Jardiance®
(empagliflozin)

EMPA-REG Outcome

A randomized, double-blind, placebo-controlled CV outcomes trial[1,2*]

CANADIAN-LED TRIAL

13 CANADIAN TRIAL SITES, ACROSS **6** PROVINCES[3]

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JARDIANCE® is indicated as an 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.[1]

CV=cardiovascular; T2D=type 2 diabetes; MI=myocardial infarction.
* EMPA-REG OUTCOME study: double-blind, placebo-controlled, event-driven study evaluating empagliflozin 10 mg and 25 mg as add-on to standard of care therapy in reducing CV events in T2D patients with ≥1 of: coronary artery disease, peripheral artery disease, historyof MI, history of stroke. Primary endpoint was time to first event in composite endpoint of CV death, non-fatal MI, or non-fatal stroke (Major Adverse Cardiovascular Events [MACE-3]).

EMPA-REG Outcome

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42 countries[2]

3.1 years

of median observation time[1,2]

7,020 patients

with T2D and established CV disease[1,2]

Established CV disease included:[1,2]

Vascular manifestations:

- Coronary artery disease (CAD)
  - Evidence of single or multi-vessel disease
- Peripheral artery disease (PAD)

Prior atherothrombotic events:

- History of MI
- History of stroke

>75% of patients had CAD

20.8% of patients had PAD
46.6% of patients had history of MI
23.3% of patients had history of stroke

The study evaluated the effect of JARDIANCE® 10 mg and 25 mg as an **add-on to standard of care (SOC) therapies**, including:[1]

CV

81% ACE inhibitors or ARBs
65% beta-blockers
43% diuretics
81% lipid-lowering agents
89% anti-thrombotic therapy

T2D

74% metformin
48% insulin
43% sulfonylurea

Investigators were encouraged to adjust glucose-lowering therapies as appropriate to achieve glycemic control and to manage other cardiovascular risks (including dyslipidemia and hypertension) according to guidelines.[2*]

ACE=angiotensin-converting enzyme; ARB=angiotensin-receptor blocker; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide 1.

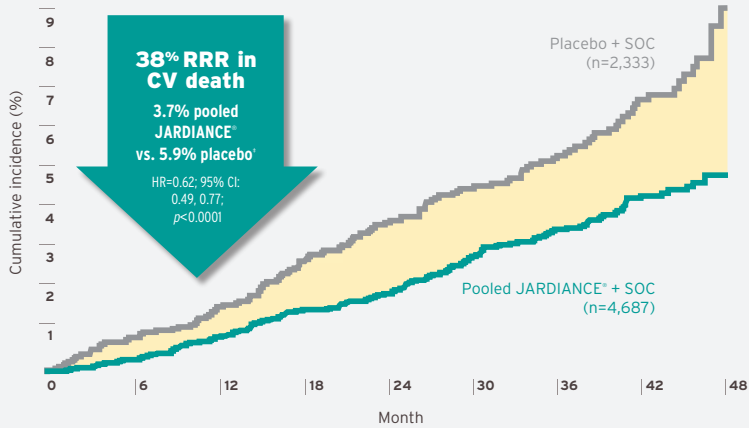
* Background glucose-lowering therapy (including metformin, insulin, sulfonylurea, DPP-4 inhibitors, thiazolidinediones, and GLP-1 agonists) remained unchanged for the first 12 weeks, after which investigators were encouraged to adjust therapy to achieve glycemic control according to local guidelines. Throughout the trial, investigators were encouraged to treat CV risk factors to achieve the best available standard of care according to local guidelines.

In patients with T2D and established CV disease

JARDIANCE®, as an adjunct to standard of care therapy*, **reduced the risk of CV death** vs. placebo[1,2†‡]

(other adjudicated endpoint)

Estimated cumulative incidence function for time to CV death



Patients at risk

Placebo	2,333	2,303	2,280	2,243	2,012	1,503	1,281	825	177
Pooled JARDIANCE®	4,687	4,651	4,608	4,556	4,128	3,079	2,617	1,722	414

Adapted from JARDIANCE® Product Monograph and Zinman B, et al.

