Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

All Wales Advice on Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors in Type 2 Diabetes and Cardiovascular Disease

September 2021

This document has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC) with support from a multidisciplinary SGLT-2 inhibitor subgroup and the All Wales Prescribing Advisory Group (AWPAG), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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1.0 INTRODUCTION

1.1 All Wales Medicines Strategy Group guidance

This document has been developed to provide healthcare professionals with information to support appropriate choice of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients with type 2 diabetes mellitus (T2DM) and cardiovascular (CV) disease.

2.0 BACKGROUND

In June 2020, the All Wales Prescribing Advisory Group (AWPAG) proposed an all Wales prescribing guideline: appropriate choice of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients with type 2 diabetes mellitus (T2DM) and cardiovascular (CV) disease. The existence of relevant National Institute for Health and Care Excellence (NICE) clinical guidelines was acknowledged but a gap was considered to exist in relation to the specific selection of SGLT-2 inhibitors.

There are currently four SGLT-2 inhibitors (canagliflozin [Invokana®][1], dapagliflozin [Forxiga®][2], empagliflozin [Jardiance®][3] and ertugliflozin▾ [Steglatro®][4]) licensed in the UK for the management of adults with T2DM. SGLT-2 inhibitors have been associated with HbA_{1c} (glycated haemoglobin) reductions making them effective treatment options for T2DM[1-4]. The mechanisms underlying the increasingly reported CV benefits of SGLT-2 inhibitors are less well understood but are considered both unrelated to the extent of glucose lowering or baseline eGFR and occur too early to be the result of weight reduction[5,6]. No head-to-head trials between SGLT-2 inhibitors have been conducted but clinical outcome data is available for four SGLT-2 inhibitors relating to their CV effects in people with T2DM[1-4]. This document provides a summary of evidence around CV risk reduction data regarding the use of SGLT-2 inhibitor medicines and focuses on specific considerations for appropriate prescribing within the T2DM management pathway.

2.1 Terminology

The term ‘sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)’ is used throughout this document to refer to canagliflozin, dapagliflozin, empagliflozin and ertugliflozin▾.

2.2 Relevant existing guidance

- Guide for non-diabetes specialist physicians and primary care teams for cardiovascular risk optimisation in patients with Type 2 diabetes and atherosclerotic cardiovascular disease (coronary artery disease, peripheral arterial disease, cerebrovascular disease) (2021)[7]
- Managing hyperglycaemia in people with diabetes and chronic kidney disease (2021)[8]
- NICE NG28 – Type 2 diabetes in adults: management (last updated 2019)[9]
- NICE NG28 – Evidence reviews for SGLT-2 inhibitors and GLP-1 mimetics (2018)[10]
- 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[5]
- Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[11]
- 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)[6]

2.2.1 NICE evidence review

An evidence review that investigated the clinical effectiveness of SGLT-2 inhibitors on CV outcomes in adults with T2DM was published by NICE in 2018[10]. It aimed to provide recommendations to supplement NICE technology appraisals on three SGLT-2 inhibitors (TA288[12], TA315[13], TA336[14] and TA418[15]), and which were reproduced in the NICE guideline on T2DM management in adults (NG28)[9]. NG28 broadly advises that treatment with SGLT-2 inhibitors can be considered alongside other glucose lowering medicines as an option at the first intensification of treatment for T2DM, in line with technology appraisal guidance, or as a first-line treatment in cases of metformin intolerance[9]. NICE does not currently make specific recommendations for glycaemia management in those with established CV disease. The evidence review comprised a systematic literature search for randomised controlled trials (RCTs) or systematic reviews of RCTs and a meta-analyses of the extracted evidence[10]. Evidence statements were prepared for two RCTs that focussed on CV outcomes, the CANVAS study (canagliflozin versus placebo) and the EMPA-REG OUTCOME study (empagliflozin versus placebo). The evidence from these two studies led the committee to make no recommendations for the use of specific drugs in patients with CV disease. The evidence review did not include the DECLARE-TIMI 58 trial, at the time this was an ongoing trial that sought to determine the effect of dapagliflozin on CV outcomes when added to current background therapy in participants with T2DM, with either established CV disease or CV risk factors[10].

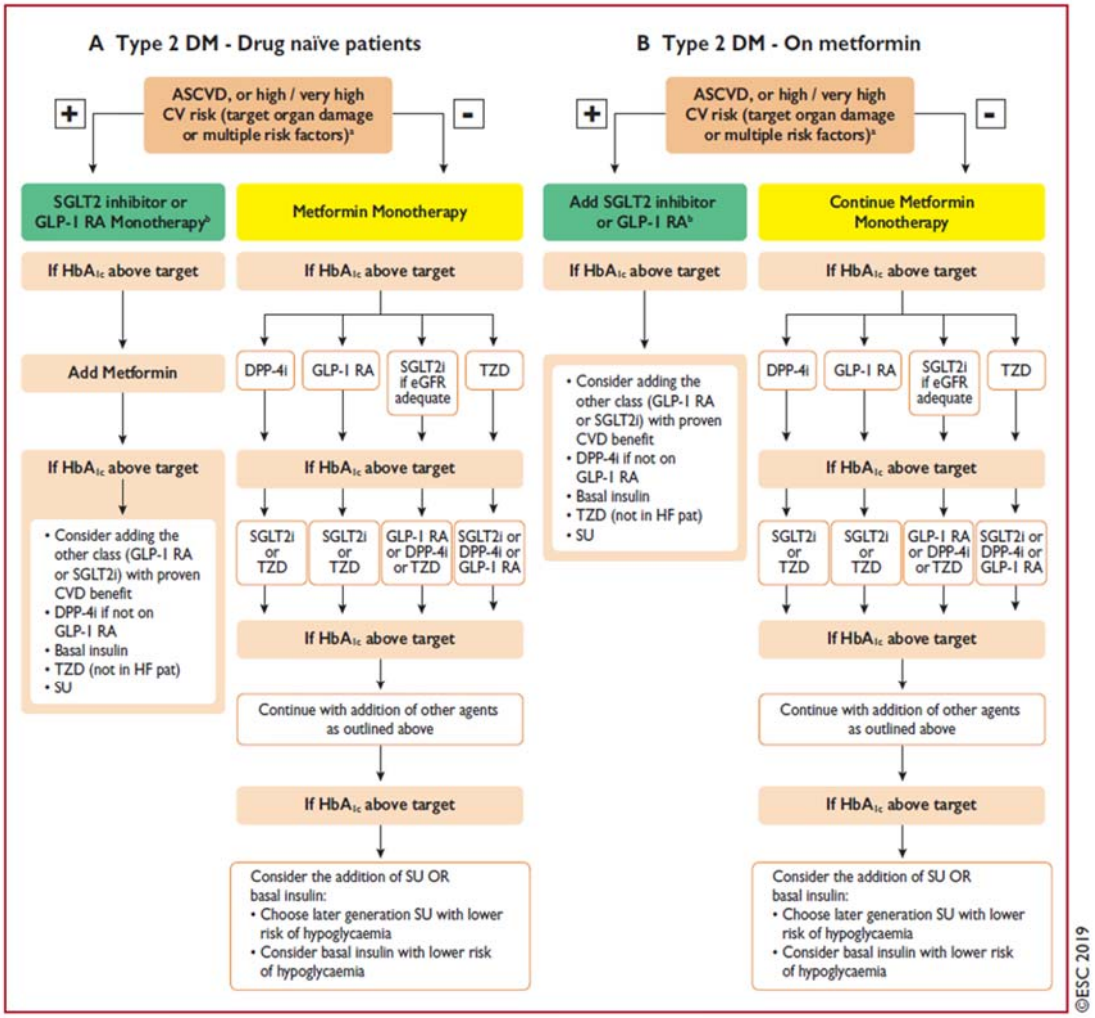
2.2.2 ADA/EASD consensus guidelines on the management of hyperglycemia

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) convened a panel to update position statements, published in 2012 and 2015, on the management of T2DM in adults[11]. A systematic evaluation of the literature since 2014 informed new recommendations that were published in 2018[11]. A further update was published in 2020, as the organisations wanted recommendations to incorporate relevant data from CV outcomes trials that had been published in 2019[5]. The recommendations currently suggest, in appropriate high risk individuals with established T2DM, the decision to treat with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or SGLT-2 inhibitor to reduce major adverse CV events (MACE), hospitalisation for heart failure (HHF), CV death, or chronic kidney disease (CKD) progression should be considered independently of baseline HbA_{1c} or individualised HbA_{1c} target[5].

2.2.3 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The European Society of Cardiology (ESC) and the EASD, similarly due to the increase in relevant data from CV outcomes trials, designed a short document to provide guidance on the management and prevention of CV disease in subjects with, and at risk of developing, T2DM[6]. The ESC guidelines in 2019 recommended SGLT-2 inhibitors and GLP-1 RA before metformin in patients with newly diagnosed T2DM who are treatment naïve and either have established CV disease or are at high CV disease risk. The document suggests individualising SGLT-2 therapy based on comorbidities and needs. A treatment algorithm for patients with T2DM and either atherosclerotic CV disease (ASCVD) or a high or very high CV risk was outlined (Figure 1)[6].

Figure 1. Treatment algorithm for patients with T2DM and ASCVD, or high/very high CV risk, for (A) drug-naïve and (B) metformin-treated patients*[6]



*Cosentino F, Grant PJ, Aboyans V, et al, 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD), European Heart Journal 2020; 41 (2): 255–323 doi:10.1093/eurheartj/ehz486. Reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology.

3.0 TABLE OF RECOMMENDATIONS ON THE ROLE OF SGLT-2 INHIBITORS IN PEOPLE WITH T2DM

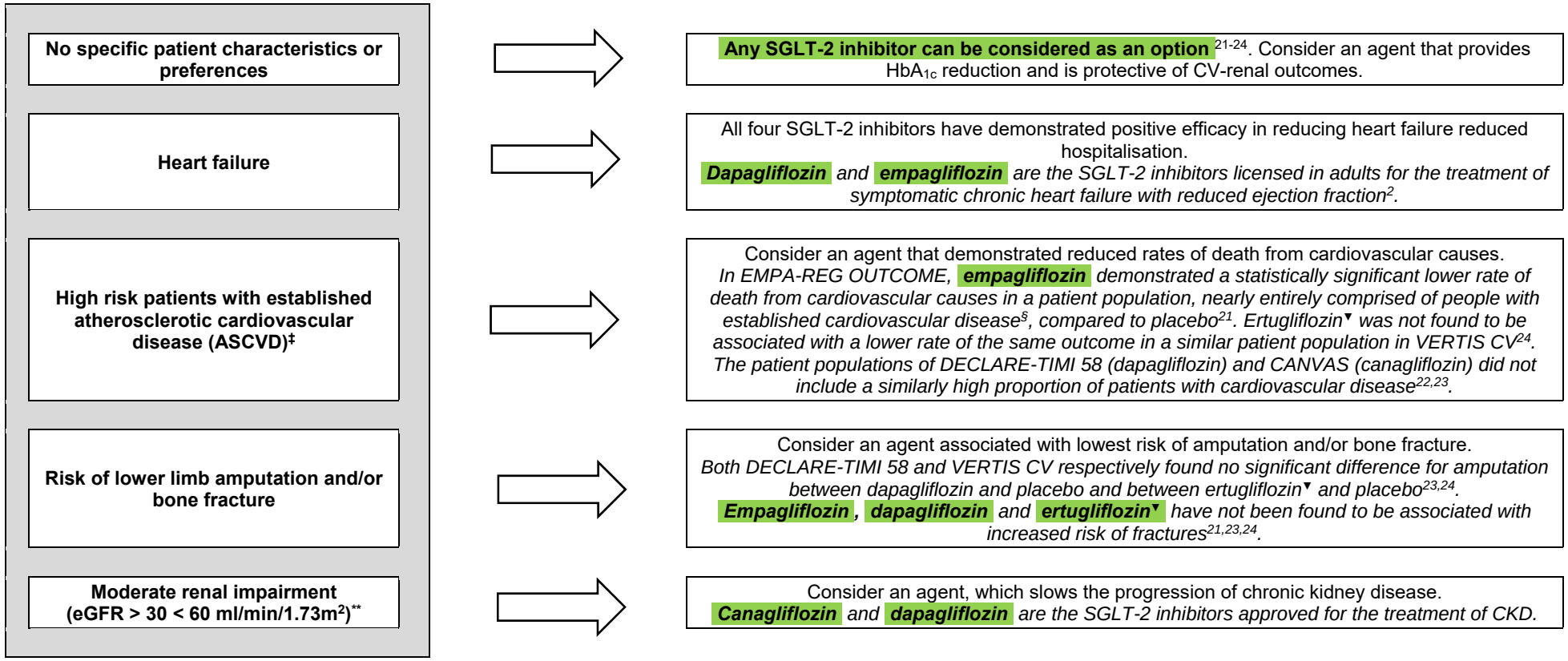
1.0	**IDENTIFICATION[1-4]**
1.1	Treatment if metformin is contraindicated or not tolerated, or in patients with inadequate glycaemic control in spite of optimal current treatment.
1.2	An SGLT-2 inhibitor as an initial drug treatment in patients with established CV or renal disease, or at high risk* of developing cardiovascular disease. Use the QRISK®2 risk assessment tool to assess CVD risk. *Defined as a QRISK®2 score more than 10% in adults with T2DM aged ≥ 40 *or* clinical judgement of an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factor in someone under 40)[16]. Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, family history (in a first-degree relative) of premature cardiovascular disease.
2.0	**CHOICE OF AGENT[1-4]**
2.1	The decision whether to start treatment with an SGLT-2 inhibitor should be made after an informed discussion between the clinician and the person with T2DM about the risks and benefits, using accredited decision aids where possible (e.g. NICE Patient Decision Aid for Type 2 Diabetes in adults). MHRA and EMA have issued warnings regarding a small risk of euglycaemic diabetic ketoacidosis (DKA). Treatment should be initiated only after an educational session with the person that includes information on the risk of DKA, signs and symptoms of early DKA and sick day rules.
2.2	CV outcome data should also be considered when making a decision on choice of SGLT-2 inhibitor. See Table 1 for information available on available SGLT-2 inhibitors. Figure 2 depicts the overall approach to selecting an SGLT-2 inhibitor for a patient with T2DM and CV disease.
3.0	**INITIATION OF AN SGLT-2 INHIBITOR[1-4]**
3.1	Please refer to Table 1 and manufacturer's full prescribing information for standard doses. When prescribing SGLT-2 inhibitors, safety and tolerability should be considered for each individual. Dose should be gradually escalated to a maximum tolerated dose in order to derive maximum HbA_{1c} reduction and aid both long-term glycaemic and risk factor control. If dapaglifozin or empagliflozin is used for treatment of symptomatic chronic HF with reduced ejection fraction no dose titration is required.
3.2	Document completion of the educational session and the advice on who to contact if not feeling well.
3.3	Emphasise advice on healthy balanced eating and encourage high fibre, low glycaemic index sources of carbohydrate in the diet, such as fruit, vegetables, wholegrains and pulses; include low fat dairy products and oily fish; and control the intake of foods containing saturated and trans-fatty acids[9].
3.4	Thrush-type genital infections are common with use of SGLT-2 inhibitors. Infections are more common early in treatment; providing information may improve continuation of treatment.
3.5	SGLT-2 inhibitors should be used with caution with loop diuretics. Check the need and whether alternative treatments could be used (e.g. for blood pressure).
3.6	Check urea and electrolyte (U&E) prior to initiation. Routine assessment of renal function within six to eight weeks of SGLT-2 inhibitor initiation is not required since there is likely to be a transient deterioration[8]. Two SGLT-2 inhibitors, empagliflozin* or ertugliflozin▼, may be initiated provided baseline eGFR ≥ 60 ml/min/1.73 m^2 (a lower cut off may be recommended for an individual by a diabetes specialist). Consider initiation with canagliflozin if baseline eGFR ≥ 45 ml/min/1.73 m^2 or ≥ 30 ml/min/1.73 m^2 provided ACR > 30 mg/mmol. Dapagliflozin can be initiated at baseline eGFR ≥ 15/ml/min/1.73 m^2. *Empagliflozin can be initiated at baseline eGFR ≥ 20 ml/min/1.73 m^2 if used for treatment of HF. If the person is taking a diuretic or is at risk of dehydration, consider monitoring blood pressure and checking U&E after starting an SGLT-2 inhibitor[17]. Note: The glycaemic efficacy of SGLT-2 inhibitors are dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment.

