National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management (medicines update)

[F1.1] Evidence reviews for subsequent pharmacological management of type 2 diabetes: 1.1.1 to 1.1.6

NICE guideline

Evidence reviews underpinning recommendations 1.9.1 to 1.9.5, 1.10.1 to 1.18.4, 1.19.1 to 1.19.3, 1.22.1 to 1.31.2 and recommendations for research in the NICE guideline

February 2026

Final

This evidence review was developed by NICE

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1. Subsequent 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 subsequent 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 subsequent treatment review considers trials where previous medication has been provided to all people and any medication is either being added to this treatment or switched with this treatment.

1.1.2. Summary of the protocol

Table 1: PICO characteristics of review question

Population	Adults (age ≥18 years) with type 2 diabetes mellitus who are currently receiving antidiabetic medication 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).
	• All doses will be pooled together.
	
	Different strategies to optimise treatment (stratify trials by the strategy used in the trial):
	• Adding a new treatment
	• Stopping a previous treatment
	• Switching to a different treatment
	
	• 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)
Comparisons	• Different strategies to optimise treatment • 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 report F2, 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 report F2, 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

Sixteen studies[17, 50, 57, 136, 164, 204, 233, 236, 237, 251, 290, 295, 336, 393, 398, 425] were included in the evidence for population model 1 (people with type 2 diabetes and heart failure). All of these trials compared an 'adding' strategy, examining the effect of adding an intervention drug to other glucose-lowering drugs. Fourteen comparisons were identified. For all the models, studies were only included if they reported outcomes at follow-up times of 24 weeks or longer. Where multiple timepoints were reported, the longest timepoint was extracted. For population model 1, the extracted timepoints ranged between 6 and 50 months.

Twenty-five studies[3, 17, 50, 52, 57, 78, 129, 132, 136, 164, 213, 214, 216, 233, 274, 277, 295, 298, 335, 347, 377, 393, 394, 398, 425] were included in the evidence for population model 2 (people with type 2 diabetes and atherosclerotic CVD). All of these trials compared an 'adding' strategy, examining the effect of adding an intervention drug to other glucose-lowering drugs. Twenty-one comparisons were identified, and the extracted follow-up time ranged between 6 and 76 months.

Twenty-seven studies[29, 50, 70, 102, 118, 138, 140, 161, 199, 201, 206, 249, 256, 259, 276, 290, 291, 301, 310, 336, 360, 370, 382, 389, 398, 406, 425] were included in the evidence for population model 3 (people with type 2 diabetes and CKD). Most of these trials compared an 'adding' strategy, examining the effect of adding an intervention drug to other glucose-lowering drugs. No trials were identified that examined a 'stopping' strategy. Twenty-one comparisons were identified, and the extracted follow-up time ranged between 5.5 and 60 months.

No evidence was identified for population model 5 (people with type 2 diabetes and lower risk for cardiovascular disease).

Three hundred and seventy one studies[1, 2, 4-28, 30-49, 51, 53-56, 58-69, 71-77, 79-101, 103-117, 119-123, 126-131, 133-135, 137, 139, 141-160, 162-198, 200, 202, 203, 205, 207-212, 215, 217-248, 252-255, 257, 258, 289, 338, 366, 409 124, 125, 250, 260-273, 275, 278-288, 292-294, 296, 297, 299, 300, 302-309, 311-337, 339-359, 361-365, 367-369, 371-376, 378-388, 390-392, 395-408, 410-425] were included in the evidence for population model 5 (people with type 2 diabetes and higher risk for cardiovascular disease. Almost all of these trials compared an 'adding' strategy, examining the effect of adding an intervention drug to other glucose-lowering drugs. Eleven comparisons included a 'switching' strategy and none compared a 'stopping' strategy. One hundred and twenty-one comparisons were identified, and the follow-up times ranged between 5.5 and 76 months.

Table 2: Summary of comparisons present in each population group in the protocol

Comparator class 1	Comparator 1	Comparator class 2	Comparator 2	Heart failure	Atherosclerotic cardiovascular disease	Chronic kidney disease	Lower cardiovascular risk	Higher cardiovascular risk
Biguanide	Metformin	Placebo	Placebo	No	No	No	No	Yes
Biguanide	Metformin modified release	Biguanide	Metformin standard release	No	No	No	No	Yes
Biguanide	Metformin	Insulin	Insulin	No	No	No	No	Yes
DPP-4 inhibitor	Alogliptin	Placebo	Placebo	Yes	Yes	No	No	Yes

DPP-4 inhibitor	Linagliptin	Placebo	Placebo	Yes	No	Yes	No	Yes
DPP-4 inhibitor	Linagliptin	Biguanide	Metformin	No	No	No	No	Yes
DPP-4 inhibitor	Saxagliptin	Placebo	Placebo	No	Yes	Yes	No	Yes
DPP-4 inhibitor	Sitagliptin	Placebo	Placebo	Yes	Yes	No	No	Yes
DPP-4 inhibitor	Sitagliptin	Biguanide	Metformin	No	No	No	No	Yes
DPP-4 inhibitor	Sitagliptin	DPP-4 inhibitor	Linagliptin	No	No	No	No	No
DPP-4 inhibitor	Sitagliptin	Insulin	Insulin	Yes	Yes	No	No	Yes
DPP-4 inhibitor	Vildagliptin	Placebo	Placebo	Yes	No	No	No	No
DPP-4 inhibitor	Vildagliptin	Biguanide	Metformin	No	No	No	No	Yes
DPP-4 inhibitor	Vildagliptin	Insulin	Insulin	No	No	No	No	Yes
DPP-4 inhibitor	Vildagliptin	DPP-4 inhibitor	Alogliptin	No	No	No	No	Yes
DPP-4 inhibitor	Vildagliptin	DPP-4 inhibitor	Saxagliptin	No	No	No	No	Yes
DPP-4 inhibitor	Vildagliptin	DPP-4 inhibitor	Sitagliptin	No	No	Yes	No	No
SGLT-2 inhibitor	Canagliflozin	Placebo	Placebo	Yes	Yes	Yes	No	Yes
SGLT-2 inhibitor	Canagliflozin	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
SGLT-2 inhibitor	Canagliflozin	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
SGLT-2 inhibitor	Canagliflozin	GLP-1 receptor agonist	Semaglutide	No	No	No	No	Yes
SGLT-2 inhibitor	Dapagliflozin	Placebo	Placebo	Yes	Yes	Yes	No	Yes
SGLT-2 inhibitor	Dapagliflozin	DPP-4 inhibitor	Saxagliptin	No	No	No	No	Yes
SGLT-2 inhibitor	Dapagliflozin	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
SGLT-2 inhibitor	Dapagliflozin	DPP-4 inhibitor	Vildagliptin	No	Yes	No	No	Yes

SGLT-2 inhibitor	Dapagliflozin	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
SGLT-2 inhibitor	Dapagliflozin	GLP-1 receptor agonist	Exenatide	No	No	No	No	Yes
SGLT-2 inhibitor	Empagliflozin	Placebo	Placebo	Yes	Yes	Yes	No	Yes
SGLT-2 inhibitor	Empagliflozin	DPP-4 inhibitor	Linagliptin	No	No	Yes	No	Yes
SGLT-2 inhibitor	Empagliflozin	DPP-4 inhibitor	Sitagliptin	No	Yes	No	No	Yes
SGLT-2 inhibitor	Empagliflozin	DPP-4 inhibitor	Vildagliptin	No	No	No	No	Yes
SGLT-2 inhibitor	Empagliflozin	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
SGLT-2 inhibitor	Empagliflozin	GLP-1 receptor agonist	Semaglutide	No	No	No	No	Yes
SGLT-2 inhibitor	Empagliflozin	Insulin	Insulin	No	No	No	No	Yes
SGLT-2 inhibitor	Ertugliflozin	Placebo	Placebo	Yes	Yes	Yes	No	Yes
SGLT-2 inhibitor	Ertugliflozin	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
GLP-1 receptor agonist	Dulaglutide	Placebo	Placebo	No	Yes	No	No	Yes
GLP-1 receptor agonist	Dulaglutide	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
GLP-1 receptor agonist	Dulaglutide	GLP-1 receptor agonist	Exenatide	No	No	No	No	Yes
GLP-1 receptor agonist	Dulaglutide	Insulin	Insulin	No	No	Yes	No	Yes
GLP-1 receptor agonist	Exenatide	Placebo	Placebo	Yes	Yes	No	No	Yes
GLP-1 receptor agonist	Exenatide	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
GLP-1 receptor agonist	Exenatide	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes

GLP-1 receptor agonist	Exenatide	Insulin	Insulin	Yes	Yes	Yes	No	Yes
GLP-1 receptor agonist	Liraglutide	Placebo	Placebo	Yes	No	Yes	No	Yes
GLP-1 receptor agonist	Liraglutide	DPP-4 inhibitor	Linagliptin	No	No	Yes	No	No
GLP-1 receptor agonist	Liraglutide	DPP-4 inhibitor	Saxagliptin	No	No	No	No	Yes
GLP-1 receptor agonist	Liraglutide	DPP-4 inhibitor	Sitagliptin	No	Yes	Yes	No	Yes
GLP-1 receptor agonist	Liraglutide	DPP-4 inhibitor	Vildagliptin	No	No	No	No	Yes
GLP-1 receptor agonist	Liraglutide	GLP-1 receptor agonist	Dulaglutide	No	No	No	No	Yes
GLP-1 receptor agonist	Liraglutide	Insulin	Insulin	Yes	Yes	No	No	Yes
GLP-1 receptor agonist	Lixisenatide	Placebo	Placebo	Yes	Yes	No	No	Yes
GLP-1 receptor agonist	Lixisenatide	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
GLP-1 receptor agonist	Lixisenatide	GLP-1 receptor agonist	Exenatide	No	No	No	No	Yes
GLP-1 receptor agonist	Lixisenatide	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
GLP-1 receptor agonist	Lixisenatide	Insulin	Insulin	No	No	No	No	Yes
GLP-1 receptor agonist	Semaglutide	Placebo	Placebo	Yes	No	Yes	No	Yes
GLP-1 receptor agonist	Semaglutide	GLP-1 receptor agonist	Dulaglutide	No	No	Yes	No	Yes
GLP-1 receptor agonist	Semaglutide	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes

GLP-1 receptor agonist	Semaglutide	GLP-1 receptor agonist	Exenatide	No	No	No	No	Yes
GLP-1 receptor agonist	Semaglutide	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
GLP-1 receptor agonist	Semaglutide; oral	GLP-1 receptor agonist	Semaglutide; subcutaneous	No	No	No	No	Yes
GLP-1 receptor agonist	Semaglutide	Insulin	Insulin	No	No	No	No	Yes
GIP/GLP-1 receptor agonist	Tirzepatide	Placebo	Placebo	No	No	No	No	Yes
GIP/GLP-1 receptor agonist	Tirzepatide	GIP/GLP-1 receptor agonist	Dulaglutide	No	No	No	No	Yes
GIP/GLP-1 receptor agonist	Tirzepatide	GIP/GLP-1 receptor agonist	Semaglutide	No	No	No	No	Yes
GIP/GLP-1 receptor agonist	Tirzepatide	Insulin	Insulin	No	Yes	No	No	Yes
Sulfonylurea	Gliclazide	DPP-4 inhibitor	Vildagliptin	No	No	No	No	Yes
Sulfonylurea	Glimepiride	Placebo	Placebo	No	No	No	No	Yes
Sulfonylurea	Glimepiride	Biguanide	Metformin	No	No	No	No	Yes
Sulfonylurea	Glimepiride	DPP-4 inhibitor	Linagliptin	No	Yes	No	No	Yes
Sulfonylurea	Glimepiride	DPP-4 inhibitor	Saxagliptin	No	No	No	No	Yes
Sulfonylurea	Glimepiride	DPP-4 inhibitor	Vildagliptin	No	No	No	No	Yes
Sulfonylurea	Glimepiride	SGLT-2 inhibitor	Canagliflozin	No	No	No	No	Yes
Sulfonylurea	Glimepiride	SGLT-2 inhibitor	Dapagliflozin	No	No	No	No	Yes
Sulfonylurea	Glimepiride	SGLT-2 inhibitor	Empagliflozin	No	No	No	No	Yes
Sulfonylurea	Glimepiride	SGLT-2 inhibitor	Ertugliflozin	No	No	No	No	Yes

Sulfonylurea	Glimepiride	GLP-1 receptor agonist	Exenatide	No	No	No	No	Yes
Sulfonylurea	Glimepiride	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
Sulfonylurea	Glimepiride	Sulfonylurea	Gliclazide	No	No	No	No	Yes
Sulfonylurea	Glimepiride	Thiazolidinedione	Pioglitazone	No	Yes	No	No	No
Sulfonylurea	Glimepiride	Insulin	Insulin	No	Yes	Yes	No	Yes
Sulfonylurea	Glipizide	Biguanide	Metformin	No	No	No	No	Yes
Sulfonylurea	Glipizide	Placebo	Placebo	No	No	No	No	Yes
Sulfonylurea	Glipizide	DPP-4 inhibitor	Alogliptin	No	No	No	No	Yes
Sulfonylurea	Glipizide	DPP-4 inhibitor	Saxagliptin	No	No	No	No	Yes
Sulfonylurea	Glipizide	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
Sulfonylurea	Glipizide	SGLT-2 inhibitor	Dapagliflozin	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	Placebo	Placebo	No	Yes	Yes	No	Yes
Thiazolidinedione	Pioglitazone	Biguanide	Metformin	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	DPP-4 inhibitor	Sitagliptin	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	DPP-4 inhibitor	Vildagliptin	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	SGLT-2 inhibitor	Dapagliflozin	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	SGLT-2 inhibitor	Empagliflozin	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	GLP-1 receptor agonist	Exenatide	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	Sulfonylurea	Gliclazide	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	Sulfonylurea	Glimepiride	No	No	No	No	Yes

Thiazolidinedione	Pioglitazone	Sulfonylurea	Glipizide	No	No	No	No	Yes
Thiazolidinedione	Pioglitazone	Insulin	Insulin	No	No	No	No	Yes
Combination	Dapagliflozin + Saxagliptin	Placebo	Placebo	No	No	Yes	No	No
Combination	Dapagliflozin + Saxagliptin	SGLT-2 inhibitor	Dapagliflozin	No	No	Yes	No	Yes
Combination	Dapagliflozin + Saxagliptin	DPP-4 inhibitor	Saxagliptin	No	No	No	No	Yes
Combination	Dapagliflozin + Saxagliptin	DPP-4 inhibitor	Sitaglipti n	No	No	No	No	Yes
Combination	Dapagliflozin + Saxagliptin	Sulfonylurea	Glimepiride	No	No	No	No	Yes
Combination	Dapagliflozin + Saxagliptin	Insulin	Insulin	No	No	No	No	Yes
Combination	Dapagliflozin + Exenatide	SGLT-2 inhibitor	Dapagliflozin	No	No	No	No	Yes
Combination	Dapagliflozin + Exenatide	GLP-1 receptor agonist	Exenatide	No	No	No	No	Yes
Combination	Empagliflozin + Liraglutide	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
Combination	Empagliflozin + Liraglutide	SGLT-2 inhibitor	Empaglif lozin	No	No	No	No	Yes
Combination	Empagliflozin + Liraglutide	Insulin	Insulin	No	No	No	No	Yes
Combination	Ertuglifl ozin +	DPP-4 inhibitor	Sitaglitpin	No	No	No	No	Yes

	Sitagliptin							
Combination	Ertugliflozin + Sitagliptin	SGLT-2 inhibitor	Ertugliflozin	No	No	No	No	Yes
Combination	Liraglutide + Metformin	Biguanide	Metformin	No	No	No	No	Yes
Combination	Glimepiride + Metformin	Biguanide	Metformin	No	No	No	No	Yes
Combination	Glimepiride + Metformin modified release	Combination	Glimepiride + Metformin standard release	No	No	No	No	Yes
Combination	Pioglitazone + Metformin	Sulfonylurea	Glimepiride	No	No	No	No	Yes
Combination	Pioglitazone + Metformin	Thiazolidinedione	Pioglitazone	No	No	No	No	Yes
Combination	Pioglitazone + Alogliptin	Thiazolidinedione	Pioglitazone	No	No	No	No	Yes
Combination	Pioglitazone + Exenatide	Thiazolidinedione	Pioglitazone	No	No	No	No	Yes
Combination	Pioglitazone + Exenatide	Insulin	Insulin	No	No	No	No	Yes
Insulin combination	IDegLira	Placebo	Placebo	No	No	No	No	Yes
Insulin combination	IDegLira	GLP-1 receptor agonist	Liraglutide	No	No	No	No	Yes
Insulin combination	IDegLira	Insulin	Insulin	No	No	No	No	Yes

Insulin combination	IGlarLixi	GLP-1 receptor agonist	Lixisenatide	No	No	No	No	Yes
Insulin combination	IGlarLixi	Insulin	Insulin	No	No	No	No	Yes

See also the study selection flow chart in report F2 (appendix C) and study evidence tables in report F2 (appendix D). The forest plots and GRADE tables can be found in reports F3-7 (forest plots in Appendix F3-6, GRADE tables in Appendix F3-5 and F7).

1.1.4.2. Excluded studies

See the excluded studies list in report F8, appendix O.

1.1.5. Summary of studies included in the effectiveness evidence

Table 3: Summary of studies included in the evidence review

Study	Population	Intervention and comparison	Outcomes	Comments
Abdul-Ghani 2017 Qatar	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 Mean age (SD): 52 (1) years Time since type 2 diabetes diagnosed: 10.7 (0.5) months	Strategy: Adding N = 231 Pioglitazone + exenatide (n=123) Insulin (n=108) Concomitant therapy: Metformin + Sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 60%	All-cause mortality, Non-fatal stroke, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, Weight change Follow up: 36 months	Study location: Qatar Sources of funding: Supported by a Qatar Foundation grant NPRP 5-273-3-079. One author's salary is paid in part by the South Texas Veterans Health Care System.
Abreu 2019 SIMPLE (NCT01966978)	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 120 Liraglutide (n=59) Insulin (n=61)	Health-related quality of life, Hypoglycaemia episodes, Severe hypoglycaemic	Study location: United States of America. Sources of

Study	Population	Intervention and comparison	Outcomes	Comments
	disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 47.4 (9.5216) years Time since type 2 diabetes diagnosed: Not stated/unclear	Concomitant therapy: Insulin determir and metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 67.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 75.80% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	episodes, HbA1c change, Weight change Follow up: 6 months	funding: Funded by a Novo Nordisk Investigator Initiated Study Grant.
Adel 2022	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Adding N = 106 Empagliflozin (n=52) Placebo (n=54) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	Cardiovascular mortality, Unstable angina, HbA1c change, Weight change Follow up: 6 months	Study location: 2 centres in Iran. Sources of funding: Medication provided free of charge by Abidi Pharmaceutical Company, Iran. Funded by the Vice Chancellor for Research of Ahvaz Jundishapur University, Iran.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear			
Ahmann 2015 NN2211-3917	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): 58.4 (10.1944) years Time since type 2 diabetes diagnosed: 12.1 (6.9516) years	Strategy: Adding N = 450 Liraglutide (n=225) Placebo (n=225) Concomitant therapy: Basal insulin +/- metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 92.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 67.40% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Multicenter trial - Argentina, Canada, Finland, Germany, India, Mexico, the Netherlands, Serbia and the United States of America. Sources of funding: Funded by Novo Nordisk.
Ahmann 2018 SUSTAIN 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	Strategy: Adding N = 813 Semaglutide (n=406) Exenatide (n=407) Concomitant therapy: Metformin, thiazolidinedione +/- sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 96.60% DPP-4 inhibitors:	Health-related quality of life, All-cause mortality, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicenter Sources of funding: Funded by Novo Nordisk A/S.

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.55 years Time since type 2 diabetes diagnosed: 9.2 years	Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 48.1%		
Ahren 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.8 (10.4881) years Time since type 2 diabetes diagnosed: 5.55 (3.9698) years	Strategy: Adding N = 107 Vildagliptin (n=56) Placebo (n=51) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality Follow up: 12 months	Study location: Multicenter. Sources of funding: Support from the Swedish Research Council.
Ahren 2013 GetGoal-M	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 680 Lixisenatide AM (n=255) Lixisenatide PM (n=255) Placebo AM and PM	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Multicenter trial - Australia, Canada, Chile, Czech Republic, Germany, Croatia, Mexico, Morocco, the

Study	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: Not stated/unclear Mean age (SD): 54.7667 (9.7156) years Time since type 2 diabetes diagnosed: 6.1 (5.1955) years	(n=170) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	change, Weight change Follow up: 5.5 months	Philippines, Romania, Russian Federation, South Africa, Spain, Ukraine, United States of America and Venezuela. Sources of funding: Funded by Sanofi.
Ahren 2014 HARMONY 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: Not stated/unclear Mean age (SD): 54.775 (9.9708) years Time since type 2 diabetes diagnosed: 6.125 (4.87) years	Strategy: Adding N = 1012 Albiglutide (n=302) Sitagliptin (n=302) Glimepiride (n=307) Placebo (n=101) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes Follow up: 24 months	Study location: Multicenter Sources of funding: Funded by GlaxoSmithKline.

Study	Population	Intervention and comparison	Outcomes	Comments
Ahren 2017 SUSTAIN 2	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): 55.1333 (10.0097) years Time since type 2 diabetes diagnosed: 6.5667 (5.1465) years	Strategy: Adding N = 1231 Semaglutide 0.5 mg (n=410) Semaglutide 1.0 mg (n=410) Sitagliptin (n=411) Concomitant therapy: Metformin ± thiazolidinedione Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 99.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 0.7%	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicenter trial - Bulgaria, Czech Republic, Hungary, Norway, Portugal, Romania, Spain, Sweden, Turkey, Ukraine, Argentina, Hong Kong, India, Japan, Mexico, Russia, South Africa and Thialand. Sources of funding: Novo Nordisk A/S.
Ando 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: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Switching N = 40 Canagliflozin (n=20) Liraglutide (n=20) Concomitant therapy: Basal insulin +/- biguanides, alpha-glucosidase inhibitors or glinides Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 3.00% Biguanides: 29.4% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear	Health-related quality of life, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Japan. Sources of funding: Supported by the Initiative for Realizing Diversity in the Research Environment 2016.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 57.05 (12.2729) years Time since type 2 diabetes diagnosed: 9.1 (6.9502) years	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Araki 2015A	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): 61.0333 (9.8358) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 336 Empagliflozin 10mg (n=136) Empagliflozin 25mg (n=137) Metformin (n=63) Concomitant therapy: Monotherapy with sulfonylurea 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: Japan (86 centres). Sources of funding: Funded by Boehringer Ingelheim and Eli Lilly and Company.
Araki 2015B	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	Strategy: Adding N = 361 Dulaglutide (0.75 mg) (n=181) Insulin glargine (n=180) Concomitant therapy: Biguanide and/or sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Falls requiring hospitalisation, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c	Study location: 35 sites in Japan Sources of funding: Sponsored by Eli Lilly K. K. Japan. Multiple authors declare funding and honoraria from numerous pharmaceutical companies

Study	Population	Intervention and comparison	Outcomes	Comments
	without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.8 (10.9062) years Time since type 2 diabetes diagnosed: 8.85 (6.4079) years	stated/unclear Biguanides: 36% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 18.5%	change, Weight change Follow up: 6 months	
Arechavaleta 2011 Sitagliptin Protocol 803	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): 56.25 (9.9026) years Time since type 2 diabetes diagnosed: 6.75 (4.7014) years	Strategy: Adding N = 1035 Sitagliptin (n=516) Glimepiride (n=519) Concomitant therapy: Metformin 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: Multicenter trial. Sources of funding: Funded by Merck Sharp & Dohme Corp.
Aroda 2016B LixiLan-L	Model 5: People with type 2 diabetes at higher risk of	Strategy: Adding N = 736 Insulin glargine +	All-cause mortality, Cardiovascular mortality,	Study location: Australia, Canada Chile, Czech

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 59.95 (9.0558) years Time since type 2 diabetes diagnosed: 12.05 (6.7521) years	lixisenatide (iGlarLix) once daily (n=367) Insulin glargine once daily (n=369) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 180.5% DPP-4 inhibitors: 4% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 15%	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Republic, Denmark, Estonia, Hungary, Lithuania, Mexico Netherlands, Poland, Romania, Russia ,Slovakia, Spain, Sweden, Ukraine Sources of funding: Sanofi
Aroda 2017 SUSTAIN 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: Not stated/unclear Mean age (SD): 56.4667 (10.4345) years Time since type 2	Strategy: Adding N = 1089 Semaglutide 0.5mg (n=362) Semaglutide 1.0mg (n=362) Insulin glargine (n=365) Concomitant therapy: Metformin ± sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 48.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear	All-cause mortality, Cardiovascular mortality, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Study location: Multicenter trial. Sources of funding: Funded by Novo Nordisk A/S.

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: 8.5667 (6.2556) years	Sulfonylureas: Not stated/unclear		
Aroda 2019A DUAL VIII	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): 56.6 (10.0501) years Time since type 2 diabetes diagnosed: 10.1 (6.1502) years	Strategy: Adding N = 1012 Insulin degludec/liraglutide (n=506) Insulin glargine (n=506) Concomitant therapy: Metformin, sulfonylurea or pioglitazone Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 0.5% Biguanides: 98% DPP-4 inhibitors: 31.5% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 64.5%	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Development of end stage kidney disease, Cardiac arrhythmia, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Multicenter trial. Sources of funding: Funded by Novo Nordisk.
Arturi 2017	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People with heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases	Strategy: Adding N = 32 Liraglutide (n=10) Sitagliptin (n=10) Glargine (n=12) Concomitant therapy: Metformin +/- sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Hospitalisation for heart failure, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: Italy Sources of funding: No funding from any specific grant from any funding agency in the public, commercial, or not-for profit sector.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60 (8.9693) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Aschner 2012 EASIE	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): 53.6 (8.7976) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 515 Sitagliptin (n=265) Insulin glargine (n=250) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 0.2% Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Non-fatal myocardial infarction, Unstable angina, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Sanofi
Attaran 2023	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 73 Pioglitazone 30 mg daily (n=36) Empagliflozin 10 mg daily (n=37) Concomitant	Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, BMI change	Study location: Iran Sources of funding: Supported by the Iran University of Medical Sciences No.

