000 (from 12 fewer to 114 more)	No outcomes identified	1 study (n=670), Very low quality, 0 fewer per 1,000 (7 fewer to 40 more)	2 studies (n=610), Moderate quality, 43 more per 1000 (15 more to 70 more)	No outcomes identified	No outcomes identified	2 studies (n=1,077), Very low quality, 7 fewer per 1,000 (30 fewer to 30 more)	2 studies (n=918), Low quality, 37 more per 1,000 (from 4 more to 112 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Exenatide	Semaglutide	Empagliflozin	Glimepiride	Glipizide	Liraglutide	Pioglitazone	Sitagliptin + metformin
Severe hypoglycaemic episodes	No outcomes identified	1 study (n=408), High quality, 0 fewer per 1,000 (14 fewer to 14 more)	1 study (n=670), Very low quality, 2 more per 1,000 (2 fewer to 7 more)	3 studies (n=915), Very low quality, 4 more per 1000 (6 fewer to 15 more)	2 studies (n=552), Very low quality, 21 more per 1,000 (from 3 fewer to 126 more)	No outcomes identified	1 study (n=751), Very low quality, 5 fewer per 1,000 (16 fewer to 5 more)	1 study (n=367), Moderate quality, 0 fewer per 1,000 (from 13 fewer to 13 more)
HbA1c change	1 study (n=360), Moderate quality, MD 0.38% lower (0.59 lower to 0.17 lower)	1 study (n=408), High quality, MD 1.35% lower (1.63 lower to 1.07 lower)	1 study (n=671), Moderate quality, MD 0.18% lower (0.2 lower to 0.16 lower)	3 studies (n=826), Low quality, MD 0.12% lower (0.21 lower to 0.03 lower)	2 studies (n=398), Low quality, MD 0.05% higher (0.29 lower to 0.39 higher)	1 study (n=40), Very low quality, MD 0.60% lower (1.57 lower to 0.37 higher)	2 studies (n=966), Very low quality, MD 0.31% lower (0.65 lower to 0.02 higher)	3 studies (n=918), Very low quality, MD 0.59% lower (1.12 lower to 0.07 lower)
Weight change	1 study (n=411), High quality, MD 1.2 kg lower (1.91 lower to 0.49 lower)	1 study (n=408), Moderate quality, MD 3.05 kg lower (3.88 lower to 2.22 lower)	1 study (n=671), Low quality, MD 2.45 kg lower (2.93 lower to 1.97 lower)	2 studies (n=782), High quality, MD 0.77 kg higher (0.31 higher to 1.24 higher)	2 studies (n=377), Moderate quality, MD 1.7 higher (1.06 higher to 2.35 higher)	1 study (n=40),Very low quality, MD 0.90 kg lower (15.40 lower to 13.60 higher)	2 studies (n=735), Low quality, MD 3.09 kg higher (1.4 higher to 4.78 higher)	1 study (n=367), Moderate quality, MD 0.4 lower (from 1.31 lower to 0.51 higher)

Outcomes for drugs compared to sitagliptin	Exenatide	Semaglutide	Empagliflozin	Glimepiride	Glipizide	Liraglutide	Pioglitazone	Sitagliptin + metformin
BMI change	No outcomes identified	1 study (n=408), High quality, MD 1.10 kg/m2 lower (1.38 lower to 0.82 lower)	No outcomes identified	1 study (n=133), Low quality, MD 0.00 kg/m2 lower (0.36 lower to 0.36 higher)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=37), Very low quality, MD 1.14 higher (0.81 lower to 3.09 higher)

1.1.7.1.10. Monotherapy and combination therapy compared to vildagliptin

Table 15: A summary matrix showing the outcomes for individual drugs and drug combinations compared to vildagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to vildagliptin	Pioglitazone	Gliclazide	Pioglitazone + Vildagliptin	Vildagliptin + Metformin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	1 study (n=1,092), Very low quality, 5 more per 1,000 (5 fewer to 35 more)	No outcomes identified	1 study (n=885), Very low quality, 2 more per 1,000 (from 2 fewer to 5 more)
Cardiovascular mortality	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to vildagliptin	Pioglitazone	Gliclazide	Pioglitazone + Vildagliptin	Vildagliptin + Metformin
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=885), Moderate quality, 0 fewer per 1,000 (from 5 fewer to 5 more)
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to vildagliptin	Pioglitazone	Gliclazide	Pioglitazone + Vildagliptin	Vildagliptin + Metformin
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=314), Very low quality, 7 fewer per 1,000 (19 fewer to 6 more)	No outcomes identified	1 study (n=445), Very low quality, 3 fewer per 1,000 (from 18 fewer to 11 more)	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=885), Moderate quality, 0 fewer per 1,000 (from 5 fewer to 5 more)
HbA1c change	1 study (n=307), Very low quality, MD 0.3% lower (0.58 lower to 0.02 lower)	1 study (n=1,092), Low quality, MD 0.13% higher (0.07 lower to 0.33 higher)	1 study (n=435), Very low quality, MD 0.7% lower (0.94 lower to 0.46 lower)	1 study (n=885), Low quality, MD 0.6% lower (0.74 lower to 0.46 lower)
Weight change	1 study (n=307), Low quality, MD 1.3 kg higher (0.47 higher to 2.13 higher)	1 study (n=1,092), Low quality, MD 0.8 kg higher (0.25 higher to 1.35 higher)	1 study (n=435), Low quality, MD 1.56kg higher (0.84 higher to 2.28 higher)	1 study (n=885), Moderate quality, MD 0.59kg lower (1.12 lower to 0.06 lower)
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

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1.1.7.1.11. Monotherapy compared to dulaglutide

Table 16: Summary table for monotherapy compared to dulaglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to dulaglutide	Glimepiride	Liraglutide	Tirzepatide
Health-related quality of life	No outcomes identified	1 study (n=417), Low quality, PAM-D21-J convenience/flexibility subscale: MD 5.64 lower (10.58 lower to 0.7 lower) PAM-D21-J perceived effectiveness subscale: MD 0.43 lower (5.74 lower to 4.88 higher) PAM-D21-J emotional effects subscale: MD 2.36 lower (4.93 lower to 0.21 higher) PAM-D21-J physical effects subscale: MD 0.66 lower (2.01 lower to 0.69 higher) IDMQ-J satisfaction subscale: MD 5.71 lower (10.14 lower to 1.28 lower) IDMQ-J ease of use subscale: MD 0.73 higher (3.03 lower to 4.49 higher) IDMQ-J lifestyle impact subscale: MD 4.21 higher (0.04 lower to 8.46 higher) IDMQ-J blood glucose control subscale: MD 2.04 lower (5.9 lower to 1.82 higher)	No outcomes identified

Outcomes for drugs compared to dulaglutide	Glimepiride	Liraglutide	Tirzepatide
All-cause mortality	1 study (n=735), Very low quality, 2 fewer per 1,000 (from 6 fewer to 2 more)	1 study (n=417), Moderate quality, 0 fewer per 1,000 (from 11 fewer to 11 more)	1 study (n=636), Moderate quality, 0 fewer per 1,000 (from 9 fewer to 9 more)
Cardiovascular mortality	1 study (n=735), Low quality, 0 fewer per 1,000 (from 6 fewer to 6 more)	1 study (n=417), Moderate quality, 0 fewer per 1,000 (from 11 fewer to 11 more)	1 study (n=636), Moderate quality, 0 fewer per 1,000 (from 9 fewer to 9 more)
3-item MACE	No outcomes identified	No outcomes identified	1 study (n=636), Very low quality, 4 fewer per 1000 (11 fewer to 33 more)
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	1 study (n=735), Very low quality, 2 fewer per 1,000 (from 6 fewer to 2 more)	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	1 study (n=636), Very low quality, 0 fewer per 1,000 (from 10 fewer to 10 more)
Unstable angina	No outcomes identified	No outcomes identified	1 study (n=636), Very low quality, 4 fewer per 1,000 (from 6 fewer to 27 more)
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to dulaglutide	Glimepiride	Liraglutide	Tirzepatide
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	1 study (n=636), Very low quality**,** 4 fewer per 1,000 (from 6 fewer to 27 more)
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=735), Low quality, 110 more per 1,000 (from 49 more to 210 more)	1 study (n=417), Very low quality, 1 more per 1,000 (from 20 fewer to 67 more)	1 study (n=636), Moderate quality, 67 fewer per 1,000 (from 69 fewer to 53 fewer)
At night hypoglycaemic episodes	1 study (n=735), Low quality, 33 more per 1000 (4 more to 166 more)	1 study (n=417), Very low quality, 0 fewer per 1,000 (from 6 fewer to 73 more)	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=735), Low quality, 0 fewer per 1,000 (from 6 fewer to 6 more)	1 study (n=417), Moderate quality, 0 fewer per 1,000 (from 11 fewer to 11 more)	1 study (n=636), Moderate quality, 0 fewer per 1,000 (from 9 fewer to 9 more)

Outcomes for drugs compared to dulaglutide	Glimepiride	Liraglutide	Tirzepatide
HbA1c change	1 study (n=720), Very low quality, MD 0.45 % higher (0.28 higher to 0.62 higher)	1 study (n=417), Low quality, MD 0.2 % higher (0 to 0.4 higher)	1 study (n=636), Moderate quality, MD 1.3 % lower (1.53 lower to 1.07 lower)
Weight change	1 study (n=720), Very low quality, MD 2.01 higher (1.55 higher to 2.47 higher)	No outcomes identified	1 study (n=636), Moderate quality, MD 7.84 kg lower (8.76 lower to 6.92 lower)
BMI change	No outcomes identified	No outcomes identified	No outcomes identified

1.1.7.1.12. Pioglitazone compared to exenatide

Table 17: Summary table for pioglitazone compared to exenatide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to exenatide	Pioglitazone
Health-related quality of life	1 study (n= 378), Moderate quality, EQ-5D MD 0.04 lower (0.07 lower to 0.01 lower)
All-cause mortality	2 studies (n = 689), High quality, 0 fewer per 1,000 (8 fewer to 8 more)
Cardiovascular mortality	2 studies (n = 689), High quality, 0 fewer per 1,000 (8 fewer to 8 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified

Outcomes for drugs compared to exenatide	Pioglitazone
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	2 studies, (n = 689), Very low quality, 31 fewer per 1000 (49 fewer to 4 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n = 278), Very low quality, 0 fewer per 1,000 (14 fewer to 14 more)
HbA1c change	2 studies (n = 583), Low quality, MD 0.09 higher (0.3 lower to 0.48 higher)
Weight change	2 studies (n = 639), High quality, MD 3.5 higher (2.9 higher to 4.1 higher)