3.7	EMA and MHRA have advised caution in using SGLT-2 inhibitors in those at risk of lower limb amputation, as a class effect cannot be ruled out.
3.8	Other glucose lowering medications including insulin and sulphonylureas should be reviewed when SGLT-2 inhibitors are started, to avoid hypoglycaemia.
3.9	Caution should be exercised with SGLT-2 inhibitors in previous lower-limb amputation. Avoid initiation with SGLT-2 inhibitors in the following patient settings: • active foot disease/ existing diabetic foot ulcers • DKA (or previous episode of DKA) • person with excess alcohol consumption or intravenous drug users • diabetes due to pancreatic disease • genetic diabetes • unwell person (acute medical illness, surgery or planned medical procedure) • pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding • cognitive impairment • history of Fournier's gangrene • conditions leading to restricted food intake or severe dehydration. Seek advice from the local diabetes team if unsure about the benefits and risks.
3.10	Provide information regarding DKA risk minimisation measures. Advise patients on signs and symptoms of DKA and provide patients with sick day guidance advice[8,18,19].
4.0	**MONITORING EFFECTS OF SGLT-2 INHIBITORS[1-4]**
4.1	Ongoing monitoring and preventative foot care advice should be provided.
4.2	Check tolerability of medication and monitor glycaemic status.
4.3	Monitor renal function annually unless eGFR < 60 ml/min/1.73m^2, if so, check eGFR every three to six months. If eGFR falls < 30 ml/min/1.73m^2, canagliflozin can be continued at the lower dose (100 mg once daily)[1] provided ACR > 30 mg/mmol. No dose adjustment is required for dapaglifozin. If eGFR persistently falls below 45 ml/min/1.73m^2, consider discontinuing empagliflozin (if used for treatment other than HF) and ertugliflozin▼[2-4] unless there are renal/cardiac indications to continue these medications for cardio-renal preservation. A diabetes specialist may also recommend a lower cut off for an individual. Note: The glycaemic efficacy of SGLT-2 inhibitors are dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment. If further glycaemic control is needed, additional glucose-lowering treatment should be considered.
4.4	Consider DKA monitoring, in line with MHRA and NICE guidelines. Patients should be advised on how to recognise the signs and symptoms of DKA such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness, and to seek prompt medical attention if symptoms of DKA develop[9,20].
4.5	Blood ketones are not routinely monitored in T2DM however consider measuring blood ketones if patient presents feeling unwell and is not eating well.
4.6	SGLT-2 inhibitors may lead to a modest decrease in blood pressure. Review diuretic and anti-hypertensive therapy periodically if hypertension improves.
4.7	Consider careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) during intercurrent conditions.
5.0	**SPECIAL CONSIDERATIONS FOR THE FRAIL AND/OR ELDERLY[1-4]**
5.1	There is limited experience of using SGLT-2 inhibitors in the elderly. Empagliflozin is not recommended in patients > 85 years old. Canagliflozin and ertugliflozin▼ should be used with caution, particularly in patients > 75 years old.
5.2	Consider side effect profile in frailty as there is an increased risk of genito-urinary infections, diuresis and weight loss.
5.3	Consult sick day guidelines in those with poor hydration/oral intake and/or reduced renal function.
5.4	Check renal function during routine baseline testing pathways for T2DM, CV disease and any concomitant medications. Monitor for volume depletion and consider more frequent monitoring if eGFR declines.

ACR: albumin/creatinine ratio; CV: cardiovascular; DKA: diabetic ketoacidosis; eGFR: estimated glomerular filtration rate; EMA: European Medicines Agency; HF: heart failure; MHRA: Medicines and Healthcare products Regulatory Agency; T2DM: type 2 diabetes mellitus

3.1 Figure 2. Patient specific characteristics to consider when choosing an SGLT-2 inhibitor for a patient with T2DM and CV disease

There are no clinical trials directly comparing SGLT-2 inhibitors and the below recommendations are based on indirect comparisons†. The choice of agent and dose should always be specific to each individual patient based on their medical history and circumstances. The guidance below can be considered in consultation with the patient/guardian/carer, and should be informed by the summaries of product characteristics (SPCs) for the relevant drug, to determine which drug options may be most appropriate for individual patients presenting with the characteristics listed. For full prescribing information consult SPC[1-4].



: highlights those options that may be most appropriate for the relevant patient characteristic (when considered in isolation).

† Due to an update in canagliflozin and dapagliflozin licensing for the treatment of CKD in patients with T2DM, data from both CREDENCE and DAPA-CKD has been used to outline one of the patient specific characteristics.
‡ A history of an acute coronary syndrome or myocardial infarction (MI), stable or unstable angina, coronary heart disease with or without revascularisation, other arterial revascularisation, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.
§ Approximately 10% of these patient populations had cardiac failure at baseline.
** The glycaemic efficacy of SGLT-2 inhibitors is reduced and likely absent in patients with moderate and severe renal impairment respectively. Refer to recommendation 4.3.

3.2 Table 1. SGLT-2 inhibitor comparison table

	canagliflozin (view SPC)	dapagliflozin (view SPC)	empagliflozin (view SPC)	ertugliflozin▼ (view SPC)
Licensed indications	Treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes.	Type 2 diabetes mellitus Treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of type 2 diabetes mellitus. Heart failure Treatment of symptomatic chronic heart failure with reduced ejection fraction in adults Treatment of chronic kidney disease in adults.	Treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes. Heart failure Treatment of symptomatic chronic heart failure with reduced ejection fraction in adults	In adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control: • as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes.
Doses	100 mg once daily (recommended starting dose). Can be increased to 300 mg dose if additional glycaemic control is needed and 100 mg once daily is tolerated.	10 mg once daily.	10 mg once daily (recommended starting dose). Can be increased to 25 mg dose if additional glycaemic control is needed and 10 mg once daily is tolerated.	5 mg once daily (recommended starting dose). Can be increased to 15 mg once daily if additional glycaemic control is needed and 5 mg once daily is tolerated.
Renal impairment (eGFR ml/min/1.73 m^2)	≥ 60 ml/min/1.73 m^2 New patients: initiate 100 mg once daily Existing patients: no dose adjustment needed ≥ 45 – < 60 ml/min/1.73 m^2 New patients: initiate 100 mg once daily Existing patients: continue at 100 mg once daily. If further glycaemic control is needed, the addition of other anti-hyperglycemic agents should be considered. ≥ 30 – < 45 ml/min/1.73 m^2 New patients: initiate 100 mg once daily provided ACR > 30 mg/mmol Existing patients: continue at 100 mg once daily provided ACR > 30 mg/mmol. If further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered. < 30 ml/min/1.73m^2 New patients: should not be initiated Existing patients: continue at 100 mg once daily if eGFR falls below 30 ml/min/1.73m^2 (provided ACR > 30 mg/mmol). Canagliflozin may be continued for cardio-renal protection until commenced on renal replacement therapy.	≥ 45 ml/min/1.73 m^2 New patients: initiate 10 mg once daily Existing patients: no dose adjustment needed ≥ 15 – < 45 ml/min/1.73 m^2 New patients: 10mg once a day Existing patients: no dose adjustment needed. Additional glucose-lowering treatment should be considered if further glycaemic control is needed. Treatment of symptomatic chronic heart failure with reduced ejection fraction Dapagliflozin can be initiated at a baseline eGFR ≥ 15 ml/min/1.73 m^2. No dose adjustment is needed. If baseline eGFR < 15 ml/min/1.73 m^2 dapagliflozin is not recommended.	≥ 60 ml/min/1.73 m^2 New patients: initiate 10 mg once daily Existing patients: no dose adjustment needed ≥ 45 – < 60 ml/min/1.73 m^2 New patients: not recommended Existing patients: dose should be maintained at 10 mg once daily < 45 ml/min/1.73 m^2 New patients: not recommended Existing patients: discontinue Treatment of symptomatic chronic heart failure with reduced ejection fraction Empagliflozin can be initiated at a baseline eGFR ≥ 20 ml/min/1.73 m^2. No dose adjustment is needed. If baseline eGFR < 20 ml/min/1.73 m^2 empagliflozin is not recommended.	≥ 60 ml/min/1.73 m^2 New patients: initiate 5 mg once daily Existing patients: no dose adjustment needed ≥ 45 – < 60 ml/min/1.73 m^2 New patients: not recommended Existing patients: maintain dose < 45 ml/min/1.73 m^2 New patients: not recommended Existing patients: discontinue

	canagliflozin (view SPC)	dapagliflozin (view SPC)	empagliflozin (view SPC)	ertugliflozin▼ (view SPC)
Hepatic Impairment	Mild/moderate – No dose adjustment. Severe – not recommended	Mild/moderate – 10mg daily Severe – start at 5mg daily, titrate to 10mg if tolerated	Mild/moderate – No dose adjustment Severe – not recommended	Mild/moderate – No dose adjustment Severe – not recommended
Drug interactions	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Enzyme inducers such as St. John's wort, rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir and efavirenz may decrease canagliflozin concentrations and may lead to decreased efficacy. Plasma digoxin concentrations may increase. No dose adjustment of digoxin is recommended but patients at risk should be monitored for digoxin toxicity. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulphonylureas may be enhanced.	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulphonylureas may be enhanced.	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Co-medication with known enzyme inducers such as rifampicin and phenytoin, may lead to decreased efficacy. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulphonylureas may be enhanced.	Effect of diuretics may be increased. Increased risk of dehydration and hypotension. Hypoglycaemic effects of insulin and insulin secretagogues, such as sulphonylureas may be enhanced.
ACR: albumin/creatinine ratio; eGFR: estimated glomerular filtration rate				

4.0 CLINICAL EVIDENCE

The research question and Population, Intervention, Comparator, Outcomes (PICO) table were adapted from those first used by NICE in February 2017 (Appendix 1)[10]. A systematic literature search was undertaken on 28-29 October 2020. The search was adapted from that performed by NICE in February 2017 and the dates were restricted to between 2017 and November 2020 to reflect this[10]. Original study papers identified within the NICE evidence appraisal were also included. Identified studies were only included if CV outcomes were reported for people with T2DM (as per the PICO table).

4.1 Included studies

Evidence for the effects of SGLT-2 inhibitors in patients with T2DM derives from four large, multicentre, randomised, double-blinded and placebo-controlled outcome trials investigating predefined CV outcomes[21-25]. Characteristics of the four RCTs, including primary outcomes, background treatments used and population characteristics of the studies, are detailed in Appendix 2. Two of the RCTs were included in the NICE evidence review, one had compared canagliflozin versus placebo (on a background of standard of care treatments for T2DM and CV disease) in patients with T2DM who either had a history of symptomatic ASCVD or had two or more specific risk factors for CV disease (the CANVAS study)[1,22]. The second RCT had compared empagliflozin versus placebo (against a background of standard care) in patients with T2DM and for which established CV disease was part of the inclusion criteria (the EMPA-REG OUTCOME study)[21]. A third RCT was identified by the NICE evidence review as yet to be published and compared dapagliflozin versus placebo (on a background of standard of care treatments for T2DM and CV disease) in patients with T2DM who either had established ASCVD or multiple risk factors for ASCVD with a creatinine clearance ≥ 60 mL/min (DECLARE-TIMI 58)[23]. Original publications for both DECLARE-TIMI 58 and a fourth RCT were identified in the literature search for this evidence summary[23-25]. The fourth RCT compared ertugliflozin▾ versus placebo (against a background of standard care) in patients with T2DM and established CV disease (VERTIS CV)[24,25]. Further characteristics of the four RCTs are detailed in Appendix 2.

4.2 Excluded studies of note

T2DM was not specified within the inclusion criteria for two studies. One RCT compared dapagliflozin versus placebo (dapagliflozin, n = 2,373; placebo, n = 2,371) in patients with New York Heart Association class II, III, or IV heart failure (HF) and an ejection fraction of 40% or less with an elevated N-terminal pro-brain natriuretic peptide level (NT-proBNP level) (DAPA-HF)[26]. The primary outcome was a composite of worsening HF (HHF or an urgent visit resulting in intravenous therapy for HF) or CV death. The DAPA-HF Phase III trial demonstrated that dapagliflozin, in addition to standard-of-care, showed a statistically significant reduction in the primary outcome. On November 3rd 2020, based on the DAPA-HF results, the European Medicine Agency extended dapagliflozin's licence to include the treatment of symptomatic chronic HF with reduced ejection fraction in adults. DAPA-HF included both patients with and without T2DM, with 42% of the patient population having a history of T2DM (dapagliflozin, n = 993; placebo, n = 990)[26].

A second RCT compared empagliflozin versus placebo (empagliflozin, n = 1,863; placebo, n = 1,867) in patients with New York Heart Association class II, III, or IV HF and an ejection fraction of 40% or less with an elevated NT-proBNP level (EMPEROR-Reduced)[27]. The primary outcome was a composite of HHF (for worsening HF) or CV death. The EMPEROR-Reduced Phase III trial demonstrated that patients in the empagliflozin group had a lower risk of CV death or HHF, and that this was primarily related to a lower risk of HHF. In July 2021, the European Medicine Agency extended empagliflozin's licence to include the treatment of symptomatic chronic heart failure with reduced ejection fraction empagliflozin indicated in adults[28].

EMPEROR-Reduced included both patients with and without T2DM, with 49.8% of the patient population having a history of diabetes mellitus, type unspecified (empagliflozin, n = 927; placebo, n = 929)[27].

4.3 Clinical effectiveness

Relevant CV outcomes were extracted from each of the four RCTs, and related post-hoc analyses, and are reported in Appendix 3. These outcomes are also described in this section and key outcomes summarised in Table 2.

4.3.1 Composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (also known as MACE)

Three of four RCTs measured a composite outcome of death from CV causes, nonfatal MI or nonfatal stroke using the number of participants with an event per 1,000 patient years (widely known as MACE) while the fourth RCT measured this composite outcome using a number of participants with an event per 100 patient years[21-24]. CANVAS found canagliflozin to be both non-inferior ($p < 0.001$) and superior ($p = 0.02$) to placebo (hazard ratio [HR] [95% CI] 0.86 [0.75–0.97])[22]. EMPA-REG OUTCOME found empagliflozin to be both non-inferior ($p < 0.001$) and superior ($p = 0.04$) to placebo (HR [95% CI] 0.86 [0.74–0.99])[21].

DECLARE-TIMI 58 found dapagliflozin to be non-inferior to placebo ($p < 0.001$)[23]. The trial was designed so that, if non-inferiority was confirmed, efficacy outcomes of MACE and the composite of CV death or HHF were tested in parallel. Dapagliflozin was not superior to placebo for MACE in that test (HR [95% CI] 0.93 [0.84–1.03], $p = 0.17$)[23]. VERTIS CV found ertugliflozin▾ to be non-inferior to placebo ($p < 0.001$) however a test of superiority was not planned for this outcome (HR [95% CI] 0.97 [0.85–1.11])[24].

4.3.2 Cardiovascular mortality and all-cause mortality

All four RCTs measured all-cause mortality[21-24]. When measuring the number of participants with an event per 1,000 patient years, a significant difference between empagliflozin and placebo was found in EMPA-REG OUTCOME (HR [95% CI] 0.68 [0.57–0.82], $p < 0.001$)[21]. CANVAS, DECLARE-TIMI 58 and VERTIS CV did not report further statistics for this outcome[22-24].

All four RCTs measured CV mortality[21-24]. When measuring the number of participants with an event per 1,000 patient years, a significant difference between empagliflozin and placebo was found in EMPA-REG OUTCOME (HR [95% CI] 0.62 [0.49–0.77], $p < 0.001$)[21]. CANVAS, DECLARE-TIMI 58 and VERTIS CV did not report further statistics for this outcome[22-24]. A publication with post-hoc analyses on EMPA-REG OUTCOME data found, when stratifying patients according to TRS-HF_{DM}, a significant difference across groups, from low to intermediate risk (absolute risk ratio [ARR] [95% CI] -2.3 [-6.0–1.4]), to high risk (ARR [95% CI] -9.1 [-17.3– -1.0]), to very high risk (ARR [95% CI] -17.6 [-28.8– -6.5]) ($p = 0.0105$)[29]. A publication with post-hoc analyses on DECLARE-TIMI 58 data found a significant difference between the use of dapagliflozin for patients with HF and reduced ejection fraction (HFrEF) when compared with patients without either HFrEF or any history of HF, when using Kaplan-Meier rates and ARR ($p = 0.012$)[30].

4.3.3 Evidence in heart failure

All four RCTs measured hospitalisation for heart failure (HHF)[21-24].