Study	Population	Intervention and comparison	Outcomes	Comments
	failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 52 (7) years Time since type 2 diabetes diagnosed: 7.95 (5.7196) years	therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: 51.40% GLP-1 receptor agonists: Not stated/unclear Insulin: 14.3% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 51.40%	Follow up: 5.5 months	IR.IUMS.REC.1398.1408. Medication provided by Abidi Pharmaceutrical company
Avilés-Santa 1999	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: Not stated/unclear Mean age (SD): 53.85 (8.6177) years Time since type 2 diabetes	Strategy: Adding N = 43 Metformin (n=21) Placebo (n=22) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Texas, US Sources of funding: Partly by Bristol-Myers Squibb

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 9.65 (5.5942) years			
Ba 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 (9.4005) years Time since type 2 diabetes diagnosed: 7 (5.1561) years	Strategy: Adding N = 498 Sitagliptin (n=249) Placebo (n=249) Concomitant therapy: Sulfonylurea ± metformin 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 53.8%	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Unstable angina, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: multicenter; 32 centers in China Sources of funding: Merck & Co. Inc. FW, LX, MEH, SSE, and RRS are all current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc. (Kenilworth, NJ, USA) and may own stock or stock options in the company. FW also reports employment at Novartis Pharmaceuticals.
Babar 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: People at higher risk of developing	Strategy: Adding N = 240 Empagliflozin (n=120) Placebo (n=120) Concomitant therapy: Metformin + sitagliptin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Pakistan Sources of funding: NR

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease Mean age (SD): 52.965 (8.8535) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Bae 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): 61.855 (9.9295) years Time since type 2 diabetes diagnosed: 13.89 (7.8705) years	Strategy: Adding N = 119 Empagliflozin (n=60) Pioglitazone (n=59) Concomitant therapy: metformin + sulfonylurea + DPP-4 inhibitor Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, BMI change Follow up: 5.5 months	Study location: Multicentre, South Korea Sources of funding: Supported by research grants from Yuhan Corporation (Pharmaceutical company)
Bailey 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	Strategy: Adding N = 546 Dapagliflozin 2.5mg (n=137) Dapagliflozin 5 mg (n=137) Dapagliflozin 10 mg (n=135) Placebo (n=137) Concomitant therapy: Metformin Antihyperglycaemic	All-cause mortality, Cardiovascular mortality, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: 80 sites across USA, Canada, Argentina, Mexico and Brazil Sources of funding: Bristol-Myers Squibb and AstraZeneca. The authors also declare

Study	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): 53.925 (9.7327) years Time since type 2 diabetes diagnosed: 19.825 (5.6411) years	treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Follow up: 23.7 months	numerous grants and honoraria from multiple pharmaceutical companies
Bailey 2016 LIRA-SWITCH	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 Mean age (SD): 56.4 (10.1577) years Time since type 2 diabetes diagnosed: 7.75 (5.9565) years	Strategy: Switching N = 406 Liraglutide (n=202) Sitagliptin (n=204) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter trial. Sources of funding: Funded by Novo Nordisk.
Bajaj 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 272 Linagliptin (n=183) Placebo (n=89)	All-cause mortality, Cardiovascular mortality, Non-fatal stroke,	Study location: 52 trial centres in Asia, Europe and North America

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 54.15 (9.2963) years Time since type 2 diabetes diagnosed: Not stated/unclear	Concomitant therapy: Metformin + pioglitazone Antihyperglycaemic treatment received: No additional information available.	Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Sources of funding: Boehringer Ingelheim. The funders participated in the study design, data collection and data analysis.
Barnett 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: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.25 (9.3773) years Time since type 2	Strategy: Adding N = 455 Saxagliptin (n=304) Placebo (n=151) Concomitant therapy: Insulin ± metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 69.00% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 100% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Funding was provided by Bristol-Myers Squibb and AstraZeneca. Au thors declare numerous grants and honoraria for multiple pharmaceutical companies.

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: 12 (7.0695) years			
Barnett 2013	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): 74.9 (4.3357) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 241 Linagliptin (n=162) Placebo (n=79) Concomitant therapy: Metformin ± sulfonylurea ± basal insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 0.3% Biguanides: 85.8% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 20.60% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 57.00%	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Unstable angina, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Sponsored by Boehringer Ingelheim
Barnett 2014 EMPA-REG RENAL - CKD2	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Adding N = 704 Stage 2 CKD - Placebo (n=97) Stage 2 CKD - Empagliflozin 10 mg (n=98) Stage 2 CKD - Empagliflozin 25 mg (n=97) Stage 3 CKD - Placebo (n=187) Stage 3 CKD - Empagliflozin 25 mg (n=188) Stage 4 CKD - Placebo (n=37) Stage 4 CKD - Empagliflozin 25 mg (n=37) Concomitant	All-cause mortality, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim, Eli Lilly

Study	Population	Intervention and comparison	Outcomes	Comments
	Includes results for a subgroup for people with different stages of chronic kidney disease. Mean age (SD): 63.225 (6.823) years Time since type 2 diabetes diagnosed: Not stated/unclear	therapy: Antidiabetes treatment excluding SGLT-2 inhibitors Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 7.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 27.2% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 4.8%		
Bergenstal 2009	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): 52.15 (10.7609) years Time since type 2 diabetes diagnosed: 8.5 (6.1033) years	Strategy: Adding N = 248 Biphasic insulin aspart once daily (n=124) Concomitant therapy: Metformin + sulfonylurea 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: 102 sites in the USA Sources of funding: The study was supported by Novo Nordisk.
Bergenstal 2010 DURATION-2	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 491 Exenatide (n=160) Sitagliptin (n=166) Pioglitazone (n=165)	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Unstable angina,	Study location: USA, India and Mexico. Sources of funding: Amylin

Study	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: Not stated/unclear Mean age (SD): 52.3333 (10.3489) years Time since type 2 diabetes diagnosed: 5.6667 (4.6858) years	Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Pharmaceuticals and Eli Lilly
Berndt-Zipfel 2013	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): 58.5 (8.0623) years Time since type 2 diabetes	Strategy: Adding N = 44 Vildagliptin (n=22) Glimepiride (n=22) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Not stated Sources of funding: Not stated

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 7.25 (7.0838) years			
Billings 2018 DUAL VII	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): 58.3 (8.8015) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 506 Insulin degludec and liraglutide fixed-ratio combination (n=252) Basal-bolus insulin (Insulin glargine and insulin aspart) (n=254) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Unstable angina, Hospitalisation for heart failure, Cardiac arrhythmia, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Trial funded by Novo Nordisk
Bizino 2019 MAGNA VICTORIA	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Mixed population	Strategy: Adding N = 49 Liraglutide (n=23) Placebo (n=26) Concomitant therapy: Metformin with or without sulfonylurea and/or insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 65%	HbA1c change, Weight change Follow up: 6 months	Study location: Trial conducted at Leiden University Medical Centre, Leiden, Netherlands Sources of funding: Novo Nordisk funded the study.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.5 (6.5509) years Time since type 2 diabetes diagnosed: 11 (6.5509) years	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 28.5%		
Blonde 2015 AWARD-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: Not stated/unclear Mean age (SD): 59.3667 (9.2374) years Time since type 2 diabetes diagnosed: 12.7333 (6.9687) years	Strategy: Adding N = 884 Duaglutide 1.5 mg (n=295) Dulaglutide 0.75 mg (n=293) Insulin glargine (n=296) Concomitant therapy: Insulin lispro with or without metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 1.1% Biguanides: 72.3% DPP-4 inhibitors: 49% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 29%	All-cause mortality, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Eli Lilly and Company
Blonde 2020 LIRA-ADD2SGLT2i	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and	Strategy: Adding N = 303 Liraglutide (n=203) Placebo (n=100) Concomitant therapy: SGLT2i +/- metformin Antihyperglycaemic treatment received:	All-cause mortality, Cardiovascular mortality, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change	Study location: Multicentre, multinational trial at 74 sites in Brazil, India, Israel, Mexico, the Russian Federation and the United States. Sources of

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 55.35 (10.0347) years Time since type 2 diabetes diagnosed: 9.85 (7.0395) years	Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 94.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 50.60% Sulfonylureas: Not stated/unclear	Follow up: 6 months	funding: Novo Nordisk
Bode 2013	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): 63.6333 (6.2386) years Time since type 2 diabetes diagnosed: 11.6667 (7.4404) years	Strategy: Adding N = 714 Canagliflozin 100 mg (n=241) Canagliflozin 300 mg (n=236) Placebo (n=237) Concomitant therapy: None or monotherapy/combination therapy (including metformin, sulfonylurea, DPP-4 inhibitor, alpha glucosidase inhibitor, GLP-1 agonist, or insulin) Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 85.3% DPP-4 inhibitors: 9.1% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 48.7%	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Multicenter Sources of funding: Study sponsored by Janssen Research & Development

Study	Population	Intervention and comparison	Outcomes	Comments
Bolinder 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: 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): 60.7 (7.5706) yrs years Time since type 2 diabetes diagnosed: 5.75 (4.9208) years	Strategy: Adding N = 180 Dapagliflozin + Metformin (n=89) Placebo + Metformin (n=91) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Conducted at 40 sites in Bulgaria, Czech Republic, Hungary, Poland, and Sweden Sources of funding: AstraZeneca and Bristol-Myers Squibb
Bolli 2008	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	Strategy: Adding N = 576 Vildagliptin 100 mg (n=295) Pioglitazone 30mg (n=281) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Worldwide. Study conducted at 118 centers; Germany (26), UK (25), USA (24), Spain (16), Italy (12), Switzerland (5), Austria (4), South Africa (3) andAustralia (3). Sources of funding: Novartis Pharmaceuticals Corporation

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular risk: Not stated/unclear Mean age (SD): 56.65 (9.4972) years Time since type 2 diabetes diagnosed: 6.4 (5.0486) years			
Bolli 2014 GetGoal-F1	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 (9.2085) years Time since type 2 diabetes diagnosed: 6 (4.4138) years (mean)	Strategy: Adding N = 482 Lixisenatide one-step dose increase (n=161) Lixisenatide two-step dose increase (n=161) Placebo (n=160) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 17.5 months	Study location: Multicenter Sources of funding: Sanofi
Bosi 2007	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart	Strategy: Adding N = 544 Vildagliptin 50 mg (n=177) Vildagliptin 100 mg (n=185) Placebo (n=182) Concomitant therapy: Metformin	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: East Hanover, New Jersey, United States. Study was conducted at 109 centers in the U.S, France, Italy and Sweden. Sources of

Study	Population	Intervention and comparison	Outcomes	Comments
	failure T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Noinformation stated/unclear Mean age (SD): 54.2 (9.8386) years Time since type 2 diabetes diagnosed: 6.2667 (5.1722) years	Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	funding: Novartis Pharmaceuticals Corporation
Brown 2020 DAPA-LVH	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): 65.5 (6.9) years Time since type 2 diabetes diagnosed: 9.25 years	Strategy: Adding N = 544 Dapagliflozin (n=32) Placebo (n=34) Concomitant therapy: Metformin with or without other antihyperglycaemic drugs Antihyperglycaemic treatment received: No additional information available.	Diabetic ketoacidosis, Hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Scotland Sources of funding: Novartis Pharmaceuticals Corporation

Study	Population	Intervention and comparison	Outcomes	Comments
Bunck 2009	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): 58.4 (1.3) years Time since type 2 diabetes diagnosed (SD): 4.9 (1.1) years	Strategy: Adding N = 69 Exenatide (n=36) Insulin glargine (n=33) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter. Sweden, Finland and the Netherlands. Sources of funding: Amylin Pharmaceuticals and Eli Lilly and Company
Buse 2004 Exenatide-113	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):	Strategy: Adding N = 377 Exenatide 10 mcg twice daily (n=129) Exenatide 5 mcg twice daily (n=125) Placebo (n=123) Concomitant therapy: Sulfonylurea 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: Not stated/unclear	Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Study location: USA (101 sites) Sources of funding: Amylin Pharmaceuticals and Eli Lilly.

Study	Population	Intervention and comparison	Outcomes	Comments
	55.3333 (10.6788) years Time since type 2 diabetes diagnosed: 6.2 (5.5749) years	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 45%		
Buse 2009 LEAD 6	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): 58.4 (1.3) years Time since type 2 diabetes diagnosed (SD): 4.9 (1.1) years	Strategy: Adding N = 464 Liraglutide (n=233) Exenatide (n=231) Concomitant therapy: Metformin and sulfonylureas Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter. Sources of funding: Novo Nordisk A/S.
Buse 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	Strategy: Adding N = 261 Exenatide 10 mcg twice daily (n=138) Placebo (n=123) Concomitant therapy: Insulin glargine with or without metformin or pioglitazone or metformin + pioglitazone Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 70.5%	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Study location: Multicenter Sources of funding: Sponsored and funded by the Alliance of Eli Lilly and Company and Amylin Pharmaceuticals.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59 (9.4842) years Time since type 2 diabetes diagnosed: 12 (7) years	DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Buse 2013 DURATION 6	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 Mean age (SD): 57 (9.5) years Time since type 2 diabetes diagnosed (SD): 8.5 (6.0) years	Strategy: Adding N = 911 Liraglutide (n=461) Exenatide (n=450) Concomitant therapy: No additional information available. Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter. Sources of funding: Novo Nordisk A/S.
Buse 2014 DUAL II	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	Strategy: Adding N = 413 IDegLira (n=207) Insulin degludec (n=206) Concomitant therapy: No additional information available. Antihyperglycaemic	Non-fatal myocardial infarction, Non-fatal stroke, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multicenter. Sources of funding: Novo Nordisk.

Study	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): 57.5 (10.1) years Time since type 2 diabetes diagnosed (SD): 10.5 (6.5) years	treatment received: No additional information available.	Follow up: 6 months	
Camerini-Davalos 1994	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 70 Glipizide 5 mg daily (n=40) Placebo (n=30) Concomitant therapy: Insulin 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: 61.20% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change Follow up: 36 months	Study location: Metropolitan Hospital Center Diabetes CLinic, New York, NY, USA Sources of funding: Supported in part by Diabetes Research Fund, New York, NY; the Michael J. Bilotto Research Fund of HOPE for Diabetes Foundation, New York, NY; the Veterans Administration Research Fund, Washington, DC; Roerig-Pfizer Pharmaceuticals, New York, NY.
Cannon 2020 VERTIS CV	Model 1: People with type 2 diabetes and heart failure	Strategy: Adding N = 8246 Ertugliflozin (n=5499)	All-cause mortality, Cardiovascular mortality, 3-point MACE, 4-point	Study location: Multicenter Sources of funding: Merck

Study	Population	Intervention and comparison	Outcomes	Comments
	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Mixed population T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Includes results for a subgroup for people with or without heart failure and with or without chronic kidney disease. Mean age (SD): 64.4 (8.0668) years Time since type 2 diabetes diagnosed: 13 (8.3334) years	Placebo (n=2747) Concomitant therapy: Monotherapy or combination therapy of any approved agent Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 76.60% DPP-4 inhibitors: 11.00% GLP-1 receptor agonists: 3.3% Insulin: 47.7% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 41%	MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Death from renal causes, Cardiac arrhythmia, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 36 months	Sharp & Dohme and Pfizer
Capehorn 2020 SUSTAIN 10	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 577 Semaglutide 1.0 mg weekly (n=290) Liraglutide 1.2 mg daily (n=287) Concomitant	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Multicenter Sources of funding: Funded by Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	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 Mean age (SD): 59.5 (10.2544) years Time since type 2 diabetes diagnosed: 9.25 (5.9044) years	therapy: Metformin, sulfonylurea or SGLT2 inhibitor monotherapy or combination therapy Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 94.8% DPP-4 inhibitors: 0.20% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 24.6% Sulfonylureas: 46.8%	change, Weight change, BMI change Follow up: 7 months	
Cefalu 2013 CANTATA-SU	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): 56.1667 (9.2354) years Time since type 2 diabetes diagnosed: 6.6 (5.3385) years	Strategy: Adding N = 1452 Glimepiride 6/8 mg daily (n=484) Canagliflozin 100 mg daily (n=483) Canagliflozin 300 mg daily (n=485) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Death from renal causes, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Funded by Janssen Research and Development, LLC

Study	Population	Intervention and comparison	Outcomes	Comments
Cefalu 2015	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.9 (7.3599) years Time since type 2 diabetes diagnosed: 12.45 (8.4548) years	Strategy: Adding N = 914 Dapagliflozin (n=455) Placebo (n=459) Concomitant therapy: Drugs excluding rosiglitazone 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: 16.80% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Progression of liver disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter trial. Sources of funding: Supported by Bristol-Myers Squibb and AstraZeneca. An author was supported in part by a grant from the National Institute of General Medical Sciences of the National Institutes of Health (1-U54-GM-104940).
Charbonnel 2006 Sitagliptin 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not	Strategy: Adding N = 701 Sitagliptin 100 mg daily (n=464) Placebo (n=237) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Funded by Merck Research Laboratories

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Mean age (SD): 54.55 (10.1691) years Time since type 2 diabetes diagnosed: 6.3 (5.1742) years			
Charbonnel 2013	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): 57.25 (10.4083) years Time since type 2 diabetes diagnosed: 7.9 (5.5454) years	Strategy: Adding N = 653 Sitagliptin 100 mg daily (n=326) Liraglutide 1.2 mg daily (n=327) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Sponsored by Merck Sharp & Dohme Corp, subsidiary of Merck & Co., Inc.
Charpentier 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	Strategy: Adding N = 299 Pioglitazone 30 mg daily (n=145) Placebo (n=154) Concomitant therapy: Metformin + sulfonylurea or metiglinide Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Hypoglycaemia episodes, HbA1c change Follow up: 7 months	Study location: France (52 hospitals, diabetology or internal medical services and 16 diabetes specialists) Sources of funding: Sponsored by Takeda France

Study	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): 59.7 (9.4466) years Time since type 2 diabetes diagnosed: 12.3 (8.4845) years	stated/unclear Biguanides: 0.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Chen 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): 62.895 (6.5404) years Time since type 2 diabetes diagnosed: 6.975 (2.3216) years	Strategy: Adding N = 73 Vildagliptin 100 mg daily (n=37) Saxagliptin 5 mg daily (n=36) Concomitant therapy: Metformin and Gliclazide Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, BMI change Follow up: 5.5 months	Study location: Guangzhou, China Sources of funding: Reports study not funded.
Chen 2017	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic	Strategy: Adding Exenatide (n=14) Insulin (n=12) Concomitant therapy: Metformin +/- sulfonylurea	All-cause mortality, HbA1c change, BMI change Follow up: 6 months	Study location: The Netherlands. Sources of funding: Supported by Eli Lilly which had a partnership with

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease T2DM and heart failure: People with heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Antihyperglycaemic treatment received: No additional information available.		Amylin, the manufacturer of exenatide at the time the trial was designed and data was collected.
Chen 2018A SUPER	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): 59.1 (8.0507) years Time since type 2 diabetes diagnosed: 13.35 (6.8667) years	Strategy: Adding N = 462 Saxagliptin + insulin (n=232) Placebo + insulin (n=230) Concomitant therapy: Insulin with or without metformin 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, BMI change Follow up: 5.5 months	Study location: China Sources of funding: Industry funding - AstraZeneca
Cho 2019	Model 5: People with type 2 diabetes at higher risk of	Strategy: Switching N = 71 Dapagliflozin 5mg	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Japan Sources of

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 63.35 (10.099) years Time since type 2 diabetes diagnosed: Not stated/unclear	(n=36) Pioglitazone 15 - 30mg (n=35) Concomitant therapy: Other hypoglycemic agents Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 15.5% Biguanides: 65.00% DPP-4 inhibitors: 52.3% GLP-1 receptor agonists: 7% Insulin: 14.00% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 26.80%	change, Weight change Follow up: 5.5 months	funding: There was no financial support for this trial.
Civera 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): 61.7 (9.7346) years Time since type 2	Strategy: Adding N = 25 Metformin (n=12) NPH insulin (n=13) Concomitant therapy: Metformin + insulin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, HbA1c change, Weight change Follow up: 5.5 months	Study location: Spain Sources of funding: No additional information

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: 9.05 (5.3506) years			
Cusi 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58 (9.5501) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 56 Canagliflozin 300 mg daily (n=26) Placebo daily (n=30) Concomitant therapy: Metformin ± DPP-4 inhibitor Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 5.5 months	Study location: USA Sources of funding: Funding by Janssen Research & Development
da Silva 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not	Strategy: Adding N = 35 Sitagliptin (n=18) NPH Insulin (n=17) Concomitant therapy: Metformin + sulfonylurea (glyburide) Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear	HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Brazil Sources of funding: São Paulo Research Foundation

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Mean age (SD): 56.75 (6.7977) years Time since type 2 diabetes diagnosed: 10.9 (6.6785) years	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%		
Dagogo-Jack 2018 VERTIS SITA2	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): 56.75 (6.7977) years Time since type 2 diabetes diagnosed: 10.9 (6.6785) years	Strategy: Adding N = 35 Ertugliflozin 15mg (n=153) Ertugliflozin 5mg (n=156) Placebo (n=153) Concomitant therapy: Metformin + a DPP-4 inhibitor or a sulfonylurea. A small number of people were on triple therapy. Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Merck & Co
Dahl 2022 SURPASS-5	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	Strategy: Adding N = 475 Tirzepatide 15 mg once weekly (n=120) Tirzepatide 10 mg once weekly (n=119) Tirzepatide 5 mg once weekly (n=116) Placebo once weekly (n=120) Concomitant therapy: Insulin +/-	All-cause mortality, Cardiovascular mortality, 4-point MACE, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 11 months	Study location: Multicenter Sources of funding: Eli Lilly and Company

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60.75 (10) years Time since type 2 diabetes diagnosed: 13.325 (7.3278) years	metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 98.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 118.80% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
D'Alessio 2015 EAGLE	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): 57.25 (8.8499) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 944 Liraglutide 0.6 mg - 1.8 mg once daily (n=470) Insulin glargine (n=474) Concomitant therapy: Metformin ± sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 1% Biguanides: 470.5% DPP-4 inhibitors: 100% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 320.5%	Non-fatal stroke, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Sanofi
Davies 2009 HEELA	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 235 Exenatide (n=118) Insulin glargine (n=117)	Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Multicentre at 36 centres in the UK Sources of funding: NR. A. K. and C. N. are

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic 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): 56.5 (9.1277) years Time since type 2 diabetes diagnosed: 8.7 (4.5015) years	Concomitant therapy: 2-3 oral drugs (metformin, sulfonylurea, thiazolidinedione) Antihyperglycaemic treatment received: No additional information available.	change, Weight change Follow up: 6 months	employees of Eli Lilly and Company
Davies 2013	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	Strategy: Adding N = 216 Exenatide 2mg once weekly (n=111) Insulin detemir titrated (2.0 IU/day to 62.0 IU/day) (n=105) Concomitant therapy: Metformin ± sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 108% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: UK Sources of funding: Eli Lilly and Company and Amylin Pharmaceutical, LLC

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 77%		
Davies 2015 SCALE Diabetes	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.8667 (10.5332) year years Time since type 2 diabetes diagnosed: 7.2 (5.4135) years	Strategy: Adding N = 846 Liraglutide 3.0mg daily (n=423) Liraglutide 1.8 mg daily (n=211) Placebo daily (n=212) Concomitant therapy: 1 to 3 drugs (metformin, thiazolidinedione, sulfonylurea) Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 158% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 3.7%	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Development of end stage kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 13 months	Study location: Multicenter Sources of funding: Novo Nordisk
Davies 2016 LIRA-RENAL	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not	Strategy: Adding N = 279 Liraglutide 1.8 mg once daily (n=140) Placebo (n=139) Concomitant therapy: Monotherapy or dual therapy combinations with metformin,	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI	Study location: Multicenter Sources of funding: Sponsored by Novo Nordisk A/S.

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 67.15 (8.1519) years Time since type 2 diabetes diagnosed: 15.05 (8.2323) years	sulfonylurea, and/or pioglitazone; or monotherapy with basal or premix insulin, or any combination of basal or premix insulin with metformin and/or pioglitazone Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 9.4% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 12.3%	change Follow up: 6 months	
Davies 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): 56.95 (8.4073) years Time since type 2 diabetes	Strategy: Adding N = 421 Placebo (n=71) Semaglutide 2.5mg (n=70) Semaglutide 5mg (n=70) Semaglutide 10mg (n=69) Semaglutide 20mg (n=70) Semaglutide 40mg standard (n=71) Semaglutide 40mg slow (n=70) Semaglutide 40mg fast (n=70) Semaglutide SC 1mg (n=69) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 84.9% DPP-4 inhibitors: Not stated/unclear	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Editorial support funded by Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 5.975 (4.2113) years	GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Davies 2021 STEP 2	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): 55.3333 (10.6773) years Time since type 2 diabetes diagnosed: 8.0333 (6.1017) years	Strategy: Adding N = 1210 Semaglutide 2.4mg (n=404) Semaglutide 1.0mg (n=403) Placebo (n=403) Concomitant therapy: Background oral antidiabetic drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 0.1% Biguanides: 91.8% DPP-4 inhibitors: 0.5% GLP-1 receptor agonists: 0.1% Insulin: Not stated/unclear SGLT-2 inhibitors: 24.8% Sulfonylureas: 25.5%	Health-related quality of life, All-cause mortality, Acute kidney injury, Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 15.7 months	Study location: Multicenter Sources of funding: Novo Nordisk
DeFronzo 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	Strategy: Adding N = 336 Exenatide 20mcg daily (n=113) Exenatide 10mcg daily (n=110) Placebo (n=113) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: 82 sites in the U.S. Sources of funding: Supported by Amylin Pharmaceuticals, San Diego, California, and Eli Lilly, Indianapolis, Indiana

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 53 (10.3705) years Time since type 2 diabetes diagnosed: 5.9 (5.5981) years	stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
DeFronzo 2009 Saxagliptin 014	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): 54.6 (9.9983) years Time since type 2 diabetes diagnosed: 6.525 (5.1043) years	Strategy: Adding N = 743 Placebo (n=179) Saxagliptin 2.5mg (n=192) Saxagliptin 5mg (n=191) Saxagliptin 10mg (n=181) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: US Sources of funding: sponsored and monitored by Bristol-Myers Squibb and AstraZeneca
DeFronzo 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 1168 Pioglitazone (n=388) Alogliptin 12.5mg + Pioglitazone (n=390) Alogliptin 25mg + Pioglitazone (n=390)	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change	Study location: Multicenter Sources of funding: Supported by Takeda Global Research & Development

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 54.5333 (9.4927) years Time since type 2 diabetes diagnosed: 6.3567 (5.4731) years	Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Follow up: 6 months	Center, Takeda Pharmaceuticals North America, Inc.
DeFronzo 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): 56.225 (9.2193) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 674 Empagliflozin 2g/linagliptin 5mg (n=134) Empagliflozin 10 mg/linagliptin 5 mg (n=135) Empagliflozin 25 mg (n=140) Empagliflozin 10 mg (n=137) Linagliptin 5 mg (n=128) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 134.8% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Hypoglycaemia episodes, HbA1c change Follow up: 12 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim and Eli Lilly and Company

Study	Population	Intervention and comparison	Outcomes	Comments
		Sulfonylureas: Not stated/unclear		
Del Prato 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): 55.3667 (9.6709) years Time since type 2 diabetes diagnosed: 5.5333 (4.9827) years	Strategy: Adding N = 2639 Alogliptin 12.5 mg (n=880) Alogliptin 25 mg (n=885) Glipizide (n=874) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 24 months	Study location: 310 study sites in North and South America, Europe, Asia, South Africa and Australia/New Zealand Sources of funding: Takeda Pharmaceuticals International, Inc.
Del Prato 2021 SURPASS-4	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear	Strategy: Adding N = 2002 Tirzepatide (n=997) Insulin (n=1005) Concomitant therapy: Metformin +/- sulfonylurea +/- SGLT-2 inhibitors Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 94.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not	All-cause mortality, Cardiovascular mortality, 4-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Multicenter Sources of funding: Funded by Eli Lilly and Company. Authors received grants and honoraria from a variety of pharmaceutical companies.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 63.6 (8.5499) years Time since type 2 diabetes diagnosed: Not stated/unclear	stated/unclear SGLT-2 inhibitors: 25.5% Sulfonylureas: 54.5%		
DePaoli 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): 55.55 (10.655) years Time since type 2 diabetes diagnosed: 8.55 (6.1) years	Strategy: Adding N = 121 Pioglitazone (n=60) Placebo (n=61) Concomitant therapy: SU +/- metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 80.20% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Not available Sources of funding: Study was funded by InteKrin Therapeutics, Inc.
Derosa 2010A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure	Strategy: Adding N = 168 Pioglitazone + vildagliptin (n=83) Glimepiride + vildagliptin (n=85) Concomitant therapy: Vildagliptin Antihyperglycaemic	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicentre study in Italy Sources of funding: NR

Study	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 Mean age (SD): 58.5 (5.5167) years Time since type 2 diabetes diagnosed: 6.5 (2.5436) years	treatment received: No additional information available.		
Derosa 2010B	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): 57.5 (5.526) years Time since type 2 diabetes diagnosed: 5.5 (2.5528) years	Strategy: Adding N = 151 Sitagliptin (n=75) Metformin (n=76) Concomitant therapy: Pioglitazone Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicentre study in Italy Sources of funding: NR
Derosa 2011B	Model 5: People with type 2 diabetes at higher risk of	Strategy: Adding N = 111 Exenatide (n=57)	Hypoglycaemia episodes, HbA1c change, Weight change, BMI	Study location: Multicentre trial in Italy

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 55.5 (6.5329) years Time since type 2 diabetes diagnosed: Not stated/unclear	Glimepiride (n=54) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	change Follow up: 12 months	Sources of funding: NR
Derosa 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.35 (8.3723)	Strategy: Adding N = 178 Sitagliptin (n=91) Placebo (n=87) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicentre study in Italy Sources of funding: University of PaviaSigma-Tau

Study	Population	Intervention and comparison	Outcomes	Comments
	years Time since type 2 diabetes diagnosed: 5.6 (2.458) months			
Derosa 2012B	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): 53.3 (7.727) years Time since type 2 diabetes diagnosed: 6.2 (3.8007) months	Strategy: Adding N = 167 Vildagliptin (n=84) Placebo (n=83) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicentre study conducted in Italy Sources of funding: NR
Derosa 2012C	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	Strategy: Adding N = 171 Exenatide (n=86) Placebo (n=85) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicentre study in Italy Sources of funding: None

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular risk: Not stated/unclear Mean age (SD): 57 (7.5038) years Time since type 2 diabetes diagnosed: 7.7 (2.9529) months			
Derosa 2014A	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): 58.5 (9.4743) years Time since type 2 diabetes diagnosed: 6.85 (4.2028) months	Strategy: Adding N = 167 Glimepiride (n=81) Vildagliptin (n=86) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Italy Sources of funding: NR
Derosa 2014B	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular	Strategy: Adding Sitagliptin (n=102) Placebo (n=103) Concomitant therapy: Oral antidiabetic drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 100% Biguanides: Not stated/unclear	HbA1c change, Weight change, BMI change Follow up: 24 months	Study location: Multicentre trial in Italy Sources of funding: NR

Study	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): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 57.7%		
Diamant 2010 DURATION-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: Not stated/unclear Mean age (SD): 58 (9.5241) years Time since type 2 diabetes diagnosed: 7.9 (6) years	Strategy: Adding N = 456 Exenatide (n=233) Insulin glargine (n=223) Concomitant therapy: Metformin ± sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 70% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Health-related quality of life, All-cause mortality, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 36 months	Study location: Multicentre trial. 72 sites across the USE, Puerto Rico, the European Union, Russia, Australia, Korea, Taiwan and Mexico Sources of funding: Amlyn Pharmaceuticals Inc and Eli Lilly and Company. Authors have received grants and honoraria from multiple pharmaceutical companies.
Diamant 2014 4B	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Strategy: Adding N = 627 Exenatide (n=315) Insulin lispro (n=312) Concomitant therapy: Metformin + insulin glargine	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Acute kidney injury, Hypoglycaemia episodes, At	Study location: Multicenter Sources of funding: Study was part of the Eli Lilly and Company / Amlyn Pharmaceuticals

Study	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): 59.45 (9.4519) years Time since type 2 diabetes diagnosed: 11 years	Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 100% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 7 months	Alliance and the Bristol-Myers Squibb / AstraZeneca Alliance. Authors received grants and honoraria from a number of different pharmaceutical companies.
Dobs 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: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.6 (9.0496) years Time since type 2 diabetes diagnosed: 9.35 (6.2278) years	Strategy: Adding N = 278 Sitagliptin (n=181) Placebo (n=97) Concomitant therapy: Metformin + PPAR gamma agonist, metformin + sulfonylurea, sulfonylurea + PPAR gamma agonist Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12.4 months	Study location: 41 sites across North and South America, Europe and Asia Sources of funding: Study sponsored by Merck Sharp and Dohme Corp. Numerous authors are current or former employees of Merk Sharp and Dohme Corp.
Dorkhan 2009	Model 5: People with type 2	Strategy: Adding N = 30	HbA1c change, BMI change	Study location: NR

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 61.15 (7.6697) years Time since type 2 diabetes diagnosed: 10.3 (6.7915) years	Pioglitazone (n=15) Insulin glargine (n=15) Concomitant therapy: Metformin with sulfonylurea or meglitinide Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%	Follow up: 6 months	Sources of funding: Study was in part financially supported by grants from Sanofi-Aventis, The Crafoord Foundation, and The Swedish Heart and Lung Association. Authors declare various honoraria's with Eli Lilly and Sanofi-Aventis. One author owns shares and stock options in NovoNordisk A/S.
Douek 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 Mean age (SD):	Strategy: Adding N = 183 Metformin (n=92) Placebo (n=91) Concomitant therapy: Insulin 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: 100% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Five hospitals in southwest England Sources of funding: Supported by the Special Trustees for the United Bristol Hospitals and the NHS Executive Southwest. Lipha Pharmaceuticals donated trial medication.

