

## EMPA-REG: CV Outcomes Trial Summary

### Empagliflozin: Cardiovascular (CV) Outcomes and Mortality in Patients with Type 2 Diabetes Mellitus (T2DM)

In patients with T2DM and at high risk of CV events, does empagliflozin reduce CV risk compared to placebo when added to standard care?

#### BOTTOM LINE <sup>1</sup>

- Empagliflozin compared to placebo in a high CV risk population:
  - Benefit: reduced risk of composite cardiovascular events (NNT=63/3yrs) and all cause death (NNT=38/3yrs)
    - The 10mg daily dose provided virtually the same benefit as the 25mg dose. Cost about \$300/100days.
    - Benefit realized despite A1C not reaching target (A1C=7.8%); mean change was approximately ≤ 0.6%
  - Harm: increased risk of genital infections in both males (NNH=29/3yrs) and females (NNH=14/3yrs). Urosepsis, although rare, was also increased with empagliflozin (~ 0.4% vs 0.1%). Overall serious adverse events (SAE) were less with empagliflozin than placebo (NNT=24). However see also “uncertainties” section for concerns raised previously.
- Of interest:
  - Empagliflozin also lowered BP (SBP ↓ 3-4mm Hg; DBP ↓1-2 mm Hg) and weight (↓ 1-2kg) more than seen in placebo group. Given the lack of CV benefits in other shorter term trials with glucose lowering agents, the benefit seen in EMPA-REG, if true, may relate to a non-glucose related mechanism.
  - Average A1C achieved in the empagliflozin group was 7.8%. The only other short-term trial (<5 years) in T2DM that found a mortality difference was ACCORD (aggressive vs standard glycemic control), which was stopped early due to a lower risk of mortality in the less aggressive control group (A1C mean ~ 7.5%).
- Remember usual care for T2DM with CVD: lifestyle, risk reduction with antihypertensive treatment, statins, ASA, & metformin.

#### BACKGROUND <sup>1</sup>

- Empagliflozin (JARDIANCE  $\square$   $\square$ ) is a sodium-glucose cotransporter 2 inhibitor (SGLT2-I) approved in 2015 for use in patients with type 2 diabetes as monotherapy or as an add-on to metformin alone, metformin + SU, pioglitazone +/- metformin, or insulin +/- metformin.
- Evidence that glucose lowering agents decrease the risk of CV events has not been convincingly shown in any study to date.<sup>1</sup> Also, some glucose lowering agents (e.g. thiazolidinediones) may increase the risk of CV events, heart failure, & other serious adverse events.

#### TRIAL BACKGROUND

**DESIGN:** Randomized, double-blind, placebo-controlled trial; allocation concealed; international, multisite; 2 week open-label run-in

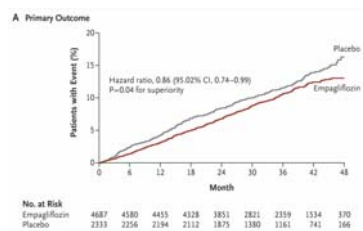
**INTERVENTION:** Empagliflozin 10mg or 25mg once daily vs. placebo, added to existing therapy. (Phase 3, noninferiority design)

**INCLUSION: T2DM, Age ≥18yrs, BMI ≤ 45, eGFR ≥30mL/min/1.73m<sup>2</sup>, established CVD, no glucose-lowering tx for ≥12wks before randomization + A1C of 7-9%, or received stable glucose-lowering tx for ≥12wks before randomization + A1C of 7-10%**

**EXCLUSION:** Uncontrolled hyperglycemia (FPG >13mmol/L), liver dx, eGFR <30mL/min/1.73m<sup>2</sup>, steroid tx, change in thyroid hormones within 6wks of informed consent, hx of cancer, ACS/TIA/stroke within prior 2 months, planned cardiac surgery within prior 3 months, bariatric surgery within the past 2 years or any GI surgery that induces chronic malabsorption, tx with anti-obesity medications 3 months prior, pre-menopausal women not practicing acceptable birth control, alcohol or drug abuse within 3 months of informed consent.