No significant difference was reported between canagliflozin and placebo in the original CANVAS publication for HHF[22]. A publication with post-hoc analyses on CANVAS programme data found a significant difference between canagliflozin and placebo for fatal HF or HHF (HR [95% CI] 0.70 [0.55–0.89], $p = 0.003$ [nominal]) and HHF (HR [95% CI] 0.67 [0.52–0.87], $p = 0.002$ [nominal])[31]. When examining the absolute risk difference (ARD) for 1,000 patients over five years (estimated as differences in

incidence rates between subgroups) between patients with a history of HF (ARD [95% CI] -70.17 [-114.34– -26.00]) and those with no history of HF (ARD [95% CI] -6.93 [-15.09–1.22]), a significant difference was found (p = 0.01) in favour of those patients with a history of HF. The same publication found a significant difference between canagliflozin and placebo for a composite outcome of CV death or HHF (HR [95% CI] 0.79 [0.67–0.91], p = 0.002). A significant difference was also found when comparing ARD (as previously described) between patients with a history of HF (ARD [95% CI] -106.97 [-171.59– -42.34]) and those with no history of HF (ARD [95% CI] -8.36 [-22.08–5.36], p = 0.003), again in favour of those patients with a history of HF[31].

When measuring the number of participants with an event per 1,000 patient years, a significant difference between empagliflozin and placebo was found in EMPA-REG OUTCOME for HHF, an exploratory outcome (HR [95% CI] 0.65 [0.50–0.85], p = 0.002 [nominal])[32]. A publication with post-hoc analyses on EMPA-REG OUTCOME data found, when stratifying patients according to a Thrombolysis in Myocardial Infarction (TIMI) Risk Score for HF in Diabetes (TRS-HF_{DM}), a significant difference across groups, from low to intermediate risk (absolute risk ratio [ARR] [95% CI] -3.8 [-8.2–0.5]), to high risk (ARR [95% CI] -11.9 [-21.8– -1.9]), to very high risk (ARR [95% CI] -24.1 [-39.1– -9.1) (p = 0.0107)[29].

No significant difference was reported between dapagliflozin and placebo in the original DECLARE-TIMI 58 publication for HHF (HR [95% CI] 0.73 [0.61–0.88])[23]. This lower rate of HHF was reflected in the lower rate of CV death or HHF (Section 4.3.4). A publication with post-hoc analyses on DECLARE-TIMI 58 data found a significant difference in ARR when comparing the subgroups of previous myocardial infarction (MI, ARR [95% CI] 1.8% [0.3%–3.2%]) and no previous MI (ARR [95% CI] 0.6% [0.1%–1.1%], p = 0.001)[33].

No test for statistical significance was reported between ertugliflozin▾ and placebo in the original VERTIS CV publication for HHF (HR [95% CI] 0.70 [0.54–0.90])[24]. A publication with pre-specified secondary analysis on VERTIS CV, measuring time to first HHF as rate with an event per 100 patient years, found significant differences in favour of ertugliflozin▾ when compared with placebo (HR [95% CI] 0.70 [0.54–0.90], p = 0.006), at 5 mg (HR [95% CI] 0.71 [0.52–0.97], p = 0.028) and at 15 mg of ertugliflozin▾ (HR [95% CI] 0.68 [0.50–0.93], p = 0.015)[34]. Significant differences were also found between groups, in favour of patients with an eGFR < 60 mL/min/1.73 m^2 (p = 0.04), patients with micro or macro albuminuria (p = 0.04), patients taking a diuretic (p = 0.02) and patients taking a loop diuretic (p = 0.01)[34].

4.3.4 Composite of cardiovascular death or hospitalisation for heart failure

All four RCTs measured a composite of CV death or HHF[21-24]. No significant difference was reported between canagliflozin and placebo in the original CANVAS publication for this outcome[22]. When measuring the number of participants with an event per 1,000 patient years, a significant difference between empagliflozin and placebo was found in EMPA-REG OUTCOME for this composite exploratory outcome (HR [95% CI] 0.66 [0.55–0.79], p < 0.001 [nominal])[21]. When measuring the rate of this outcome between dapagliflozin and placebo, a significant difference was found in DECLARE-TIMI 58 (HR [95% CI] 0.83 [0.73–0.95], p = 0.005)[23]. No significant difference was found between ertugliflozin▾ and placebo in VERTIS CV for this outcome (HR [95% CI] 0.88 [0.75–1.03], p = 0.11)[24].

4.3.5 Evidence in myocardial infarction

CANVAS and EMPA-REG OUTCOME measured non-fatal myocardial infarction (MI) by comparing the number of participants with an event per 1,000 patient years while VERTIS CV measured this composite outcome using a number of participants with an event per 100 patient years[21,22,24]. EMPA-REG OUTCOME did not find a significant difference between empagliflozin use and placebo while the other two studies did not

report further statistics for this outcome[21,22,24]. A secondary analysis of selected total events of EMPA-REG OUTCOME data found a significant difference in relative risk reduction of total MI events (fatal or non-fatal) for empagliflozin use (risk ratio [RR] [95% CI] 0.79 [0.67–1.15]; p = 0.049)[35]. Post-hoc analyses of DECLARE-TIMI 58 data measured a composite of fatal or non-fatal MI finding a significant difference in absolute risk reduction (ARR) between the subgroups, patients with previous MI (ARR [95% CI] 2.5% [0.5%–4.5%]) and patients with no previous MI (ARR [95% CI] 0% [-0.6%–0.6%], p = 0.019)[33]. A second publication which stratified patients according to length of time with a diagnosis of T2DM, found a significant difference in fatal or non-fatal MI across the five groups, ≤ 5 years (HR [95% CI] 1.11 [0.81–1.52]), 5–10 years (HR [95% CI] 0.97 [0.74–1.28]), 10–15 years (HR [95% CI] 0.88 [0.67–1.15]), 15–20 years (HR [95% CI] 0.82 [0.58–1.15]) and > 20 years (HR [95% CI] 0.66 [0.47–0.92], p = 0.019)[36].

4.3.6 Evidence in stroke

CANVAS and EMPA-REG OUTCOME measured fatal or non-fatal stroke in their original publications by comparing the number of participants with an event per 1,000 patient years while VERTIS CV measured this composite outcome using a number of participants with an event per 100 patient years[21,22,24]. No significant difference was found for EMPA-REG OUTCOME data while no further statistics were reported for CANVAS and VERTIS CV data[21,22,24].

Post-hoc analyses of CANVAS data and DECLARE-TIMI 58 data measured fatal stroke by either comparing the number of participants with an event per 1,000 patient years or the rate of stroke in subgroups of patients (with or without HF and reduced ejection fraction) respectively[30,37]. No significant difference was found for CANVAS data while no further statistics were reported for DECLARE-TIMI 58[30,37].

CANVAS, EMPA-REG OUTCOME and VERTIS CV all measured non-fatal stroke by comparing the number of participants with an event per 1,000 patient years[21,22,24]. Again, EMPA-REG OUTCOME did not find a significant difference between empagliflozin use and placebo while the other two studies did not report further statistics for this outcome[21,22,24].

A publication with post-hoc analyses for CANVAS programme data found a significant difference in haemorrhagic stroke between canagliflozin and placebo (HR [95% CI] 0.43 [0.20–0.89], p = 0.02)[37]. This outcome was not reported for the other trials. The same publication, when stratifying patients according to eGFR, found a significant difference across the three groups in relation to fewer stroke events per 1,000 patient years, 30 to < 60 ml/min/1.73 m^2 (HR [95% CI] 0.50 [0.30–0.83]), 60 to < 90 ml/min/1.73 m^2 (HR [95% CI] 0.89 [0.65–1.21]) and ≥ 90 ml/min/1.73 m^2 (HR [95% CI] 1.42 [0.86–2.36], p = 0.005)[37].

A publication with post-hoc analyses for DECLARE-TIMI 58 data in ischaemic stroke, where patients were stratified according to length of time with a diagnosis of T2DM, found a significant difference across the five groups, ≤ 5 years (HR [95% CI] 1.32 [0.89–1.98]), 5–10 years (HR [95% CI] 1.08 [0.75–1.56]), 10–15 years (HR [95% CI] 1.07 [0.74–1.54]), 15–20 years (HR [95% CI] 0.89 [0.55–1.42]) and > 20 years (HR [95% CI] 0.61 [0.38–1.00], p = 0.015)[36]. This outcome was also reported for CANVAS in a post-hoc analysis but no significant difference was found[37].

4.3.7 Risk of lower limb amputation

CANVAS, DECLARE-TIMI 58 and VERTIS CV all measured amputation prospectively[22-24]. CANVAS measured amputation by comparing the number of participants with an event per 1,000 patient years and found a significant difference between canagliflozin use and placebo (HR [95% CI] 1.97 [1.41–2.75], p < 0.001)[22]. DECLARE-TIMI 58 found no significant difference between dapagliflozin use and

placebo for this outcome (HR [95% CI] 1.09 [0.84–1.40], p = 0.53)[23]. VERTIS CV also found no significant difference between ertugliflozin▾ use and placebo for this outcome but did not report an exact figure (Risk difference [95% CI] 0.1 [–0.1– 0.3])[24]. A post-hoc analysis of EMPA-REG OUTCOME found no significant difference between empagliflozin use (pooled) and placebo for this outcome (HR [95% CI] 1.00 [0.70–1.44])[38].

Table 2. Summary of SGLT-2 inhibitor CV outcomes

Outcome (HR [95% CI]) in T2DM	Empagliflozin (EMPA-REG OUTCOME)	Canagliflozin (CANVAS)	Dapagliflozin (DECLARE-TIMI 58)	Ertugliflozin▾ (VERTIS CV)
CV death, non-fatal MI or non-fatal stroke (MACE)	0.86 (0.74 -0.99); p < 0.001 for non-inferiority; p = 0.04 for superiority[21]	0.86 (0.75–0.97); p < 0.001 for non-inferiority; p = 0.02 for superiority[22]	0.93 (0.84–1.03); p < 0.001 for non-inferiority; p = 0.17 for superiority [23]	0.97 (0.85–1.11); p < 0.001 for non-inferiority; further statistics not reported [24]
CV death	0.62 (0.49–0.77); p < 0.001[21]	0.88 (0.70–1.10)[22]	0.98 (0.82–1.17)[23]	0.92 (0.77–1.11)[24]
Hospitalisation for heart failure	0.65 (0.50–0.85); p = 0.002[21]	0.67 (0.52–0.87)[22]	0.73 (0.61–0.88)[23]	0.70 (0.54–0.90)[24]
CV death or hospitalisation for heart failure	0.66 (0.55–0.79); p < 0.001[21]	0.78 (0.67–0.91); p = 0.4584[22]	0.83 (0.73–0.95); p = 0.005 for superiority[23]	0.88 (0.75–1.03); p = 0.11 for superiority[24]
All-cause mortality	0.68 (0.57–0.82); p < 0.001[21]	0.87 (0.74–1.01)[22]	0.93 (0.82–1.04)[23]	0.93 (0.80–1.08)[24]
Fatal or non-fatal MI	0.87 (0.70–1.09); p = 0.23[21]	0.89 (0.73–1.09)[22]	0.89 (0.77–1.01)[23]	1.04 (0.86–1.26)[24]
Fatal or non-fatal stroke	1.18 (0.89–1.56); p = 0.26[21]	0.87 (0.69–1.09); p = 0.23[22,37*]	1.01 (0.84–1.21)†	1.06 (0.82–1.37)[24]

*includes statistics from secondary publications
†reported as ischaemic stroke in text
CV: cardiovascular; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NR: not reported; T2DM: type 2 diabetes mellitus

4.4 Safety

The adverse reactions of SGLT-2 inhibitors are broadly similar. The most common adverse drug reactions, as reported by the RCTs, are hypoglycaemia and urogenital infection (urinary tract infections [UTIs] and candidal infection)[21-24]. Adverse drug reactions related to volume depletion (such as dehydration, hypovolaemia and hypotension) have also been reported. Rare cases of diabetic ketoacidosis (DKA) have been reported in clinical trials and post-marketing of SGLT-2 inhibitors; cases of DKA were reported in all four RCTs included in this evidence review[21-24]. Adverse events in CANVAS attributed to canagliflozin included increased risk of amputations (primarily at the level of the toe or metatarsal), fracture and genital infection, although there was evidence of heterogeneity between the CANVAS and CANVAS-R populations for fracture[22]. CREDENCE, an RCT comparing canagliflozin versus placebo in patients with T2DM and albuminuric CKD, found both the risk of lower-limb amputation (HR [95% CI] 1.11 [0.79–1.56]) and also the rate of fracture (HR [95% CI] 0.98 [0.70–1.37]) to not be significant between treatment groups[39]. The authors did not report p values for these outcomes as they were not included in the hierarchical-testing strategy[39]. EMPA-REG OUTCOME did not look at lower-limb amputations associated with empagliflozin use[21]. In March 2017 the Medicines and Healthcare products Regulatory Agency (MHRA) warned that canagliflozin increased the risk of lower-limb amputation (mainly toes) in patients with T2DM[40]. Evidence does not show an increased risk for dapagliflozin and empagliflozin, but the risk may be a class effect[40]. An increased risk of bone fractures has been reported with canagliflozin, and decreases in bone mineral density at the hip and lumbar spine[8,41].

4.4.1 MHRA Drug Safety Updates

MHRA Drug Safety update April 2016: SGLT-2 inhibitors: updated advice on the management of the risk of diabetic ketoacidosis[20].

MHRA Drug Safety update June 2016: Canagliflozin (Invokana, Vokanamet): signal of increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients[41].

MHRA Drug Safety update March 2017: SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)[40]

MHRA Drug Safety update February 2019: SGLT-2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum). Fournier's gangrene is a rare but this serious bacterial infection needs urgent treatment[42].

MHRA Drug Safety update March 2020: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness[43]

5.0 RENAL EFFECTS OF SGLT-2 INHIBITORS

5.1 Relevant existing guidance

The Association of British Clinical Diabetologists updated recommendations on the management of hyperglycaemia in adults with diabetic kidney disease in 2021. A review of the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase was carried out in December 2020 and an evidence grading system applied to the recommendations. This guideline, Clinical practice guidelines for the management of hyperglycaemia in adults with diabetic kidney disease, is endorsed by the Renal Association. The document currently outlines 14 recommendations relating to SGLT-2 inhibitor use summarising licensing status and clinical trial evidence of canagliflozin, dapagliflozin, empagliflozin and ertugliflozin▾. The authors recommend SGLT-2 inhibitors are considered in all individuals with T2DM with an eGFR ≥ 30 ml/min/1.73 m^2, irrespective of glycaemic control, recognising that it is currently off-licence to do so.

NICE updated guidelines for the care and treatment of people with, or at risk of developing, CKD in 2021 (NG203)[44]. It combines the following NICE guidelines using multiple evidence reviews to inform recommendations: chronic kidney disease in adults, assessment and management (CG182); chronic kidney disease (stage 4 or 5), management of hyperphosphataemia (CG157); and chronic kidney disease, managing anaemia (NG8). Based on the evidence, the guidelines state that SGLT-2 inhibitors reduce the risk of end-stage renal disease, mortality and hospitalisation in adults with T2DM. It recommends that, for adults with CKD and T2DM, an SGLT-2 inhibitor should be offered in addition to an ACE inhibitor or an ARB, if they have an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisations (including relevant eGFR thresholds)[45].

5.2 Key renal dedicated SGLT-2 inhibitor trials and renal outcomes

Due to the interrelated relationship between T2DM, CKD and CV risk, two RCTs have been described below as they include evidence that supports some of the prescribing guideline recommendations (featured within Section 5 and Figure 2). Renal outcomes reported in CANVAS, DECLARE-TIMI 58 and VERTIS CV are also described below.

One RCT compared canagliflozin versus placebo (canagliflozin, n = 2,202; placebo, n = 2,199) in patients with T2DM and albuminuric CKD (CREDENCE)[39]. The primary outcome was a composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an eGFR of < 15 ml per minute per 1.73 m^2 sustained for at least 30 days), doubling of the serum creatinine level from baseline sustained for at

least 30 days, or death from renal or CV disease. This was measured using the number of participants with an event per 1,000 patient years. The CREDENCE Phase III trial demonstrated that canagliflozin, in addition to standard-of-care, showed a statistically significant reduction in the primary outcome, with a 30% lower relative risk for patients in the canagliflozin group (HR [95% CI] 0.70 [0.59–0.82], p = 0.00001)[39]. A secondary outcome, a composite of end-stage kidney disease, doubling of the serum creatinine level or renal death, demonstrated a statistically significant lower relative risk for patients in the canagliflozin group (HR [95% CI] 0.66 [0.53–0.81], p < 0.001). End-stage kidney disease, when separate from the composite primary outcome, demonstrated a statistically significant lower relative risk for patients in the canagliflozin group (HR [95% CI] 0.68 [0.54–0.86], p = 0.002). On June 26th 2020, based on the CREDENCE results, the European Medicine Agency extended canagliflozin's licence to include the treatment of diabetic kidney disease as an add on to standard-of-care[46].