Study	Population	Intervention and comparison	Outcomes	Comments
	58 (8.325) years Time since type 2 diabetes diagnosed: 9.5 (5.2) years			
Dungan 2014 AWARD-6	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): 56.65 (9.6052) years Time since type 2 diabetes diagnosed: 7.2 (5.4) years	Strategy: Adding N = 599 Dulaglutide (n=299) Liraglutide (n=300) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Falls requiring hospitalisation, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Sponsored by Eli Lilly and Company. Authors state numerous grants and honoraria from multiple pharmaceutical companies.
Dungan 2016 AWARD-8	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	Strategy: Adding N = 300 Dulaglutide (n=240) Placebo (n=60) Concomitant therapy: Glimepiride Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not	All-cause mortality, Non-fatal stroke, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: NR Sources of funding: Funded by Eli Lilly and Company. First author declares funding and honoraria from multiple pharmaceutical companies

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.95 (9.71) years Time since type 2 diabetes diagnosis: 7.3 (5.0386) years	stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%		
Ferdinand 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 atherosclerotic 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): 56.85 (9.3) years Time since type 2 diabetes diagnosed: 9.3 (7.0668) years	Strategy: Adding N = 150 Empagliflozin (n=78) Placebo (n=72) Concomitant therapy: None or stable oral hypoglycemic drug Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Persistent signs of worsening kidney disease, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: 92 centers in the United States Sources of funding: Boehringer Ingelheim
Fernandez 2008	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 20 Pioglitazone (n=10) Placebo (n=10) Concomitant therapy: insulin	Hypoglycaemia episodes, HbA1c change Follow up: 8.3 months	Study location: Texas, the US Sources of funding: American Diabetes Association Take

Study	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: Not stated/unclear Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: No additional information available.		da Pharmaceuticals
Ferrannini 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 atherosclerotic 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):	Strategy: Adding N = 2789 Vildagliptin (n=1396) Glimepiride (n=1393) Concomitant therapy: metformin + placebo Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Cardiac arrhythmia, Hypoglycaemia episodes, HbA1c change Follow up: 12 months	Study location: Germany, United States Sources of funding: Novartis Pharmaceuticals

Study	Population	Intervention and comparison	Outcomes	Comments
	57.48 (9.1705) years Time since type 2 diabetes diagnosed: 5.73 (5.1056) years			
Filozof 2010a	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): 59.45 (10.0483) years Time since type 2 diabetes diagnosed: 6.6 (5.1991) years	Strategy: Adding N = 1007 Vildagliptin (n=513) Gliclazide (n=494) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, HbA1c change, Weight change Follow up: 12 months	Study location: Unclear, but appears to be Switzerland and France Sources of funding: Novartis Pharmaceuticals
Filozof 2010b	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	Strategy: Adding N = 914 Vildagliptin (n=456) metformin (n=458) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Acute kidney injury, Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: Germany, United States Sources of funding: Novartis Pharmaceuticals

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.95 (9.8911) years Time since type 2 diabetes diagnosed: 4.65 (4.9251) years			
Fioretto 2018 DERIVE	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 321 Dapagliflozin 10 mg once daily (n=160) Placebo (n=161) Concomitant therapy: Stable glucose-lowering therapy (diet, exercise +oral anti-diabetic drug [excluding SGLT2-inhibitors] and/or long/intermediate/mixed insulin) Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 66.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 49.80% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 40.8%	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hospitalisation for heart failure, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: International (88 sites in Bulgaria, Canada, Czech Republic, Italy, Poland, Spain, Sweden, USA). Sources of funding: Funded by AstraZeneca and supported by grant from National Institutes of Health, Grant/Award Number: UL1TR001111.
Fonseca 2007	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and	Strategy: Adding N = 296 vildagliptin (n=144) placebo (n=152) Concomitant therapy: insulin Antihyperglycaemic treatment received: No additional	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Germany (ten), Finland (five), Spain (four) and the USA (49) Sources of funding: Novartis Pharmaceuticals

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 59.25 (10.5598) years Time since type 2 diabetes diagnosed: 14.65 (8.4979) years	information available.	Follow up: 9 months	
Fonseca 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: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.05 (9.0556) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 313 Sitagliptin (n=157) Placebo (n=156) Concomitant therapy: Pioglitazone + metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Merck Sharp & Dohme LLC
Forst 2005	Model 5: People with type 2 diabetes at higher risk of	Strategy: Adding N = 173 Pioglitazone (n=89)	HbA1c change	Study location: Unclear: appears to be Germany

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 62.6 (7.9304) months years Time since type 2 diabetes diagnosed: 85.75 (86.8345) months	glimepiride (n=84) Concomitant therapy: other antidiabetic medication Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	Sources of funding: TAKEDA Germany
Forst 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): 57.3333 (10.0701) years Time since type 2	Strategy: Adding N = 342 Canagliflozin 100 mg (n=113) Canagliflozin 300 mg (n=114) Placebo/Sitagliptin (n=115) Concomitant therapy: metformin + pioglitazone Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, HbA1c change, Weight change Follow up: 6 months	Study location: Canada, Finland, France, Germany, Greece, India, Mexico, Spain, Thailand, United Kingdom, United States Sources of funding: Janssen Research & Development, LLC

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: 10.5333 (6.9493) years			
Forst 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): 66.75 (10.881) years Time since type 2 diabetes diagnosed: 7.95 (5.1347) years	Strategy: Adding N = 161 Vildagliptin (n=82) NPH insulin (n=79) Concomitant therapy: Glimepiride Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Germany Sources of funding: Novartis Pharma GmbH
Frias 2016 DURATION-8	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	Strategy: Adding N = 695 Exenatide 2 mg weekly + Dapagliflozin 10 mg daily (n=231) Exenatide 2 mg weekly + Placebo (n=231) Dapagliflozin 10 mg daily + Placebo (n=233) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional	All-cause mortality, Cardiovascular mortality, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Multicenter Sources of funding: AstraZeneca

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 54.3333 (9.6763) years Time since type 2 diabetes diagnosed: 7.3667 (5.6711) years	information available.		
Frias 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.95 (7.0827) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 318 Tirzepatide 1 mg (n=53) Tirzepatide 5 mg (n=55) Tirzepatide 10 mg (n=52) Tirzepatide 15 mg (n=53) Dulaglutide 1.5 mg (n=54) Placebo (n=51) Concomitant therapy: Current metformin treatment continued Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: 47 sites in Poland, Puerto Rico, Slovakia, and USA Sources of funding: Eli Lilly and Company
Frias 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	Strategy: Adding N = 444 Saxagliptin + Dapagliflozin (n=227) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional	All-cause mortality, Hospitalisation for heart failure, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: 87 centres in Germany, the Czech Republic, Hungary, Mexico, Poland, Romania, Russia, Sweden, the UK and the United States. Sources of

Study	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): 56.1 (9.6707) years Time since type 2 diabetes diagnosed: 7.8 (6.4491) years	information available.	Follow up: 36 months	funding: AstraZeneca
Frias 2021 SURPASS-2	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): 56.575 (10.4287) years Time since type 2 diabetes diagnosed: 8.625 (6.455) years	Strategy: Adding N = 1878 Tirzepatide 5 mg (n=470) Tirzepatide 10 mg (n=469) Tirzepatide 15 mg (n=470) Semaglutide 1 mg (n=469) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 9 months	Study location: 128 sites in the United States, Argentina, Australia, Brazil, Canada, Israel, Mexico, and the United Kingdom Sources of funding: Eili Lilly
Frias 2023	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 103 Dulaglutide (n=50) Placebo (n=53) Concomitant	All-cause mortality, Cardiovascular mortality, Cardiac arrhythmia, Diabetic ketoacidosis,	Study location: The US, Hungary, Poland, and Slovakia Sources of

Study	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: Not stated/unclear Mean age (SD): 58.55 (9.8458) years Time since type 2 diabetes diagnosed: Not stated/unclear	therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	funding: Eli Lilly and Company
Fujioka 2003	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): 54.3333 years Time since type 2 diabetes diagnosed: 3 years	Strategy: Switching N = 217 Extended release metformin (1000 mg) (n=75) Extended release metformin (1500 mg) (n=71) Immediate release formulin (1000mg) (n=71) Concomitant therapy: None Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes Follow up: 5.5 months	Study location: 42 centres in the United States Sources of funding: NR

Study	Population	Intervention and comparison	Outcomes	Comments
Gadde 2017 DURATION-NEO-2	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): 53.7 (9.4888) years Time since type 2 diabetes diagnosed: 8.3667 (5.6986) years	Strategy: Adding N = 364 Exenatide QWS-AI (n=181) Sitagliptin (100 mg) (n=122) Placebo (n=61) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6.5 months	Study location: 81 centres in the USA Sources of funding: AstraZeneca. Primary author delcares funding from Bristol-Myers Squibb, Eisai and the NIDDK. A second author was an employee of Bristol-Myers Squibb during the conduct of the study and two further authors are employees of AstraZeneca
Galindo 2023	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	Strategy: Adding N = 145 Insulin degludec/liraglutide (n=72) Basal-bolus Insulin (n=73) Concomitant therapy: Oral agents +/or basal insulin 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	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: US Sources of funding: Grant funding: National Institutes of Health (NIH) and National Institute of Diabetes and Digestive and Kidney DiseaseNovo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 54.15 (9.9006) years Time since type 2 diabetes diagnosed: Not stated/unclear	Insulin: 15.1% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Galle 2012	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 69.25 (8.1689) years Time since type 2 diabetes diagnosed: 13.1 (9.057) years	Strategy: Adding N = 39 Pioglitazone 30 mg once daily (n=20) Placebo (n=19) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 6 months	Study location: Germany (12 sites) Sources of funding: Sponsored by TAKEDA Pharma GmbH, Aachen, Germany
Gallwitz 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	Strategy: Adding N = 363 Exenatide (n=182) Insulin aspart 70/30 (n=181) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor	Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: 68 sites in Germany Sources of funding: Two authors are employed by Lilly Deutschland, Germany, a further author is employed by Eli Lilly Austria.

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57 (9.9503) years Time since type 2 diabetes diagnosed: 5 (4.5263) years	agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Gallwitz 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.8 (9.4) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 1551 Linagliptin (n=776) Glimepiride (n=775) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Falls requiring hospitalisation, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim. Multiple authors declare funding and honoraria with numerous pharmaceutical companies
Gallwitz 2012B EUREXA	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular	Strategy: Adding N = 1029 Exenatide (n=515) Glimegiride (n=514) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change	Study location: Multicenter Sources of funding: Eli Lilly and Company; Amlyn Pharmaceuticals. Multiple authors declare funding and honoraria with numerous

Study	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): 56 (9.561) years Time since type 2 diabetes diagnosed: 5.65 (4.5571) years	Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Follow up: 36 months	pharmaceutical companies
Gao 2023 SURPASS-AP-Combo	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.125 (11.3268) years Time since type 2 diabetes diagnosed: 7.655 (5.734) years	Strategy: Adding N = 917 Tirzepatide 5mg (n=230) Tirzepatide 10mg (n=228) Tirzepatide 15mg (n=229) Insulin glargine (n=230) Concomitant therapy: Metformin +/- sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 52.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, 4-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 9 months	Study location: Multicentre trial (Asia-Pacific region). Sources of funding: Funded by Eli Lilly and Company.
Garber 2007	Model 5: People with type 2 diabetes at higher risk of	Strategy: Adding N = 463 Vildagliptin 50 mg	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: USA and Romania

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease T2DM and heart failure: without hear 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): 54.266 (9.333) years Time since type 2 diabetes diagnosis: 4.7 (4.6) years	daily (n=147) Vildagliptin 100 mg daily (n=158) Placebo (n=158) Concomitant therapy: Pioglitazone 45 mg daily Antihyperglycaemic treatment received: No additional information available.	change Follow up: 5.5 months	Sources of funding: Novartis Pharmaceuticals Corporation 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.
Garber 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): 58.2333 (10.7333) years Time since type 2	Strategy: Adding N = 515 Vildagliptin 50 mg daily (n=170) Vildagliptin 100 mg daily (n=169) Placebo (n=176) Concomitant therapy: Glimepiride 4mg daily Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, hypoglycaemia episodes, severe hypoglycaemia episodes, HbA1c change, weight change Follow up: 5.5 months	Study location: USA, Sweden, Finland, Argentina, and Lithuania Sources of funding: Novartis Pharmaceuticals 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.

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosis: 7.133 (5.433) years			
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 Mean age (SD): 53.4 (10.9) years Time since type 2 diabetes diagnosed: 5.4 (5.2) years	Strategy: Adding N = 917 Liraglutide 1.2mg (n=251) Liraglutide 1.8mg (n=247) Glimepiride (n=248) Concomitant therapy: No additional information Antihyperglycaemic treatment received: No additional information	HbA1c change Follow up: 12 months	Study location: USA and Mexico. Sources of funding: Novo Nordisk.
Garvey 2020 SCALE Insulin	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	Strategy: Adding N = 396 Liraglutide (n=198) Placebo (n=198) Concomitant therapy: Insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 0.5% Biguanides: 88.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 91.9% SGLT-2 inhibitors:	Health-related quality of life, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 13 months	Study location: 53 sites globally Sources of funding: Study was sponsored by Novo Nordisk. The authors declare multiple research grants and honoraria funded by multiple pharmaceutical companies

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular risk: Not stated/unclear Mean age (SD): 56.75 (10.8593) years Time since type 2 diabetes diagnosed: 12.1 (6.8502) years	22.2% Sulfonylureas: 35.1%		
Garvey 2023 SURMOUNT-2	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.2 (10.6) years Time since type 2 diabetes diagnosed: 8.5333 (6.5058) years	Strategy: Adding N = 938 Tirzepatide 10mg (n=312) Tirzepatide 15mg (n=311) Placebo (n=315) Concomitant therapy: Biguanide, sulfonylureas, SGLT-2 inhibitors, thiazolidinediones and alpha-glucosidase inhibitors Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 0.8% Biguanides: 88.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 20.4% Sulfonylureas: 26.6%	Health-related quality of life, All-cause mortality, 3-point MACE, Persistent signs of worsening kidney disease, Cardiac arrhythmia, Progression of liver disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 18 months	Study location: Multicenter trial. Sources of funding: Funded by Eli Lilly and Company.
Genovese 2013 PRISMA	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart	Strategy: Adding N = 213 Pioglitazone (n=110) Placebo (n=103) Concomitant therapy: Metformin Antihyperglycaemic treatment received:	All-cause mortality, Cardiovascular mortality, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Italy Sources of funding: Takeda Italia SpA, Rome, Italy

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 57.4 (8.409) years Time since type 2 diabetes diagnosed: 5.75 (5.0989) years	No additional information available.		
Gerstein 2019A REWIND	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease 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 Includes results for a subgroup for	Strategy: Adding N = 9901 Dulaglutide (n=4949) Placebo (n=4952) Concomitant therapy: Antihyperglycemic therapy except DPP-4 inhibitor or GLP-1 receptor agonist Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 81.2% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 23.80% SGLT-2 inhibitors: 0.1% Sulfonylureas: 46%	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Cardiac arrhythmia, Progression of liver disease, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 64.8 months	Study location: Multicenter Sources of funding: Eli Lilley & Co.

Study	Population	Intervention and comparison	Outcomes	Comments
	people with atherosclerotic cardiovascular disease. Mean age (SD): 66.2 (6.5) years Time since type 2 diabetes diagnosed: 10.55 (7.2502) years			
Giorgino 2015 AWARD-2	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): 56.6667 (9.3503) years Time since type 2 diabetes diagnosed: 9 (6) years	Strategy: Adding N = 807 Dulaglutide 1.5 mg (n=273) Dulaglutide 0.75 mg (n=272) Insulin glargine (n=262) Concomitant therapy: Metformin + glimepiride Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 17.7 months	Study location: NR Sources of funding: Eli Lilly and Company
Giugliano 1993	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular	Strategy: Adding N = 50 Metformin (n=27) Placebo (n=23) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional	HbA1c change Follow up: 6 months	Study location: Unclear - authors were based in Italy Sources of funding: NR

Study	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): 11.6 (1.2468) years Time since type 2 diabetes diagnosed: 11.7 (1.2) years	information available.		
Gohari 2022 EMPA-CARD	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.84 (7.9196) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 95 Empagliflozin 10 mg (n=47) Placebo (n=48) Concomitant therapy: Background oral antidiabetic drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 96.80% DPP-4 inhibitors: 12.60% GLP-1 receptor agonists: Not stated/unclear Insulin: 7.4% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 31.60%	All-cause mortality, Cardiovascular mortality, HbA1c change Follow up: 6 months	Study location: Iran Sources of funding: Dr. Abidi Pharmaceutical company and Zanja University Medical Sciences (Grant Number: 1602001000)
Göke 2010	Model 5: People with type 2 diabetes at higher risk of	Strategy: Adding N = 858 Saxagliptin (n=428)	All-cause mortality, Cardiovascular mortality,	Study location: International, multicentre trial taking place at

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 57.55 (10.3153) years Time since type 2 diabetes diagnosed: 5.45 (4.6013) years	Glipizide (n=430) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 46.80% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 24 months	130 study sites in Germany, Finland, United Kingdom, Hungary, India, South Korea, Netherlands, Norway, Russia, Slovakia and Vietnam. Sources of funding: Bristol-Myers Squibb and AstraZeneca
Goodman 2009	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): 54.8 (10.4914) years Time since type 2	Strategy: Adding N = 370 Vildagliptin AM (n=125) Vildagliptin PM (n=123) Placebo (n=122) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Multicentre trial conducted at 67 centres in the USA and Europe Sources of funding: Novartis Pharmaceutical Corporation

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: Not stated/unclear			
Gough 2014 DUAL-I	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 (9.9266) years Time since type 2 diabetes diagnosed: 6.9333 (5.4147) years	Strategy: Adding N = 1660 Insulin degludec + liraglutide once daily (n=833) Insulin degludec titrated once daily (n=413) Liraglutide 1.8 mg once daily (n=414) Concomitant therapy: Metformin ± pioglitazone Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 457.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Novo Nordisk
Gram 2011 South Danish Diabetes Study	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	Strategy: Adding N = 184 NPH Insulin titrated + placebo twice daily (n=46) NPH insulin titrated + metformin 1000-2000 mg daily (n=45) Insulin aspart titrated + placebo twice daily (n=48) Insulin aspart titrated + metformin 1000-2000 mg daily (n=45) Concomitant therapy: Insulin Antihyperglycaemic treatment received:	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Denmark Sources of funding: No additional information.

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 56.1 (8.2332) years Time since type 2 diabetes diagnosed: 8.325 (4.6241) years	No additional information available.		
Green 2015 TECOS	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Includes results for a subgroup for people with or without heart failure. Mean age (SD): 65.45 (7.9502) years Time since type 2 diabetes	Strategy: Adding N = 14671 Sitagliptin (n=7332) Placebo (n=7339) Concomitant therapy: Monotherapy or combination therapy of any approved agent Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 81.6% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 23.2% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 45.3%	All-cause mortality, Cardiovascular mortality, 3-point MACE, 4-point MACE, Non-fatal myocardial infarction, Unstable angina, Hospitalisation for heart failure, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Severe hypoglycaemic episodes, HbA1c change Follow up: 36 months	Study location: Multicenter Sources of funding: Merck Sharp & Dohme;

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 11.6 (8.1) years			
Grey 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): not stated/unclear Time since type 2 diabetes diagnosed: not stated/unclear	Strategy: Adding Pioglitazone (n=43) Placebo (n=43) Concomitant therapy: Insulin and / or other oral hypoglycaemic 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: 20% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change, Weight change Follow up: 12 months	Study location: NR Sources of funding: Grant support from the Health Research Council of New Zealand. Two authors declare funding from multiple pharmaceutical companies
Groop 2017 MARLINA-T2D	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Adding N = 360 Linagliptin 5mg once daily (n=182) Placebo (n=178) Concomitant therapy: Antidiabetic drugs including insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 34.2% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 31.6%	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Development of end stage kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: International (Canada, Denmark, Finland, France, Germany, Japan, the Philippines, South Korea, Spain, Taiwan, USA and Vietnam) Sources of funding: Supported by the Boehringer Ingelheim and Eli Lilly and Company, Diabetes Alliance.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 60.55 (9.6603) years Time since type 2 diabetes diagnosed: Not stated/unclear	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Group 2022 The GRADE Study	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	Strategy: Adding N = 5047 Glimepiride (n=1254) Liraglutide (n=1262) Sitagliptin (n=1268) Insulin glargine (n=1263) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, 3-point MACE, Hospitalisation for heart failure, Severe hypoglycaemic episodes, HbA1c change Follow up: 60 months	Study location: 36 clinical centres - it appeared that these were based in the US Sources of funding: National Institute of Diabetes and Digestive and Kidney Diseases and others. The manufacturers contributed trial medications under clinical-trial agreements with the NIDDK but had no role in the design, conduct, or analysis of the trial: donated medications and supplies were from Becton Dickinson, Bristol Myers Squibb, Merck, Novo Nordisk, Roche Diagnostics, and Sanofi.
Grunberger 2018 VERTIS RENAL	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic	Strategy: Adding N = 467 Ertugliflozin 15 mg once daily (n=155) Ertugliflozin 5 mg once daily (n=158) Placebo (n=154) Concomitant therapy: Antihyperglycemic therapy (monotherapy or combination therapy including sulfonylureas or insulin)	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Merck Sharp & Dohme Corp. subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Pfizer Inc.

Study	Population	Intervention and comparison	Outcomes	Comments
	kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 67.2333 (8.5679) years Time since type 2 diabetes diagnosed: 14.1667 (8.5452) years	Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 24.6% DPP-4 inhibitors: 13.5% GLP-1 receptor agonists: 2.8% Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 40.2%		
Gu 2019 SPECIFY	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): 53.5 (9.4501) years Time since type 2 diabetes diagnosed: 5.05 (4.3046) years	Strategy: Adding N = 388 Saxagliptin (n=194) Glimepiride (n=194) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 11 months	Study location: 11 sites in China Sources of funding: AstraZeneca
Guja 2017 DURATION-7	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 464 Exenatide (n=233) Placebo (n=231) Concomitant therapy: Metformin, insulin	All-cause mortality, Cardiovascular mortality, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Multicenter Sources of funding: AstraZeneca

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 57.7 (9.6691) years Time since type 2 diabetes diagnosed: 11.3 (6.356) years	Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 51.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 3.9%	change, Weight change Follow up: 6.4 months	
Gullaksen 2023 SEMPA	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): 13.5 (67.5463) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 40 Empagliflozin (n=20) Placebo (n=20) Concomitant therapy: None reported Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 90% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 25% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Weight change Follow up: 7.3 months	Study location: Denmark Sources of funding: Novo Nordisk Foundation, Central Denmark Region Research Fund and Danish Medical Associations Research Foundation
Guo 2020	Model 5: People with type 2	Strategy: Adding N = 96	All-cause mortality,	Study location: China

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 52.5667 (6.5977) years Time since type 2 diabetes diagnosed: Not stated/unclear	Insulin glargine (n=32) Liraglutide (n=32) Placebo (n=32) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Sources of funding: Natural Science Foundation of Fujian Province and 900 Hospital of the Joint Logistics Team Internal Hospital Project
Gurkan 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): 52.65 (7.1263)	Strategy: Adding N = 34 Exenatide (n=17) Insulin glargine (n=17) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Turkey Sources of funding: None

Study	Population	Intervention and comparison	Outcomes	Comments
	years Time since type 2 diabetes diagnosed: 7.235 (3.7931) years			
Guzman 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): 57.45 (8.5079) years Time since type 2 diabetes diagnosed: 10.55 (6.3755) years	Strategy: Adding N = 109 Sitagliptin (n=41) Placebo (n=68) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Eli Lilly and Company
Handelsman 2019	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	Strategy: Adding N = 461 Dapagliflozin + saxagliptin (n=232) Sitagliptin (n=229) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Acute kidney injury, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Hungary, Mexico, Poland, Romania, South Africa and the USA Sources of funding: Bristol-Myers Squibb and AstraZeneca

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.85 (9.2543) years Time since type 2 diabetes diagnosed: 8.05 (5.4574) years			
Hanefeld 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60 (8.4089) years Time since type 2 diabetes diagnosed: 7.05 (5.6) years	Strategy: Adding N = 639 Pioglitazone 15-45 mg daily (n=319) Metformin 850-2550 mg daily (n=320) Concomitant therapy: Sulfonylurea 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 31%	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: International (Canada, Belgium, Denmark, Estonia, Finland, Hungary, Italy, Lithuania, Netherlands, Slovak Republic, Sweden, UK) Sources of funding: Takeda Europe R&D Centre and Eli Lilly and Company, USA
Hanefeld 2011 PIOCOMB	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic	Strategy: Adding N = 121 Metformin (n=42) Pioglitazone (n=40) Pioglitazone + metformin (n=39) Concomitant therapy: Insulin glargine Antihyperglycaemic	Hypoglycaemia episodes, HbA1c change Follow up: 6 months	Study location: Germany Sources of funding: NR

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 63 (7.4347) years Time since type 2 diabetes diagnosed: 11.0333 (6.1358) years	treatment received: No additional information available.		
Hao 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: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 51.85 (11.251) years Time since type 2 diabetes diagnosed: 6.3 (5.652) years	Strategy: Adding N = 360 Liraglutide 1.2mg/d (n=180) Dapagliflozin 10mg (n=180) Concomitant therapy: Metformin +/-SU Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Non-fatal myocardial infarction, Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: China Sources of funding: Supported by the Exceptional Young Talents Fostering Foundation 2021 of the Tianjin Fourth Central Hospital

Study	Population	Intervention and comparison	Outcomes	Comments
Haring 2013 EMPA-REG METSU	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): 57.1 (9.2327) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 669 Empagliflozin 25 mg (n=218) Empagliflozin 10 mg (n=226) Placebo (n=225) Concomitant therapy: Metformin + sulfonylurea 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 Sources of funding: Boehringer Ingelheim and Eli Lilly and Company
Haring 2014 EMPA-REG MET	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	Strategy: Adding N = 638 Empagliflozin 10 mg (n=217) Empagliflozin 25 mg (n=214) Placebo (n=207) Concomitant therapy: Metformin 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: Boehringer Ingelheim and Eli Lilly

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 55.7 (9.9379) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Harreiter 2021 EXENDA	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): 60.15 (8.0081) years Time since type 2 diabetes diagnosed: 6.55 (4.9741) years	Strategy: Adding N = 30 Exenatide (n=16) Placebo (n=14) Concomitant therapy: Metformin and dapagliflozin Antihyperglycaemic treatment received: No additional information available.	Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Austria Sources of funding: AstraZeneca
Hartemann-Heurtier 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	Strategy: Adding N = 28 Pioglitazone (n=14) Insulin (n=14) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: France Sources of funding: Public funds from Assistance Publique des Hopitaux de Paris.

