Potential Mechanisms of Cardiovascular Benefit for Empagliflozin

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Disclosure

Consulting: Many pharmaceutical companies

Clinical Trials: Amgen, AstraZeneca, Eli Lilly, Novartis, Novo Nordisk, The Medicines Company, Cerenis, Orexigen, Takeda, Vivus, and Pfizer.

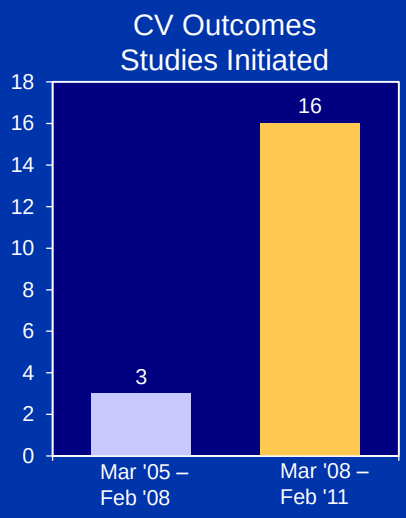
Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.

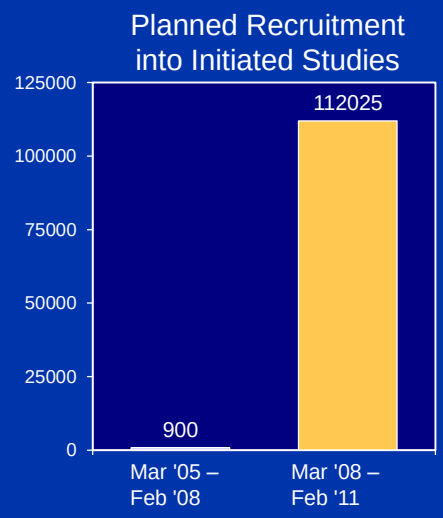
The Context for EmpaReg: An Editorial Comment

- 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.