A second RCT compared dapagliflozin versus placebo (dapagliflozin, n = 2,151; placebo, n = 2,152) in patients with or without T2DM who had an eGFR of 25 to 75 ml per minute per 1.73 m^2 of body-surface-area and a urinary-to-creatinine ratio or 200 to 5,000 (DAPA-CKD)[47]. The primary outcome was a composite of the first occurrence of any of the following: a decline of at least 50% in e GFR, the onset of end-stage kidney disease (defined as maintenance dialysis for ≥ 28 days, kidney transplantation, or an eGFR of < 15 ml per minute per 1.73 m^2 confirmed by a second measurement after ≥ 28 days), or death from renal or CV causes. This was measured in a time-to-event analysis. The DAPA-CKD Phase III trial demonstrated that dapagliflozin, in addition to standard-of-care, showed a statistically significant reduction in the primary outcome (HR [95% CI] 0.61 [0.51–0.72], p < 0.001). A secondary outcome, a composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal causes, demonstrated a statistically significant lower relative risk of 44% for patients in the dapagliflozin group (HR [95% CI] 0.56 [0.45–0.68], p < 0.001). No test for statistical significance was reported between dapagliflozin and placebo for end-stage kidney disease, when separate from the composite primary outcome (HR [95% CI] 0.64 [0.50–0.82]). The proportion of people in each group with T2DM was similar (dapagliflozin, n = 1,455; placebo, n = 1,451)[47]. On 9th August 2021, based on DAPA CKD results, the Medicines and Healthcare products Regulatory Agency extended dapagliflozin's to include the treatment of chronic kidney disease in adults[48].

VERTIS measured a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level, a secondary outcome, by comparing the number of participants with an event per 100 patient years between ertugliflozin▾ and placebo (HR [95% CI] 0.81 [0.63–1.04]); no test for statistical significance was reported[24].

CANVAS measured the progression of albuminuria, a secondary outcome, by comparing the number of participants with an event per 1,000 patient years between canagliflozin and placebo (HR [95% CI] 0.73 [0.67–0.79]); no test for statistical significance was reported[22].

DECLARE TIMI 58 measured a composite of a sustained decline in eGFR of at least 40%, new end-stage renal disease, or death from renal or CV causes, a secondary outcome, by comparing the number of participants with an event per 1,000 patient years between dapagliflozin and placebo (HR [95% CI] 0.76 [0.67–0.87]; p < 0.001)[23]. An additional pre-specified composite outcome, including all of the criteria of the former outcome excluding death from CV causes, also demonstrated a lower relative risk for patients in the dapagliflozin group (HR [95% CI] 0.53 [0.43–0.66]; p < 0.0001)[23].

REFERENCES

1. Napp Pharmaceuticals Limited. Invokana®. Summary of Product Characteristics. Jul 2020. Available at: https://www.medicines.org.uk/emc/product/8855/smpc. Accessed Dec 2020.
2. AstraZeneca UK Limited. Forxiga®. Summary of Product Characteristics. Nov 2020. Available at: https://www.medicines.org.uk/emc/product/7607/smpc. Accessed Dec 2020.
3. Boehringer Ingelheim Limited. Jardiance®. Summary of Product Characteristics. Oct 2020. Available at: https://www.medicines.org.uk/emc/product/5441/smpc. Accessed Dec 2020.
4. Merck Sharp & Dohme Limited. Steglatro®. Summary of Product Characteristics. Aug 2020. Available at: https://www.medicines.org.uk/emc/product/10099/smpc. Accessed Dec 2020.
5. Buse JB, Wexler DJ, Tsapas A et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2020;43:487-493. Available at: https://doi.org/10.2337/dci19-0066. Accessed Jan 2021.
6. Cosentino F, Grant PJ, Aboyans V et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European Heart Journal.* 2020;41:255-323. Available at: https://doi.org/10.1093/eurheartj/ehz486. Accessed Jan 2021.
7. Cardio-Renal-Metabolic (CaReMeUK) Partnership. Guide for non-diabetes specialist physicians and primary care teams for cardiovascular risk optimisation in patients with Type 2 diabetes and atherosclerotic cardiovascular disease (coronary artery disease, peripheral arterial disease, cerebrovascular disease). Apr 2021. Available at: https://www.guidelines.co.uk/cardiovascular/caremeuk-cardiovascular-risk-optimisation-algorithm/455896.article. Accessed Jun 2021.
8. Association of British Clinical Diabetologists and The Renal Association. Managing hyperglycaemia in people with diabetes and chronic kidney disease. . Feb 2021. Available at: https://renal.org/sites/renal.org/files/Managing%20hyperglycaemia%20in%20people%20with%20DKD_final%20draft.pdf. Accessed Jun 2021.
9. National Institute for Health and Care Excellence. NICE Guideline, NG28. Type 2 diabetes in adults: management. Aug 2019. Available at: https://www.nice.org.uk/guidance/ng28. Accessed Dec 2020.
10. National Institute for Health and Care Excellence. NICE Guideline Evidence Review, NG28. Evidence reviews for SGLT-2 inhibitors and GLP-1 mimetics. Mar 2018. Available at: https://www.nice.org.uk/guidance/ng28/evidence/march-2018-evidence-reviews-for-sglt2-inhibitors-and-glp1-mimetics-pdf-4783687597. Accessed Dec 2020.
11. Davies MJ, D'Alessio DA, Fradkin J et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2018;44. Available at: https://doi.org/10.2337/dci18-0033. Accessed Jan 2021.
12. National Institute for Health and Care Excellence. Technology Appraisal 288. Dapagliflozin in combination therapy for treating type 2 diabetes. Nov 2016. Available at: https://www.nice.org.uk/guidance/ta288. Accessed Dec 2020.
13. National Institute for Health and Care Excellence. Technology Appraisal 315. Canagliflozin in combination therapy for treating type 2 diabetes. Jun 2014. Available at: https://www.nice.org.uk/guidance/TA315. Accessed Dec 2020.
14. National Institute for Health and Care Excellence. Technology Appraisal 336. Empagliflozin in combination therapy for treating type 2 diabetes. Mar 2015. Available at: https://www.nice.org.uk/guidance/TA336. Accessed Dec 2020.

15. National Institute for Health and Care Excellence. Technology Appraisal 418. Dapagliflozin in triple therapy for treating type 2 diabetes. Nov 2016. Available at: https://www.nice.org.uk/guidance/TA418. Accessed Dec 2020.
16. National Institute for Health and Care Excellence. NICE Guideline, CG181. Cardiovascular disease: risk assessment and reduction, including lipid modification. September 2016. Available at: https://www.nice.org.uk/guidance/cg181/chapter/1-Recommendations. Accessed Sept 2021.
17. Dashora U, Patel D, Nagi D et al. SGLT-2 inhibitors in people with type 2 diabetes: An educational resource for health professionals. *ABCD (DIABETES CARE) LTD.* 2020. Available at: https://abcd.care/sites/abcd.care/files/site_uploads/Resources/Position-Papers/SGLT2-inhibitors-ABCD.pdf. Accessed Feb 2021.
18. Diabetes UK. What is DKA (Diabetic Ketoacidosis)? Nov 2019. Available at: https://www.diabetes.org.uk/guide-to-diabetes/complications/diabetic_ketoacidosis. Accessed Jun 2021.
19. Diabetes UK. Diabetes when you're unwell. Jan 2017. Available at: https://www.diabetes.org.uk/guide-to-diabetes/life-with-diabetes/illness. Accessed Jun 2021.
20. Medicines and Healthcare products Regulatory Agency. SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis. Apr 2016. Available at: https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis. Accessed Dec 2020.
21. Zinman B, Inzucchi SE, Lachin JM et al. Empagliflozin and Cerebrovascular Events in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk. *Stroke.* 2017;48:1218-1225. Available at: http://dx.doi.org/10.1161/STROKEAHA.116.015756. Accessed Dec 2020.
22. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England Journal Of Medicine.* 2017;377:644-657. Available at: http://doi.org/10.1056/NEJMoa1611925. Accessed Dec 2020.
23. Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *The New England Journal Of Medicine.* 2019;380:347-357. Available at: http://dx.doi.org/10.1056/NEJMoa1812389. Accessed Dec 2020.
24. Cannon CP, Pratley R, Dagogo-Jack S et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *The New England Journal Of Medicine.* 2020;383:1425-1435. Available at: http://dx.doi.org/10.1056/NEJMoa2004967. Accessed Dec 2020.
25. Cannon CP, McGuire DK, Pratley R et al. Design and baseline characteristics of the eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV). *American Heart Journal.* 2018;206:11-23. Available at: http://dx.doi.org/10.1016/j.ahj.2018.08.016. Accessed Dec 2020.
26. McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *The New England Journal Of Medicine.* 2019;381(21):1995-2008. Available at: http://dx.doi.org/10.1056/NEJMoa1911303. Accessed Dec 2020.
27. Packer M, Anker SD, Butler J et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *The New England Journal Of Medicine.* 2020;383:1413-1424. Available at: https://doi.org/10.1056/NEJMoa2022190. Accessed Jan 2021.
28. European Medicines Agency. Committee for Medicinal Products for Human Use: Jardiance®. Procedure No. EMEA/H/C/002677/II/0055. July 2021. Available at: https://www.ema.europa.eu/en/documents/variation-report/jardiance-h-c-002677-ii-0055-epar-assessment-report-variation_en.pdf. Accessed Aug 2021.

29. Verma S, Sharma A, Zinman B et al. Empagliflozin reduces the risk of mortality and hospitalization for heart failure across Thrombolysis In Myocardial Infarction Risk Score for Heart Failure in Diabetes categories: Post hoc analysis of the EMPA-REG OUTCOME trial. *Diabetes, Obesity & Metabolism.* 2020;22:1141-1150. Available at: http://dx.doi.org/10.1111/dom.14015. Accessed Dec 2020.
30. Kato ET, Silverman MG, Mosenzon O et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation.* 2019;139:2528-2536. Available at: http://dx.doi.org/10.1161/CIRCULATIONAHA.119.040130. Accessed Dec 2020.
31. Rådholm K, Figtree G, Perkovic V et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus. Results From the CANVAS Program. *Circulation.* 2018;138:458-468. Available at: http://dx.doi.org/10.1161/CIRCULATIONAHA.118.034222. Accessed Dec 2020.
32. Zinman B, Wanner C, Lachin JM et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine.* 2015;373:2117-2128. Available at: http://dx.doi.org/10.1056/NEJMoa1504720. Accessed Jun 2021.
33. Furtado RHM, Bonaca MP, Raz I et al. Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction. Subanalysis From the DECLARE-TIMI 58 Trial. *Circulation.* 2019;139:2516-2527. Available at: http://dx.doi.org/10.1161/CIRCULATIONAHA.119.039996. Accessed Dec 2020.
34. Cosentino F, Cannon CP, Cherney DZI et al. Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients with Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERTIS CV Trial. *Circulation.* 2020;142:2205-2215. Available at: http://dx.doi.org/10.1161/CIRCULATIONAHA.120.050255. Accessed Dec 2020.
35. McGuire DK, Zinman B, Inzucchi SE et al. Effects of empagliflozin on first and recurrent clinical events in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a secondary analysis of the EMPA-REG OUTCOME trial. *The Lancet Diabetes & Endocrinology.* 2020;8:949-959. Available at: https://doi.org/10.1016/S2213-8587(20)30344-2. Accessed Jun 2021.
36. Bajaj HS, Raz I, Mosenzon O et al. Cardiovascular and renal benefits of dapagliflozin in patients with short and long-standing type 2 diabetes: Analysis from the DECLARE-TIMI 58 trial. *Diabetes, Obesity & Metabolism.* 2020;22:1122-1131. Available at: http://dx.doi.org/10.1111/dom.14011. Accessed Dec 2020.
37. Zhou Z, Lindley RI, Rådholm K et al. Canagliflozin and Stroke in Type 2 Diabetes Mellitus. Results From the Randomized CANVAS Program Trials. *Stroke.* 2019;50:396-404. Available at: http://dx.doi.org/10.1161/STROKEAHA.118.023009. Accessed Dec 2020.
38. Inzucchi SE, Iliev H, Pfarr E et al. Empagliflozin and Assessment of Lower-Limb Amputations in the EMPA-REG OUTCOME Trial. *Diabetes Care.* 2018;41. Available at: https://doi.org/10.2337/dc17-1551. Accessed Jun 2021.
39. Perkovic V, Jardine MJ, Neal B et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *The New England Journal Of Medicine.* 2019;380:2295-2306. Available at: http://doi.org/10.1056/NEJMoa1811744. Accessed Jan 2021.
40. Medicines and Healthcare products Regulatory Agency. SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes). Mar 2017. Available at: https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-increased-risk-of-lower-limb-amputation-mainly-toes. Accessed Dec 2020.
41. Medicines and Healthcare products Regulatory Agency. Canagliflozin (Invokana▼, Vokanamet▼): signal of increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients. Jun 2016. Available at: https://www.gov.uk/drug-safety-update/canagliflozin-invokana-

vokanamet-signal-of-increased-risk-of-lower-extremity-amputations-observed-in-trial-in-high-cardiovascular-risk-patients. Accessed Dec 2020.

42. Medicines and Healthcare products Regulatory Agency. SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum). Feb 2019. Available at: https://www.gov.uk/drug-safety-update/sglt2-inhibitors-reports-of-fournier-s-gangrene-necrotising-fasciitis-of-the-genitalia-or-perineum. Accessed Dec 2020.
43. Medicines and Healthcare products Regulatory Agency. SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness. Mar 2020. Available at: https://www.gov.uk/drug-safety-update/sglt2-inhibitors-monitor-ketones-in-blood-during-treatment-interruption-for-surgical-procedures-or-acute-serious-medical-illness. Accessed Jan 2021.
44. National Institute for Health and Care Excellence. NICE Guideline, NG203. Chronic kidney disease: assessment and management. August 2021. Available at: https://www.nice.org.uk/guidance/cg181/chapter/1-Recommendations. Accessed Sept 2021.
45. National Institute for Health and Care Excellence. NICE Evidence. Chronic kidney disease: assessment and management (update). In development [GID-NG10118]. Aug 2021. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ng10118. Accessed Jun 2021.
46. European Medicines Agency. Assessment Report: Invokana®. Procedure No.: EMEA/H/C002649. Jun 2020. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/invokana. Accessed Jun 2021.
47. Heerspink HJL, Stefánsson BV, CorreaRotter R et al. Dapagliflozin in Patients with Chronic Kidney Disease. *The New England Journal Of Medicine.* 2020;383:1436-1446. Available at: http://dx.doi.org/10.1056/NEJMoa2024816. Accessed Jun 2021.
48. Pharmatimes online. AZ's Forxiga gains EC, MHRA approvals for chronic kidney disease. Aug 2021. Available at: https://www.pharmatimes.com/news/azs_forxiga_gains_ec,_mhra_approvals_for_chronic_kidney_disease_1374412. Accessed August 2021.

APPENDIX 1: PICO TABLE

Population	Adults (aged 18 years and older) with Type 2 diabetes mellitus.
Intervention	Sodium-glucose cotransporter-2 inhibitors (SGLT-2), including: • Canaglifozin • Dapaglifozin • Empaglifozin • Ertugliflozin▾ In mono, dual or triple therapy or as an add-on to insulin therapy
Comparator	There will be a stepwise approach to comparators: 1. Studies that compare SGLT-2 inhibitors to each other (active comparators within class) 2. If no studies that identify SGLT-2 inhibitor v another SGLT-2 inhibitor, then comparators of usual care, no treatment or placebo will be used.
Outcomes	Cardiovascular outcomes: • Cardiovascular mortality • Fatal MI • Non-fatal MI • Fatal stroke • Non-fatal stroke • Heart failure • Lower limb amputation
Study design	RCT
Exclusion criteria	English language only. Published studies, full text only.

