Common Drug Review
Clinical Review Report

October 2016

Drug	Empagliflozin (Jardiance)
Indication	Adjunct to diet, exercise and standard care therapy to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease who have inadequate glycemic control
Listing request	As per indication
Dosage form (s)	10 mg and 25 mg tablets
NOC date	July 27, 2016
Manufacturer	Boehringer Ingelheim (Canada) Ltd.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

Adj	adjusted
AE	adverse event
ANCOVA	analysis of covariance
CDA	Canadian Diabetes Association
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CK-MB	creatine kinase - muscle/brain
CV	cardiovascular
DPP-4	dipeptidyl peptidase-4
ECG	Electrocardiogram
FDA	Food and Drug Administration
GLP-1	glucagon-like peptide-1
A1C	glycated hemoglobin
HR	hazard ratio
LOCF	last observation carried forward
MI	myocardial infarction
mITT	modified intention-to-treat
OC	observed case
PP	per-protocol
RCT	randomized controlled trial
RR	relative risk
RRT	renal replacement therapy
SAE	serious adverse event
SBP	systolic blood pressure
SGLT-2	sodium-glucose cotransporter-2
UTI	urinary tract infection

EXECUTIVE SUMMARY

Introduction

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels at both the microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral artery disease, cardiovascular [CV] disease) levels. Type 2 diabetes mellitus is more common than type 1, accounting for approximately 90% of cases of diabetes.[1] In Canada, the prevalence of diabetes was 6.8% (2.4 million Canadians) in 2009, and is expected to rise to 3.7 million people by 2019.[2] People with diabetes are more likely to be hospitalized and to experience complications requiring specialist care. By 2020, the diabetes-associated costs to the Canadian health care system will be an estimated $16.9 billion per year.[1]

Empagliflozin is an inhibitor of sodium-glucose cotransporter-2 (SGLT-2). It reduces the renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thus increasing urinary glucose excretion.[3]

The manufacturer has received approval for empagliflozin as an adjunct to diet, exercise, and standard care therapy to reduce the incidence of CV death in patients with type 2 diabetes mellitus and established CV disease who have inadequate glycemic control. The recommended dose is 10 mg or 25 mg once daily.[3]

Empagliflozin is also indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance. It is also indicated as an add-on therapy when metformin used alone does not provide adequate glycemic control. It can be used in combination with metformin, metformin and a sulfonylurea, pioglitazone (alone or with metformin), or basal or prandial insulin (alone or with metformin).[3]

In 2015, empagliflozin was reviewed by the CADTH Canadian Drug Expert Committee (CDEC). The committee recommended that empagliflozin be listed for the treatment of type 2 diabetes if the following clinical criteria and conditions are met:

- Added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.
- The drug plan cost of treatment with empagliflozin should not exceed the drug plan cost of treatment with the least costly option from within the SGLT-2 inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor classes.[4]

Indication under review
Adjunct to diet, exercise and standard care therapy to reduce the incidence of CV death in patients with type 2 diabetes mellitus and established CV disease who have inadequate glycemic control
Listing criteria requested by sponsor
As per indication

The objective of this report is to perform a systematic review of the beneficial and harmful effects of empagliflozin 10 mg and 25 mg tablets as adjunct to standard care therapy in patients with type 2 diabetes and high CV risk, to reduce the risk of all-cause mortality by reducing CV deaths and CV deaths or hospitalization, for heart failure (HF).

Results and interpretation

Included studies

A single randomized, double-blind (DB), non-inferiority trial met the inclusion criteria (N = 7,020). The EMPA-REG OUTCOME study was designed to assess the CV safety of empagliflozin 10 mg and 25 mg daily (as add-on therapy to standard care) versus placebo in patients with type 2 diabetes and high CV risk. The primary outcome was time to first occurrence of CV death, non-fatal myocardial infarction (MI) (excluding silent MI), or non-fatal stroke, with a non-inferiority margin of 1.3 for the hazard ratio (HR). If non-inferiority was achieved, superiority versus placebo was tested next in the statistical hierarchy. In this event-driven trial, patients were followed until a minimum of 691 primary composite outcome events had been reported (median follow-up of 3.1 years).

The mean age of included patients was 63 years; the majority were male (72%) and Caucasian (72%), with a history of coronary artery disease (76%) or stroke (23%), and had diabetes for more than 10 years (57%). The baseline mean glycated hemoglobin (A1C) was 8.1%; 70% of patients were taking two or more antidiabetic medications, and 48% were on insulin. Overall 95%, 90%, and 81% of patients were taking antihypertensive, anticoagulant, or lipid-lowering medications, respectively, at baseline.

The trial had a number of limitations that could affect the internal validity, such as the rigour of outcome ascertainment, lack of control of type 1 error due to the high number of exploratory and post-hoc comparisons, and potential confounding after randomization. Of note, the indication and manufacturer's listing request are not the full primary outcome in the study, as the request represents only a component of the entire composite outcome.

Efficacy

The pooled empagliflozin 10 mg and 25 mg daily dosage group was non-inferior to placebo for the primary outcome of time to first occurrence of CV death, non-fatal MI, or non-fatal stroke, and for the key secondary outcome, which also included hospitalization for unstable angina. Superiority over placebo was demonstrated for the primary outcome (adjusted [adj] HR = 0.86; 95% confidence interval [CI], 0.74 to 0.99, one-sided *P* = 0.019), but not the key secondary outcome (adj HR = 0.89; 95% CI, 0.78 to 1.01). Differences between treatments were mainly due to a reduction in CV deaths observed with empagliflozin (3.7%) compared with placebo (5.9%) (adj HR = 0.62; 95% CI, 0.49 to 0.77). All-cause mortality was also reduced for empagliflozin (5.7%) versus placebo (8.3%), largely due to differences in CV mortality. Numerically more patients on empagliflozin had a non-fatal stroke (3.5% versus 3.0%), and fewer patients had a non-fatal MI (4.5% versus 5.2%) compared with placebo, but the clinical importance of the differences is unclear. Of note, the analysis of mortality and the individual components of the composite outcomes were outside of the statistical hierarchy and therefore were subject to type 1 error.

The incidence of hospitalization for unstable angina was the same for both treatment groups (2.8%); numerically fewer patients underwent a coronary revascularization procedure in the empagliflozin group than in the placebo group (7.0% versus 8.0%). Fewer patients in the empagliflozin group had a hospitalization for HF compared with placebo (2.7% versus 4.1%; adj HR = 0.65; 95% CI, 0.50 to 0.85).

The proportion of patients who reported a microvascular event (which included initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or "new or worsening nephropathy") was lower in the empagliflozin group versus the placebo group (14.0% versus 20.5%). Most microvascular events were renal-related, with new-onset macroalbuminuria contributing the majority of the "new or worsening nephropathy" events. New-onset albuminuria was reported in 51% of patients in both the empagliflozin and placebo groups.

Modest differences were observed between empagliflozin and placebo for the mean change in A1C (–0.4% to –0.6%), weight (–1.2 kg to –2.3 kg), and blood pressure (systolic blood pressure ([SBP]: –3 mm Hg to –4 mm Hg, diastolic blood pressure (DBP]: –0.9 mm Hg to –1.5 mm Hg). It is difficult to attribute these changes directly to empagliflozin given that investigators were encouraged to modify background antidiabetic therapies, blood pressure medications, and other CV-prevention medications according to local standards of care.

There are a number of issues to consider when interpreting the findings of the EMPA-REG OUTCOME study. First, the trial was designed to test the safety of empagliflozin, not to establish its benefit for a specific outcome. US Food and Drug Administration (FDA) briefing documents state that the collection of event data was less rigorous than in an efficacy trial designed to test a specific hypothesis.[5] Of the 309 CV-related deaths, 124 (40%) were presumed CV deaths, as the events were unassessable. In sensitivity analyses, after excluding the unassessable deaths from the primary outcome, empagliflozin was non-inferior to placebo, but was no longer superior.[5] Misclassification of events is not likely to bias the results in favour of one treatment over the other (assuming that blinding was maintained), but may underestimate the true incidence of events and the potential power for specific end points. Second, there was no control for type 1 error across the numerous exploratory outcomes analyzed, including the individual components of the primary outcome, HF, and microvascular outcomes; therefore, the statistically significant differences should be interpreted with caution as some may be due to chance due to the high probability of type 1 errors in this study. There was no adjudication of silent MI, microvascular events, or renal events, and results may be subject to bias due to the substantial proportion of patients who were excluded or missing from some of these outcomes (12% to 49%). There were no scheduled ophthalmic examinations in the trial; thus, retinopathy-related events may have been under-reported. The definition of renal events may have captured acute or temporary changes in renal function, and may not reflect irreversible loss of renal function.[5] Third, the CV outcomes may have been confounded by differences between groups in the management of CV risk factors. Laboratory and clinical measurements of weight, glycemic control, and blood pressure were available to investigators and may have unblinded participants to treatment allocation. There was some differential use of background antidiabetic and antihypertensive therapies reported in the trial, although details (such as dosing information) were lacking. Lastly, there was some unblinding of CV results, as interim data were made available to support regulatory approvals, and numerous changes were made to the protocol and statistical analysis plan over the course of the trial (including renal events and hospitalization for HF), although the implications of these issues are unclear.

Harms

The adverse events (AEs) reported in the EMPA-REG OUTCOME study were similar to those identified in previous empagliflozin clinical trials.[3,5] In the three-year EMPA-REG OUTCOME study, serious adverse events (SAEs) were reported in 37% and 39% of patients in the empagliflozin groups and in 42% of patients in the placebo group. The percentage of patients who withdrew from treatment due to adverse events (WDAEs) was similar in the placebo group (19%) and the empagliflozin groups (18% and 17%).

Genital infections were reported more frequently in the empagliflozin groups (6%) compared with placebo (2%), and were more common in women than men. Hypoglycemia (28%) and urinary tract infections (UTIs) (18%) were the most commonly reported AEs, but the incidence was similar for all groups. The frequency of lower-limb amputations was similar in the empagliflozin and placebo groups; however, data on amputations was not systematically collected during the trial. Thus, the events were likely under-reported. The product monograph for empagliflozin includes warnings regarding the risk of volume depletion for patients on the drug, but in this trial the frequency was similar for both treatment groups (5%). Ketoacidosis was rare (empagliflozin, n = 4; placebo, n = 1), although the acidosis in all four empagliflozin patients was classified as an SAE. In general, no substantial dose-related differences in the occurrence of AEs were identified for the 10 mg and 25 mg doses of empagliflozin.

Conclusions

Based on data from one randomized controlled trial (RCT), add-on therapy with empagliflozin did not increase the risk of major CV adverse events (MACE) compared with standard care in patients with inadequate glycemic control of long-standing type 2 diabetes and high CV risk.

The impact of empagliflozin on MI, stroke, hospitalization for HF, or renal or other microvascular outcomes is unclear, given the limitations of the trial such as the rigour of outcome ascertainment, lack of control of type 1 error, and potential confounding after randomization. Based on exploratory analyses, empagliflozin may reduce CV mortality, but concerns over the methodologic rigour of the trial would also apply to this outcome.

Empagliflozin was associated with an increased frequency of genital infections. No new safety signals were identified; however, the study was not designed to detect rare AEs, such as diabetic ketoacidosis or lower-limb amputation, which have been linked to SGLT-2 inhibitors. The safety and efficacy of empagliflozin beyond 2.6 years of therapy is unknown.

TABLE 1: SUMMARY OF RESULTS

OUTCOME	EMPA-REG OUTCOME			
Time to First Event	**Placebo (N = 2,333) n (%)**	**Empagliflozin Pooled (N = 4,687) n (%)**	**Adj HR (95% CI)[a] Versus Placebo**	***P* Value**
CV mortality, MI, or stroke[b]	282 (12.1)	491 (10.5)	0.86 (0.74 to 0.99)	Non-inferiority $P < 0.0001$ Superiority (1-sided) $P = 0.019$ (2-sided) $P = 0.038$[c]
CV mortality, MI, stroke, or hospitalization for unstable angina[b]	333 (14.3)	599 (12.8)	0.89 (0.78 to 1.01)	Non-inferiority $P < 0.0001$ Superiority (1-sided) $P = 0.040$ (NS) (2-sided) $P = 0.080$[c]
CV mortality	137 (5.9)	172 (3.7)	0.62 (0.49 to 0.77)	< 0.0001[c]
MI (fatal/non-fatal)[b]	126 (5.4)	223 (4.8)	0.87 (0.70 to 1.09)	0.23[c]
Stroke (fatal/non-fatal)	69 (3.0)	164 (3.5)	1.18 (0.89 to 1.56)	0.26[c]
HF requiring hospitalization	95 (4.1)	126 (2.7)	0.65 (0.50 to 0.85)	0.0017[c]
Composite microvascular event[d]	424 (20.5)	577 (14.0)	0.62 (0.54 to 0.70)	< 0.0001[c]
	Placebo (N = 2,333) n (%)	**Empagliflozin 10 mg (N = 2,345) n (%)**	**Empagliflozin 25 mg (N = 2,342) n (%)**	
Withdrawals	67 (2.9)	81 (3.5)	63 (2.7)	
Patients with ≥ 1 SAE	988 (42)	876 (37)	913 (39)	
AEs leading to discontinuation of study drug	453 (19)	416 (18)	397 (17)	
Genital infection	42 (1.8)	153 (6.5)	148 (6.3)	
Volume depletion	115 (4.9)	115 (4.9)	124 (5.3)	

Adj = adjusted; AE = adverse event; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; NS = not statistically significant; SAE = serious adverse event.

[a] Model included age, sex, baseline body mass index (BMI) (categorical), baseline A1C (categorical), baseline eGFR (categorical), geographical region, and treatment.

[b] Excluding silent MI.

[c] Outside the statistical testing hierarchy, and therefore at risk of type 1 error.

[d] Initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or "new or worsening nephropathy;" placebo, N = 2,068; empagliflozin, N = 4,132.

Source: Clinical Study Report.[6]

1. INTRODUCTION

1.1 Disease prevalence and incidence

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). The persistent, elevated blood glucose causes damage to blood vessels on both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral artery disease, cardiovascular [CV] disease) levels. There are two main subtypes of diabetes mellitus, type 1, in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2, in which cells are unresponsive to insulin. Type 2 diabetes mellitus is more common than type 1, accounting for approximately 90% of cases of diabetes.[1] The etiology of type 1 diabetes is unknown, although the onset is typically early in life. In contrast, the onset of type 2 diabetes is typically later in life, although this is changing with the current epidemic of childhood obesity in Western societies. Poor diet, minimal exercise, and associated weight gain are considered to be risk factors for type 2 diabetes.[2] There is overlap between the two conditions. Most notably, patients with type 2 diabetes, who, in the initial stages of their disease, are able to secrete insulin, or may be hyperinsulinemic, can progress to a stage where insulin secretion is reduced, similar to type 1 diabetes.

Diabetes is a chronic metabolic disease with significant health impacts. The incidence of diabetes is increasing at a dramatic rate around the world. The International Diabetes Federation estimated that 371 million people had diabetes in 2012, and the prevalence expected to increase to 552 million by 2030.[7] In Canada, the prevalence of diabetes was 6.8% (2.4 million Canadians) in 2009, and is expected to rise to 3.7 million people by 2019.[2] People with diabetes are more likely to be hospitalized and to experience complications requiring specialist care. By 2020, the diabetes-associated costs to the Canadian health care system will be an estimated $16.9 billion per year.[1]

1.2 Standards of therapy

There are many classes of drugs used to treat type 2 diabetes (Table 5, Table 6). Metformin is widely considered to be the first-line drug of choice, with other drug classes added to metformin or used in combination with each other in patients unable to achieve therapeutic targets.[8] These therapies include sulfonylureas and incretins, which comprise dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. Other drug classes include the thiazolidinediones, which have had considerable safety issues, prescribing restrictions, and market withdrawals since their arrival on the market in the 1990s; the meglitinides, which act in a similar manner to the sulfonylureas; and the alpha-glucosidase inhibitors, which have a simple mechanism (they block glucose absorption) and are typically used in combination with other agents. Insulin and insulin analogues can be used in rapid-acting, intermediate-acting, or longer-acting forms, and are all administered by injection. The 2016 Canadian guidelines on the management of type 2 diabetes recommend, for patients with clinical CV disease in whom glycemic targets are not met, that empagliflozin be added to antihyperglycemic therapy to reduce the risk of CV and all-cause mortality.[9]

As a result of CV safety concerns with the thiazolidinediones, the US Food and Drug Administration (FDA) issued a Guidance for Industry on the evaluation of CV risk for new antidiabetic therapies for type 2 diabetes.[10] Of the CV outcome studies published to date, the GLP-1 analogues (liraglutide and lixisenatide), DPP-4 inhibitors (saxagliptin, sitagliptin, and alogliptin), and insulin analogues (insulin glargine) were shown to be non-inferior to placebo in terms of CV adverse events (AEs).[11-16] Of these, liraglutide also showed superiority over placebo in the time to CV death, non-fatal MI (including silent MI), or non-fatal stroke.[11] Pioglitazone, a thiazolidinedione, also has evidence suggesting CV benefits.[17]

1.3 Drug

Empagliflozin is an inhibitor of sodium-glucose cotransporter-2 (SGLT-2), the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thus increasing urinary glucose excretion.[3]

The manufacturer has received approval for empagliflozin as an adjunct to diet, exercise, and standard care therapy to reduce the incidence of CV death in patients with type 2 diabetes mellitus and established CV disease who have inadequate glycemic control. The recommended dose is 10 mg or 25 mg once daily.[3]

Empagliflozin is also indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance, or as an add-on therapy when metformin used alone does not provide adequate glycemic control. It can be used in combination with the following:

- metformin
- metformin and a sulfonylurea
- pioglitazone (alone or with metformin)
- basal or prandial insulin (alone or with metformin).[3]

In 2015, empagliflozin was reviewed by the CADTH Canadian Drug Expert Committee (CDEC). The committee recommended that empagliflozin be listed for the treatment of type 2 diabetes if the following clinical criteria and conditions are met:

- Added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.
- The drug plan cost of treatment with empagliflozin should not exceed the drug plan cost of treatment with the least costly option from within the SGLT-2 inhibitor and DPP-4 inhibitor classes.[4]

Indication under review
Adjunct to diet, exercise and standard care therapy to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease who have inadequate glycemic control
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF SGLT-2 INHIBITORS, METFORMIN, AND SULFONYLUREAS

	SGLT-2 INHIBITORS	BIGUANIDES (METFORMIN)	SULFONYLUREAS
Mechanism of Action	Inhibits the SGLT-2 transporter in the kidney, leading to increased glucose excretion	• Reduces gluconeogenesis • Increases conversion of glucose to glycogen • Increases degradation of glucose	Promotes insulin secretion by binding to the sulfonylurea receptor (SUR-1)
Indication[a]	**Empagliflozin** **In adults with T2DM** - As an adjunct to diet and exercise to improve glycemic control in patients whom metformin is inappropriate due to contraindications or intolerance. - To improve glycemic control when metformin, used alone or along with diet and exercise, does not provide adequate glycemic control. Empagliflozin is to be used in combination with metformin, metformin and a sulfonylurea, pioglitazone (alone or with metformin), basal or prandial insulin (alone or with metformin). *New indication*: As an adjunct to diet, exercise, and standard care therapy, to reduce the incidence of CV death in patients with T2DM and established CV disease who have inadequate glycemic control. **Canagliflozin** **In T2DM:** - As monotherapy in patients for whom metformin is inappropriate. - In combination with metformin or a sulfonylurea when diet and exercise plus monotherapy with one of these agents does not provide adequate glycemic control. - In combination with metformin and either a sulfonylurea or pioglitazone[b] when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control. - Combination therapy with insulin (with or without metformin) when diet, exercise, and therapy with insulin (with or without metformin) do not provide adequate glycemic control. **Dapagliflozin** **In adults with T2DM:** - An adjunct to diet and exercise to improve glycemic control in patients for whom metformin is inappropriate due to contraindications or intolerance. - To improve glycemic control in combination with metformin, a	T2DM that cannot be controlled by proper dietary management, exercise, and weight reduction, or when insulin therapy is not appropriate. Treatment of obese patients with diabetes.	T2DM in adults, alone or in combination with other antihyperglycemic agents, as an adjunct to diet and exercise.

	SGLT-2 INHIBITORS	BIGUANIDES (METFORMIN)	SULFONYLUREAS
	sulfonylurea, metformin and a sulfonylurea, sitagliptin (alone or with metformin), insulin (alone or with metformin), when metformin alone or the existing therapy listed above, along with diet and exercise, does not provide adequate glycemic control.		
Route of Administration	Oral	Oral	Oral
Recommended Dose	Empagliflozin: 10 mg to 25 mg once daily Canagliflozin: 100 mg to 300 mg once daily Dapagliflozin: 5 mg to 10 mg once daily	850 mg to 1,000 mg twice daily	Varies by drug
Serious Side Effects/Safety Issues	Contraindications: Renally impaired patients with eGFR less than 45 mL/min/1.73 m^2, patients with end-stage renal disease, or patients on dialysis. Warnings and precautions: - reduced intravascular volume - hypoglycemia when combined with antihyperglycemics - increase in LDL-C - hyperkalemia - impaired renal function - diabetic ketoacidosis - genital infections and UTIs - amputation	Contraindications: - acute or chronic metabolic acidosis including diabetic ketoacidosis - severe renal impairment Warnings: - lactic acidosis (rare)	Contraindications: - ketoacidosis - severe liver or renal impairment Precautions: - hypoglycemia

CV = cardiovascular; DPP-4 = dipeptidyl peptidase 4; eGFR = glomerular filtration rate; LDL-C = low-density lipoprotein-cholesterol; SGLT-2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus; SUR-1 = sulfonylurea receptor; UTI = urinary tract infection.

[a] Health Canada indication.

[b] Health Canada–approved combination for canagliflozin and empagliflozin, but not dapagliflozin.

Source: Product monographs from e-CPS.[8]

TABLE 3: KEY CHARACTERISTICS OF GLP-1 ANALOGUES, THIAZOLIDINEDIONES, DPP-4 INHIBITORS, AND INSULIN/INSULIN ANALOGUES

	GLP-1 ANALOGUES	THIAZOLIDINEDIONES (PIOGLITAZONE)	DPP-4 INHIBITORS	INSULIN/INSULIN ANALOGUES
Mechanism of Action	Stimulates GLP-1, which leads to: - insulin secretion - inhibition of glucagon release - delayed gastric emptying - reduced food intake	PPAR-gamma agonists, which leads to - increased uptake of FFA - increased uptake of glucose - reduced glucose synthesis	Increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1, leading to: - insulin secretion - inhibition of glucagon release - delayed gastric emptying - reduced food intake	Substitute for endogenously secreted insulin.
Indication[a]	**Liraglutide:** T2DM in combination with metformin or metformin and a sulfonylurea, when these drugs, along with diet and exercise, do not provide adequate glycemic control; T2DM in combination with metformin and a basal insulin, when liraglutide and metformin, along with diet and exercise, do not provide adequate glycemic control. **Albiglutide**: T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with metformin, metformin and a sulfonylurea, or basal insulin with oral antidiabetic therapies. **Exenatide (twice daily):** T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with metformin, a sulfonylurea, or metformin and a sulfonylurea. **Exenatide (extended-release, once weekly):** T2DM that cannot be adequately	T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with a sulfonylurea or metformin when monotherapy fails to adequately control blood glucose.	**Saxagliptin:** T2DM in combination with metformin or a sulfonylurea, or insulin (with or without metformin) or metformin and a sulfonylurea, when these drugs used alone, along with diet and exercise, do not provide adequate glycemic control. **Sitagliptin:** T2DM as monotherapy, or in combination with metformin or a sulfonylurea and metformin, or insulin (with or without metformin) or pioglitazone, or metformin and pioglitazone, when these drugs, along with diet and exercise, do not provide adequate glycemic control. **Linagliptin:** T2DM as monotherapy or in combination with metformin or a sulfonylurea, or metformin and a sulfonylurea, when these drugs, along with diet and exercise, do not provide adequate glycemic control **Alogliptin:** T2DM to improve glycemic control in adult patients with T2DM: • as monotherapy as an adjunct to diet	Patients with T2DM who require insulin for control of hyperglycemia.

	GLP-1 Analogues	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	Insulin/Insulin Analogues
	controlled by diet and exercise alone. May be used in combination with metformin, a sulfonylurea, metformin and a sulfonylurea, or insulin glargine. **Dulaglutide:** T2DM that cannot be adequately controlled by diet and exercise alone. May be used in combination with metformin, metformin and a sulfonylurea, or prandial insulin with metformin.		and exercise in patients for whom metformin is inappropriate due to contraindications or intolerance. • in combination with metformin, a sulfonylurea, pioglitazone, pioglitazone plus metformin, or insulin (with or without metformin), when diet and exercise plus glycemic therapies do not provide adequate glycemic control.	
Route of Administration	Subcutaneous	Oral	Oral	Subcutaneous
Recommended Dose	Varies by drug	15 mg to 30 mg once daily	Varies by drug	Titrated
Serious Side Effects/Safety Issues	Warnings and precautions: - thyroid cancer - prolonged PR interval - hypoglycemia (when combined with sulfonylurea) - pancreatitis Contraindications: - personal or family history of MTC - patients with MEN2	Serious warnings: - bone fractures in women - fluid retention Warnings and precautions: - bladder cancer - HF - hepatitis/hepatic failure	Contraindications: - DKA Warnings and precautions: - HF - pancreatitis - immune suppression	Serious warnings and precautions: - hypoglycemia - immune responses

DKA = diabetic ketoacidosis; DPP-4 = Dipeptidyl peptidase 4; FFA = free fatty acid; GLP-1 = Glucagon-like peptide 1; HF = heart failure; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid carcinoma; PPAR = peroxisome proliferator-activated receptor; PR interval = in electrocardiography, the interval extending from the onset of atrial depolarization until the onset of ventricular depolarization; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

Source: Product monographs from e-CPS.[8]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of empagliflozin 10 mg and 25 mg tablets as adjunct to standard care in patients with type 2 diabetes and high CV risk, to reduce the risk of all-cause mortality by reducing CV death, and CV death or hospitalization, for heart failure (HF).

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

PATIENT POPULATION	Adults with T2DM Subgroups: • age • race • baseline A1C • eGFR • T2DM duration • background diabetic therapy • history of HF • history of ischemic heart disease
INTERVENTION	Empagliflozin 10 mg and 25 mg once daily
COMPARATORS	When used alone or in combination with: • placebo • metformin • sulfonylureas • other SGLT-2 inhibitors • incretins (DPP-4 inhibitors, GLP-1 analogues) • thiazolidinediones • meglitinides • insulin/insulin analogues • alpha-glucosidase inhibitors
OUTCOMES	***Key efficacy outcomes:*** • mortality (all-cause, CV-related) • MI • stroke • HF • hospitalization (CV-related, all-cause) • diabetes-related microvascular morbidity, including blindness • HRQoL[a] ***Other efficacy outcomes:*** • glycemic control (e.g., A1C, FPG) [a] • blood pressure[a] • body weight[a] • health care resource utilization

	Harms outcomes: AEs, SAEs, WDAEs, hypoglycemia[a], diabetic ketoacidosis, volume depletion, genital infections, UTIs, renal failure, amputation
STUDY DESIGN	Published and unpublished phase 3 RCTs

AE = adverse events; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide 1; A1C = glycated hemoglobin; HF = heart failure; HRQoL = health-related quality of life; MI = myocardial infarction; RCT = randomized controlled trial; SAE = serious adverse event; SGLT-2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus; UTI = urinary tract infection; WDAE = withdrawal due to adverse events.