**POPULATION at baseline** ..... n = 7,020: age 63 ± 8.8yrs; ~71% ♂; eGFR ~74 ± 21(mL/min/1.73m<sup>2</sup>)

- Presence of CV Risk Factors ..... (includes: CAD 76%, hx MI 47%, CABG 25%, hx stroke 23%, PAD, single/multi-vessel CAD 57%, HF 10%): ~99%
- A1C; BMI; Weight: ..... ~8.07% ± 0.85; BMI (kg/m<sup>2</sup>): 30.6 ± 5.3; Weight (kg): ~86 ± 19
- Time Since Diagnosis of T2DM: ..... ≤1yr ~2.6%; >1-5yr ~15.5%; >5-10yr ~24.8%; >10yr ~57.2%
- Race/Ethnicity: ..... White ~72%; Asian ~22%; African-American/Black ~5.1%; Other ~1.0%
- Other Glucose Lowering Tx: ..... Metformin ~74%; Insulin ~48% (median daily dose~53 IU); SU~42%; DPP4-I~11%; TZD ~4%; GLP1-A~3%; monox~30% vs dual tx~49%
- Anti-HTN Tx: ..... Total ~95% {ACEI/ARB~80%; BB~65%; Diuretics~43%; CCBs~33%}
- Lipid-Lowering Tx: ..... Total ~81% {Statins~77%; Fibrates~9%; Ezetimibe~4%}
- Other : ..... ASA~83%; SBP ~ 135.5 ± 17mmHg; DBP~76.7±10



#### RESULTS

follow-up: Mean 3yrs/Median 3.1yrs

CLINICAL ENDPOINTS ITT ANALYSIS	NON-INFERIORITY DATA		SUPERIORITY DATA		{NNT/H = number needed to Treat for Benefit / Harm}		COMMENTS	
	EMPAGLIFLOZIN (10MG & 25MG) n=4687	PLACEBO n=2333	HR (95% CI)	P VALUE	ARR/ARI	NNT/NNH /3.1YRS		
<b>PRIMARY ENDPOINT</b>								
Death from CV causes, non-fatal MI, or non-fatal stroke	10.5% (n=490)	12.1% (n=282)	0.86 (0.74-0.99)	<0.001 0.04	↓1.6%	63	<ul style="list-style-type: none"> <li>• A1C ↓ by 0.6% or less.</li> <li>• Systolic BP ↓ by 3-4mmHg</li> <li>• Weight ↓ by 1-2 kg</li> </ul>	
<b>SECONDARY ENDPOINTS</b>								
1° endpoint plus hospitalization for unstable angina	12.8% (n=599)	14.3% (n=333)	0.89 (0.78-1.01)	<0.001 0.08	↓1.5%	67		
All-cause Death	5.7% (n=269)	8.3% (n=194)	0.68 (0.57-0.82)	<0.001	↓2.6%	38		
CV Death	3.7% (n=172)	5.9% (n=137)	0.62 (0.49-0.77)	<0.001	↓2.2%	45		
Hospitalization for HF	2.7% (n=126)	4.1% (n=95)	0.65 (0.50-0.85)	0.002	↓1.4%	71		
Hospitalization for HF or death from CV causes excluding fatal stroke	5.7% (n=265)	8.5% (n=198)	0.66 (0.55-0.79)	<0.001	↓2.8%	36	Consistent benefit on HF endpoints whether HF pre-existent or not.	

Non-significant 2° outcomes; Trend for better outcome on empagliflozin: fatal or non-fatal MI excluding silent MI, non-fatal MI, silent MI, hospitalization for unstable angina, coronary revascularization procedure, and TIA. Trend for worse on empagliflozin: fatal or nonfatal stroke, silent MI.

