Potential Mechanisms of Cardiovascular Benefit for Empagliflozin

Steven E. Nissen MD MACC
Chairman, Department of Cardiovascular Medicine
Cleveland Clinic

Disclosure

Consulting: Many pharmaceutical companies
Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.

The Context for EmpaReg: An Editorial Comment

• During the last decade, the cardiovascular and diabetes communities have come a long way together. Although CV disease is the leading cause of death in diabetes:

  – Prior to 2008, there existed no comparative effectiveness trials evaluating macrovascular outcomes for diabetes drugs.

• A pivotal recommendation by the FDA Endocrine and Metabolism Panel in 2008 led to a controversial diabetes guidance and an explosion of CV outcome trials.

• We are now reaping the harvest from that courageous decision.
New era of research on outcomes with diabetes drugs

Regarding Empagliflozin: A Caveat

- It is impossible to “prove” the mechanism of benefit for most drugs, particularly agents with complex biological effects such as SGLT2 inhibitors.

- Accordingly, we can only speculate about potential explanations for the favorable cardiovascular effects observed with empagliflozin.

The Principle of Occam’s Razor

The simplest of several hypotheses is generally the best in accounting for unexplained facts.
Effect of Empagliflozin on Death, Stroke, and MI

HR 0.86
(95% CI 0.74, 0.99)

\[ P=0.04 \]

Reasonably Well-Understood Mechanisms

- Reduction in glycemia without an increase in insulin levels
- Decrease in blood pressure without sympathetic activation
  - Improved cardiac function due to left ventricular unloading
  - Reduced ischemia due to lowered oxygen demand (reduced rate-pressure product)
- Favorable effects on body weight
  - With reduced visceral adiposity
More Speculative Beneficial Effects

- Chronic sodium depletion
- Reduction in oxidative stress
- Reduction in uric acid levels
- Increased glucagon levels
- Increased HDL-cholesterol with minimal LDL increase
- Alteration in cardiac metabolism

EmpaReg: Cardiovascular Risk at Baseline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (N = 2333)</th>
<th>Pooled Empagliflozin (N = 4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>75.6%</td>
<td>46.5%</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>47.1%</td>
<td>46.5%</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>46.4%</td>
<td>46.7%</td>
</tr>
<tr>
<td>Coronary bypass graft surgery</td>
<td>24.1%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>23.7%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>20.5%</td>
<td>21.0%</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>10.5%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>
Effect of Empagliflozin on HbA1c Levels

Estimated mean difference = 0.4%

UKPDS: Impact of HbA1c on CV Outcomes

Fatal and Non-fatal MI

P < 0.0001
14% increase per 1%

Hazard Ratio

Fatal and Non-fatal Stroke

P < 0.035
12% increase per 1%

Hazard Ratio

Amputation/Death from PVD

P < 0.0001
43% increase per 1%

Hazard Ratio

Heart Failure

P < 0.021
16% increase per 1%

Hazard Ratio

UKPDS Brit Med J 2000;321:405
UKPDS: HbA1c vs. Rates for Myocardial Infarction and Microvascular Complications

![Graph showing the adjusted incidence of myocardial infarction and microvascular endpoints vs. updated mean HbA1c concentration.]

Adjusted Incidence per 1,000 Person Years (%)


Comparative Rates of Severe Hypoglycemia

Proportion of Patients with at Least One Event Each Year

In the EmpaReg trial, identical rates of hypoglycemia were observed for empagliflozin and placebo.
Effect of Empagliflozin on Systolic Blood Pressure

Adjusted mean systolic blood pressure over weeks for placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg groups.

Effect of Empagliflozin on 24-hour Ambulatory Blood Pressure (Mean Baseline 131 mm Hg)

Mean change from baseline in 24-hour SBP (mmHg) for placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg groups.

Difference vs. placebo: -3.44 mmHg for Empagliflozin 10 mg and -4.16 mmHg for Empagliflozin 25 mg.
P < 0.001 for both.

Blood Pressure Reduction and CV outcome

Insights derived from UKPS

UK Prospective Diabetes Study. BMJ 1998:317

Rates of MI and Microvascular Endpoints by Systolic Blood Pressure: UKPDS

Adjusted for age, sex, and ethnic group
Concept

• The benefits of blood pressure reduction are highly dependent on the characteristics of the population studied.

• In the case of EmpaReg, a very high cardiovascular risk population was studied.

CAMELOT Study Design

Comparison of Amlodipine versus Enalapril to Limit Ischemic Occurrences of Thrombosis

2000 Patients

PTCA & Angiogram

Amlodipine 10 mg

Enalapril 20 mg

Placebo

100 sites

24 Months

Prospective, Randomized, Double Blind, Multicenter

Endpoints: CHD Death, Resuscitated Arrest, Nonfatal MI, Stroke, TIA, CABG, Revascularization, Unstable Angina, Hospitalized CHF

Systolic Pressure: All Three Treatment Groups

Mean difference 4.8 mmHg

CAMELOT: Time to Major Cardiovascular Event

Amlodipine vs. Placebo
HR = 0.69 (95% CI 0.54-0.88)
P = 0.003

Meta-Analysis: Cardiovascular Outcomes in Placebo-Controlled Trials of Thiazide Diuretics