[a] Outcomes identified as important by patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Jardiance (empagliflozin).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on May 26, 2016. Regular alerts were established to update the search until the meeting of the CDEC on September 21, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were

resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in section 3.2.

3. RESULTS

3.1 Findings from the literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5: Details of Included Studies and described in Section 3.2.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

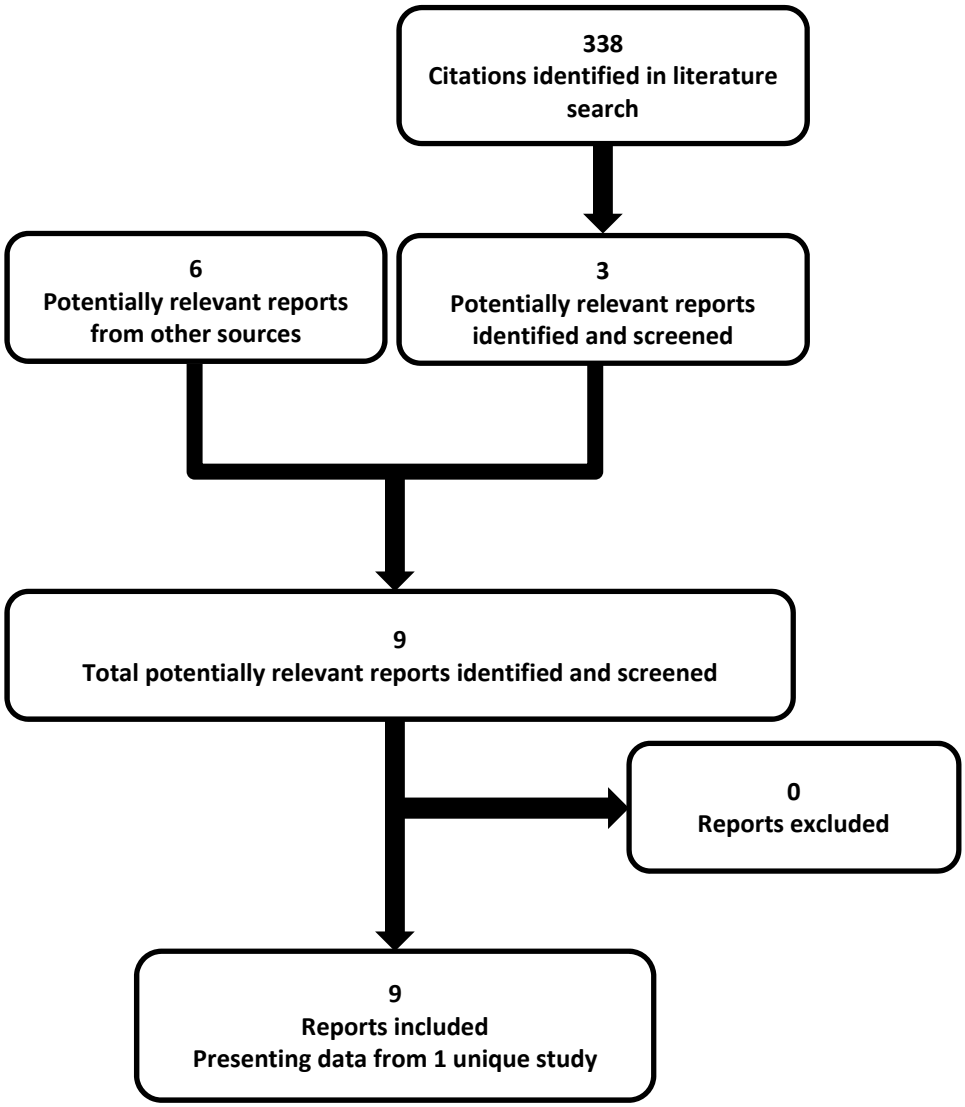


TABLE 5: DETAILS OF INCLUDED STUDIES

		EMPA-REG OUTCOME (STUDY 1245.25)
DESIGNS AND POPULATIONS	**Study Design**	DB RCT, non-inferiority study
	Locations	Europe, North America, South America, Asia, South Africa, Australia, New Zealand
	Randomized (N)	7,028
	Inclusion Criteria	-Adults with T2DM and who had insufficient glycemic control despite diet and exercise, and were either drug-naive or receiving any antidiabetic background therapy -High CV risk defined as one of the following: • history of MI • multi-vessel coronary artery disease in two or more major coronary arteries (irrespective of revascularization status) • single vessel coronary artery disease with significant stenosis and either a positive non-invasive stress test or discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection • last episode of unstable angina > 2 months prior with confirmed evidence of coronary multi-vessel or single vessel disease • history of ischemic or hemorrhagic stroke • occlusive peripheral artery disease [a] - A1C ≥ 7% and ≤ 10% at baseline for patients on antidiabetic medications and ≥ 7% and ≤ 9% for drug-naive patients - BMI ≤ 45 kg/m^2 - no change to diabetes therapy in past 12 weeks[b]
	Exclusion Criteria	• uncontrolled hyperglycemia (FPG > 13.3 mmol/L) during run-in period • acute coronary syndrome, stroke, TIA within two months prior to informed consent • planned cardiac surgery or angioplasty within three months • impaired renal function (eGFR < 30 mL/min/1.73m^2) • blood dyscrasias or disorders causing hemolysis or unstable RBC • liver disease (liver enzymes > 3 times the ULN)
DRUGS	**Intervention**	Empagliflozin 10 mg daily or empagliflozin 25 mg daily, as add-on therapy to standard care of diabetes, hypertension, and high cholesterol.
	Comparator(s)	Placebo As add-on therapy to standard care of diabetes, hypertension, and high cholesterol.
DURATION	**Phase**	3
	Run-in	Two-week, OL, placebo, run-in
	DB	Event-driven trial (691 primary composite outcome events)
	Follow-up	30 days
OUTCOMES	**Primary End Point**	Time to first occurrence of CV death, non-fatal MI or non-fatal stroke (pooled empagliflozin groups versus placebo)
	Other End Points	Key secondary outcome: Time to first occurrence of the following: • CV death, non-fatal MI or stroke, or hospitalization for unstable angina Additional secondary outcomes: • Individual components of the key secondary outcome • occurrence of and time to silent MI

		EMPA-REG OUTCOME (STUDY 1245.25)
		• HR requiring hospitalization • all-cause mortality • TIA • coronary revascularization procedure • microvascular complications • glycemic control • blood pressure • weight • harms.
NOTES	**Publications**	Zinman 2015[18,19]

A1C = glycated hemoglobin; BMI = body mass index; CV = cardiovascular; DB = double-blind; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; MI = myocardial infarction; OL = open-label; RBC = red blood cells; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; ULN = upper limit of normal.
[a] Documented previous limb angioplasty, stenting, or bypass surgery; or previous limb or foot amputation due to circulatory insufficiency; or angiographic evidence of significant (> 50%) peripheral artery stenosis in at least one limb; or evidence from a non-invasive measurement of significant (> 50% or as reported as hemodynamically significant) peripheral artery stenosis in at least one limb; or ankle brachial index of < 0.9 in at least one limb.
[b] Insulin total daily dose was not changed by more than 10% daily within the 12 weeks before randomization.
Note: Seven additional reports were included (CDR submission,[20] FDA reports,[5,21,22] Zinman 2014,[23] Wanner 2016,[24,25] Fitchett 2015.[26,27]).
Source: Clinical Study Report.[6]

3.2 Included studies

3.2.1 Description of studies

The EMPA-REG OUTCOME trial was a randomized, double-blind (DB), event-driven trial designed to assess the safety of empagliflozin 10 mg and 25 mg daily versus placebo in terms of major cardiovascular (CV) events (CV death, MI, or stroke) in patients with type 2 diabetes and high CV risk (N = 7,028). The primary outcome was to test the non-inferiority of empagliflozin versus placebo based on a hazard ratio (HR) non-inferiority margin of 1.3.

Eligible patients underwent a two-week open-label (OL), placebo, run-in period, during which time the background glucose-lowering treatments were unchanged. Those who continued to meet the inclusion criteria were randomized 1:1:1 to empagliflozin 10 mg, 25 mg, or placebo once daily. A computer-generated, random sequence and interactive voice or Web-response system was used to randomize patients. Randomization was stratified by glycated hemoglobin (A1C) levels (< 8.5% or ≥ 8.5%), body mass index (BMI) (< 30 or ≥ 30 kg/m^2), renal function (eGFR 30 mL/min/1.73m^2 to 59 mL/min/1.73m^2, 60 mL/min/1.73m^2 to 89 mL/min/1.73m^2, or ≥ 90 mL/min/1.73m^2) and region, using a block size of six per strata. Patients were followed until the planned 691 primary outcome events had occurred. The median duration of follow-up was 3.07 years, 3.15 years, and 3.16 years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively. Overall, 88% of patients were followed for at least two years, and 53% were followed for at least three years.

3.2.2 Populations

a) Inclusion and exclusion criteria

Enrolled patients had type 2 diabetes with inadequate glycemic control on diet and exercise, and had received either no glucose-lowering medications or had been on stable glucose-lowering therapies over

the previous 12 weeks. The patients were also required to have one or more CV risk factors, including a history of MI, coronary artery disease, unstable angina, stroke, or peripheral vascular disease (Table 5).

The trial excluded patients with liver disease or impaired renal function (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2), and those with an acute coronary syndrome, stroke, or transient ischemic attack (TIA) in the two months prior to giving informed consent.

b) Baseline characteristics

The patients enrolled in the EMPA-REG study had a mean age of 63 years, of which 45% were 65 years or older and 9% were 75 years or older (Table 6). The majority of patients were male (72%) and Caucasian (72%), had a history of coronary artery disease (76%), and had had diabetes for more than 10 years (57%). The distribution of patient characteristics was similar across treatment groups.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

CHARACTERISTIC	EMPA-REG OUTCOME		
	PLACEBO (N = 2,333)	EMPAGLIFLOZIN 10 MG (N = 2,345)	EMPAGLIFLOZIN 25 MG (N = 2,343)
Male, n (%)	1,680 (72)	1,653 (71)	1,683 (72)
Age, years, mean (SD)	63.2 (8.8)	63.0 (8.6)	63.2 (8.6)
Race, n (%)			
Caucasian	1,678 (72)	1,707 (73)	1,696 (72)
Asian	511 (22)	505 (22)	501 (21)
Black/African-American	120 (5)	119 (5)	118 (5)
American Indian/Alaska Native	20 (0.9)	11 (0.5)	23 (1.0)
Pacific Islander/Native Hawaiian	4 (0.2)	3 (0.1)	3 (0.1)
A1C %, mean (SD)	8.1 (0.84)	8.1 (0.86)	8.1 (0.84)
A1C category, n (%)			
< 8%	1,156 (50)	1,188 (51)	1,151 (49)
8% to < 9%	795 (34)	730 (31)	804 (34)
≥ 9%	382 (16)	426 (18)	386 (17)
BMI kg/m^2, mean (SD)	30.7 (5.2)	30.6 (5.2)	30.6 (5.3)
eGFR mL/min/1.73m^2, mean (SD)	73.8 (21.1)	74.3 (21.8)	74.0 (21.4)
Years since diabetes diagnosis, n (%)			
≤ 1 year	52 (2)	68 (3)	60 (3)
> 1 to 5 years	371 (16)	338 (14)	374 (16)
> 5 to 10 years	571 (25)	585 (25)	590 (25)
> 10 years	1339 (57)	1,354 (58)	1,318 (56)
Region, n (%)			
Europe	959 (41)	966 (41)	960 (41)
North America/Australia/ New Zealand	462 (20)	466 (20)	466 (20)
Asia	450 (19)	447 (19)	450 (19)
Latin America	360 (15)	359 (15)	362 (16)
Africa	102 (4)	107 (5)	104 (4)
CV Risk Factors, n (%)[a]			

Characteristic	EMPA-REG OUTCOME		
	Placebo (N = 2,333)	Empagliflozin 10 mg (N = 2,345)	Empagliflozin 25 mg (N = 2,343)
Coronary artery disease	1,763 (76)	1,782 (76)	1,763 (75)
History of MI	1,083 (46)	1,107 (47)	1,083 (46)
Stroke	553 (24)	535 (23)	549 (23)
Peripheral artery disease	479 (21)	465 (20)	517 (22)
Prior medical history (within 6 months), n (%)			
Hypertension	2,153 (92)	2,134 (91)	2,132 (91)
Diabetic neuropathy	727 (31)	735 (31)	735 (31)
Diabetic retinopathy	523 (22)	521 (22)	502 (21)
Diabetic nephropathy	467 (20)	444 (19)	460 (20)
UTI[b]	130 (6)	161 (7)	155 (7)
Diabetic foot	145 (6)	127 (5)	136 (6)
Genital infection[b]	43 (2)	36 (2)	34 (2)
HF[c]	244 (11)	240 (10)	222 (10)

BMI = body mass index; CV = cardiovascular; A1C = glycated hemoglobin; HF = heart failure; SD = standard deviation; UTI = urinary tract infection.
[a] In total, 26, 12, and 18 patients in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively, did not have a documented CV risk factor according to the protocol inclusion criteria. These patients continued in the trial and their data were analyzed.
[b] Chronic or recurrent infections.
[c] Proportion with HF at baseline was based on standardized Medical Dictionary for Regulatory Activities (MedDRA) query using free-text information collected on the case report form.
Source: Clinical Study Report.[6]

Overall, 98% of patients enrolled were taking one or more antidiabetic medications at baseline (Table 7), of which metformin (74%), insulin (48%), and sulfonylureas (43%) were the most commonly prescribed. Approximately half of patients were taking two antidiabetic medications (49%), while 30% were taking one medication and 20% were taking three or more medications. Other key medications are summarized in Table 7. The frequency of medications used was similar between groups.

Table 7: Summary of Medications at Baseline

Characteristic	EMPA-REG OUTCOME		
	Placebo (N = 2,333)	Empagliflozin 10 mg (N = 2,345)	Empagliflozin 25 mg (N = 2,342)
Antihypertensives, n (%)	2,221 (95)	2,227 (95)	2,219 (95)
ACEI/ARB	1,868 (80)	1,896 (81)	1,902 (81)
Beta-blocker	1,498 (64)	1,530 (65)	1,526 (65)
Diuretic	988 (42)	1,036 (44)	1,011 (43)
Calcium channel blocker	788 (34)	781 (33)	748 (32)
Mineralocorticoid receptor antagonists	136 (6)	157 (7)	148 (6)
Renin inhibitor	19 (< 1)	16 (< 1)	11 (< 1)
Other	191 (8)	193 (8)	190 (8)
Anticoagulants, n (%)	2,090 (90)	2,098 (90)	2,064 (88)
Platelet aggregation inhibitor (oral)	2003 (86)	2016 (86)	2003 (86)

CHARACTERISTIC	EMPA-REG OUTCOME		
	PLACEBO (N = 2,333)	EMPAGLIFLOZIN 10 MG (N = 2,345)	EMPAGLIFLOZIN 25 MG (N = 2,342)
Lipid-lowering Agents, n (%)	1,864 (80)	1926 (82)	1,894 (81)
Statins	1,773 (76)	1,827 (78)	1,803 (77)
Antidiabetic Drugs, n (%)			
No background therapy	36 (1.5)	46 (2.0)	47 (2.0)
Any background therapy	2,297 (99)	2,299 (98)	2,295 (98)
Metformin	1,734 (74)	1,729 (74)	1,730 (74)
Insulin	1,135 (49)	1,132 (48)	1,120 (48)
Sulfonylurea	992 (43)	985 (42)	1,029 (44)
DPP-4 inhibitor	267 (11)	282 (12)	247 (11)
Thiazolidinedione	101 (4)	96 (4)	102 (4)
GLP-1 agonist	70 (3)	68 (3)	58 (3)
Metformin daily dose, mg, (median IQR)	2000 (1,000 to 2000)	1,700 (1,000 to 2000)	1,700 (1,000 to 2000)
Insulin daily dose, IU, (median IQR)	52.0 (32.0 to 83.0)	52.5 (32.0 to 80.5)	54.0 (34.0 to 82.0)
Patients on one medication, n (%)	691 (30)	704 (30)	676 (29)
Insulin only	326 (14)	317 (14)	309 (13)
Metformin only	234 (10)	264 (11)	242 (10)
Patients with two medications, n (%)	1,148 (49)	1,110 (47)	1,149 (49)
Metformin + insulin	506 (22)	448 (19)	464 (20)
Metformin + sulfonylurea	461 (20)	443 (19)	480 (21)
Patients with three medications, n (%)	387 (17)	419 (18)	411 (18)
Metformin + sulfonylurea + insulin	123 (5)	149 (6)	146 (6)
Patient with ≥ four medications, n (%)	71 (3)	66 (3)	59 (3)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DPP-4 = dipeptidyl peptidase-4; GLP-1 agonist = glucagon-like peptide-1 agonist; IU = international units.
Source: Clinical Study Report.[6]

3.2.3 Interventions

In the EMPA-REG OUTCOME study, patients received either empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily. A double-dummy design was used to maintain blinding.

Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization, unless the patient had a fasting plasma glucose (FPG) level > 13.3 mmol/L that was confirmed by a second test. After the initial 12 weeks, background therapy could be modified or new treatments could be added (except other SGLT-2 inhibitors) at the investigator's discretion and according to local guidelines. Investigators were encouraged to treat CV risk factors (e.g., blood pressure, lipids) according to the local standard of care.

All patients were to receive counselling on diet and exercise at each study visit. Treatment with anti-obesity drugs or systemic steroids (more than two weeks' duration) were prohibited due to their influence on glucose metabolism. Patients who used restricted drugs remained in the study, and if

necessary, the study drug could be temporarily discontinued and restarted at the investigator's discretion. Treatment interruptions of more than seven consecutive days were recorded.

3.2.4 Outcomes

The outcomes of interest to the review are listed below. The text in italics identifies outcomes that were added or modified based on protocol amendments during the EMPA-REG OUTCOME study (i.e., after patients had already been enrolled in the trial).

The primary and key secondary efficacy outcomes were the time to first occurrence of:

- CV death, non-fatal MI, or non-fatal stroke (excluding silent MI)
- CV death, non-fatal MI, non-fatal stroke (excluding silent MI), or hospitalization for unstable angina for the pooled empagliflozin groups versus placebo. The primary and key secondary outcomes were analyzed first for non-inferiority, then for superiority.

The other secondary and exploratory outcomes of interest in this review included the following:

Time to first occurrence of:

- silent MI (determined by an electrocardiogram [ECG] measurement in patients with no symptoms suggestive of MI, analyzed in patients without silent MI or relevant cardiac conduction effects at baseline and available baseline and post-baseline ECG measurements)
- HF requiring hospitalization (adjudicated)
- new-onset albuminuria (urine albumin/creatinine ratio [UACR] ≥ 30 mg/g)
- new-onset macroalbuminuria (UACR > 300 mg/g)
- composite microvascular outcome defined as initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or new or worsening nephropathy (new-onset macroalbuminuria, doubling of serum creatinine with eGFR ≤ 45 mL/min/1.73m^2, initiation of renal replacement therapy, or death due to renal disease)
- CV death
- all-cause mortality
- MI (fatal or non-fatal MI)
- non-fatal MI
- hospitalization for unstable angina
- coronary revascularization procedure
- stroke (fatal or non-fatal stroke)
- non-fatal stroke
- TIA.

Change from baseline in:

- A1C, FPG
- body weight
- systolic blood pressure (SBP), diastolic blood pressure (DBP).

Two blinded, independent committees adjudicated all CV events and neurologic events, including deaths and suspected events of myocardial ischemia, stroke, HF, and coronary revascularization procedures. There was no adjudication of silent MI or microvascular events. Details on the definitions of events are discussed in Appendix 5.

Patients who stopped treatment early continued to be followed for CV outcomes or vital status (using publicly available data sources for those who were lost to follow-up).

Patient visits were scheduled every four weeks for the first 16 weeks after randomization, then every 12 weeks until one year, and then every 14 weeks until the end of the study. The final visit was conducted 30 days after the end of the trial. Information on scheduling of ECG and other investigations is described in Appendix 5, Table 17. No specific ophthalmic examinations were performed as part of the assessment of vitreous hemorrhage or diabetes-related blindness, or of the initiation of retinal photocoagulation, which were all part of the composite microvascular outcome.[28] These outcomes, as well as initiation of renal replacement therapy, were captured based on the Medical Dictionary for Regulatory Activities (MedDRA) queries of reported AEs or concomitant therapies.[28] In addition, some patients did not receive an ECG at baseline prior to study drug initiation.

Adverse events (AEs) were defined as any undesirable medical occurrence in a patient who was administered a pharmaceutical product in a clinical investigation, whether or not considered causally related to the product. AE reporting began after patients gave consent, irrespective of the start of study medications, and included events that occurred up to seven days after the last dose of the study medication.

Serious adverse events (SAEs) were any AEs that were life-threatening or resulted in death, required or prolonged hospitalization, resulted in persistent or significant disability, were congenital anomalies, or were deemed serious based on medical judgment.

Hypoglycemic events were to be reported if the patient's plasma glucose was ≤ 3.9 mmol/L. Events were considered to be an AE if the patient showed symptoms of hypoglycemia, required assistance, had a plasma glucose concentration of less than 3.0 mmol/L, or if the investigator considered the event to be an AE.

3.2.5 Statistical analysis

The primary composite outcome and secondary time-to-event outcomes were analyzed using a Cox proportional hazard model with factors for treatment (pooled empagliflozin doses versus placebo), age, sex, baseline body mass index (BMI) (< 30 kg/m^2 or ≥ 30 kg/m^2), baseline A1C (< 8.5% or ≥ 8.5%), baseline eGFR (≥ 90 mL/min, 60 mL/min to ≤ 89 mL/min, or ≤ 59 mL/min), and region. There was no imputation for missing data.

Corrections for multiple testing were applied to the primary and key secondary outcome only. A four-step hierarchical testing procedure was applied, comparing the pooled empagliflozin doses versus placebo:

- non-inferiority of the primary composite outcome (time to CV death, MI, or stroke)
- non-inferiority of the key secondary outcome (time to CV death, MI, stroke, or hospitalization for unstable angina)
- superiority of the primary composite outcome
- superiority of the key secondary outcome.

Based on the final statistical plan, a non-inferiority margin of 1.3 was selected, which was consistent with FDA guidelines.[10] If the upper limit of the HR (95.02%) confidence interval [CI]) did not exceed 1.3, empagliflozin was to be considered non-inferior to placebo. For the superiority test, empagliflozin was to be considered superior if the upper bound of the 95.02% CI was less than 1.0. Statistical tests were

one-sided with a significance level of 0.0249. One interim analysis was conducted to support regulatory approvals, and a Haybittle-Peto correction was used to maintain the one-sided significance level of 0.025. For the one-sided non-inferiority and superiority analyses, 95.02% CI were reported, based on the reduced alpha level of 0.0249 from the interim analysis. The primary non-inferiority assessment was analyzed based on a modified intention-to-treat (mITT) population, and with the per-protocol (PP) and on-treatment set (OS) as a sensitivity analysis. Other time-to-event analyses were based on the mITT population. Patients without an event were censored at the individual day of trial completion (i.e., at the end of the study or on the patient's last assessment date). Kaplan-Meier estimates were calculated, as were cumulative incidence function estimates corrected for non-CV death as a competing risk. Based on the 2:1 allocation ratio and the planned 691 primary outcome events, the study had 90% power for a non-inferiority margin of 1.3 with a one-sided significance level of 2.5%. With a sample size of 7,000 patients (accrued over two years), the trial was expected to continue for eight years, assuming the yearly event rate was 1.5%.

Changes in continuous outcomes over time were analyzed using a mixed-model repeated measures (MMRM) approach with the fixed, categorical effects of treatment, week, treatment-by-week interaction, and the covariates of baseline efficacy end point, baseline A1C, baseline body mass index (BMI), baseline eGFR, geographical region, and baseline efficacy end point-by-week interaction and baseline A1C-by-week interaction. Analyses were performed using any data obtained on treatment until rescue therapy (observed-case [OC] analysis) as well as any data obtained during treatment, post-treatment, and after intake of rescue medication (observed case–after discontinuation [OC-AD] analysis), with no imputation for missing data. MMRM models were analyzed up to 12 weeks (during which background antidiabetic medications were to remain unchanged) and up to week 94 (this time-point was not-pre-specified, but calculated after the close-out date of the trial had been decided). Continuous data were analyzed using analysis of covariance (ANCOVA) models and last observation carried forward (LOCF) for missing data.

A number of pre-specified subgroup analyses were conducted, including subgroups based on age, race, baseline A1C, and eGFR, time since diabetes diagnosis, and CV risk factors. Post-hoc analyses were conducted based on history of HF and antidiabetic medications at baseline.

Two-sided statistical tests and CIs were estimated (alpha = 0.05) for all outcomes that were not part of the hierarchical statistical testing procedure and for all subgroup analyses; no corrections for multiplicity of testing were applied.

The trial ran from August 26, 2010 to April 21, 2015. It underwent a number of changes to the protocol and statistical analysis plan after patients had been randomized. The statistical analysis plan was modified after the interim analysis and was finalized May 21, 2015. Interim data from this trial (up to August 31, 2012) was used to support a new drug application and to conduct a meta-analysis with other phase 2 and phase 3 studies for a global submission to health authorities. The manufacturer reports that access to the interim data were restricted, and that the analysis was conducted by an independent team.

TABLE 8: KEY PROTOCOL AND STATISTICAL ANALYSIS CHANGES

Protocol Amendment 1: September 22, 2010 (one month after first patient enrolled) • CV outcome events were exempt from the expedited, unblinded reporting process if they occurred during the randomized treatment period.
Protocol Amendment 2: April 22, 2011 (eight months after first patient enrolled) • The inclusion criteria for the maximum A1C in treatment-naive patients changed from 8.0% to 9.0%. • The definition of patients at high CV risk included those with single vessel coronary disease, and the criteria for unstable angina, peripheral vascular disease, and multi-vessel disease were clarified. • Age and sex were added as covariates to the statistical models. • Some study end points were clarified or added (e.g., composite microvascular outcome, time to hospitalization for unstable angina).
Protocol Amendment 3: December 29, 2011 (16 months after first patient enrolled) • The non-inferiority margin for the primary outcome changed from 1.8 to 1.3. The planned number of patients enrolled increased from 4,000 to 7,000, and the required number patients with a primary outcome event increased from 137 to 691, in order to ensure a power of 90%. • The hierarchical statistical testing procedure was modified to reflect the changes in primary and secondary outcomes (see above for final plan). • An interim analysis was added to support a New Drug Application in addition to the previously planned meta-analysis to assess the CV safety profile of empagliflozin. A Haybittle-Peto boundary was used to maintain the alpha at 0.025. • The primary outcome was clarified to exclude silent MI. • Previous renal-related outcome changed to new-onset microalbuminuria and macroalbuminuria as defined above. • Death from renal disease was added as part of the composite "new or worsening nephropathy" outcome.
Statistical Analysis Amendments: (after the interim analysis and prior to the final database lock) • Additional CV end points were analyzed (e.g., adjudicated hospitalization for HF or CV death [excluding fatal stroke]). • Addition of an on-treatment analysis (OS population) of primary, secondary, and other CV outcomes (pooled empagliflozin and individual doses). • A cumulative incidence function, accounting for competing risks was added to primary outcomes, and key secondary outcomes, and hospitalization for HF was added as a sensitivity analysis. • Clarification of specific outcomes was provided (such as death due to renal disease or silent MI, macroalbuminuria defined as UACR > 300 mg/g). • Changes were made to the analysis of SBP, DBP, weight, and FPG, and a number of microvascular- related outcomes were added. • Specific safety outcomes were added, based on requests from the FDA. • Diabetic ketoacidosis and venous thrombotic and embolic events were added as safety outcomes. • Time-adjusted analyses and subgroup analyses of AEs were added. • Addition of new subgroup analyses (e.g., based on baseline therapies).
Clinical Event Committee Charter (which defined the outcomes and adjudication of CV events): Over the course of the trial, changes were made to the definitions of outcomes, such as the following: The definition of stroke: • removed "amaurosis fugax" (transient complete/partial loss of vision in one eye) from the definition of stroke; • removed subdural hematoma from the definition of hemorrhagic stroke. The definition of "hospitalization for HF" was changed to include the following: • initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy; and • up-titration of oral diuretic or intravenous therapy, if already on therapy. The definition of hospitalization for HF or unstable angina was changed from "requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or

a date change if the time of admission/discharge is not available)" to "the date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit."
- Changes were also made to streamline the collection and determination of cause of death, after deficiencies were identified by the Data Monitoring Committee in July 2013.