Result of FDA Policy Change

New era of research on outcomes with diabetes drugs





Bethel MA and Sourij H. *Curr Cardiol Rep* 2012;14:59–69

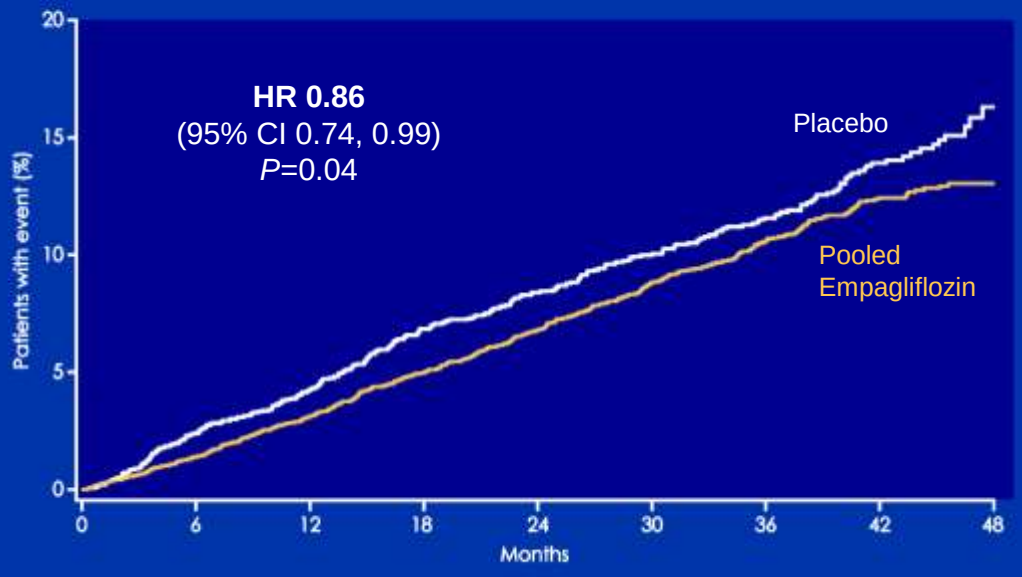
Regarding Empagliflozin: A Caveat

- 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



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

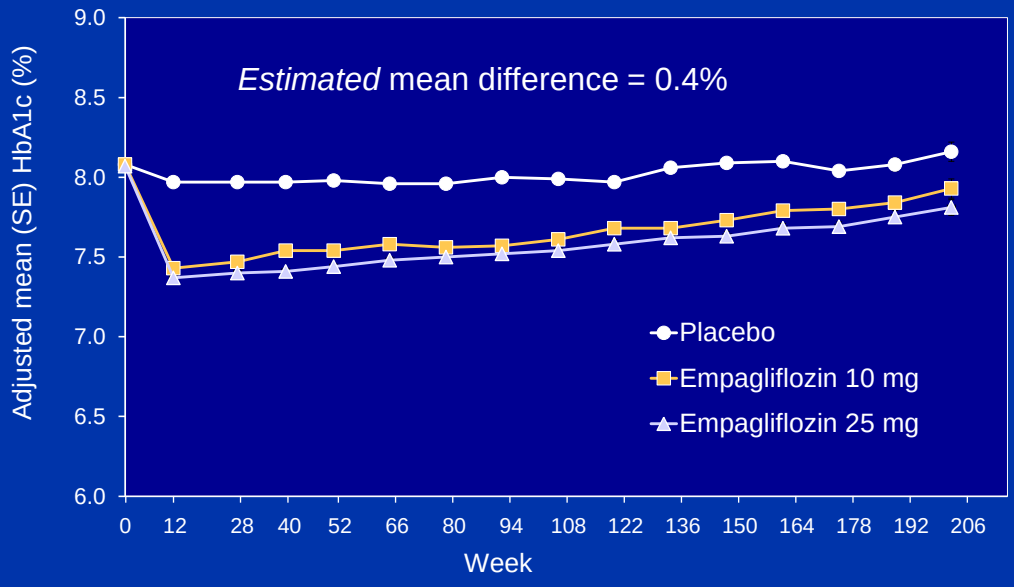
More Speculative Beneficial Effects

- 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

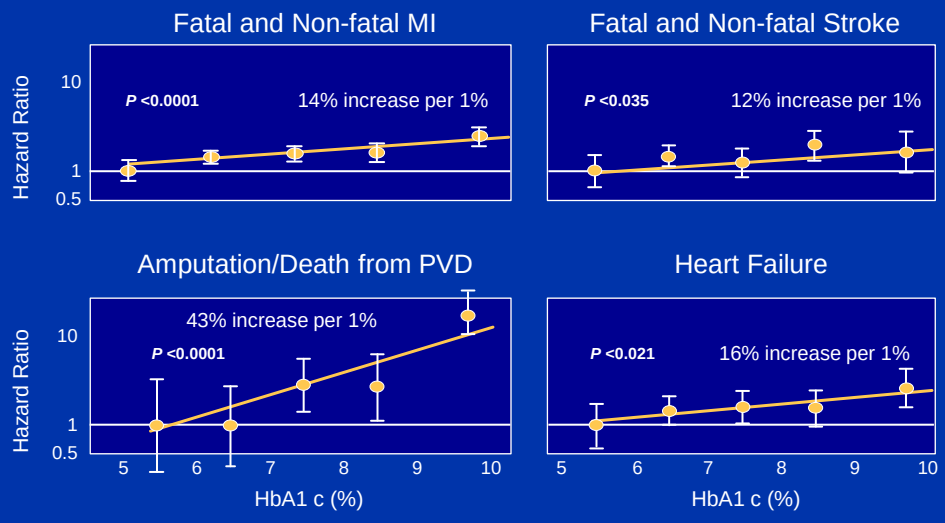
EmpaReg: Cardiovascular Risk at Baseline

	Placebo (N = 2333)	Pooled Empagliflozin N= 4687)
Coronary artery disease	75.6%	46.5%
Multivessel CAD	47.1%	46.5%
History of myocardial infarction	46.4%	46.7%
Coronary bypass graft surgery	24.1%	25.1%
Prior stroke	23.7%	23.1%
Peripheral arterial disease	20.5%	21.0%
History of heart failure	10.5%	9.9%