Outcomes for drugs compared to exenatide	Pioglitazone
BMI change	1 study = 228, Low quality, MD 1.3 higher (1.02 higher to 1.58 higher)

1.1.7.1.13. Monotherapy compared to liraglutide

Table 18: Summary table for individual therapies compared to liraglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to liraglutide	Semaglutide	Pioglitazone
Health-related quality of life	1 study (n=191), Very low quality, SF-36v2 acute version physical component subscale: MD 1.02 higher (2.02lower to 0.01 lower) SF-36v2 acute version mental component subscale: MD 0.57 higher (2.07 lower to 0.93 higher)	No outcomes identified
All-cause mortality	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more	No outcomes identified
Cardiovascular mortality	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more)	No outcomes identified

Outcomes for drugs compared to liraglutide	Semaglutide	Pioglitazone
Non-fatal myocardial infarction	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more)	No outcomes identified
Unstable angina	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more)	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified
Acute kidney injury	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more)	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more)	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=194), Very low quality, 63 fewer per 1,000 (from 91 fewer to 24 more)	1 study (n = 60), Very low quality, 33 more per 1,000 (from 27 fewer to 663 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified

Outcomes for drugs compared to liraglutide	Semaglutide	Pioglitazone
Severe hypoglycaemic episodes	1 study (n=194), Very low quality, 0 fewer per 1,000 (from 30 fewer to 30 more	1 study (n = 60), Very low quality, 0 fewer per 1,000 (from 63 fewer to 63 more)
HbA1c change	1 study (n=187), Low quality, MD 0.07 % lower (0.3 lower to 0.16 higher)	1 study (n=60), Very low quality, MD 0.4 higher (0.39 lower to 1.19 higher)
Weight change	1 study (n=187), Very low quality, MD 1.22 lower (1.94 lower to 0.5 lower)	1 study (n=60), Low quality, MD 9.9 higher (4.89 higher to 14.91 higher)
BMI change	No outcomes identified	1 study (n=60), Low quality, MD 3.6 higher (1.78 higher to 5.42 higher)

1.1.7.1.14. Canagliflozin + metformin compared to canagliflozin

Table 19: Summary table for monotherapy and combination therapy compared to canagliflozin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to canagliflozin	Canagliflozin + metformin
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=949), Low quality, 0 fewer per 1,000 (4 fewer to 4 more)
Cardiovascular mortality	1 study (n=949), Very low quality, 0 fewer per 1,000 (4 fewer to 4 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	1 study (n=949), Very low quality, 0 more per 1,000 (2 fewer to 32 more)

Outcomes for drugs compared to canagliflozin	Canagliflozin + metformin
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	1 study (n=949), Very low quality, 2 more per 1,000 (from 2 fewer to 6 more)
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	1 study (n=949), Very low quality, 2 fewer per 1,000 (6 fewer to 2 more)
Diabetic ketoacidosis	1 study (n= 949), Very low quality, 2 fewer per 1,000 (6 fewer to 2 more)
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=949), Very low quality, 15 more per 1,000 (8 fewer to 57 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=949), Low quality, 0 fewer per 1,000 (4 fewer to 4 more)
HbA1c change	1 study (n=935), Very low quality, MD 0.37 % lower (0.51 lower to 0.23 lower)
Weight change	1 study (n=945), Low quality, MD 0.4 kg lower (0.99 lower to 0.19 higher)
BMI change	No outcomes identified

1

1.1.7.1.15. Dapagliflozin + metformin compared to dapagliflozin

Table 20: Summary table for dapagliflozin + metformin compared to dapagliflozin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to dapagliflozin	Dapagliflozin + metformin
Health-related quality of life	No outcomes identified
All-cause mortality	2 studies (n=827), Very low quality, 2 fewer per 1,000 (from 10 fewer to 6 more)
Cardiovascular mortality	2 studies (n=827), Low quality, 2 fewer per 1,000 (from 10 fewer to 6 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified

Outcomes for drugs compared to dapagliflozin	Dapagliflozin + metformin
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	2 studies (n=827), High quality, 20 more per 1,000 (from 2 more to 90 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	2 studies (n=827), High quality, 0 fewer per 1,000 (from 7 fewer to 7 more)
HbA1c change	2 studies (n=799), Low quality, MD 0.69 % lower (0.82 lower to 0.51 lower)
Weight change	2 studies (n=823), High quality, MD 0.32 kg lower (0.79 lower to 0.14 higher)
BMI change	No outcomes identified

1.1.7.1.16. Combination therapy compared to empagliflozin

Table 21: Summary table for combination therapy compared to empagliflozin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to Empagliflozin	Empagliflozin + metformin	Empagliflozin + linagliptin
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=1019), High quality, 0 fewer per 1,000 (5 fewer to 5 more)	2 studies (n=447), Low quality, 0 fewer per 1,000 (12 fewer to 12 more)
Cardiovascular mortality	1 study (n=1019), High quality, 0 fewer per 1,000 (5 fewer to 5 more)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified

Outcomes for drugs compared to Empagliflozin	Empagliflozin + metformin	Empagliflozin + linagliptin
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	2 studies (n=447), Very low quality, 4 fewer per 1,000 (20 fewer to 11 more)
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=1019), Low quality, 4 more per 1,000 (4 fewer to 43 more)	No outcomes identified

Outcomes for drugs compared to Empagliflozin	Empagliflozin + metformin	Empagliflozin + linagliptin
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	2 studies (n=447), Very low quality, 4 fewer per 1,000 (from 20 fewer to 11 more)
HbA1c change	1 study (n=854), High quality, MD 0.69 % lower (0.83 lower to 0.55 lower)	2 studies (n=447), Very low quality, MD 0.7% lower (0.93 lower to 0.46 lower)
Weight change	No outcomes identified	No outcomes identified
BMI change	No outcomes identified	No outcomes identified

1.1.7.1.17. Monotherapy compared to gliclazide

Table 22: A summary matrix showing the outcomes for individual drugs and drug combinations compared to gliclazide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities (model 5)

Outcomes for drugs compared to gliclazide	Liraglutide	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	1 study (n = 40), Very low quality, 0 fewer per 1,000 (from 92 fewer to 92 more)
Cardiovascular mortality	No outcomes identified	1 study (n = 40), Very low quality, 0 fewer per 1,000 (from 92 fewer to 92 more)
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified

Outcomes for drugs compared to gliclazide	Liraglutide	Pioglitazone
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	1 study (n = 40), Very low quality, 0 fewer per 1,000 (from 90 fewer to 90 more)
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	1 study (n = 40), Very low quality, 0 fewer per 1,000 (from 90 fewer to 90 more)
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=62), Very low quality, 63 fewer per 1,000 (146 fewer to 21 more)	2 studies (n = 1310), Very low quality, 58 fewer per 1,000 (from 85 fewer to 31 fewer)

Outcomes for drugs compared to gliclazide	Liraglutide	Pioglitazone
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	No outcomes identified
HbA1c change	1 study (n=62), Very low quality, MD 0.4% lower (1.38 lower to 0.58 higher)	3 studies (n=1,875), Very low quality, MD 0.32% lower (0.63 lower to 0.02 lower)
Weight change	1 study (n=56), Very low quality, MD 2.04 kg lower (8.42 lower to 4.34 higher)	2 studies (n=605), Very low quality, MD 4.56 Kg lower (20.39 lower to 11.26 higher)
BMI change	1 study (n=56), Very low quality, MD 1.1 kg/m2 lower (2.49 lower to 0.29 higher)	1 study (n=38), Very low quality, MD 1.53 Kg/m2 lower (4.65 lower to 1.59 higher)

1.1.7.1.18. Monotherapy and combination therapy compared to glimepiride

Table 23: A summary matrix showing the outcomes for individual drugs and drug combinations compared to glimepiride for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to glimepiride	Liraglutide	Pioglitazone	Sitagliptin + metformin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	No outcomes identified	1 study (n=290), Very low quality, 0 fewer per 1,000 (13 fewer to 13 more)
Cardiovascular mortality	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to glimepiride	Liraglutide	Pioglitazone	Sitagliptin + metformin
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to glimepiride	Liraglutide	Pioglitazone	Sitagliptin + metformin
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	2 studies (n=266), Very low quality, 22 fewer per 1,000 (from 47 fewer to 49 more)	1 study (n=290), Low quality, 147 fewer per 1,000 (175 to 86 fewer)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	No outcomes identified	1 study (n=290), Very low quality, 7 fewer per 1,000 (21 fewer to 7 more)
HbA1c change	1 study (n=272), Very low quality, MD 0.51% lower (0.84 lower to 0.18 lower)	1 study (n=75), Very low quality, MD 0.2 higher (0.23 lower to 0.63 higher)	1 study (n=290), Low quality, MD 0.78% lower (0.96 lower to 0.6 lower)

Outcomes for drugs compared to glimepiride	Liraglutide	Pioglitazone	Sitagliptin + metformin
Weight change	No outcomes identified	1 study (n=191), Very low quality, MD 0.2 lower (3.92 lower to 3.52 higher)	1 study (n=290), Very low quality, MD 1.72 kg lower (2.74 lower to 0.7 lower)
BMI change	No outcomes identified	2 studies (n=266), Very low quality, MD 0.44 higher (0.51 lower to 1.39 higher)	No outcomes identified

1.1.7.1.19. Gliclazide + saxagliptin compared to saxagliptin + metformin

Table 24: A summary matrix showing the outcomes for gliclazide + saxagliptin compared to saxagliptin + metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to saxagliptin + metformin	Gliclazide + saxagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=432), High quality, 0 fewer per 1000 (9 fewer to 9 more)
Cardiovascular mortality	1 study (n=432), High quality, 0 fewer per 1000 (9 fewer to 9 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified

Outcomes for drugs compared to saxagliptin + metformin	Gliclazide + saxagliptin
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=432), Low quality, 56 more per 1000 (2 more to 162 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=432), High quality, MD 0.10% higher (0.11 lower to 0.31 higher)
Weight change	No outcomes identified
BMI change	1 study (n=432), Low quality, MD 1.00 kg/m2 higher (0.92 lower to 2.92 higher)

1

1.1.7.1.20. Glimepiride + metformin compared to canagliflozin + metformin

Table 25: A summary matrix showing the outcomes for glimepiride + metformin compared to canagliflozin + metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to canagliflozin + metformin	Glimepiride + metformin
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified

Outcomes for drugs compared to canagliflozin + metformin	Glimepiride + metformin
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	No outcomes identified
Weight change	1 study (n=25), Low quality, MD 1.57 higher (0.80 higher to 2.34 higher)
BMI change	No outcomes identified