AE = adverse event; CV = cardiovascular; DBP = diastolic blood pressure; FDA = Food and Drug Administration; FPG = fasting plasma glucose; A1C = glycated hemoglobin; HF = heart failure; MI = myocardial infarction; OS = on-treatment set (population); SBP = systolic blood pressure; UACR = urine albumin-to-creatinine ratio.
Source: Clinical Study Report,[6] FDA Briefing Document.[5]

a) Analysis populations

The primary, secondary, other CV, and safety outcomes were based on the treated set, a modified intention-to-treat population (mITT). This included all randomized patients who received at least one dose of study medication (analyzed according to the randomized treatment).

The full-analysis set included all randomized patients who received at least one dose of study medication and who had a baseline A1C value. This population was used to evaluate the change from baseline in A1C. The composite microvascular and renal outcomes were analyzed in treated patients who did not have macroalbuminuria at baseline, who had available measurements of serum creatinine at baseline and post-baseline, and who had post-baseline measurements of the UACR, unless patients who did not fulfill these criteria had at least one of the other components of this composite outcome.

The PP set included patients who received at least one dose of study medication and did not have any important protocol violations.

The OS set included patients who received at least 30 days of study medication and any events that occurred no later than 30 days after the last dose of study drug.

Other analysis populations included the OC set, which used any data obtained on treatment until rescue therapy, and the OC-AD set, which included any data obtained during treatment, post-treatment, and after intake of rescue medication.

3.3 Patient disposition

Of the 11,531 patients screened, 7,020 (61%) were randomized and treated in the EMPA-REG study (Table 9). Limited information was provided on the reasons for failing screening. Approximately 3% of patients did not complete the study, and follow-up for the primary outcome was not available for the entire study period. Vital status was unknown for 53 patients (0.8%), with similar frequencies across treatment groups.

More patients stopped treatment prematurely in the placebo (29%) than the empagliflozin groups (23% to 24%). The most commonly reported reasons were due to AEs, patient refusal, and 'other reasons' as per Table 9.

TABLE 9: PATIENT DISPOSITION

	EMPA-REG OUTCOME		
	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
Screened, N	11,531		
Entered Run-in Period, N (%)	7,610 (66)		
Randomized, N (%)	7,028 (61)[a]		
	2,337	2,347	2,344
Treated, N (%)	7,020 (61)[b]		
	2,333	2,345	2,342
Discontinued, N (%)	67 (2.9)	81 (3.5)	63 (2.7)
Consent withdrawn	31 (1.3)	41 (1.7)	30 (1.3)
Site closure	25 (1.1)	30 (1.3)	26 (1.1)
Lost to follow-up for MACE	11 (0.5)	10 (0.4)	7 (0.3)
Vital Status Unknown, N (%)	17 (0.7)	21 (0.9)	15 (0.6)
Discontinued Study Medication, N (%)	683 (29)	555 (24)	542 (23)
AE	303 (13)	267 (11)	273 (12)
Lack of efficacy[c]	11 (< 1)	1 (< 1)	0
Non-compliance	15 (< 1)	15 (< 1)	12 (< 1)
Lost to follow-up	15 (< 1)	9 (< 1)	6 (< 1)
Patient refusal	172 (7)	118 (5)	122 (5)
Other	162 (7)	142 (6)	125 (5)
Reason missing	5 (< 1)	3 (< 1)	4 (< 1)
mITT, N	2,333 (99.8)	2,345 (99.9)	2,342 (99.9)
PP, N	2,316 (99.1)	2,332 (99.4)	2,322 (99.1)
Safety, N	2,333 (99.8)	2,345 (99.9)	2,342 (99.9)

AE = adverse event; MACE = major adverse cardiovascular event; mITT = modified intention-to-treat; PP = per-protocol.
[a] In total, 4,503 patients were screened but were not randomized (inclusion/exclusion criteria not met, n = 3,811; consent withdrawn, n = 342; other, n = 350).
[b] Eight patients were randomized in error and were not treated (four in placebo group and two in each of the empagliflozin groups) due to uncontrolled hyperglycemia during run-in (n = 5), impaired renal function (n = 1), did not have high CV risk (n = 1), and aggravated renal failure requiring therapy during run-in (n = 1).
[c] Hyperglycemia above protocol-defined level despite use of rescue therapy.
Source: Clinical Study Report.[6]

3.4 Exposure to study treatments

The median treatment exposure (including temporary off-treatment periods) was 2.57, 2.61, and 2.61 years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively. The majority of patients were treated for two or more years (71%, 75%, and 75% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively), but less than half of patients were treated for three or more years (39%, 41%, and 43%, respectively).

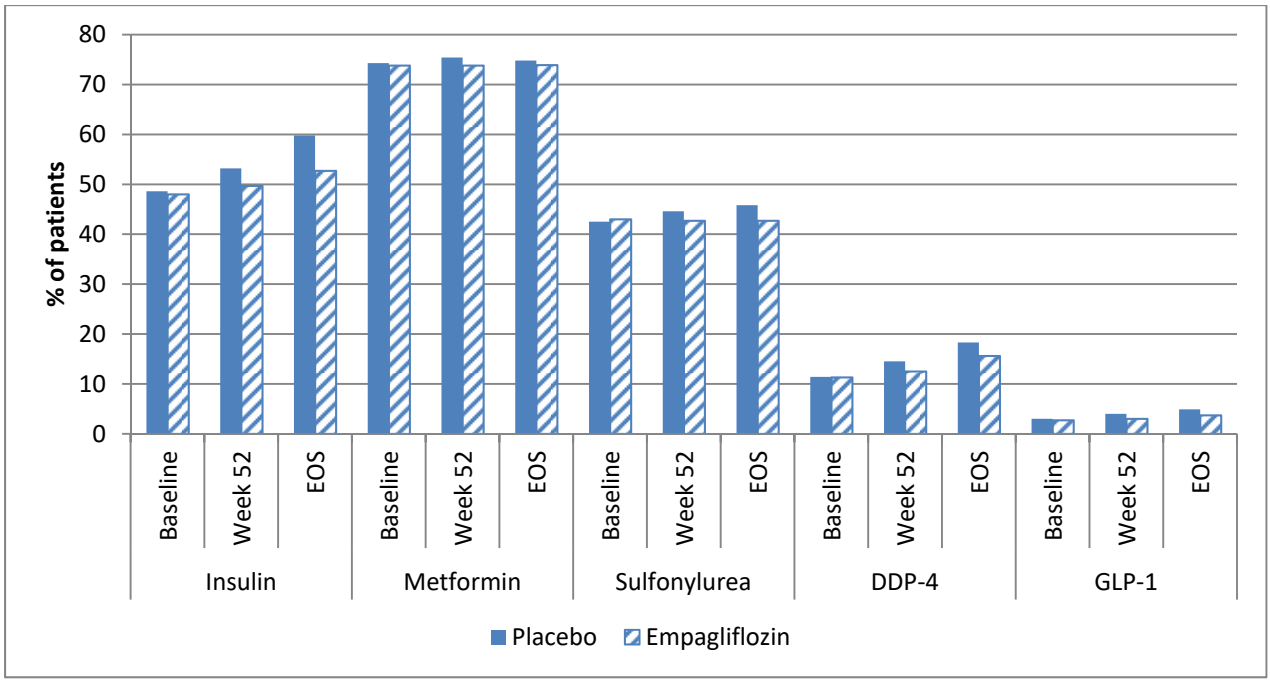
More patients in the placebo group (54%) required rescue antidiabetic drug therapy compared with the empagliflozin groups (32% or 33%). Rescue therapy included increases in the dose of background therapy or additional antidiabetic drugs (Table 10). The proportion of patients on different antidiabetic therapies during the course of the study is presented in Figure 2. By the last patient visit, 60% of the placebo group versus 53% of the empagliflozin groups were receiving insulin.

TABLE 10: CHANGES TO ANTIDIABETIC THERAPY AFTER RANDOMIZATION

TREATMENT CHANGE	EMPA-REG OUTCOME		
	PLACEBO (N = 2,333)	EMPAGLIFLOZIN 10 MG (N = 2,344)	EMPAGLIFLOZIN 25 MG (N = 2,341)
RESCUE THERAPY[A]	n (%)	n (%)	n (%)
Any rescue therapy	1,265 (54)	777 (33)	745 (32)
Increase in dose of background medications	931 (40)	555 (24)	537 (23)
Additional antidiabetic medication	631 (27)	364 (16)	328 (14)
Insulin	221 (10)	110 (5)	87 (4)
Metformin	96 (4)	69 (3)	60 (3)
Sulfonylurea	147 (6)	79 (3)	61 (3)
DPP-4 inhibitor	151 (7)	106 (5)	88 (4)
Thiazolidinedione	60 (3)	17 (< 1)	29 (1)
GLP-1 agonist	51 (2)	22 (1)	31 (1)
OTHER CHANGES[B]			
Decrease in background therapy dose	542 (23)	634 (27)	651 (28)

DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists.
[a] Any increase in dose of background therapy (> 10% of total daily insulin dose), or addition of other antidiabetic agents for seven or more days or until treatment discontinuation.
[b] For seven or more days or until treatment discontinuation.
Source: Clinical Study Report.[6]

FIGURE 2: NON-STUDY ANTIDIABETIC MEDICATIONS



EOS = end of study/last patient visit; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists.
Source: Clinical Study Report.[6]

More patients in the placebo group than in the empagliflozin groups started an antihypertensive agent after randomization (51% versus 44% and 45%, respectively) (Appendix 4, Table 18). The proportion of patients who started lipid-lowering therapy or antiplatelet therapy was similar among groups. Of note, the percentages reported in Table 18 do not take into consideration the treatments taken at baseline and those that may have stopped or had a change in dose post-baseline.

3.5 Critical appraisal

3.5.1 Internal validity

The EMPA-REG OUTCOME trial used accepted methods to randomize patient and conceal allocation, using a computer-generated, random sequence, and interactive voice or Web-response system. The baseline patient characteristics and the use of background therapies appear to be similar among groups. A double-dummy design was used to blind participants to the treatment received. Some unblinding did occur, as the interim data analysis, which was also included in a meta-analysis of empagliflozin trials, was made available to regulatory agencies to support empagliflozin's new drug submissions.[5,22] An estimated 230 individuals had access to the interim CV data.[5] How access to the interim data or the results of the meta-analysis may have influenced the study is unknown, but protocol changes were noted after the conduct of these interim analyses and meta-analysis. Of note, the manufacturer states that no changes were made to the primary or key secondary outcome after the interim analysis, and that the definition of CV death (including presumed CV death) remained unchanged throughout the entire trial. However, changes to definitions of other outcomes of interest were modified after the interim analysis. Given that SGLT-2 inhibitors are known to reduce A1C and have modest reductions on blood pressure and weight, there was potential for unbinding in the study, as investigators and patients were aware of laboratory and clinical data throughout the trial. Changes in these parameters could have influenced the use of other agents known to reduce CV events (e.g., angiotensin-converting enzyme

inhibitors, statins) as the trial progressed, as investigators were instructed to modify antidiabetic therapies (after the initial 12 weeks) and other CV medication over the course of the trial according to local standards of care. Limited information on medication changes throughout the trial was available for the EMPA-REG study. The AE profile was not likely to have significantly compromised blinding; however, those affected by urogenital AEs could have surmised that the allocated treatment was empagliflozin, given that these events are known to occur with the SGLT-2 inhibitor class drugs.

The study was designed to assess the CV safety of empagliflozin; the primary and key secondary outcomes, as well as the non-inferiority margin of 1.3, were consistent with FDA guidelines.[10] The key CV events were adjudicated by independent, blinded outcome committees. FDA briefing documents state that the collection of event data was less rigorous in this safety trial than in an efficacy trial designed to test a specific hypothesis.[5] No formal clinical assessments were performed at the time of a potential outcome event; thus, adjudication was based on the data available, rather than on a prescribed set of information.[5] FDA reviewers stated that adjudication of non-fatal events or the cause of death may be problematic, given the lack of rigorous information available.[5] If several events occurred in close proximity, a judgment was made as to the principal condition; a subsequent death may not have been attributed to the correct qualifying event. This may have impacted the percentage of deaths classified as CV deaths.[5] Overall, 40% of CV deaths reported in the EMPA-REG study could not be assessed and were assigned to be "presumed CV deaths." Other unassessable events are summarized in Appendix 4, Table 19. The proportions showed [redacted] FDA reviewers also identified issues with the definition of hospitalization for HF; due to a lack of specificity, it may have captured patients with other conditions.[5] Misclassification of events may not bias the study in favour of one treatment (assuming that blinding was maintained), but it may underestimate the true incidence of events, and may reduce the power to detect differences for specific end points.

The definitions of key CV and renal outcomes used in the EMPA-REG study varied from those used historically, and in some cases may have underestimated or overestimated events. Although the differences are unlikely to have biased the trial in favour of one treatment group, they may be important when comparing the results of the EMPA-REG study with other CV outcome trials (Appendix 5). The exclusion of silent MI from the primary composite outcome should be considered when interpreting the findings. Although the trial included a composite outcome for microvascular complications of diabetes, this composite included only renal and ophthalmic outcomes; there was no assessment of diabetes-related neuropathy. Also of note, there were no scheduled ophthalmic examinations during the trial. Ophthalmic events (initiation of retinal photocoagulation, vitreous hemorrhage, or diabetes-related blindness) were based on queries of reported AEs or concomitant treatments, and thus may not capture all patients with diabetes-related ophthalmic complications. As a result, the composite microvascular outcome was based mainly on laboratory tests of renal function, which was assessed at regular intervals during the trial. The definition of events for "new and worsening nephropathy" was not consistent with those typically used to establish the efficacy of drugs for diabetic nephropathy; also, according to the FDA reviewer, it was not designed well enough to capture irreversible loss of renal function.[5] Confirmation of a change in renal function was not required; thus, the events captured also included acute or temporary changes in renal function (including short-term dialysis for an acute kidney injury).[5] Furthermore, the renal-related outcomes were among the key protocol changes noted in the trial design after patients were randomized.

Numerous additional protocol and statistical analyses plan changes were made during the trial and after the interim data analysis had been shared with regulatory agencies (Table 8). Several exploratory

outcomes and subgroup analyses were added to the protocol, and some of these have been selectively reported in published articles (e.g., renal or HF-related outcomes).[18,24,26] It is not possible to know the potential impact of these protocol changes on the study's findings.

Methods to control type 1 error were employed for the interim analysis, the primary outcomes, and the key secondary outcomes. However, the numerous other outcomes, including multiple composite outcomes as well as individual components of the composites and the subgroup analyses had no control of multiplicity; thus, statistically significant results should be interpreted with caution. Of note, the primary outcome of the trial does not address the manufacturer's requested listing, and the submitted Health Canada indication is based on an exploratory outcome, namely CV mortality, which was outside the statistical testing hierarchy in the EMPA-REG study and is highly susceptible to type 1 error due to multiplicity of testing.

The time-to-event outcomes were assessed using a Cox proportional hazards model that was adjusted for age and sex, plus the stratification variables applied at randomization. The Cox model takes into consideration the length of follow-up of patients; however, this method assesses only the time to the first occurrence of an event; the drug's effect on subsequent, recurrent events was not assessed. Also of note, the sample sizes were small for some subgroup and may lack the statistical power to detect differences.

The statistical methods used to test the non-inferiority and superiority of the primary outcomes and key secondary outcomes were based on one-sided tests and 95.02% CI. Two-sided superiority tests were also conducted that showed consistent results, but these were outside the statistical hierarchy. Furthermore, the analysis of the primary non-inferiority outcome was based on the mITT population (randomized patients who had received at least one dose of study drug), not the PP population, which is generally more conservative in a non-inferiority study.

The continuous outcomes (e.g., A1C) were presented[18] using a MMRM analysis even though ANCOVA/LOCF was specified as the main analysis in the protocol; however, the results were generally consistent between the two approaches. Data were analyzed up to week 12 and week 96; however, the 96-week time-point was not-pre-specified, but was calculated after the close-out date of the trial had been decided.

Relatively few patients discontinued the study early (placebo, 2.9%; empagliflozin, 3.1%), had unknown status for non-fatal major CV events (placebo, 2.1%; empagliflozin, 2.3%), or had an unknown vital status (placebo, 0.7%; empagliflozin, 0.8%); the percentages were generally similar between groups. Data were incomplete for some outcomes. The results may be subject to bias due to the substantial extent of missing or excluded patients, which ranged from 12% (composite microvascular outcome) to 49% (silent MI). There was no imputation of missing data, and patients with incomplete follow-up were censored at the time of last assessment for the time-to-event analyses. Data for silent MI should be interpreted with caution given that the outcome was a) not adjudicated, b) was reported for only half of the patients enrolled, and c) excluded patients with silent MI or relevant cardiac conduction defects at baseline, those without post-baseline ECG measurements, and those with only post-baseline ECG measurements with cardiac conduction defects.

3.5.2 External validity

The findings of the trial apply to a specific subset of patients with diabetes, namely a secondary prevention population (i.e., approximately half of the patients enrolled had a prior MI, and a quarter of the patients had had a prior stroke) who were well managed, were receiving evidence-based CV medications, and who had long-standing diabetes. The patients enrolled had inadequate glycemic control, even though 70% were taking two or more antidiabetic medications, and approximately half were using insulin. Caution should be used when generalizing the findings to other diabetes patients, such as those without established CV disease or those with a more recent diagnosis of diabetes, as the absolute effects may not be as substantial in lower-risk populations.

Other potential external validity issues include the substantial percentage of patients who failed screening (40%), for which few details were available. Also, there were a limited number of Canadian patients (< 2%) included, although 17% of those enrolled were from the US. Sample sizes were small for some subpopulations of interest (e.g., Black patients); therefore, there may be generalizability limitations. Patients with HF were not a pre-specified subgroup in the trial; thus, any data from these patients should be interpreted with caution.

The patients enrolled in the trial were predominantly male (72%); thus, women may be under-represented. This may have some implications for the external validity, given than women with diabetes may develop CV disease later than men. Therefore, the rate of CV disease observed for this age group in the trial may be higher than in the general population,[29] and the rate of genital infections, which affect mostly females, may be lower in the trial than in general population.

The median empagliflozin exposure duration was 2.6 years; thus, the risks and benefits of longer-term treatment durations are uncertain.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See *0 for detailed efficacy data.*

No information on health-related quality of life was reported in the EMPA-REG OUTCOME study.

3.6.1 CV Mortality, MI, or stroke

In the primary outcome analysis, fewer patients in the pooled empagliflozin group experienced a major cardiovascular adverse event (MACE) defined as first occurrence of CV death, non-fatal MI, or non-fatal stroke,than in the placebo group (10.5% versus 12.1%, respectively) (Table 11). Empagliflozin was non-inferior to placebo, as the upper bounds of the 95.02 % CI did not exceed the non-inferiority margin of 1.3 with either the mITT or the PP analysis (mITT: adj HR = 0.86; 95% CI, 0.74 to 0.99) (Figure 3). Empagliflozin was superior to placebo based on the one-sided (P = 0.019) and two-sided tests (P = 0.038, outside the statistical hierarchy).

The two doses of empagliflozin showed results similar to the pooled group, although the 95% CI were wider (Table 11). The Kaplan-Meier graph of the time to first occurrence of CV death, MI, or stroke (excluding silent MI) is presented in Figure 4. In this graph, separation between the groups appeared by approximately six months.

The primary outcome included 124 presumed CV deaths that were not assessable based on the data available. Empagliflozin was non-inferior but was not superior to placebo in a sensitivity analysis that

excluded all non-assessable CV deaths from the primary composite outcome (adj HR = 0.90; 95% CI, 0.77 to 1.06).[5]

The primary analysis was analyzed by numerous subgroups, and those specified in the CDR review protocol have been presented in Appendix 4, Table 20. Overall, there were four subgroups where the interaction *P* value was statistically significant: age, baseline A1C, weight, and history of hypertension. No difference between groups was reported for the subgroup < 65 year of age (adj HR = 1.04; 95% CI, 0.84 to 1.29) and with baseline A1C ≥ 8.5% (adj HR = 1.14; 95% CI, 0.86 to 1.50), whereas those ≥ 65 years of age (adj HR = 0.71; 95% CI, 0.59 to 0.87) and with an A1C < 8.5% showed a treatment effect with empagliflozin (adj HR = 0.76; 95% CI, 0.64 to 0.90). Some variability in treatment effect was also observed between subgroups (e.g., race, baseline eGFR, antidiabetic medications at baseline), although the interaction terms were not significant and some subgroups were small. HF was not a pre-specified subgroup in the EMPA-REG study and the post-hoc analysis did not report data for the primary outcome.[26]

TABLE 11: MAJOR CV EVENTS (ADJUDICATED)

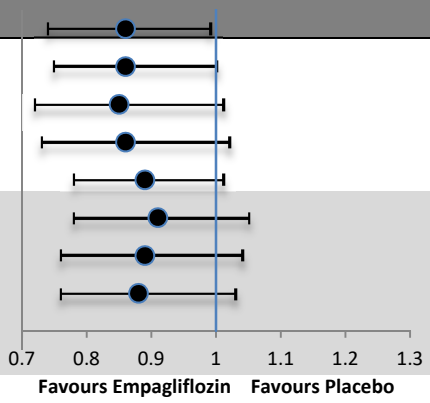
OUTCOME	EMPA-REG OUTCOME			
TIME TO FIRST EVENT	Placebo (N = 2,333)	Empagliflozin Pooled (N = 4,687)	Empagliflozin 10 mg (N = 2,345)	Empagliflozin 25 mg (N = 2,342)
CV DEATH, MI, OR STROKE (EXCLUDING SILENT MI)				
n (%)	282 (12.1)	490 (10.5)	243 (10.4)	247 (10.5)
Incidence rate/1,000 years at risk	43.9	37.4	37.1	37.7
Adj HR (95% CI) versus placebo[a]		0.86 (0.74 to 0.99)[b]	0.85 (0.72 to 1.01)	0.86 (0.73 to 1.02)
Non-inferiority *P* value[c]		< 0.0001		
Superiority *P* value[d]		0.019		
P value (2-sided)[e]		0.038	0.067	0.087
COMPONENTS[F,G]				
CV death, n (%)	107 (4.6)	143 (3.1)		
Non-fatal MI, n (%)	120 (5.1)	208 (4.4)		
Non-fatal stroke, n (%)	55 (2.4)	142 (3.0)		
CV DEATH, MI, STROKE, OR HOSPITALIZATION FOR UNSTABLE ANGINA (EXCLUDING SILENT MI)				
n (%)	333 (14.3)	599 (12.8)	300 (12.8)	299 (12.8)
Incidence rate/1,000 years at risk	52.5	46.4	46.6	46.3
Adj HR (95% CI) versus placebo[a]		0.89 (0.78 to 1.01)[b]	0.89 (0.76 to 1.04)	0.88 (0.76 to 1.03)
Non-inferiority *P* value[c]		< 0.0001		
Superiority *P* value[d]		0.040 (NS)		
P value (2-sided)[e]		0.080	0.15	0.12
COMPONENTS[F,G]				

OUTCOME	EMPA-REG OUTCOME			
TIME TO FIRST EVENT	Placebo (N = 2,333)	Empagliflozin Pooled (N = 4,687)	Empagliflozin 10 mg (N = 2,345)	Empagliflozin 25 mg (N = 2,342)
CV death, n (%)	104 (4.5)	142 (3.0)		
Non-fatal MI, n (%)	116 (5.0)	200 (4.3)		
Non-fatal stroke, n (%)	55 (2.4)	140 (3.0)		
Hospitalization for unstable angina, n (%)	61 (2.6)	120 (2.6)		

Adj = adjusted; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NS = not statistically significant.
[a] Model included age, sex, baseline BMI (categorical), baseline A1C (categorical), baseline eGFR (categorical), geographical region, and treatment.
[b] 95.02% CIs reported, based on the reduced alpha level of 0.0249 resulting from the interim analysis.
[c] *P* value for HR ≥ 1.3 (1-sided).
[d] *P* value for HR ≥ 1.0 (1-sided).
[e] *P* value for HR = 1.0 (2-sided). Outside the statistical testing hierarchy.
[f] Outside the statistical testing hierarchy.
[g] Patients could be reported with multiple events if a non-fatal MI and non-fatal stroke occurred on the same day.
Source: Clinical Study Report.[6]

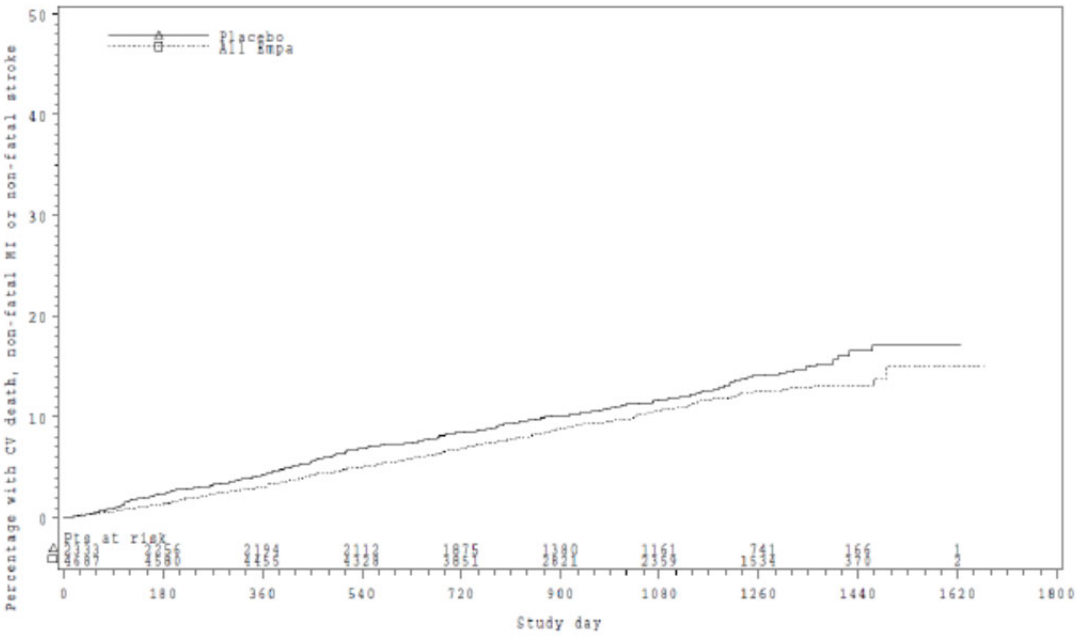
FIGURE 3: PRIMARY AND KEY SECONDARY OUTCOMES

Outcome	Analysis	Intervention Versus Placebo	Adj HR (95% CI)
MACE[a]	mITT	Empagliflozin (pooled)	0.86 (0.74 to 0.99)
	PP	Empagliflozin (pooled)	0.86 (0.75 to 1.00)
	mITT	Empagliflozin 10 mg	0.85 (0.72 to 1.01)
	mITT	Empagliflozin 25 mg	0.86 (0.73 to 1.02)
MACE Plus[b]	mITT	Empagliflozin (pooled)	0.89 (0.78 to 1.01)
	OS[c]	Empagliflozin (pooled)	0.91 (0.78 to 1.05)
	mITT	Empagliflozin 10 mg	0.89 (0.76 to 1.04)
	mITT	Empagliflozin 25 mg	0.88 (0.76 to 1.03)



Adj = adjusted; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; mITT = modified intention-to-treat; OS = on-treatment set; PP = per-protocol.
[a] Time to first occurrence of CV death, MI, or stroke.
[b] Time to first occurrence of CV death, MI, stroke, or hospitalization for unstable angina.
[c] Including events up to 30 days after the last dose of study drug.
Source: Clinical Study Report.[6]

FIGURE 4: KAPLAN-MEIER ESTIMATION OF TIME TO FIRST OCCURRENCE OF CV DEATH, MI, OR STROKE



EMPA = empagliflozin; CV = cardiovascular; MI = myocardial infarction.
Source: Clinical Study Report.[6]

3.6.2 CV death, MI, stroke, or hospitalization for unstable angina

Based on the time to first occurrence of CV mortality, MI, stroke, or hospitalization for unstable angina, empagliflozin was non-inferior to placebo (mITT: adj HR = 0.89; 95% CI, 0.78 to 1.01) based on a non-inferiority margin of 1.3; however, no statistically significant differences were detected between groups in the superiority analysis (Table 11). Similar results were observed based on the on-treatment analysis and when each dose of empagliflozin was analyzed separately (Figure 3).