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60 (10) years Time since type 2 diabetes diagnosed: 12 (5.3033) years			
Hattori 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.75 (11.0809) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 102 Empagliflozin (n=51) Placebo (n=51) Concomitant therapy: Medical treatment other than SGLT2 inhibitors Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 14.7% Biguanides: 23.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 20.6%	HbA1c change, BMI change Follow up: 12 months	Study location: Japan Sources of funding: None
Heine 2005	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and	Strategy: Adding N = 549 Exenatide (n=282) Insulin glargine (n=267) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic	Health-related quality of life, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Eli Lilly and Company, Inc., and Amylin Pharmaceuticals, Inc.

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 58.9 (9.1471) years Time since type 2 diabetes diagnosed: 9.55 (5.856) years	treatment received: No additional information available.		
Heise 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): 61.7333 (6.802) years Time since type 2 diabetes diagnosed: 11.3067 (6.1568) years	Strategy: Adding N = 117 Tirzepatide (n=45) Semaglutide (n=44) Placebo (n=28) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6.5 months	Study location: 2 centres in Germany Sources of funding: Eli Lilly
Henriksen 2011	Model 5: People with type 2 diabetes at higher risk of	Strategy: Adding N = 211 Pioglitazone (n=102)	All-cause mortality, Cardiovascular mortality, Non-	Study location: Denmark, Sweden, Finland,

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 60.5 (8.1964) years Time since type 2 diabetes diagnosed: 13.2 (7.3485) years	Placebo (n=109) Concomitant therapy: Insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 20.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 1.5%	fatal myocardial infarction, HbA1c change, Weight change Follow up: 6 months	Sources of funding: Den Danske Forskningsfond [Authors were also employees of and owned stocks in Nordic Bioscience]
Hermansen 2007 - Stratum 1 Sitagliptin 035	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): 54.8 (10.2501) years	Strategy: Adding N = 212 Stratum 1 - Sitagliptin (n=106) Stratum 1 - Placebo (n=106) Concomitant therapy: Glimepiride 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: Methods state that the study is multinational, but no further information provided Sources of funding: Merck & Co. Inc

Study	Population	Intervention and comparison	Outcomes	Comments
	Time since type 2 diabetes diagnosed: 7.6 (5.7987) years			
Hermansen 2007 - Stratum 2 Sitagliptin 035	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): 57.15 (8.8495) years Time since type 2 diabetes diagnosed: 9.95 (6.2669) years	Strategy: Adding N = 229 Stratum 2 - Sitagliptin (n=116) Stratum 2 - Placebo (n=113) Concomitant therapy: Glimepiride + metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Methods state that the study is multinational, but no further information provided Sources of funding: Merck & Co. Inc
Hiramatsu 2018	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not	Strategy: Switching N = 139 Liraglutide 0.9 mg daily (n=45) Sitagliptin 50 mg daily (n=49) Linagliptin 5 mg daily (n=45) Concomitant therapy: None, insulin, alphaglucosidase inhibitor, or glinide Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 11.2% Biguanides: Not stated/unclear	All-cause mortality, Non-fatal myocardial infarction, Hospitalisation for heart failure, Development of end stage kidney disease, Cardiac arrhythmia, HbA1c change, BMI change Follow up: 48 months	Study location: Konan City, Japan Sources of funding: None reported

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Mean age (SD): 69.8 (7.4292) years Time since type 2 diabetes diagnosed: 8.7667 (6.3418) years	DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 9.2% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Hollander 2009 CV181-013	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): 54.0333 (10.1333) years Time since type 2 diabetes diagnosed: 5.2 (5.2079) years	Strategy: Adding N = 565 Saxagliptin 2.5 mg (n=195) Saxagliptin 5 mg (n=186) Placebo (n=184) Concomitant therapy: Thiazolidinedione Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 17.5 months	Study location: Multicentre study in the US Sources of funding: Bristol-Myers Squibb and AstraZeneca
Hollander 2018 VERTIS SU	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	Strategy: Adding N = 1326 Ertugliflozin 15 mg (n=441) Ertugliflozin 5 mg (n=448) Glimepiride (n=437) Concomitant therapy: Metformin and sitagliptin Antihyperglycaemic treatment received:	All-cause mortality, Cardiovascular mortality, Acute kidney injury, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multicenter Sources of funding: Merck Sharp & Dohme Corp (subsidiary of Merck & Co.) and Pfizer Inc.

Study	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): 58.2 (9.6062) years Time since type 2 diabetes diagnosed: 7.4667 (5.6672) years	No additional information available.	Follow up: 12 months	
Holman 2017 EXSCEL	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease 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: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease	Strategy: Adding N = 14752 Exenatide (n=7356) Placebo (n=7396) Concomitant therapy: Up to three oral glucose-lowering agents or insulin plus two oral glucose-lowering agents Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 76.6% DPP-4 inhibitors: 15.00% GLP-1 receptor agonists: 0% Insulin: 13.8% SGLT-2 inhibitors: 1.00% Sulfonylureas: 36.60%	All-cause mortality, Cardiovascular mortality, 3-point MACE, Unstable angina, Hospitalisation for heart failure, Development of end stage kidney disease, Death from renal causes, Cardiac arrhythmia, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 38.4 months	Study location: Multicenter Sources of funding: Amylin Pharmaceuticals

Study	Population	Intervention and comparison	Outcomes	Comments
	Includes results for a subgroup for people with heart failure and atherosclerotic cardiovascular disease. Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear			
Home 2015 HARMONY 5	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): 55.7 (9.4576) years Time since type 2 diabetes diagnosed: 9.25 (6.1) years	Strategy: Adding N = 404 Pioglitazone (n=288) Placebo (n=116) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, 3-point MACE, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: sponsored by GlaxoSmithKline.
Hong 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Strategy: Adding N = 140 Sitagliptin (100 mg) (n=70) Insulin (n=70) Concomitant therapy: Insulin	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Korea Sources of funding: National Rearsch Foundation grant funded by the Korean government and

Study	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): 59.2 (13.6655) years Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 37% Biguanides: 43.6% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 24.2%		from a grant from the Seoul National University Bindang Hospital
Hong 2023	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): 58.5 (9.5216) years Time since type 2 diabetes diagnosed: 12.4667 (7.0271) years	Strategy: Adding N = 78 Dapagliflozin 10 mg daily (n=26) Sitagliptin 100 mg daily (n=26) Lobeglitazone 0.5 mg daily (n=26) Concomitant therapy: Metformin + a sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%	Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, BMI change Follow up: 24 months	Study location: Seongnam, Gyeonggi, South Korea Sources of funding: Supported by grants from the Korean Diabetes Association (S.L., 2015F-7) and Seoul National University Bundang Hospital (14-2015-0014)

Study	Population	Intervention and comparison	Outcomes	Comments
Husain 2019 PIONEER 6	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: Mixed population T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 66 (7) years Time since type 2 diabetes diagnosed: 14.9 (8.5) years	Strategy: Adding N = 3183 Semaglutide (n=1591) Placebo (n=1592) Concomitant therapy: Standard of care Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 2.5% Biguanides: 77.40% DPP-4 inhibitors: 0.00% GLP-1 receptor agonists: 0.00% Insulin: 60.6% SGLT-2 inhibitors: 9.6% Sulfonylureas: 32.20%	All-cause mortality, Cardiovascular mortality, 3-point MACE, 5-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Severe hypoglycaemic episodes Follow up: 15.9 months	Study location: Multicenter Sources of funding: Novo Nordisk
Iacobellis 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	Strategy: Adding N = 95 Liraglutide (n=54) Control (n=41) Concomitant therapy: None (all people received metformin before entering the trial) Antihyperglycaemic treatment received: No additional information available.	HbA1c change, BMI change Follow up: 6 months	Study location: US - Report describes that screening occurred at the University of Miami Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 51 (10) years Time since type 2 diabetes diagnosed: 3.65 (3.4434) years			
Iacobellis 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): 51.5 (10.0499) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 100 Dapagliflozin (n=50) Placebo (n=50) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: US - report states that participants were screened at the University of Miami Sources of funding: AstraZeneca
Iijima 2023	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	Strategy: Switching N = 32 Semaglutide (n=16) Dulaglutide (n=16) Concomitant therapy: No additional information. Antihyperglycaemic treatment received: No additional	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Japan Sources of funding: Not stated/unclear

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.1 (11.4) years Time since type 2 diabetes diagnosed (SD): 12.9 (10.7) years	information available.		
Ikonomidis 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: People without chronic kidney disease T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 57.5 (9.5131) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 160 Insulin (n=40) Liraglutide (n=40) Empagliflozin (n=40) Liraglutide + Empagliflozin (n=40) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Study reports that recruitments was conducted at Attikon Hospital in Athens, Greece Sources of funding: Report states there were no sources of funding
Inagaki 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 427 2 mg Exenatide QW (n=215)	All-cause mortality, Cardiovascular mortality, Non-fatal stroke,	Study location: Japan Sources of funding: Eli Lilly

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 56.755 (10.8035) years Time since type 2 diabetes diagnosed: 9.035 (6.0253) years	Insulin glargine (n=212) Concomitant therapy: Biguanide ± thiazolidinedione ± sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 67% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	and Company and Amylin Pharmaceuticals Inc. Three authors are employees of Eli Lilly, two others have have received funding or honoraria from multiple pharmaceutical companies
Inagaki 2013	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): 60.5 (10.8269) years Time since type 2 diabetes	Strategy: Adding N = 352 Linagliptin 5mg (n=228) Metformin (n=124) Concomitant therapy: Monotherapy with a sulfonylurea or α glucosidase inhibitor Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 41.1% Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 59.00%	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: 43 centres in Japan Sources of funding: Medical writing funded by Boehringer Ingelheim. Five of the authors are employed by Boehringer Ingelheim. Authors declare multiple funding from numerous pharmaceutical companies

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: Not stated/unclear			
Jabbour 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): 54.9 (10.3003) years Time since type 2 diabetes diagnosed: 5.67 (5.1424) years	Strategy: Adding N = 451 Dapagliflozin 10 mg (n=225) Placebo (n=226) Concomitant therapy: Sitagliptin ± metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: Not stated/unclear DPP-4 inhibitors: 49.40% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 11 months	Study location: Conducted in Argentina, Germany, Mexico, Poland, UK and the US Sources of funding: Funded by AstraZeneca and Bristol-Myers Squibb. A number of authors are stockholders and/or employees of AstraZeneca. Primary author belongs to speakers' bureaus for Eli Lilly and Company and Amlyn.
Ji 2016B VISION	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	Strategy: Adding N = 3084 Vildagliptin (n=2573) Metformin (n=511) Concomitant therapy: Metformin 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: 127 medical centres in China Sources of funding: Study funded by Novartis Pharmaceuticals. Two authors are also employees of Novartis Pharmaceuticals.

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Mean age (SD): 56.35 (10.6334) years Time since type 2 diabetes diagnosed: 4.2 (4.2167) years			
Ji 2019 VERTIS Asia	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): 56.4333 (9.1013) years Time since type 2 diabetes diagnosed: 6.9667 (5.0666) years	Strategy: Adding N = 506 Ertugliflozin 5 mg (n=170) Ertugliflozin 15 mg (n=169) Placebo (n=167) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 4.6% Biguanides: 100% DPP-4 inhibitors: 2.6% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 19.4%	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicentre from China, Hong Kong, Republic of Korea, Philippines and Taiwan Sources of funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., USA, in collaboration with Pfizer Inc., USA. Several authors are employees of Merck Sharp and Dohme and Pfizer
Ji 2021A SUSTAIN China	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	Strategy: Adding N = 868 Semaglutide 0.5 mg (n=288) Semaglutide 1.0 mg (n=290) Sitagliptin (100 mg) (n=290) Concomitant therapy: Metformin Antihyperglycaemic treatment received:	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 8.1 months	Study location: 65 sites in Brazil, China, Hong Kong, Taiwan, Republic of Korea, South Africa and Ukraine Sources of funding: Trial was funded by Novo Nordisk A/S Denmark. Multiple authors

Study	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): 53.0333 (10.8072) years Time since type 2 diabetes diagnosed: 6.3667 (5.1702) years	Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 99.8% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		declare employment and funding from Novo Nordisk
Ji 2023	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): 60.2333 (8.2885) years Time since type 2 diabetes diagnosed: 14.6433 (7.2422) years	Strategy: Adding N = 219 Empagliflozin 10 mg (n=73) Empagliflozin 25 mg (n=73) Placebo (n=73) Concomitant therapy: Insulin Insulin ± up to 2 additional OADs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 29.7% Biguanides: 68% DPP-4 inhibitors: 5.9% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 8.7%	Acute kidney injury, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: 24 centres in China Sources of funding: Funded by Boehringer Ingelheim. Two of the authors are also employees of Boehringer Ingelheim.
Joubert 2021 EXEPUMP	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 46 Exenatide (n=28) Placebo (n=18)	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hospitalisation	Study location: Not clear, likely to be France Sources of

Study	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: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.5 (7.4024) years Time since type 2 diabetes diagnosed: 6.45 (5.8754) years	Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	funding: AstraZeneca
Kadowaki 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): 58.0667 (9.9449) years Time since type 2 diabetes	Strategy: Adding N = 181 Exenatide 5 ug (n=72) Exenatide 10 ug (n=73) Placebo (n=36) Concomitant therapy: SU monotherapy, combination therapy with SU and BG, or SU and TZD 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: Not stated/unclear SGLT-2 inhibitors:	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Japan Sources of funding: Amylin Pharmaceuticals and Eli Lilly and Company

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed:12.0 (6.5653) years	Not stated/unclear Sulfonylureas: 8.4%		
Kadowaki 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): 57.2 (9.2005) years Time since type 2 diabetes diagnosed: 7.42 (6.1522) years	Strategy: Adding N = 138 Canagliflozin (n=70) Placebo (n=68) Concomitant therapy: Teneligliptin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Mulitcentre Sources of funding: Mitsubishi Tanabe Pharma Corporation. Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Kaku 2009A	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	Strategy: Adding N = 169 Pioglitazone + Metformin (n=83) Placebo + Metformin (n=86) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change Follow up: 6.5 months	Study location: Japan Sources of funding: Takeda Pharmaceutical Co., Ltd

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 52.5 (8.0589) years Time since type 2 diabetes diagnosed: 5.05 (4.4098) years			
Kaku 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.6667 (10.347) years Time since type 2 diabetes diagnosed: 10.3333 (6.9814) years	Strategy: Adding N = 264 Liraglutide 0.6 mg (n=88) Liraglutide 0.9 mg (n=88) Placebo (n=88) Concomitant therapy: Sulfonylurea 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 69.7%	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Japan Sources of funding: Novo Nordisk Pharmaceuticals Ltd
Kaku 2019A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic	Strategy: Adding N = 819 Insulin degludec/liraglutide once daily (n=275) Degludec once daily (n=271) Liraglutide once daily (n=273) Concomitant therapy: OADs	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Japan Sources of funding: Novo Nordisk funded medical writing and editorial support. Two Novo Nordisk employees also provided review

Study	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): 57.1667 (10.0682) years Time since type 2 diabetes diagnosed: Not stated/unclear	aligned with Japanese clinical practice guidelines: α-glucosidase inhibitors; thiazolidinediones; sodium-glucose co-transporter-2 inhibitors; glinides; metformin; or sulfonylureas Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 40.7% Biguanides: 46.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 61% Sulfonylureas: 42.3%		and input to the manuscript.
Kanazawa 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 Mean age (SD): 66.5 (10) years Time since type 2 diabetes	Strategy: Adding N = 45 Pioglitazone (n=22) Metformin (n=23) Concomitant therapy: Insulin, Sulfonylurea, Alpha-glucosidase inhibitor Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 11.20% Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 55.5% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 24.5%	HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Shimane University Hospital, Japan Sources of funding: Supported by the Alumni Association of Shimane University School of Medicine and from the Ministry of Science, Education and Culture of Japan

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 13 (10.073) years			
Kaneto 2020 LixiLan JP-L	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): 66.5 (10) years Time since type 2 diabetes diagnosed: 13 (10.073) years	Strategy: Adding N = 512 IGlarLixi (n=255) Insulin glargine (n=257) Concomitant therapy: No additional information. Antihyperglycaemic treatment received: No additional information.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Japan Sources of funding: Sanofi
Kang 2021	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease	Strategy: Adding N = 159 Exenatide 10/20 mcg daily (n=79) Insulin glargine (n=80) Concomitant therapy: Metformin or sulfonylurea or both Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 29.6% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not	HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Chongqing, China Sources of funding: Supported by Project 2014YLC20 of the Xinqiao Hospital, and Project ctstc2015shmszx 120014 and ctstc2015jcsf100 03 of the Chongqing Science and Technology Commission.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 48.5 (9.0644) years Time since type 2 diabetes diagnosed: Not stated/unclear	stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 13.8%		
Kawamori 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.9 (10.2122) years Time since type 2 diabetes diagnosed: 8.85 (6.8491) years	Strategy: Adding N = 275 Empagliflozin (n=182) Placebo (n=93) Concomitant therapy: Linagliptin Antihyperglycaemic treatment received: No additional information available.	Cardiovascular mortality, Non-fatal stroke, Hospitalisation for heart failure, Acute kidney injury, Diabetic ketoacidosis, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 12 months	Study location: 40 sites in Japan Sources of funding: Funded by Boehringer Ingelheim and Eli Lilly and Company. Boehringer Ingelheim International GmbH and Nippon Boehringer Ingelheim Co. Ltd were involved in the study design, data collection, data analysis and preparation of the manuscript. A number of authors are employees of Boehringer Ingelheim and others disclose receiving multiple honoraria and funding grants from numerous pharmaceutical companies
Kellerer 2022 SUSTAIN 11	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and	Strategy: Adding N = 1748 Semaglutide (n=874) Insulin aspart (n=874) Concomitant therapy: Metformin. Antihyperglycaemic treatment received:	Health-related quality of life, All-cause mortality, Unstable angina, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change	Study location: Multicenter Sources of funding: Novo Nordisk A/S

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 61.2 (9.5) years Time since type 2 diabetes diagnosed: 13.4 (6.7) years	No additional information.	Follow up: 12 months	
Kendall 2005 Exendin-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: Not stated/unclear Mean age (SD): 55.3333 (9.6773) years Time since type 2 diabetes diagnosed: 8.9333 (6.1689) years	Strategy: Adding N = 733 Exenatide 20 mcg daily (n=241) Exenatide 10 mcg daily (n=245) Placebo (n=247) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6.9 months	Study location: USA (91 sites) Sources of funding: Supported by Amylin Pharmaceuticals, CA, USA and Eli Lilly, IN, USA.
Kesavadev 2017 SWIM	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 440 Glimepiride 1-3 mg daily (n=221)	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight	Study location: Kerala, India Sources of funding: Funded

Study	Population	Intervention and comparison	Outcomes	Comments
	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: Not stated/unclear Mean age (SD): 50.6 (7.2349) years Time since type 2 diabetes diagnosed: 15.315 (7.265) years	Sitagliptin 100 mg daily (n=219) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	change, BMI change Follow up: 12 months	by grant from Merck & Co., Inc.
Khaloo 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Adding N = 250 Pioglitazone 30 mg daily (n=125) Sitagliptin 100 mg daily (n=125) Concomitant therapy: Metformin + Gliclazide Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Vali-Asr Hospital, Tehran, Iran Sources of funding: Reports that study did not 'receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors'

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 61.75 (8.1502) years Time since type 2 diabetes diagnosed: 12.8 (6.5593) years			
Khan 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: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 50.85 (8.6026) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 120 Empagliflozin 10/20 mg daily (n=60) Vildagliptin 50/100 mg daily (n=60) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change Follow up: 5.5 months	Study location: Karachi, Pakistan Sources of funding: Sponsored by Primary Care Diabetes Association, Pakistan
Kim 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	Strategy: Switching N = 168 Glimepiride + metformin sustained release (n=86) Glimepiride + metformin immediate release (n=82) Concomitant therapy: None Antihyperglycaemic	Hypoglycaemia episodes, At night hypoglycaemic episodes Follow up: 5.5 months	Study location: 11 centres in the Republic of Korea Sources of funding: HANDOK Pharm aceuticals

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: Mixed population T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.8 (9.6119) years Time since type 2 diabetes diagnosed: 10.4 (6.8606) years	treatment received: No additional information available.		
Kim 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): 59.6 (9.757) years Time since type 2 diabetes diagnosed: 10.15 (7.5045) years	Strategy: Adding N = 135 Pioglitazone 15 mg daily (n=69) Glimepiride 2 mg daily (n=66) Concomitant therapy: Metformin + Alogliptin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: 100% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Falls requiring hospitalisation, Hypoglycaemia episodes, HbA1c change Follow up: 6 months	Study location: Korea Sources of funding: This study was funded by Takeda Pharmaceuticals Korea Co.
Kimura 2023 COMING	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not	Strategy: Adding N = 120 Dulaglutide (n=59) Semaglutide (n=61) Concomitant therapy: Various	Health-related quality of life, Hospitalisation for heart failure, Diabetic ketoacidosis, Progression of liver disease,	Study location: Japan Sources of funding: Supported by Research Project Grants from the

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.7 (10.7586) years Time since type 2 diabetes diagnosed: 13.9 (7.4176) years	previous treatments Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 3.8% Biguanides: 84.1% DPP-4 inhibitors: 75.60% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 64.4% Sulfonylureas: 22.4%	Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Kawasaki Medical School (R03B-058 and R04B-009).
Kinoshita 2020	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): 58.5667 years Time since type 2 diabetes diagnosed: 7.2333 years	Strategy: Adding N = 110 Pioglitazone 7.5-15 mg daily (n=36) Glimepiride 0.5-1 mg daily (n=34) Dapagliflozin 5 mg daily (n=40) Concomitant therapy: Background anti-diabetic drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 12.3% Biguanides: Not stated/unclear DPP-4 inhibitors: 66.2% GLP-1 receptor agonists: 1% Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6.5 months	Study location: Japan (7 hospitals) Sources of funding: Supported in part by Research Project Grant 29G-002, Kawasaki Medical School, Japan.
Kohan 2014	Model 3: People with type 2	Strategy: Adding N = 352	All-cause mortality,	Study location: 111 sites in

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 67 (8.4654) years Time since type 2 diabetes diagnosed: 16.9333 (9.5345) years	Dapagliflozin 5mg (n=83) Dapagliflozin 10mg (n=85) Placebo (n=184) Concomitant therapy: Antidiabetic drugs including insulin 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: 65.1% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 25%	Cardiovascular mortality, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	United States, Argentina, Canada, India, Mexico, Peru, Italy, Australia, France, Spain, Denmark, Puerto Rico, and Singapore. Sources of funding: Bristol-Myers Squibb and AstraZeneca-supported study
Komorizono 2020 J-LINK	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Adding N = 50 Linagliptin (n=25) Metformin (n=25) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, HbA1c change, Weight change Follow up: 12 months	Study location: 10 medical institutions in Kagoshima, Japan Sources of funding: Boehringer Ingelheim and Eli Lilly Company

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 52.5 (10.5043) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Kooy 2009 HOME	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): 61.5 (10.5093) years Time since type 2 diabetes diagnosed: 13 (8.5173) years	Strategy: Adding N = 390 Metformin (n=196) Placebo (n=194) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, HbA1c change, Weight change, BMI change Follow up: 52 months	Study location: 3 sites in the Netherlands Study location: 108 sites in 16 countries in Asia, Europe and North and South America Sources of funding: Supported by grants from Altana; Lifescan; E. Merck/Sante´; Merck, Sharpe, & Dohme; and Novo Nordisk
Kosiborod 2024	Model 1: People with type 2 diabetes and heart failure T2DM and atherosclerotic heart disease: Not stated/unclear T2DM and chronic kidney disease: not stated/unclear T2DM and higher cardiovascular	Strategy: Adding N = 616 Semaglutide 2.4 mg weekly (n=310) Placebo (n=306) Concomitant therapy: Pre-existing treatment Antihyperglycaemic treatment received: Alpha-glucosidase	All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Acute kidney injury, Hypoglycaemia, Severe hypoglycaemic episodes, HbA1c change, Weight change	Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: not stated/unclear Mean age (SD): not stated/unclear Time since type 2 diabetes diagnosed: not stated/unclear	inhibitors: Not stated/unclear Biguanides:71.9% DPP-4 inhibitors: 14.9% GLP-1 receptor agonists: 0% Insulin: 20.8% SGLT-2 inhibitors: 32.8% Sulfonylureas: 17.5%	Follow up: 12 months	
Kothny 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: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.2 (9.9989) years Time since type 2 diabetes diagnosed: 13.05 (7.4091) years	Strategy: Adding N = 449 Vildagliptin 50 mg daily (n=228) Placebo (n=221) Concomitant therapy: Insulin ± metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 61.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 60.6% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Multicentre trial conducted in Europe, Asia, Australia and Central America Sources of funding: Novartis Pharmaceuticals corporation for which two authors are also employees. Several authors declared honoraria for multiple pharmaceutical companies
Kothny 2015	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not	Strategy: Adding N = 148 Vildagliptin (n=83) Sitagliptin (n=65) Concomitant therapy: Pre-existing	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change	Study location: 6 centres in Brazil and 81 centres in the US Sources of funding: Novartis Pharma

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 66.8 (9.1593) years Time since type 2 diabetes diagnosed: 19.25 (10.2266) years	treatment 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: 61.7% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 10.8%	Follow up: 5.5 months	
Kovacs 2014 EMPA-REG PIO	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): 54.5 (9.7838) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 498 Empagliflozin 10 mg (n=165) Empagliflozin 25 mg (n=168) Placebo (n=165) Concomitant therapy: Pioglitazone ± Metformin 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 17.6 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim and Eli Lilly. A number of authors are employees of Boehringer Ingelheim