APPENDIX 2: CLINICAL STUDY SUMMARIES

Original study (Secondary published analyses)	Study nickname and identifier number	Type of Study	Population	Intervention	Comparison	Outcomes (cardiovascular)
Neal et al. 2017 (Radholm et al. 2018, Matthews et al. 2019, Zhou et al. 2019)	CANVAS, NCT01032629 CANVAS-R, NCT01989754	Randomised controlled trial Mean follow-up of 188.2 weeks Multi-centre study (667 centres across 30 countries)	N = 10,142; 4330 in CANVAS and 5,812 in CANVAS-R Inclusion criteria: patients with type 2 diabetes (glycated haemoglobin level, ≥ 7.0% and ≤ 10.5%), either 30 years or older with a history of symptomatic atherosclerotic cardiovascular disease or 50 years or older with two or more of the following risk factors for cardiovascular disease: duration of diabetes of at least 10 years, systolic blood pressure higher than 140 mm Hg while they were receiving one or more antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or high-density lipoprotein cholesterol level of less than 1 mmol per litre (38.7 mg per decilitre). eGFR at entry of more than 30 ml per minute per 1.73 m^2 of body-surface area Mean age: 63.3 years (SD ± 8.3 years) Mean disease duration: 13.5 years Sex: 35.8% female, 64.2% male CVD history: 64.8% canagliflozin, 66.7% placebo ASCVD history (coronary, cerebrovascular, peripheral): 71.2% canagliflozin, 73.5% placebo Mean eGFR (SD): 76.5 ml/min/1.73 m (± 20.5), n = 10,140	Canagliflozin; 100 mg per day or 300 mg per day (n = 5,795). Background therapy: Standard of care. Regimens not specified.	Placebo (n = 4,347). Background therapy: Standard of care. Regimens not specified.	- **Primary outcome**: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke - Cardiovascular mortality - Non-fatal myocardial infarction - Non-fatal stroke - Hospitalisation for heart failure - Lower limb amputation - All-cause mortality

Original study (Secondary published analyses)	Study nickname and identifier number	Type of Study	Population	Intervention	Comparison	Outcomes (cardiovascular)
Zinman et al. 2017 (Fitchett et al. 2018, Fitchett et al. 2019, Pellicori et al. 2020, Verma et al. 2020)	EMPA-REG OUTCOME, NCT01131676	Randomised controlled trial Median observation time of 3.1 years Multi-centre study (590 centres across 42 countries)	N = 7,028 Inclusion criteria: patients with type 2 diabetes, ≥ 18 years, body-mass index ≤ 45 kg/m^2, estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area, established cardiovascular disease and no glucose-lowering agents for at least 12 weeks before randomisation and HbA1c level ≥ 7% ≤ 9% or stable glucose-lowering therapy for at least 12 weeks before randomisation and HbA1c level of ≥ 7% ≤ 10% Mean age empagliflozin: 63.1 years (SD ± 8.6 years) Mean age placebo: 63.2 years (SD ± 8.8 years) Disease duration empagliflozin: 57% > 10 years, 43% < 10 years Disease duration placebo: 57.4% > 10 years, 42.6% < 10 years Sex empagliflozin: 28.8% female, 71.2% male Sex placebo: 28% female, 72% male CV disease risk factor (either CAD, multi vessel CAD, history of MI, coronary artery bypass graft, history of stroke, PAD, single vessel CAD, cardiac failure): 99.4% empagliflozin, 98.9% placebo eGFR < 60 mL/min/1.73 m: 25.9% of patient population	Empagliflozin; 10 mg per day (n = 2,345), 25 mg per day (n = 2,342), used against a background of standard care.	Placebo (n = 2,333), used against a background of standard care.	- **Primary outcome**: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke - Cardiovascular mortality - Fatal acute myocardial infarction (not separated from non-fatal myocardial infarction) - Non-fatal myocardial infarction - Non-fatal silent myocardial infarction - Fatal stroke (not separated from non-fatal stroke) - Non-fatal stroke - Fatal heart failure - Non-fatal heart failure - Hospitalisation for heart failure - Coronary revascularisation procedure - All-cause mortality
Wiviott et al. 2019 (Furtado et al. 2019, Kato et	DECLARE-TIMI 58, NCT01730534	Randomised controlled trial	N = 17,160	Dapagliflozin; 10 mg per day. Background	Placebo. Background therapy:	- **Primary outcome one**: MACE, defined as cardiovascular

Original study (Secondary published analyses)	Study nickname and identifier number	Type of Study	Population	Intervention	Comparison	Outcomes (cardiovascular)
al. 2019, Baja et al. 2020)		Median follow-up of 4.2 years Multi-centre study (807 centres across 34 countries)	Inclusion criteria: ≥ 40 years with type 2 diabetes with either established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD. Glycated haemoglobin level ≥ 6.5% < 12.0% and a creatinine clearance ≥ 60 mL/min Median age (SD): 63.9 years (6.8) for dapagliflozin; 64.0 years (6.8) for placebo Disease duration (IQR): 11 years (6–16) Sex: 36.9% female, 63.1% male for dapagliflozin; 37.9% female, 62.1% male for placebo Established ASCVD (unclear how defined): 40.5% for dapagliflozin; 40.8% for placebo Mean eGFR: 85.2 mL/min/1.73m^2	therapy: Standard of Care.	Standard of Care.	death, myocardial infarction or ischaemic stroke - **Primary outcome two**: composite cardiovascular death or hospitalisation due to heart failure - All-cause mortality - Composite of cardiovascular death, myocardial infarction, and ischemic stroke
Cannon et al. 2018, Cannon et al. 2020 (Cosentino et al. 2020)	VERTIS CV, NCT01986881	Randomised controlled trial Mean follow up of 3.5 years Multi-centre study (567 centres across 34 countries)	N = 8,246 Inclusion criteria: ≥ 40 years with type 2 diabetes (with a glycated haemoglobin level of 7% to 10.5%) and established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral arterial systems Mean age: 64.4 years Mean disease duration: 13 years Sex: 29.7% female, 70.3% male for ertugliflozin▾; 30.7% female, 69.3% male for placebo	Ertugliflozin▾; 5 mg per day (n = 2,752), 15 mg per day (n = 2,747), added to background standard-of-care treatment.	Placebo (n = 2,747), added to background standard-of-care treatment.	- **Primary outcome**: MACE, defined as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (a major adverse cardiovascular event) - A composite of death from cardiovascular causes or hospitalization for heart failure - Death from cardiovascular causes

Original study (Secondary published analyses)	Study nickname and identifier number	Type of Study	Population	Intervention	Comparison	Outcomes (cardiovascular)
			Mean eGFR (SD): 76.1 (± 20.9) ml/min/1.73 m^2 for ertugliflozin▾ (n = 5498), 75.7 (± 20.8) ml/min/1.73 m^2 for placebo Established ASCVD was not reported beyond it being part of the inclusion criteria and exclusion from the study if this criteria was not met.			
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HF: heart failure; IQR: interquartile range; SD: standard deviation						

APPENDIX 3: CLINICAL STUDY CARDIOVASCULAR OUTCOMES

Study	Medicine	Trial	Outcome	Comments
Cardiovascular mortality				
Neal et al. 2017	Canagliflozin	CANVAS programme	11.6 participants with an event per 1,000 patient years for canagliflozin 12.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.88 (0.70–1.10)	No further statistics reported for this outcome
Radholm et al. 2018	Canagliflozin	CANVAS programme	History of HF 24.3 participants with an event per 1,000 patient years for canagliflozin 31.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.72 (0.51–1.02) No history of HF 9.8 participants with an event per 1,000 patient years for canagliflozin 9.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.95 (0.76–1.20) Interaction between groups, p = 0.17 Absolute risk difference over five years (95% CI) per 1,000 patient years History of HF -36.40 (-85.01– -12.21) No history of HF -0.31 (-11.39–10.78) Interaction between groups, p = 0.16	CV death
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	12.4 participants with an event per 1,000 patient years for empagliflozin 20.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.62 (0.49–0.77); p < 0.001	
Fitchett et al. 2018	Empagliflozin	EMPA-REG OUTCOME	Low to average risk 8.2 participants with an event per 1,000 patient years for empagliflozin 12.4 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.65 (0.45–0.94) High risk 15.4 participants with an event per 1,000 patient years for empagliflozin 27.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.57 (0.38–0.88) Very high risk 23.6 participants with an event per 1,000 patient years for empagliflozin 47.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.49 (0.24–1.02)	Five-year risk according to baseline Health ABC risk score and then classified as low-to-average (< 10%), high (10-20%) and very high (≥ 20%)

Study	Medicine	Trial	Outcome	Comments
			Interaction between groups, p = 0.7660	
Fitchett et al. 2019	Empagliflozin	EMPA-REG OUTCOME	Prior MI or stroke at baseline 14.5 participants with an event per 1,000 patient years for empagliflozin 24.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.60 (0.46–0.77) No prior MI or stroke at baseline 8.5 participants with an event per 1,000 patient years for empagliflozin 12.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.69 (0.43–1.10) Interaction between groups, p = 0.6182	
Verma et al. 2020	Empagliflozin	EMPA-REG OUTCOME	Low to intermediate risk 9.1 participants with an event per 1,000 patient years for empagliflozin 6.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.75 (0.48–1.18) ARR (95% CI) -2.3 (-6.0, 1.4) NNT 149 High risk 22.7 participants with an event per 1,000 patient years for empagliflozin 13.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.60 (0.39–0.92) ARR (95% CI) -9.1 (-17.3, -1.0) NNT 39 Very high risk 41.2 participants with an event per 1,000 patient years for empagliflozin 23.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.56 (0.41–0.78) ARR (95% CI) -17.6 (-28.8, -6.5) NNT 21 Interaction between groups, p = 0.0105	TRS-HF_{DM} attributes one point to AF, CAD, eGFR < 60 mL/min/ 1.73m^2 and UACR 30-300 mg/g, and two points to prior HF and UACR > 300 mg/g, thus a maximum of seven points is possible. Three categories were defined: low-intermediate, high and very high risk as scores of 0-1, 2 and ≥ 3 points respectively. Patients were stratified based on baseline TRS-HF_{DM} score.

Study	Medicine	Trial	Outcome	Comments
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	7.0 participants with an event per 1,000 patient years for dapagliflozin 7.1 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.98 (0.82–1.17)	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Dapagliflozin 7.2% KM rate for patients with heart failure and reduced ejection fraction 2.5% KM rate for patients without either heart failure with reduced ejection fraction or any history of heart failure 3.1% KM rate patients with heart failure without known reduced ejection fraction 2.1% KM rate no history of heart failure Placebo 12.4% KM rate for patients with heart failure and reduced ejection fraction 2.3% KM rate for patients without either heart failure with reduced ejection fraction or any history of heart failure 3.2% KM rate patients with heart failure without known reduced ejection fraction 2.1% KM rate no history of heart failure Absolute risk reduction 5.2 for patients with heart failure and reduced ejection fraction HR (95% CI) 0.55 (0.34–0.90) -0.2 patients without either heart failure with reduced ejection fraction or any history of heart failure HR (95% CI) 1.08 (0.89–1.31) 0.1 patients with heart failure without known reduced ejection fraction HR (95% CI) 1.41 (0.93–2.13) 0.0 no history of heart failure HR (95% CI) 1.01 (0.81–1.25) P = 0.012 between patients with heart failure and reduced ejection fraction and patients without either heart failure with reduced ejection fraction or any history of heart failure	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	Previous MI 4.9% events for dapagliflozin 5.3% events for placebo HR (95% CI) 0.92 (0.69–1.23) No previous MI 2.3% events for dapagliflozin 2.3% events for placebo HR (95% CI) 1.03 (0.82–1.28) Between group interaction, p = 0.56 Absolute risk reduction (95% CI) Previous MI	

Study	Medicine	Trial	Outcome	Comments
			0.4% (-1.0%–1.9%) No previous MI 0.1% (-0.6%–0.4%) Between group interaction, p = 0.50	
Bajaj et al. 2020	Dapagliflozin	DECLARE TIMI 58	≤ 5 years 2.5% events for dapagliflozin 3.0% events for placebo ARR (95% CI) 0.4% (-0.6%–1.5%) HR (95% CI) 0.84 (0.58–1.24) 5–10 years 2.4% events for dapagliflozin 2.3% events for placebo ARR (95% CI) -0.1% (-0.9%–0.8%) HR (95% CI) 1.03 (0.71–1.50) 10–15 years 2.9% events for dapagliflozin 2.6% events for placebo ARR (95% CI) -0.3% (-1.3%–0.7%) HR (95% CI) 1.11 (0.76–1.62) 15–20 years 3.7% events for dapagliflozin 3.0% events for placebo ARR (95% CI) -0.7% (-2.1%–0.8%) HR (95% CI) 1.20 (0.77–1.85) > 20 years 3.4% events for dapagliflozin 4.4% events for placebo ARR (95% CI) 1.0% (-0.6%–2.6%) HR (95% CI) 0.76 (0.50–1.17) Between group interaction, p = 0.974	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	1.8 participants with an event per 100 patient years for ertugliflozin▾ 1.9 participants with an event per 100 patient years for placebo HR (95% CI) 0.92 (0.77–1.11)	No further statistics reported for this outcome
Fatal myocardial infarction				

Study	Medicine	Trial	Outcome	Comments
Neal et al. 2017	Canagliflozin	CANVAS programme	NR	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	NR	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Dapagliflozin 0.3% of patients with heart failure and reduced ejection fraction (n = 318) 0.3% of patients without either heart failure with reduced ejection fraction or any history of heart failure (n = 8,264) Placebo 1.4% of patients with heart failure and reduced ejection fraction (n = 353) 0.4% of patients without either heart failure with reduced ejection fraction or any history of heart failure (n = 8,264)	No further statistics reported for this outcome
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	NR	
Non-fatal myocardial infarction				
Neal et al. 2017	Canagliflozin	CANVAS programme	9.74 participants with an event per 1,000 patient years for canagliflozin 11.61 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.85 (0.69–1.05)	No further statistics reported for this outcome
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	16.0 participants with an event per 1,000 patient years for empagliflozin 18.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.87 (0.70–1.09); p = 0.22	Excludes silent MI
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	NR	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	1.7 participants with an event per 100 patient years for ertugliflozin▾ 1.6 participants with an event per 100 patient years for placebo HR (95% CI) 1.04 (0.86–1.27)	No further statistics reported for this outcome
Fatal or non-fatal myocardial infarction				
Radholm et al. 2018	Canagliflozin	CANVAS programme	History of HF 13.4 participants with an event per 1,000 patient years for canagliflozin 11.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.11 (0.65–1.89) No history of HF 10.9 participants with an event per 1,000 patient years for canagliflozin 12.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.86 (0.69–1.06) Interaction between groups, p = 0.36 Absolute risk difference over five years (95% CI) per 1,000 patient years History of HF 9.27 (-23.11–41.64)	

Study	Medicine	Trial	Outcome	Comments
			No history of HF -9.41 (-22.01–3.19) Interaction between groups, p = 0.29	
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	11.7 participants with an event per 1,000 patient years for dapagliflozin 13.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.89 (0.77–1.01)	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	Previous MI 9.2% events for dapagliflozin 11.7% events for placebo HR (95% CI) 0.78 (0.63–0.95) No previous MI 3.4% events for dapagliflozin 3.4% events for placebo HR (95% CI) 0.99 (0.83–1.19) Between group interaction, p = 0.82 Absolute risk reduction (95% CI) Previous MI 2.5% (0.5%–4.5%) No previous MI 0.0% (-0.6%–0.6%) Between group interaction, p = 0.019	
Bajaj et al. 2020	Dapagliflozin	DECLARE TIMI 58	≤ 5 years 4.2% events for dapagliflozin 3.8% events for placebo ARR (95% CI) -0.4% (-1.7%–0.8%) HR (95% CI) 1.11 (0.81–1.52) 5–10 years 4.1% events for dapagliflozin 4.3% events for placebo ARR (95% CI) 0.2% (-0.9%–1.3%) HR (95% CI) 0.97 (0.74–1.28) 10–15 years 4.8% events for dapagliflozin 5.5% events for placebo	

Study	Medicine	Trial	Outcome	Comments
			ARR (95% CI) 0.7% (-0.7%–2.1%) HR (95% CI) 0.88 (0.67–1.15) 15–20 years 4.9% events for dapagliflozin 5.8% events for placebo ARR (95% CI) 0.9% (-0.9%–2.7%) HR (95% CI) 0.82 (0.58–1.15) > 20 years 5.4% events for dapagliflozin 7.8% events for placebo ARR (95% CI) 2.4% (0.3%–4.4%) HR (95% CI) 0.66 (0.47–0.92) Between group interaction, p = 0.019	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	1.8 participants with an event per 100 patient years for ertugliflozin▾ 1.7 participants with an event per 100 patient years for placebo HR (95% CI) 1.04 (0.86–1.26)	No further statistics reported for this outcome
Fatal stroke				
Neal et al. 2017	Canagliflozin	CANVAS programme	NR	
Zhou et al. 2019	Canagliflozin	CANVAS programme	0.95 participants with an event per 1,000 patient years for canagliflozin 1.18 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.84 (0.44–1.59); p = 0.59	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	NR	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Dapagliflozin 0.9% of patients with heart failure and reduced ejection fraction (n = 318) 0.3% of patients without either heart failure with reduced ejection fraction or any history of heart failure (n = 8,264) Placebo 1.1% of patients with heart failure and reduced ejection fraction (n = 353) 0.3% of patients without either heart failure with reduced ejection fraction or any history of heart failure (n = 8,264)	No further statistics reported for this outcome
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	NR	
Non-fatal stroke				