3.6.3 Mortality

All-cause and CV-related mortality were reported as secondary outcomes (outside the statistical testing hierarchy) in the EMPA-REG study (Table 12). Fewer patients in the empagliflozin group died due to CV causes than in the placebo group (3.7% versus 5.9%) (adj HR = 0.62; 95% CI, 0.49 to 0.77). The analysis of all-cause mortality showed similar results (adj HR = 0.68; 95% CI, 0.57 to 0.82).

The adjudicated CV deaths were reported according to subcategory (Table 12). The most frequently reported events for placebo versus empagliflozin groups were fatal event not assessable (2.3% versus 1.5%), sudden death (1.6% versus 1.1%), and worsening of HF (0.8% versus 0.2%). A sensitivity analysis excluding the non-assessable CV deaths (n = 124) showed similar results as reported in Table 12 (CV death: Adj HR = 0.59; 95% CI, 0.44 to 0.79; all-cause mortality: HR = 0.68; 95% CI, 0.57 to 0.82).[5]

TABLE 12: MORTALITY (ADJUDICATED)

OUTCOME	EMPA-REG OUTCOME	
TIME TO FIRST EVENT	**Placebo N = 2,333**	**Empagliflozin Pooled N = 4,687**
ALL-CAUSE MORTALITY		
n (%)	194 (8.3)	269 (5.7)
Incidence rate/1,000 years at risk	28.6	19.4
Adj HR (95% CI) versus placebo[a]		0.68 (0.57 to 0.82)
P value		< 0.0001[b]
CV DEATH		
n (%)	137 (5.9)	172 (3.7)
Incidence rate/1,000 years at risk	20.2	12.4
Adj HR (95% CI) versus placebo[a]		0.62 (0.49 to 0.77)
P value		< 0.0001 [b]
CV DEATH BY SUBCATEGORY		
Acute MI, n (%)	11 (0.5)	15 (0.3)
Sudden death, n (%)	38 (1.6)	53 (1.1)
Worsening of HF, n (%)	19 (0.8)	11 (0.2)
Cardiogenic shock, n (%)	3 (0.1)	3 (0.1)
Stroke, n (%)	11 (0.5)	16 (0.3)
Other CV death, n (%)	2 (0.1)	3 (0.1)
Fatal event not assessable, n (%)	53 (2.3)	71 (1.5)

Adj = adjusted; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio MI = myocardial infarction.
[a] Model included age, sex, baseline body mass index (BMI) (categorical), baseline A1C (categorical), baseline eGFR (categorical), geographical region, and treatment.
[b] Outside the statistical testing hierarchy. Two-sided *P* value, alpha = 0.05.
Source: Clinical Study Report.[6]

3.6.4 MI

Numerically fewer patients experienced a non-fatal MI (5.2% versus 4.5%), or a fatal/non-fatal MI (5.4% versus 4.8%) in the pooled empagliflozin group compared with the placebo group (Table 13), although the HR CIs for both analyses included the null value and were not statistically significant.

Silent MI was reported numerically more frequently in the empagliflozin group than placebo group (adj HR = 1.28; 95% CI, 0.70 to 2.33)(Table 13). The subset of patients analyzed for the time to CV death, stroke, or MI including silent MI reported events in 21.4% and 19.6% of placebo and empagliflozin groups, respectively (adj HR = 0.92; 95% CI, 0.79 to 1.06). Of note, silent MI was not an adjudicated event and was assessed for 51% of patients, excluding those with silent MI or relevant cardiac conduction effects at baseline and those with no baseline or post-baseline ECG measurements.

3.6.5 Stroke or TIA

Numerically more patients in the empagliflozin group experienced a non-fatal stroke (3.2% versus 2.6%) or a fatal/non-fatal stroke (3.5% versus 3.0%) than in the placebo group (Table 13). TIA was reported infrequently during the trial, and the proportion of patients with a TIA (0.8% versus 1%) was generally similar between groups.

Most of the adjudicated stroke events were ischemic strokes (58 of the 60 of non-fatal strokes in the placebo group and 140 of the 150 of the non-fatal strokes in the empagliflozin group). In both the placebo and pooled empagliflozin groups, 0.3% of patients had more than one stroke event, and 1.2% and 1.4% of patients, respectively, had a non-fatal stroke that resulted in persistent or significant disability. Of note, there was no adjudication of the second or subsequent stroke events, and there was no requirement to assess or report disability during the trial.

TABLE 13: OTHER ADJUDICATED CV OUTCOMES

OUTCOME	EMPA-REG OUTCOME	
Time to First Event	**Placebo (N = 2,333)**	**Empagliflozin Pooled (N = 4,687)**
MI (FATAL/NON-FATAL)[A]		
n (%)	126 (5.4)	223 (4.8)
Incidence rate/1,000 years at risk	19.3	16.8
Adj HR (95% CI) versus placebo[b]		0.87 (0.70 to 1.09)
P value		0.23[c]
NON-FATAL MI[A]		
n (%)	121 (5.2)	213 (4.5)
Incidence rate/1,000 years at risk	18.5	16.0
Adj HR (95% CI) versus placebo[b]		0.87 (0.70 to 1.09)
P value		0.22[c]
SILENT MI[D]	**N = 1,211**	**N = 2,378**
n (%)	15 (1.2)	38 (1.6)
Incidence rate/1,000 years at risk	5.4	7.0
Adj HR (95% CI) versus placebo[b]		1.28 (0.70 to 2.33)
P value		0.42[c]
STROKE (FATAL/NON-FATAL)[E]		
n (%)	69 (3.0)	164 (3.5)
Incidence rate/1,000 years at risk	10.5	12.3
Adj HR (95% CI) versus placebo[b]		1.18 (0.89 to 1.56)
P value		0.26[c]
NON-FATAL STROKE		
n (%)	60 (2.6)	150 (3.2)
Incidence rate/1,000 years at risk	9.1	11.2
Adj HR (95% CI) versus placebo[b]		1.24 (0.92 to 1.67)
P value		0.16[c]
TIA		
n (%)	23 (1.0)	39 (0.8)
Incidence rate/1,000 years at risk	3.5	2.9

OUTCOME	EMPA-REG OUTCOME	
Time to First Event	**Placebo (N = 2,333)**	**Empagliflozin Pooled (N = 4,687)**
Adj HR (95% CI) versus placebo[b]		0.85 (0.51 to 1.42)
P value		0.54[c]
HOSPITALIZATION FOR UNSTABLE ANGINA		
n (%)	66 (2.8)	133 (2.8)
Incidence rate/1,000 years at risk	10.0	10.0
Adj HR (95% CI) versus placebo[b]		0.99 (0.74 to 1.34)
P value		0.97[c]
CORONARY REVASCULARIZATION PROCEDURES		
n (%)	186 (8.0)	329 (7.0)
Incidence rate/1,000 years at risk	29.1	25.1
Adj HR (95% CI) versus placebo[b]		0.86 (0.72 to 1.04)
P value		0.11[c]
HF REQUIRING HOSPITALIZATION		
n (%)	95 (4.1)	126 (2.7)
Incidence rate/1,000 years at risk	14.5	9.4
Adj HR (95% CI) versus placebo[b]		0.65 (0.50 to 0.85)
P value		0.0017[c]

Adj = adjusted; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; TIA = transient ischemic attack.
[a] Excluding silent MI.
[b] Model included age, sex, baseline body mass index (BMI) (categorical), baseline A1C (categorical), baseline eGFR (categorical), geographical region, and treatment.
[c] Outside the statistical testing hierarchy. Two-sided *P* value, alpha = 0.05.
[d] This secondary outcome was not adjudicated. Time to major adverse cardiac event (MACE) including silent MI: placebo, 21.4%; empagliflozin, 19.6%. HR = 0.92; 95% CI, 0.79 to 1.06, *P* = 0.23 (placebo N = 1,378, empagliflozin N = 2,674).
[e] The proportion of patients with a stroke was similar for the empagliflozin 10 mg (3.6%) and 25 mg dose groups (3.4%).
Source: Clinical Study Report.[6]

3.6.6 Other CV outcomes

The incidence of hospitalization for unstable angina was the same for both treatment groups (2.8%); numerically fewer patients underwent a coronary revascularization procedure in the empagliflozin group than in the placebo group (7.0% versus 8.0%) (Table 13).

Fewer patients in the empagliflozin group had a hospitalization for HF compared with placebo (2.7% versus 4.1%, adj HR = 0.65; 95% CI, 0.50 to 0.85). Of note, these outcomes were outside the statistical hierarchy and were considered exploratory.

3.6.7 Microvascular outcomes

The proportion of patients who reported a microvascular event (which included initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or "new or worsening nephropathy") was lower in the empagliflozin versus placebo group (14.0% versus 20.5%) (Table 14). Most microvascular events were renal-related, with new-onset macroalbuminuria contributing the majority of the new or worsening nephropathy events.

New-onset albuminuria was reported in 51% of patients in the empagliflozin and placebo groups, and initiation of renal replacement therapy was reported in 0.6% of the placebo group compared with 0.3% of the empagliflozin group (Table 14). Diabetes-related blindness was reported infrequently (0.1%), with the same incidence in both groups (Table 14).

Of note, data for the renal-related outcomes were not reported for all patients in the trial (limited to 59% to 89% of the overall study population), and excluded patients such as those with albuminuria or macroalbuminuria at baseline or with missing laboratory data. No further details were available.

TABLE 14: MICROVASCULAR OUTCOMES

OUTCOME	EMPA-REG OUTCOME	
TIME TO FIRST EVENT	**Placebo (N = 2,333)**	**Empagliflozin Pooled (N = 4,687)**
COMPOSITE MICROVASCULAR EVENT[A]	**N = 2,068**	**N = 4,132**
n (%)	424 (20.5)	577 (14.0)
Incidence rate/1,000 years at risk	83.6	52.8
Adj HR (95% CI) versus placebo[b]		0.62 (0.54 to 0.70)
P value		< 0.0001[c]
NEW OR WORSENING NEPHROPATHY[D]	**N = 2,061**	**N = 4,124**
n (%)	388 (18.8)	525 (12.7)
Incidence rate/1,000 years at risk	76.0	47.8
Adj HR (95% CI) versus placebo[b]		0.61 (0.53 to 0.70)
P value		< 0.0001[c]
NEW-ONSET MACROALBUMINURIA (UACR > 300 MG/G)	**N = 2,033**	**N = 4,091**
n (%)	330 (16.2)	459 (11.2)
Incidence rate/1,000 years at risk	64.9	41.8
Adj HR (95% CI) versus placebo[b]		0.62 (0.54 to 0.72)
P value		< 0.0001[c]
NEW-ONSET ALBUMINURIA (UACR ≥ 30 MG/G)	**N = 1,374**	**N = 2,779**
n (%)	703 (51.2)	1,430 (51.5)
Incidence rate/1,000 years at risk	266.0	252.5
Adj HR (95% CI) versus placebo[b]		0.95 (0.87 to 1.04)
P value		0.25[c]
INITIATION OF CONTINUOUS RENAL REPLACEMENT THERAPY	**N = 2,333**	**N = 4,687**
n (%)	14 (0.6)	13 (0.3)
Incidence rate/1,000 years at risk	2.1	1.0

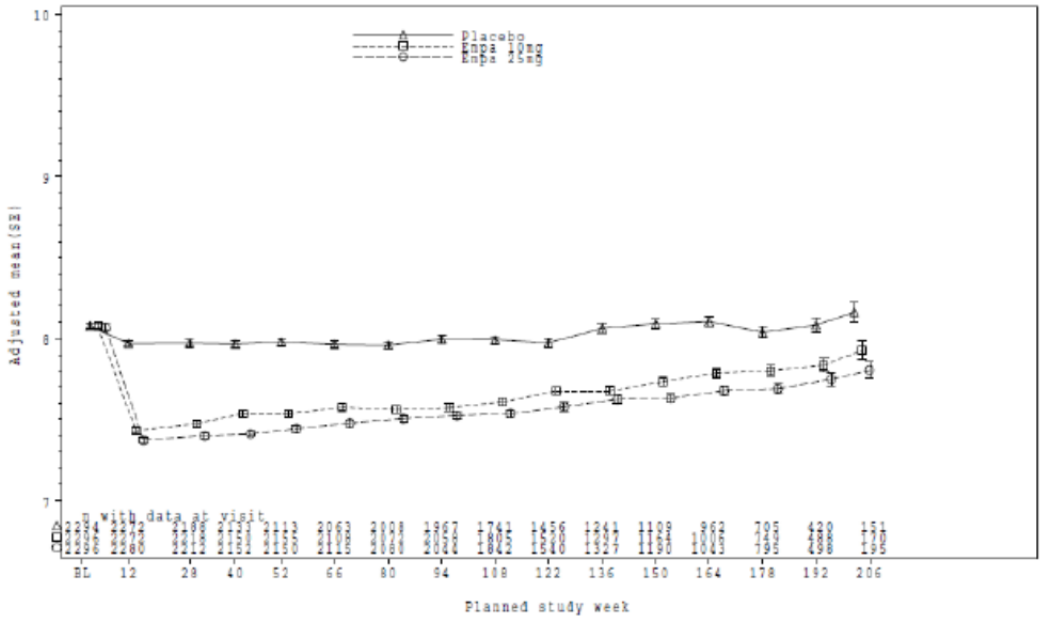
OUTCOME	EMPA-REG OUTCOME	
TIME TO FIRST EVENT	**Placebo (N = 2,333)**	**Empagliflozin Pooled (N = 4,687)**
Adj HR (95% CI) versus placebo[b]		0.45 (0.21 to 0.97)
P value		0.04[c]
DIABETES-RELATED BLINDNESS[E]	**N = 2,333**	**N = 4,687**
n (%)	2 (0.1)	4 (0.1)
Incidence rate/1,000 years at risk	0.3	0.3

Adj = adjusted; CI = confidence interval; HR = hazard ratio; UACR = urine albumin-to-creatinine ratio.
[a] Defined as the time to first occurrence of initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or "new or worsening nephropathy."
[b] Model included age, sex, baseline body mass index (BMI) (categorical), baseline A1C (categorical), baseline eGFR (categorical), geographical region, and treatment.
[c] Outside the statistical testing hierarchy. Two-sided *P* value, alpha = 0.05.
[d] Part of the composite microvascular outcome and includes new-onset macroalbuminuria, doubling of serum creatinine with eGFR ≤ 45 mL/min/1.73m^2, initiation of renal replacement therapy, or death due to renal disease.
[e] HR not calculated due to the low number of events.
Source: Clinical Study Report,[6]

3.6.8 A1C, BP, and weight

The mean baseline A1C levels were 8.1% in all treatment groups. Modest differences in the mean A1C were reported for empagliflozin versus placebo at 12 weeks (–0.5% to –0.6%) and at 94 weeks (–0.4% to –0.5%) (Appendix 4, Table 21). The adjusted mean A1C during the study, presented Figure 5, shows similar A1C levels for the two empagliflozin groups. The findings were similar for the changes to FPG levels, which are summarized in Appendix 4, Table 22. Of note, changes to background antidiabetic therapy were allowed at the investigator's discretion after the initial 12 weeks.

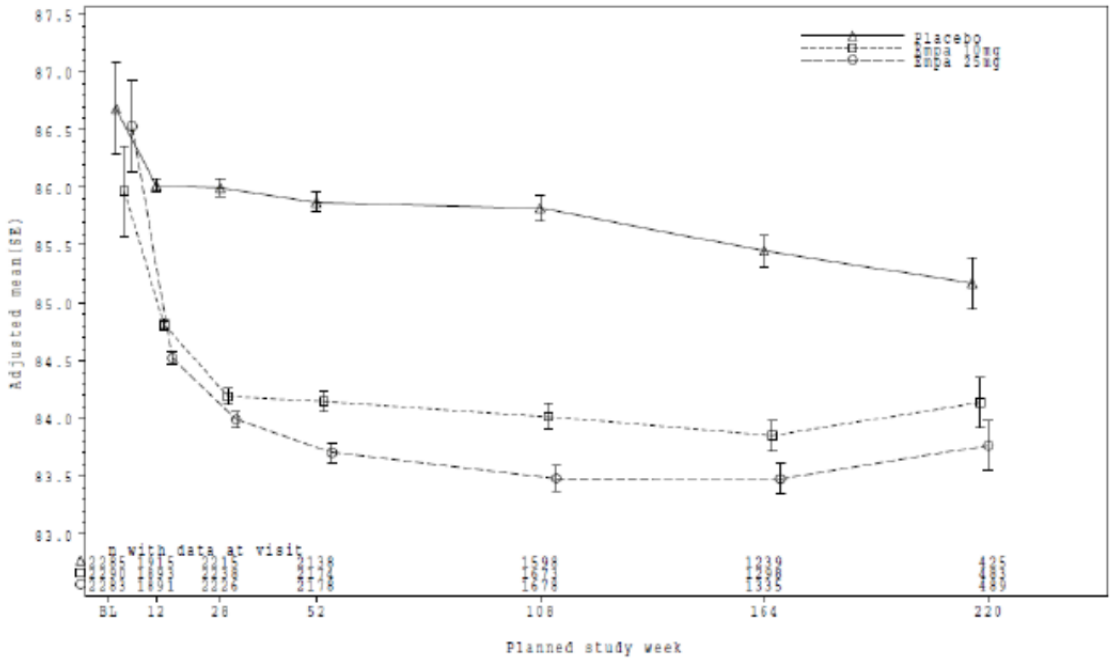
FIGURE 5: ADJUSTED MEAN A1C (%) OVER TIME (MMRM OC-AD)



EMPA = empagliflozin; A1C = glycated hemoglobin; MMRM (OC-AD) = mixed-model repeated measure (observed case–after discontinuation); SE = standard error.
Source: Clinical Study Report, page 222.[6]

The mean body weight declined in both the placebo and empagliflozin groups during the study (Figure 6). The adjusted mean differences were –1.2 kg and –1.5 kg at week 12, –1.7 kg and –2.2 kg at week 52, and –1.8 kg and –2.3 kg at week 108 in the empagliflozin 10 mg and empagliflozin 25 mg groups, respectively, compared with placebo (Appendix 4,Table 23).

FIGURE 6: ADJUSTED MEAN BODY WEIGHT (KG) OVER TIME (MMRM OC-AD)

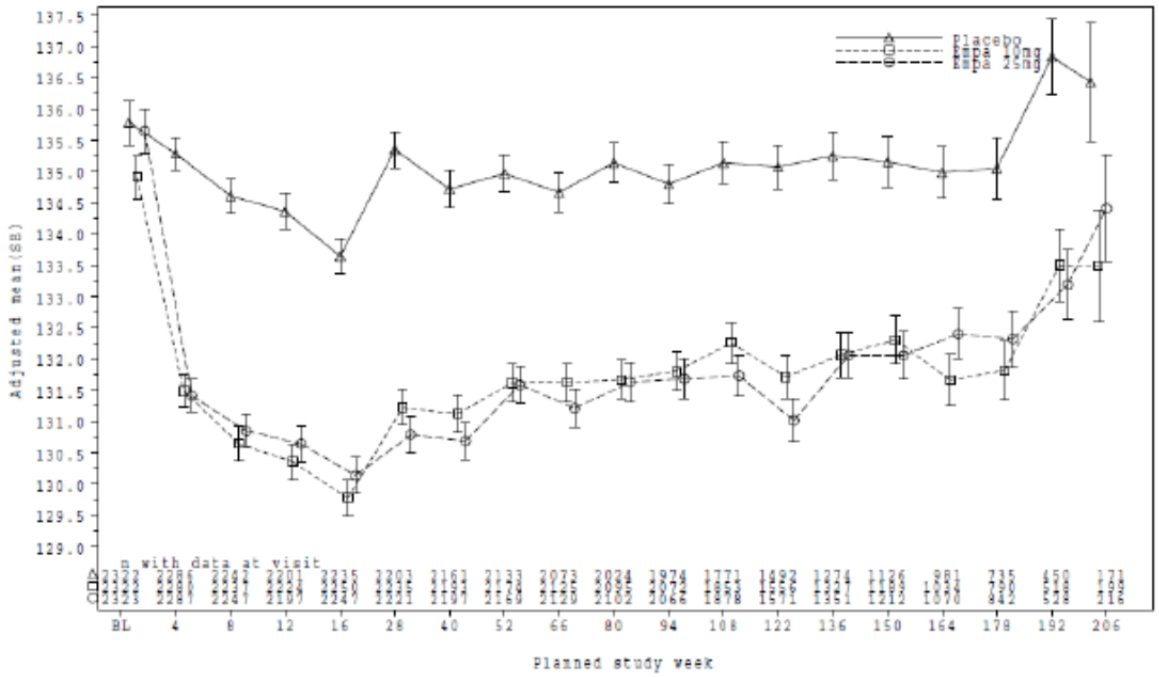


EMPA = empagliflozin; MMRM (OC-AD) = mixed-model repeated measure (observed case–after discontinuation); SE = standard error.
Source: Clinical Study Report, page 224.[6]

The changes in SBP and DBP are presented in Figure 7 and Figure 8. The difference between empagliflozin and placebo in mean SBP observed at 12 weeks (–4 mm Hg) was generally sustained over the study (–3 mm Hg at week 94) (Appendix 4, Table 24). A trend of declining DBP was observed for the empagliflozin and placebo groups; the adjusted mean differences between groups ranged from –0.9 to –1.5 mm Hg at weeks 12 and 94 (Appendix 4, Table 25). Of note, changes to background hypertension therapy were allowed at the investigator's discretion.

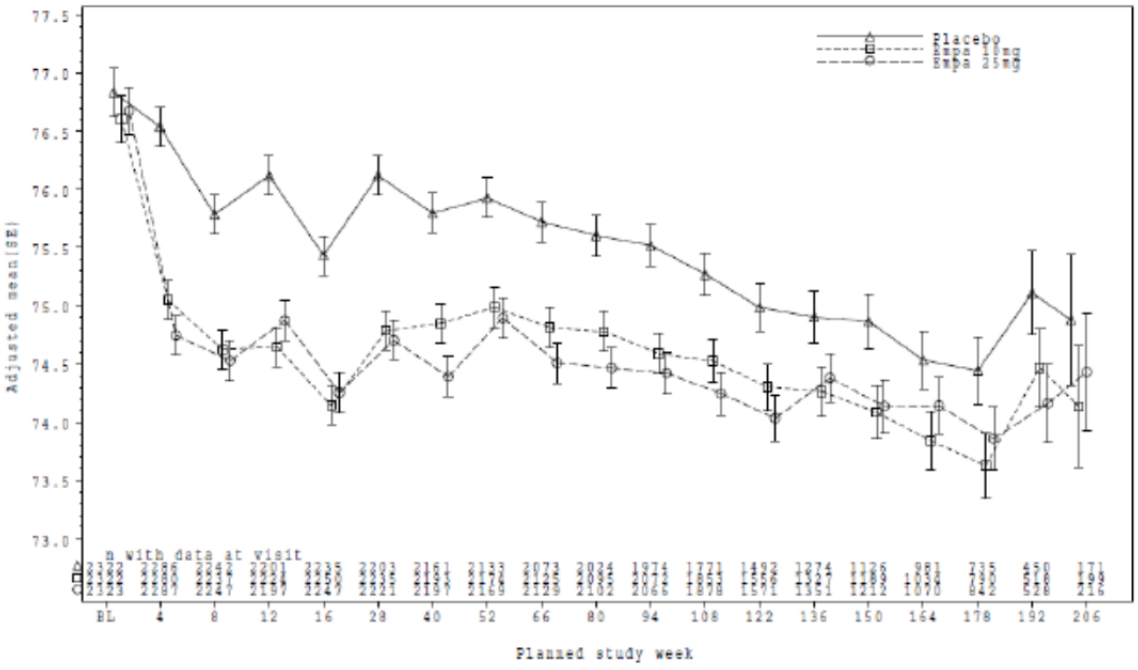
The ANCOVA/LOCF analyses of change from baseline in A1C, FPG, weight, and blood pressure yielded similar results to the MMRM models.

FIGURE 7: ADJUSTED MEAN SBP (MM HG) OVER TIME (MMRM OC-AD)



EMPA = empagliflozin; MMRM (OC-AD) = mixed-model repeated measure (observed case–after discontinuation); SBP = systolic blood pressure; SE = standard error.
Source: Clinical Study Report, page 225.[6]

FIGURE 8: ADJUSTED MEAN DBP (MM HG) OVER TIME (MMRM OC-AD)



EMPA = empagliflozin; MMRM (OC-AD) = mixed-model repeated measure (observed case–after discontinuation); SBP = systolic blood pressure; SE = standard error.
Source: Clinical Study Report, page 227.[6]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). *See 0 for detailed harms data.*

3.7.1 Adverse events

Most patients reported one or more AE during the trial (placebo 92%, empagliflozin 90%) (Table 15). The frequency of the more common AEs was similar between groups, except for hyperglycemia and peripheral edema, which were reported more frequently in the placebo group.

3.7.2 Serious adverse events

SAEs were reported in 42%, 37%, and 39% of the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively (Table 15). Cardiac disorders (14% to 17%), infections (8% to 9%), and nervous system disorders (6% to 7%) were the most commonly reported SAEs.

3.7.3 Withdrawals due to adverse events

The proportion of patients who withdrew from treatment due to adverse events (WDAE) was generally similar in the placebo (19%) and in the empagliflozin group (17% and 18%) (Table 15). CV-related events and infections were the most common events leading to discontinuation.