Study	Population	Intervention and comparison	Outcomes	Comments
Koyama 2014 PioRAGE	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 64.9 years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 63 Pioglitazone (n=31) Glimepiride (n=32) Concomitant therapy: Sulfonylurea or glinide or no treatment Antihyperglycaemic treatment received: No additional information available.	Non-fatal myocardial infarction, Non-fatal stroke, HbA1c change, Weight change Follow up: 5.5 months	Study location: Japan Sources of funding: Ministry of Education, Culture, Sports, Science and Technology, Japan.
Langenfeld 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular	Strategy: Adding N = 179 Pioglitazone 45 mg daily (n=92) Glimepiride 1-6 mg daily (n=87) Concomitant therapy: Background anti-diabetic drugs Antihyperglycaemic treatment received: No additional information available.	Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, BMI change Follow up: 5.5 months	Study location: Germany Sources of funding: Unrestricted grant from Takeda Pharma GmbH, Germany

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 62.5 (7.5307) years Time since type 2 diabetes diagnosed: 7.15 (7.2536) years			
Lavalle-Gonzalez 2013A	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 atherosclerotic cardiovascular disease T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.4 (9.5) years Time since type 2 diabetes diagnosed (SD): 6.9 (5.3) years	Strategy: Adding N = 1284 Canagliflozin 300mg (n=367) Canagliflozin 100mg (n=368) Sitagliptin (n=366) Placebo (n=183) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Janssen Research & Development, LLC
Lavalle-Gonzalez 2013B	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and	Strategy: Adding N = 1284 Canagliflozin 300mg (n=367) Canagliflozin 100mg (n=368) Sitagliptin (n=366) Placebo (n=183) Concomitant therapy: Metformin	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemia episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Janssen Research & Development, LLC

Study	Population	Intervention and comparison	Outcomes	Comments
	atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular disease T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.4 (9.5) years Time since type 2 diabetes diagnosed (SD): 6.9 (5.3) years	Antihyperglycaemic treatment received: No additional information available.		
Ledesma 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 72.4 (5.3558) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 302 Linagliptin 20 mg daily (n=151) Placebo (n=151) Concomitant therapy: Basal insulin 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: 28.00% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, 4-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Supported by Boehringer Ingelheim and Eli Lilly & Co. and the Diabetes Alliance.
Lee 2013B	Model 2: People with type 2	Strategy: Adding N = 121	All-cause mortality, Non-	Study location: South Korea

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 61.1 (9.145) years Time since type 2 diabetes diagnosed: 5.765 (6.7493) years	Pioglitazone 15 mg (n=60) Placebo (n=61) Concomitant therapy: pre-existing treatment: insulin , metformin , glimepride , sulfonylurea , α-glycosidase inhibitor Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 2.5% Biguanides: 34.80% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 10.00% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 61.20%	fatal myocardial infarction, HbA1c change Follow up: 12 months	Sources of funding: This study was supported by a grant from the Korean Heath Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A070001).
Lee 2022 DISTINCTION	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	Strategy: Adding N = 60 Dapagliflozin 10 mg daily (n=30) Sitagliptin 100 mg daily (n=30) Concomitant therapy: Insulin +/- metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear	Diabetic ketoacidosis, HbA1c change, Weight change Follow up: 5.5 months	Study location: Hong Kong, P.R. of China Sources of funding: Supported in part by funding from AstraZeneca, and from Endowment Fund awarded to Dr K.C.-B. Tan.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 58.75 (9.0529) years Time since type 2 diabetes diagnosed: 18.2 (9.0455) years	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Leiter 2014	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 63.75 (7.3055) years Time since type 2 diabetes diagnosed: 13.25 (8.3008) years	Strategy: Adding N = 962 Dapagliflozin 10 mg (n=480) Placebo (n=482) Concomitant therapy: Pre-existing treatment excluding rosiglitazone 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: 94.5% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Canada, Australia, Chile, Argentina, and five European countries (not specified) Sources of funding: Funded by Astra Zeneca and Bristol-Myers Squibb
Li 2014A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic	Strategy: Adding N = 203 Liraglutide (n=68) Saxagliptin (n=68) Vildagliptin (n=67) Concomitant therapy: Metformin ± sulfonylurea ± alpha-glucosidase inhibitor or thiazolidinedione Antihyperglycaemic	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Metabolic Disease Hospital of Tianjin Medical University, China Sources of funding: NR

Study	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): 47.1 (10.6557) years Time since type 2 diabetes diagnosed: 5.5333 (2.5818) years	treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 12.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 9.1%		
Li 2014B	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 46.6333 (10.2368) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 208 Saxagliptin (n=71) Vildagliptin (n=69) Sitagliptin (n=68) Concomitant therapy: Metformin + oral hypoglycaemic agent Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change Follow up: 5.5 months	Study location: Tianjin. China Sources of funding: Supported by the National Nature Science Foundation of China and grants from Tianjin Health Bureau Technology Fund

Study	Population	Intervention and comparison	Outcomes	Comments
Li 2014C	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.55 (12.3482) years Time since type 2 diabetes diagnosed: 15.5 (5.946) years	Strategy: Adding N = 56 Glimepiride (n=29) Insulin (higher doses) (n=27) Concomitant therapy: Continuation of insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 36.4% Biguanides: 49.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Tianjin, China Sources of funding: National Nature Science Foundation of China, Tianjin Health Bureau Technology, Science and Technology Development Foundation of Tianjin Advanced College
Li 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney	Strategy: Adding N = 33 Vildagliptin 50 mg twice daily (n=17) Placebo twice daily (n=16) Concomitant therapy: Insulin +/- Metformin Antihyperglycaemic treatment received: No additional information available.	Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: China Sources of funding: Science and Technology Support Program of Jiangsu Province (CN) (no. BL2014010) and by the China Postdoctoral Science Foundation (no. 2015M581829).

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.4 (8.3961) year years Time since type 2 diabetes diagnosed: Not stated/unclear			
Lind 2015 MDI Liraglutide	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): 40 (64.5653) years Time since type 2 diabetes diagnosed: 17.15 (7.8458) years	Strategy: Adding N = 124 Liraglutide 0.6 mg - 1.8 mg daily (n=64) Placebo (n=60) Concomitant therapy: Insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 71.00% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 100% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Sweden Sources of funding: NovoNordisk provided financial support and study drugs but did not play a role in the design and execution of the trial.
Lingvay 2016 DUAL V	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People	Strategy: Adding N = 557 Insulin Degludec/Liraglutide 50 U/1.8 mg once daily (n=278) Insulin glargine once daily (n=279)	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal stroke, HbA1c change, Weight change	Study location: Multicenter Sources of funding: NovoNordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	without heart failure T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.75 (9.5528) years Time since type 2 diabetes diagnosed: 11.485 (7.0271) years	Concomitant therapy: Insulin glargine + metformin Antihyperglycaemic treatment received: No additional information available.	Follow up: 6 months	
Lingvay 2019 SUSTAIN 8	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Mixed population T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.6 (10.9018)	Strategy: Adding N = 788 Semaglutide 1.0 mg once weekly (n=394) Canagliflozin 300 mg once daily (n=394) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 394% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	years Time since type 2 diabetes diagnosed: 7.35 (5.6555) years			
Liu 2013	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): 59.1 (8.6052) years Time since type 2 diabetes diagnosed: 7.8 (4.1049) years	Strategy: Adding N = 120 Pioglitazone 30 mg daily (n=60) Sitagliptin 100 mg daily (n=60) Concomitant therapy: Metformin or sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 91%	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Taiwan Sources of funding: The study was supported by the Mackay Memorial Hospital. The sponsor of the study was not directly involved in study design.
Liu 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	Strategy: Adding N = 106 Linagliptin (n=53) Empagliflozin (n=53) Concomitant therapy: Insulin +/- OAD Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Single centre Sources of funding: NR

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular risk: Not stated/unclear Mean age (SD): 58.55 (10.3005) years Time since type 2 diabetes diagnosed: 11.85 (6.1502) years	stated/unclear Insulin: 100% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Liutkus 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 Mean age (SD): 54.5 (8.3383) years Time since type 2 diabetes diagnosed: 6.35 (4.3341) years	Strategy: Adding N = 165 Exenatide 10 mcg twice daily (n=111) Placebo (n=54) Concomitant therapy: Metformin and thiazolidinedione 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: This study was sponsored by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company.
Ludvik 2018 AWARD-10	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular	Strategy: Adding N = 424 dulaglutide 1.5 mg (n=142) dulaglutide 0.75 mg (n=142) placebo (n=140) Concomitant therapy: SGLT2 inhibitor +/- metformin	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Unstable angina, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight	Study location: Austria, Czechia, Germany, Hungary, Israel, Mexico, Puerto Rico, Spain, United States Sources of funding: Eli Lilly and Company

Study	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): 57.2733 (9.3205) years Time since type 2 diabetes diagnosed: 9.3767 (6.1526) years	Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 95.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	change Follow up: 5.5 months	
Ludvik 2021 SURPASS-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: Not stated/unclear Mean age (SD): 57.45 (10.0253) years Time since type 2 diabetes diagnosed: 8.3 (6.2256) years	Strategy: Adding N = 1444 Tirzepatide (n=1079) Insulin degludec (n=365) Concomitant therapy: Metformin alone or in combination with an SGLT2 inhibitor Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 68% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, 4-point MACE, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multinational - Argentina, Austria, Greece, Hungary, Italy, Poland, Puerto Rico, Romania, South Korea, Spain, Taiwan, Ukraine, USA Sources of funding: Conducted by employees and shareholders of Eli Lilly and Company
Lukashevich 2011 moderate renal impairment	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 294 Moderate RI: Vildagliptin (n=165) Moderate RI:	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes	Study location: 108 centres worldwide Sources of funding: Four of

Study	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: Not stated/unclear Mean age (SD): 68.7 (8.1764) years Time since type 2 diabetes diagnosed: 15.1 (9.505) years	Placebo (n=129) Concomitant therapy: Untreated or treated with sulfonylurea, α glucosidase inhibitor, thiazolidinedione, insulin, meglitinide, or combination 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: 55.20% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Follow up: 52 months	the five authors are employees of Novartis. The remaining authors declares honoraria and funding from multiple pharmaceutical companies Lukashevic 2011 moderate renal impairment and severe renal impairment are the same study, just reporting different populations.
Lukashevich 2011 severe renal impairment	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): 64.3 (9.9331) years Time since type 2	Strategy: Adding N = 221 Severe RI: Vildagliptin (n=124) Severe RI: Placebo (n=97) Concomitant therapy: Untreated or treated with sulfonylurea, α glucosidase inhibitor, thiazolidinedione, insulin, meglitinide, or combination 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	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes Follow up: 52 months	Study location: 108 centres worldwide Sources of funding: Four of the five authors are employees of Novartis. The remaining authors declares honoraria and funding from multiple pharmaceutical companies Lukashevic 2011 moderate renal impairment and severe renal impairment are the same study, just reporting different populations.

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: 18.15 (9.052) years	Insulin: 69.1% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Lukashevich 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: Mixed population T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.15 (10.6623) years Time since type 2 diabetes diagnosed: 7.3 (6.1499) years	Strategy: Adding N = 318 Vildagliptin 50 mg (n=158) Placebo (n=160) Concomitant therapy: Metformin + glimepiride Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes Follow up: 5.5 months	Study location: Australia, Germany,Hungary, India, Italy, Mexico, Philippines, Romania Sources of funding: Novartis Pharmaceuticals Corporation
Lundby-Christensen 2016 CIMT	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	Strategy: Adding N = 412 Metformin (n=206) Placebo (n=206) Concomitant therapy: Insulin 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	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 18 months	Study location: Eight hospitals in the greater Copenhagen region Sources of funding: Novo Nordisk A/S. Numerous authors declare multiple funding and honoraria from numerous pharmaceutical companies

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular risk: Not stated/unclear Mean age (SD): 60.65 (8.9022) years Time since type 2 diabetes diagnosed: 12.85 (6.3518) years	Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 28.5%		
Macauley 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): 62.05 (1.2349) years Time since type 2 diabetes diagnosed: 5.7 (0.7) years	Strategy: Adding N = 44 Vildagliptin 50 mg twice daily (n=22) Placebo twice daily (n=22) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: UK Sources of funding: Novartis Pharma AG
Mahaffey 2018 CANVAS/CANVAS-R	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease Model 5: People with type 2 diabetes at higher	Strategy: Adding N = 10142 Canagliflozin (n=5795) Placebo (n=4347) Concomitant therapy: Monotherapy or combination therapy of any approved agent	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Persistent signs of worsening kidney disease, Development of	Study location: Multicenter Sources of funding: Supported by Janssen Research & Development, LLC. Medical writing support was funded by Janssen Global Services, LLC.

Study	Population	Intervention and comparison	Outcomes	Comments
	risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and 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 Includes results for a subgroup for people with or without heart failure and with atherosclerotic cardiovascular disease. Mean age (SD): 63.35 (8.2573) years Time since type 2 diabetes diagnosed: 13.6 (7.743) years	Antihyperglycaemic treatment received: No additional information available.	end stage kidney disease, Cardiac arrhythmia, HbA1c change, Weight change Follow up: 43 months	Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corp.
Marre 2009 LEAD-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	Strategy: Adding N = 809 Liraglutide 0.6 mg daily (n=233) Liraglutide 1.2 mg daily (n=228) Liraglutide 1.8 mg daily (n=234) Placebo daily (n=114) Concomitant therapy: Oral drugs Antihyperglycaemic treatment received: Alpha-glucosidase	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.925 (9.6989) years Time since type 2 diabetes diagnosed: Not stated/unclear	inhibitors: Not stated/unclear Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 202.20%		
Marso 2016A LEADER	Model 1: People with type 2 diabetes and heart failure 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: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Includes results for a subgroup for people with or without heart failure. Mean age (SD): 64.3 (7.2) years Time since type 2 diabetes diagnosed: 12.85 (8.0502) years	Strategy: Adding N = 9340 Liraglutide (n=4668) Placebo (n=4672) Concomitant therapy: One or more drugs, insulin, or combination Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 2.8% Biguanides: 76.40% DPP-4 inhibitors: 0.1% GLP-1 receptor agonists: 0.00% Insulin: 44.60% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 50.7%	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Death from renal causes, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 42 months	Study location: Multicenter Sources of funding: Novo Nordisk and the National Institutes of Health

Study	Population	Intervention and comparison	Outcomes	Comments
Marso 2016B SUSTAIN 6	Model 1: People with type 2 diabetes and heart failure 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 Includes results for a subgroup for people with or without heart failure. Mean age (SD): 64.625 (5.2152) years Time since type 2 diabetes diagnosed: 13.9 (5.7153) years	Strategy: Adding N = 6594 Semaglutide 0.5 mg (n=826) Semaglutide 1.0 mg (n=822) Placebo 0.5 mg (n=824) Placebo 1.0 mg (n=825) Semaglutide 0.5mg and 1.0mg combined (n=1648) Placebo 0.5mg and 1.0mg combined (n=1649) Concomitant therapy: No more than two oral hypoglycemic drugs ± basal or premixed insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 1.3% Biguanides: 73.2% DPP-4 inhibitors: 0.1% GLP-1 receptor agonists: Not stated/unclear Insulin: 58% SGLT-2 inhibitors: 0.1% Sulfonylureas: 42.8%	Health-related quality of life, All-cause mortality, Cardiovascular mortality, 3-point MACE, 5-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Cardiac arrhythmia, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 25.2 months	Study location: Multicenter Sources of funding: Novo Nordisk
Mathieu 2014 BEGIN: VICTOZA ADD-ON	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure	Strategy: Adding N = 177 Insulin degludec/Liraglutide (n=88) Insulin degludec/Insulin aspart (n=89) Concomitant therapy: Metformin	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multicenter Sources of funding: Novo Nordisk A/S

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular disease T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 61.0 (9.1) years Time since type 2 diabetes diagnosed (SD): 12.4 (6.5) years	Antihyperglycaemic treatment received: No additional information.	Follow up: 6 months	
Mathieu 2015A	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 atherosclerotic cardiovascular disease T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.8 (9.3) years Time since type 2 diabetes	Strategy: Adding N = 660 Sitagliptin (n=330) Placebo (n=330) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Merck & Co

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed (SD): 13.5 (6.2) years			
Mathieu 2015B	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): 55.1 (9.1) years Time since type 2 diabetes diagnosed (SD): 7.6 (6.2) years	Strategy: Adding N = 320 Dapagliflozin (n=160) Placebo (n=160) Concomitant therapy: Saxagliptin + Metformin Antihyperglycaemic treatment received: No additional information.	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 6 months	Study location: Multicenter Sources of funding: Bristol-Myers Squibb and AstraZeneca.
Matthaei 2015A	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	Strategy: Adding N = 315 Saxagliptin 5 mg daily (n=153) Placebo daily (n=162) Concomitant therapy: Metformin + dapagliflozin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: USA Puerto Rico, Canada, R omania, Russia, Poland, Czech Republic, Mexico . Hungary Sources of funding: Bristol-Myers Squibb and Astra Zeneca

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 54.6 (9.5461) years Time since type 2 diabetes diagnosed: 7.75 (6.4109) years			
Matthaei 2015B	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): 61 (9.4533) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 218 Dapagliflozin 10 mg daily (n=109) Placebo (n=109) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: North America (Canada) and Europe (Czech Republic, Germany, Poland, Slovak Republic, and Spain) Sources of funding: Bristol-Myers Squibb and AstraZeneca
Matthews 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: Not stated/unclear T2DM and	Strategy: Adding N = 632 Pioglitazone 15-45 mg daily (n=319) Gliclazide 80-320 mg daily (n=313) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: International (75 centres in Australia, Bulgaria, Czech Republic, France, Germany, Greece, Latvia, Poland, Romania, Turkey) Sources of funding: Takeda Europe R&D Centre and Eli

Study	Population	Intervention and comparison	Outcomes	Comments
	chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.5 (9.1015) years Time since type 2 diabetes diagnosed: 5.65 (5.1) years			Lilly and Company, USA
Matthews 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Mixed population T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.5 (9.1301) years Time since type 2 diabetes diagnosed: 5.7 (5.1012) years	Strategy: Adding N = 3118 Glimepiride 2-6 mg (n=1556) Vildagliptin 50 mg (n=1562) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 1559% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: The study was conducted in 402 sites. Sources of funding: Novartis Pharmaceutical Corporation
Mattoo 2005	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 289 Pioglitazone 30 mg daily (n=142) Placebo (n=147)	All-cause mortality, Hypoglycaemia episodes, HbA1c change, Weight change	Study location: Not available Sources of funding: Sponsored by Eli

Study	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: Not stated/unclear Mean age (SD): 58.85 (6.6792) years Time since type 2 diabetes diagnosed: 162.15 (77.3725) months	Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	Follow up: 6 months	Lilly and Company, Indianapolis, Indiana, and Takeda Europe R&D Centre, London, United Kingdom.
Mazzone 2006 CHICAGO	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): 59.6 (8.1002) years Time since type 2	Strategy: Adding N = 462 Pioglitazone 15 - 45 mg daily (n=232) Glimepiride 1-4 mg daily (n=230) Concomitant therapy: Metformin ± sulfonylurea ± insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 70.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 29% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 76%	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, Weight change Follow up: 18 months	Study location: US, Chicago at 28 clinical sites. Sources of funding: Takeda Pharmaceuticals North America Inc, Lincolnshire, Ill, sponsored and funded this study and provided the study drugs.

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: 7.75 (7.2128) years			
McCluskey 2004	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): 55.5 (8.5493) years Time since type 2 diabetes diagnosed: 5.9 (7.403) years	Strategy: Adding N = 40 Glimepiride 2-8 mg daily (n=25) Placebo daily (n=15) Concomitant therapy: Rosiglitazone Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 7 months	Study location: US (17 sites) Sources of funding: No additional information.
McGuire 2025	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	Strategy: Adding N = 9650 Semaglutide (n=4825) Placebo (n=4825) Concomitant therapy: Metformin 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: Not	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Unstable angina, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 47.5 months	Study location: 33 countries in Africa, Asia, Europe, Latin and North America, and the Middle East Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 66.1 (7.6) years Time since type 2 diabetes diagnosed: 15.4 (8.8) years	stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
McGill 2013	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 64.45 (10.2854) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 133 Linagliptin (n=68) Placebo (n=65) Concomitant therapy: Insulin, sulfonylurea, glinides, pioglitazone, and α-glucosidase inhibitors 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: 64.1% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 12%	All-cause mortality, Non-fatal myocardial infarction, Non-fatal stroke, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim
McMurray 2018 VIVIDD	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	Strategy: Adding N = 254 Vildagliptin (n=128) Placebo (n=126) Concomitant therapy: Drug therapy, if any Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 2% Biguanides: 34.6% DPP-4 inhibitors: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hospitalisation for heart failure, Cardiac arrhythmia, Hypoglycaemia episodes, HbA1c change Follow up: 12 months	Study location: Czechia, Denmark, Estonia, Germany, Greece, Guatemala, India, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Singapore, Slovakia [Taken from Clinicaltials.gov]

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 63.15 (9.3818) years Time since type 2 diabetes diagnosed: 9.3 (7.9526) years	GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 50.00%		Sources of funding: Novartis
Meneghini 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 52.35 (10.1997) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 247 Pioglitazone 15 mg - 45 mg daily (n=126) Insulin glargine titrated (n=121) Concomitant therapy: Metformin or sulfonylurea 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 26%	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 11 months	Study location: US Sources of funding: One of the authors is employed by Sanofi Aventis group and editorial support was also provided by the Sanofi Aventis U.S. group which suggests that they provided at least some funding towards the study.
Meneilly 2017 GetGoal-O	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 350 Lixisenatide (n=176) Placebo (n=174) Concomitant therapy: Permitted	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic	Study location: Multicenter Sources of funding: Sanofi. Numerous authors declare funding and

Study	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: Not stated/unclear Mean age (SD): 74.2 (3.9019) years Time since type 2 diabetes diagnosed: 14.1 (7.6042) years	therapies were metformin, sulfonylurea (except glibenclamide >10 mg and gliclazide >160 mg), meglitininde (excet repaglinide >6 mg), pioglitazone, and basal insulin) Antihyperglycaemic treatment received: No additional information available.	episodes, HbA1c change, Weight change Follow up: 5.5 months	honoraria from multiple pharmaceutical companies
Miras 2019 GRAVITAS	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 (8.9876) years Time since type 2 diabetes diagnosed: 18 (7.3485) years	Strategy: Adding N = 80 Liraglutide (n=53) Placebo (n=27) Concomitant therapy: Oral glucose lowering agents and or insulin 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: 25% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Health-related quality of life, All-cause mortality, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: London, UK Sources of funding: JP Moulton Charitable Foundation. Liraglutide and Placebo pens provided by Novo Nordisk. Multiple authors declare funding and honoraria from numerous pharmaceutical companies
Moeinzadeh 2021	Model 3: People with type 2	Strategy: Adding N = 136	HbA1c change, Weight change	Study location: Iran

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60.11 (12.986) years Time since type 2 diabetes diagnosed:Not stated/unclear	Linagliptin (n=68) Placebo (n=68) Concomitant therapy: Current glucose-lowering drugs 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: 19.80% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Follow up: 6 months	Sources of funding: NR
Moon 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): 53.1 (8.3435) years	Strategy: Adding N = 75 Glimepiride 1-8 mg daily (n=36) Insulin glargine daily (n=39) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 11 months	Study location: Korea Sources of funding: NR

Study	Population	Intervention and comparison	Outcomes	Comments
	Time since type 2 diabetes diagnosed: 87.3 (66.0836) months			
Morikawa 2011 APRIME	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.45 (1.6593) years Time since type 2 diabetes diagnosed: 10.55 (1.1573) years	Strategy: Adding N = 63 Pioglitazone (n=32) Metformin (n=31) Concomitant therapy: Insulin or oral hypoglycemic agents other than thiazolidinediones/metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 19% Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 62.00%	All-cause mortality, Unstable angina, Persistent signs of worsening kidney disease, HbA1c change Follow up: 12 months	Study location: Japan Sources of funding: Takeda Pharmaceutical Company, Japan
Mosenzon 2019 PIONEER 5	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney	Strategy: Adding N = 324 Semaglutide (n=163) Placebo (n=161) Concomitant therapy: Metformin, a sulfonylurea, or both; or basal insulin with or without metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 74.60%	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change	Study location: 88 sites in Denmark, Finland, Israel, Poland, Russia, Sweden, the UK, and the USA Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 70.5 (8) years Time since type 2 diabetes diagnosed: 14 (8.0262) years	DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 40.40%	Follow up: 6 months	
Moses 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): 57 (10.589) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 257 Saxagliptin 5 mg daily (n=129) Placebo daily (n=128) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Bristol-Myers Squibb and Astra Zeneca
Moses 2017	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear	Strategy: Adding N = 427 Sitagliptin 100 mg daily (n=213) Placebo once daily (n=214) Concomitant therapy: Metformin + glimepiride/gliclazide	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: USA Sources of funding: Merck & Co., Inc. (Kenilworth, NJ, USA).

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.9 (9.9052) years Time since type 2 diabetes diagnosed: 7.75 (5.3501) years	Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	
Muller-Wieland 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.4 (8.5909) years Time since type 2	Strategy: Adding N = 939 Dapagliflozin (n=314) Dapagliflozin + Saxagliptin (n=312) Glimepiride (n=313) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: 194 centres in Germany, the Czech Republic, Hungary, Poland and Slovakia Sources of funding: AstraZeneca; Numerous authors declare honoraria and funding from multiple pharmaceutical companies.

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: 6.9667 (5.4109) years			
Nahra 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): 56.4 (9.6498) years Time since type 2 diabetes diagnosed: 7.6 (5.5722) years	Strategy: Adding N = 222 Liraglutide (n=110) Placebo (n=112) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, HbA1c change, Weight change Follow up: 12.5 months	Study location: Multicenter Sources of funding: AstraZeneca. A number of authors are also employees of AstraZeneca
Nakaguchi 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	Strategy: Adding N = 61 Liraglutide (n=30) Empagliflozin (n=31) Concomitant therapy: Insulin +/- OAD Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 22.80% Biguanides: 37.60% DPP-4 inhibitors: 42.7% GLP-1 receptor agonists: Not stated/unclear Insulin: 100% SGLT-2 inhibitors:	Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Yokahama Japan Sources of funding: Self-procurement with no subsidy

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 66.75 (9.2576) years Time since type 2 diabetes diagnosed: 18.9 (10.0022) years	Not stated/unclear Sulfonylureas: 1.60%		
Nauck 2007A	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): 58.5 (9) years Time since type 2 diabetes diagnosed: 9.9 (6.2507) years	Strategy: Adding N = 501 Exenatide (n=253) Insulin (n=248) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Industry initiated study. A number of authors are employees of Eli Lilly and Amlyn Pharmaceuticals or declare funding and / or honoraria from Eli Lilly and Amlyn Pharmaceuticals
Nauck 2007B Sitagliptin 024	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	Strategy: Adding N = 1172 Sitagliptin (n=588) Glipizide (n=584) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Multinational study Sources of funding: Merck & Co.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.7 (9.5524) years Time since type 2 diabetes diagnosed: 6.35 (5.7618) years			
Nauck 2009A	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): 55 (11) years Time since type 2 diabetes diagnosed: 6 (4.6271) years	Strategy: Adding N = 527 Alogliptin 12.5 mg (n=213) Alogliptin 25 mg (n=210) Placebo (n=104) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Takeda Global Research and Development Center, Inc. A number of authors are employees of Takeda Global Research and Development Center, Inc. The primary author declares honoraria from numerous pharmaceutical companies
Nauck 2009B LEAD-2	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 1091 Liraglutide 0.6 mg (n=242) Liraglutide 1.2 mg (n=241) Liraglutide 1.8 mg (n=242)	Death from renal causes, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change	Study location: Multicenter Sources of funding: A number of authors were supported by Novo Nordisk.