Effect of Empagliflozin on HbA1c Levels

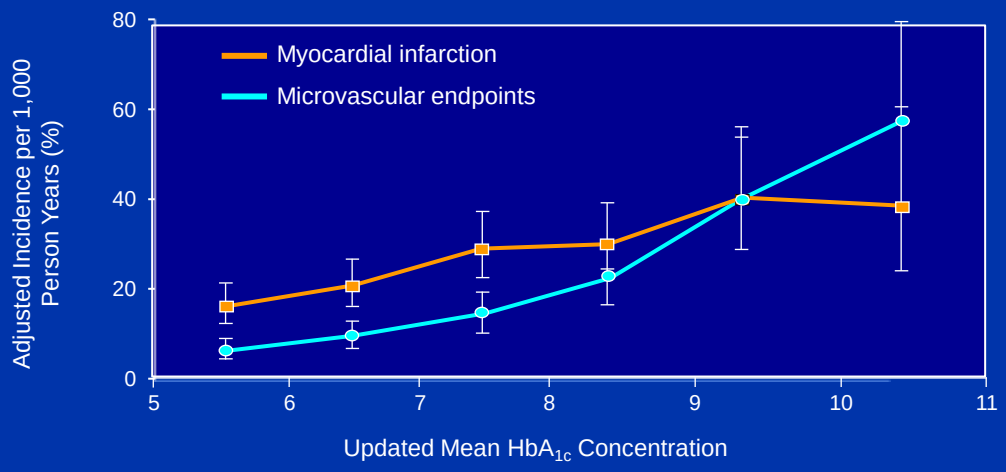


UKPDS: Impact of HbA1c on CV Outcomes



UKPDS Brit Med J 2000;321:405

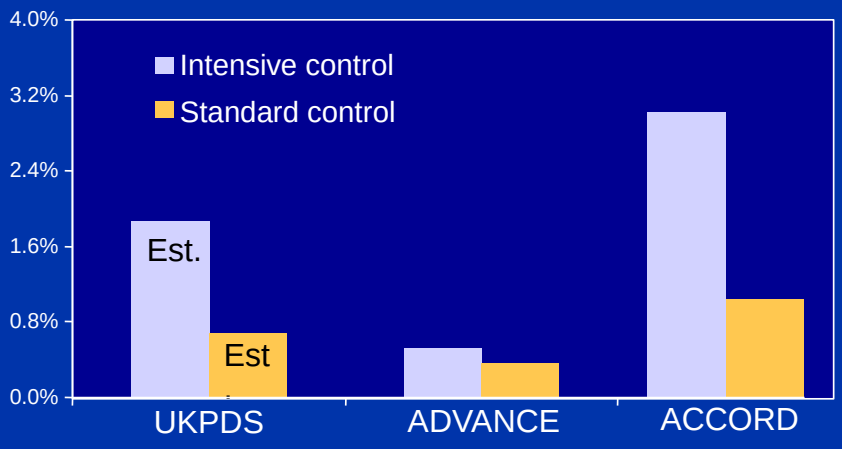
UKPDS: HbA1c vs. Rates for Myocardial Infarction and Microvascular Complications



Stratton IM, et al. *BMJ.* 2000;321:405–412; reproduced with permission from the BMJ Publishing Group.

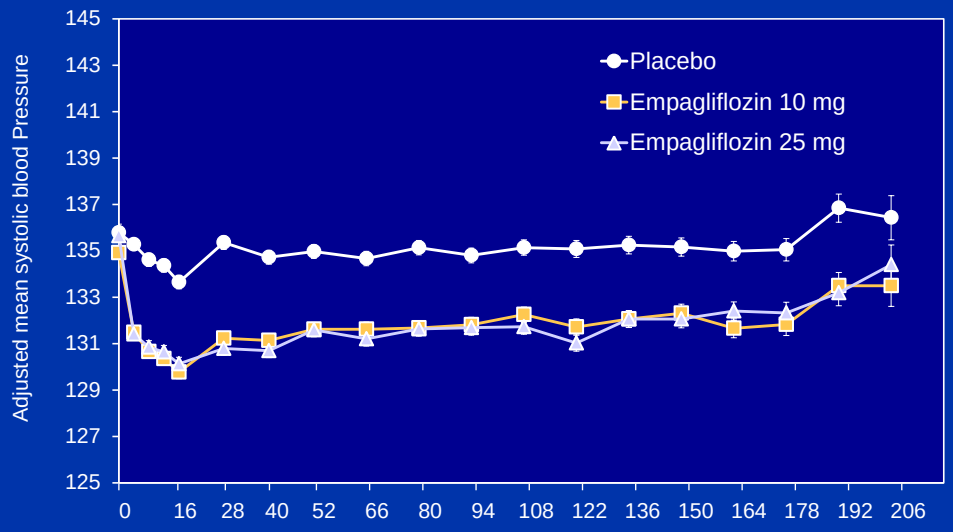
Comparative Rates of Severe Hypoglycemia