Study	Medicine	Trial	Outcome	Comments
Neal et al. 2017	Canagliflozin	CANVAS programme	7.12 participants with an event per 1,000 patient years for canagliflozin 8.39 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.90 (0.71–1.15)	No further statistics reported for this outcome
Zhou et al. 2019	Canagliflozin	CANVAS programme	7.12 participants with an event per 1,000 patient years for canagliflozin 8.39 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.90 (0.71–1.15); p = 0.40	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	11.2 participants with an event per 1,000 patient years for empagliflozin 9.1 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.24 (0.92–1.67); p = 0.16	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	NR	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▼	VERTIS CV	0.8 participants with an event per 100 patient years for ertugliflozin▼ 0.8 participants with an event per 100 patient years for placebo HR (95% CI) 1.00 (0.76–1.32)	No further statistics reported for this outcome
Ischemic stroke				
Zhou et al. 2019	Canagliflozin	CANVAS programme	6.70 participants with an event per 1,000 patient years for canagliflozin 7.51 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.95 (0.74–1.22); p = 0.69	
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	6.9 participants with an event per 1,000 patient years for dapagliflozin 6.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.01 (0.84–1.21)	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	Previous MI 3.7% events for dapagliflozin 3.9% events for placebo HR (95% CI) 0.93 (0.66–1.30) No previous MI 2.5% events for dapagliflozin 2.4% events for placebo HR (95% CI) 1.05 (0.85–1.30) Between group interaction, p = 0.54 Absolute risk reduction (95% CI) Previous MI 0.3% (-1.0%–1.5%) No previous MI -0.1% (-0.7%–0.4%) Between group interaction, p = 0.56	
Bajaj et al. 2020	Dapagliflozin	DECLARE TIMI 58	≤ 5 years 2.9% events for dapagliflozin 2.2% events for placebo	

Study	Medicine	Trial	Outcome	Comments
			ARR (95% CI) -0.8% (-1.8%–0.2%) HR (95% CI) 1.32 (0.89–1.98) 5–10 years 2.6% events for dapagliflozin 2.4% events for placebo ARR (95% CI) -0.2% (-1.1%–0.7%) HR (95% CI) 1.08 (0.75–1.56) 10–15 years 3.0% events for dapagliflozin 2.8% events for placebo ARR (95% CI) -0.2% (-1.2%–0.9%) HR (95% CI) 1.07 (0.74–1.54) 15–20 years 2.6% events for dapagliflozin 2.9% events for placebo ARR (95% CI) 0.3% (-1.0%–1.6%) HR (95% CI) 0.89 (0.55–1.42) > 20 years 2.5% events for dapagliflozin 3.8% events for placebo ARR (95% CI) 1.4% (-0.1%–2.8%) HR (95% CI) 0.61 (0.38–1.00) Between group interaction, p = 0.015	
Haemorrhagic stroke				
Zhou et al. 2019	Canagliflozin	CANVAS programme	0.53 participants with an event per 1,000 patient years for canagliflozin 1.29 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.43 (0.20–0.89); p = 0.02	
Fatal or non-fatal stroke				
Neal et al. 2017	Canagliflozin	CANVAS programme	7.9 participants with an event per 1,000 patient years for canagliflozin 9.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.87 (0.69–1.09)	
Radholm et al. 2018	Canagliflozin	CANVAS programme	History of HF 12.0 participants with an event per 1,000 patient years for canagliflozin 15.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.84 (0.51–1.39)	

Study	Medicine	Trial	Outcome	Comments
			No history of HF 7.3 participants with an event per 1,000 patient years for canagliflozin 8.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.88 (0.68–1.14) Interaction between groups, p = 0.57 Absolute risk difference over five years (95% CI) per 1,000 patient years History of HF -19.46 (-54.45–15.53) No history of HF -6.36 (-16.65–3.93) Interaction between groups, p = 0.48	
Zhou et al. 2019	Canagliflozin	CANVAS programme	7.93 participants with an event per 1,000 patient years for canagliflozin 9.62 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.87 (0.69–1.09); p = 0.23	
Zhou et al. 2019	Canagliflozin	CANVAS programme	30 to < 60 ml/min/1.73 m^2 6.6 participants with an event per 1,000 patient years for canagliflozin 14.52 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.50 (0.30–0.83) 60 to < 90 ml/min/1.73 m^2 7.69 participants with an event per 1,000 patient years for canagliflozin 9.32 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.84 (0.65–1.21) ≥ 90 ml/min/1.73 m^2 9.47 participants with an event per 1,000 patient years for canagliflozin 6.62 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.42 (0.86–2.36) Interaction between groups, p = 0.005	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	12.3 participants with an event per 1,000 patient years for empagliflozin 10.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.18 (0.89–1.56); p = 0.26	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	1.0 participants with an event per 100 patient years for ertugliflozin▾ 0.9 participants with an event per 100 patient years for placebo HR (95% CI) 1.06 (0.82–1.37)	
Heart failure				

Study	Medicine	Trial	Outcome	Comments
Neal et al. 2017	Canagliflozin	CANVAS programme	5.50 participants with an event per 1,000 patient years for canagliflozin 8.68 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.67 (0.52–0.87)	Hospitalisation for HF; no further statistics reported for this outcome
Radholm et al. 2018	Canagliflozin	CANVAS programme	6.4 participants with an event per 1,000 patient years for canagliflozin 9.7 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.70 (0.55–0.89); p = 0.003	Fatal or hospitalisation for HF
Radholm et al. 2018	Canagliflozin	CANVAS programme	1.2 participants with an event per 1,000 patient years for canagliflozin 1.4 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.89 (0.49–1.60); p = 0.69	Fatal HF
Radholm et al. 2018	Canagliflozin	CANVAS programme	5.5 participants with an event per 1,000 patient years for canagliflozin 8.7 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.67 (0.52–0.87); p = 0.002	Hospitalisation for HF (further statistics reported)
Radholm et al. 2018	Canagliflozin	CANVAS programme	History of HF 14.1 participants with an event per 1,000 patient years for canagliflozin 28.1 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.51 (0.33–0.78) No history of HF 4.3 participants with an event per 1,000 patient years for canagliflozin 5.7 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.79 (0.57–1.09) Interaction between groups, p = 0.47 Absolute risk difference over five years (95% CI) per 1,000 patient years History of HF -70.17 (-114.34– -26.00) No history of HF -6.93 (-15.09–1.22) Interaction between groups, p = 0.01	Hospitalisation for HF
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	9.4 participants with an event per 1,000 patient years for empagliflozin 14.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.65 (0.50–0.85); p = 0.002	Hospitalisation for HF
Fitchett et al. 2018	Empagliflozin	EMPA-REG OUTCOME	Low to average risk 4.9 participants with an event per 1,000 patient years for empagliflozin 6.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.71 (0.44–1.14) High risk 7.9 participants with an event per 1,000 patient years for empagliflozin	Five-year risk according to baseline Health ABC risk score and then classified as low-to-average (< 10%), high (10–

Study	Medicine	Trial	Outcome	Comments
			18.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.42 (0.24–0.73) Very high risk 19.0 participants with an event per 1,000 patient years for empagliflozin 33.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.61 (0.26–1.45) Interaction between groups, p = 0.3822	20%) and very high (≥ 20%)
Fitchett et al. 2019	Empagliflozin	EMPA-REG OUTCOME	Prior MI or stroke at baseline 10.8 participants with an event per 1,000 patient years for empagliflozin 15.7 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.68 (0.50–0.94) No prior MI or stroke at baseline 6.8 participants with an event per 1,000 patient years for empagliflozin 12.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.57 (0.35–0.95) Interaction between groups, p = 0.5610	
Pellicori et al. 2020	Empagliflozin	EMPA-REG OUTCOME	Events less than six months from randomisation 0.9% of events with HF at baseline with empagliflozin (n = 462) 5.7% of events with HF at baseline with placebo (n = 244) HR (95% CI) 0.15 (0.05–0.45) 0.2% of events without HF at baseline with empagliflozin (n = 4225) 0.6% of events without HF at baseline with placebo (n = 2089) HR (95% CI) 0.37 (0.16–0.88) Interaction between groups, p = 0.199 Events less than one year from randomisation 3.2% of events with HF at baseline with empagliflozin (n = 462) 6.6% of events with HF at baseline with placebo (n = 244) HR (95% CI) 0.48 (0.24–0.97) 0.4% of events without HF at baseline with empagliflozin (n = 4225) 0.9% of events without HF at baseline with placebo (n = 2089) HR (95% CI) 0.47 (0.24–0.91) Interaction between groups, p = 0.965	HF outcome data assessed by Cox regression models at six months and one year after randomisation in people with or without HF at baseline

Study	Medicine	Trial	Outcome	Comments
Verma et al. 2020	Empagliflozin	EMPA-REG OUTCOME	Low to intermediate risk 5.4 participants with an event per 1,000 patient years for empagliflozin 2.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.53 (0.28–1.01) ARR (95% CI) -2.5 (-5.3, -0.3) NNT 135 High risk 13.5 participants with an event per 1,000 patient years for empagliflozin 8.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.68 (0.40–1.17) ARR (95% CI) -4.6 (-11.0, 1.9) NNT 76 Very high risk 35.8 participants with an event per 1,000 patient years for empagliflozin 24.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.67 (0.48–0.96) ARR (95% CI) -11.5 (-22.5, -0.6) NNT 32 Interaction between groups, p = 0.1171	Hospitalisation for HF. TRS-HF_{DM} attributes one point to AF, CAD, eGFR < 60 mL/min/ 1.73m^2 and UACR 30-300 mg/g, and two points to prior HF and UACR > 300 mg/g, thus a maximum of seven points is possible. Three categories were defined: low-intermediate, high and very high risk as scores of 0-1, 2 and ≥ 3 points respectively. Patients were stratified based on baseline TRS-HF_{DM} score.
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	6.2 participants with an event per 1,000 patient years for dapagliflozin 8.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.73 (0.61–0.88)	Hospitalisation for HF
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Dapagliflozin 13.5% KM rate for patients with heart failure and reduced ejection fraction 2.1% KM rate for patients without either heart failure with reduced ejection fraction or any history of heart failure 4.5% KM rate patients with heart failure without known reduced ejection fraction 1.5% KM rate no history of heart failure Placebo 19% KM rate for patients with heart failure and reduced ejection fraction 2.7% KM rate for patients without either heart failure with reduced ejection fraction or any history of heart failure	Hospitalisation for HF

Study	Medicine	Trial	Outcome	Comments
			5.2% KM rate patients with heart failure without known reduced ejection fraction 2.0% KM rate no history of heart failure Absolute risk reduction 5.5 for patients with heart failure and reduced ejection fraction HR (95% CI) 0.64 (0.43–0.95) 0.6 patients without either heart failure with reduced ejection fraction or any history of heart failure HR (95% CI) 0.76 (0.62–0.92) 0.7 patients with heart failure without known reduced ejection fraction HR (95% CI) 0.72 (0.50–1.04) 0.5 patients with no history of heart failure HR (95% CI) 0.77 (0.60–0.97) P = 0.449 between patients with heart failure and reduced ejection fraction and patients without either heart failure with reduced ejection fraction or any history of heart failure	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	Previous MI 4.6% events for dapagliflozin 6.3% events for placebo HR (95% CI) 0.71 (0.53–0.94) No previous MI 1.9% events for dapagliflozin 2.5% events for placebo HR (95% CI) 0.75 (0.60–0.94) Between group interaction, p = 0.77 Absolute risk reduction (95% CI) Previous MI 1.8% (0.3%–3.2%) No previous MI 0.6% (0.1%–1.1%) Between group interaction, p = 0.001	
Bajaj et al. 2020	Dapagliflozin	DECLARE TIMI 58	≤ 5 years 1.9% events for dapagliflozin 2.4% events for placebo ARR (95% CI) 0.5% (-0.5%–1.4%) HR (95% CI) 0.80 (0.52–1.23) 5–10 years 2.3% events for dapagliflozin	

Study	Medicine	Trial	Outcome	Comments
			2.9% events for placebo ARR (95% CI) 0.7% (-0.3%–1.6%) HR (95% CI) 0.79 (0.55–1.13) 10–15 years 2.3% events for dapagliflozin 3.2% events for placebo ARR (95% CI) 0.9% (-0.2%–1.9%) HR (95% CI) 0.72 (0.49–1.06) 15–20 years 2.9% events for dapagliflozin 4.4% events for placebo ARR (95% CI) 1.5% (0.0%–3.0%) HR (95% CI) 0.64 (0.42–0.97) > 20 years 3.7% events for dapagliflozin 5.0% events for placebo ARR (95% CI) 1.3% (-0.4%–3.0%) HR (95% CI) 0.72 (0.48–1.08) Between group interaction, p = 0.534	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	0.7 participants with an event per 100 patient years for ertugliflozin▾ 1.1 participants with an event per 100 patient years for placebo HR (95% CI) 0.70 (0.54–0.90)	No further statistics reported for this outcome
Cosentino et al. 2020	Ertugliflozin▾	VERTIS CV	0.73 rate with an event per 100 patient years for ertugliflozin▾ 1.05 rate with an event per 100 patient years for placebo HR (95% CI) 0.70 (0.54–0.90) P = 0.006 0.75 rate with an event per 100 patient years for ertugliflozin▾ (5 mg) 1.05 rate with an event per 100 patient years for placebo HR (95% CI) 0.71 (0.52–0.97) P = 0.028 0.72 rate with an event per 100 patient years for ertugliflozin▾ (15 mg) 1.05 rate with an event per 100 patient years for placebo HR (95% CI) 0.68 (0.50–0.93) P = 0.015	Time to first hospitalisation for heart failure

Study	Medicine	Trial	Outcome	Comments
Cosentino et al. 2020	Ertugliflozin▾	VERTIS CV	History of HF 1.69 rate with an event per 100 patient years for ertugliflozin▾ 2.62 rate with an event per 100 patient years for placebo HR (95% CI) 0.63 (0.44–0.90) No history of HF 0.47 rate with an event per 100 patient years for ertugliflozin▾ 0.60 rate with an event per 100 patient years for placebo HR (95% CI) 0.79 (0.54–1.15) Interaction between groups, p = 0.40 Ejection fraction ≤ 45% 1.75 rate with an event per 100 patient years for ertugliflozin▾ 3.66 rate with an event per 100 patient years for placebo HR (95% CI) 0.48 (0.30–0.76) Ejection fraction > 45% 0.70 rate with an event per 100 patient years for ertugliflozin▾ 0.81 rate with an event per 100 patient years for placebo HR (95% CI) 0.86 (0.58–1.29) Unknown 0.49 rate with an event per 100 patient years for ertugliflozin▾ 0.65 rate with an event per 100 patient years for placebo HR (95% CI) 0.75 (0.45–1.25) Interaction between groups, p = 0.15	Time to first hospitalisation for heart failure
Cosentino et al. 2020	Ertugliflozin▾	VERTIS CV	HF and ejection fraction ≤ 45% 3.33 rate with an event per 100 patient years for ertugliflozin▾ 5.57 rate with an event per 100 patient years for placebo HR (95% CI) 0.60 (0.36–1.00) HF and ejection fraction > 45% 1.29 rate with an event per 100 patient years for ertugliflozin▾ 1.84 rate with an event per 100 patient years for placebo HR (95% CI) 0.70 (0.39–1.26) HF and EF unknown 0.86 rate with an event per 100 patient years for ertugliflozin▾ 1.66 rate with an event per 100 patient years for placebo	Time to first hospitalisation for heart failure

Study	Medicine	Trial	Outcome	Comments
			HR (95% CI) 0.52 (0.21–1.31) No HF and ejection fraction ≤ 45% 0.36 rate with an event per 100 patient years for ertugliflozin▾ 2.02 rate with an event per 100 patient years for placebo HR (95% CI) 0.18 (0.06–0.55) No HF and ejection fraction > 45% 0.52 rate with an event per 100 patient years for ertugliflozin▾ 0.51 rate with an event per 100 patient years for placebo HR (95% CI) 1.02 (0.58–1.79) No HF and EF unknown 0.43 rate with an event per 100 patient years for ertugliflozin▾ 0.46 rate with an event per 100 patient years for placebo HR (95% CI) 0.94 (0.50–1.76) Interaction between groups, p = 0.11	
Cosentino et al. 2020	Ertugliflozin▾	VERTIS CV	eGFR < 60 mL/min/1.73 m^2 1.14 rate with an event per 100 patient years for ertugliflozin▾ 2.27 rate with an event per 100 patient years for placebo HR (95% CI) 0.50 (0.33–0.76) eGFR ≥ 60 mL/min/1.73 m^2 0.63 rate with an event per 100 patient years for ertugliflozin▾ 0.73 rate with an event per 100 patient years for placebo HR (95% CI) 0.86 (0.62–1.21) Interaction between groups, p = 0.04 Albuminuria normal 0.46 rate with an event per 100 patient years for ertugliflozin▾ 0.41 rate with an event per 100 patient years for placebo HR (95% CI) 1.12 (0.69–1.83) Albuminuria micro 0.83 rate with an event per 100 patient years for ertugliflozin▾ 1.62 rate with an event per 100 patient years for placebo HR (95% CI) 0.51 (0.34–0.77) Albuminuria macro 2.26 rate with an event per 100 patient years for ertugliflozin▾	Time to first hospitalisation for heart failure