TABLE 15: HARMS

	EMPA-REG OUTCOME		
ADVERSE EVENTS[A]	**Placebo (N = 2,333)**	**Empagliflozin 10 mg (N = 2,345)**	**Empagliflozin 25 mg (N = 2,342)**
Subjects with > 0 AEs, n (%)	2,139 (92)	2,112 (90)	2,118 (90)
Most common AEs[b]			
UTI	352 (15)	347 (15)	347 (15)
Nasopharyngitis	217 (9)	210 (9)	220 (9)
Upper respiratory tract infection	201 (9)	192 (8)	177 (8)
Bronchitis	170 (7)	134 (6)	122 (5)
Influenza	167 (7)	134 (6)	149 (6)
Hypoglycemia	686 (29)	696 (30)	674 (29)
Hyperglycemia	431 (19)	220 (9)	205 (9)
Back pain	155 (7)	152 (7)	174 (7)
Arthralgia	132 (6)	108 (5)	151 (6)
Pain in extremity	136 (6)	117 (5)	106 (5)
Diarrhea	175 (8)	150 (6)	148 (6)
Constipation	112 (5)	93 (4)	121 (5)
Dizziness	153 (7)	178 (8)	178 (8)
Headache	125 (5)	101 (4)	124 (5)
Peripheral edema	159 (7)	84 (4)	76 (3)
Chest pain	108 (5)	113 (5)	119 (5)
Cough	146 (6)	119 (5)	108 (5)
Hypertension	216 (9)	158 (7)	182 (8)
Cataract	119 (5)	90 (4)	100 (4)
Anemia	121 (5)	81 (4)	81 (4)

	EMPA-REG OUTCOME		
ADVERSE EVENTS[A]	**Placebo (N = 2,333)**	**Empagliflozin 10 mg (N = 2,345)**	**Empagliflozin 25 mg (N = 2,342)**
SAEs			
Subjects with > 0 SAEs, n (%)	988 (42)	876 (37)	913 (39)
Most common SAEs by system organ class			
Cardiac disorders	398 (17)	320 (14)	332 (14)
Infections and infestations	213 (9)	175 (8)	185 (8)
Nervous system disorders	159 (7)	146 (6)	160 (7)
Vascular disorders	116 (5)	80 (3)	111 (5)
General disorders and administration site conditions	94 (4)	80 (3)	74 (3)
Renal and urinary disorders	73 (3)	60 (3)	52 (2)
WDAEs			
AEs leading to discontinuation of study drug, n (%)	453 (19)	416 (18)	397 (17)
Most common reasons			
MI	20 (0.9)	19 (0.8)	16 (0.7)
Acute MI	17 (0.7)	14 (0.6)	15 (0.6)
Cardiac failure	16 (0.7)	9 (0.4)	5 (0.2)
Cardiac arrest	11 (0.5)	3 (0.1)	2 (0.1)
Unstable angina	8 (0.3)	15 (0.6)	9 (0.4)
Cerebrovascular accident	6 (0.3)	12 (0.5)	12 (0.5)
UTIs	7 (0.3)	17 (0.7)	11 (0.5)
Pneumonia	14 (0.6)	10 (0.4)	7 (0.3)
Renal impairment	10 (0.4)	10 (0.4)	16 (0.7)

AE = adverse event; MI = myocardial infarction; SAE = serious adverse event; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] From first intake of study drug to last intake of study drug plus seven days.

[b] Frequency > 5%.

Source: Clinical Study Report.[6]

3.7.4 Notable harms

UTI was reported by 18% of patients per group, and the incidence of more severe infections was generally similar between groups (Table 16). The incidence was higher for females (41%, 36%, and 37%) than for males (9%, 11%, and 10%) in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively. The incidence was also higher among older patients and those with greater renal impairment, but was generally similar between the placebo and empagliflozin groups.

More patients in empagliflozin groups (6.3% to 6.5%) than in the placebo group (1.8%) experienced a genital infection, or stopped treatment due to a genital infection (0.6% to 0.8% versus 0.1%, respectively) (Table 16). Genital infections were also reported more frequently among women than men; for both sexes the reporting of genital infection was higher in the empagliflozin groups (women 9.2% to 10.8%; men 4.6% to 5.4%), than in the placebo group (women 2.6%; men 1.5%).

Decreased renal function was reported as an AE by 6.6% of patients in the placebo group and by 5.2% or 5.3% of those in the empagliflozin groups (Table 16). Ketoacidosis was reported in four patients who

received empagliflozin and by one patient on placebo. For all four empagliflozin patients, ketoacidosis was an SAE. No notable differences in the frequency of volume depletion or hypoglycemia were observed (Table 16).

The manufacturer provided information on the number of patients with lower-limb amputation, which showed a similar frequency across groups (Table 16). As this was not a pre-specified event of interest, the data were collected from narrative reports of concomitant treatments or AEs, and likely underestimate the true incidence.

TABLE 16: NOTABLE HARMS

	EMPA-REG OUTCOME		
Notable AEs,[a] n (%)	**Placebo (N = 2,333)**	**Empagliflozin 10 mg (N = 2,345)**	**Empagliflozin 25 mg (N = 2,342)**
UTI	423 (18)	426 (18)	416 (18)
Leading to treatment discontinuation	10 (0.4)	22 (0.9)	19 (0.8)
SAE (required hospitalization)	29 (1.2)	24 (1.0)	34 (1.5)
Complicated UTI[bc]	41 (1.8)	34 (1.4)	48 (2.0)
Urosepsis[d]	5 (0.2)	7 (0.3)	12 (0.7)
Genital Infection	42 (1.8)	153 (6.5)	148 (6.3)
Leading to treatment discontinuation	2 (0.1)	19 (0.8)	14 (0.6)
SAE	3 (0.1)	5 (0.2)	4 (0.2)
Decreased Renal Function	155 (6.6)	121 (5.2)	125 (5.3)
Leading to treatment discontinuation	24 (1.0)	19 (0.8)	22 (0.9)
SAE	46 (2.0)	31 (1.3)	26 (1.1)
Renal failure	42 (1.8)	23 (1.0)	31 (1.3)
Diabetic Ketoacidosis	1 (< 0.1)	3 (0.1)	1 (< 0.1)
Leading to treatment discontinuation	0	2 (0.1)	0
SAE	0	3 (0.1)	1 (< 0.1)
Volume Depletion[e]	115 (4.9)	115 (4.9)	124 (5.3)
Leading to treatment discontinuation	7 (0.3)	1 (< 0.1)	4 (0.2)
SAE	24 (1.0)	19 (0.8)	26 (1.1)
Lower-limb Amputation[f]	44 (1.9)	42 (1.8)	47 (2.0)
Diabetic foot infection	8 (0.3)	9 (0.4)	9 (0.4)
Venous embolic and thrombotic events	20 (0.9)	9 (0.4)	21 (0.9)
Confirmed Hypoglycemia[g]	650 (28)	656 (28)	647 (28)
Symptomatic	523 (22)	527 (23)	515 (22)
Asymptomatic	289 (12)	277 (12)	289 (12)

	EMPA-REG OUTCOME		
Notable AEs,[a] n (%)	**Placebo (N = 2,333)**	**Empagliflozin 10 mg (N = 2,345)**	**Empagliflozin 25 mg (N = 2,342)**
Hypoglycemia Severity (Worst Episode)			
Requiring assistance	36 (2)	33 (1)	30 (1)
Symptomatic and plasma glucose < 54 mg/dL (< 3.0 mmol/L)	259 (11)	257 (11)	265 (11)
Symptomatic and plasma glucose ≥ 54 mg/dL and ≤ 70 mg/dL (≥ 3.0 mmol/L and ≤ 3.9 mmol/L)	231 (10)	240 (10)	220 (9)
Asymptomatic and plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L)	124 (5)	126 (5)	132 (6)

AE = adverse event; SAE = serious adverse event; UTI = urinary tract infection.
[a] Notable harms were based on standardized Medical Dictionary for Regulatory Activities (MedDRA) or Boehringer Ingelheim MedDRA queries of related AE terms. Events that occurred from first intake of study drug to last intake of study drug + seven days were included.
[b] Includes urinary infection-related SAE, serious and non-serious pyelonephritis, and urosepsis.
[c] An additional four patients likely experienced urosepsis (two placebo, one each empagliflozin 10 mg and empagliflozin 25 mg) but were not captured in the complicated UTI MedDRA query (reported as sepsis or Escherichia sepsis but the source of infection was likely the urinary tract).
[d] Two patients and one patient in the empagliflozin 10 mg and empagliflozin 25 mg groups, respectively, died from urosepsis compared with none in the placebo group.
[e] Includes hypotension, orthostatic hypotension, syncope but not dizziness, or presyncope.
[f] The number of patients with a lower-limb amputation was based on a post-hoc analysis of free-text AE and concomitant treatment data. As this was not a pre-defined event of interest, the events reported are uncertain and likely underestimated.
[g] Patients could be counted more than once. A confirmed hypoglycemia AE was defined as either a plasma glucose concentration ≤ 70 mg/dL or "the patient required assistance."
Sources: Clinical Study Report.[6] Data from the manufacturer.[28]

4. DISCUSSION

4.1 Summary of available evidence

The available data were limited to a single, randomized, DB, non-inferiority trial (EMPA-REG OUTCOME, N = 7,020), designed to assess the safety of empagliflozin 10 mg and empagliflozin 25 mg daily versus placebo in terms of major cardiovascular (CV) events (CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) in patients with type 2 diabetes and high CV risk. In this event-driven trial, patients were followed until a minimum of 691 primary composite outcome events was reported (median follow-up 3.1 years). The trial had a number of limitations that could have affected the internal validity, such as the rigour of outcome ascertainment, lack of control of type 1 error, and potential confounding after randomization. Also of note, the primary outcome in the study does not address the manufacturer's listing request.

4.2 Interpretation of results

4.2.1 Efficacy

The primary objective the study was to exclude the possibility that empagliflozin increased CV risk by 30% or more compared with standard-of-care, glucose-lowering medications. The pooled empagliflozin 10 mg and empagliflozin 25 mg daily dosage group was non-inferior to placebo for the time to first occurrence of CV death, non-fatal MI ,or non-fatal stroke, and for the key secondary outcome, which also included hospitalization for unstable angina. Superiority over placebo was demonstrated for the primary outcome (adj hazard ratio [HR] = 0.86; 95% CI, 0.74 to 0.99, one-sided *P* = 0.019), but not for the key secondary outcome. The differences between treatments were mainly due to a reduction in CV deaths observed with empagliflozin (3.7%) compared with placebo (5.9%) (adj HR = 0.62; 95% CI, 0.49 to 0.77). All-cause mortality was also reduced for empagliflozin (5.7%) versus placebo (8.3%), largely due to differences in CV mortality. Numerically more patients on empagliflozin had a non-fatal stroke (3.5% versus 3.0%) and fewer patients had a non-fatal MI (4.5% versus 5.2%) compared with placebo, but the clinical importance of the differences is unclear. Of note, the analysis of mortality and individual components of the composite outcomes were outside of the statistical hierarchy and were subject to type 1 error.

There are a number of issues to consider when interpreting the findings of the EMPA-REG study. First, the trial was designed to test the safety of empagliflozin, not to establish benefit. FDA briefing documents state that the collection of event data in the EMPA-REG study was less rigorous than in an efficacy trial designed to test a specific hypothesis.[5] No formal clinical assessments were performed at the time of a potential outcome event; thus, adjudication was based on the information available, rather than a prescribed set of data.[5] The lack of rigorous information could have made the determination of non-fatal events, such as stroke, particularly challenging. The Data Monitoring Committee (July 2014) identified problems in adjudicating the cause of death, and initiated a change to the Clinical Event Committee charter to improve the collection of source documents.[5] FDA reviewers noted that despite these changes to the charter, the source documents were often incomplete, and the adjudication of events could be difficult.[5] If several events occurred in close proximity, a judgment was made as to the principal condition; death may have been under-reported if it followed a prolonged illness with an earlier qualifying event (e.g., non-fatal stroke).[5] Of the 309 CV-related deaths, 124 (40%) were presumed to be CV deaths, as the events were unassessable. In sensitivity analyses, excluding the unassessable deaths from the primary outcome, empagliflozin was non-inferior to placebo but was no longer superior.[5] Misclassification of events is not likely to bias the results in favour of one treatment or the other as long as blinding is maintained, but may underestimate the true incidence of events. However,

there was potential for unblinding in this trial, as interim CV data were made available to support regulatory approvals. Second, there was no control for type 1 error across the numerous exploratory outcomes analyzed, including the individual components of the primary outcome; therefore, the statistically significant differences should be interpreted with caution as some may have been due to chance.

FDA reviewers noted that regional differences in the identification and treatment of strokes, and imbalances between treatment groups in co-morbid conditions (e.g., atrial fibrillation), may have compromised the interpretation of stroke events.[5] Stroke-related disability was not collected at fixed time points during the study; thus, it is unclear whether disabling strokes were avoided or whether fewer deaths from stroke resulted in more disabled patients.[5]

Numerous differences were noted between the outcome definitions used in the EMPA-REG study and standardized definitions (Appendix 5), although the impact of these differences on the trial's results is unclear. Silent MI was excluded from the primary outcome, which may be important when comparing the EMPA-REG study finding to other CV-prevention trials. Although data on silent MI were reported, the results should be interpreted with caution because of a lack of complete event ascertainment and adjudication of events, and because analyses were limited to those patients with complete baseline and post-baseline electrocardiogram (ECG) data. It is unclear whether the exclusion of silent MI was a late protocol change or whether exclusion was intended from the start of the trial.

Empagliflozin was associated with a lower risk of hospitalization for HF compared with placebo, as well as a reduced risk of microvascular and renal AEs; however, there are a number of issues with these data. First, FDA reviewers stated that few conclusions can be drawn from the HF findings in the EMPA-REG study, and that there are limitations to the applicability of these results to patients with diabetes and HF.[5] Patients with HF were not a pre-specified subgroup for the trial, and data important to the interpretation of the results were not collected (e.g., ejection fraction or New York Heart Association [NYHA] functional class). Furthermore, patients were not required to be taking evidence-based treatments for HF. The definition of hospitalization for HF lacked specificity, and may have included patients without HF.[5] Second, there were no planned ophthalmic examinations and no systematic collection of ophthalmic events; thus, diabetes-related retinopathy may have been under-reported. Third, the measurement of renal function captured acute, reversible changes as well as chronic changes; thus, the clinical relevance of the findings is unclear. Progression to end-stage renal disease would have been a more clinically relevant outcome. Fourth, the definition and analysis plan for HF hospitalization and microvascular and renal outcomes changed over the course of the study, although the implications of these changes are unclear.

Modest differences were observed between empagliflozin and placebo for the mean change in glycated hemoglobin (A1C) (–0.4% to –0.6%), weight (–1.2 kg to –2.3 kg), SBP (–3 mm Hg to –4 mm Hg), and DBP (–0.9 mm Hg to –1.5 mm Hg). It is difficult attribute these changes directly to empagliflozin, given that investigators were encouraged to modify antidiabetic therapies, blood pressure medications, and other CV-prevention medications according to local standards of care. All patients were monitored regularly and received diet and exercise counselling at every study visit, which may explain the observed trends such as the decrease in weight for placebo as well as empagliflozin. The trial was designed to minimize differences in glycemic control (after 12 weeks) and other CV risk factors; however, differences in these parameters persisted, and may have unblinded patients or investigators to treatment allocation. Although limited or no information was available on the dosing of background therapies in the trial, there was some differential use of medications after randomization, and patients in the placebo group

were more likely to have received rescue antidiabetic medications and new antihypertensive drugs than those in the empagliflozin groups. It is possible that the differences in the management of blood pressure, glycemic control, and weight confounded the CV outcomes, but the direction of bias is difficult to establish.

The EMPA-REG study is the first published CV outcomes trial related to an SGLT-2 inhibitor, but two other trials are underway.[30,31] The CANVAS (canagliflozin) and DECLARE-TIMI 58 (dapagliflozin) trials are expected to be completed in 2017 and 2019, respectively, and their results may determine whether the CV effects observed with empagliflozin are attributable to a class effect.[30,31] At present, there is no direct or indirect evidence comparing CV outcomes for empagliflozin with other antidiabetic medications. Recently, the LEADER trial was published, which reported a statistically significant difference between liraglutide 1.8 mg subcutaneous injection daily versus placebo for the time to CV death, non-fatal MI (including silent MI), or non-fatal stroke (HR = 0.87; 95% CI, 0.78 to 0.97; $P < 0.001$ for non-inferiority, $P = 0.01$ for superiority).[11] It is not clear how the LEADER and EMPA-REG OUTCOME trials' finding will have an impact on clinical practice. Of note, the population enrolled in the EMPA-REG study should be considered when generalizing the findings to Canadians with diabetes. The included patients had long-standing diabetes (70% were on two or more antidiabetic medications) and established CV disease (half had a prior MI and a quarter had a prior stroke) for which they were receiving evidence-based CV medications; therefore, they may be considered more advanced than many patients who had inadequate glycemic control on a first-line agent.

4.2.2 Harms

The AEs reported in the EMPA-REG study were similar to those identified in previous empagliflozin clinical trials.[3,5] In the three-year EMPA-REG study, SAEs were reported in 37% and 39% of patients in the empagliflozin groups and in 42% of patients in the placebo group. The percentage of patients who stopped treatment due to AEs was similar in the placebo group (19%) and the empagliflozin groups (18% and 17%).

Genital infections were reported more frequently in the empagliflozin groups (6%) compared with placebo (2%), and were more common in women than men. Similar findings were reported in a recent meta-analysis, which showed an increased risk of genital infection with other SGLT-2 inhibitors (Appendix 6). Hypoglycemia (28%) and urinary tract infections (UTIs) (18%) were the most commonly reported AEs, but the incidence was similar for all groups. CDR requested information on the frequency of lower-limb amputations due to recent FDA warnings of an increased risk associated with canagliflozin, another SGLT-2 inhibitor.[32] The data supplied by the manufacturer showed no increased risk during the EMPA-REG study;[28] however, data on amputations was not systematically collected during the trial, and thus the events were likely under-reported. The product monograph includes warnings regarding the risk of volume depletion for patients on empagliflozin, but in this trial the frequency was similar for placebo and empagliflozin (5%). Ketoacidosis was rare (empagliflozin, n = 4; placebo, n = 1); although the acidosis in all four empagliflozin patients was classified as an SAE. In general, no substantial dose-related differences in the occurrence of AEs were identified for the 10 mg and 25 mg doses of empagliflozin.

4.3 Potential place in therapy[1]

Compared with patients with type 2 diabetes in the 20th century, patients with type 2 diabetes now have a wide choice of drugs with a low risk of hypoglycemia and a low or reduced risk of weight gain. SGLT-2 inhibitors have added to this choice, with additional benefits for blood pressure reduction. Similar to other members of the class, empagliflozin is a good choice for people with hypertensions who wish to avoid weight gain and hypoglycemia.

The Canadian Diabetes Association (CDA) has identified EMPA-REG OUTCOME as a practice-changing study;[9] however, it is not clear whether the benefits shown in the older, longer-duration, prior CV disease group studied would apply to a younger group of type 2 diabetes patients with a shorter duration of diabetes and without clinically evident CV disease.

A concern about the use of SGLT-2 inhibitors is that they cause hemoconcentration. Dehydration has long been associated with increased stroke risk, and has been shown to increase the stroke risk in patients with atrial fibrillation by 60%.[33] The EMPA-REG study showed a small but not statistically significant increase in non-fatal strokes (3.2% for empagliflozin versus 2.6% for placebo). Physicians should therefore consider carefully the risks and benefits in prescribing it to patients at high risk of stroke, such as those with atrial fibrillation.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

Based on data from one randomized controlled trial (RCT), add-on therapy with empagliflozin did not increase the risk of major CV adverse events (MACE) compared with standard care in patients with inadequate glycemic control of long-standing type 2 diabetes and high CV risk.

The impact of empagliflozin on MI, stroke, hospitalization for HF, or renal or other microvascular outcomes is unclear, given the limitations of the trial such as the rigour of outcome ascertainment, lack of control of type 1 error, and potential confounding after randomization. Based on exploratory analyses, empagliflozin may reduce CV mortality, but concerns over the methodologic rigour of the trial would also apply to this outcome.

Empagliflozin was associated with an increased frequency of genital infections. No new safety signals were identified; however, the study was not designed to detect rare AEs, such as diabetic ketoacidosis or lower-limb amputation, which have been linked to SGLT-2 inhibitors. The safety and efficacy of empagliflozin beyond 2.6 years of therapy is unknown.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups.

1. Brief description of patient group(s) supplying input

The Canadian Diabetes Association (CDA) provides education and services, advocates on behalf of people with diabetes, supports research, and translates research into practical applications. The Association is supported in its efforts by a community-based network of volunteers, employees, health care professionals, researchers, and partners.

The CDA solicits and receives unrestricted educational grants from multiple manufacturers and vendors of medications, supplies, and devices for diabetes and its complications; these sources are listed in Figure 9. These funds are used to help the CDA support community programs and services for people with diabetes and to fund research and advocacy across Canada. The CDA declared no conflicts of interest in the preparation of this submission.

2. Condition-related information

The CDA solicited patient input through two previously conducted surveys distributed through social media and email blasts for a previous CADTH Common Drug Review (CDR) submission for empagliflozin. The first survey was conducted in August 2014 on 376 patients with type 2 diabetes and their caregivers to identify the impacts of diabetes and the aspects of diabetes they want medications to address. The second survey was conducted in April 2015 and gathered information from 424 individuals (349 patients with diabetes and 75 caregivers) about their experiences with current drug therapies (including empagliflozin) and their expectations of diabetes treatment. Approximately 4% of patients (14 of 349 respondents) had taken empagliflozin.

Type 2 diabetes is a chronic, progressive condition that occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced. Common symptoms of diabetes include fatigue, thirst, and weight change. High blood glucose levels can cause long-term complications such as blindness, heart disease, kidney problems, nerve damage, and erectile dysfunction.

The majority of patients with type 2 diabetes indicated that daily fluctuations in blood glucose were the most important aspect of diabetes to control during the day and overnight. The fluctuations have an impact on the ability to work and on interactions with friends and family, and they cause stress and worry as well as the ability to participate in normal activities of daily living. Uncontrolled diabetes and the stigma associated with the disease can result in a reduced quality of life. Respondents frequently emphasized the psychological and emotional impact of diabetes on their lives (effect on stress, anxiety, adjusting to changes in diet and lifestyle, medication and treatment management, as well as relationships with family) as well as fatigue, and lack of energy. A patient noted: “Having diabetes makes me useless. I have no energy or strength to enjoy life anymore. I can’t do partial jobs around the house. I can’t enjoy sports anymore. Diabetes has instill (sic) a fear in me.”

3. Current therapy-related information

Management of diabetes includes lifestyle changes (diet, exercise, and stress management). A large proportion of patients with type 2 diabetes fail to achieve optimal glycemic control, which places them at risk for both acute and chronic diabetes complications. Initial therapy is most often with metformin,

but over time, most patients will require the addition of a second or third agent to reach glycemic targets. Many of the currently available second-line therapies cause significant weight gain, while their ability to achieve optimal glycemic control may be limited by hypoglycemia. As one patient reported, "The most distressing side effect of all of the diabetes drugs is they make you gain weight or prevent weight loss. It is annoying to be told to lose weight then handed a drug that prevents weight loss." The majority of respondents (63%; n = 218 of 397) stated that they were satisfied or very satisfied with their current therapies, whereas 18% indicated dissatisfaction. Patients indicated that current therapies were better or much better at maintaining target blood glucose and A1C levels. However, 38% of respondents reported that they found avoiding low blood glucose with current therapies "the same," "worse," or "much worse." More than 90% of respondents indicated that keeping blood glucose at satisfactory levels and avoiding hypoglycemia throughout the day and overnight were "quite important" or "very important."

At least half of the patients surveyed reported that several side effects were "the same," "worse," or "much worse" with current therapies, including weight gain (52% of respondents), gastrointestinal effects (57% of respondents), dehydration (59% of respondents), and urinary tract/yeast infection (55% of respondents). The vast majority of respondents indicated that avoiding these side effects and reducing high blood pressure are important to them.

The CDA reported other important aspects for consideration when selecting medications, such as avoiding kidney strain, heart problems, and depression. Some respondents simply wanted drugs to "allow them to lead as normal a life as possible" and to provide a "life without concerns about complications because of diabetes."

4. Expectations about the drug being reviewed

Empagliflozin belongs to a new class of drugs that lowers blood glucose and also causes a reduction in blood pressure and weight loss through inhibition of subtype 2 sodium-glucose transport protein (SGLT-2). Of 349 diabetes patients who participated in the second survey, 14 respondents had had experience with empagliflozin. In addition, 136 patients reported experience with other drugs from the same class (i.e., canagliflozin [Invokana] or dapagliflozin [Forxiga]). Patients who had taken empagliflozin noted its effectiveness in keeping blood glucose levels at target, decreasing side effects (diarrhea, stomach ache, losing weight), and providing "better quality of life" from their perspective. A patient who used empagliflozin in a past trial and is now on another class of drugs expressed that "it worked…[other drugs] cause weight gain and do not work as well as empagliflozin." The CDA noted that the results of the first published cardiovascular (CV) outcome trial of this drug class demonstrated lower rates of CV-related hospitalization and mortality in patients treated with empagliflozin, and that the availability of empagliflozin offers an alternative treatment option for people with type 2 diabetes as well as those at higher risk for CV events.

People who have not had experience with empagliflozin expressed several expectations of new drugs for diabetes management. They indicated that ideal new therapies would result in maintenance of blood glucose levels, fewer instances of hypoglycemia, better A1C, minimal side effects without increased risks of renal damage, slowed progression of disease and associated complications, better blood pressure, reduction of other diabetes medications, fewer or less frequent insulin injections, weight loss or no weight gain, reduced depression, and fear, and ultimately effective management of diabetes or even a cure for their diabetes.

While all patients want to manage their blood glucose levels, avoid hypoglycemia, avoid long-term complications, and live a healthy life, a large number of respondents also hope to reduce the number of drugs taken, as well as insulin injections. One respondent stated: “I hope one day to be able to take only one or two medications to control my diabetes rather than the three injectables and two tablet medications I take now.”

Patients also indicated the need for affordable access to new medications for diabetes through lower drug costs or full coverage by public drug plans. More than 66% of respondents who have taken empagliflozin indicated that its availability is important to people living with type 2 diabetes. Among respondents who are on diabetes medications, 57% (n = 179 out of 316) indicated it is important for empagliflozin to be available. While most of these respondents have not had direct experience with empagliflozin, they indicated the importance to provide alternatives and options to patients. As noted by a respondent: “Open access to this new class of diabetes therapy [would allow] physicians and patients [to] have the flexibility to find the most effective and safe "mix" of drugs to maintain control of diabetes. Diabetes changes over time, and everyone needs different medications at different times of their life with diabetes.”