1.1.7.1.21. Pioglitazone + metformin compared to glimepiride + metformin

Table 26: A summary matrix showing the outcomes for pioglitazone + metformin compared to glimepiride + metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to glimepiride + metformin	Pioglitazone + metformin
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified

Outcomes for drugs compared to glimepiride + metformin	Pioglitazone + metformin
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=135), Low quality, 16 fewer per 1,000 (40 fewer to 123 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=135), Moderate quality, MD 0.6 % lower (0.72 lower to 0.48 lower)
Weight change	No outcomes identified

Outcomes for drugs compared to glimepiride + metformin	Pioglitazone + metformin
BMI change	1 study (n=135), High quality, MD 1.5 kg/m^2 lower (2.11 lower to 0.89 lower)

1.1.7.1.22. Monotherapy and combination therapy compared to pioglitazone

Table 27: A summary matrix showing the outcomes for individual drugs and drug combinations compared to pioglitazone for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to pioglitazone	Exenatide	Sitagliptin + metformin	Glimepiride + metformin	Pioglitazone + metformin	Pioglitazone + alogliptin	Pioglitazone + linagliptin	Pioglitazone + sitagliptin	Pioglitazone + vildagliptin
Health-related quality of life	1 study (n=411), Moderate quality, MD 0.04 higher (0.01 higher to 0.07 higher)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=411), High quality, MD 0 fewer per 1,000 (10 fewer to 10 more)	No outcomes identified	No outcomes identified	1 study (n=391), Very low quality, 0 fewer per 1,000 (10 fewer to 10 more)	No outcomes identified	No outcomes identified	1 study (n=317), Very low quality, 6 more per 1,000 (6 fewer to 18 more)	No outcomes identified
Cardiovascular mortality	1 study (n=411), High quality, MD 0	No outcomes identified	No outcomes identified	1 study (n=391), Low quality, 0	No outcomes identified	No outcomes identified	1 study (n=317), Very low quality, 6	No outcomes identified

Outcomes for drugs compared to pioglitazone	Exenatide	Sitagliptin + metformin	Glimepiride + metformin	Pioglitazone + metformin	Pioglitazone + alogliptin	Pioglitazone + linagliptin	Pioglitazone + sitagliptin	Pioglitazone + vildagliptin
	fewer per 1,000 (10 fewer to 10 more)			fewer per 1,000 (10 fewer to 10 more)			more per 1,000 (6 fewer to 18 more)	
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=801), Very low quality, 0 more per 1000 (4 fewer to 31 more)	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=391), Very low quality, 5 fewer per 1,000 (16 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to pioglitazone	Exenatide	Sitagliptin + metformin	Glimepiride + metformin	Pioglitazone + metformin	Pioglitazone + alogliptin	Pioglitazone + linagliptin	Pioglitazone + sitagliptin	Pioglitazone + vildagliptin
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to pioglitazone	Exenatide	Sitagliptin + metformin	Glimepiride + metformin	Pioglitazone + metformin	Pioglitazone + alogliptin	Pioglitazone + linagliptin	Pioglitazone + sitagliptin	Pioglitazone + vildagliptin
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=411), Low quality, 16 more per 1,000 (16 fewer to 98 more)	1 study (n=517), Very low quality, 41 more per 1,000 (1 fewer to 127 more)	1 study (n=133), Very low quality, 50 more per 1,000 (10 fewer to 100 more)	2 studies (n=529), Very low quality, 7 more per 1,000 (2 fewer to 66 more)	No outcomes identified	1 study (n=801), Very low quality, 2 fewer per 1,000 (9 fewer to 25 more)	1 study (n=317), Very low quality, 24 more per 1,000 (1 more to 48 more)	1 study (n=453), Very low quality, 3 more per 1,000 (3 fewer to 10 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	1 study (n=522), Low quality, 0	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=801), Very low quality, 3	1 study (n=317), Very low quality, 0	No outcomes identified

Outcomes for drugs compared to pioglitazone	Exenatide	Sitagliptin + metformin	Glimepiride + metformin	Pioglitazone + metformin	Pioglitazone + alogliptin	Pioglitazone + linagliptin	Pioglitazone + sitagliptin	Pioglitazone + vildagliptin
		fewer per 1,000 (7 fewer to 7 more)				more per 1,000 (2 fewer to 8 more)	fewer per 1,000 (12 fewer to 12 more)	
HbA1c change	1 study (n=411), High quality, MD 0.1 % higher (0.09 lower to 0.29 higher)	1 study (n=499), Very low quality, MD 0.5% lower (0.68 lower to 0.32 lower)	1 study (n=135), Moderate quality, MD 0.4 % lower (0.59 lower to 0.21 lower)	2 studies (n=488), High quality, MD 0.97 % lower (1.13 lower to 0.81 lower)	1 study (n=490), low quality, MD 0.49% lower (0.69 lower to 0.29 lower)	1 study (n=801), Moderate quality, MD 0.32 % lower (0.45 lower to 0.19 lower)	1 study (n=310), Very low quality, MD 0.5 % lower (0.71 lower to 0.29 lower)	1 study (n=442), Very low quality, MD 0.4 % lower (0.64 lower to 0.16 lower)
Weight change	1 study (n=411), High quality, MD 3.5 kg lower (4.21 lower to 2.79 lower)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=490), moderate quality, MD 0.64 kg higher (0.08 lower to 1.36 higher)	1 study (n=530), Moderate quality, MD 1.21 kg lower (2.26 lower to 0.16 lower)	1 study (n=317), Low quality, MD 0.7 kg higher (0.74 lower to 2.14 higher)	1 study (n=442), low quality, MD 0.26 higher (0.46 lower to 0.98 higher)
BMI change	No outcomes identified	No outcomes identified	1 study (n=135), High quality, MD 1.7 kg/m2 higher (1.1 higher to 2.3 higher)	No outcomes identified		No outcomes identified	No outcomes identified	No outcomes identified

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1.1.7.1.23. Monotherapy compared to insulin

Table 28: A summary matrix showing the outcomes for individual drugs compared to insulin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to insulin	Metformin	Exenatide	Tolbutamide	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	1 study (n=280), Very low quality, 0 fewer per 1,000 (from 14 fewer to 14 more)	1 study (n=618), Very low quality, 55 more per 1,000 (from 2 more to 138 more)	1 study (n=274), Very low quality, 0 fewer per 1,000 (from 14 fewer to 14 more)
Cardiovascular mortality	No outcomes identified	1 study (n=280), Very low quality, 0 fewer per 1,000 (from 14 fewer to 14 more)	1 study (n=618) Very low quality, 67 more per 1,000 (15 more to 155 more)	1 study (n=278), Very low quality, 0 fewer per 1,000 (from 14 fewer to 14 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Exenatide	Tolbutamide	Pioglitazone
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	1 study (n=566), Very low quality, 11 more per 1,000 (19 fewer to 74 more)	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	1 study (n=585), Very low quality, 4 more per 1,000 (33 fewer to 69 more)	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Exenatide	Tolbutamide	Pioglitazone
Hypoglycaemia episodes	1 study (n=75), Very low quality, 248 fewer per 1,000 (319 fewer to 52 fewer)	2 studies (n=356), Very low quality, 47 fewer per 1,000 (from 87 fewer to 25 more)	No outcomes identified	1 study (n=274), Very low quality, 94 fewer per 1,000 (from 116 fewer to 34 fewer)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	
Severe hypoglycaemic episodes	1 study (n=75), Very low quality, 0 fewer per 1,000 (51 fewer to 51 more)	2 studies (n=356), Low quality, 0 fewer per 1,000 (from 16 fewer to 16 more)	No outcomes identified	1 study (n=278), Very low quality, 0 fewer per 1,000 (from 14 fewer to 14 more)
HbA1c change	1 study (n=75), Low quality MD 0.2 % higher (0.05 lower to 0.45 higher)	2 studies (n=295), Very low quality, MD 0.36 % lower (0.9 lower to 0.18 higher)	No outcomes identified	1 study (n=232), Low quality, MD 0.2 higher (0.08 lower to 0.48 higher)
Weight change	No outcomes identified	2 studies (n=295), Low quality, MD 4.33 kg lower (5.19 lower to 3.47 lower)	No outcomes identified	1 study (n=232), Low quality, MD 1 lower (1.98 lower to 0.02 lower)
BMI change	No outcomes identified	2 studies (n=295), Very low quality, MD 1.65 kg/m2 lower (1.91 lower to 1.40 lower)	No outcomes identified	1 study (n=232), Low quality, MD 0.4 lower (0.68 lower to 0.12 lower)

See report E2, appendix F for full GRADE tables.

1.1.8. Economic evidence

See report F1, section 1.1.10 for details of economic model

1.1.8.1. Included studies

Two health economic studies with relevant comparisons were included in this review: 1 comparing no treatment (placebo), metformin, pioglitazone, repaglinide, sitagliptin, sulfonylurea and vildagliptin[85]; and 1 comparing metformin plus drugs from cardiovascular outcome trials (alogliptin, canagliflozin, dapagliflozin, dulaglutide, empagliflozin, ertugliflozin, exenatide, linagliptin, liraglutide, lixisenatide; pioglitazone, saxagliptin, semaglutide (injection), semaglutide (oral) and sitagliptin) to metformin alone[86]. These are summarised in the health economic evidence profile below (Table 4) and the health economic evidence tables in Appendix H.

No health economic studies were included that related to tirzepatide.