Study	Medicine	Trial	Outcome	Comments
			3.87 rate with an event per 100 patient years for placebo HR (95% CI) 0.58 (0.35–0.95) Interaction between groups, p = 0.04 Diuretic 1.19 rate with an event per 100 patient years for ertugliflozin▾ 2.05 rate with an event per 100 patient years for placebo HR (95% CI) 0.58 (0.43–0.78) Not diuretic 0.41 rate with an event per 100 patient years for ertugliflozin▾ 0.35 rate with an event per 100 patient years for placebo HR (95% CI) 1.18 (0.69–2.02) Interaction between groups, p = 0.02 Loop diuretic 2.14 rate with an event per 100 patient years for ertugliflozin▾ 4.37 rate with an event per 100 patient years for placebo HR (95% CI) 0.49 (0.34–0.71) No loop diuretic 0.50 rate per 1,000 patient years for ertugliflozin▾ 0.52 rate with an event per 1,000 patient years for placebo HR (95% CI) 0.97 (0.67–1.41) Interaction between groups, p = 0.01	
Cardiovascular death or hospitalisation for heart failure				
Neal et al. 2017	Canagliflozin	CANVAS programme	16.3 participants with an event per 1,000 patient years for canagliflozin 20.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.78 (0.67–0.91)	
Radholm et al. 2018	Canagliflozin	CANVAS programme	16.3 participants with an event per 1,000 patient years for canagliflozin 20.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.78 (0.67–0.91); p = 0.002	
Radholm et al. 2018	Canagliflozin	CANVAS programme	History of HF 35.4 participants with an event per 1,000 patient years for canagliflozin 56.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.61 (0.46–0.80)	

Study	Medicine	Trial	Outcome	Comments
			No history of HF 13.6 participants with an event per 1,000 patient years for canagliflozin 15.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.87 (0.72–1.06) Interaction between groups, p = 0.02 Absolute risk difference over five years (95% CI) per 1,000 patient years History of HF -106.97 (-171.59– -42.34) No history of HF -8.36 (-22.08–5.36) Interaction between groups, p = 0.003	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	19.7 participants with an event per 1,000 patient years for empagliflozin 30.1 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.66 (0.55–0.79); p < 0.001	
Fitchett et al. 2018	Empagliflozin	EMPA-REG OUTCOME	Low to average risk 12.0 participants with an event per 1,000 patient years for empagliflozin 16.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.71 (0.52–0.96) High risk 20.7 participants with an event per 1,000 patient years for empagliflozin 40.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.52 (0.36–0.75) Very high risk 38.0 participants with an event per 1,000 patient years for empagliflozin 70.0 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.55 (0.30–1.00) Interaction between groups, p = 0.4280	Five-year risk according to baseline Health ABC risk score and then classified as low-to-average (< 10%), high (10–20%) and very high (≥ 20%)
Fitchett et al. 2019	Empagliflozin	EMPA-REG OUTCOME	Prior MI or stroke at baseline 22.4 participants with an event per 1,000 patient years for empagliflozin 34.7 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.64 (0.52–0.80) No prior MI or stroke at baseline 14.6 participants with an event per 1,000 patient years for empagliflozin 21.7 participants with an event per 1,000 patient years for placebo	

Study	Medicine	Trial	Outcome	Comments
			HR (95% CI) 0.69 (0.48–0.99) Interaction between groups, p = 0.7696	
Pellicori et al. 2020	Empagliflozin	EMPA-REG OUTCOME	Events less than six months from randomisation 1.3% of events with HF at baseline with empagliflozin (n = 462) 7.0% of events with HF at baseline with placebo (n = 244) HR (95% CI) 0.18 (0.07–0.45) 0.5% of events without HF at baseline with empagliflozin (n = 4225) 1.1% of events without HF at baseline with placebo (n = 2089) HR (95% CI) 0.43 (0.24–0.77) Interaction between groups, p = 0.118 Events less than one year from randomisation 4.8% of events with HF at baseline with empagliflozin (n = 462) 9.0% of events with HF at baseline with placebo (n = 244) HR (95% CI) 0.50 (0.28–0.91) 1.1% of events without HF at baseline with empagliflozin (n = 4225) 2.0% of events without HF at baseline with placebo (n = 2089) HR (95% CI) 0.54 (0.36–0.83) Interaction between groups, p = 0.843	HF outcome data assessed by Cox regression models at six months and one year after randomisation in people with or without HF at baseline
Verma et al. 2020	Empagliflozin	EMPA-REG OUTCOME	Low to intermediate risk 12.2 participants with an event per 1,000 patient years for empagliflozin 8.4 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.69 (0.46–1.03) ARR (95% CI) -3.8 (-8.2, 0.5) NNT 91 High risk 32.5 participants with an event per 1,000 patient years for empagliflozin 20.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.65 (0.45–0.92) ARR (95% CI) -11.9 (-21.8, -1.9) NNT 31 Very high risk 67.6 participants with an event per 1,000 patient years for empagliflozin 43.5 participants with an event per 1,000 patient years for placebo	TRS-HF_{DM} attributes one point to AF, CAD, eGFR < 60 mL/min/ 1.73m^2 and UACR 30-300 mg/g, and two points to prior HF and UACR > 300 mg/g, thus a maximum of seven points is possible. Three categories were defined:

Study	Medicine	Trial	Outcome	Comments
			HR (95% CI) 0.64 (0.49–0.82) ARR (95% CI) -24.1 (-39.1, -9.1) NNT 17 Interaction across groups, p = 0.0107	low-intermediate, high and very high risk as scores of 0-1, 2 and ≥ 3 points respectively. Patients were stratified based on baseline TRS-HF_{DM} score.
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	12.2 participants with an event per 1,000 patient years for dapagliflozin 14.7 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.83 (0.73–0.95) P = 0.005 Risk group (number of events/number of patients) ASCVD 272/3474 for dapagliflozin 325/3500 for placebo HR (95% CI) 0.83 (0.71–0.98) MRF 145/5108 for dapagliflozin 171/5078 for placebo HR (95% CI) 0.84 (0.67–1.04) Interaction between groups, p = 0.99 History of HF (number of events/number of patients) 142/852 for dapagliflozin 172/872 for placebo HR (95% CI) 0.79 (0.63–0.99) No history of HF 275/7730 for dapagliflozin 324/7706 for placebo HR (95% CI) 0.84 (0.72–0.99) Interaction between groups, p = 0.60	
Bajaj et al. 2020	Dapagliflozin	DECLARE TIMI 58	≤ 5 years	

Study	Medicine	Trial	Outcome	Comments
			4.1% events for dapagliflozin 5.2% events for placebo ARR (95% CI) 1.0% (-0.3%–2.4%) HR (95% CI) 0.79 (0.58–1.06) 5–10 years 4.2% events for dapagliflozin 4.9% events for placebo ARR (95% CI) 0.7% (-0.5%–1.9%) HR (95% CI) 0.86 (0.66–1.13) 10–15 years 4.9% events for dapagliflozin 5.3% events for placebo ARR (95% CI) 0.4% (-1.0%–1.7%) HR (95% CI) 0.92 (0.70–1.22) 15–20 years 5.9% events for dapagliflozin 7.0% events for placebo ARR (95% CI) 1.1% (-0.8%–3.1%) HR (95% CI) 0.81 (0.59–1.11) > 20 years 6.3% events for dapagliflozin 8.2% events for placebo ARR (95% CI) 1.9% (-0.3%–4.0%) HR (95% CI) 0.75 (0.55–1.03) Between group interaction, p = 0.760	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	Previous MI 8.6% events for dapagliflozin 10.5% events for placebo HR (95% CI) 0.81 (0.65–1.00) No previous MI 3.9% events for dapagliflozin 4.5% events for placebo HR (95% CI) 0.85 (0.72–1.00) Between group interaction, p = 0.69	

Study	Medicine	Trial	Outcome	Comments
			Absolute risk reduction (95% CI) Previous MI 1.9% (0%–3.8%) No previous MI 0.6% (0%–1.3%) Between group interaction, p = 0.010	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	8.1% of the ertugliflozin▾ group 9.1% of the placebo group HR (95% CI) 0.88 (0.75–1.03) P = 0.11	
Cosentino et al. 2020	Ertugliflozin▾	VERTIS CV	2.34 participants with an event per 100 patient years for ertugliflozin▾ 2.66 participants with an event per 100 patient years for placebo HR (95% CI) 0.88 (0.75–1.03) P = 0.109 2.36 participants with an event per 100 patient years for ertugliflozin▾ (5 mg) 2.66 participants with an event per 100 patient years for placebo HR (95% CI) 0.89 (0.74–1.06) P = 0.190 2.33 participants with an event per 100 patient years for ertugliflozin▾ (15 mg) 2.66 participants with an event per 100 patient years for placebo HR (95% CI) 0.88 (0.73–1.05) P = 0.150	Time to first hospitalisation for heart failure
Amputation				
Neal et al. 2017	Canagliflozin	CANVAS programme	6.3 participants with an event per 1,000 patient years for canagliflozin 3.4 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.97 (1.41–2.75); p < 0.001	All amputation including major and minor
Matthews et al. 2019	Canagliflozin	CANVAS	4.48 participants with an event per 1,000 patient years for canagliflozin 2.44 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.94 (1.31–2.88)	Minor
Matthews et al. 2019	Canagliflozin	CANVAS	1.82 participants with an event per 1,000 patient years for canagliflozin 0.93 participants with an event per 1,000 patient years for placebo HR (95% CI) 2.03 (1.08–3.82)	Major
Matthews et al. 2019	Canagliflozin	CANVAS	6.17 participants with an event per 1,000 patient years for canagliflozin 2.76 participants with an event per 1,000 patient years for placebo HR (95% CI) 2.24 (1.36–3.69)	100 mg canagliflozin
Matthews et al. 2019	Canagliflozin	CANVAS	5.54 participants with an event per 1,000 patient years for canagliflozin 2.76 participants with an event per 1,000 patient years for placebo HR (95% CI) 2.01 (1.20–3.34)	300 mg canagliflozin

Study	Medicine	Trial	Outcome	Comments
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	NR	
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	1.4% for dapagliflozin 1.3% for placebo HR (95% CI) 1.09 (0.84–1.40); p = 0.53	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Patients with heart failure and reduced ejection fraction 3.6% of patients taking dapagliflozin (n = 317) 2.4% of patients taking placebo (n = 353) HR (95% CI) 1.59 (0.62–4.11); p = 0.337 (Cox's) Patients without either heart failure with reduced ejection fraction or any history of heart failure 1.4% of patients taking dapagliflozin (n = 8,256) 1.3% of patients taking placebo (n = 8,216) HR (95% CI) 1.05 (0.81–1.37); p = 0.708 (Cox's) P interaction = 0.387	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	2% of patients taking 5 mg ertugliflozin▾ (n = 2,746) 2.1% of patients taking 15 mg ertugliflozin▾ (n = 2,747) 1.6% of patients taking placebo (n = 2,745)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	0.6 exposure-adjusted incidence rate per 100 patient years for pooled ertugliflozin▾ 0.5 exposure-adjusted incidence rate per 100 patient years for placebo Risk difference (95% CI) 0.1 (–0.1, 0.3)	
Composite score (of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), widely known as MACE				
Neal et al. 2017	Canagliflozin	CANVAS programme	26.9 participants with an event per 1,000 patient years for canagliflozin 31.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.86 (0.75–0.97); p < 0.001 for non-inferiority; p = 0.02 for superiority	
Neal et al. 2017	Canagliflozin	CANVAS programme	Age < 65 years 22.0 participants with an event per 1,000 patient years for canagliflozin 23.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.91 (0.76–1.10) Age ≥ 65 years 33.8 participants with an event per 1,000 patient years for canagliflozin 42.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.80 (0.67–0.95) Interaction between groups, p = 0.26	
Neal et al. 2017	Canagliflozin	CANVAS programme	Glycated haemoglobin < 8.5% 24.7 participants with an event per 1,000 patient years for canagliflozin 26.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.94 (0.77–1.15)	

Study	Medicine	Trial	Outcome	Comments
			Glycated haemoglobin ≥ 8.5% 28.8 participants with an event per 1,000 patient years for canagliflozin 35.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.80 (0.68–0.94) Interaction between groups, p = 0.29	
Neal et al. 2017	Canagliflozin	CANVAS programme	BMI < 30 25.6 participants with an event per 1,000 patient years for canagliflozin 27.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.97 (0.79–1.20) BMI ≥ 30 27.8 participants with an event per 1,000 patient years for canagliflozin 34.0 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.79 (0.67–0.93) Interaction between groups, p = 0.29	
Neal et al. 2017	Canagliflozin	CANVAS programme	eGFR 30 < 60 ml/min/1.73 m^2 36.4 participants with an event per 1,000 patient years for canagliflozin 49.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.70 (0.55–0.90) 60 < 90 ml/min/1.73 m^2 26.8 participants with an event per 1,000 patient years for canagliflozin 29.0 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.95 (0.80–1.13) ≥ 90 ml/min/1.73 m^2 20.8 participants with an event per 1,000 patient years for canagliflozin 23.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.84 (0.62–1.12) Interaction between groups, p = 0.20	
Neal et al. 2017	Canagliflozin	CANVAS programme	History of CV disease 34.1 participants with an event per 1,000 patient years for canagliflozin 41.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.82 (0.72–0.95) No history of CV disease 15.8 participants with an event per 1,000 patient years for canagliflozin 15.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.98 (0.74–1.30)	

Study	Medicine	Trial	Outcome	Comments
			Interaction between groups, p = 0.18	
Neal et al. 2017	Canagliflozin	CANVAS programme	History of heart failure 42.2 participants with an event per 1,000 patient years for canagliflozin 51.4 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.80 (0.61–1.05) No history of heart failure 24.8 participants with an event per 1,000 patient years for canagliflozin 28.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.79 (0.76–1.01) Interaction between groups, p = 0.51	
Neal et al. 2017	Canagliflozin	CANVAS programme	History of peripheral vascular disease 33.9 participants with an event per 1,000 patient years for canagliflozin 43.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.75 (0.58–0.97) No history of peripheral vascular disease 25.4 participants with an event per 1,000 patient years for canagliflozin 28.8 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.89 (0.77–1.03) Interaction between groups, p = 0.47	
Neal et al. 2017	Canagliflozin	CANVAS programme	Beta-blocker use 29.5 participants with an event per 1,000 patient years for canagliflozin 39.0 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.75 (0.64–0.88) No beta-blocker use 24.2 participants with an event per 1,000 patient years for canagliflozin 23.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 1.04 (0.85–1.28) Interaction between groups, p = 0.01	
Neal et al. 2017	Canagliflozin	CANVAS programme	Diuretic use 27.6 participants with an event per 1,000 patient years for canagliflozin 41.0 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.66 (0.56–0.79) No diuretic use 26.4 participants with an event per 1,000 patient years for canagliflozin 24.0 participants with an event per 1,000 patient years for placebo	

Study	Medicine	Trial	Outcome	Comments
			HR (95% CI) 1.11 (0.93–1.34) Interaction between groups, p < 0.001	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	37.4 participants with an event per 1,000 patient years for empagliflozin 43.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.86 (0.74–0.99); p < 0.001 for non-inferiority; p = 0.04 for superiority	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	Age < 65 years HR (95% CI) 1.04 (0.84–1.20) Age ≥ 65 years HR (95% CI) 0.71 (0.59–0.87) Interaction between groups, p = 0.01	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	Glycated haemoglobin < 8.5% HR (95% CI) 0.76 (0.64–0.90) Glycated haemoglobin ≥ 8.5% HR (95% CI) 1.14 (0.86–1.50) Interaction between groups, p = 0.01	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	BMI < 30 HR (95% CI) 0.74 (0.60–0.91) BMI ≥ 30 HR (95% CI) 0.98 (0.80–1.21) Interaction between groups, p = 0.06	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	eGFR < 60 ml/min/1.73 m^2 HR (95% CI) 0.88 (0.69–1.13) 60 < 90 ml/min/1.73 m^2 HR (95% CI) 0.76 (0.61–0.94) ≥ 90 ml/min/1.73 m^2 HR (95% CI) 1.10 (0.77–1.57) Interaction between groups, p = 0.20	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	Beta-blocker use HR (95% CI) 0.83 (0.70–1.00) No beta-blocker use HR (95% CI) 0.90 (0.70–1.17)	