FIGURE 9: ORGANIZATIONS AND FOUNDATIONS THAT MADE DONATIONS TO THE CANADIAN DIABETES ASSOCIATION IN 2015. [34]

Corporate Supporters $5,000 – $24,999

Abakhan & Associates Inc.
ADI Development Group
Agway Metals Inc.
Alberta Blue Cross
AM Roofing Simcoe-Bluewater Ltd.
Army Navy & Airforce BC
Ascensia Diabetes Care
Associated Auto Auction Ltd.
Association Portugaise d'Aylmer
ATB Financial
ATCO Electric
ATCO Gas
B&T Estevan Gun Show Corp.
Bank of Nova Scotia
Basant Motors
Bazil Developments Inc.
Benevity Inc.
Bermuda Tan
Beverly Charity Classic Golf – Hamilton
Boulangerie St-Méthode
Briarlane Direct Property Management Inc.
Calgary Roadrunners Club
Cameco Corporation
Canada's Building Trades Unions
Capital Cosmopolitan Club
Cenovus Energy Inc.
Chadi & Company
Chartwell Seniors Housing Reit
CMG Computer Modelling Group Ltd.
Connect Hearing
Construction Labour Relations Association NL
Cooperators – Cumis
Cornerstone Properties Ltd.
Dairy Farmers
Dakota Dunes Community Development Corporation
Dauphin Clinic Pharmacy
Egli's Sheep Farm Ltd.
Engineering Society B, Faculty of Engineering
Excelleris Technologies Inc.
Ford Drive 4UR Community & School Program
Forest City Road Races
Fraternal Order of Eagles – BC Provincial Auxiliary
Gamma Dynacare Medical Laboratories
General Mills Canada Ntl.
General Presidents' Maintenance Committee
Gerrie Electric Wholesale Ltd.
Gibbons Ride & Drive – Brantford
Giffen-Mack Funeral Home
HCI Holdings
Holy Spirit Charitable Society
Husky Energy Lloyd Charitable Campaign
Impact Security
International Credit Experts
Irish Society of Westman
Iupat Canadian Regional Conference
Janzen's Pharmacy
Jarrod Oils Ltd.
John Zubick Ltd.
Kal Tire
Kinsmen BC
Kinsmen Club of Saskatoon
Kinsmen Club of Thunder Bay (Hill City Kinsmen)
Kiwanis Club of Vancouver
Kiwanis Clubs of BC
Knights Therapeutics
Leon's Furniture Ltd.
Leslie Street (FGH) Inc.
Manitoba Association of Health Care Professionals
Manitoba Health
Manitoba Housing and Community Development
Marshes Golf Club
Matec Consultants Limited
Medtronic of Canada Ltd.
Mihealth Global Systems Inc.
Nashwaaksis Lions Club Inc.
Northern (#468)
Northland Properties Corporation
Ontario Automotive Recyclers Association
Ontario Pork
PD Management & Services Inc.
PricewaterhouseCoopers LLP
RBC Dominion Securities
Regina Capital Cosmopolitan Club
Regina Queen City Kinsmen
Resources Development Trades Council
Richmond Hill Italian Social Club
Roche
Rosmar Drywall Ltd.
Royal Canadian Legion BC
Royal Regina Golf Club (Ladies Section)
Royal Scenic Holidays Ltd.
Saskatchewan Indian Gaming Authority
Saskatoon Downtown Lions Club
SaskCanola
Shaw Communications Inc.
Sherwood Co-Op Association
Signex Manufacting Inc.
Skyway Canada Ltd.
Sudbury Rocks Running Club
Sunrise Soya Foods
Sun-Rype Products Ltd.
Tangerine
TD Waterhouse Canada Inc.
Teck Resources
Telus
Thunder Bay Real Estate Board
UBC Alpha Gamma Delta
Universal Collision Centre
Vale Newfoundland & Labrador Ltd.
Vancouver Courier
Wellington Laboratories Inc.
World Health Edmonton
Zone 6 Lions Clubs

Corporate Supporters $25,000 – $49,999

Alberta Building Trades
Blistex
Brandt Tractor Inc.
Connect Marketing Group
Egg Farmers
GlaxoSmithKline Inc.
Group SEB – T-Fal
Lions Clubs of BC
Lions Clubs of Saskatchewan
MEDEC (Diabetes Committee)
Rogers Communications
Rogers Radio Vancouver
Rubicon Pharmacies Canada Inc.
Taste of Kingston
Ventas Inc.

Corporate Supporters $50,000 – $99,999

Abbott Nutrition
Canola
First Nations Health Authority
J&J Consumer
Lions Clubs of Canada

Corporate Supporters $ 100,000 – $174,999

Eli Lilly Canada Inc.
Janssen Inc.
Loblaws
MEDT
Nestle Canada
Provincial Health Services Authority
Royal Bank of Canada
Sanofi – Aventis Canada Ltd.
The North West Company LP

Diabetes Champion $175,000 – $249,999

Bayer Inc.
Merck Canada Inc.

Diabetes Catalyst $250,000 – $349,999

LifeScan Canada Ltd.
Shaw Media
Sun Life Financial

Diabetes Visionary $400,000+

AstraZeneca
Novo Nordisk Canada Inc.

Foundations

Airlie Foundation
Alice & Murray Maitland Foundation
Alpha Gamma Delta Foundation
Aqueduct Foundation
AWB Charitable Foundation
Brantford Community Foundation – City of Brantford
Brian & Susan Thomas Foundation
Burrows Colden Family Foundation
Butler Family Foundation
Cal Wenzel Family Foundation
Calgary Shaw Charity Classic Foundation
Cambridge & North Dumfries Community Foundation
Canadian MedicAlert Foundation
Cenovus Employee Foundation
Chickadee Trust
Chimp Foundation
Colin & Lois Pritchard Foundation
Community Foundation for Kingston & Area
Community Foundation of Ottawa-Carleton
Crabtree Foundation
Deloitte Foundation Canada
Edmonton Community Foundation
Edwards Charitable Foundation
EnCana Cares Foundation
Ernst Hansch Foundation/ Terracon Development
Eva T. Villanueva Charitable Fund at the Strategic Charitable Giving Foundation
Flaman Foundation
Fleming Foundation
Fredericton Community Foundation Inc.
G Grant & Dorothy F Armstrong Foundation
Gift Funds Canada
Gill Family Charitable Trust
Glenn's Helping Hand Foundation Inc.
Greygates Foundation
Halifax Protestant Infants' Foundation
Halifax Youth Foundation
Hamber Foundation
Harry P. Ward Foundation
Infinity Community Fund
Jewish Community Foundation
Jewish Foundation of Manitoba
John M. & Bernice Parrott Foundation Inc.
KPMG Foundation
Lagniappe Foundation
Leslie & Irene Dube Foundation
Manitoba Hydro Charitable Fund
Medavie Health Foundation
Mister Blake Foundation
Napanee District Community Foundation
Newfound Foundation
NL Retired Teachers Foundation
Northern Ontario Heritage Fund Corporation
NWM Private Giving Foundation
Oakville Community Foundation
Orville & Alvera Woolacott Foundation
PepsiCo Foundation
Prince Albert & Area Community Foundation
Private Giving Foundation
Raymond James Canada Foundation
RBC Foundation
Rexall Foundation
Salesforce Foundation
Saskatchewan Community Initiatives Fund
Saskatoon Community Foundation
Sayal Charitable Foundation
Scotiabank Community Program
Sherry & Sean Bourne Family Charitable Foundation
South Saskatchewan Community Foundation Inc.
Strategic Charitable Giving Foundation
The Barrett Family Foundation
The Brockville Community Foundation
The Calgary Foundation
The Charles Norcliffe Baker & Thelma Scott Baker Foundation
The Chatham-Kent Community Foundation
The Dr. Charles & Margaret Brown Foundation
The Edith Lando Charitable Foundation
The Guelph Community Foundation
The Gyro Club of Vancouver Charitable Foundation
The Home Depot Foundation
The Horn Family Fund
The John and Judy Bragg Family Foundation
The Kitchener & Waterloo Community Foundation
The Lawrason Foundation
The Mariano Elia Foundation
The Poker for Diabetes Foundation
The Ryley Family Foundation
The Tenaquip Foundation
The Virmani Family Charitable Foundation
The Walker Lynch Foundation
The WB Family Foundation
The Winnipeg Foundation
Toronto Star Fresh Air Fund
Valero Energy Foundation of Canada
Vancouver Foundation – Ann Claire Angus Fund
Vancouver Foundation – McFarlane-Karp Fund
Victoria Foundation
VOCM Cares Foundation
William James Henderson Foundation
Windsor Foundation

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 26, 2016
Alerts:	Weekly search updates until September 21, 2016
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(jardiance* or empagliflozin* or BI-10773 or BI10773 or HDC1R2M35U).ti,ab,ot,rn,hw,nm,kf.
2	864070-44-0.rn,nm.
3	1 or 2
4	3 use pmez
5	*empagliflozin/
6	(jardiance* or empagliflozin* or BI-10773 or BI10773 or HDC1R2M35U).ti,ab,kw.
7	5 or 6
8	7 use oemezd
9	4 or 8
10	remove duplicates from 9
11	conference abstract.pt.
12	10 not 11

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	May 2016
Keywords:	Jardiance, empagliflozin
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

No studies were excluded in the second stage of screening, after reviewing the full-text articles of potentially relevant studies.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 17: STUDY VISITS AND OUTCOME ASSESSMENTS IN EMPA-REG OUTCOME STUDY

TEST	TREATMENT VISITS DURING DB PERIOD (WEEK)									FOLLOW-UP PERIOD	
	0	4	8	12	16	28	40	52	Every 14 Weeks to FV	EOS Visit	30 Days After FV
Physical exam[a]						x		x	x	x	
BP, pulse	x	x	x	x	x	x	x	x	x	x	x
Weight	x			x		x		x	x	x	x
12-lead ECG[b]	x					x		x	x	x	
A1C	x			x		x	x	x	x	x	
FPG	x	x		x		x		x	x	x	x
Home blood glucose monitoring[c]	x	x	x	x	x	x	x	x	x	x	x
Safety laboratory test[d]	x			x		x		x	x	x	x
Lipid panel	x	x				x		x	x	x	x
Ophthalmic exams	No scheduled examinations as part of the study procedures.										

BP = blood pressure; DB = double-blind; ECG = electrocardiogram; EOS = end of study; FPG = fasting plasma glucose; FV = final visit; A1C = glycated hemoglobin.
[a] Also conducted at placebo run-in visit, two weeks prior to randomization.
[b] In addition, ECG was to be recorded in case of cardiac symptoms indicating rhythm disorders or cardiac ischemia.
[c] Recommended daily monitoring during run-in and follow-up periods and weekly monitoring during the treatment period, or as needed for hypoglycemia or hyperglycemia-related symptoms.
[d] Includes hematology, clinical chemistry (e.g., serum creatinine, electrolytes, liver enzymes, creatine kinase, bicarbonate), lipids, and urinalysis (ketones, albumin, creatinine, white blood cells/leukocytes, red blood cells /erythrocytes). Urine culture test was triggered by positive leukocyte esterase and/or nitrite in a semi-quantitative/dipstick test.
Source: Clinical Study Report.[6]

TABLE 18: OTHER MEDICATIONS INTRODUCED AFTER RANDOMIZATION

DRUG	EMPA-REG OUTCOME		
	PLACEBO (N = 2,333)	EMPAGLIFLOZIN 10 MG (N = 2,345)	EMPAGLIFLOZIN 25 MG (N = 2,342)
Antihypertensives, n (%)[a]	1,190 (51)	1,030 (44)	1,058 (45)
ACEI/ARB	702 (30)	602 (26)	622 (27)
Beta-blocker	481 (21)	420 (18)	438 (19)
Diuretic	608 (26)	429 (18)	470 (20)
Calcium channel blocker	481 (21)	311 (13)	361 (15)
Mineralocorticoid receptor antagonists	136 (6)	87 (4)	90 (4)
Renin inhibitor	6 (< 1)	5 (< 1)	4 (< 1)
Other	165 (7)	129 (6)	145 (6)
Anticoagulants, n (%)[a]	708 (30)	663 (28)	677 (29)
Platelet aggregation inhibitor (oral)	518 (22)	499 (21)	476 (20)

Drug	EMPA-REG OUTCOME		
	Placebo (N = 2,333)	Empagliflozin 10 mg (N = 2,345)	Empagliflozin 25 mg (N = 2,342)
Lipid-lowering Agents, n (%)[a]	719 (31)	673 (29)	693 (30)
Statins	601 (26)	574 (25)	571 (24)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.
[a] The percentages reported do not take into consideration treatments taken at baseline and those that may have stopped or had a change in dose after baseline.
Source: Clinical Study Report.[6]

Table 19: CV Adjudication Results

	Placebo (N = 2,333)	Empagliflozin Pooled (N = 4,687)
Number of patients with confirmed CV event, n (%)	473 (20.3)	814 (17.4)
Number of patients with no confirmed non-fatal CV event and confirmed fatal event is not assessable, n (%)	[redacted]	[redacted]
Not assessable (patients with no confirmed event with/without fatal event not assessable and at least one non-fatal event not assessable), n (%)	[redacted]	[redacted]

CV = cardiovascular.
Source: Clinical Study Report.[6]

Table 20: Subgroup Analyses of Time to CV Death, First Occurrence of MI or Stroke

Subgroup	EMPA-REG OUTCOME			
Time to First Occcurence of CV Death, MI, or Stroke	**Placebo n/N (%)**	**Empagliflozin Pooled n/N (%)**	**Adj HR (95% CI)[a]**	**Interaction Term *P* Value**
Overall Population	282/2,333 (12.1)	490/4,687 (10.5)	0.86 (0.74 to 0.99)	NA
Age				
< 65 years	121/1,297 (9.3)	251/2,596 (9.7)	1.04 (0.84 to 1.29)	0.013
≥ 65 years	161/1,036 (15.5)	239/2,091 (11.4)	0.71 (0.59 to 0.87)	
Race				
Caucasian	205/1,678 (12.2)	366/3,403 (10.8)	0.88 (0.74 to 1.04)	0.087
Black/African-American	12/120 (11.7)	39/237 (16.5)	1.48 (0.80 to 2.72)	
Asian	58/511 (11.4)	79/1,006 (7.9)	0.68 (0.48 to 0.95)	
Other	5/24 (20.8)	6/40 (15.0)	NR[b]	
Baseline A1C				
< 8.5%	209/1607 (13.0)	322/3212 (10.0)	0.76 (0.64 to 0.90)	0.015
≥ 8.5%	73/726 (10.1)	168/1475 (11.4)	1.14 (0.86 to 1.50)	
Baseline eGFR				
≥ 90 mL/min/1.73 m^2	44/488 (9.0)	102/1,050 (9.7)	1.10 (0.77 to 1.57)	0.20

Subgroup	EMPA-REG OUTCOME			
Time to First Occcurence of CV Death, MI, or Stroke	**Placebo n/N (%)**	**Empagliflozin Pooled n/N (%)**	**Adj HR (95% CI)[a]**	**Interaction Term *P* Value**
Overall Population	282/2,333 (12.1)	490/4,687 (10.5)	0.86 (0.74 to 0.99)	NA
60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2	139/1,238 (11.2)	212/2,425 (8.7)	0.76 (0.61 to 0.94)	
< 60 mL/min/1.73 m^2	99/607 (16.3)	176/1,212 (14.5)	0.88 (0.69 to 1.13)	
CV Risk Factor(s) at Baseline				
Cerebrovascular disease only	29/325 (8.9)	65/635 (10.2)	1.15 (0.74 to 1.78)	0.53
Coronary artery disease only	152/1,340 (11.3)	261/2,732 (9.6)	0.83 (0.68 to 1.02)	
Peripheral artery disease only	12/191 (6.3)	25/412 (6.1)	0.94 (0.47 to 1.88)	
Two or three risk factors	87/451 (19.3)	137/878 (15.6)	0.79 (0.61 to 1.04)	
No CV risk factors	2/26 (7.7)	2/30 (6.7)	NR[b]	
Time Since Diabetes Diagnosis				
≤ 5 years	42/423 (9.9)	72/840 (8.6)	0.85 (0.58 to 1.24)	0.83
> 5 to 10 years	63/571 (11.0)	106/1,175 (9.0)	0.79 (0.58 to 1.08)	
> 10 years	177/1,339 (13.2)	312/2,672 (11.7)	0.89 (0.74 to 1.06)	
Metformin at Baseline[c]				
No	93/599 (15.5)	146/1,228 (11.9)	0.72 (0.56 to 0.94)	0.14
Yes	189/1,734 (10.9)	344/3,459 (9.9)	0.92 (0.77 to 1.10)	
Sulfonylurea at Baseline[c]				
No	173/1,341 (12.9)	295/2,673 (11.0)	0.85 (0.70 to 1.02)	0.83
Yes	109/992 (11.0)	195/2,014 (9.7)	0.87 (0.69 to 1.11)	
Insulin at Baseline[c]				
No	140/1,198 (11.7)	225/2,435 (9.2)	0.79 (0.64 to 0.97)	0.28
Yes	142/1,135 (12.5)	265/2,252 (11.8)	0.93 (0.75 to 1.13)	
Thiazolidinediones at Baseline[c]				
No	271/2,232 (12.1)	467/4,489 (10.4)	0.85 (0.73 to 0.98)	0.44
Yes	11/101 (10.9)	23/198 (11.6)	1.13 (0.55 to 2.31)	
DPP-4 Inhibitor at Baseline[c]				
No	254/2,066 (12.3)	423/4,158 (10.2)	0.81 (0.70 to 0.95)	0.061
Yes	28/267 (10.5)	67/529 (12.7)	1.27 (0.82 to 1.98)	

Adj = adjusted; CI = confidence interval; CV = cardiovascular; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate: A1C = glycated hemoglobin; HR = hazard ratio; MI = myocardial infarction; NA = not applicable.
[a] Model included age, sex, baseline body mass index (BMI) (categorical), baseline A1C (categorical), baseline eGFR (categorical), geographical region, treatment, subgroup, and treatment by subgroup interaction.
[b] Subgroup was not included in the model.
[c] Post-hoc subgroup analysis.
Source: Clinical Study Report.[6]

TABLE 21: CHANGE FROM BASELINE IN A1C

VISIT/TREATMENT GROUP	N	A1C (%)[A, B]		
		BASELINE MEAN (SE)	CHANGE FROM BASELINE ADJ MEAN (SE)	DIFFERENCE FROM PLACEBO ADJ MEAN (95% CI), *P* VALUE
Week 12				
Placebo	2,272	8.08 (0.02)	–0.11 (0.02)	
Empagliflozin 10 mg	2,272	8.08 (0.02)	–0.65 (0.02)	–0.54 (–0.58 to –0.49), *P* < 0.0001
Empagliflozin 25 mg	2,280	8.07 (0.02)	–0.71 (0.02)	–0.60 (–0.64 to –0.55), *P* < 0.0001
Week 94				
Placebo	1,967	8.08 (0.02)	–0.08 (0.02)	
Empagliflozin 10 mg	2,058	8.08 (0.02)	–0.50 (0.02)	–0.42 (–0.48 to –0.36), *P* < 0.0001
Empagliflozin 25 mg	2044	8.07 (0.02)	–0.55 (0.02)	–0.47 (–0.54 to –0.41), *P* < 0.0001

Adj = adjusted; CI = confidence interval; A1C = glycated hemoglobin; MMRM FAS (OC-AD) = mixed-model repeated measure, full-analysis set (observed case–after discontinuation); SE = standard error.
[a] MMRM FAS (OC-AD). Outside the statistical testing hierarchy. Two-sided *P* values, alpha = 0.05.
[b] Model include, treatment, baseline A1C (continuous), baseline body mass index (BMI) (categorical), baseline eGFR (categorical), week reachable for A1C, geographical region, visit, visit by treatment interaction, and baseline A1C by visit interaction.
Source: Clinical Study Report.[6]

TABLE 22: CHANGE FROM BASELINE IN FASTING PLASMA GLUCOSE

VISIT/TREATMENT GROUP	N	FPG (MG/DL)[A, B]		
		BASELINE MEAN (SE)	CHANGE FROM BASELINE ADJ MEAN (SE)	DIFFERENCE FROM PLACEBO ADJ MEAN (95% CI), *P* VALUE
Week 12				
Placebo	2,226	153.5 (0.9)	5.2 (0.8)	
Empagliflozin 10 mg	2,228	153.2 (0.9)	–15.2 (0.8)	–20.4 (–22.6 to –18.2), *P* < 0.0001
Empagliflozin 25 mg	2,234	151.8 (0.9)	–18.6 (0.8)	–23.8 (–26.0 to –21.6), *P* < 0.0001
Week 94				
Placebo	1,934	153.5 (0.9)	8.1 (1.0)	
Empagliflozin 10 mg	2,030	153.2 (0.9)	–9.1 (1.0)	–17.3 (–19.9 to –14.6), *P* < 0.0001
Empagliflozin 25 mg	2,030	151.8 (0.9)	–12.7 (1.0)	–20.8 (–23.5 to –18.2), *P* < 0.0001

Adj = adjusted; CI = confidence interval; FPG = fasting plasma glucose; MMRM FAS (OC-AD) = mixed-model repeated measure, full-analysis set (observed case–after discontinuation); SE = standard error.
[a] MMRM FAS (OC-AD). Outside the statistical testing hierarchy. Two-sided *P* values, alpha = 0.05.
[b] Model includes treatment, baseline FPG, baseline A1C, baseline eGFR (categorical), geographical region, baseline body mass index (BMI) (categorical), week reachable glucose, visit, visit by treatment interaction, baseline A1C by visit interaction, baseline FPG by visit interaction.
Source: Clinical Study Report.[6]

TABLE 23: CHANGE FROM BASELINE IN WEIGHT

VISIT/TREATMENT GROUP	N	WEIGHT (KG)[A, B]		
		BASELINE MEAN (SE)	CHANGE FROM BASELINE ADJ MEAN (SE)	DIFFERENCE FROM PLACEBO ADJ MEAN (95% CI)
Week 12				
Placebo	1,915	86.7 (0.4)	–0.2 (0.06)	
Empagliflozin 10 mg	1,893	86.0 (0.4)	–1.4 (0.06)	–1.2 (–1.4 to –1.1), *P* < 0.0001
Empagliflozin 25 mg	1,891	86.5 (0.4)	–1.7 (0.06)	–1.5 (–1.7 to –1.3), *P* < 0.0001
Week 52				
Placebo	2,138	86.7 (0.4)	–0.3 (0.09)	
Empagliflozin 10 mg	2,174	86.0 (0.4)	–2.1 (0.09)	–1.7 (–2.0 to –1.5), *P* < 0.0001
Empagliflozin 25 mg	2,178	86.5 (0.4)	–2.5 (0.09)	–2.2 (–2.4 to –1.9), *P* < 0.0001
Week 108				
Placebo	1,598	86.7 (0.4)	–0.4 (0.11)	
Empagliflozin 10 mg	1,673	86.0 (0.4)	–2.2 (0.11)	–1.8 (–2.1 to –1.5), *P* < 0.0001
Empagliflozin 25 mg	1,678	86.5 (0.4)	–2.7 (0.11)	–2.3 (–2.7 to –2.0), *P* < 0.0001

Adj = adjusted; CI = confidence interval; MMRM FAS (OC-AD) = mixed-model repeated measure, full-analysis set (observed case–after discontinuation); SE = standard error.

[a] MMRM FAS (OC-AD). Outside the statistical testing hierarchy. Two-sided *P* values, alpha = 0.05.

[b] Model includes treatment, baseline weight, baseline A1C, baseline eGFR (categorical), geographical region, baseline body mass index (BMI) (categorical), week reachable weight, visit, visit by treatment interaction, baseline A1C by visit interaction, baseline weight by visit interaction.

Source: Clinical Study Report.[6]

TABLE 24: CHANGE FROM BASELINE IN SBP

VISIT/TREATMENT GROUP	N	SBP (MM HG)[A, B]		
		BASELINE MEAN (SE)	CHANGE FROM BASELINE ADJ MEAN (SE)	DIFFERENCE FROM PLACEBO ADJ MEAN (95% CI)
Week 12				
Placebo	2,201	135.8 (0.4)	–1.0 (0.3)	
Empagliflozin 10 mg	2,224	134.9 (0.4)	–5.0 (0.3)	–4.0 (–4.8 to –3.2), *P* < 0.0001
Empagliflozin 25 mg	2,197	135.7 (0.4)	–4.7 (0.3)	–3.7 (–4.5 to –2.9), *P* < 0.0001
Week 94				
Placebo	1,974	135.8 (0.4)	–0.5 (0.3)	
Empagliflozin 10 mg	2,072	134.9 (0.4)	–3.5 (0.3)	–3.0 (–3.9 to –2.1), *P* < 0.0001
Empagliflozin 25 mg	2,066	135.7 (0.4)	–3.6 (0.3)	–3.1 (–4.0 to –2.2), *P* < 0.0001

Adj = adjusted; CI = confidence interval; SBP = systolic blood pressure; MMRM FAS (OC-AD) = mixed-model repeated measure, full-analysis set (observed case–after discontinuation); SE = standard error.
[a] MMRM FAS (OC-AD). Outside the statistical testing hierarchy. Two-sided *P* values, alpha = 0.05.
[b] Model includes treatment, baseline SBP, baseline A1C, baseline body mass index (BMI) (categorical), baseline eGFR (categorical), geographical region, week reachable vital signs, visit, visit by treatment interaction, baseline A1C by visit interaction, baseline SBP by visit interaction.
Source: Clinical Study Report.[6]

TABLE 25: CHANGE FROM BASELINE IN DBP

VISIT/TREATMENT GROUP	N	DBP (MM HG)[A, B]		
		BASELINE MEAN (SE)	CHANGE FROM BASELINE ADJ MEAN (SE)	DIFFERENCE FROM PLACEBO ADJ MEAN (95% CI)
Week 12				
Placebo	2,201	76.8 (0.2)	–0.5 (0.2)	
Empagliflozin 10 mg	2,224	76.6 (0.2)	–2.0 (0.2)	–1.5 (–1.9 to –1.0), *P* < 0.0001
Empagliflozin 25 mg	2,197	76.7 (0.2)	–1.8 (0.2)	–1.2 (–1.7 to –0.8), *P* < 0.0001
Week 94				
Placebo	1,974	76.8 (0.2)	–1.1 (0.2)	
Empagliflozin 10 mg	2,072	76.6 (0.2)	–2.0 (0.2)	–0.9 (–1.4 to –0.4), *P* = 0.0005
Empagliflozin 25 mg	2,066	76.7 (0.2)	–2.1 (0.2)	–1.0 (–1.5 to –0.5), *P* < 0.0001