1.1.8.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.9. Summary of included economic evidence

Table 29: Health economic evidence profile: Metformin versus any other drug during initial therapy

Study	Applicability	Limitations	Other comments	Cost effectiveness and uncertainty
NICE 2015[85] (UK)	Directly applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic model (UKPDS OM1) based on network meta-analysis of RCTs • Cost-utility analysis (QALYs) • Population: Adults aged 18 years and over with type 2 diabetes • Comparators: 1.No treatment (placebo) 2.Metformin 3.Pioglitazone 4.Repaglinide 5.Sitagliptin 6.Sulfonylurea 7.Vildagliptin Time horizon: lifetime/ 40 years	**Intervention in order of cost** / **Inc. costs versus metformin[(c)]** / **Inc. QALYs versus metformin** / **Cost per QALY gained versus metformin** Metformin Repaglinide: £48 / -0.059 / Dominated Pioglitazone: £163 / -0.060 / Dominated Sulfonylurea: £330 / -0.082 / Dominated No treatment (placebo): £794 / -0.121 / Dominated Sitagliptin: £1,207 / -0.043 / Dominated Vildagliptin: £1,377 / -0.074 / Dominated Probability Intervention 2 cost effective versus all other interventions (£20K/30K threshold): 88%/86% Metformin remained the most cost-effective treatment option when 2-year treatment effects data for HbA1c and weight change were applied.
NICE 2022[86] (UK)	Directly applicable [(a)]	Potentially serious limitations[(b)]	• Two-part probabilistic model that builds upon the UKPDS OM2 model, based on network meta-analysis of RCTs • Cost-utility analysis (QALYs) • Population: Adults aged 18 years and over with type 2 diabetes	**Intervention in order of cost** / **Inc. cost versus metformin** / **Inc. QALYs versus metformin** / **Cost per QALY gained versus metformin** Metformin Pioglitazone + metformin: £1,647 / -0.097 / Dominated Alogliptin + metformin: £4,496 / -0.062 / Dominated Ertugliflozin + metformin: £4,751 / 0.198 / £24,004

Study	Applicability	Limitations	Other comments	Cost effectiveness and uncertainty

- Comparators: CVOT drugs plus metformin were compared to metformin alone
- Time horizon: lifetime/40 years

Linagliptin + metformin	£5,248	0.021	£248,971
Sitagliptin + metformin	£5,822	0.033	£177,546
Dapagliflozin + metformin	£5,834	0.367	£15,899
Empagliflozin + metformin	£6,220	0.244	£25,526
Saxagliptin + metformin	£6,241	-0.27	Dominated
Canagliflozin + metformin	£6,920	0.226	£30,664
Lixisenatide + metformin	£8,977	-0.291	Dominated
Semaglutide (injection) + metformin	£12,565	0.473	£26,552
Dulaglutide + metformin	£12,589	0.161	£78,166
Exenatide + metformin	£12,881	0.064	£202,472
Semaglutide (oral) + metformin	£14,325	-0.323	Dominated
Liraglutide + metformin	£18,913	-0.004	Dominated

Subgroup analyses were also conducted for those:

1. with a BMI of greater than or equal to 30kg/m2
2. at high risk of a CV event who have not had a prior event
3. who have had a prior CV event
4. combination of numbers 2 and 3 above

The costs per QALY gained did differ between subgroups and treatments generally became more cost-effective with increasing CV risk. However, the differences were small.

Study	Applicability	Limitations	Other comments	Cost effectiveness and uncertainty
				Analysis of uncertainty: • There were no analyses of uncertainty presented for the addition of CVOT drugs to metformin.

Abbreviations: CV= cardiovascular; CVOT= cardiovascular outcome trial; GLP-1= glucagon-like peptide; HbA1c= glycated haemoglobin; ICER= incremental cost-effectiveness ratio; Inc= incremental; OM1= outcomes model 1; OM2= outcomes model 2; QALY= quality-adjusted life years; RCT= randomised controlled trial; UKPDS= United Kingdom prospective diabetes study

(a) Newer GLP-1 agonists and SGLT-2 inhibitors are missing from the analysis. Tirzepatide is also missing from the analysis.

(b) NPH insulin was modelled within the treatment intensification regimen, however it is not a commonly used insulin type. The validity of HbA1c as a surrogate marker used to predict cardiovascular outcomes and mortality has been questioned. Sources of costs are dated and do not accurately reflect current NHS conditions. The proportion of hypoglycaemic episodes that are severe (2%) - and therefore incur costs to the NHS - was assumed to be the same across all treatments.

(c) 2012/13 costs/UK pounds. Cost components incorporated: Drug costs, drug consumables (needles, self-monitoring blood glucose strips and lancets, sharps bins), staff time for GLP-1 and insulin initiation, diabetes-related complications costs

(d) Only cardiovascular outcome trial (CVOT) drugs are included in the incremental analysis; other drug classes such as sulfonylureas and insulin are included as background treatments only. Tirzepatide is also missing from the analysis.

(e) NPH insulin was modelled within the treatment intensification regimen, however it is not a commonly used insulin type. Probabilistic analysis was only conducted for the second intensification stage due to a lack of time. The analysis assumes that non-cardiovascular treatment-related outcomes are the same between comparator arms. The timing of treatment intensification does not differ between different treatment options, meaning that between-treatment effects on HbA1c are not fully captured.

(f) 2020/21 costs/UK pounds. Cost components incorporated: Drug costs, drug consumables (needles, self-monitoring blood glucose strips and lancets [for sulfonylureas and insulins only], sharps bins), staff time for GLP-1 and insulin drug class initiation, diabetes-related complications

NG28 (2015)

All treatments reduced complications and increased QALYs compared with no treatment. However, there was very little difference in complication rates between therapies, in part due to small differences in change to HbA1c between treatments. Metformin dominated all other interventions in the base case as it had the greatest impact on weight loss, which resulted in increased QALYs.

NG28 update (2022)

Six interventions were dominated by metformin alone when added to metformin during initial therapy, meaning their addition reduced QALYs. The reason varied by treatment.

Alogliptin was associated with event hazard ratios (point estimates) greater than one for heart failure (HF) and myocardial infarction (MI), while saxagliptin had event hazard ratios greater than one for HF, stroke and ischaemic heart disease (IHD). These differences appear to account for their dominance by metformin alone.

While the event hazard ratios for pioglitazone were lower than one for myocardial infarction and stroke, its association with severe hypoglycaemic events appeared to negate its beneficial cardiovascular affects.

The remaining three dominated interventions (liraglutide, lixisenatide and oral semaglutide) were all from the GLP-1 receptor agonist drug class.

- Liraglutide had event hazard ratios of less than one for all of HF, IHD, MI and stroke. It reduced weight and reduced hypos. But all of the benefit was negated by the disutility associated with daily injection.
- Lixisenatide had event hazard ratios greater than one for IHD, MI and stroke, and an event hazard ratio of less than one for HF. Like liraglutide, it must also be injected daily.
- Oral semaglutide was associated with more IHD and MI events, and fewer HF and stroke and a high hypoglycaemia rate.

1.1.9.1. Unit costs of standard release and modified release metformin

Table 14 presents the unit costs for standard release and modified release metformin. The price listed is the lowest Drug Tariff Price for each type of medication as listed in the BNF (accessed 28/01/2025). Metformin modified release costs approximately twice as much as standard release. Assuming a daily dose of 2g per day (the maximum of the range listed in the BNF) opting for modified release over standard release metformin leads to an annual increase in prescribing costs of £13.

Table 30. Unit costs of Metformin

Treatment	Pack size and dosage	Unit price	Cost per tablet	Cost per year
Metformin Standard Release	56 x 500mg	£1.28	£0.02	£33.37
Metformin Modified Release	56 x 1g	£3.52	£0.04	£46.02

For a population of 0.24 million, the number of newly diagnosed as estimated by NHS England (Incidence and prevalence of diabetes), prescribing modified release metformin over standard release metformin would equate to a cost increase of £2 million per year. For a prevalent population of 2 million, the additional prescribing costs would be £16.5 million a year if all were prescribed modified release metformin over standard release metformin. This is unlikely to be the additional cost of recommending modified release metformin as some individuals will already be prescribed metformin modified release and not all individuals will necessarily switch to it.

Modified release metformin is associated with lower adverse events than standard release metformin in particular gastrointestinal events. Assuming a cost per GP appointment of £49, the cost estimated by PSSRU 2023 (including qualification costs), for metformin modified release to be cost neutral, with regards to prescribing costs, 1 GP appointment for every 5 people needs to be averted every year.

This analysis does not capture any of the health benefits and potential savings associated with modified release metformin. Modified release metformin has a lower number of adverse events, can be taken less frequently and consequently leads to higher adherence with the treatment regimen. Greater adherence to treatment will improve the benefits of metformin treatment. This will lead to better control of diabetes, preventing the need to escalate to additional treatments and avoiding cardio-renal events and reducing the costs associated with both. Lower adverse events and better health outcomes will also lead to additional QALYs.

1.1.10. Evidence statements

1.1.10.1. Economic

- One cost-utility analysis reported that metformin dominated no treatment (placebo), pioglitazone, repaglinide, sitagliptin, sulfonylureas and vildagliptin, with an 88% probability of being cost effective versus all at a £20,000 per QALY gained threshold. This analysis was assessed as directly applicable with potentially serious limitations.
- One cost-utility analysis reported that metformin alone was cost effective at £20,000 per QALY versus metformin plus combinations of various cardiovascular outcome trial drugs ((alogliptin, canagliflozin, dulaglutide, empagliflozin, ertugliflozin, exenatide, linagliptin, liraglutide, lixisenatide; pioglitazone, saxagliptin, semaglutide (injection), semaglutide (oral) and sitagliptin), except for dapagliflozin plus metformin (ICER: £15,899). This analysis was assessed as directly applicable with potentially serious limitations.

1.1.11. The committee's discussion and interpretation of the evidence

For more information, please see the committee discussion document.

1.1.12. Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and the recommendation for research on treatment strategies for people with type 2 diabetes and frailty, access to SGLT-2 inhibitors and management of early onset type 2 diabetes. Other evidence supporting these recommendations can be found in the evidence reviews on subsequent therapy (evidence review F).

1.1.13. References

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Appendices

Appendix A Review protocols

A.1 Review protocol for the initial pharmacological management of type 2 diabetes

ID	Field	Content
0.	PROSPERO registration number	CRD42023416862
1.	Review title	For different population subgroups, which individual and/or combinations of pharmacological therapies are most clinically and cost effective as initial treatment for the management of type 2 diabetes?
2.	Review question	For different population subgroups, which individual and/or combinations of pharmacological therapies are most clinically and cost effective as initial treatment for the management of type 2 diabetes.
3.	Objective	Historically initial pharmacological treatment for type 2 diabetes has included metformin and sulfonylureas. Metformin has been the initial treatment for a long period of time and has been an effective treatment for many people. As a more holistic approach to type 2 diabetes treatment has been adopted and more treatments have developed, more options have been available that may be better suited to different people at different times. This review will aim to ask what the best initial treatment is for people with type 2 diabetes in different population subgroups.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Study design RCT and SR filters will be applied • No date limit will be set • English language studies • Human studies • Conference abstracts will be excluded from the search results

		Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Pharmacological treatments for people with type 2 diabetes mellitus
6.	Population	Inclusion: • Adults (age ≥18 years) with type 2 diabetes mellitus The population will be stratified into different groups, these include: • People with type 2 diabetes mellitus and heart failure o People with type 2 diabetes mellitus and heart failure o People with type 2 diabetes mellitus and no heart failure o Mixed population o Not stated/unclear • People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease o People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease o People with type 2 diabetes mellitus and no atherosclerotic cardiovascular disease o Mixed population o Not stated/unclear • People with type 2 diabetes mellitus and chronic kidney disease o People with type 2 diabetes mellitus and chronic kidney disease o People with type 2 diabetes mellitus and no chronic kidney disease o Mixed population o Not stated/unclear

		• People with type 2 diabetes mellitus and high cardiovascular risk
		  ○ People with type 2 diabetes mellitus and high cardiovascular risk
		  ○ People with type 2 diabetes mellitus and not at high cardiovascular risk
		  ○ Mixed population
		  ○ Not stated/unclear
		
		After the protocol was submitted, it was agreed that five population models would be obtained from these stratifications:
		• People with type 2 diabetes and chronic heart failure
		• People with type 2 diabetes and atherosclerotic cardiovascular disease
		• People with type 2 diabetes and chronic kidney disease
		• People with type 2 diabetes and low cardiovascular risk with no other comorbidities
		• People with type 2 diabetes and high or mixed/unclear cardiovascular risk with no other comorbidities
		
		Exclusion:
		• Children and young people (age <18 years) with type 2 diabetes mellitus
		• Pregnant people with type 2 diabetes mellitus
		• People with type 1 diabetes mellitus
		• People with type 2 diabetes mellitus who are hyperglycaemic and require rescue treatment

7.	Intervention	Pharmacological therapies for people with type 2 diabetes.
		• All therapies will be examined on an individual drug level (rather than a class level).
		• All doses will be pooled together.
		