**TABLE 2: ADVERSE EVENTS (AE)**

CLINICAL ENDPOINTS	EMPAGLIFLOZIN	EMPAGLIFLOZIN		PLACEBO n=2333	P VALUE	ARR/ARI (POOLED)	NNT/NNH /3.1yrs	COMMENTS
	POOLED n=4687	10MG n=2345	25MG n=2342					
Severe AE	23.5% (n=1100)	22.9% (n=536)	24.1% (n=564)	25.4% (n=592)	<0.05	↓ 1.9%	53	Proportion of patients with confirmed hypoglycemic events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture and volume depletion were similar in the two study groups  Urosepsis greater in empagliflozin group (0.4% vs 0.1%) <sup>FDA warning</sup>  NOTE: AE due to placebo should take into account differences in usual care in placebo group, ie. higher rate of insulin use, gliclazide use, etc.
Serious AE (Any)	38.2% (n=1789)	37.4% (n=876)	39.0% (n=913)	42.3% (n=988)	<0.001	↓ 4.1%	24	
Serious AE (Death)	3.8% (n=176)	4.1% (n=97)	3.4% (n=79)	5.1% (n=119)	<0.01	↓ 1.3%	77	
AE leading to D/C of study drug	17.3% (n=813)	17.7% (n=416)	17.0% (n=397)	19.4% (n=453)	<0.01	↓ 2.1%	48	
UTI (♀)	36.4% (n=492)	35.5% (n=246)	37.3% (n=246)	40.6% (n=265)	<0.05	↓ 4.2%	24	
UTI (♂)	10.5% (n=350)	10.9% (n=180)	10.1% (n=170)	9.4% (n=158)	—	—	—	
Genital Infection (♀)	10.0% (n=135)	9.2% (n=64)	10.8% (n=71)	2.6% (n=17)	<0.001	↑ 7.4%	14	
Genital Infection (♂)	5.0% (n=166)	5.4% (n=89)	4.6% (n=77)	1.5% (n=25)	<0.001	↑ 3.5%	29	
Acute Renal Failure	5.2% (n=246)	5.2% (n=121)	5.3% (n=125)	6.6% (n=155)	<0.01	↓ 1.4%	71	
Acute Kidney Injury	1.0% (n=45)	1.1% (n=26)	0.8% (n=19)	1.6% (n=37)	<0.05	↓ 0.6%	167	

Non-significant AE include: confirmed hypoglycemic AE, complicated UTI, volume depletion, diabetic ketoacidosis, thromboembolic event, bone fracture

**STRENGTHS, LIMITATIONS, & UNCERTAINTIES**

**STRENGTHS:**

- Important trial examining SGLT2-I and CV efficacy & safety outcomes.
- Trial size fairly large. Baseline demographics were well balanced between placebo and empagliflozin groups.
- Primary outcome and death from CV were largely consistent (homogeneity) within subgroups. However, some pts age <65, A1C >8.5%, on TZD did worse with empa vs. placebo for primary outcome. Those with Black/African-American ancestry also did worse with empa vs. placebo for primary outcome.
- >99% of patients had established CVD and were treated in regards to lipid-lowering therapy and antihypertensive medications.<sup>1</sup>
- Few patients lost to follow-up: 97% completed study & 99% had known vital status.

**LIMITATIONS:**

- 25.4% of patients prematurely discontinued a study drug<sup>1</sup> (23.4% in empagliflozin vs. 29.3% in placebo); this is despite the 2 week open-label run-in which would eliminate most who do not tolerate the drug acutely.
- Lack of a dose-response curve (10mg arm and 25mg had equivalent outcomes).
- Funded by Boehringer Ingelheim & Eli Lilly; employees had active role on steering committee, & in analysis of data & writing.