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 56.75 (8.9876) years Time since type 2 diabetes diagnosed: 7.5 (4.7111) years	Glimepiride (n=244) Placebo (n=122) Concomitant therapy: Metformin +/- OADs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 31.2% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 3.8%	Follow up: 24 months	Numerous authors declare funding and honoraria
Nauck 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.5 (9.5144) years Time since type 2 diabetes	Strategy: Adding N = 814 Dapagliflozin (n=406) Glipizide (n=408) Concomitant therapy: Metformin ± oral agent Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 66.40% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 48 months	Study location: Multicenter Sources of funding: Supported by AstraZeneca and Bristol-Myers Squibb

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 6.5 (5.5239) years			
Nauck 2014 Dulaglutide v Placebo AWARD-5	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): 54.25 (9.846) year years Time since type 2 diabetes diagnosed: 7 (5.2959) years	Strategy: Adding N = 1098 Dulaglutide 1.5 mg weekly (n=304) Dulaglutide 0.75 mg weekly (n=302) Sitagliptin 100 mg daily (n=315) Placebo daily (n=177) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Severe hypoglycaemic episodes, HbA1c change Follow up: 24 months	Study location: US, Canada, France, Germany, India, Korea, Mexico, Poland, Puerto Rico, Romania, Russian, Spain and Taiwan. Sources of funding: Eli Lilly and company
Nauck 2016B	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	Strategy: Adding N = 404 Liraglutide (n=202) Lixisenatide (n=202) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear	Cardiac arrhythmia, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Sponsored by Novo Nordisk A/S

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 56.2 (10.3044) years Time since type 2 diabetes diagnosed: 6.4 (5.1522) years	Sulfonylureas: Not stated/unclear		
Nesti 2022 EMPA-HEART	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 61.7 (9.8624) years Time since type 2 diabetes diagnosed: 9.45 (7.9421) years	Strategy: Adding N = 56 Empagliflozin (n=27) Sitagliptin (n=29) Concomitant therapy: Metformin and or basal insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 91% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 28.5% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change, Weight change Follow up: 6 months	Study location: Single centre in Pisa, Italy. Sources of funding: Supported at 49% by an unrestricted grant from Boehringer Ingelheim
Ning 2016	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure T2DM and	Strategy: Adding N = 293 Vildagliptin (n=146) Placebo (n=147) Concomitant therapy: Metformin ± insulin Antihyperglycaemic treatment received: Alpha-glucosidase	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: 22 centres in China, Thailand, Philippines, and Singapore Sources of funding: Novartis Pharma AG (Basel, Switzerland). Five authors were also employed by

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 58.1 (9.3542) years Time since type 2 diabetes diagnosed: 11.3 (7.0054) years	inhibitors: Not stated/unclear Biguanides: 71.00% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		Novartis and may be eligible for Novartis stock and stock options
Nissen 2008 PERISCOPE	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.85 (9.252) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 543 Glimepiride (n=273) Pioglitazone (n=270) Concomitant therapy: 1-2 oral drugs excluding thiazolidinedione Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 64.40% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 20.6% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, 3-point MACE, 5-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 18 months	Study location: Multicenter trial. Sources of funding: Financially supported by Takeda Pharmaceuticals North America Inc.
Nogueira 2014	Model 5: People with type 2	Strategy: Adding N = 35	HbA1c change, Weight change,	Study location: Unclear- appears

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 56.75 (6.7977) years Time since type 2 diabetes diagnosed: 10.9 (6.6785)	Sitagliptin (n=18) Insulin NPH (n=17) Concomitant therapy: Metformin; Glyburide Antihyperglycaemic treatment received: No additional information available.	BMI change Follow up: 5.5 months	to be Brazil Sources of funding: grants from Fundação de Amparo à Pesquisa do Estado de São Paulo. (FAPESP)
Nowicki 2011A	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 66.5 (8.7092) years	Strategy: Adding N = 170 Saxagliptin (n=85) Placebo (n=85) Concomitant therapy: Excluded metformin therapy, and previous or current DPP-4 inhibitor or GLP1 receptor agonist 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: 75.3% SGLT-2 inhibitors:	All-cause mortality, Development of end stage kidney disease, Hypoglycaemia episodes, HbA1c change Follow up: 12 months	Study location: Multi-centre - Belarus, Croatia, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Ukraine, USA Sources of funding: Bristol-Myers Squibb and AstraZeneca

Study	Population	Intervention and comparison	Outcomes	Comments
	Time since type 2 diabetes diagnosed: 16.65 (8.0156) years	Not stated/unclear Sulfonylureas: 25.3%		
Oh 2021 ELITE	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 64.95 (8.4296) years Time since type 2 diabetes diagnosed: 74.2 (69.9855) months	Strategy: Adding N = 97 Empagliflozin 10 mg (n=48) Sitagliptin 100 mg (n=49) Concomitant therapy: Metformin, sulfonylurea, pioglitazone Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 67% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 33%	HbA1c change, Weight change Follow up: 6 months	Study location: South Korea Sources of funding: No information available.
Ohira 2014A	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	Strategy: Adding N = 60 Pioglitazone (n=30) Glimepiride (n=30) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Not available Sources of funding: NR

Study	Population	Intervention and comparison	Outcomes	Comments
	chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.965 (10.3284) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Ohira 2014B	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): 60.37 (11.6992) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 70 Sitagliptin + metformin (n=35) Metformin (n=35) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Japan Sources of funding: NR
Owens 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Strategy: Adding N = 1058 Linagliptin (n=793) Placebo (n=265) Concomitant therapy: Metformin + sulfonylurea	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim

Study	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): 57.95 (9.8504) years Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: No additional information available.		
Pan 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.1333 (9.7696) years Time since type 2 diabetes diagnosed: 5.03 (4.6019) years	Strategy: Adding N = 438 Vildagliptin 50 mg qd (n=148) Vildagliptin 50 mg bid (n=146) Placebo (n=144) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Multicentre trial in China Sources of funding: Novartis Beijing

Study	Population	Intervention and comparison	Outcomes	Comments
Pan 2014 GetGoal-M-Asia	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 Mean age (SD): 54.8 (10.4002) years Time since type 2 diabetes diagnosed: 6.65 (4.7008) years	Strategy: Adding N = 391 Lixisenatide 20 mcg daily (n=196) Placebo (n=195) Concomitant therapy: Metformin ± sulfonylurea 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: 5.5 months	Study location: Multicenter Sources of funding: Funded by Sanofi, France.
Papathanassiou 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease	Strategy: Adding N = 28 Pioglitazone 30 mg daily (n=14) Glimepiride 4 mg daily (n=14) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Ioannina, Greece Sources of funding: Funded in part by Michaelidion Cardiac Center, University of Ioannina, Ioannina, Greece

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 63.2 (7.2502) years Time since type 2 diabetes diagnosed: 5.3 (5.254) years			
Park 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.7 (8.1994) years Time since type 2 diabetes diagnosed: 5 (5.1499) years	Strategy: Adding N = 67 Pioglitazone 15 mg daily (n=34) Metformin 1000 mg daily (n=33) Concomitant therapy: Glimepiride or other sulfonylurea Antihyperglycaemic treatment received: No additional information available.	HbA1c change, BMI change Follow up: 5.5 months	Study location: Seoul, South Korea Sources of funding: Supported by Faculty research grant of Yonsei University College of Medicine for 2007 and Yonsei University College of Medicine, Internal Medicine Research Grant 2007.
Park 2014	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and	Strategy: Adding N = 99 Metformin (n=33) Glimepiride (n=34) Metformin + Glimepiride (n=32) Concomitant therapy: Insulin glargine	Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multicentre trial in Korea Sources of funding: Sanofi-Korea

Study	Population	Intervention and comparison	Outcomes	Comments
	atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: No information Mean age (SD): 56.6333 (10.2084) years Time since type 2 diabetes diagnosed: 12 (6.6126) years	Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	
Park 2023 BEYOND	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): 55.15 (9.1512) years Time since type 2 diabetes diagnosed: 6.25 (4.8503) years	Strategy: Adding N = 124 Dapagliflozin (n=62) Glimepiride (n=62) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: 14 centres in Korea Sources of funding: AstraZeneca
Pasquel 2021	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 287 Liraglutide (n=140) Insulin glargine	All-cause mortality, Acute kidney injury, Hypoglycaemia episodes, Severe	Study location: United States Sources of

Study	Population	Intervention and comparison	Outcomes	Comments
	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 (10.4056) years Time since type 2 diabetes diagnosed: 9.65 (8.4909) years	(n=147) Concomitant therapy: Existing antidiabetic treatment 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: 15% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	funding: Novo Nordisk
Perkovic 2019 CREDENCE	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 without heart failure T2DM and atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Includes results for a subgroup for people with or	Strategy: Adding N = 4401 Canagliflozin (n=2202) Placebo (n=2199) Concomitant therapy: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, 3-point MACE, 5-point MACE, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Death from renal causes, Diabetic ketoacidosis, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 31.44 months	Study location: Multicenter Sources of funding: Janssen Research & Development, LLC

Study	Population	Intervention and comparison	Outcomes	Comments
	without heart failure. Mean age (SD): 63.05 (9.2) years Time since type 2 diabetes diagnosed: 15.75 (8.6502) years			
Perkovic 2024 FLOW	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 66.7 (9.0) years Time since type 2 diabetes diagnosed: Majority at 15 years and greater	Strategy: Adding N = 3533 Semaglutide (subcutaneous) (n=1767) Placebo (n=1766) Concomitant therapy: Renin-angiotensin system inhibitor (antihypertensive). Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 51.9% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 61.3% SGLT-2 inhibitors: 15.6% Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Death from renal causes, Cardiac arrhythmia, Diabetic ketoacidosis, Severe hypoglycaemic episodes, HbA1c change, Weight Change Follow up: 40.8 months	Study location: Multicenter Sources of funding: Novo Nordisk.
Pei 2021 DUAL II China	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	Strategy: Adding N = 453 IDegLira (n=302) Insulin degludec (n=151) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: China and Hong Kong Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.8 (9.9) years Time since type 2 diabetes diagnosed: 11.5 (6.0) years			
Petrica 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 Mean age (SD): 57.85 (7.1415) years Time since type 2 diabetes diagnosed: 10.085 (4.4597) years	Strategy: Adding N = 78 Pioglitazone (n=39) Glimepiride (n=39) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change, BMI change Follow up: 12 months	Study location: Department of Diabetes and Metabolic Diseases, Romania Sources of funding: NR
Pfützner 2005 PIONEER	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People	Strategy: Adding N = 173 Pioglitazone (n=89) Glimepiride (n=84) Concomitant therapy: Any oral antidiabetic excluding	Hospitalisation for heart failure, Severe hypoglycaemic episodes, HbA1c change, BMI change Follow up: 6 months	Study location: Clinical Department of the Institute for Clinical Research and Development, Mainz, Germany Sources of

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 62.6 (7.9304) years Time since type 2 diabetes diagnosed: 7.15 (7.2543) years	thiazolidinedione treatment for the pioglitazone arm and metformin for the glimepiride arm Antihyperglycaemic treatment received: No additional information available.		funding: Takeda Pharma, Germany. A number of authors declare funding and honoraria from Takeda Pharma.
Pfützner 2011B PIOfix	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): 62.6 (7.9304) years Time since type 2 diabetes diagnosed: 7.15 (7.2543) years	Strategy: Adding N = 288 Pioglitazone + Metformin (n=146) Glimepiride + Metformin (n=142) Concomitant therapy: No additional information. Antihyperglycaemic treatment received: No additional information available.	Hospitalisation for heart failure, Acute kidney injury, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Germany Sources of funding: Takeda Pharma.

Study	Population	Intervention and comparison	Outcomes	Comments
Pfeffer 2015 ELIXA	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic 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 Includes results for a subgroup for people with or without heart failure. Mean age (SD): 60.25 (9.6501) years Time since type 2 diabetes diagnosed: 9.3 (8.2502) years	Strategy: Adding N = 6068 Lixisenatide (n=3034) Placebo (n=3034) Concomitant therapy: Antidiabetic medications with the exception of other incretin therapies Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 66.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 39.1% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 33.00%	All-cause mortality, Cardiovascular mortality, 4-point MACE, 5-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 25 months	Study location: Multicenter Sources of funding: Funded by Sanofi
Philis-Tsimikas 2013 BEGIN	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 458 Sitagliptin 100 mg daily (n=229) Insulin degludec 100 U/mL daily (n=229) Concomitant	All-cause mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Multicenter Sources of funding: Funded by Novo Nordisk, A/S, Denmark.

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 55.65 (10.8167) years Time since type 2 diabetes diagnosed: 7.75 (6.0519) years	therapy: Background oral antidiabetic drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 25.00% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	change, Weight change Follow up: 6 months	
Philis-Tsimikas 2019 DUAL IX	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): 56.65 (10.3005) years Time since type 2 diabetes diagnosed: 9.55 (6.2502) years	Strategy: Adding N = 420 Insulin degludec/liraglutide daily titrated (n=210) Insulin glargine U100 daily titrated (n=210) Concomitant therapy: SGLT2 inhibitor ± other oral antidiabetic drugs Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Acute kidney injury, Persistent signs of worsening kidney disease, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Sponsored by Novo Nordisk, A/D, Denmark.
Phrommintikul 2019	Model 2: People with type 2	Strategy: Adding Dapagliflozin 10 mg	All-cause mortality,	Study location: Thailand

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic 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): 63.22 (7.91) years Time since type 2 diabetes diagnosed: Not stated/unclear	(n=25) Vildagliptin 50 - 100 mg (n=24) Concomitant therapy: Metformin and or sulfonylurea and or thiazoledinedione Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 89.80% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 75.4%	Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Sources of funding: Thailand research fund
Pieber 2019 PIONEER 7	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	Strategy: Adding N = 504 Semaglutide 3-14 mg daily (n=253) Sitagliptin 100 mg daily (n=251) Concomitant therapy: One or two glucose-lowering drugs (metformin, sulfonylureas, sodium glucose co-transporter-2 [SGLT2] inhibitors, or thiazolidinediones) Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Acute kidney injury, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicenter Sources of funding: Funded by Novo Nordisk A/S, Denmark.

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Mean age (SD): 57.4 (9.9012) years Time since type 2 diabetes diagnosed: 8.8 (6.2504) years	stated/unclear Biguanides: 37.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 0.7% Sulfonylureas: 1.5%		
Pinget 2013 GetGoal-P	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): 55.65 (9.5) years Time since type 2 diabetes diagnosed: 8.1 (5.4672)	Strategy: Adding N = 484 Lixisenatide 80 mcg daily (n=323) Placebo (n=161) Concomitant therapy: Pioglitazone ± metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 81% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Sanofi
Pollock 2019 DELIGHT	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and	Strategy: Adding N = 448 Dapagliflozin + Saxagliptin (n=155) Dapagliflozin (n=145) Placebo (n=148) Concomitant therapy: Stable glucose-lowering therapy Antihyperglycaemic	All-cause mortality, Persistent signs of worsening kidney disease, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multi-centre, multi-national study conducted at 116 research centres in Australia, Canada, Japan, South Korea, Mexico, South Africa, Spain, Taiwan and the USA. Sources of

Study	Population	Intervention and comparison	Outcomes	Comments
	chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 64.4667 (8.7802) years Time since type 2 diabetes diagnosed: Not stated/unclear	treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 60.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 71.3% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 32.7%	Follow up: 5.5 months	funding: Astra Zeneca
Pozzilli 2017 AWARD-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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60.4 (9.8046) years Time since type 2 diabetes diagnosed: 13.15 (7.6007) years	Strategy: Adding N = 300 Dulaglutide 1.5 mg weekly (n=150) Placebo (n=150) Concomitant therapy: Insulin glargine ± metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 88.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6.5 months	Study location: International (Czech Republic, Hungary, Italy, Puerto Rico, UK, USA Sources of funding: Sponsored by Eli Lilly and Co., Indianapolis, IN, USA.
Pratley 2009A Alogliptin Study 009	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 493 Alogliptin 12.5 mg (n=197) Alogliptin 25 mg (n=199) Placebo (n=97)	All-cause mortality, Non-fatal myocardial infarction, Hospitalisation for heart failure, Hypoglycaemia episodes, Weight change	Study location: 125 sites in the regions of United States, Western Europe, Australia and New Zealand, Latin America, plus Hungary, India

Study	Population	Intervention and comparison	Outcomes	Comments
	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: No information Mean age (SD): 55.3667 (10.0118) years Time since type 2 diabetes diagnosed: 7.6333 (5.7552) years	Concomitant therapy: Thiazolidinedione ± metformin and or sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 56.4% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 20.7%	Follow up: 6 months	and South Africa Sources of funding: Financial support provided by Takeda Global Research and Development Center, Inc,. USA.
Pratley 2009B Alogliptin Study 007	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): 56.7 (11.138) years Time since type 2 diabetes diagnosed: 7.7 (5.9103) years	Strategy: Adding N = 500 Alogliptin 12.5 mg (n=203) Alogliptin 25 mg (n=198) Placebo (n=99) Concomitant therapy: Sulfonylurea 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: Argentina, Australia, Brazil, Chile, Dominican Republic, Guatemala, India, Mexico, Netherlands, New Zealand, Peru, Poland, South Africa, United Kingdom, United States Sources of funding: Takeda

Study	Population	Intervention and comparison	Outcomes	Comments
Pratley 2010 1860-LIRA-DPP-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: Not stated/unclear Mean age (SD): 55.3 (9.24) years Time since type 2 diabetes diagnosed: 6.2333 (5.1132) years	Strategy: Adding N = 665 Liraglutide 1.2 mg (n=225) Liraglutide 1.8 mg (n=221) Sitagliptin (n=219) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Funded by Novo Nordisk, Denmark. Numerous authors declare funding and honoraria from numerous pharmaceutical companies
Pratley 2018A VERTIS FACTORIAL	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	Strategy: Adding N = 1233 Ertugliflozin 5 mg (n=250) Ertugliflozin 15 mg (n=248) Sitagliptin 100 mg (n=247) Ertugliflozin 5 mg + Sitagliptin 100 mg (n=243) Ertugliflozin 15 mg + Sitagliptin 100 mg (n=245) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc and Pfizer Inc.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 55.1 (9.1115) years Time since type 2 diabetes diagnosed: 6.9 (5.36) years			
Pratley 2018B SUSTAIN 7	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): 55.5 (10.6267) years Time since type 2 diabetes diagnosed: 7.4 (5.6771) years	Strategy: Adding N = 1201 Semaglutide 0.5 mg (n=301) Dulaglutide 0.75 mg (n=300) Semaglutide 1.0 mg (n=300) Dulaglutide 1.5 mg (n=300) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 10.5 months	Study location: Multicenter Sources of funding: Novo Nordisk. Numerous authors declare honoraria and funding from multiple pharmaceutical companies
Pratley 2019 PIONEER 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	Strategy: Adding N = 711 Semaglutide (n=285) Liraglutide (n=284) Placebo (n=142) Concomitant therapy: Metfomin ± SGLT2 inhibitor Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Acute kidney injury, Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicenter Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.3333 (10) years Time since type 2 diabetes diagnosed: 7.6333 (5.5032) years			
Punthakee 2012 TIDE	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): 66.35 (6.7167) years Time since type 2 diabetes diagnosed: 8.6 (6.6) years	Strategy: Adding N = 933 Pioglitazone (n=392) Placebo (n=541) Concomitant therapy: Two or fewer glucose-lowering drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 81% DPP-4 inhibitors: 2.4% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 47%	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Persistent signs of worsening kidney disease, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.4 months	Study location: Multicenter Sources of funding: GlaxoSmithKline
Raman 2022	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart	Strategy: Adding N = 107 Empagliflozin + insulin (n=52) Linagliptin + insulin (n=55)	Hypoglycaemia episodes, HbA1c change Follow up: 12 months	Study location: Eastern India Sources of funding: Unclear. Statement that the authors

Study	Population	Intervention and comparison	Outcomes	Comments
	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: Not stated/unclear Mean age (SD): 62.45 (7.4943) years Time since type 2 diabetes diagnosed: 13.415 (5.5487) years	Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.		received no financial support for the research, authorship, and /or publication of this article.
Raz 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): 54.85 (9.5) years Time since type 2 diabetes diagnosed: 7.85 (5.9368) years	Strategy: Adding N = 190 Sitagliptin (n=96) Placebo (n=94) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 52.1% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change Follow up: 6.9 months	Study location: Multinational trial Sources of funding: Merck & Co.

Study	Population	Intervention and comparison	Outcomes	Comments
Retnakaran 2010 BEST	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	Strategy: Switching N = 21 Sitagliptin (n=10) Placebo (n=11) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 42.80% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 4.60%	Hypoglycaemia episodes Follow up: 11.2 months	Study location: Canada Sources of funding: Samuel Lunenfeld Research Institute, Mount Sinai Hospital
Ridderstrale 2014 EMPA-REG H2H-SU	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):	Strategy: Adding N = 1545 Glimepiride 1 - 4 mg once daily (n=780) Empagliflozin 25 mg once daily (n=765) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 772.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 48 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim - involved in the study design, data gathering and analysis. Eli-Lilly co-sponsored the trial but was not involved in the study design, and data gathering analysis.

Study	Population	Intervention and comparison	Outcomes	Comments
	55.95 (10.3506) year years Time since type 2 diabetes diagnosed: Not stated/unclear	Sulfonylureas: Not stated/unclear		
Riddle 1998 Glimepiride Combination Group 1998	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 (8) years Time since type 2 diabetes diagnosed: 7 (4) years	Strategy: Adding N = 145 Glimepiride 16 mg daily (n=72) Placebo (n=73) Concomitant therapy: NPH Insulin 70%/Regular insulin 30% 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: 5.5 months	Study location: Not reported but probably USA (multisite) Sources of funding: Funded by Hoechst Marion Roussel Pharmaceuticals.
Riddle 2013A GetGoal-L	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	Strategy: Adding N = 496 Lixisenatide (n=329) Placebo (n=167) Concomitant therapy: Insulin ± metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 21% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Sanofi

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular risk: Not stated/unclear Mean age (SD): 57 (10) years Time since type 2 diabetes diagnosed: 12.45 (6.7729) years	Insulin: 50% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Riddle 2013B GetGoal-Duo-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): 56 (10) years Time since type 2 diabetes diagnosed: 9.15 (5.9008) years	Strategy: Adding N = 446 Lixisenatide (n=223) Placebo (n=223) Concomitant therapy: Insulin + Metformin ± thiazolidinedione + insulin 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 Sources of funding: Sanofi
Roberts 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	Strategy: Adding N = 170 Glimepiride 2-8 mg daily (n=85) Placebo (n=85) Concomitant therapy: Metformin and a thiazolidinedione Antihyperglycaemic treatment received: No additional	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change	Study location: USA (multisite) Sources of funding: Supported by Aventis Pharmaceuticals, Bridgewater, NJ, USA; Innovus Research Inc., Medford, MA, USA performed health-related

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.45 (9.9005) years Time since type 2 diabetes diagnosed: 8.3 (5.9266) years	information available.	Follow up: 6 months	quality of life analysis.
Rodbard 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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.45 (9.7063) years Time since type 2 diabetes diagnosed: 9.95 (5.6543) years	Strategy: Adding N = 213 Canagliflozin 100 mg/300 mg titrated (n=107) Placebo (n=106) Concomitant therapy: Metformin + sitagliptin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Supported by Janssen Research and Development, LLC
Rodbard 2017 DUAL IV	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 435 Insulin degludec/liraglutide	All-cause mortality, Non-fatal myocardial infarction, Hypoglycaemia	Study location: Multicenter Sources of funding:

Study	Population	Intervention and comparison	Outcomes	Comments
	disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 59.7 (10.0179) years Time since type 2 diabetes diagnosed: Not stated/unclear	titrated (n=289) Placebo (n=146) Concomitant therapy: Sulfonylurea 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 11%	episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Sponsored by Novo Nordisk.
Rodbard 2018 SUSTAIN 5	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Adding N = 397 Semaglutide 1.0 mg weekly (n=132) Semaglutide 0.5 mg weekly (n=132) Placebo (n=133) Concomitant therapy: Basal insulin with or without metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 86.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 53.8% SGLT-2 inhibitors:	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hospitalisation for heart failure, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: International (90 sites in Germany, Japan, Serbia, Slovakia, and USA) Sources of funding: Funded by Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Not stated/unclear Sulfonylureas: 0.3%		
Rodbard 2019 PIONEER 2	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): 57.5 (10) years Time since type 2 diabetes diagnosed: 7.45 (6.0558) years	Strategy: Adding N = 822 Empagliflozin 25 mg daily (n=410) Semaglutide 14 mg (n=412) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Hospitalisation for heart failure, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Multicenter Sources of funding: Novo Nordisk A/S, Denmark.
Roden 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	Strategy: Adding N = 353 Pioglitazone (n=316) Metformin (n=597) Concomitant therapy: Sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Weight change Follow up: 12 months	Study location: Europe and Canada. Sources of funding: Eli Lily and Company and Takeda Europe R&D.