		• Biguanides
		  ○ Metformin hydrochloride standard release
		  ○ Metformin hydrochloride slow release
		• DPP-4 inhibitors
		  ○ Alogliptin (Vipidia)
		  ○ Linagliptin (Trajenta)
		  ○ Saxagliptin (Onglyza)
		  ○ Sitagliptin (Januvia)
		  ○ Vildagliptin (Galvus)
		• GLP-1 receptor agonist
		  ○ Dulaglutide (Trulicity)

		○ Exenatide (Byetta) ○ Liraglutide (Victoza) ○ Lixisenatide (Lyxumia) ○ Semaglutide (Rybelsus, Ozempic) • Dual GIP/GLP-1 receptor co-agonists ○ Tirzepatide (Mounjaro) • SGLT2 inhibitors ○ Canagliflozin (Invokana) ○ Dapagliflozin (Forxiga) ○ Empagliflozin (Jardiance) ○ Ertugliflozin (Steglatro) • Sulfonylureas ○ Gliclazide ○ Glimepiride ○ Glipizide ○ Tolbutamide • Thiazolidinediones ○ Pioglitazone • Combinations of therapies listed above (combinations may include medicines being given separately or combination products) • After the protocol was submitted it was agreed that IDegLira (insulin degludec and liraglutide) and IGlarLixi (insulin glargine and lixisenatide) would be included as combinations that would be looked at in this category even though insulin is a comparator.
8.	Comparator	• Different pharmacological therapies listed in the intervention section to each other • An oral formulation compared with an injectable formulation of the same medication • Insulin (all types and doses pooled together in the same drug class) • Placebo
9.	Types of study to be included	Systematic reviews (SRs) of randomised-controlled trials Randomised-controlled trials (RCTs) Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	• Non-randomised trial evidence (including observational, cohort, case-control and case series studies, uncontrolled or single arm trials), narrative reviews, conference abstracts, letters, editorials and trial protocols. • Studies including a mixed population of people with type 1 and 2 diabetes, unless subgroup analyses were reported or 85% or more of the study population have type 2 diabetes.

		• Studies including a mixed population of people with and without diabetes will be excluded. • Comparisons with unlicensed modes of delivery (for example, inhaled insulin). • Crossover trials (a crossover trial will only be included if the duration of one or both interventions is at least 24 weeks and there is a washout period of at least 6 weeks between interventions). • Trials where there is unclear washout of existing drug treatments, where a proportion or all participants continued previous medicines that will likely confound study results (papers were excluded unless this represented a small proportion of patients that is less than 5%). • Trials that have a treatment and follow up period of less than 24 weeks. • Systematic reviews that did not include at least one RCT of at least 24 weeks duration. • Dose finding trials where both arms would be combined in a single node in the NMA. (Three arm trials may be included if they connect to the network and provide useful information. • Trials of Treatments which are not available, or no longer available, in the UK including: o Glibenclamide o Chlorpropamide o Nateglinide o Miglitol o Omarigliptin o Albiglutide o Rosiglitazone • Trials of treatments that are rarely used in the UK, including: o Repaglinide o Acarbose • Trials of combinations of drugs which include one or more drug that is not available in the UK, no longer available in the UK. • Trials of a combined formulation of drugs which is not available in the UK. • Trials that were not reported in English.
11.	Context	The 2021 update focussed on the cardiovascular benefits of different pharmacological therapies for type 2 diabetes. The evidence included in this review will take a holistic view of the wider potential benefits of the treatments. This may affect which medicines

		should be offered, and which combinations should be used at each stage of treatment.
12.	Primary outcomes (critical outcomes)	Outcomes will be extracted in this review for inclusion in the review. The final time point (end point of the trial) reported will be extracted and used in the analysis where possible. Where outcomes are reported as time-to-event and dichotomous values, both time-to-event and dichotomous values will be extracted. **Outcomes to be extracted for use in this review** All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Health-related quality of life (continuous outcomes): o EQ-5D o SF-6D o SF-36 o SF-12 o Other utility measures (AQOL, HUI, 15D, QWB) o HASMID-10 o Diabetes Quality of life o Diabetes Quality of life questionnaire o Diabetes Quality of life Clinical Trial Questionnaire o Audit of Diabetes Dependent Quality of Life o Diabetes-39 o Diabetes Health Profile o DAWN2 Impact of Diabetes Profile o Diabetes Impact Measurement Scales o QoLHYPO • All-cause mortality (time-to-event/dichotomous outcome) • Cardiovascular mortality (time-to-event/dichotomous outcome) • Major Cardiovascular Events (MACE) (where multiple MACE values are reported [for example: 3-item MACE and 4-item MACE], the highest number MACE value will be prioritised) (time-to-event/dichotomous outcome) o 3-item MACE o 4-item MACE o 5-item MACE

		• Events making up MACE (time-to-event/dichotomous outcomes):
		  ○ Non-fatal stroke
		  ○ Non-fatal myocardial infarction
		  ○ Unstable angina
		  ○ Hospitalisation for heart failure
		• Renal events (time-to-event/dichotomous outcome):
		  ○ Acute kidney injury
		  ○ Persistent signs of worsening kidney disease (including doubling of serum creatinine)
		  ○ Development of end stage kidney disease (including need for renal replacement therapy and transplant)
		  ○ Death from renal cause
		• Serious adverse events (time-to-event/dichotomous outcome):
		  ○ Cardiac arrhythmia (including atrial fibrillation)
		  ○ Diabetic ketoacidosis
		  ○ Falls requiring hospitalisation
		• Progression of liver disease (to non-alcoholic fatty liver disease, to fibrosis, to cirrhosis, to end stage liver disease) (time-to-event/dichotomous outcome)
		• Remission (time-to-event/dichotomous outcome)
		• Acute diabetic complications (time-to-event/dichotomous outcome):
		  ○ Hypoglycaemia episodes
		  ○ At night hypoglycaemic episodes
		  ○ Severe hypoglycaemic episodes
		• Continuous outcomes:
		  ○ HbA1c change (absolute change scores prioritised over percentage change scores)
		  ○ Weight change
		  ○ BMI change

13.	Data extraction (selection and coding)	EndNote will be used for reference management, citations and bibliographies. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. EPPI will be used for sifting. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow or equivalent. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager. Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. When different studies present continuous data measuring the same outcomes but using different numerical scales these outcomes will be converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, this will be achieved using standardised mean differences (SMDs, Hedges' g). Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias,

		indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Network meta-analysis (NMAs) may be used to synthesise direct evidence about pairs of interventions that originate from two or more separate studies and indirect evidence. WinBUGS will be used for network meta-analysis, if possible given the data identified. The quality of the NMA networks will be assessed using a modified form of GRADE.

16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present:
		
		• People with frailty
		  ○ People with frailty
		  ○ People without frailty
		  ○ Mixed population
		  ○ Not stated/unclear
		• Onset of type 2 diabetes mellitus
		  ○ Early onset type 2 diabetes mellitus first diagnosed at age below 40 years of age
		  ○ People with type 2 diabetes mellitus first diagnosed at age above 40 years of age
		  ○ Mixed population
		  ○ Not stated/unclear
		• People with non-alcoholic fatty liver disease
		  ○ People with non-alcoholic fatty liver disease
		  ○ People without non-alcoholic fatty liver disease
		  ○ Mixed population
		  ○ Not stated/unclear
		• People with obesity
		  ○ People with obesity (for people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background BMI ≥27.5, for people not in the groups listed before BMI ≥30)
		  ○ People without obesity (for people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background BMI <27.5, for people not in the groups listed before BMI <30)
		  ○ Mixed population
		  ○ Not stated/unclear
		• eGFR category at baseline
		  ○ eGFR ≥30mL/min/1.73m^2

<table>
<tr><td></td><td></td><td colspan="3">○ eGFR 15-29mL/min/1.73m^2
○ eGFR <15mL/min/1.73m^2
○ Mixed population
○ Not stated/unclear
• Albuminuria category at baseline
○ A1 (ACR <30mg/g or <3mg/mmol)
○ A2 (ACR 30-300 mg/g or 3-30mg/mmol)
○ A3 (ACR >300mg/g or >30mgmmol)
○ Mixed population
○ Not stated/unclear</td></tr>
<tr><td rowspan="7">17.</td><td rowspan="7">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
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<tr><td>19.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3">10/01/2023</td></tr>
<tr><td>21.</td><td>Anticipated completion date</td><td colspan="3">01/12/2024</td></tr>
<tr><td rowspan="8">22.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
<tr><td>Data extraction</td><td>☑</td><td>☑</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☑</td><td>☑</td></tr>
<tr><td>Data analysis</td><td>☑</td><td>☑</td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact
Guideline Development Team NGC

5b Named contact e-mail
t2diabetesadults@nice.org.uk</td></tr>
</table>

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
24.	Review team members	From NICE: Serena Carville (Guideline lead) George Wood (Medicines analyst) Emily Terrazas-Cruz (Senior research fellow) Tayyaba Mumtaz (Trainee technical analyst) Nancy Pursey (Trainee technical analyst) David Wonderling (Head of health economics) Muksitur Rahman (Health economics analyst) Joseph Runicles (Information specialist) Sarah Glover (Information specialist) Amy Crisp (Senior project manager)
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10336
28.	Other registration details	N/A
29.	Reference/URL for published protocol	N/A
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Adults; Biguanides; DPP-4 inhibitors; GLP-1 receptor agonists; Initial; Intervention; Pharmacological; SGLT2 inhibitors; Sulfonylureas; Thiazolidinediones; Type 2 Diabetes Mellitus	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Below is the health economic review protocol. This sets out how published cost effectiveness evidence will be identified for the guideline and the criteria for inclusion/exclusion.