**UNCERTAINTIES:**

- Trials with other glucose-lowering agents have shown neutral or poor CV outcomes (e.g. SAVOR-TIMI 53, EXAMINE, TECOS, ELIXA); why would this trial have better results? (Is the difference real or due to chance?)
- If the benefit found represents a true benefit, was the mechanism possibly related to the reduction in BP? Benefit appeared earlier in trial than would be expected if attributable to glycemic control alone. In addition, the achieved A1C in the empagliflozin group was around 7.8% - only about 0.6% lower than the placebo group, and much higher than generally recommended in current diabetes guidelines.
- Disproportionally greater use of insulin & SU in placebo group supporting hypothesis that hyperinsulinemia associated with harm.
- Were some of the benefits of this drug actually due to placebo group getting more dangerous drugs (e.g. pioglitazone, etc) as part of the "usual care" group? More people in the placebo group got insulin, DPP4s, sulphonylureas, metformin, TZDs, and GLP1s; 3x as many patients received a TZD in the placebo group (although absolute numbers were low). A subgroup analysis states these extra drugs weren't driving the results; however, it would only have taken a few extra negative events in the placebo group to change the results of this study.
- Is this a class effect? Awaiting other outcome trials - e.g. **CANVAS** canagliflozin, **DECLARE** dapagliflozin - to see if the other SGLT2 inhibitors have the same apparent CV benefits.
- What is the applicability of these results to patients with diabetes but no CVD (primary prevention)?
- Are SGLT2 inhibitors safe in those with renal dysfunction (CKD > stage 3)? Concerns have been raised about acute kidney injury.
- FDA Committee meeting June/16: discussion about the 124 non-assessable deaths & adjudicated as presumed CV deaths that occurred in the trial & if that would alter the results.  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM508422.pdf>
- Several concerns regarding serious adverse effects with empagliflozin use have been raised outside of this trial:
  - Euglycemic diabetic ketoacidosis and urosepsis with SGLT2 inhibitors (FDA Dec 2015).
  - Fractures (canagliflozin) and reduced bone mineral density (FDA Sep 2015).
  - Acute kidney injury (canagliflozin & dapagliflozin) FDA June/16

**RELATED RxFiles LINKS**

- RxFiles Diabetes Agents Outcomes Table: <http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf>
- RxFiles Diabetes – Landmark Trials and Links: <http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf>

X = non-formulary in SK ⊕ = not covered by NIHB ⊖ = Exceptional Drug Status in SK ♀ = female ♂ = male AE = adverse event ACS = acute coronary syndrome BMI = body mass index CAD = coronary artery disease CVD = cardiovascular disease DPP4-I = dipeptidyl peptidase-4 inhibitor dx = disease GI = gastrointestinal GLP1-A = glucagon-like peptide-1 agonist HF = heart failure MI = myocardial infarction PAD = peripheral artery disease SGLT2-I = sodium glucose cotransporter 2 inhibitor SU = sulphonylurea T2DM = type 2 diabetes mellitus TIA = transient ischemic attack tx = treatment TZD = thiazolidinedione UTI = urinary tract infection

**References:**

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2. Ceriello A, Genovese S, Mannucci E, Gronda E. Understanding EMPA-REG OUTCOME. Lancet Diabetes Endocrinol. 2015 Dec;3(12):929-930.
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**Additional references:**

Health Canada May/16 SGLT2 Inhibitors [INVOKANA (canagliflozin), FORXIGA (dapagliflozin), XIGDUO (dapagliflozin/metformin), JARDIANCE (empagliflozin)] - Risk of Diabetic Ketoacidosis - Janssen Inc., Boehringer Ingelheim (Canada) Ltd. Serious, sometimes life-threatening and fatal cases of diabetic ketoacidosis (DKA) have been reported in patients on sodium glucose co-transporter 2 (SGLT2) inhibitors for type 1 and type 2 diabetes. In a number of these cases, the presentation of the condition was atypical with only moderately increased blood glucose levels observed. SGLT2 inhibitors are NOT indicated for treatment of type 1 diabetes mellitus and should not be used in type 1 diabetes.

Mancia G, Cannon CP, Tikkanen I, et al. Impact of Empagliflozin on Blood Pressure in Patients With Type 2 Diabetes Mellitus and Hypertension by Background Antihypertensive Medication. (Empa-Reg) Hypertension.2016 ;68 :000-000.

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Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and **progression of kidney disease** in type 2 diabetes. (Empa-Reg Outcome) N Engl J Med. DOI: 10.1056/NEJMoa1515920.

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