Demonstrated NNT with JARDIANCE® for 3 years to prevent one CV death

NNT=46

JARDIANCE® demonstrated 14% RRR in the MACE-3 primary analysis vs. placebo (10.5% pooled JARDIANCE® [n=490] vs. 12.1% placebo [n=282]).[1,2‡]

HR=0.86; 95% CI: 0.74, 0.99; *p*=0.0382

There was no significant change in non-fatal MI or non-fatal stroke.[1]

RRR=relative risk reduction; HR=hazard ratio; CI=confidence interval; NNT=number needed to treat.

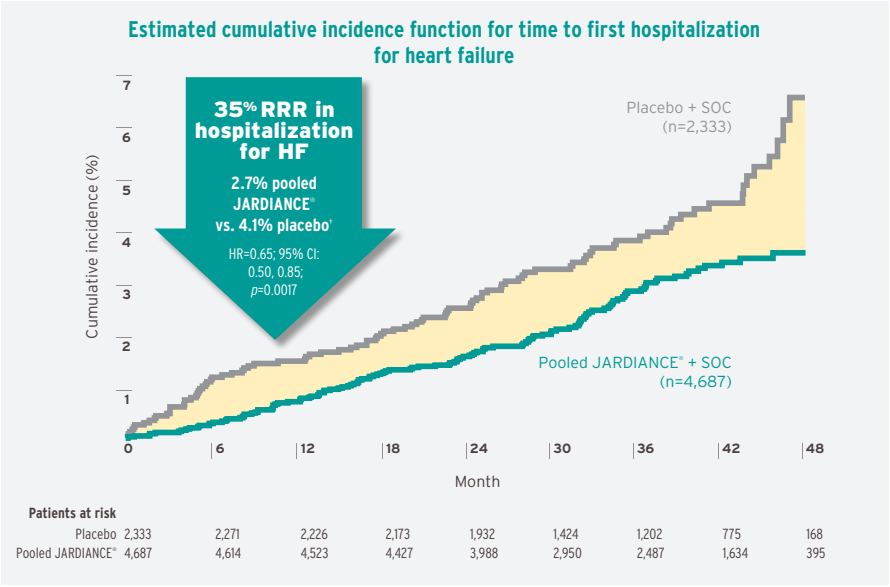
* Baseline therapies included: renin angiotensin system inhibitors (81%), beta-blockers (65%), diuretics (43%), anti-thrombotic therapy (89%), lipid-lowering medication (81%), metformin (74%), insulin (48%), sulfonylurea (43%).

† EMPA-REG OUTCOME study: double-blind, placebo-controlled, event-driven study evaluating empagliflozin 10 mg and 25 mg as add-on to standard of care therapy in reducing CV events in T2D patients with ≥1 of: coronary artery disease, peripheral artery disease, history of MI, history of stroke. Primary endpoint was time to first event in composite endpoint of CV death, non-fatal MI, or non-fatal stroke (Major Adverse Cardiovascular Events [MACE-3]).

‡ Pre-specified pooled analysis of JARDIANCE® 10 and 25 mg vs. placebo in the treated set (patients receiving ≥1 dose of study drug).

In patients with T2D and established CV disease

JARDIANCE®, as an adjunct to standard of care therapy*, **reduced the risk of heart failure requiring hospitalization** vs. placebo[1,2†‡] (other adjudicated endpoint)



Adapted from JARDIANCE® Product Monograph and Zinman B, et al.

Demonstrated NNT with JARDIANCE® for 3 years to prevent one hospitalization for HF

NNT=72

HF=heart failure.

* Baseline therapies included: renin angiotensin system inhibitors (81%), beta-blockers (65%), diuretics (43%), anti-thrombotic therapy (89%), lipid-lowering medication (81%), metformin (74%), insulin (48%), sulfonylurea (43%).