Table 31: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018) • International HTA database (INAHTA) – all years Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2008 (including those included in the previous guideline), abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2008 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (https://www.nice.org.uk/process/pmg20/chapter/introduction) **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and

	methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2008 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2008 will be rated as 'Not applicable'. • Studies published before 2008 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Number of interventions:* • Studies presenting results for multiple comparators of interest will be included in the review. • Studies presenting results of pair-wise analyses only will be excluded from the review. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.(NICE2014)

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Q1.1 For different population subgroups, which individual and/or combinations of pharmacological therapies are most clinically and cost effective as initial treatment for the management of type 2 diabetes?

Table 1: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 21 March 2024	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 21 March 2024	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2024 Issue 3 of 12 CENTRAL to 2024 Issue 3 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 21 March 2024	Systematic review studies Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

	exp Diabetes Mellitus, Type 2/

	(type adj4 ("2" or "II" or two) adj4 diabet*).tw.
	((matur* or adult* or slow*) adj4 onset* adj4 diabet*).tw.
	(("ketosis resistant" or "ketosis prone" or stable) adj4 diabet*).tw.
	(("non insulin" or noninsulin) adj4 depend* adj4 diabet*).tw.
	(NIDDM or T2DM or DM2).tw.
	or/1-6
	letter/
	editorial/
	news/
	exp historical article/
	Anecdotes as Topic/
	comment/
	case reports/
	(letter or comment*).ti.
	or/8-15
	randomized controlled trial/ or random*.ti,ab.
	16 not 17
	animals/ not humans/
	exp Animals, Laboratory/
	exp Animal Experimentation/
	exp Models, Animal/
	exp Rodentia/
	(rat or rats or mouse or mice or rodent*).ti.
	or/18-24
	7 not 25
	limit 26 to english language
	exp Glucagon-Like Peptide 1/
	"glucagon like peptide 1".tw.
	("GLP 1" or "GLP1").tw.
	Exenatide/
	(Exenatide* or Byetta or Bydureon or Saxenda).tw.
	(Liraglutide* or Victoza).tw.
	(Dulaglutide* or Trulicity).tw.
	(Semaglutide* or Ozempic or Rybelsus).tw.
	(Lixisenatide* or Lyxumia).tw.
	(tirzepatide* or mounjaro).tw.
	Sodium-Glucose Transporter 2 Inhibitors/
	"Sodium-Glucose Transporter 2".tw.
	("Sodium-Glucose cotransporter 2" or "Sodium-Glucose co transporter 2").tw.
	(SGLT* or gliflozin*).tw.
	Canagliflozin/
	(Canagliflozin* or Invokana or Dapagliflozin or Forxiga or Ertugliflozin or Steglatro or Empagliflozin or Jardiance or Glyxambi).tw.

	exp Sulfonylurea Compounds/tu [Therapeutic Use]
	(Sulfonylurea* or Sulphonylurea*).tw.
	(Gliclazide* or Diamicron).tw.
	(Glimepiride* or Amaryl).tw.
	(Glipizide* or Minodiab).tw.
	Tolbutamide*.tw.
	Thiazolidinediones/
	(Thiazolidinedione* or Glitazone*).tw.
	Pioglitazone/
	(Pioglitazone* or Actos).tw.
	exp Dipeptidyl-Peptidase IV Inhibitors/ or Dipeptidyl Peptidase 4/
	("Dipeptidyl-Peptidase IV Inhibitor*" or "Dipeptidyl Peptidase 4 Inhibitor").tw.
	(DPP* adj2 ("4" or "iv")).tw.
	gliptin*.tw.
	(Saxagliptin* or Onglyza or Komboglyze or Qtern).tw.
	Vildagliptin/
	(Vildagliptin* or Galvus).tw.
	Sitagliptin/
	(Sitagliptin* or Januvia).tw.
	(Alogliptin* or Vipdomet).tw.
	Linagliptin/
	(Linagliptin* or Trajenta or Jentadueto).tw.
	Metformin/
	(Metformin* or Glucophage).tw.
	(Competact or Janumet or Eucreas or Synjardy or Vokanamet or Xigduo).tw.
	Biguanides/
	Biguanide*.tw.
	or/28-70
	randomized controlled trial.pt.
	controlled clinical trial.pt.
	randomi#ed.ti,ab.
	placebo.ab.
	randomly.ti,ab.
	Clinical Trials as topic.sh.
	trial.ti.
	or/72-78
	Meta-Analysis/
	exp Meta-Analysis as Topic/
	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

	(search* adj4 literature).ab.
	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
	cochrane.jw.
	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
	or/80-89
	27 and 71
	91 and (79 or 90)

Embase (Ovid) search terms

	non insulin dependent diabetes mellitus/
	(type adj4 ("2" or "II" or two) adj4 diabet*).tw.
	((matur* or adult* or slow*) adj4 onset* adj4 diabet*).tw.
	(("ketosis resistant" or "ketosis prone" or stable) adj4 diabet*).tw.
	(("non insulin" or noninsulin) adj4 depend* adj4 diabet*).tw.
	(NIDDM or T2DM or DM2).tw.
	or/1-6
	letter.pt. or letter/
	note.pt.
	editorial.pt.
	case report/ or case study/
	(letter or comment*).ti.
	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
	or/8-13
	randomized controlled trial/ or random*.ti,ab.
	14 not 15
	animal/ not human/
	nonhuman/
	exp Animal Experiment/
	exp Experimental Animal/
	animal model/
	exp Rodent/
	(rat or rats or mouse or mice or rodent*).ti.
	or/16-23
	7 not 24
	limit 25 to english language
	"glucagon like peptide 1".tw.
	*glucagon like peptide 1/
	("GLP 1" or "GLP1").tw.
	*exendin 4/
	(Exenatide* or Byetta or Bydureon or Saxenda).tw.
	*liraglutide/
	(Liraglutide* or Victoza).tw.

	*dulaglutide/
	(Dulaglutide* or Trulicity).tw.
	*semaglutide/
	(Semaglutide* or Ozempic or Rybelsus).tw.
	*lixisenatide/
	(Lixisenatide* or Lyxumia).tw.
	*tirzepatide/
	(tirzepatide* or mounjaro).tw.
	*sodium glucose cotransporter 2 Inhibitor/
	"Sodium-Glucose Transporter 2".tw.
	("Sodium-Glucose cotransporter 2" or "Sodium-Glucose co transporter 2").tw.
	(SGLT* or gliflozin*).tw.
	*canagliflozin/
	(Canagliflozin* or Invokana or Dapagliflozin or Forxiga or Ertugliflozin or Steglatro or Empagliflozin or Jardiance or Glyxambi).tw.
	sulfonylurea derivative/dt [Drug Therapy]
	(Sulfonylurea* or Sulphonylurea*).tw.
	*gliclazide/
	(Gliclazide* or Diamicron).tw.
	*glimepiride/
	(Glimepiride* or Amaryl).tw.
	*glipizide/
	(Glipizide* or Minodiab).tw.
	*tolbutamide/
	Tolbutamide*.tw.
	*2,4 thiazolidinedione derivative/ or *Glitazone derivative/
	(Thiazolidinedione* or Glitazone*).tw.
	*pioglitazone/
	(Pioglitazone* or Actos).tw.
	*dipeptidyl peptidase IV inhibitor/
	*dipeptidyl peptidase IV/
	("Dipeptidyl-Peptidase IV Inhibitor*" or "Dipeptidyl Peptidase 4 Inhibitor").tw.
	(DPP* adj2 ("4" or "iv")).tw.
	gliptin*.tw.
	*saxagliptin/
	(Saxagliptin* or Onglyza or Komboglyze or Qtern).tw.
	*vildagliptin/
	(Vildagliptin* or Galvus).tw.
	*sitagliptin/
	(Sitagliptin* or Januvia).tw.
	*alogliptin/
	(Alogliptin* or Vipdomet).tw.
	*linagliptin/

	(Linagliptin* or Trajenta or Jentadueto).tw.
	*metformin/
	*dapagliflozin plus metformin/ or *linagliptin plus metformin/ or *metformin/ or *dapagliflozin plus metformin plus saxagliptin/ or *ertugliflozin plus metformin/ or *glipizide plus metformin/ or *metformin plus pioglitazone/ or *metformin plus vildagliptin/ or *metformin plus saxagliptin/ or *empagliflozin plus linagliptin plus metformin/ or *alogliptin plus metformin/ or *glimepiride plus metformin/ or *empagliflozin plus metformin/ or *metformin plus sitagliptin/ or *canagliflozin plus metformin/
	(Metformin* or Glucophage).tw.
	(Competact or Janumet or Eucreas or Synjardy or Vokanamet or Xigduo).tw.
	*biguanide derivative/
	Biguanide*.tw.
	or/27-82
	random*.ti,ab.
	factorial*.ti,ab.
	(crossover* or cross over*).ti,ab.
	((doubl* or singl*) adj blind*).ti,ab.
	(assign* or allocat* or volunteer* or placebo*).ti,ab.
	crossover procedure/
	single blind procedure/
	randomized controlled trial/
	double blind procedure/
	or/84-92
	systematic review/
	meta-analysis/
	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
	(search* adj4 literature).ab.
	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
	cochrane.jw.
	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
	or/94-103
	26 and 83
	105 and (93 or 104)

Cochrane Library (Wiley) search terms

	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
	(type near/4 ("2" or "II" or two) near/4 diabet*):ti,ab
	((matur* or adult* or slow*) near/4 onset* near/4 diabet*):ti,ab