Study	Medicine	Trial	Outcome	Comments
			Interaction between groups, p = 0.61	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	Diuretic use HR (95% CI) 0.88 (0.71–1.07) No diuretic use HR (95% CI) 0.83 (0.67–1.02) Interaction between groups, p = 0.72	
Fitchett et al. 2019	Empagliflozin	EMPA-REG OUTCOME	Prior MI or stroke at baseline 42.2 participants with an event per 1,000 patient years for empagliflozin 50.0 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.84 (0.71–1.00) No prior MI or stroke at baseline 28.5 participants with an event per 1,000 patient years for empagliflozin 32.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.88 (0.66–1.18) Interaction between groups, p = 0.7859	
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	22.6 participants with an event per 1,000 patient years for dapagliflozin 24.2 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.93 (0.84–1.03); p < 0.001 for non-inferiority; p = 0.17 for superiority Risk group (number of events/number of patients) ASCVD 483/3474 for dapagliflozin 537/3500 for placebo HR (95% CI) 0.90 (0.79–1.02) MRF 273/5108 for dapagliflozin 266/5078 for placebo HR (95% CI) 1.01 (0.86–1.20) Interaction between groups, p = 0.25 History of HF (number of events/number of patients) 153/852 for dapagliflozin 151/872 for placebo HR (95% CI) 1.01 (0.81–1.27)	

Study	Medicine	Trial	Outcome	Comments
			No history of HF 603/7730 for dapagliflozin 652/7706 for placebo HR (95% CI) 0.92 (0.82–1.02) Interaction between groups, p = 0.46	
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	eGFR < 60 ml/min/1.73 m^2 HR (95% CI) 0.92 (0.69–1.23) 60 < 90 ml/min/1.73 m^2 HR (95% CI) 0.95 (0.82–1.09) ≥ 90 ml/min/1.73 m^2 HR (95% CI) 0.94 (0.80–1.10) Interaction between groups, p = 0.99	
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	History of heart failure HR (95% CI) 1.01 (0.81–1.27) No history of heart failure HR (95% CI) 0.92 (0.82–1.02) Interaction between groups, p = 0.46	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	NR	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	Previous MI 15.2% events for dapagliflozin 17.8% events for placebo HR (95% CI) 0.84 (0.72–0.99); p = 0.039 No previous MI 7.1% events for dapagliflozin 7.1% events for placebo HR (95% CI) 1.00 (0.88–1.13); p = 0.97 Between group interaction, p = 0.107 Absolute risk reduction (95% CI) Previous MI 2.6% (0.1%–5.0%) No previous MI 0.0% (-0.9%–0.8%)	

Study	Medicine	Trial	Outcome	Comments
			Between group interaction, p = 0.048	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	≤ 12 months 13.8% events for dapagliflozin 20.3% events for placebo HR (95% CI) 0.66 (0.42–1.03) > 12 to 24 months 11.8% events for dapagliflozin 25.7% events for placebo HR (95% CI) 0.42 (0.25–0.71) > 24 to 36 months 15.8% events for dapagliflozin 18.8% events for placebo HR (95% CI) 0.83 (0.50–1.40) > 36 months 15.8% events for dapagliflozin 15.8% events for placebo HR (95% CI) 1.01 (0.82–1.23) Between group interaction, p = 0.007	Previous MI
Bajaj et al. 2020	Dapagliflozin	DECLARE TIMI 58	≤ 5 years 8.5% events for dapagliflozin 7.8% events for placebo ARR (95% CI) -0.7% (-2.4%–1.1%) HR (95% CI) 1.08 (0.87–1.35) 5–10 years 8.0% events for dapagliflozin 7.9% events for placebo ARR (95% CI) -0.1% (-1.6%–1.5%) HR (95% CI) 1.02 (0.83–1.25) 10–15 years 9.1% events for dapagliflozin 9.7% events for placebo ARR (95% CI) 0.6% (-1.2%–2.4%) HR (95% CI) 0.94 (0.77–1.15) 15–20 years	

Study	Medicine	Trial	Outcome	Comments
			9.6% events for dapagliflozin 10.2% events for placebo ARR (95% CI) 0.6% (-1.8%–2.9%) HR (95% CI) 0.92 (0.71–1.18) > 20 years 9.7% events for dapagliflozin 13.6% events for placebo ARR (95% CI) 3.9% (1.2%–6.5%) HR (95% CI) 0.67 (0.52–0.86) Between group interaction, p = 0.004	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	3.9 participants with an event per 100 patient years for ertugliflozin▾ 4.0 participants with an event per 100 patient years for placebo HR (95% CI) 0.97 (0.85–1.11); p < 0.001for non-inferiority	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	Age < 65 years 2.96 participants with an event per 100 patient years for ertugliflozin▾ 3.31 participants with an event per 100 patient years for placebo HR (95% CI) 0.90 (0.73–1.10) Age ≥ 65 years 4.89 participants with an event per 100 patient years for ertugliflozin▾ 4.77 participants with an event per 100 patient years for placebo HR (95% CI) 1.03 (0.86–1.22)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	Glycated haemoglobin < 8.5% 3.72 participants with an event per 100 patient years for ertugliflozin▾ 3.69 participants with an event per 100 patient years for placebo HR (95% CI) 1.01 (0.85–1.20) Glycated haemoglobin ≥ 8.5% 4.19 participants with an event per 100 patient years for ertugliflozin▾ 4.54 participants with an event per 100 patient years for placebo HR (95% CI) 0.92 (0.75–1.14)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	BMI < 30 3.76 participants with an event per 100 patient years for ertugliflozin▾ 3.98 participants with an event per 100 patient years for placebo HR (95% CI) 0.95 (0.76–1.17) BMI ≥ 30 3.98 participants with an event per 100 patient years for ertugliflozin▾	

Study	Medicine	Trial	Outcome	Comments
			4.04 participants with an event per 100 patient years for placebo HR (95% CI) 0.99 (0.84–1.17)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	eGFR 30 < 60 ml/min/1.73 m^2 5.59 participants with an event per 100 patient years for ertugliflozin▾ 5.17 participants with an event per 100 patient years for placebo HR (95% CI) 1.08 (0.84–1.40) 60 < 90 ml/min/1.73 m^2 3.82 participants with an event per 100 patient years for ertugliflozin▾ 3.97 participants with an event per 100 patient years for placebo HR (95% CI) 0.96 (0.80–1.16) ≥ 90 ml/min/1.73 m^2 2.73 participants with an event per 100 patient years for ertugliflozin▾ 3.19 participants with an event per 100 patient years for placebo HR (95% CI) 0.86 (0.64–1.16)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	History of heart failure 5.15 participants with an event per 100 patient years for ertugliflozin▾ 4.89 participants with an event per 100 patient years for placebo HR (95% CI) 1.05 (0.82–1.35) No history of heart failure 3.53 participants with an event per 100 patient years for ertugliflozin▾ 3.74 participants with an event per 100 patient years for placebo HR (95% CI) 0.95 (0.81–1.11)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	Beta-blocker use 4.04 participants with an event per 100 patient years for ertugliflozin▾ 4.16 participants with an event per 100 patient years for placebo HR (95% CI) 0.97 (0.83–1.14) No beta-blocker use 3.59 participants with an event per 100 patient years for ertugliflozin▾ 3.70 participants with an event per 100 patient years for placebo HR (95% CI) 0.97 (0.76–1.24)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	Diuretic use 4.70 participants with an event per 100 patient years for ertugliflozin▾ 4.91 participants with an event per 100 patient years for placebo HR (95% CI) 0.96 (0.80–1.16)	

Study	Medicine	Trial	Outcome	Comments
			No diuretic use 3.31 participants with an event per 100 patient years for ertugliflozin▾ 3.37 participants with an event per 100 patient years for placebo HR (95% CI) 0.98 (0.81–1.19)	
All-cause mortality				
Neal et al. 2017	Canagliflozin	CANVAS programme	17.31 participants with an event per 1,000 patient years for canagliflozin 19.50 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.87 (0.74–1.01)	No further statistics reported for this outcome
Radholm et al. 2018	Canagliflozin	CANVAS programme	History of HF 29.2 participants with an event per 1,000 patient years for canagliflozin 38.7 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.70 (0.51–0.96) No history of HF 15.6 participants with an event per 1,000 patient years for canagliflozin 16.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.93 (0.78–1.11) Interaction between groups, p = 0.16 Absolute risk difference over five years (95% CI) per 1,000 patient years History of HF -47.40 (-101.05–6.24) No history of HF -4.13 (-18.31–10.06) Interaction between groups, p = 0.13	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	19.4 participants with an event per 1,000 patient years for empagliflozin 28.6 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.68 (0.57–0.82); p < 0.001	
Verma et al. 2020	Empagliflozin	EMPA-REG OUTCOME	Low to intermediate risk 16.1 participants with an event per 1,000 patient years for empagliflozin 10.9 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.68 (0.48–0.97) ARR (95% CI) -5.2 (-10.1, -0.3) NNT 67 High risk 32.3 participants with an event per 1,000 patient years for empagliflozin 21.4 participants with an event per 1,000 patient years for placebo	TRS-HF_{DM} attributes one point to AF, CAD, eGFR < 60 mL/min/ 1.73m^2 and UACR 30-300 mg/g, and two points to prior HF and

Study	Medicine	Trial	Outcome	Comments
			HR (95% CI) 0.67 (0.47–0.95) ARR (95% CI) -10.8 (-20.6, -1.0) NNT 34 Very high risk 51.4 participants with an event per 1,000 patient years for empagliflozin 36.0 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.69 (0.52–0.91) ARR (95% CI) -15.4 (-28.2, -2.6) NNT 25 Interaction across risk groups, p = 0.1442	UACR > 300 mg/g, thus a maximum of seven points is possible. Three categories were defined: low-intermediate, high and very high risk as scores of 0-1, 2 and ≥ 3 points respectively. Patients were stratified based on baseline TRS-HF_{DM} score.
Fitchett et al. 2019	Empagliflozin	EMPA-REG OUTCOME	Prior MI or stroke at baseline 21.1 participants with an event per 1,000 patient years for empagliflozin 32.5 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.65 (0.52–0.80) No prior MI or stroke at baseline 16.4 participants with an event per 1,000 patient years for empagliflozin 21.3 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.78 (0.55–1.11) Interaction between groups, p = 0.3808	
Wiviott et al. 2019	Dapagliflozin	DECLARE TIMI 58	15.1 participants with an event per 1,000 patient years for dapagliflozin 16.4 participants with an event per 1,000 patient years for placebo HR (95% CI) 0.93 (0.82–1.04)	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Dapagliflozin 11.3% KM rate for patients with heart failure and reduced ejection fraction 5.5% KM rate for patients without either heart failure with reduced ejection fraction or any history of heart failure 6.3% KM rate for patients with heart failure without known reduced ejection fraction 5.0% KM rate for no history of heart failure Placebo 17.7% KM rate for patients with heart failure and reduced ejection fraction 5.4% KM rate for patients without either heart failure with reduced ejection fraction or any history of heart failure	

Study	Medicine	Trial	Outcome	Comments
			6.2% KM rate for patients with heart failure without known reduced ejection fraction 4.9% KM rate for no history of heart failure Absolute risk reduction 6.4 for patients with heart failure and reduced ejection fraction HR (95% CI) 0.59 (0.40–0.88) -0.1 patients without either heart failure with reduced ejection fraction or any history of heart failure HR (95% CI) 0.97 (0.86–1.10) -0.1 patients with heart failure without known reduced ejection fraction HR (95% CI) 1.02 (0.75–1.38) -0.1 patients with no history of heart failure HR (95% CI) 0.96 (0.84–1.10) P = 0.016 between patients with heart failure and reduced ejection fraction and patients without either heart failure with reduced ejection fraction or any history of heart failure	
Furtado et al. 2019	Dapagliflozin	DECLARE TIMI 58	Previous MI 8.6% events for dapagliflozin 10.3% events for placebo HR (95% CI) 0.83 (0.67–1.03) No previous MI 5.5% events for dapagliflozin 5.7% events for placebo HR (95% CI) 0.97 (0.85–1.12) Between group interaction, p = 0.22 Absolute risk reduction (95% CI) Previous MI 1.7% (-0.2%–3.7%) No previous MI 0.1% (-0.6%–0.9%) Between group interaction, p = 0.084	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	2.4 participants with an event per 100 patient years for ertugliflozin▾ 2.6 participants with an event per 100 patient years for placebo HR (95% CI) 0.93 (0.80–1.08)	No further statistics reported for this outcome

Abbreviations: AF: atrial fibrillation; ARR: absolute risk reduction; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CI: confidence interval; CV cardiovascular; EF ejection fraction; eGFR: estimated glomerular filtration rate; HF heart failure; HR hazard ratio; KM Kaplan Meier; MI myocardial infarction; MRF multiple risk factors; NNT number needed to treat; NR not reported; TRS-HF_{DM}: Thrombolysis In Myocardial Infarction (TIMI) Risk Score for Heart Failure in Diabetes; UACR: urine albumin to creatine ratio

APPENDIX 4: ADVERSE EVENTS

Study	Medicine	Trial	Outcome	Comment
Urinary tract infections				
Neal et al. 2017	Canagliflozin	CANVAS programme	NR for the CANVAS programme	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	Event consistent with urinary tract infection: 18% of patients taking empagliflozin 18.1% of patients taking placebo Event consistent with urinary tract infection male: 10.5% of patients taking empagliflozin 9.4% of patients taking placebo Event consistent with urinary tract infection female: 36.4% of patients taking empagliflozin 40.6% of patients taking placebo P < 0.05	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Patients with heart failure and reduced ejection fraction 1.1% of patients taking dapagliflozin 0.4% of patients taking placebo HR (95% CI) 1.45 (0.24–8.68) Patients without either heart failure with reduced ejection fraction or any history of heart failure 1.7% of patients taking dapagliflozin 1.8% of patients taking placebo HR (95% CI) 0.92 (0.72–1.17)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▼	VERTIS CV	12.2% of patients taking 5 mg ertugliflozin▼; 2.1 risk difference compared with placebo (0.4–3.7), p = 0.02 12.0% of patients taking 15 mg ertugliflozin▼; 1.8 risk difference compared with placebo (0.2–3.5), p = 0.03 10.2% of patients taking placebo	
Genital infections				
Neal et al. 2017	Canagliflozin	CANVAS programme	34.9 participants with an event per 1,000 patient years for canagliflozin 10.8 participants with an event per 1,000 patient years for placebo p < 0.001	Female NR
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	Event consistent with genital infection: 6.4% of patients taking empagliflozin 1.8% of patients taking placebo P < 0.001 Event consistent with genital tract infection male: 5.0% of patients taking empagliflozin	

Study	Medicine	Trial	Outcome	Comment
			1.5% of patients taking placebo P < 0.001 Event consistent with genital tract infection female: 10.0% of patients taking empagliflozin 2.6% of patients taking placebo P < 0.001	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Patients with heart failure and reduced ejection fraction 1.1% of patients taking dapagliflozin 0% of patients taking placebo - Patients without either heart failure with reduced ejection fraction or any history of heart failure 0.9% of patients taking dapagliflozin 0.1% of patients taking placebo HR (95% CI) 8.01 (4.01–16.01), p < 0.001	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▾	VERTIS CV	Genital mycotic infection in men 4.4% of patients taking 5 mg ertugliflozin▾; 3.3 risk difference compared with placebo (2.3–4.3), p < 0.001 5.1% of patients taking 15 mg ertugliflozin▾; 4.0 risk difference compared with placebo (2.9–5.1), p < 0.001 1.2% of patients taking placebo Genital mycotic infection in women 6% of patients taking 5 mg ertugliflozin▾; 3.6 risk difference compared with placebo (1.8–5.7), p < 0.001 7.8% of patients taking 15 mg ertugliflozin▾; 5.4 risk difference compared with placebo (3.4–7.7), p < 0.001 2.4% of patients taking placebo	
Fracture				
Neal et al. 2017	Canagliflozin	CANVAS programme	15.4 participants with an event per 1,000 patient years for canagliflozin 11.9 participants with an event per 1,000 patient years for placebo p = 0.02	
Zinman et al. 2017	Empagliflozin	EMPA-REG OUTCOME	3.8% of patients taking empagliflozin 3.9% of patients taking placebo	
Kato et al. 2019	Dapagliflozin	DECLARE TIMI 58	Patients with heart failure and reduced ejection fraction 7.7% of patients taking dapagliflozin 6.6% of patients taking placebo HR (95% CI) 1.20 (0.66–2.19) Patients without either heart failure with reduced ejection fraction or any history of heart failure 5.3% of patients taking dapagliflozin	

Study	Medicine	Trial	Outcome	Comment
			5.0% of patients taking placebo HR (95% CI) 1.03 (0.9–1.18)	
Cannon et al. 2018, Cannon et al. 2020	Ertugliflozin▼	VERTIS CV	3.6% of patients taking 5 mg ertugliflozin▼ 3.7% of patients taking 15 mg ertugliflozin▼ 3.6% of patients taking placebo	
Abbreviations: CI: confidence interval; HR: hazard ratio; NR: not reported				