Adj = adjusted; CI = confidence interval; DBP = diastolic blood pressure; MMRM FAS (OC-AD) = mixed-model repeated measure, full-analysis set (observed case–after discontinuation); SE = standard error.
[a] MMRM FAS (OC-AD). Outside the statistical testing hierarchy. Two-sided *P* values, alpha = 0.05.
[b] Model includes treatment, baseline DBP, baseline A1C, baseline body mass index (BMI) (categorical), baseline eGFR (categorical), geographical region, week reachable vital signs, visit, visit by treatment interaction, baseline A1C by visit interaction, baseline DBP by visit interaction.
Source: Clinical Study Report.[6]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim: To evaluate whether standard definitions for cardiovascular and renal end points were utilized in the EMPA-REG OUTCOME trial.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
CV mortality	Sudden cardiac death	Death that occurs unexpectedly in a previously stable patient and includes the following: • witnessed and instantaneous without new or worsening symptoms • witnessed within 60 min of the onset of new or worsening cardiac symptoms • witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording or witnessed on a monitor by either a medic or paramedic) • patient unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who dies within 24 hours without identification of a non-cardiac etiology • unwitnessed death and there is no conclusive evidence of another, non-CV, cause of death (i.e., presumed CV death).	Death that occurs unexpectedly and not within 30 days of an acute MI and includes the following: • witnessed and occurring without new or worsening symptoms • witnessed within 60 min of the onset of new or worsening cardiac symptoms • witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on ICD review) • death after unsuccessful resuscitation from cardiac arrest (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest) or after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology • unwitnessed death in a patient seen alive and clinically stable ≤ 24 hours before being found dead without any evidence supporting a specific non-CV cause of death (information about the patient's clinical status preceding death should be provided if available).	The standard definition includes a 30-day threshold for association of death to an MI, whereas the trial definition does not include any time frame. **Note**: Although differences exist between the definitions, it is uncertain whether the changes would have affected the outcomes.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
	Sudden death due to acute MI	Sudden death occurring up to 14 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) and where there is no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.	Death by any CV mechanism (arrhythmia, sudden death, HF, stroke, pulmonary embolus, PAD) within 30 days after an acute MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. Note: Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus.	• Generally, the standard definition appears to be more inclusive than the definition used in the trial. ○ The standard definition includes a 30-day threshold instead of a 14-day threshold for association of death to an MI. **Note**: The classification of death occurring 15 days following an MI is unclear. Although differences exist between the definitions, it is uncertain whether the changes and uncertainties would have affected the outcomes.
	Death due to HF or cardiogenic shock	• Death occurring in the context of clinically worsening symptoms and/or signs of CHF without evidence of another cause of death. • New or worsening signs and/or symptoms of CHF including any of the following: ○ new or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF ○ HF symptoms or signs requiring continuous intravenous therapy or	• Death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology. • New or worsening symptoms due to HF, the patient should have at least at least one of the following on presentation: ○ dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough in supine position, tachypnea) ○ decreased exercise tolerance (reduced ability to perform activities that involve dynamic	• Generally, the standard definition appears to be more inclusive than the definition used in the trial. ○ Only the trial definition requires new or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		oxygen administration ○ confinement to bed predominantly due to HF symptoms ○ pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF ○ cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF. • Cardiogenic shock is defined as SBP < 90 mm Hg for more than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion: ○ cool, clammy skin ○ oliguria (urine output < 30 mL/hour) ○ altered sensorium ○ cardiac index < 2.2 L/min/m^2. • Cardiogenic shock can also be defined in the presence of SBP ≥ 90 mm Hg or for a time period < 1 hour if the BP measurement or the time period is influenced by the presence of positive inotropic or vasopressor agents alone and/or with mechanical support < 1 hour. The outcome of cardiogenic	movement of large skeletal muscles because of symptoms of dyspnea or fatigue) ○ fatigue (usually described as feeling a lack of energy and motivation in both mental and physical activities, easily tiring and not being able to complete usual activities, and sometimes accompanied by dizziness, lightheadedness) ○ worsened end-organ perfusion (worsening cerebral, renal, liver, abdominal, or gastrointestinal, peripheral circulatory function manifested by symptoms such as dizziness, lightheadedness, syncope, confusion, altered mental status, restlessness, decline in cognitive state, nausea, vomiting, abdominal pain, abdominal fullness, abdominal discomfort or abdominal tenderness, cold clammy extremities, discoloration of extremities or lips, jaundice, pain in extremities, reduced urine output, darkening of urine color, chest pain, and/or palpitations) ○ other symptoms of volume overload (swelling of lower extremities; swelling or indentation of pressure marks in areas of fluid accumulation such as the legs, ankles, or lower back; an increase in abdominal girth, right-	**Note**: Considering that the standard definition may have a higher occurrence rate of HF, it is possible that the occurrences of HF may be artificially deflated in the trial. It is unclear whether patients captured under the standard HF definition are captured elsewhere in the trial. Although differences exist between the definitions, it is uncertain whether the changes and uncertainties would have affected the outcomes. Trial definitions and standard definitions for cardiogenic shock are similar.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study outcome. This category will include sudden death occurring during an admission for worsening HF.	sided abdominal fullness, discomfort, or tenderness; an increase in body weight; oozing and development of skin breakdown in lower extremities). • Cardiogenic shock is defined as sustained (> 30 min) episode of SBP < 90 mm Hg and/or cardiac index < 2.2 L/min/m2 determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., intra-aortic balloon pump, extracorporeal circulatory support, ventricular assist device) to maintain BP and cardiac index above those specified levels.	
	Death due to stroke, cerebrovascular event	Death occurring up to 30 days after a stroke that is either due to the stroke or caused by complication of the stroke.	Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Note: Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.	• Generally, the standard definition appears to be more inclusive than the definition used in the trial. ○ The trial definition includes a 30- day threshold for associating death to a stroke, whereas the standard definition does not include any time frame. **Note**: The classification of death occurring 30 days following a stroke is unclear. Although differences exist

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
				between the definitions, it is unclear whether the changes and uncertainties would have affected the outcomes.
	Death due to other CV causes	Death must be due to a fully documented CV cause not included in the above categories (e.g., dysrhythmia, pulmonary embolism, or CV intervention). Death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation will be classified as "death due to other CV cause."	CV death not included in the above categories but with specific, known cause (e.g., PE, PAD).	**Note**: Trial definitions and standard definitions appear to be similar.
MI (non-fatal)	Criterion A: Spontaneous MI (type 1)	To identify a type 1 MI, patients should demonstrate spontaneous symptoms of myocardial ischemia unprovoked by supply/demand inequity, together with ≥ 1 of the following criteria: • Cardiac biomarker elevation: Troponin is the preferred marker for use to adjudicate the presence of acute MI. At least one value should show a rise and/or fall above the lowest cut-point providing 10% imprecision (typically the upper reference limit for the troponin run per standard of clinical care). Creatine kinase - muscle/brain (CK-MB) is a secondary choice to troponin; a rise of CK-MB above the local upper reference limit would be consistent with myocardial injury. • ECG changes consistent with new ischemic changes: ○ ECG changes indicative of new ischemia (new ST-T changes or new	Spontaneous clinical syndrome related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection, with resulting intraluminal thrombus, and leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. This classification requires: • detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least one value > 99th percentile of the URL, and • at least one of the following: ○ symptoms of myocardial ischemia ○ new or presumed new significant ST–T changes or new LBBB on the ECG ○ development of pathological Q waves on the ECG ○ imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality	• Generally, the standard definition appears to be more inclusive than the definition used in the trial. ○ Trial definition requires symptoms of MI in addition to one or more of the defined criteria; whereas, the standard definition does not require symptoms of MI. ○ The standard definition considers the inclusion of R waves for the development of pathological waves on the ECG, whereas the trial definition does not consider them.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		LBBB) or ECG manifestations of acute myocardial ischemia (in absence of LVH and LBBB) ○ development of pathological Q waves in the ECG ▪ any Q wave in leads V2 to V3 ≥ 0.02 seconds or QS complex in leads V2 and V3 ▪ Q wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads 1, 2, aVL, aVF, or V4 to V6 in any two leads of a contiguous lead grouping (1, aVL, V6; V4 to V6; 2, 3, and aVF) ○ ST elevation: New ST elevation at the J point in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2 to V3 and/or ≥ 0.1 mV in other leads ○ ST depression and T wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1 • Imaging evidence of new non-viable myocardium or new wall-motion abnormality.	○ identification of an intracoronary thrombus by angiography or autopsy. • Notes: One or more coronary arteries may be involved. The patient may have underlying severe CAD but on occasion may have non-obstructive CAD. • ST elevation: New (or presumed new) ST elevation at the J point in 2 contiguous leads with the following cut points: ≥ 0.1 mV in all leads other than leads V2 to V3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years of age; ≥ 0.25 mV in men < 40 years of age, or ≥ 0.15 mV in women. • ST depression and T wave changes: new (or presumed new) horizontal or down-sloping ST-segment depression ≥ 0.05 mV in two contiguous leads and/or T inversion ≥ 0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio > 1.) • Development of pathological waves on the ECG: ○ new (or presumed new) a) Q wave in leads V2 to V3 ≥ 0.02 s or QS complex in leads V2 and V3 ○ Q wave ≥ 0.03 s and ≥ 0.1 mV deep or QS complex in leads 1, 2, aVL, aVF, or V4 to V6 in any two leads of a contiguous lead grouping (1, aVL; V1 to V6; 2, 3, aVF; V7 to V9)	**Note**: Considering that the standard definition may have a higher occurrence rate of MI, it is possible that the occurrences of MI may be artificially deflated in the trial. It is unclear whether patients captured in under the standard MI definition are captured elsewhere in the trial. Although differences exist between the definitions, it is uncertain whether the changes and uncertainties would affect the outcomes.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
			○ R wave ≥ 0.04 s in V1 to V2 and R/S ratio ≥ 1 with a concordant positive T wave in the absence of a conduction defect.	
	Criterion B: "Demand"-related (type 2) MI	• Patients with type 2 MI should be considered with similar diagnostic criteria as a type 1 MI; however, type 2 MI should be considered present when myocardial ischemia and infarction are consequent to supply/demand inequity, rather than a spontaneous plaque rupture and coronary thrombosis.	• Spontaneous clinical syndrome where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand (e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachyarrhythmias/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH). This classification requires: ○ detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least one value > 99th percentile of the URL, and ○ at least one of the following: ▪ symptoms of myocardial ischemia ▪ new or presumed new significant ST–T changes or new LBBB on the ECG ▪ development of pathological Q waves on the ECG ▪ imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality.	**Note:** Trial definitions and standard definitions appear to be similar.
	Type 3	NA	Death where symptoms suggestive of myocardial ischemia are present, and with (presumed) new ischemic changes	**Note**: No trial definition provided. Presumed to be classified as death due to MI.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
			or new LBBB on ECG, but where death occurs before cardiac biomarkers can be obtained or could rise or (in rare cases) were not collected.	
	Criterion C: PCI-related MI (type 4a/4b)	• For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers > 3 × 99th percentile URL (troponin or CK-MB > 3 × 99th percentile URL) are consistent with PCI-related MI. • If the cardiac biomarker is elevated prior to PCI, a ≥ 20% increase of the value in the second cardiac biomarker sample within 24 hours of PCI and documentation that cardiac biomarker values were decreasing (two samples ≥ 6 hours apart) prior to the suspected recurrent MI is consistent with PCI-related MI. • Symptoms of cardiac ischemia are not required. • Type 4c MI associated with stent thrombosis and restenosis: NA.	• MI associated with and occurring within 48 hours of PCI, with elevation of cardiac biomarker values to > 5 × 99th percentile of the URL in patients with normal baseline values (≤ 99th percentile URL), or a rise of cardiac biomarker values ≥ 20% if baseline values are elevated and are stable or falling. This classification also requires at least one of the following: ○ symptoms suggestive of myocardial ischemia (i.e., prolonged ischemia ≥ 20 min) ○ new ischemic changes on ECG or new LBBB ○ Angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or no flow or embolization ○ imaging evidence of new loss of viable myocardium or new regional wall-motion abnormality. • MI associated with stent thrombosis as detected by coronary angiography or at autopsy, where symptoms suggestive of myocardial ischemia are present, and with a rise and/or fall of cardiac biomarker values, with at least one value > 99th percentile of the URL.	• There are considerable differences between the trial and standard definitions. ○ The standard definition includes an MI with threshold of 48 hours and an increases of biomarkers > 5 × 99th percentile of the URL following PCI, whereas the trial includes a threshold of 24 hours and increases of biomarkers > 3 × 99th percentile of the URL. ○ The standard definition requires the above condition in addition to one or more of the defined criteria, whereas the trial definition does not. ○ The standard definition includes MI associated with sent thrombosis, whereas the trial definition does not. **Note**: Although differences exist between the definitions, it is uncertain

Outcome	Components	Trial Definition	Standard Definition[35-38]	Variation Compared With Standard Definition
			• MI associated with stent restenosis as detected by coronary angiography or at autopsy, occurring > 48 hours after PCI, without evidence of stent thrombosis but with symptoms suggestive of myocardial ischemia, and with elevation of cardiac biomarker values to > 99th percentile of the URL. This classification also requires the following: ○ does not meet criteria for any other classification of MI ○ presence of a ≥ 50% stenosis at the site of previous successful stent PCI or a complex lesion and no other significant obstructive CAD of greater severity following: ▪ initially successful stent deployment, or ▪ dilation of a coronary artery stenosis with balloon angioplasty to < 50% stenosis	whether the changes and uncertainties would affect the outcomes. No trial definition provided for type 4c.
	Criterion D: CABG-related MI (type 5)	• For CABG in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of periprocedural myocardial necrosis. By convention, an increase of biomarkers > 5 × 99th percentile URL (troponin or CK-MB > 5 × 99th percentile URL) plus at least one of the following: ○ new pathological Q waves in at least two contiguous leads on the electrocardiogram that persist	• MI associated with and occurring within 48 hours of CABG surgery, with elevation of cardiac biomarker values to > 10 × 99th percentile of the URL in patients with normal baseline cardiac biomarker values (≤ 99th percentile URL). This classification also requires at least one of the following: ○ new pathological Q waves, new LBBB on ECG ○ angiographic new graft or new native coronary artery occlusion ○ imaging evidence of new loss of	• There are considerable differences between the trial and standard definitions. ○ The standard definition includes an MI with threshold of 48 hours and an increases of biomarkers > 10 × 99th percentile of the URL following CABG, whereas the trial includes a threshold of 72 hours

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		through 30 days or new LBBB ○ angiographically documented new graft or native coronary artery occlusion ○ imaging evidence of new loss of viable myocardium is consistent with CABG-related MI • If the cardiac biomarker is elevated prior to CABG, a ≥ 20% increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples ≥ 6 hours apart) prior to the suspected recurrent MI plus new pathological Q waves in ≥ two contiguous leads on the ECG or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a periprocedural MI after CABG. • Symptoms of cardiac ischemia are not required.	viable myocardium or new regional wall-motion abnormality.	and increases of biomarkers > 5 × 99th percentile of the URL. ○ The trial definition requires new pathological Q waves to persist for 30 days, whereas the standard definition does not. **Note**: Although differences exist between the definitions, it is uncertain whether the changes and uncertainties would have affected the outcomes.
Stroke		Rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumour, or infection). Available neuroimaging studies are considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke.	An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. • The term "stroke" should be broadly used to include all of the following: ○ Definition of CNS infarction: CNS infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on:	**Note:** Trial definitions and standard definitions appear to be similar.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		• For the diagnosis of stroke, the following four criteria should be fulfilled: ○ Rapid onset of a focal/global neurological deficit with at least one of the following: ▪ change in level of consciousness ▪ hemiplegia ▪ hemiparesis ▪ numbness or sensory loss affecting one side of the body ▪ dysphasia/aphasia ▪ hemianopia (loss of half of the field of vision of one or both eyes) ▪ other new neurological sign(s)/symptom(s) consistent with stroke NOTE: If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation. ○ Duration of a focal/global neurological deficit ≥ 24 hours or < 24 hours if this is because of at least one of the following therapeutic interventions: ▪ pharmacologic (i.e., thrombolytic drug administration) ▪ non-pharmacologic (i.e., neurointerventional procedure [e.g., intracranial angioplasty]) **or**	▪ pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or ▪ clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and other etiologies excluded. (Note: CNS infarction includes hemorrhagic infarctions, types 1 and 2; see "Hemorrhagic Infarction.") ○ Definition of ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. (Note: Evidence of CNS infarction is defined above.) ○ Definition of silent CNS infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion. ○ Definition of intracerebral hemorrhage: A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. (Note: Intracerebral hemorrhage includes parenchymal hemorrhages after CNS infarction, types 1 and 2 — see "Hemorrhagic Infarction.") ○ Definition of stroke caused by	

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		▪ Available brain imaging clearly documents a new hemorrhage or infarct. **or** ▪ The neurological deficit results in death. ○ No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycemia, peripheral lesion) ○ Confirmation of the diagnosis by at least one of the following: ▪ neurology or neurosurgical specialist ▪ brain imaging procedure (at least one of the following): – CT scan – MRI scan – cerebral vessel angiography ▪ lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) • If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus is mandatory. • If the acute focal signs represent a worsening of a previous deficit, these signs must have either	intracerebral hemorrhage: Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. ○ Definition of silent cerebral hemorrhage: A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion. ○ Definition of subarachnoid hemorrhage: Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord). ○ Definition of stroke caused by subarachnoid hemorrhage: Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma. ○ Definition of stroke caused by cerebral venous thrombosis:	

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		○ persisted for more than one week **or** ○ persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding • Strokes are sub-classified as follows: ○ Ischemic: A stroke caused by an arterial obstruction due to a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic strokes with hemorrhagic transformation. ○ Hemorrhagic: A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category includes strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. ○ Not assessable: The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.	Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke. ○ Definition of stroke, not otherwise specified: An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above. • Strokes are sub-classified as follows: ○ Ischemic: An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Note: Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke. ○ Hemorrhagic: An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Note: Subdural hematomas are intracranial hemorrhagic events and not strokes.	

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
			○ Undetermined: An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.	
HF requiring hospitalization		The date of this event is the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. HF requiring hospitalization is defined as an event that meets all of the following criteria: • Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available) • Clinical manifestations of HF (new or worsening) including at least one of the following: ○ dyspnea ○ orthopnea ○ paroxysmal nocturnal dyspnea ○ edema ○ pulmonary basilar crackles ○ jugular venous distension ○ third heart sound or gallop rhythm ○ radiological evidence of worsening HF	An event where the patient is admitted to the hospital with a primary diagnosis of HF where the length of stay is at least 24 hours (or extends over a calendar date if the hospital admission and discharge times are unavailable), where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF. • Documentation of new or worsening symptoms of HF on patient presentation. Criterion for new or worsening symptoms due to HF is to have at least one of the following on presentation: ○ dyspnea ○ decreased exercise tolerance ○ fatigue ○ worsened end-organ perfusion ○ volume overload • Documentation of new or worsening physical examination findings of HF on patient presentation. Criterion for	• Generally, trial definitions and standard definitions appear to be similar with the exception of the following. ○ The trial definition requires a length of stay of at least 12 hours, whereas the standard definition requires a 24-hour stay. **Note**: Although differences exist between the definitions, it is uncertain whether the changes and uncertainties would affect the outcomes.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
		• Additional/increased therapy: at least one of the following: ○ initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy ○ up-titration of oral diuretic or intravenous therapy, if already on therapy ○ initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of HF Changes in biomarker (e.g., brain natriuretic peptide) consistent with CHF will support this diagnosis.	new or worsening objective findings due to HF includes at least two physical examination findings or one physical examination finding and at least one laboratory criterion. Physical examination findings include new or worsened: ○ peripheral edema ○ increasing abdominal distention or ascites ○ pulmonary rales/crackles/crepitations ○ increased jugular venous pressure and/or hepatojugular reflux ○ S3 gallop ○ clinically significant or rapid weight gain. • Documentation of new or worsening laboratory evidence of HF obtained within 24 hours of patient presentation. Criteria for new or worsening objective findings due to HF includes at least two physical examination findings or one physical examination finding and at least one laboratory criterion. Laboratory criteria include new or worsened: ○ increase in HF biomarker ○ radiological evidence of pulmonary congestion ○ non-invasive diagnostic evidence of HF ○ invasive diagnostic evidence of HF • Initiation or intensification of treatment specifically for HF. The	

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
			criterion is that the patient receives initiation or intensification of treatment specifically for HF, including at least one of the following: ○ augmentation in oral diuretic therapy ○ intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator) ○ mechanical or surgical intervention	
New-onset albuminuria		Cases of new-onset albuminuria were identified as UACR ≥ 30 mg/g.	• Cases of new-onset albuminuria were identified as UACR ≥ 30 mg/g.	**Note:** Trial definitions and standard definitions appear to be similar.
New-onset macroalbuminuria		Cases of new-onset macroalbuminuria were identified as any UACR > 300 mg/g.	Cases of new-onset macroalbuminuria were identified as any UACR > 300 mg/day.	**Note:** Trial definitions and standard definitions appear to be similar.
Initiation of continuous renal replacement therapy		The definition of initiation of continuous RRT was not clear; however, not all of the RRT events reflected "end-stage" disease as some of the events included temporary dialysis for acute kidney injury (i.e., includes acute and chronic kidney disease).	The definition of initiation of continuous RRT when the trial initiated was: When patients reach stage 5 CKD (eGFR < 15 mL/min/1.73 m^2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning RRT. Particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5. Since then the definition for Initiation of continuous RRT has been changed to: The decision to initiate maintenance dialysis in patients who choose to do so should be based primarily upon an	• There are considerable differences between the trial and standard definitions. ○ The trial definition seems to include acute and chronic kidney disease, whereas the standard definitions appear to only include end-stage chronic renal disease. **Note**: Although differences exist between the definitions, it is uncertain whether the changes and uncertainties would affect the outcomes.

OUTCOME	COMPONENTS	TRIAL DEFINITION	STANDARD DEFINITION[35-38]	VARIATION COMPARED WITH STANDARD DEFINITION
			assessment of signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy rather than on a specific level of kidney function in the absence of such signs and symptoms.	
New or worsening nephropathy		Cases of new or worsening nephropathy, defined as the following: • new-onset macroalbuminuria • doubling of serum creatinine with an eGFR (MDRD) ≤ 45 mL/min/1.73m^2, without requiring confirmation that the decline in renal function persisted after a specified time period. • initiation of continuous RRT • death due to renal disease.	Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decrease GFR, manifest by either: • pathological abnormalities or • markers of kidney damage including abnormalities in the composition of the blood or urine or abnormalities in imaging tests. GFR < 60 mL/min/1.73m^2 for ≥ 3 months with or without kidney damage.	• There are considerable differences between the trial and standard definitions (i.e., trial definition includes mixed types of kidney disease, including acute and reversible kidney injury, microalbuminuria, and conditions for serum creatinine, contrary to the standard definition). ○ The standard definition requires kidney damage for at least three months, whereas the trial definition does not include a timeframe and considers acute kidney injury. ○ The trial definition includes microalbuminuria, whereas the standard definition does not. ○ The trial definition requires a doubling of

Outcome	Components	Trial Definition	Standard Definition[35-38]	Variation Compared With Standard Definition
				serum creatinine and an eGFR of ≤ 45 mL/min/1.73m^2, with no confirmation of persistence, whereas the standard definition requires GFR < 60 mL/min/1.73m^2 for at least three months. **Note**: Although differences exist between the definitions, it is uncertain whether the changes and uncertainties would affect the outcomes.

BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; CEC = Clinical Event Committee; CHF = congestive heart failure; CK = creatine kinase; CKD = chronic kidney disease; CNS = central nervous system; CT = computed tomography; cTn = cardiac troponin; CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; J point = the end of the S wave on the ECG; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MDRD = Modification of Diet in Renal Disease; MI = myocardial infarction; MRI = magnetic resonance imaging; NA = not available; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PE = pulmonary embolism; Q wave = one of three waves in the QRS complex on the ECG; QS complex = Q/S wave on the ECG; R wave = one of three waves in the QRS complex on the ECG; RRT = renal replacement therapy; R/S ratio = the ratio of the R wave to the S wave on the ECG; S wave = one of three waves in the QRS complex on the ECG; SBP = systolic blood pressure; ST elevation = elevation of the section of the ECG between the end of the S wave and the beginning of the T wave; ST-T = ST segment–T wave; T wave = a wave visible on the ECG, representing ventricular repolarization; UACR = urine albumin-to-creatinine ratio; URL = upper reference limit.

Summary and conclusion

Generally, the definitions of the outcomes included in the trials are not always consistent with the standard definitions.[35-38] Although differences do exist among the definitions, it is uncertain whether the variations would have affected the outcomes. In a briefing document completed by FDA reviewers,[5] some concerns were raised with the definitions utilized in the trials for both CV and renal outcomes. Generally, the FDA reviewers commented on the various amendments to the end points throughout the trial, and noted that some end points were added or amended at later stages during the trial. The FDA reviewers highlighted that more than one-third of all CV deaths were labelled as "fatal event not assessable," defined as all deaths not attributed to the specified categories and not attributed to a non-CV cause. The FDA noted that it is not clear whether these events are truly CV deaths. The FDA reviewers also highlighted that only a subset of "silent MI" were adjudicated and included in the primary analysis, and that using this definition is limiting due to the lack of complete event ascertainment and adjudication; therefore, the meaningfulness of analyses including this event in the three-point major adverse cardiac event (MACE) end point is uncertain. However, the FDA reviewers also noted uncertainty with regard to the consideration of these events in the overall interpretation of the trial results.

With regard to HF and stroke outcomes, the FDA reviewers noted that they were both exploratory and not corrected for type 1 error, that the trial was not designed to appropriately assess the outcomes (e.g., insufficient data collection), and that these factors limit the conclusions that can be drawn from the results. In addition, the FDA reviewers also noted that, due to an amendment to the definition of HF, it is possible that some of the events that were categorized as HF may not have reflected HF.

Regarding renal end points, the FDA reviewers noted that there were too few clinical events to truly conclude whether there were any differences between therapies, and that not all of the renal replacement therapy events reflected "end-stage" disease (i.e., some renal replacement therapy events included temporary dialysis for acute kidney injury), making any conclusions uncertain. In addition, the FDA reviewers noted that renal end points (e.g., new or worsening nephropathy) results are mostly driven by laboratory test findings (i.e., albuminuria), which may not be reflective of clinical outcomes in diabetic nephropathy (i.e., includes acute and reversible nephropathy); consequently, the validity of these end points is unclear. In addition, no confirmation of doubling of serum creatinine was required for the evaluation of permanent loss of renal function, thereby also capturing acute reversible changes rather than chronic irreversible changes; this further compromised the validity of renal outcomes. The FDA also highlighted that "new or worsening nephropathy" is also included as a criterion for the composite microvascular end point; therefore, any uncertainties corresponding to the validity of the outcomes are carried over.

In general, there are several variances between universally accepted definitions of the outcomes and the outcomes used in this trial. This, combined with the less rigorous data collection and issues around the ascertainment of outcomes in the trial, introduces significant uncertainty and makes inferences on the effect of empagliflozin on these outcomes difficult.

APPENDIX 6: SUMMARY OF OTHER STUDIES

Aim

To provide a summary and appraisal of the systematic reviews, meta-analysis, and indirect treatment comparisons of the effect of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on cardiovascular (CV) events, death, and safety in adults with type 2 diabetes.

Findings

A search was completed by CDR using the MEDLINE (1946 to present) and Embase (1974 to present). After two independent reviewers screened the literature search results, one systematic review comparing the efficacy and safety of SGLT-2 inhibitors and placebo or other comparators in patients with type 2 diabetes was identified (Wu et al.).[39] A second systematic review and indirect treatment comparison was identified from other sources (Palmer et al.).[40]

Summary of systematic review by Wu et al.[39]

Study design

The objective of the systematic review and meta-analysis by Wu et al. was to establish the effects of SGLT-2 inhibitors on CV events, death, and safety outcomes in adults with type 2 diabetes, both as a class effect and separately for individual drugs.

The submission documents to the US Food and Drug Administration (FDA), the European Medicines Agency, and the Japanese Pharmaceutical and Medical Devices Agency (up to September 30, 2015), as well as a systematic literature search using the PRISMA statement, were used to collect data for the meta-analysis conducted by Wu et al. The systematic review included the MEDLINE, Embase, and The Cochrane Library databases, and searched for published studies between January 1, 1950 and September 30, 2015 using relevant words associated with "randomized trials," "SGLT-2," in addition to the individual drug names. No language restrictions were used. Two investigators independently reviewed the submission documents to the regulatory agencies as well as the titles and abstracts in the systematic literature search for inclusion into the meta-analysis. However, only one investigator subsequently reviewed the full texts for inclusion. The same two investigators also extracted the data from the all of the included studies. Two other investigators independently performed a quality assessment on all the included studies identified in the systematic literature search using the Jadad scale. However, no quality assessment was possible for the data included from the regulatory submissions, given their abbreviated nature. Any disagreements were settled by consultation between the investigators. Duplicates, trials including combination treatments (e.g., SGLT-2 in combination with metformin), trials with seven or fewer days of follow-up, trials that did not report outcomes of interest, and pooled data sets were excluded.

The primary efficacy outcome of the systematic review included major adverse cardiovascular events (MACE), which consisted of cardiovascular (CV) death, non-fatal myocardial infarction (MI), and non-fatal stroke. The secondary outcomes included MACE plus (MACE in addition to admission to hospital for unstable angina), heart failure (HF), and all-cause mortality. Safety outcomes included urinary tract infection (UTI), genital infection, cancer, bone fracture, volume depletion, venous thromboembolism, hypoglycemia, acidosis, and kidney disease. Relative risks (RRs) with respect to hypoglycemia associated with SGLT-2 inhibition with low-to-moderate heterogeneity (monotherapy and in combination with insulin) were assessed using fixed-effect models; whereas, those with high degrees of heterogeneity (in combination with metformin or sulfonylurea) were assessed using random-effects models using

DerSimonian and Laird methods. The definitions for all safety outcomes were consistent among all of the included studies, except for the definitions of volume depletion and kidney disease.