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60 (8) years Time since type 2 diabetes diagnosed: 7 (5.6) years			
Rosenstock 2006 Sitagliptin 019	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): 56.25 (10.7587) years Time since type 2 diabetes diagnosed: 6.1 (5.5533) years	Strategy: Adding N = 353 Sitagliptin (n=175) Placebo (n=178) Concomitant therapy: Pioglitazone 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: Multinational study Sources of funding: Merck & Co., Inc.
Rosenstock 2009B	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart failure	Strategy: Adding N = 390 Alogliptin 12.5 mg (n=131) Alogliptin 25 mg (n=129) Placebo (n=130) Concomitant therapy: Insulin ± metformin	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multicenter Sources of funding: Unclear, appears that the study could have been funded by Takeda Pharmaceuticals

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.4333 (10.2042) years Time since type 2 diabetes diagnosed: 12.5667 (6.8808) years	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: 41.3% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Follow up: 6 months	
Rosenstock 2012 Study MB102030	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): 53.5 (10.9064) years Time since type 2 diabetes diagnosed:	Strategy: Adding N = 420 Dapagliflozin 5 mg (n=141) Dapagliflozin 10 mg (n=140) Placebo (n=139) Concomitant therapy: Pioglitazone 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 11 months	Study location: 105 sites in Argentina, Canada, India, Mexico, Peru, Philippines, Taiwan, and United States Sources of funding: Bristol-Myers Squibb and AstraZeneca. Numerous authors declare funding and honoraria from multiple pharmaceutical companies

Study	Population	Intervention and comparison	Outcomes	Comments
	5.4867 (5.6489) years			
Rosenstock 2013 GetGoal-X	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): 57.5 (10.0) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 420 Dapagliflozin 5 mg (n=141) Dapagliflozin 10 mg (n=140) Placebo (n=139) Concomitant therapy: Pioglitazone Antihyperglycaemic treatment received: No additional information	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Sanofi
Rosenstock 2014A GetGoal-S	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear	Strategy: Adding N = 859 Lixisenatide (n=573) Placebo (n=286) Concomitant therapy: Sulfonylurea ± metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 84.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Sanofi

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.4 (9.9008) years Time since type 2 diabetes diagnosed: 9.45 (6.0672) years	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%		
Rosenstock 2014B EMPA-REG MDI	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.6667 (9.4198) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 563 Empagliflozin 10 mg (n=186) Empagliflozin 25 mg (n=189) Placebo (n=188) Concomitant therapy: Insulin ± metformin 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: 29% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim and Eli Lilly. A number of authors are employees of Boehringer Ingelheim and others declare funding and honoraria from multiple pharmaceutical companies
Rosenstock 2015A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Strategy: Adding N = 534 Dapagliflozin + Saxagliptin (n=179) Saxagliptin + Placebo (n=176) Dapagliflozin + Placebo (n=179)	All-cause mortality, Cardiovascular mortality, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic	Study location: Canada, Mexico, Poland, Puerto Rico, Republic of Korea, Romania, South Africa; United States Sources of funding: Bristol-

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54 (10) years Time since type 2 diabetes diagnosed: 7.5667 (5.3033) years	Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	episodes, HbA1c change, Weight change Follow up: 5.5 months	Myers Squibb and AstraZeneca
Rosenstock 2015B EMPA-REG BASAL	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.8667 (9.8921) years Time since type 2	Strategy: Adding N = 494 Empagliflozin 25 mg (n=155) Empagliflozin 10 mg (n=169) Placebo (n=170) Concomitant therapy: Insulin ± metformin ± sulfonylurea 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	All-cause mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 18 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim and Eli Lilly and Company

Study	Population	Intervention and comparison	Outcomes	Comments
	diabetes diagnosed: Not stated/unclear			
Rosenstock 2016A GetGoal-Duo-2	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): 59.8 (8.9101) years Time since type 2 diabetes diagnosed: 12.2 (6.6693) years	Strategy: Adding N = 894 Lixisenatide (n=298) Insulin glulisine QD (n=298) Insulin glulisine TID (n=298) Concomitant therapy: Metformin + insulin glargine Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 87.3% DPP-4 inhibitors: 12.1% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 46.1%	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Sanofi
Rosenstock 2016B LixiLan-O	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	Strategy: Adding N = 1170 Lixisenatide/Insulin glargine (n=469) Lixisenatide (n=234) Insulin glargine (n=467) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: Not stated/unclear DPP-4 inhibitors: 2.4% GLP-1 receptor agonists: Not	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 7 months	Study location: Multicenter Sources of funding: Sanofi

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Mean age (SD): 58.4 (9.3053) years Time since type 2 diabetes diagnosed: 8.8333 (5.7077) years	stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 0.3% Sulfonylureas: 53.7%		
Rosenstock 2016C LixiLan PoC	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):56.75 (9.45) years Time since type 2 diabetes diagnosed: 6.7 (4.8) years	Strategy: Adding Lixisentatide + Insulin glargine (n=161) Insulin glargine (n=162) Concomitant therapy: Metformin 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 Sources of funding: Sanofi
Rosenstock 2018A FREEDOM-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	Strategy: Adding N = 441 Exenatide 40 mcg/day (n=147) Exenatide 60 mcg/day (n=151) Placebo (n=143) Concomitant therapy: Diet and exercise alone or with metformin, sulfonylureas or pioglitazone monotherapy or in	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 9.1 months	Study location: 126 clinical sites in the U.S. Sources of funding: Intarcia Therapeutics

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.9667 (9.6836) years Time since type 2 diabetes diagnosed: 8.8667 (6.3867) years	combination Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 41.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 3.5%		
Rosenstock 2018B VERTIS MET	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): 56.6667 (8.7471) years Time since type 2 diabetes diagnosed: 8 (5.9789) years	Strategy: Adding N = 621 Empagliflozin 5 mg (n=207) Empagliflozin 15 mg (n=205) Placebo (n=209) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 99.8% DPP-4 inhibitors: 3.4% GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, HbA1c change Follow up: 6 months	Study location: North America, South America, Europe, Asia, South Africa, Australia, New Zealand Sources of funding: Study funded by Pfizer.Numerous authors declare funding and honoraria from multiple pharmaceutical companies
Rosenstock 2019A CARMELINA	Model 1: People with type 2 diabetes and heart failure Model 3: People with type 2 diabetes and	Strategy: Adding N = 6991 Linagliptin (n=3499) Placebo (n=3492) Concomitant therapy: Additional	All-cause mortality, Cardiovascular mortality, 3-point MACE, 4-point MACE, Non-fatal myocardial infarction, Non-	Study location: Multicenter Sources of funding: Study was sponsored by Boehringer

Study	Population	Intervention and comparison	Outcomes	Comments
	chronic kidney disease Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Mixed population 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 Includes results for a subgroup for people with or without heart failure and with or without chronic kidney disease. Mean age (SD): 65.85 (9.1) years Time since type 2 diabetes diagnosed: 14.75 (9.4513) years	medications except DPP-4 inhibitors, GLP 1 receptor agonists or SGLT-2 inhibitors Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 54.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 58% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 32.1%	fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Death from renal causes, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 26.4 months	Ingelheim and Eli Lilly.
Rosenstock 2019B CAROLINA	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 6033 Linagliptin (n=3023) Glimepiride (n=3010) Concomitant therapy: Additional medications including adjustment of background therapy, or addition of pioglitazone, metformin, alpha glucosidase inhibitor	All-cause mortality, Cardiovascular mortality, 3-point MACE, 4-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c	Study location: Multicenter Sources of funding: Boehringer Institute and Eli Lilly and Company.

Study	Population	Intervention and comparison	Outcomes	Comments
	failure: People without heart failure T2DM and 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 Includes results for a subgroup for people with atherosclerotic cardiovascular disease. Mean age (SD): 64.05 (9.5) years Time since type 2 diabetes diagnosed: Not stated/unclear	or basal insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 3.20% Biguanides: 83.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 28.5%	change, Weight change Follow up: 75.6 months	
Rosenstock 2019C PIONEER 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: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear	Strategy: Adding N = 1864 Semaglutide 3 mg/d (n=466) Semaglutide 7 mg/d (n=466) Semaglutide 14 mg/d (n=465) Sitagliptin 100 mg/d (n=467) Concomitant therapy: Metformin with or without sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Death from renal causes, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change	Study location: Multicenter Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 57.75 (10) years Time since type 2 diabetes diagnosed: 8.55 (6.0012) years		Follow up: 18 months	
Rosenstock 2019D	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.7 (10.5073) years Time since type 2 diabetes diagnosed: 7.6333 (6.1369) years	Strategy: Adding N = 883 Dapagliflozin + Saxagliptin (n=293) Dapagliflozin (n=294) Saxagliptin (n=296) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: 119 centres in Canada, the Czech Republic, Germany, Mexico, Russia, and the USA Sources of funding: AstraZeneca
Rosenstock 2023 SURPASS-6	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic	Strategy: Adding N = 1425 Tirzepatide (n=717) insulin lispro (n=708) Concomitant therapy: No additional information Antihyperglycaemic	All-cause mortality, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Globally - 135 centers in Argentina, Belgium, Brazil, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Romania, Russia, Slovakia, Spain, Turkey,

Study	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): 58.8 (9.7504) years Time since type 2 diabetes diagnosed: 13.8 (7.3001) years	treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 84.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		and the US Sources of funding: Eli Lilly and Company
Roussel 2019 CompoSIT-I	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): 58.35 (9.6001) years Time since type 2 diabetes diagnosed: 10.75 (6.85) years	Strategy: Adding N = 743 Sitagliptin (n=373) Placebo (n=370) Concomitant therapy: Insulin, Metformin with or without DPP-4 inhibitor and/or sulfonylurea 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: Multicenter Sources of funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. The lead author declares support from multiple pharmaceutical companies and numerous authors are employees of Merck Sharp & Dohme Corp
Russell-Jones 2009 LEAD-5 met+SU	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 581 Liraglutide 1.8 mg daily (n=232) Placebo (n=115)	Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic	Study location: Multicenter Sources of funding: Funded

Study	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: Not stated/unclear Mean age (SD): 57.5333 (9.9342) years Time since type 2 diabetes diagnosed: 9.4333 (6.1268) years	Insulin glargine (n=234) Concomitant therapy: Metformin + glimepiride Antihyperglycaemic treatment received: No additional information available.	episodes, HbA1c change, Weight change Follow up: 6 months	by Novo Nordisk A/S
Sathyanarayana 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): 52 years Time since type 2 diabetes	Strategy: Adding N = 21 Pioglitazone 30 - 45 mg daily + Exenatide 10 µg twice daily (n=11) Pioglitazone 30 mg - 45 mg daily (n=10) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 81% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: US Sources of funding: Amylin Pharmaceuticals and Eli-Lilly supported the research through grants.

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: Not stated/unclear			
Savvidou 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: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.95 (7.1502) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 110 Exenatide (n=55) Insulin (n=55) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Medical Center of Diabetes Mellitus in ‘‘Papageorgiou’’ University Hospital of Thessaloniki, Greece Sources of funding: None
Schernthaner 2013 CANTATA-D2	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	Strategy: Adding N = 756 Canagliflozin (n=378) Sitagliptin (n=378) Concomitant therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: Multicenter Sources of funding: Janssen Global Services, LLC.

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 56.65 (9.4512) years Time since type 2 diabetes diagnosed: 9.55 (6.2008) years	stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 30%		
Schernthaner 2015A GENERATION	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): 72.6 (5.552) years Time since type 2 diabetes diagnosed: 7.6 (6.2032) years	Strategy: Adding N = 720 Saxaglitpin (n=360) Glimepiride (n=360) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: AstraZeneca and Bristol-Myers Squibb
Scirica 2013 SAVOR-TIMI 53	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart	Strategy: Adding N = 16492 Saxagliptin (n=8280) Placebo (n=8212) Concomitant therapy: Antihyperglycemic therapy except DPP-4 inhibitor or GLP-1 receptor agonist Antihyperglycaemic treatment received: Alpha-glucosidase	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Persistent signs of worsening kidney disease, Development of end stage kidney	Study location: Multicenter Sources of funding: AstraZeneca and Bristol-Myers Squibb.

Study	Population	Intervention and comparison	Outcomes	Comments
	failure: People without heart failure T2DM and 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 Includes results for a subgroup for people with atherosclerotic cardiovascular disease. Mean age (SD): 65.05 (8.5499) years Time since type 2 diabetes diagnosed: Not stated/unclear	inhibitors: Not stated/unclear Biguanides: 69.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 41.4% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 40.20%	disease, Death from renal causes, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 25.2 months	
Scott 2018 CompoSIT-R	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	Strategy: Adding N = 614 Sitagliptin (n=307) Dapagliflozin (n=307) Concomitant therapy: Metformin with or without a sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 71.3% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors:	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 67.15 (8.5501) years Time since type 2 diabetes diagnosed: 10.6 (7.2028) years	Not stated/unclear Sulfonylureas: Not stated/unclear		
Seino 2012 GetGoal-L Asia	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): 58.35 (10.1496) years Time since type 2 diabetes diagnosed: 13.9 (7.7) years	Strategy: Adding N = 311 Lixisenatide (n=154) Placebo (n=157) Concomitant therapy: Insulin ± sulfonylurea Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Sanofi
Seino 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	Strategy: Adding N = 257 Liraglutide (n=127) Placebo (n=130) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 8.3 months	Study location: 23 sites in Japan Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60.55 (11.1528) years Time since type 2 diabetes diagnosed: 14.505 (8.7445) years			
Seino 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): 55.5 (10.5946) years Time since type 2 diabetes diagnosed: 9.15 (4.9672) years	Strategy: Adding N = 141 Sitagliptin (n=70) Placebo (n=71) Concomitant therapy: Ipragliflozin 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: MSD K.K., a subsidiary of Merck & Co
Shankar 2017A	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People without heart	Strategy: Adding N = 467 Sitagliptin (n=234) Placebo (n=233) Concomitant therapy: Insulin with or without metformin Antihyperglycaemic	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic	Study location: China Sources of funding: Merck & Co

Study	Population	Intervention and comparison	Outcomes	Comments
	failure T2DM and atherosclerotic cardiovascular disease: People without atherosclerotic cardiovascular disease T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.7 (8.8) years Time since type 2 diabetes diagnosed: 11.2 (5.4) years	treatment received: No additional information available.	episodes, HbA1c change, Weight change Follow up: 6 months	
Sivalingam 2023	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): 69.95 (8.0327) years Time since type 2 diabetes diagnosed: 18.5 (10.5119) years	Strategy: Adding N = 60 Semaglutide (n=30) Placebo (n=30) Concomitant therapy: Empagliflozin 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: 0% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 50%	All-cause mortality, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Copenhagen, Denmark Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
Skrivanek 2014 AWARD-5	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): 54.75 (7.1388) years Time since type 2 diabetes diagnosed: 7 (3.3578) years	Strategy: Adding N = 135 Dulaglutide 0.25 mg once weekly (n=24) Dulaglutide 0.5 mg once weekly (n=25) Dulaglutide 0.75 mg once weekly (n=21) Dulaglutide 1.0 mg once weekly (n=10) Dulaglutide 1.5 mg once weekly (n=25) Dulaglutide 2.0 mg once weekly (n=30) Dulaglutide 3.0 mg once weekly (n=15) Sitagliptin 100 mg daily (n=42) Placebo daily/weekly (n=38) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change, Weight change Follow up: 12 months	Study location: US Sources of funding: Eli Lily and company
Softeland 2017 NA	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	Strategy: Adding N = 333 Empagliflozin 10 mg once daily (n=112) Empagliflozin 25 mg once daily (n=111) Placebo (n=110) Concomitant therapy: Meformin + linagliptin, Placebo Antihyperglycaemic treatment received: No additional	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Multicenter Sources of funding: Funded by Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance

Study	Population	Intervention and comparison	Outcomes	Comments
	chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.2 (9.7338) years Time since type 2 diabetes diagnosed: Not stated/unclear	information available.		
Sone 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.6667 (10.079) years Time since type 2 diabetes diagnosed: 13.8 (8.0144) years	Strategy: Adding N = 269 Empagliflozin 10 mg daily (n=89) Empagliflozin 25 mg daily (n=90) Placebo (n=90) Concomitant therapy: Insulin 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: 72.4% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Unstable angina, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Japan (51 sites) Sources of funding: Supported by Nippon Boehringer Ingelheim Co. Ltd.
Sridhar 2013	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People	Strategy: Adding N = 50 Pioglitazone 30 mg daily (n=25) Placebo (n=25) Concomitant therapy: Glimepiride + metformin	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: India Sources of funding: Drug and placebo tablets provided by Sun Pharmaceutical

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 45.95 (6.5376) years Time since type 2 diabetes diagnosed: 2.55 (1.9105) years	Antihyperglycaemic treatment received: No additional information available.		Industries Ltd, Mumbai, India.
Strain 2013 INTERVAL	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): 74.75 (4.1527) years Time since type 2 diabetes diagnosed: 11.4 (7.4169) years	Strategy: Adding N = 278 Vildagliptin (n=139) Placebo (n=139) Concomitant therapy: Oral drugs Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Progression of liver disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: Multicenter (Belgium, Bulgaria, Germany, Finland, Slovakia, Spain and the UK). Sources of funding: Funded by Novartis Pharma AG.
Strojek 2011	Model 5: People with type 2	Strategy: Adding N = 592	All-cause mortality,	Study location: Multicenter

Study	Population	Intervention and comparison	Outcomes	Comments
	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 Mean age (SD): 59.825 (9.5999) years Time since type 2 diabetes diagnosed: 7.425 (5.7299) years	Dapagliflozin 2.5 mg daily (n=154) Dapagliflozin 5 mg daily (n=142) Dapagliflozin 10 mg daily (n=151) Placebo (n=145) Concomitant therapy: Glimepiride Antihyperglycaemic treatment received: No additional information available.	Cardiovascular mortality, Non-fatal stroke, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Sources of funding: Astra Zenaca and Bristol-Myers Squib funded medical writing and editorial assistance.
Su 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): 48.14 (13.0642)	Strategy: Adding N = 600 Vildagliptin 100 mg daily (n=300) Placebo daily (n=300) Concomitant therapy: Metformin + alpha glucosidase inhibitor Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: China Sources of funding: No additional information.

Study	Population	Intervention and comparison	Outcomes	Comments
	years Time since type 2 diabetes diagnosed: Not stated/unclear			
Takahashi 2023	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Switching N = 110 Liraglutide 0.9-1.8 mg daily (n=20) Semaglutide 0.25-1.0 mg weekly A (n=20) Dulaglutide 0.75 mg weekly (n=35) Semaglutide 0.25-1.0 mg weekly B (n=35) Concomitant therapy: NA Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 15.7% Biguanides: 87.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: 43.20% Insulin: 51.40% SGLT-2 inhibitors: 77.8% Sulfonylureas: 23.20%	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Japan (8 hospital sites) Sources of funding: Research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Takihata 2013 COMPASS	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	Strategy: Adding N = 130 Pioglitazone 15 mg daily (n=65) Sitagliptin 50 mg daily (n=65) Concomitant therapy: Metformin ± sulfonylurea 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: Grants-in-Aid for Scientific Research (B) 21390282 and (B) 24390235 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, a Grant for the Strategic Japanese-Danish Cooperative Program on Molecular Diabetology from

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 60.5 (8.5586) years Time since type 2 diabetes diagnosed: Not stated/unclear			the Japan Science and Technology Agency, a Grant-in-Aid from the Uehara Memorial Foundation to one author, and a Grant-in-Aid from the Joint Research Association for Japanese Diabetes to another author.
Tan 2004 GLAD	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): 55.4 (8.6797) years Time since type 2 diabetes diagnosed: 6.65 (6.7529) years	Strategy: Switching N = 244 Pioglitazone (n=121) Glimepiride (n=123) Concomitant therapy: NA Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 20.9% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 54.60% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Hypoglycaemia episodes, HbA1c change Follow up: 12 months	Study location: 16 centres in Mexico Sources of funding: This work relates to Eli Lilly and Company protocol H6E-MC-GLAD. The main author is an employee of Eli Lilly and Company
Tanaka 2017	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear	Strategy: Switching N = 132 Alogliptin (n=64) Vildagliptin (n=68) Concomitant therapy: Existing treatment (except for sitagliptin which was switched for study	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: Japan Sources of funding: None declared

Study	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 Mean age (SD): 66.45 (10.0465) years Time since type 2 diabetes diagnosed: 11.25 (9.221) years	drug) Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 15% Biguanides: 55.2% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 28.20%		
Tanaka 2019 EMBLEM	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 64.9 (10.4) years Time since type 2 diabetes diagnosed: 13.2 (10.9) years	Strategy: Adding Empagliflozin (n=58) Placebo (n=59) Concomitant therapy: Standard therapy Antihyperglycaemic treatment received: No additional information available.	HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Japan. Sources of funding: Funded by Boehringer Ingelheim and Eli Lilly and Company.
Taskinen 2011	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 700 Linagliptin 5mg daily (n=523)	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight	Study location: Multicenter Sources of funding: Funded

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 56.55 (10.3076) years Time since type 2 diabetes diagnosed: Not stated/unclear	Placebo (n=177) Concomitant therapy: Metformin with or without one other blood-glucose lowering drug Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 68.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	change Follow up: 5.5 months	by Boehringer Ingelheim.
Terauchi 2020 LixiLan JP-O2	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): 59.7 (10.7) years Time since type 2 diabetes	Strategy: Adding N = 226 Linagliptin 5 mg daily (n=106) Placebo (n=120) Concomitant therapy: Background blood-glucose lowering drug monotherapy Antihyperglycaemic treatment received: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Japan Sources of funding: Sanofi

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: Not stated/unclear			
Thrasher 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): 53.9 (9.9942) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 226 Linagliptin 5 mg daily (n=106) Placebo (n=120) Concomitant therapy: Background blood-glucose lowering drug monotherapy Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 78.00% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 20.40%	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: USA Sources of funding: Funded by Boehringer Ingelheim Inc
Tinahones 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	Strategy: Adding N = 226 Linagliptin 5 mg + Empagliflozin 10 mg (n=126) (study 1) Linagliptin 5 mg + Empagliflozin 25 mg (n=114) (study 2) Placebo + Empagliflozin 10mg (n=130) (study 1) Placebo + Empagliflozin 25 mg (n=112) (study 2) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multicenter Sources of funding: Boehringer Ingelheim and Eli Lilly & Co.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 59.7 (10.7) years Time since type 2 diabetes diagnosed: Not stated/unclear			
Tripathy 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: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.5 (2.5289) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 29 Pioglitazone 15 mg daily (n=15) Placebo (n=14) Concomitant therapy: Metformin with or without a sulfonylurea Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 60.6% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Texas, USA Sources of funding: Funded by Takeda.
Tuttle 2018 AWARD-7	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney	Strategy: Adding N = 577 Dulaglutide 1.5 mg weekly (n=193) Dulaglutide 0.75 mg weekly (n=190) Insulin glargine (n=194) Concomitant therapy: Insulin lispro +/- hypoglycaemic agent	All-cause mortality, Cardiovascular mortality, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Death from renal causes, Hypoglycaemia episodes, At night hypoglycaemic	Study location: Multicenter Sources of funding: Eli Lilly and Co.

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 64.5667 (8.6012) years Time since type 2 diabetes diagnosed: 18.1 (8.7331) years	Antihyperglycaemic treatment received: No additional information available.	episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	
Umpierrez 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 48.9 (10.4997) years Time since type 2 diabetes diagnosed: 5.4 (5.1247) years	Strategy: Adding N = 210 Pioglitazone 30-45 mg daily (n=109) Glimepiride 2-8 mg daily (n=101) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Hospitalisation for heart failure, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: USA (51 diabetes centres) Sources of funding: Sponsored by Sanofi-Aventis, Bridgewater, NJ, USA.
Vähätalo 2007	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Strategy: Adding Glipizide (n=15) Metformin (n=26) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional	HbA1c change, Weight change Follow up: 12 months	Study location: Finland. Sources of funding: No additional information.

Study	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	information available.		
van der Meer 2009 PIRAMID	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): 56.6 (0.9513) years Time since type 2 diabetes diagnosed: 3.5 years	Strategy: Adding N = 78 Pioglitazone (n=39) Metformin (n=39) Concomitant therapy: Glimepiride 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 100%	Hospitalisation for heart failure, HbA1c change, Weight change Follow up: 5.5 months	Study location: The study was performed at two institutes in The Netherlands Sources of funding: Supported by Eli Lilly, the Netherlands, which has a partnership with Takeda, the manufacturer of pioglitazone. Metformin tablets and matching placebos were provided by Merck, the Netherlands. Multiple authors report receiving funding from numerous pharmaceutical companies
van Eyk 2019	Model 5: People with type 2 diabetes at higher risk of cardiovascular	Strategy: Adding N = 47 Liraglutide (n=22) Placebo (n=25)	HbA1c change, Weight change, BMI change	Study location: The Netherlands Sources of funding: The

Study	Population	Intervention and comparison	Outcomes	Comments
	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 Mean age (SD): 55 (9.9833) years Time since type 2 diabetes diagnosed: 18 (10) years	Concomitant therapy: Concomitant treatment with metformin, sulfonylurea derivatives and insulin was optional Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	study was funded by Novo Nordisk (Bagsvaerd, Denmark) Roba Metals B.V. Ijsselstein and the Cardio Vascular Imaging Group, Leiden University Medical Centre (Leiden, The Netherlands).
van Gaal 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): 43.05 (4.9539) years Time since type 2 diabetes	Strategy: Adding N = 319 Lixisenatide 20 mcg daily (n=158) Sitagliptin 100 mg daily (n=161) Concomitant therapy: Metformin 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 (Australia, Brazil, Canada, Chile, Guatemala, Mexico, Peru, Poland, Romania, Russian Federation, Ukraine, USA) Sources of funding: Funded/supported by Sanofi

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 4.4 (3.7516) years			
Vanderheiden 2016A	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): 54.15 (7.3773) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 71 Liraglutide 1.8 mg daily (n=35) Placebo (n=36) Concomitant therapy: Insulin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Texas, USA Sources of funding: Funded by Novo Nordisk
Verma 2019 EMPA-HEART CardioLink-6	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear	Strategy: Adding N = 97 Empagliflozin (n=49) Placebo (n=48) Concomitant therapy: Metformin +/- insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 94% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 25% SGLT-2 inhibitors: Not stated/unclear	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Persistent signs of worsening kidney disease, Cardiac arrhythmia, Diabetic ketoacidosis, Progression of liver disease, HbA1c change, Weight change, BMI change	Study location: Canada. Sources of funding: Boehringer Ingelheim (Canada) Ltd.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Sulfonylureas: Not stated/unclear	Follow up: 6 months	
Vianna 2018 BoneGLIC	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): 61.9 (5.8758) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 42 Vildagliptin 100 mg (n=21) Gliclazide MR 120mg (n=21) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: One centre, Brazil Sources of funding: investigator-initiated trial research funds from Novartis Pharmaceuticals
Vilsboll 2010 Sitagliptin Study 051	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular	Strategy: Adding N = 641 Sitagliptin 100 mg daily (n=322) Placebo (n=319) Concomitant therapy: Insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Unstable angina, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multicenter Sources of funding: Funded by Merck & Co., Inc.

Study	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): 57.75 (9.2001) years Time since type 2 diabetes diagnosed: 12.5 (6.5215) years	stated/unclear Biguanides: 72% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Follow up: 5.5 months	
Vilsboll 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 55.5 (9.5749) years Time since type 2 diabetes diagnosed: 9.45 (6.3525) years	Strategy: Adding N = 641 Dapagliflozin 10 mg daily + Saxagliptin 5 mg daily (n=322) Insulin (n=319) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 0.20% Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: 0.40% Insulin: 0.40% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Acute kidney injury, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Funded by AstraZeneca.
Wägner 2019 LIPER2	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease	Strategy: Adding N = 24 Liraglutide (n=12) Placebo (n=12) Concomitant	HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Single centre Sources of funding: Funding and Drug

Study	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: Not stated/unclear Mean age (SD): 52.9 (11.9275) years Time since type 2 diabetes diagnosed: 8.71 (5.8588) years	therapy: Use of other glucose lowering agents Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 41.7% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 41.7%		supplies; Novo Nordisk
Wada 2022	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 62.45 (10.8042) years Time since type 2 diabetes diagnosed: 15.96 (8.8116) years	Strategy: Adding N = 308 Canagliflozin (n=154) Placebo (n=154) Concomitant therapy: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, 3-point MACE, 5-point MACE, Hospitalisation for heart failure, Diabetic ketoacidosis, Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 25 months	Study location: Japan Sources of funding: Mitsubishi Tanabe Pharma Corporation

Study	Population	Intervention and comparison	Outcomes	Comments
Wang 2016B	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): 55.8 (10.086) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 306 Linagliptin 5 mg daily (n=205) Placebo (n=101) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 4% Biguanides: 65.2% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 27.80%	All-cause mortality, Cardiovascular mortality, 5-point MACE, Non-fatal myocardial infarction, Hospitalisation for heart failure, Development of end stage kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: International (19 centres in China, Philippines and Malaysia) Sources of funding: Funded by Boehringer Ingelheim
Wang 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	Strategy: Adding N = 380 Sitagliptin 100 mg daily (n=191) Placebo (n=189) Concomitant therapy: Acarbose Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 190% Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear	Hypoglycaemia episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: China, Romania, Kore, Malaysia, India, Philippines Sources of funding: Merck & Co., Inc., Kenilworth, NJ, USA

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 57.15 (9.2033) years Time since type 2 diabetes diagnosed: 7.8 (5.313) years	Sulfonylureas: Not stated/unclear		
Wang 2019B	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): 54.9667 (9.6045) years Time since type 2 diabetes diagnosed: 8.1333 (5.1387) years	Strategy: Adding N = 774 Dulaglutide 0.75 mg (n=257) Dulaglutide 1.5 mg (n=258) Insulin (n=259) Concomitant therapy: Metformin and /or a SU Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 40.7% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 11.7%	All-cause mortality, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: 45 sites in China, Russia, Mexico and South Korea Sources of funding: Elli Lilly and Company. A number of authors are employees of Elli Lilly and Company
Wang 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	Strategy: Adding N = 95 Exenatide (n=49) Insulin (n=46) Concomitant therapy: existing oral antidiabetic therapy Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 46.00% DPP-4 inhibitors:	HbA1c change, Weight change Follow up: 5.5 months	Study location: Nantong University, Nantong, China Sources of funding: AstraZeneca and 3SBio Inc.