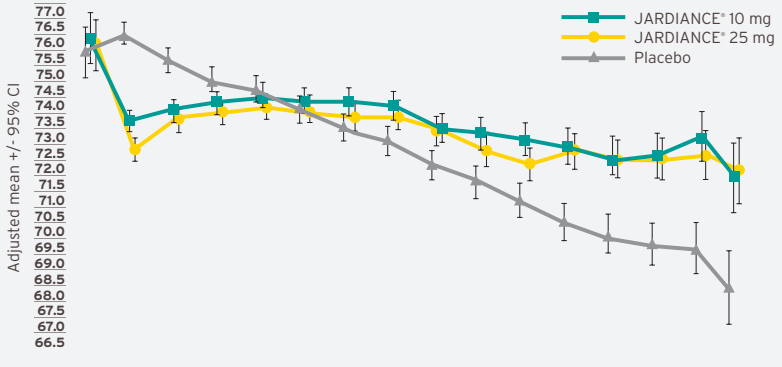
† EMPA-REG OUTCOME study: double-blind, placebo-controlled, event-driven study evaluating empagliflozin 10 mg and 25 mg as add-on to standard of care therapy in reducing CV events in T2D patients with ≥1 of: coronary artery disease, peripheral artery disease, history of MI, history of stroke. Primary endpoint was time to first event in composite endpoint of CV death, non-fatal MI, or non-fatal stroke (Major Adverse Cardiovascular Events [MACE-3]).

‡ Pre-specified pooled analysis of JARDIANCE® 10 and 25 mg vs. placebo in the treated set (patients receiving ≥1 dose of study drug).

RENAL CONSIDERATIONS

In the EMPA-REG CV outcomes trial, mean eGFR for JARDIANCE® groups showed initial decrease, then stabilized, whereas mean eGFR for placebo showed progressive decline.[1]

Time profile plot adjusted mean eGFR – JARDIANCE® 10 mg and 25 mg vs. placebo



n with data at visit

Placebo	2,323	2,295	2,267	2,205	2,121	2,064	1,927	1,981	1,763	1,479	1,262	1,123	977	731	448	171
JARDIANCE® 10 mg	2,322	2,290	2,264	2,235	2,162	2,114	2,012	2,064	1,839	1,540	1,314	1,180	1,024	785	513	193
JARDIANCE® 25 mg	2,322	2,288	2,269	2,216	2,156	2,111	2,006	2,067	1,871	1,563	1,340	1,207	1,063	838	524	216

Adapted from JARDIANCE® Product Monograph.

Increases in serum sodium and serum phosphate above upper limit of normal and decreases in serum potassium and serum bicarbonate below lower limit of normal occurred more frequently in patients receiving JARDIANCE® than those receiving placebo.

In the overall population, increases in serum creatinine and decreases in eGFR:[1]
In a pool of four placebo-controlled trials, mean change from baseline for:
- eGFR (mL/min/1.73 m^2) at Week 24 was -0.55, -1.41 and -0.32
- creatinine (µmol/L) was 0.66, 1.28 and 0.35

for JARDIANCE® 10 mg, 25 mg and placebo, respectively.

JARDIANCE® can be used in patients with eGFR 30 mL/min/1.73 m^2 and above[1]

JARDIANCE® is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease and patients on dialysis. The glucose-lowering benefit of JARDIANCE® decreases with declining renal function.

Assess renal function prior to and regularly during JARDIANCE® treatment. In patients with eGFR <60 mL/min/1.73 m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended (especially if eGFR <45 mL/min/1.73 m^2). Discontinue if eGFR falls below 30 mL/min/1.73 m^2 during treatment.

There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors.

eGFR=estimated glomerular filtration rate; BL=baseline.

Indications and clinical use not discussed elsewhere in the piece

Monotherapy: JARDIANCE® (empagliflozin) is 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.

Add-on combination: JARDIANCE® is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control, when metformin used alone does not provide adequate glycemic control, in combination with: metformin, metformin and a sulfonylurea, pioglitazone (alone or with metformin), linagliptin and metformin, basal or prandial insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

Important limitation of use: Use of JARDIANCE® with insulin mix (regular or analogue mix) has not been studied. Therefore, JARDIANCE® should not be used with insulin mix.

Contraindications

- Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease and patients on dialysis

Most serious warnings and precautions

Diabetic ketoacidosis (DKA): Cases of DKA, a serious, life-threatening condition requiring urgent hospitalization, have been reported for JARDIANCE® or other SGLT2i, including fatal cases for patients taking JARDIANCE® and atypical cases with blood glucose <13.9 mmol/L (250 mg/dL). Consider the risk of DKA if non-specific symptoms occur, regardless of blood glucose level, and **immediately discontinue JARDIANCE® and assess for DKA**. JARDIANCE® should not be used for the treatment of DKA or in patients with a history of DKA. JARDIANCE® is not indicated, and should not be used, in patients with type 1 diabetes.