The reported CV outcomes and death are based on data collected from the submissions made to the regulatory agencies, as well as the published scientific literature. It was unclear whether the data included in regulatory submissions were double-counted in the systematic literature search data; therefore, estimates based on each data source (i.e., estimates using each set of data separately in addition to the estimate using the combined data) were used to address this issue. RRs with 95% confidence intervals (CIs) were estimated for all of the included outcomes and were pooled across studies using fixed-effects models and inverse-variance weighting. Heterogeneity was measured using the I^2 statistic with the corresponding *P* value. The likelihood of demonstrating a difference beyond chance were considered low, moderate, or high when associated with heterogeneity ≤ 25%, 26% ≤ I^2 ≤ 75% and 76% ≤ I^2 ≤ 100%, respectively, with a corresponding *P* value of 0.05. If significant heterogeneity was present, a sensitivity analysis was performed using a random-effects model. A single analysis was performed for the primary and secondary outcomes using the combined data from the regulatory submissions and the data from the systematic literature search, whereas two separate analyses were performed for the safety outcomes using the data extracted from the regulatory submissions separately from the data from the systematic literature search. Comparisons of the included SGLT-2 inhibitors with placebo and other comparators were done separately. Trials in which the outcome was not detected in any of the treatment groups were excluded from the analysis for that outcome.

Results

Regulatory submissions provided data on 37,525 individuals, while 57 published trials provided data on 33,385 individuals. The mean age ranged between 12.8 years to 68.4 years, the percentage of women ranged from 14% to 56%, and follow-up ranged between 1.3 weeks to 161 weeks.

Efficacy

All outcomes were informed solely by empagliflozin and canagliflozin, with the exception of HF (informed by empagliflozin only) and all-cause mortality (informed by canagliflozin, dapagliflozin, and empagliflozin). Class effects for efficacy outcomes were mostly informed by the data for empagliflozin (71% of MACE events, 72% of MACE plus events, and 89% of CV events) and canagliflozin (15% of MACE events, 15% of MACE plus events, and 11% of CV events).

Generally, SGLT-2 inhibition is associated with a reduced RR for the following:

- MACE events (RR = 0.84; 95% CI, 0.75 to 0.95; *P* = 0.006; I^2 = 44%)
- MACE plus events (RR = 0.85; 95% CI, 0.77 to 0.95; *P* = 0.008; I^2 = 24%)
- CV death (RR = 0.63; 95% CI, 0.51 to 0.77; *P* < 0.0001; I^2 = 0%)
- hospitalization due to HF (RR = 0.65; 95% CI, 0.50 to 0.85; *P* = 0.002; I^2 = 0%)
- all-cause mortality (RR = 0.71; 95% CI, 0.61 to 0.83; *P* < 0.0001; I^2 = 0%).

There were no clear associations between SGLT-2 inhibition and the RR for non-fatal MI (RR = 0.88; 95% CI, 0.72 to 1.07; *P* = 0.18, I^2 = 0%), or hospitalization due to unstable angina (RR = 0.95; 95% CI, 0.73 to 1.23]; *P* = 0.70, I^2 = 0%). However, SGLT-2 inhibition was associated with an increased RR for non-fatal stroke (RR = 1.30; 95% CI, 0.1.00 to 1.68; *P* = 0.049, I^2 = 0%). Heterogeneity was considered low for all outcomes with the exception of MACE (moderate heterogeneity I^2 = 44%). A sensitivity analysis was performed using a random-effects model for this outcome, resulting in a non-significant RR of 0.82 (95% CI, 0.67 to 1.01; *P* = 0.066). RRs corresponding to efficacy outcomes are detailed in Table 26.

TABLE 26: EFFECT OF SGLT-2 INHIBITION ON EFFICACY OUTCOMES (WU 2016)

OUTCOME				
	SGLT-2 (n/N)	Control[a] (n/N)	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)
MACE				
Canagliflozin	104/6,396	53/3,327	1.02 (0.74 to 1.42)	0.84 (0.75 to 0.99)[b] I^2 = 44%
Dapagliflozin	73/5,936	62/3,403	0.67 (0.48 to 0.94)	
Empagliflozin	490/4,687	282/2,333	0.86 (0.75 to 0.99)	
MACE PLUS				
Canagliflozin	130/6,395	71/3,327	0.95 (0.72 to 1.27)	0.85 (0.77 to 0.95) I^2 = 24%
Dapagliflozin	97/5,936	81/3,403	0.69 (0.51 to 0.92)	
Empagliflozin	621/7,082	359/3,547	0.87 (0.77 to 0.98)	
CV DEATH				
Canagliflozin	21/6,396	16/3327	0.68 (0.36 to 1.31)	0.63 (0.51 to 0.77) I^2 = 0%
Empagliflozin	172/4,687	137/2333	0.62 (0.50 to 0.78)	
NON-FATAL MI				
Canagliflozin	45/6,396	27/3,327	0.87 (0.54 to 1.39)	0.88 (0.72 to 1.07) I^2 = 0%
Empagliflozin	213/4,687	121/2,333	0.88 (0.70 to 1.09)	
NON-FATAL STROKE				
Canagliflozin	47/6,396	16/3,327	1.53 (0.87 to 2.69)	1.30 (1.00 to 1.68) I^2 = 0%
Empagliflozin	150/4,687	60/2,333	1.24 (0.93 to 1.67)	
HOSPITALIZATION DUE TO UNSTABLE ANGINA				
Canagliflozin	26/6,396	18/3,327	0.75 (0.41 to 1.37)	0.95 (0.73 to 1.23) I^2 = 0%
Empagliflozin	133/4,687	66/2,333	1.00 (0.75 to 1.34)	
HOSPITALIZATION DUE TO HF				
Empagliflozin	126/4,687	95/2,333	0.65 (0.50 to 0.85)	NA
ALL-CAUSE DEATH				
Canagliflozin	49/6,177	37/3,262	0.70 (0.46 to 1.07)	0.71 (0.61 to 0.83) I^2 = 0%
Dapagliflozin	37/5,936	24/2,403	0.88 (0.53 to 1.48)	
Empagliflozin	278/7,082	201/3,647	0.69 (0.58 to 0.82)	

CV = cardiovascular; HF = heart failure; MACE = major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); MACE plus = MACE and admission to hospital for unstable angina; MI = myocardial infarction; NA = not applicable; SGLT-2 = sodium-glucose cotransporter-2.

[a] Comparators include placebo, sitagliptin, placebo in combination with sitagliptin, glimepiride, glipizide, placebo in combination with metformin.

[b] Pooled class effect includes other SGLT-2 not approved in Canada.

Note: Data for each drug were extracted from regulatory submission documents or fixed-effects meta-analysis of effect estimates from multiple sources. SGLT-2 class effect analyses were obtained using fixed-effect models.

Reproduced with permission from the publisher for: Figure 2, Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundstrom J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2016 May;4(5):411-9.[39]

Safety

Two separate analyses were performed for the safety outcomes to address the potential of double-counting AEs; the first utilizes the data extracted from the regulatory submissions only, and the second utilizes the data from the systematic literature search only.

SGLT-2 inhibition is associated with an increase in the RR for genital infection in both the regulatory submission analysis and the systematic literature search analysis (RR = 4.75; 95% CI, 4.00 to 5.63; I^2 = 59%) and (RR = 2.88; 95% CI; 2.48 to 3.34; I^2 = 79%), respectively. SGLT-2 inhibition was also associated with an increased RR for UTIs (RR = 1.15; 95% CI, 1.06 to 1.26; I^2 = 0%) and volume depletion (RR = 1.53; 95% CI, 1.27 to 1.83; I^2 = 40%) in the regulatory submission analysis but not in the systematic literature search analysis.

There were no clear associations between SGLT-2 inhibition and cancer, bone fracture, hypoglycemia, venous thromboembolism, acidosis, or kidney disease in either of the analyses. However, RRs corresponding to safety outcomes are detailed in Table 27.

The RR for hypoglycemia was not increased with SGLT-2 inhibition as a monotherapy or as an add-on therapy to either metformin or insulin; however, SGLT-2 inhibition was associated with an increased RR for hypoglycemia when combined with a sulfonylurea (RR = 1.82; 95% CI, 1.05 to 3.16; I^2 = 79%). RRs for hypoglycemia stratified by background therapy are detailed in Table 28.

TABLE 27: EFFECT OF SGLT-2 INHIBITION ON SAFETY OUTCOMES (WU 2016)

OUTCOME	REGULATORY SUBMISSION ANALYSIS				SYSTEMATIC LITERATURE SEARCH			
	SGLT-2 (n/N)	Control[a] (n/N)	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)	SGLT-2 (n/N)	Control[a] (n/N)	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)
UTI								
Canagliflozin	504/6,177	218/3,262	1.22 (1.05 to 1.42)	1.15 (1.06 to 1.26)[b] I^2 = 0%	204/2,473	86/1,236	1.15 (0.90 to 1.47)	1.02 (0.95 to 1.10) I^2 = 45%[c]
Dapagliflozin	110/2,360	81/2,295	1.32 (1.00 to 1.75)		335/4,305	159/2,541	1.29 (1.07 to 1.56)	
Empagliflozin	730/8,232	380/4,676	1.09 (0.97 to 1.23)		128/9,213	713/4,768	0.96 (0.88 to 1.05)	
GENITAL INFECTION								
Canagliflozin	669/6,177	72/3,262	4.91 (3.86 to 6.23)	4.75 (4.00 to 5.63) I^2 = 59%[c]	450/3,858	117/1,822	2.59 (1.96 to 3.42)	2.88 (2.48 to 3.34) I^2 = 79%[c]
Dapagliflozin	130/2,360	14/2,295	9.03 (5.22 to 15.62)		381/5,464	54/3,017	3.22 (2.42 to 4.30)	
Empagliflozin	378/8,232	52/4,676	4.13 (3.10 to 5.51)		567/9,213	101/4,768	3.10 (2.47 to 3.88)	
CANCER								
Canagliflozin	18/6,648	14/3,640	0.70 (0.35 to 1.41)	1.07 (0.85 to 1.34) I^2 = 0%	NR	NR	NR	0.72 (0.34 to 1.54) I^2 = 0%
Dapagliflozin	89/5,936	51/3,403	1.00 (0.71 to 1.41)		11/1,316	13/1,046	0.74 (0.33 to 1.66)	
Empagliflozin	88/8,232	42/4,676	1.19 (0.83 to 1.72)		1/375	0/188	1.51 (0.06 to 36.84)	
BONE FRACTURE								
Canagliflozin	129/6,396	53/3,327	1.27 (0.92 to 1.74)	0.99 (0.82 to 1.21) I^2 = 29%	20/656	6/327	1.66 (0.67 to 4.09)	0.96 (0.78 to 1.18) I^2 = 21%
Dapagliflozin	23/2,026	32/1,956	0.69 (0.41 to 1.18)		28/1,431	11/934	1.08 (0.49 to 2.38)	
Empagliflozin	110/8,232	72/4,676	0.87 (0.65 to 1.17)		206/6,208	124/3,597	0.92 (0.74 to 1.16)	

Outcome	Regulatory Submission Analysis				Systematic Literature Search			
	SGLT-2 (n/N)	Control[a] (n/N)	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)	SGLT-2 (n/N)	Control[a] (n/N)	Relative Risk (95% CI)	Pooled Relative Risk (95% CI)
Volume Depletion								
Canagliflozin	240/6,177	78/3,262	1.62 (1.26 to 2.09)	1.53 (1.27 to 1.83) I^2 = 40%	65/2,812	16/1,319	1.77 (1.03 to 3.03)	1.16 (0.98 to 1.38) I^2 = 0%
Dapagliflozin	27/2,360	17/2,295	1.54 (0.84 to 2.83)		77/3,738	31/2,409	1.36 (0.89 to 2.09)	
Empagliflozin	119/8,232	57/4,676	1.19 (0.87 to 1.62)		296/7,678	136/3,998	1.07 (0.88 to 1.31)	
Thromboembolism								
Canagliflozin	13/6177	5/3,262	1.37 (0.49 to 3.85)	1.54 (0.0.63 to 3.79)	NR	NR	NR	NR
Dapagliflozin	2/5,936	1/3,403	1.15 (0.10 to 12.64)	I^2 = 0%	NR	NR	NR	
NR[d]					30/4,687	20/2333	0.75 (0.42 to 1.31)	
Hypoglycemia								
Canagliflozin	884/3,343	401/1,658	1.09 (0.99 to 1.21)	1.00 (0.94 to 1.07) I^2 = 67%[c]	710/3,461	484/1,729	0.96 (0.87 to 1.07)	0.95 (0.91 to 1.00) I^2 = 89%[c]
Dapagliflozin	324/2,360	284/2,295	1.11 (0.96 to 1.29)		660/5,364	487/3,331	0.95 (0.86 to 1.05)	
Empagliflozin	958/8,232	614/4,676	0.89 (0.81 to 0.97)		1,778/8,709	1,104/4,529	0.94 (0.89 to 1.01)	
Acidosis								
NR	1/1,630	0/311	0.57 (0.02 to 14.10)		4/4,687	1/2,333	1.99 (0.22 to 17.80)	
Kidney Disease								
Canagliflozin	27/6,177	13/3,262	1.10 (0.57 to 2.12)	1.21 (0.91 to 1.62) I^2 = 10%	NR	NR	NR	0.83 (0.69 to 1.00) I^2 = 6%
Dapagliflozin	3/5,936	0/3,403	4.01 (0.21 to 77.68)		46/2,388	16/1,622	1.32 (0.74 to 2.35)	
Empagliflozin	99/8,232	40/4,676	1.41 (0.98 to		246/4,687	155/2,333	0.79 (0.65 to	

OUTCOME	REGULATORY SUBMISSION ANALYSIS				SYSTEMATIC LITERATURE SEARCH			
	SGLT-2 (n/N)	**Control[a] (n/N)**	**Relative Risk (95% CI)**	**Pooled Relative Risk (95% CI)**	**SGLT-2 (n/N)**	**Control[a] (n/N)**	**Relative Risk (95% CI)**	**Pooled Relative Risk (95% CI)**
			2.03)				0.96)	

CI = confidence interval; NR = not reported; SGLT-2 = sodium-glucose cotransporter-2; UTI = urinary tract infection.
[a] Comparators include placebo, sitagliptin, placebo in combination with sitagliptin, glimepiride, glipizide, placebo in combination with metformin and placebo in combination with hydrochlorothiazide.
[b] Pooled class effect includes SGLT-2 not identified in the table and not approved in Canada.
[c] *P* value < 0.05 for heterogeneity.
[d] Data for only one unidentified SGLT-2 included.
Note: Data for each drug were extracted from regulatory submission documents or fixed-effects meta-analysis of effect estimates from multiple sources. SGLT-2 class effect analyses were obtained using fixed-effect models.
Source: Wu.[39]

TABLE 28: EFFECT OF SGLT-2 INHIBITION ON HYPOGLYCEMIA STRATIFIED BY BACKGROUND THERAPY

BACKGROUND THERAPY	TRIALS	POOLED RELATIVE RISK (95% CI)	HETEROGENEITY (I^2)
None	13	0.87 (0.56 to 1.33)	0%
Metformin	10	0.47 (0.22 to 1.01)	89%
Insulin	10[a]	1.03 (0.98 to 1.08)	31%
Sulfonylurea	5[b]	1.82 (1.05 to 3.16)	79%

CI = confidence interval; SGLT = sodium-glucose cotransporter-2 (inhibitors).
[a] One of the studies included a combination of insulin and metformin as background therapy.
[b] Three of the studies included a combination of sulfonylurea and metformin as background therapy.
Note: RRs associated to SGLT-2 inhibition with low-to-moderate heterogeneity (monotherapy and in combination with insulin) were assessed using fixed-effect models, whereas those with high degrees of heterogeneity (in combination with metformin or sulfonylurea) were assessed using random-effects models using DerSimonian and Laird methods.
Reproduced with permission from the publisher for: Table Hypoglycaemia, Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundstrom J, et al. Supplement: Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2016 May;4(5):411-9.[39]

Limitations

Although the systematic review and meta-analysis by Wu et al. satisfied the PRISMA statement, there are some inherent limitations. First, the meta-analysis appears to pool results using an unconventional method, whereby the numbers of crude events for a given outcome from each study are first combined using simple counts/summation, rather than the result of an outcome being pooled across all included trials. No meta-analytic technique was used to first pool these crude events or to determine whether initial pooling of events by specific drug was appropriate. The pooling of the crude events across studies was then used to evaluate the RR for the drug in question (i.e., there were 57 potential studies involved, yet all data were combined and entered into the meta-analysis as a single crude pooled effect for each drug). The meta-analysis conducted by Wu et al. does not provide any information to justify the use of the alternate method, which may be susceptible to Simpson's paradox (a biased result when data are improperly pooled, creating uncertainty in the end points. In addition to the unconventional pooling methodology for the crude events, the weighting methodology of the pooled trials was not properly described for the efficacy outcomes. It is unclear whether appropriate weighting of trials can be established using the unconventional pooling methodology. Inappropriate weighting per cent distribution of the pooled trials can make it difficult to assess the efficacy and safety of the SGLT-2 class effect. The pooling of the trials in the meta-analysis may have not always been appropriate, whereby some of the pooled trials did not include common comparators (i.e., some trials used placebo as a comparator while other trials used active comparators) or trial results with fundamentally different patient characteristics were pooled (e.g., one trial of the included trials had a mean participant age of 12.8 years, despite the requested indication in adults).

Additionally, some of the trials did not include consistent definitions for the measured outcomes (i.e., some trials used different definitions for volume depletion and kidney disease). Also, the Methods section lacked any information related to definitions of MACE and MACE plus outcomes (i.e., which outcomes were included in these composites), and it remains unclear whether their definitions were consistent across the included trials. Some of the included trials also considered different trial durations ranging between 1.3 weeks and 161 weeks. Given that MACE outcomes are typically longer-term end points, shorter trials included in the meta-analysis have the potential to bias the results. Furthermore, it is unclear whether any of the MACE outcomes were properly adjudicated in the original trials included in the meta-analysis; if not, this can lead to uncertainty with respect to the outcomes and therefore

uncertainty in the efficacy. These inconsistencies can make it difficult to assess the efficacy and safety of SGLT-2 inhibition, and could have added to some of the heterogeneity observed for various end points.

Although a considerable number of the pooled outcomes demonstrated moderate-to-high heterogeneity, all analyses pooled the results of the included trials using fixed-effect models instead of random-effect models, with the exception of the primary MACE outcome. The pooling of heterogeneous results for the remaining outcomes using fixed-effect models may not have been appropriate and could have resulted in an artificial narrowing of the CIs. Despite the fact that a considerable number of end points demonstrated heterogeneity, no sensitivity analyses were performed to investigate their cause.

Some of the pooled analyses included a limited number of studies to inform the end point, which can further add to the variability of the results. Furthermore, in general, there were relatively few events reported for some of the relevant end points, which can also add to the variability of the results.

The quality assessment of the included data for the meta-analyses was primarily based on the Jadad scale. This tool does not account for many of the essential points required when performing a critical appraisal of a randomized control trial, which may create uncertainty associated with the quality of the included trials. In addition, the Jadad scale identified several trials that did not describe the randomization methodology and did not report key baseline characteristics of the included populations, such as age and gender, which may increase the uncertainty associated to any confounders. It is unclear whether any further quality assessments were conducted on the trials to be included in the meta-analysis. Furthermore, no sensitivity analyses were performed on the data extracted from literature or the regulatory submissions, and no quality assessments were conducted on the data extracted from the regulatory submissions.

Finally, in some end points, pooled class effects either included SGLT-2 inhibitors not approved in Canada (e.g., ertugliflozin, ipragliflozin, luseogliflozin and tofogliflozin) or included unidentified SGLT-2 inhibitors, which may limit the generalizability of the efficacy and safety results to the Canadian population.

Summary of systematic review by Palmer et al.[40]

Study design

The systematic review and indirect treatment comparison by Palmer et al.[40] were conducted to estimate the relative efficacy and safety of glucose-lowering drugs for the treatment of type 2 diabetes in adults. The review included randomized controlled trials (RCTs) with a minimum duration of 24 weeks that compared two glucose-lower drug classes from the following: metformin, sulfonylurea, thiazolidinedione, dipeptyl peptidase-4 (DPP-4) inhibitor, SGLT-2 inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, insulin, meglitinide, or alpha-glucosidase inhibitor.[40] The primary outcome was CV mortality, and secondary outcomes included all-cause mortality, MI, stroke, A1C, treatment failure (lack of efficacy or need for rescue treatment), serious adverse events (SAEs), hypoglycemia, and body weight.

A literature search of The Cochrane Library Central Register of Controlled Trials, MEDLINE, and Embase was conducted (no language restrictions). Two reviewers independently screened articles, extracted data, and assessed the quality of included trials using the Cochrane Risk of Bias tool.

Conventional random-effects meta-analysis and frequentist random-effects network meta-analyses (NMA) were conducted, and results were reported as odds ratios and/or risk differences for

dichotomous outcomes and as standardized mean differences for continuous outcomes. Separate analyses were conducted for drugs given as monotherapy, in combination with metformin (dual therapy), or in combination with metformin and a sulfonylurea (triple therapy). Drugs were analyzed by drug class, rather than as individual agents, and no limits with regard to doses of glucose-lowering treatments were specified in the review methods.

Prior to pooling studies, the study characteristics, setting, and patient characteristics on the trials were qualitatively compared to determine whether studies were sufficiently similar for NMA. Heterogeneity in each NMA was evaluated by comparing the common heterogeneity variance for the network (tau) with an empirical distribution of heterogeneity variance (tau of 0.5 to 1.0 = high heterogeneity, tau > 1.0 = extreme heterogeneity). Inconsistency of direct and indirect evidence was evaluated based on the loop specific inconsistency factor and a qualitative comparison of direct and indirect effect estimates. Meta-regression analyses were conducted for glycated hemoglobin (A1C), weight, and hypoglycemia for the potential effect modifiers including study level baseline age, A1C, weight, duration of diabetes, and duration of treatment.

Results

A total of 301 randomized controlled trials (RCTs) met the systematic review inclusion criteria; of these, 177 trials (N = 56,598) were for monotherapy, 109 trials (N = 53,030) were for dual therapy, and 29 trials (N = 10,598) were for triple therapy regimens. The mean study duration ranged from 24 weeks to 76.8 months (median 6 months). The authors rated a number of the trials with a high or unclear risk of bias for randomization (69% of trials), allocation concealment (77%), blinding or participants/investigators (32%) or outcome assessors (93%), completeness of outcome reporting (60%), and selective outcome reporting (58%).

Of the included studies, 25, 26 and five trials, respectively, were included in the NMA of CV mortality for the monotherapy, dual therapy, and triple therapy analyses.[40] There were no statistically significant differences in CV mortality between drug classes, including SGLT-2 inhibitors, when used as monotherapy, dual therapy, or triple therapy.[40] SGLT-2 inhibitor monotherapy did not show statistically significant differences in all-cause mortality, MI, stroke, A1C, weight, SAEs, or hypoglycemia, compared with metformin monotherapy (Table 29). However, in the analysis of dual therapy, SGLT-2 inhibitors plus metformin showed statistically significant results for weight and hypoglycemia versus sulfonylurea plus metformin. Other outcomes for dual therapy showed no statistically significant differences between SGLT-2 inhibitors plus metformin and sulfonylureas plus metformin.

The network of evidence for triple therapy was sparse; due to the lack of data, no analysis of MI or stroke was possible. There was considerable uncertainty in the mortality results as demonstrated by the wide CIs (Table 29). No statistically significant differences were found between SGLT-2 inhibitors and thiazolidinediones, as add-on therapy to metformin plus a sulfonylurea, for the change in A1C or risk of SAEs or hypoglycemia. The analysis of change in body weight showed a small significant difference between groups, favouring SGLT-2 inhibitor more than thiazolidinedione triple therapy (Table 29).

Inconsistency was identified for some drug comparisons (hypoglycemia and weight [dual therapy]; hypoglycemia and A1C [triple therapy]); however, due to the wide CIs for the inconsistency factor, robust conclusions about inconsistency could not be made. There was evidence for high heterogeneity for the analysis of A1C for dual therapy. The results for the meta-regression analyses were generally consistent with primary NMA results.

TABLE 29: NMA RESULTS FOR SGLT-2 INHIBITORS (PALMER 2016)

Outcome	Monotherapy	Dual therapy	Triple therapy
	SGLT-2 Versus Metformin	SGLT-2 + Metformin Versus SU + Metformin	SGLT-2 + Metformin + SU Versus Thiazolidinedione + Metformin + SU
CV mortality OR (95% CI)[a]	0.75 (0.14 to 3.96)	0.86 (0.14 to 5.27)	3.69 (0.05 to 258)
All-cause mortality OR (95% CI)[a]	0.84 (0.22 to 3.21)	0.83 (0.37 to 1.86)	2.16 (0.10 to 45.2)
MI OR (95% CI)[a]	0.63 (0.06 to 6.24)	0.42 (0.12 to 1.48)	NA
Stroke OR (95% CI)[a]	0.70 (0.05 to 9.71)	2.75 (0.76 to 10.0)	NA
A1C SMD (95% CI)[b]	0.18 (–0.15 to 0.51)	0.17 (–0.49 to 0.82)	0.12 (–1.12 to 1.35)
Weight SMD (95% CI)[b]	–0.06 (–0.22 to 0.08)	–0.96 (–1.46 to –0.47)	–0.33 (–0.59 to –0.07)
SAE OR (95% CI)[a]	1.24 (0.81 to 1.92)	0.92 (0.73 to 1.15)	0.53 (0.27 to 1.06)
Hypoglycemia OR (95% CI)[a]	0.63 (0.30 to 1.32)	0.12 (0.08 to 0.18)	0.86 (0.48 to 1.54)

CI = confidence interval; CV = cardiovascular; A1C = glycated hemoglobin; MI = myocardial infarction; NA = not assessable; OR = odds ratio; SAE = serious adverse event; SGLT-2 = sodium-glucose cotransporter-2 inhibitor; SMD = standardized mean difference; SU = sulfonylurea.

[a] An OR greater than 1 indicates that the outcome is more likely with SGLT-2 treatment than control.

[b] An SMD greater than 0 indicates higher weight or A1C at the end of treatment for SGLT-2 treatment versus control. An SMD of 0.2 is considered to be a small difference between treatments, an SMD of 0.5 is considered to be a moderate difference, and an SMD of 0.8 is considered to be a large difference.

Source: Palmer et al.[40]

Limitations

The review excluded a number of key CV outcome trials in type 2 diabetes, including EMPA-REG OUTCOME (empagliflozin),[18] LEADER (liraglutide),[11] TECOS (sitagliptin),[12] and SAVOR-TIMI 53 (saxagliptin),[14] because these trials did not analyze the treatments as monotherapy or as added to metformin. Only a minority of the included studies reported on CV mortality, and in many trials, no events occurred. Also, treatment effects were estimated for each drug class; thus, the indirect treatment comparison does not provide information on the comparative efficacy of empagliflozin specifically.

Conclusions

Significant limitations to the methodology of the systematic review and meta-analysis by Wu et al.[39], including the pooling of crude events rather than using traditional meta-analytical methods, as well as combining heterogeneous data, limit the ability to draw any conclusions. Too many uncertainties exist to determine whether the statistical results of this meta-analysis are valid.

The indirect treatment comparison by Palmer et al.[40] found no statistically significant differences between SGLT-2 inhibitors and other glucose-lowering drugs for mortality, MI, or stroke in adults with type 2 diabetes; however, the exclusion of key CV outcome trials limits the findings.

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