Study	Population	Intervention and comparison	Outcomes	Comments
	chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.235 (10.9911) years Time since type 2 diabetes diagnosed: Not stated/unclear	Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 36.8%		
Wang 2020B	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 56.05 (8.462) years Time since type 2 diabetes diagnosed: 11.15 (6.6121) years	Strategy: Adding N = 92 Exenatide 10 mcg twice daily (n=46) Insulin lispro thrice daily (n=46) Concomitant therapy: Insulin glargine Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 26.1% Biguanides: 38.00% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 75% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 15.2%	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: 4 hospitals in Guangzhou, China Sources of funding: AstraZeneca China and 3SBio Inc. funded study and provided drugs and examination items during follow up.
Wang 2020C	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear	Strategy: Adding N = 60 Sitagliptin (n=30) Liraglutide (n=30) Concomitant therapy: existing oral antidiabetic therapy Antihyperglycaemic	HbA1c change Follow up: 6 months	Study location: Linyi Peoples Hospital, Linyi, China Sources of funding: NR

Study	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: People at higher risk of developing cardiovascular disease Mean age (SD): 66.65 (6.5276) years Time since type 2 diabetes diagnosed: 8.59 (2.857) years	treatment received: No additional information available.		
Wang 2022B	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 atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 54.7667 (10.2503) years	Strategy: Adding N = 720 Insulin degludec/liraglutide once daily (n=361) Insulin degludec once daily (n=179) Liraglutide 1.8 mg once daily (n=180) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Unstable angina, Hypoglycaemia episodes, At night hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: China Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	Time since type 2 diabetes diagnosed: Not stated/unclear			
Wang 2023 AWARD-CHN3	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): 58.05 (9.4016) years Time since type 2 diabetes diagnosed: 11.8 (6.4703) years	Strategy: Adding N = 291 Dulaglutide 5 mg once weekly (n=144) Placebo once weekly (n=147) Concomitant therapy: Basal insluin glargine + metformin +/or acarbose Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 13.5% Biguanides: 76% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Acute kidney injury, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6.4 months	Study location: China Sources of funding: Eli Lilly and Company
Watada 2019 DUAL II Japan	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	Strategy: Adding N = 210 Insulin degludec/liraglutide titrated twice weekly (n=105) Insulin degludec titrated twice weekly (n=105) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, HbA1c change, Weight change Follow up: 6 months	Study location: Japan (Multicentre trial, 38 sites) Sources of funding: Funded by Novo Nordisk A/S

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 56.05 (10.202) years Time since type 2 diabetes diagnosed: 14.05 (7.6268) years			
Webb 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: People at higher risk of developing cardiovascular disease Mean age (SD): 44.1 (6.4734) years Time since type 2 diabetes diagnosed: 4.45 (4.4503) years	Strategy: Adding N = 76 Liraglutide 0.6-1.8 mg weekly (n=38) Sitagliptin 100 mg daily (n=38) Concomitant therapy: Metformin and/or a sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Non-fatal myocardial infarction, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: Diabetes Research Centre, University of Leicester, Leicester, UK Sources of funding: Funded by Novo Nordisk and supported by NIHR Leicester Biomedical Research Center, the NIHR CLAHRC-East Midlands, the NIHR Leicester Clinical Research Facility and The NIHR Leicester Clinical Trial Unit.
White 2013 EXAMINE	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease	Strategy: Adding N = 5380 Alogliptin (n=2701) Placebo (n=2679) Concomitant therapy: Anti-diabetic therapy other than DPP-4 inhibitor or GLP-1 receptor agonist	All-cause mortality, Cardiovascular mortality, 3-point MACE, 4-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure,	Study location: Multicenter Sources of funding: Takeda Development Center Americas

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and heart failure: Mixed population T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Includes results for a subgroup for people with or without heart failure. Mean age (SD): Not stated/unclear Time since type 2 diabetes diagnosed: Not stated/unclear	Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 66.2% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 29.80% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 46.60%	Development of end stage kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 18 months	
Wilcox 2008 PROactive	Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear	Strategy: Adding N = 5238 Pioglitazone (n=2605) Placebo (n=2633) Concomitant therapy: Oral agents ± insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 10% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 0.20% SGLT-2 inhibitors:	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, Cardiac arrhythmia, Hypoglycaemia episodes Follow up: 34.5 months	Study location: Multicenter Sources of funding: Takeda Europe R&D Centre Ltd, London, United Kingdom, and Eli Lilly and Company, Indianapolis, IN.

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Mean age (SD): 61.75 (7.7012) years Time since type 2 diabetes diagnosed: Not stated/unclear	Not stated/unclear Sulfonylureas: 19.5%		
Wilding 2012 Dapagliflozin 006	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 Mean age (SD): 59.3 (8.2289) years Time since type 2 diabetes diagnosed: 13.6 (7.269) years	Strategy: Adding N = 807 Dapagliflozin 10 mg daily (n=196) Dapagliflozin 5/10 mg daily (n=212) Dapagliflozin 2.5 mg daily (n=202) Placebo (n=197) Concomitant therapy: Insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 40.00% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Persistent signs of worsening kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 24 months	Study location: Multicenter Sources of funding: Sponsored by Bristol-Myers Squibb and AstraZeneca.
Wilding 2013A CANTATA-MSU	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Strategy: Adding N = 469 Canagliflozin 100 mg (n=157) Canagliflozin 300 mg (n=156) Placebo (n=156) Concomitant	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: Multicenter Sources of funding: Janssen Research & Development, LLC

Study	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): 56.7667 (9.2827) years Time since type 2 diabetes diagnosed: 9.5667 (6.2795) years	therapy: Metformin + sulfonylurea Antihyperglycaemic treatment received: No additional information available.	Follow up: 12 months	
Wilding 2013B	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 (9.345) year years Time since type 2 diabetes diagnosed: 5.95 (4.8924) years	Strategy: Adding N = 182 Glipizide 5-20 mg (n=94) Placebo (n=88) Concomitant therapy: metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 100% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes Follow up: 6 months	Study location: 92 sites in: Germany, Hungary, Latvia, Lithuania, Poland, Romania, Sweden, UK, Chile, Mexico, Peru Sources of funding: Astra Zeneca

Study	Population	Intervention and comparison	Outcomes	Comments
Wiviott 2019 DECLARE-TIMI 58	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease Model 3: People with type 2 diabetes and chronic kidney disease 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: Not stated/unclear T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Includes results for a subgroup for people with or without chronic kidney disease, heart failure and people with atherosclerotic cardiovascular disease. Mean age (SD): 63.95 (6.8) years Time since type 2 diabetes	Strategy: Adding N = 17160 Dapagliflozin (n=8582) Placebo (n=8578) Concomitant therapy: Use of other glucose lowering agents at discretion (other than SGLT-2 inhibitor, pioglitazone or rosiglitazone Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 82% DPP-4 inhibitors: 16.8% GLP-1 receptor agonists: 4.40% Insulin: 40.9% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 42.60%	All-cause mortality, Cardiovascular mortality, 3-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Death from renal causes, Cardiac arrhythmia, Diabetic ketoacidosis, Progression of liver disease, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 50.4 months	Study location: Multicenter Sources of funding: Funded by AstraZeneca

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: Not stated/unclear			
Wu 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: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 60.2 (9.6496) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 93 Metformin 1500 mg daily (n=47) Pioglitazone 15 mg daily (n=46) Concomitant therapy: Hypoglycaemic drugs (not specified) other than biguanides and thiazolidinediones 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: 26.9% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 24.7%	HbA1c change, BMI change Follow up: 12 months	Study location: China Sources of funding: No additional information.
Wysham 2014 AWARD-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	Strategy: Adding N = 976 Dulaglutide 1.5 mg once weekly (n=279) Dulaglutide 0.75 mg once weekly (n=280) Exenatide 10 micrograms twice daily (n=276) Placebo twice daily (n=141) Concomitant therapy: Metformin + thiazolidinedione Antihyperglycaemic treatment received: No additional	All-cause mortality, Cardiovascular mortality, Severe hypoglycaemic episodes, HbA1c change Follow up: 12 months	Study location: USA Sources of funding: Eli Lilly and company

Study	Population	Intervention and comparison	Outcomes	Comments
	risk: Not stated/unclear Mean age (SD): 55.5 (9.7235) year years Time since type 2 diabetes diagnosed: 9 (5.7308) years	information available.		
Xiao 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 53.855 (3.5036) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 120 Pioglitazone 15-45 mg daily (n=40) Glipizide 5-10 mg daily (n=40) Insulin (n=40) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	HbA1c change Follow up: 5.5 months	Study location: Anhui, China Sources of funding: Financially supported by the Natural Science Foundation of Anhui Province (09B117)
Xiao 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	Strategy: Adding N = 41 Glimepiride 4 mg daily (n=18) Sitagliptin 100 mg daily (n=23) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional	Non-fatal myocardial infarction, Non-fatal stroke, Hospitalisation for heart failure, HbA1c change, Weight change Follow up: 5.5 months	Study location: Qilu Hospital, Shandong University, Jinan, China Sources of funding: Supported by grants from special funds for scientific research projects of clinical

Study	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): 68.9 (6.3879) years Time since type 2 diabetes diagnosed: Not stated/unclear	information available.		medicine of the Chinese Medical Association (grant no. 13060990484), the Medicine Health Care Science and Technology Development Project Program of Shandong Province (grant no. 2013WSC02036), Science Foundation of Qilu Hospital of Shandong University (grant no. 2015QLMS11) and Fundamental Research Funds of Shandong University (2601017561601 2).
Xu 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): 53.4 (9.8502) years Time since type 2 diabetes	Strategy: Adding N = 1103 Glimepiride (n=551) Gliclazide (n=552) Concomitant therapy: Metformin + sitagliptin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina, Diabetic ketoacidosis, Falls requiring hospitalisation, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: 237 centres across 25 provinces in China Sources of funding: Merck & Co., Inc.

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 5.65 (4.3011) years			
Yabe 2020 PIONEER 10	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): 58.75 (10.1676) years Time since type 2 diabetes diagnosed: 9.425 (6.3286) years	Strategy: Adding N = 458 Semaglutide 3 mg weekly (n=131) Semaglutide 7 mg daily (n=132) Semaglutide 14 mg daily (n=130) Dulaglutide 0.75 mg weekly (n=65) Concomitant therapy: Glucose-lowering drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 17% Biguanides: Not stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 17% Sulfonylureas: 32%	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Acute kidney injury, Death from renal causes, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: Japan (36 clinics and hospitals) Sources of funding: Funded by Novo Nordisk, Denmark.
Yabe 2023 EMPA-ELDERLY	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	Strategy: Adding N = 127 Empagliflozin (n=64) Placebo (n=63) Concomitant therapy: DPP-4 inhibitors, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors and/or meglitinides Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 6.3% Biguanides: 51.20% DPP-4 inhibitors: 67.7% GLP-1 receptor	Health-related quality of life, All-cause mortality, Persistent signs of worsening kidney disease, Diabetic ketoacidosis, Progression of liver disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 12 months	Study location: Japan. Sources of funding: Sponsored by Nippon Boehringer Ingelheim Co. Ltd and Eli Lilly K.K.

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 74.1 (5.0002) years Time since type 2 diabetes diagnosed: 12.1 (7.9081) years	agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 7.80%		
Yale 2013 DIA3004	Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: Not stated/unclear T2DM and atherosclerotic cardiovascular disease: Mixed population T2DM and chronic kidney disease: People with chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 68.5333 (8.2675) years Time since type 2 diabetes diagnosed: 16.3333 (8.5194) years	Strategy: Adding N = 269 Canagliflozin 100 (n=90) Canagliflozin 300 (n=89) Placebo (n=90) Concomitant therapy: None, monotherapy or combination therapy Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 1.5% DPP-4 inhibitors: 7.5% GLP-1 receptor agonists: Not stated/unclear Insulin: 74% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 31.2%	All-cause mortality, HbA1c change, Weight change Follow up: 12 months	Study location: Multicenter Sources of funding: Janssen Research & Development, LLC.
Yan 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: Not stated/unclear T2DM and	Strategy: Adding N = 75 Liraglutide 1.8 mg daily (n=24) Sitagliptin 100 mg daily (n=27) Insulin glargine (n=24) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: China (10 centres) Sources of funding: Supported by investigator-initiated trial research funds from Novo Nordisk, National Natural Science Foundation of China (81770821), Pearl River S&T

Study	Population	Intervention and comparison	Outcomes	Comments
	chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 44.8 (8.8922) years Time since type 2 diabetes diagnosed: 4.4667 (3.9492) years	information available.		Nova Program of Guangzhou (201610010175) and Guangdong High-Level Talents Special Support Program (2016TQ03R590)
Yang 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): 54.1 (10.25) years Time since type 2 diabetes diagnosed: 5.1 (4.5242) years	Strategy: Adding N = 570 Saxagliptin 5 mg daily (n=283) Placebo (n=287) Concomitant therapy: Metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 79.20% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: International (40 sites in China, India, South Korea) Sources of funding: Funded by AstraZeneca LP and Bristol-Myers Squibb.
Yang 2012	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: People	Strategy: Adding N = 395 Sitagliptin 100 mg daily (n=197) Placebo (n=198) Concomitant therapy: Metformin	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change	Study location: China (17 sites) Sources of funding: Funded by Merck Sharp & Dohme Corp., subsidiary of Merck & Co, Inc.

Study	Population	Intervention and comparison	Outcomes	Comments
	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): 54.6 (9.4095) years Time since type 2 diabetes diagnosed: 6.85 (4.5014) years	Antihyperglycaemic treatment received: No additional information available.	Follow up: 5.5 months	
Yang 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: People without atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.5 (9.5596) years Time since type 2 diabetes	Strategy: Adding N = 279 Vildagliptin 50 mg daily (n=143) Placebo (n=136) Concomitant therapy: Glimepiride Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 5.5 months	Study location: China (multisite trial) Sources of funding: Novartis Pharmaceuticals

Study	Population	Intervention and comparison	Outcomes	Comments
	diagnosed: 6.9 (4.3635) years			
Yang 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): 53.7333 (9.2712) years Time since type 2 diabetes diagnosed: 4.9333 (4.2834) years	Strategy: Adding N = 444 Dapagliflozin 10 mg daily (n=152) Dapagliflozin 5 mg daily (n=147) Placebo (n=145) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Development of end stage kidney disease, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: International (32 sites in China, India and South Korea) Sources of funding: Funded by Bristol-Myers Squibb, NJ, USA, and AstraZeneca, MD, USA
Yang 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: Not stated/unclear T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not	Strategy: Adding N = 272 Dapagliflozin 10 mg daily (n=139) Placebo (n=133) Concomitant therapy: Insulin with or without oral antidiabetic drugs Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: 13.2% Biguanides: 45.2% DPP-4 inhibitors: 5.5% GLP-1 receptor agonists: Not stated/unclear Insulin: 39.7%	All-cause mortality, Cardiovascular mortality, Non-fatal myocardial infarction, Development of end stage kidney disease, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: International (28 sites in China, Singapore and South Korea) Sources of funding: Funded by AstraZeneca

Study	Population	Intervention and comparison	Outcomes	Comments
	stated/unclear Mean age (SD): 57.55 (8.6481) years Time since type 2 diabetes diagnosed: 12.45 (6.96) years	SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 11%		
Yang 2018B GetGoal-L-C	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): 55.1 (9.5084) years Time since type 2 diabetes diagnosed: 10.25 (6.1502) years	Strategy: Adding N = 448 Lixisenatide 20 mcg daily (n=224) Placebo (n=224) Concomitant therapy: Insulin with or without metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 88.6% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 82.80% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: International (51 centres in China, India, South Korea and Russian Federation) Sources of funding: Funded by Sanofi
Yang 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	Strategy: Adding N = 206 Linagliptin 5 mg daily (n=104) Placebo (n=102) Concomitant therapy: Insulin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: Not	All-cause mortality, Cardiovascular mortality, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 5.5 months	Study location: China (25 sites) Sources of funding: Funded by Boehringer Ingelheim

Study	Population	Intervention and comparison	Outcomes	Comments
	T2DM and chronic kidney disease: Not stated/unclear T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 58.6 (10.0597) years Time since type 2 diabetes diagnosed: Not stated/unclear	stated/unclear DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 30.2% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear		
Yang 2022 LixiLan-O-AP	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 (9.7) years Time since type 2 diabetes diagnosed: Not stated/unclear	Strategy: Adding N = 206 IGlarLixi (n=351) Insulin glargine (n=350) Lixisenatide (n=177) Concomitant therapy: All people had the opportunity to receive a second oral antihyperglycaemic drug Antihyperglycaemic treatment received: No additional information	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: Sanofi
Yki-Järvinen 2013	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not	Strategy: Adding N = 1261 Linagliptin 5 mg daily (n=631) Placebo (n=630) Concomitant therapy: Insulin ± metformin and/or	All-cause mortality, Cardiovascular mortality, 5-point MACE, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight	Study location: Multicenter Sources of funding: Sponsored by Boehringer Ingelheim.

Study	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): 60.05 (9.9501) years Time since type 2 diabetes diagnosed: Not stated/unclear	thiazolidinedione Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 75.60% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	change Follow up: 12 months	
Yokoyama 2014 JDDM 33	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 Mean age (SD): 61.3 (9.1609) years Time since type 2 diabetes diagnosed: 11.335 (6.9523) years	Strategy: Adding N = 99 Liraglutide 0.9 mg daily (n=50) Sitagliptin 50-100 mg daily (n=49) Concomitant therapy: Sulfonylurea 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: Not stated/unclear SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 46.40%	Health-related quality of life, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 5.5 months	Study location: Japan (21 primary care centres) Sources of funding: Supported by Japan Diabetes Foundation.

Study	Population	Intervention and comparison	Outcomes	Comments
Yuan 2022 LixiLan-L-CN	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): 57.45 (9.0064) years Time since type 2 diabetes diagnosed: 12.35 (6.1003) years	Strategy: Adding N = 426 iGlarLixi (n=212) Insulin glargine (n=214) Concomitant therapy: Background oral antidiabetic treatment Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 78.20% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: 85% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: Not stated/unclear	All-cause mortality, Cardiovascular mortality, Death from renal causes, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6.9 months	Study location: China (44 centres) Sources of funding: Funded by Sanofi, Paris, France.
Zang 2016 LIRA-DPP-4 CHINA	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	Strategy: Adding N = 368 Liraglutide 1.8 mg daily (n=184) Sitagliptin 100 mg daily (n=184) Concomitant therapy: Metformin Antihyperglycaemic treatment received: No additional information available.	All-cause mortality, Cardiovascular mortality, Non-fatal stroke, Cardiac arrhythmia, Diabetic ketoacidosis, Hypoglycaemia episodes, At night hypoglycaemic episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 6 months	Study location: China (25 sites) Sources of funding: Funded by Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	Mean age (SD): 51.55 (10.851) years Time since type 2 diabetes diagnosed: 5.25 (4.9254) years			
Zhang 2020B	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): 58.44 (12.97) years Time since type 2 diabetes diagnosed: 7.38 (5.7114) years	Strategy: Adding N = 59 Exenatide 5-10 Î¼g twice daily (n=27) Insulin (initially 0.2-0.4 IU/Kg then titrated) daily (n=32) Concomitant therapy: Any antihyperglycaemic other than sulfunylurea and nateglinide Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI change Follow up: 12 months	Study location: China Sources of funding: Astra Zeneca and 3SBioInc.
Zhao 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	Strategy: Adding N = 100 Sitagliptin (n=50) Placebo (n=50) Concomitant therapy: Insulin, exenatide or metformin Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, HbA1c change, Weight change, BMI change Follow up: 9 months	Study location: China. Sources of funding: None declared.

Study	Population	Intervention and comparison	Outcomes	Comments
	disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 68.45 (7.9627) years Time since type 2 diabetes diagnosed: 5.65 (4.4045) years			
Zinman 2009 LEAD-4 Met+TZD	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): 53.6667 (29.4694) years Time since type 2 diabetes diagnosed: 9 (6) years	Strategy: Adding N = 533 Liraglutide 1.2 mg (n=178) Liraglutide 1.8 mg (n=178) Placebo (n=177) Concomitant therapy: Metformin + TZD Antihyperglycaemic treatment received: No additional information available.	Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change Follow up: 6 months	Study location: Multi-centre (96 sites) study conducted in the USA and Canada. Sources of funding: Funding source not clearly stated. Statistical and writing assistance was provided by staff from Novo Nordisk.
Zinman 2015 EMPA-REG OUTCOME	Model 1: People with type 2 diabetes and heart failure Model 2: People with type 2 diabetes and atherosclerotic	Strategy: Adding N = 7020 Empagliflozin (n=4687) Placebo (n=2333) Concomitant therapy: No or stable glucose lowering	All-cause mortality, Cardiovascular mortality, 3-point MACE, 4-point MACE, Non-fatal myocardial infarction, Non-fatal stroke, Unstable angina,	Study location: Multicenter Sources of funding: Supported by Boehringer Ingelheim and Eli Lilly

Study	Population	Intervention and comparison	Outcomes	Comments
	cardiovascular disease Model 3: People with type 2 diabetes and chronic kidney disease T2DM and heart failure: People without heart failure T2DM and atherosclerotic cardiovascular disease: People with atherosclerotic cardiovascular diseases T2DM and chronic kidney disease: Mixed population T2DM and higher cardiovascular risk: People at higher risk of developing cardiovascular disease Includes results for a subgroup for people with or without heart failure and with or without chronic kidney disease. Mean age (SD): 63.15 (8.667) years Time since type 2 diabetes diagnosed: Not stated/unclear	therapy Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 74.00% DPP-4 inhibitors: 11.40% GLP-1 receptor agonists: 2.80% Insulin: 48.3% SGLT-2 inhibitors: Not stated/unclear Sulfonylureas: 42.80%	Hospitalisation for heart failure, Acute kidney injury, Persistent signs of worsening kidney disease, Development of end stage kidney disease, Diabetic ketoacidosis, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change Follow up: 36 months	
Zinman 2019A SUSTAIN 9	Model 5: People with type 2 diabetes at higher risk of cardiovascular disease T2DM and heart failure: Not stated/unclear T2DM and	Strategy: Adding N = 302 Semaglutide 1.0 mg (n=151) Placebo (n=151) Concomitant therapy: SGLT-2 inhibitor as monotherapy or with a sulfonylurea or	Health-related quality of life, All-cause mortality, Cardiovascular mortality, Acute kidney injury, Hypoglycaemia episodes, Severe hypoglycaemic episodes, HbA1c change, Weight change, BMI	Study location: Multicenter Sources of funding: Novo Nordisk

Study	Population	Intervention and comparison	Outcomes	Comments
	atherosclerotic cardiovascular disease: Not stated/unclear T2DM and chronic kidney disease: People without chronic kidney disease T2DM and higher cardiovascular risk: Not stated/unclear Mean age (SD): 57.05 (9.5189) years Time since type 2 diabetes diagnosed: 9.7 (6.1033) years	metformin Antihyperglycaemic treatment received: Alpha-glucosidase inhibitors: Not stated/unclear Biguanides: 71.5% DPP-4 inhibitors: Not stated/unclear GLP-1 receptor agonists: Not stated/unclear Insulin: Not stated/unclear SGLT-2 inhibitors: 99.60% Sulfonylureas: 12.9%	change Follow up: 7 months	
Zinman 2019B PIONEER 8	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): 60.5 (9.7576) years Time since type 2 diabetes diagnosed: 15.05 (8.1036) years	Strategy: Adding N = 730 Semaglutide 3 mg (n=184) Semaglutide 7 mg (n=181) Semaglutide 14 mg (n=181) Placebo (n=184) Concomitant therapy: Insulin +/- metformin Antihyperglycaemic treatment received: No additional information available.	Health-related quality of life, All-cause 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: 12 months	Study location: Multicenter Sources of funding: PIONEER 8 was funded by Novo Nordisk A/S Denmark.

1 See report 1.2 B, appendix D for full evidence tables.

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

Table 4: Summary of effectiveness evidence (network meta-analysis) - people with type 2 diabetes and heart failure

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Cardiovascular mortality at 33 months	7	RCT	9128	See report F14	Not serious	Not serious	Not serious	Very serious[a]	**Low**
3-point MACE at 36 months	8	RCT	11956	See report F9	Not serious	Not serious	Not serious	Serious[b]	**Moderate**
Non-fatal myocardial infarction at 38 months	3	RCT	4924	See report F9	Serious[c]	Not serious	Not serious	Very serious[a]	**Very low**
Non-fatal stroke at 32 months	4	RCT	5178	See report F9	Serious	Not serious	Not serious	Very serious[a]	**Very Low**
Hospitalisation for heart failure at 32 months	11	RCT	15739	See report F14	Not serious	Not serious	Not serious	Very serious[a]	**Low**
HbA1c change at 9 months	2	RCT	55	See report F9	Serious[c]	Not serious	Not serious	Very serious[a]	**Very low**

Footnotes:

a) Downgraded by 2 increments as a significant proportion of inputs or measures produced by the network meta-analysis showed imprecision that had a substantial impact on the ability of the committee to draw conclusions from the results of the analysis.

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.

c) Downgraded by 1 increment as greater than 33.3% of the studies in the meta-analysis were at high or moderate risk of bias.

Table 5: Summary of effectiveness evidence (network meta-analysis) - people with type 2 diabetes and cardiovascular disease

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Cardiovascular mortality at 27 months	12	RCT	62776	See report F9	Serious[a]	No serious	No serious	Serious[b]	**Low**

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3-point MACE at 40 months	12	RCT	83664	See report F9	Not serious	Not serious	Not serious	Serious[b]	**Moderate**
Hospitalisation for heart failure at 29 months	11	RCT	62683	See report F9	Not serious	Not serious	Not serious	Very serious	**Low**
Non-fatal myocardial infarction at 28 months	11	RCT	55863	See report F9	Very serious[c]	Not serious	Not serious	Serious[c]	**Very low**
Non-fatal stroke at 31 months	8	RCT	41022	See report F9	Not serious	Not serious	Not serious	Very serious[c]	**Low**
Unstable angina at 24 months	7	RCT	42392	See report F9	Very serious[d]	Not serious	Not serious	Very serious[c]	**Very low**
HbA1c change at 18 months	18	RCT	34325	See report F9	Very serious[d]	Not serious	Not serious	Serious[c]	**Very low**
Weight change at 8 months	5	RCT	1888	See report F9	Very serious[d]	Not serious	Not serious	Not serious	**Low**

Footnotes:

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

Table 6: Summary of effectiveness evidence (network meta-analysis) - people with type 2 diabetes and chronic kidney disease

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Cardiovascular mortality at 22 months	9	RCT	14523	See report F9	Not serious	Not serious	Not serious	Very serious[a]	**Low**

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3-point MACE at 35 months	3	RCT	10593	See report F9	Serious[b]	Not serious	Not serious	Serious[c]	**Low**
Non-fatal myocardial infarction at 22 months	3	RCT	632	See report F9	Very serious[d]	Not serious	Not serious	Very serious[a]	**Very low**
Non-fatal stroke at 8 months	3	RCT	731	See report F9	Serious[b]	Not serious	Not serious	Very serious[a]	**Very low**
Hospitalisation for heart failure at 27 months	9	RCT	18277	See report F9	Not serious	Not serious	Not serious	Very serious[a]	**Low**
Development of end stage kidney disease at 22 months	3	RCT	4823	See report F9	Serious[b]	Not serious	Not serious	Very serious[a]	**Very low**
HbA1c change at 14 months	24	RCT	10109	See report F9	Very serious[d]	Not serious	Not serious	Serious[c]	**Very low**
Weight change at 12 months	6	RCT	1883	See report F9	Very serious[d]	Not serious	Not serious	Very serious[a]	**Very low**

Footnotes:

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

Table 7: Summary of effectiveness evidence (network meta-analysis) - people with type 2 diabetes and high cardiovascular risk

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Cardiovascular mortality at 15.9 months	84	RCT	164385	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**

Outcome	No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3-point MACE at 31.3 months	17	RCT	106710	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**
4-point MACE at 22.2 months	7	RCT	20290	See report F10	Not serious	Not serious	Not serious	Very serious[b]	**Low**
5-point MACE at 18.5 months	3	RCT	7741	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**
Non-fatal myocardial infarction at 15.1 months	48	RCT	111619	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**
Non-fatal stroke at 15.6 months	47	RCT	106740	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**
Unstable angina at 19.6 months	29	RCT	105389	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**
Hospitalisation for heart failure (base case) at 22.8 months	33	RCT	118970	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**
Hospitalisation for heart failure (sensitivity analysis) at 22.8 months	33	RCT	120217	See report F10	Not serious	Not serious	Not serious	Very serious[b]	**Low**
Development of end stage kidney disease at 34.7 months	9	RCT	85882	See report F10	Not serious	Not serious	Not serious	Serious[a]	**Moderate**
HbA1c change at 10 months	335	RCT	264168	See report F11-F12	Very serious[c]	Not serious	Not serious	Not serious	**Low**
HbA1c change (regression analysis) at 10 months	308	RCT	224786	See report F11-F12	Very serious[c]	Not serious	Not serious	Not serious	**Low**
Weight change at 9 months	173	RCT	105529	See report F11, F13	Very serious[c]	Not serious	Not serious	Serious[a]	**Very low**

Note: Unless specified, the GRADE rating for the base case and sensitivity analyses are the same. The base case values are reported in the table.

Footnotes:

a) 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.

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

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