	(("ketosis resistant" or "ketosis prone" or stable) near/4 diabet*):ti,ab
	(("non insulin" or noninsulin) near/4 depend* near/4 diabet*):ti,ab
	(NIDDM or T2DM or DM2):ti,ab
	(or #1-#6)
	MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees
	"glucagon like peptide 1":ti,ab
	("GLP 1" or "GLP1"):ti,ab
	MeSH descriptor: [Exenatide] this term only
	(Exenatide* or Byetta or Bydureon or Saxenda):ti,ab
	(Liraglutide* or Victoza):ti,ab
	(Dulaglutide* or Trulicity):ti,ab
	(Semaglutide* or Ozempic or Rybelsus):ti,ab
	(Lixisenatide* or Lyxumia):ti,ab
	(tirzepatide* or mounjaro):ti,ab
	MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] this term only
	"Sodium-Glucose Transporter 2":ti,ab
	("Sodium-Glucose cotransporter 2" or "Sodium-Glucose co transporter 2"):ti,ab
	(SGLT* or gliflozin*):ti,ab
	MeSH descriptor: [Canagliflozin] this term only
	(Canagliflozin* or Invokana or Dapagliflozin or Forxiga or Ertugliflozin or Steglatro or Empagliflozin or Jardiance or Glyxambi):ti,ab
	MeSH descriptor: [Sulfonylurea Compounds] explode all trees
	(Sulfonylurea* or Sulphonylurea*):ti,ab
	(Gliclazide* or Diamicron):ti,ab
	(Glimepiride* or Amaryl):ti,ab
	(Glipizide* or Minodiab):ti,ab
	Tolbutamide*:ti,ab
	MeSH descriptor: [Thiazolidinediones] this term only
	(Thiazolidinedione* or Glitazone*):ti,ab
	MeSH descriptor: [Pioglitazone] this term only
	(Pioglitazone* or Actos):ti,ab
	MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] explode all trees
	MeSH descriptor: [Dipeptidyl Peptidase 4] this term only
	(Dipeptidyl NEXT Peptidase NEXT IV NEXT Inhibitor* or Dipeptidyl NEXT Peptidase NEXT 4 NEXT Inhibitor*):ti,ab
	(DPP* NEAR/2 ("4" or "iv")):ti,ab
	gliptin*:ti,ab
	(Saxagliptin* or Onglyza or Komboglyze or Qtern):ti,ab
	MeSH descriptor: [Vildagliptin] this term only
	(Vildagliptin* or Galvus):ti,ab
	MeSH descriptor: [Sitagliptin Phosphate] this term only
	(Sitagliptin* or Januvia):ti,ab
	(Alogliptin* or Vipdomet):ti,ab
	MeSH descriptor: [Linagliptin] this term only

	(Linagliptin* or Trajenta or Jentadueto):ti,ab
	MeSH descriptor: [Metformin] this term only
	(Metformin* or Glucophage):ti,ab
	(Competact or Janumet or Eucreas or Synjardy or Vokanamet or Xigduo):ti,ab
	MeSH descriptor: [Biguanides] this term only
	Biguanide*:ti,ab
	(or #8-#51)
	#7 and #52
	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or eudract* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
	#53 not #54
	conference:pt
	#55 not #56 with Cochrane Library publication date Between Oct 2023 and Mar 2024, in Cochrane Reviews, Cochrane Protocols, Trials

Epistemonikos search terms

	(title:((type AND ("2" OR "II" OR two) AND diabet*)) OR abstract:((type AND ("2" OR "II" OR two) AND diabet*))) OR (title:(((matur* OR adult* OR slow*) AND onset* AND diabet*)) OR abstract:(((matur* OR adult* OR slow*) AND onset* AND diabet*))) OR (title:((("ketosis resistant" OR "ketosis prone" OR stable) AND diabet*)) OR abstract:((("ketosis resistant" OR "ketosis prone" OR stable) AND diabet*))) OR (title:((("non insulin" OR noninsulin) AND depend* AND diabet*)) OR abstract:((("non insulin" OR noninsulin) AND depend* AND diabet*))) OR (title:((NIDDM OR T2DM OR DM2)) OR abstract:((NIDDM OR T2DM OR DM2)))
	(title:("glucagon like peptide 1") OR abstract:("glucagon like peptide 1")) OR (title:(("GLP 1" OR "GLP1")) OR abstract:(("GLP 1" OR "GLP1"))) OR (title:((Exenatide* OR Byetta OR Bydureon OR Saxenda)) OR abstract:((Exenatide* OR Byetta OR Bydureon OR Saxenda))) OR (title:((Liraglutide* OR Victoza)) OR abstract:((Liraglutide* OR Victoza))) OR (title:((Dulaglutide* OR Trulicity)) OR abstract:((Dulaglutide* OR Trulicity))) OR (title:((Semaglutide* OR Ozempic OR Rybelsus)) OR abstract:((Semaglutide* OR Ozempic OR Rybelsus))) OR (title:((Lixisenatide* OR Lyxumia)) OR abstract:((Lixisenatide* OR Lyxumia))) OR (title:((tirzepatide* OR mounjaro)) OR abstract:((tirzepatide* OR mounjaro))) OR (title:("Sodium-Glucose Transporter 2") OR abstract:("Sodium-Glucose Transporter 2")) OR (title:(("Sodium-Glucose cotransporter 2" OR "Sodium-Glucose co transporter 2")) OR abstract:(("Sodium-Glucose cotransporter 2" OR "Sodium-Glucose co transporter 2"))) OR (title:((SGLT* OR gliflozin*)) OR abstract:((SGLT* OR gliflozin*))) OR (title:((Canagliflozin* OR Invokana OR Dapagliflozin OR Forxiga OR Ertugliflozin OR Steglatro OR Empagliflozin OR Jardiance OR Glyxambi)) OR abstract:((Canagliflozin* OR Invokana OR Dapagliflozin OR Forxiga OR Ertugliflozin OR Steglatro OR Empagliflozin OR Jardiance OR Glyxambi))) OR (title:((Sulfonylurea* OR Sulphonylurea*)) OR abstract:((Sulfonylurea* OR Sulphonylurea*))) OR (title:((Gliclazide* OR Diamicron)) OR abstract:((Gliclazide* OR Diamicron))) OR (title:((Glimepiride* OR Amaryl)) OR abstract:((Glimepiride* OR Amaryl))) OR (title:((Glipizide* OR Minodiab)) OR abstract:((Glipizide* OR Minodiab))) OR (title:(Tolbutamide*) OR abstract:(Tolbutamide*)) OR (title:((Thiazolidinedione* OR Glitazone*)) OR abstract:((Thiazolidinedione* OR Glitazone*))) OR (title:((Pioglitazone* OR Actos)) OR abstract:((Pioglitazone* OR Actos))) OR (title:((Dipeptidyl*)) OR abstract:((Dipeptidyl*))) OR (title:((DPP* AND

	("4" OR "iv"))) OR abstract:((DPP* AND ("4" OR "iv")))) OR (title:(gliptin*) OR abstract:(gliptin*)) OR (title:((Saxagliptin* OR Onglyza OR Komboglyze OR Qtern)) OR abstract:((Saxagliptin* OR Onglyza OR Komboglyze OR Qtern))) OR (title:((Vildagliptin* OR Galvus)) OR abstract:((Vildagliptin* OR Galvus))) OR (title:((Sitagliptin* OR Januvia)) OR abstract:((Sitagliptin* OR Januvia))) OR (title:((Alogliptin* OR Vipdomet)) OR abstract:((Alogliptin* OR Vipdomet))) OR (title:((Linagliptin* OR Trajenta OR Jentadueto)) OR abstract:((Linagliptin* OR Trajenta OR Jentadueto))) OR (title:((Metformin* OR Glucophage)) OR abstract:((Metformin* OR Glucophage))) OR (title:((Competact OR Janumet OR Eucreas OR Synjardy OR Vokanamet OR Xigduo)) OR abstract:((Competact OR Janumet OR Eucreas OR Synjardy OR Vokanamet OR Xigduo))) OR (title:(Biguanide*) OR abstract:(Biguanide*))))
	1 AND 2

B.1.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad type 2 diabetes population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 08 November 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 08 November 2022	
Embase (OVID)	Health Economics 1 January 2014 – 08 November 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 08 November 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	NA
Health Technology Assessment Database (HTA)	Inception – 31st March 2018	NA

(Centre for Research and Dissemination – CRD)		
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 08 November 2022	English language

Medline (Ovid) search terms

	exp Diabetes Mellitus, Type 2/
	(Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).tw.
	((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabetic*)).tw.
	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).tw.
	((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).tw.
	NIDDM.tw.
	or/1-6
	letter/
	editorial/
	news/
	exp historical article/
	Anecdotes as Topic/
	comment/
	case report/
	(letter or comment*).ti.
	or/8-15
	randomized controlled trial/ or random*.ti,ab.
	16 not 17
	animals/ not humans/
	exp Animals, Laboratory/
	exp Animal Experimentation/
	exp Models, Animal/
	exp Rodentia/
	(rat or rats or mouse or mice or rodent*).ti.
	or/18-24
	7 not 25
	limit 26 to english language
	exp Glucagon-Like Peptide 1/
	(Glucagon* adj Like adj Peptide adj "1").tw.
	(GLP* adj "1").tw.
	GLP1*.tw.
	Exenatide/

	(Exenatide* or Byetta* or Bydureon* or Saxenda*).tw.
	(Liraglutide* or Victoza*).tw.
	(Dulaglutide* or Trulicity*).tw.
	(Semaglutide* or Ozempic* or Rybelsus*).tw.
	(Lixisenatide* or Lyxumia*).tw.
	(tirzepatide* or Mounjaro).tw.
	Sodium-Glucose Transporter 2/
	(Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw.
	(Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw.
	(SGLT* or gliflozin*).tw.
	Canagliflozin/
	(Canagliflozin* or Invokana* or Dapagliflozin* or Forxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or Glyxambi*).tw.
	exp Sulfonylurea Compounds/tu [Therapeutic Use]
	(Sulfonylurea* or Sulphonylurea*).tw.
	(Gliclazide* or Diamicron*).tw.
	(Glimepiride* or Amaryl*).tw.
	(Glipizide* or Minodiab*).tw.
	Tolbutamide*.tw.
	Thiazolidinediones/
	(Thiazolidinedione* or Glitazone*).tw.
	Pioglitazone/
	(Pioglitazone* or Actos*).tw.
	exp Dipeptidyl-Peptidase IV Inhibitors/ or Dipeptidyl Peptidase 4/
	(Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw.
	(DPP* adj2 ("4" or "iv")).tw.
	gliptin*.tw.
	(Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw.
	(Vildagliptin* or Galvus*).tw.
	(Sitagliptin* or Januvia*).tw.
	(Alogliptin* or Vipdomet*).tw.
	(Linagliptin* or Trajenta* or Jentadueto*).tw.
	Metformin/
	(Metformin* or Glucophage*).tw.
	(Competact* or Janumet* or Eucreas* or Synjardy* or Vokanamet* or Xigduo*).tw.
	Biguanides/
	Biguanide*.tw.
	exp Glycoside Hydrolase Inhibitors/
	glycosid*.tw.
	(glycosyl adj4 hydrolases).tw.
	(((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or intestinal) adj4 alpha-amylase adj4 inhibitor*).tw.