Other relevant warnings and precautions

- Not recommended in volume-depleted patients; drops in blood pressure; monitor volume status and electrolytes
- Caution in patients at high risk for cerebrovascular accidents
- Temporarily discontinue in situations predisposing to ketoacidosis
- Caution when reducing concomitant insulin dose
- Hypoglycemia when used in combination with insulin secretagogues or insulin
- Risk and monitoring of LDL-C increases
- Genital mycotic infections
- Urinary tract infections
- Necrotizing fasciitis of the perineum (Fournier's gangrene)
- Caution in patients with elevated hematocrit
- Not recommended in patients with severe hepatic impairment
- Serious hypersensitivity reactions
- Intravascular volume contraction, increases in serum creatinine, decreases eGFR; assess renal function prior to initiation and regularly during treatment thereafter; monitor renal function with concomitant drug use; more intensive monitoring if eGFR <60 mL/min/1.73 m^2 (especially if eGFR <45 mL/min/1.73 m^2); discontinue if eGFR <30 mL/min/1.73 m^2
- Acute kidney injury
- Use in settings of reduced oral intake or fluid loss
- Do not use during pregnancy or breastfeeding
- Do not use in patients <18 years; caution in patients ≥65 years and ≥75 years; not recommended in patients ≥85 years
- Patients will test positive for glucose in urine

For more information

Refer to the Product Monograph at www.JardiancePM.ca for important information relating to adverse events, drug interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling 1-800-263-5103 ext. 84633.

SGLT2i=sodium-glucose co-transporter 2 inhibitors; LDL-C=low-density lipoprotein cholesterol.

References: 1. JARDIANCE® Product Monograph, Boehringer Ingelheim (Canada) Ltd., April 15, 2020. **2.** Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;373(22):2117–28. **3.** U.S. National Library of Medicine – ClinicalTrials.gov. BI 10773 (Empagliflozin) Cardiovascular outcome event trial in type 2 diabetes mellitus patients (EMPA-REG OUTCOME). Available at: https://clinicaltrials.gov/ct2/show/study/NCT01131676?term=EMPA-REG+OUTCOME&draw=2&rank=1&show_locs=Y#locn. **4.** U.S. National Library of Medicine – ClinicalTrials.gov. EMPA-KIDNEY (The study of heart and kidney protection with empagliflozin). Available at: https://clinicaltrials.gov/ct2/show/NCT03594110. **5.** U.S. National Library of Medicine – ClinicalTrials.gov. A study to test the effect of empagliflozin in patients who are in hospital for acute heart failure. Available at: https://clinicaltrials.gov/ct2/show/NCT04157751?term=EMPULSE&draw=1&rank=1. **6.** U.S. National Library of Medicine – ClinicalTrials.gov. Empagliflozin and cardiac remodelling in people without diabetes (EMPA-HEART 2). Available at: https://clinicaltrials.gov/ct2/show/NCT04461041?term=NCT04461041&draw=2&rank=1.

ONGOING TRIALS

Follow along the empagliflozin journey, study by study...

Name	Objective
EMPA-KIDNEY[4]	To evaluate the effect of empagliflozin on kidney disease progression or CV death vs. placebo on top of SOC in patients with pre-existing chronic kidney disease *NOTE: empagliflozin is not indicated for the treatment of kidney disease*
EMPULSE[5]	To evaluate the effect of in-hospital administration of empagliflozin on HF-related clinical events and patient-reported outcomes (death, HFE and KCCQ-TSS) as a measure of health status (symptoms and physical limitations) in patients hospitalized for acute HF (de novo or decompensated chronic HF) after initial stabilization *NOTE: empagliflozin is not indicated for the treatment of acute heart failure*
EMPA-HEART 2[6]	To evaluate the effects of empagliflozin on cardiac structure, function and circulating biomarkers in patients with CV risk factors, but without diabetes *NOTE: empagliflozin is not indicated for the treatment of patients without T2D or patients with CV risk factors*

HFE=heart failure event; KCCQ-TSS=Kansas City Cardiomyopathy Questionnaire – Total Summary Score; LV=left ventricular; cMRI=cardiac magnetic resonance imaging.

EMP-CA-101093
EMP-LI-101093

Boehringer Ingelheim

Lilly