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>RR (95% CI)</th>
<th>$i^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>0.67 (0.56-0.81)</td>
<td>37%</td>
</tr>
<tr>
<td>Thiazide-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary events</td>
<td>0.81 (0.63-1.05)</td>
<td>38%</td>
</tr>
<tr>
<td>Thiazide-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>0.52 (0.38-0.69)</td>
<td>25%</td>
</tr>
<tr>
<td>Thiazide-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.36 (0.16-0.84)</td>
<td>14%</td>
</tr>
<tr>
<td>Thiazide-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.86 (0.75-1.00)</td>
<td>12%</td>
</tr>
<tr>
<td>Thiazide-type</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors thiazide  Favors placebo

Rik et al. Hypertension. 2015;65:1033-1040

SGLT2 Inhibitors vs. Diuretics:

- Like diuretics, SGLT2 inhibitors result in transient natriuresis, increased urine volume, reduction in plasma volume with some degree of RAS activation.

- Unlike diuretics, these drugs produce glucosuria:
  - Osmotic diuresis, caloric loss and glucose-lowering (thiazide diuretics tend to increase blood glucose)
  - Lowering of uric acid (thiazides increase uric acid)
  - Increased sodium delivery to macula densa
  - No changes in serum potassium
  - Possibly no activation of sympathetic tone
Diurnal Pattern in Hourly Mean Systolic BP during 12-week ABPM Study With Empagliflozin

Absence of Sympathetic Activation

The blood pressure reduction in the EmpaReg Trial was not accompanied by reflex increases in sympathetic activity.
Effect of Empagliflozin on Heart Rate

Adjusted mean (SE) heart rate (bpm)

Week

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg

Effect of Empagliflozin on Rate-Pressure Product in Two Treatment Cohorts

Change in Rate-Pressure Product

P < 0.001 for both cohorts

Diabetes, Obesity and Metabolism 17: 1180–1193, 2015
Importance of Rate Pressure Product

Myocardial Oxygen Demand

\[ \text{MVO}_2 = 0.08 (HR \times BP \times 10^{-2}) - 0.15 \]

\( r = 0.83 \)


Effect of Empagliflozin on Body Weight

Adjusted mean weight (kg)

Week

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg
Cardiovascular Outcomes: Look Ahead

Percent of Patients with a Cardiovascular Event (%)

HR = 0.95
95% CI 0.83-1.09
P = 0.51

Effect of Empagliflozin on Waist Circumference

A surrogate for visceral fat?

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg
Change in Fat and Lean Mass over Two Years
Glimepiride vs. Empagliflozin with Metformin

<table>
<thead>
<tr>
<th>Percent Change after Two Years Treatment</th>
<th>Glimepiride</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>0.4</td>
<td>-1.9</td>
</tr>
<tr>
<td>Lean</td>
<td>1.0</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

Ridderstråle et al. Lancet Diabetes Endocrinol 2014

Effect of Weight Reduction on C-reactive Protein

Arch Intern Med. 2007;167:31-39
Effect of Empagliflozin on LDL-Cholesterol

Effect of Empagliflozin on HDL-Cholesterol
Effect of Empagliflozin on Cardiovascular Death

HR 0.62
(95% CI 0.49, 0.77)
$\ p<0.0001$

Emerging Risk Factor Collaborative: Years of Life Lost Due to Diabetes

HR for all cause mortality 1.80 (mean adjusted years lost 6.0)

BP Reduction and All-Cause Mortality

ADVANCE

Cumulative incidence (%)

Follow-up (months)

Relative risk reduction 14%
95% CI 2-25%
p=0.025

Effect of Empagliflozin on Death by Cause

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 2333)</th>
<th>Pooled Empagliflozin (N= 4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiovascular deaths</td>
<td>5.9%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Worsening of heart failure</td>
<td>0.8%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Other cardiovascular death</td>
<td>2.4%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
Effect of Empagliflozin on CHF Hospitalization

HR 0.65
(95% CI 0.50, 0.85)
p = 0.002

Many Unanswered Questions

• Do the results of the EmpaReg Trial reflect a “class effect”?

• Will other ongoing SGLT2 inhibitor trials show similar or different cardiovascular effects?
  – These agents are all different in subtle ways, particularly the balance of SGLT2 and SGLT1 inhibition.

• How do we explain the large reduction in cardiovascular death and hospitalization for heart failure.
Multifactorial Management in Diabetes
The STENO 2 Study – 13 Years of Follow-Up

*Composite endpoint: CV-death, MI or stroke, CABG or PCI, limb amputation or vascular surgery*

Cumulative incidence of CV events (%)

Conventional therapy

Intensive therapy

A Final Thought

The courageous decision by the FDA Panel to require cardiovascular outcome trials for diabetes drugs has yielded a large number of high quality clinical trials. EmpaReg is the first to show a favorable macrovascular effect, but it won’t be the last. Recently, another agent, liraglutide was reported to show favorable effects. These developments portend a huge change in the outlook for patients with diabetes, ushering an era where we can finally offer glucose-lowering therapies with the promise of longer life with freedom from cardiovascular morbidity.