	((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw.
	Acarbose/
	(Acarbose* or Glucobay*).tw.
	exp Insulins/ad, tu [Administration & Dosage, Therapeutic Use]
	exp Insulin/ad, tu [Administration & Dosage, Therapeutic Use]
	Insulin Infusion Systems/
	(Insulin* adj4 (treat* or therap* or administrat* or dos* or human* or analogue* or biphasic* or basal* or protamine* or isophane* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion*)).tw.
	(Insulin* adj4 (Intermediate* or shortact* or short-act* or short act* or longact* or long-act* or long act* or ultralong* or ultra-long* or ultra long* or rapidact* or rapid-act* or rapid act*)).tw.
	(Actrapid* or Humulin* or Hypurin*).tw.
	Aspart*.tw.
	(Glulisine* or Apidra*).tw.
	(Lispro* or Humalog*).tw.
	(Insulin* adj4 zinc* adj4 (suspension* or protamine*)).tw.
	(Detemir* or Levemir*).tw.
	(Glargine* or Lantus* or Toujeo*).tw.
	(Degludec* or Tresiba*).tw.
	(Isophane* or Insulatard* or Insuman* or Novomix*).tw.
	(Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw.
	(LY2963016 or Abasaglar* or MYK-1501D or MYK1501D or Semglee*).tw.
	Biosimilar pharmaceuticals/
	(biosimilar* or biologics).tw.
	Nateglinide/
	(Meglitinide* or Repaglinide* or Nateglinide*).tw.
	or/28-94
	Economics/
	Value of life/
	exp "Costs and Cost Analysis"/
	exp Economics, Hospital/
	exp Economics, Medical/
	Economics, Nursing/
	Economics, Pharmaceutical/
	exp "Fees and Charges"/
	exp Budgets/
	budget*.ti,ab.
	cost*.ti.
	(economic* or pharmaco?economic*).ti.
	(price* or pricing*).ti,ab.
	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

	(financ* or fee or fees).ti,ab.
	(value adj2 (money or monetary)).ti,ab.
	or/97-112
	quality-adjusted life years/
	sickness impact profile/
	(quality adj2 (wellbeing or well being)).ti,ab.
	sickness impact profile.ti,ab.
	disability adjusted life.ti,ab.
	(qal* or qtime* or qwb* or daly*).ti,ab.
	(euroqol* or eq5d* or eq 5*).ti,ab.
	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
	(hui or hui1 or hui2 or hui3).ti,ab.
	(health* year* equivalent* or hye or hyes).ti,ab.
	discrete choice*.ti,ab.
	rosser.ti,ab.
	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
	or/114-132
	27 and 96
	113 and 134
	133 and 134

Embase (Ovid) search terms

	exp Diabetes Mellitus, Type 2/
	(Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).tw.
	((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabetic*)).tw.
	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).tw.
	((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).tw.
	NIDDM.tw.
	or/1-6
	letter.pt. or letter/
	note.pt.
	editorial.pt.
	case report/ or case study/
	(letter or comment*).ti.
	(conference abstract or conference paper).pt.
	or/8-13

	randomized controlled trial/ or random*.ti,ab.
	14 not 15
	animal/ not human/
	nonhuman/
	exp Animal Experiment/
	exp Experimental Animal/
	animal model/
	exp Rodent/
	(rat or rats or mouse or mice or rodent*).ti.
	or/16-23
	7 not 24
	limit 25 to english language
	*Glucagon Like Peptide 1/
	(Glucagon* adj Like adj Peptide adj "1").tw.
	(GLP* adj "1").tw.
	GLP1*.tw.
	*Exenatide/
	*Exendin 4/
	(Exenatide* or Byetta* or Bydureon* or Saxenda*).tw.
	*Liraglutide/
	(Liraglutide* or Victoza*).tw.
	*Dulaglutide/
	(Dulaglutide* or Trulicity*).tw.
	*Semaglutide/
	(Semaglutide* or Ozempic* or Rybelsus*).tw.
	*Lixisenatide/
	(Lixisenatide* or Lyxumia*).tw.
	(tirzepatide* or Mounjaro).tw.
	*Sodium-Glucose Cotransporter 2/
	(Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw.
	(Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw.
	(SGLT* or gliflozin*).tw.
	*Canagliflozin/ or *Dapagliflozin/ or *dapagliflozin plus saxagliptin/ or *dapagliflozin plus metformin plus saxagliptin/ or *Empagliflozin/ or *Empagliflozin plus Metformin/
	(Canagliflozin* or Invokana* or Dapagliflozin* or Forxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or Glyxambi*).tw.
	exp *Sulfonylurea Derivative/dt [Drug Therapy]
	(Sulfonylurea* or Sulphonylurea*).tw.
	(Gliclazide* or Diamicron*).tw.
	(Glimepiride* or Amaryl*).tw.
	(Glipizide* or Minodiab*).tw.
	Tolbutamide*.tw.

	*2,4 Thiazolidinedione Derivative/ or *Glitazone Derivative/
	(Thiazolidinedione* or Glitazone*).tw.
	*Pioglitazone/ or *pioglitazone plus sitagliptin/
	(Pioglitazone* or Actos*).tw.
	*Dipeptidyl Peptidase IV Inhibitor/
	(Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw.
	(DPP* adj2 ("4" or "iv")).tw.
	gliptin*.tw.
	*Saxagliptin/
	(Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw.
	*Vildagliptin/ or *Metformin plus Vildagliptin/
	(Vildagliptin* or Galvus*).tw.
	*Sitagliptin/ or *metformin plus sitagliptin/ or *simvastatin plus sitagliptin/ or *pioglitazone plus sitagliptin/ or *ertugliflozin plus sitagliptin/
	(Sitagliptin* or Januvia*).tw.
	*Alogliptin/ or *alogliptin plus metformin/ or *alogliptin plus pioglitazone/
	(Alogliptin* or Vipdomet*).tw.
	*Linagliptin/ or *empagliflozin plus linagliptin/ or *linagliptin plus metformin/
	(Linagliptin* or Trajenta* or Jentadueto*).tw.
	*Metformin/ or *metformin plus sitagliptin/ or *metformin plus repaglinide/ or *metformin plus vildagliptin/ or *metformin plus pioglitazone/ or *metformin plus rosiglitazone/ or *metformin 4 chlorophenoxyacetate/ or *metformin plus saxagliptin/ or *metformin embonate/ or *metformin glycinate/
	(Metformin* or Glucophage*).tw.
	(Competact* or Janumet* or Eucreas* or Synjardy* or Vokanamet* or Xigduo*).tw.
	*Biguanide Derivative/
	Biguanide*.tw.
	exp *glycosidase inhibitor/
	glycosid*.tw.
	(glycosyl adj4 hydrolases).tw.
	((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or (intestinal adj4 alpha-amylase adj4 inhibitor*)).tw.
	((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw.
	*Acarbose/
	(Acarbose* or Glucobay*).tw.
	exp *insulin/ad, do [Drug Administration, Drug Dose]
	exp *Insulin Derivative/ad, do [Drug Administration, Drug Dose]
	*Insulin Infusion/
	insulin aspart plus insulin degludec/ or insulin degludec plus liraglutide/ or insulin aspart/ or insulin glulisine/ or insulin lispro/ or insulin detemir/ or insulin glargine plus lixisenatide/ or insulin glargine/ or insulin glargine plus lixisenatide/ or insulin glargine/
	(Insulin* adj4 (treat* or therap* or administrat* or dos* or human* or analogue* or biphasic* or basal* or protamine* or isophane* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion*)).tw.

	(Insulin* adj4 (Intermediate* or shortact* or short-act* or short act* or longact* or long-act* or long act* or ultralong* or ultra-long* or ultra long* or rapidact* or rapid-act* or rapid act*)).tw.
	(Actrapid* or Humulin* or Hypurin*).tw.
	Aspart*.tw.
	(Glulisine* or Apidra*).tw.
	(Lispro* or Humalog*).tw.
	(Insulin* adj4 zinc* adj4 (suspension* or protamine*)).tw.
	(Detemir* or Levemir*).tw.
	(Glargine* or Lantus* or Toujeo*).tw.
	(Degludec* or Tresiba*).tw.
	(Isophane* or Insulatard* or Insuman* or Novomix*).tw.
	(Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw.
	(LY2963016 or Abasaglar* or MYK-1501D or MYK1501D or Semglee*).tw.
	*Biosimilar Agent/
	(biosimilar* or biologics).tw.
	*Meglitinide/ or *Repaglinide/ or *Nateglinide/
	(Meglitinide* or Repaglinide* or Nateglinide*).tw.
	or/27-105
	26 and 106
	health economics/
	exp economic evaluation/
	exp health care cost/
	exp fee/
	budget/
	funding/
	budget*.ti,ab.
	cost*.ti.
	(economic* or pharmaco?economic*).ti.
	(price* or pricing*).ti,ab.
	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
	(financ* or fee or fees).ti,ab.
	(value adj2 (money or monetary)).ti,ab.
	or/108-120
	quality adjusted life year/
	"quality of life index"/
	short form 12/ or short form 20/ or short form 36/ or short form 8/
	sickness impact profile/
	(quality adj2 (wellbeing or well being)).ti,ab.
	sickness impact profile.ti,ab.
	disability adjusted life.ti,ab.
	(qal* or qtime* or qwb* or daly*).ti,ab.

	(euroqol* or eq5d* or eq 5*).ti,ab.
	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
	(hui or hui1 or hui2 or hui3).ti,ab.
	(health* year* equivalent* or hye or hyes).ti,ab.
	discrete choice*.ti,ab.
	rosser.ti,ab.
	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
	or/122-142
	107 and 121
	107 and 143

NHS EED and HTA (CRD) search terms

	(MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES)
	((Type*) NEAR4 ("2" or "II" or two*) NEAR4 (diabete* or diabetic*))
	((Maturit* or adult* or slow*) NEAR4 (onset*) NEAR4 (diabete* or diabetic*))
	((Ketosis-resistant* or stable*) NEAR4 (diabete* or diabetic*))
	((Non-insulin* or Non insulin* or Noninsulin*) NEAR4 (depend*) NEAR4 (diabete* or diabetic*))
	((NIDDM))
	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

INAHTA search terms

1.	((Type* AND ("2" or "II" or two*) AND (diabete* or diabetic*))) OR (Diabetes Mellitus, Type 2)[mh] OR (((Maturit* or adult* or slow*) AND onset* AND (diabete* or diabetic*))) OR (((Ketosis-resistant* or stable*) AND (diabete* or diabetic*))) OR (((Non-insulin* or Non insulin* or Noninsulin*) AND depend* AND (diabete* or diabetic*))) OR (NIDDM)
2.	limit English language 2015-2022

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review