Proportion of Patients with at Least One Event Each Year

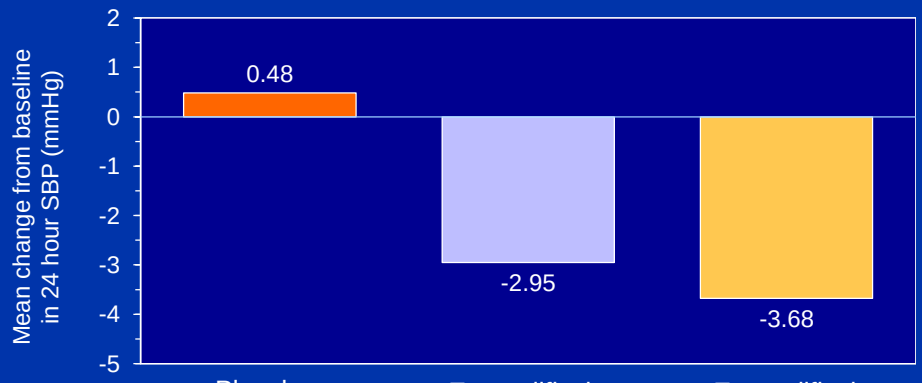


In the EmpaReg trial, identical rates of hypoglycemia were observed for empagliflozin and placebo

Effect of Empagliflozin on Systolic Blood Pressure



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



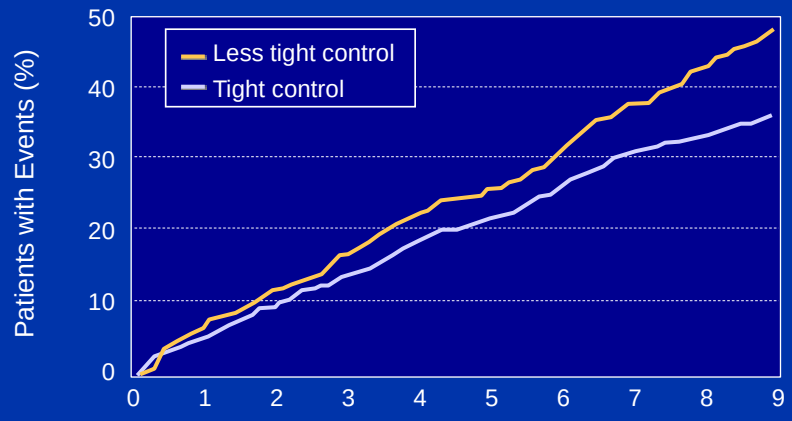
Difference vs. placebo -3.44 mmHg -4.16 mmHg

P <0.001 for both

Tikkanen I *et al*. *Diabetes Care* 2015;38:420–428.

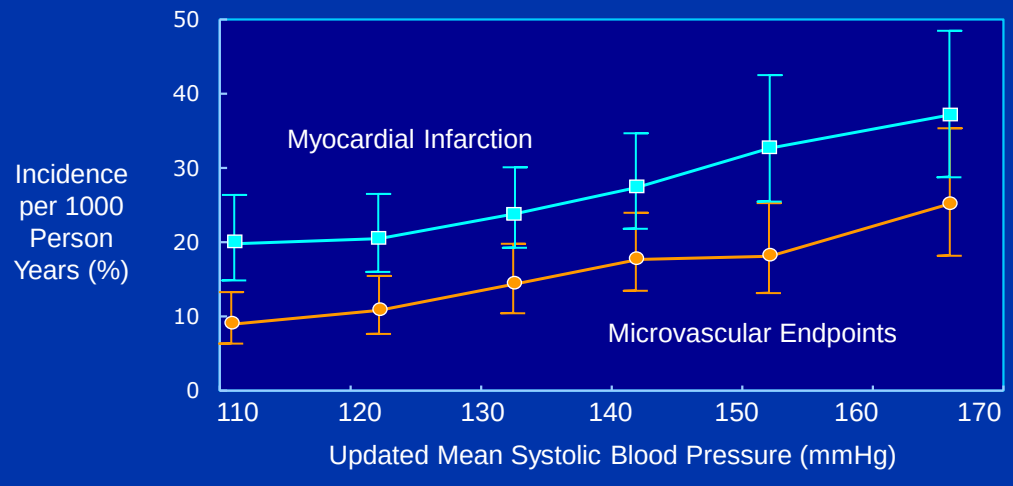
Blood Pressure Reduction and CV outcome

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

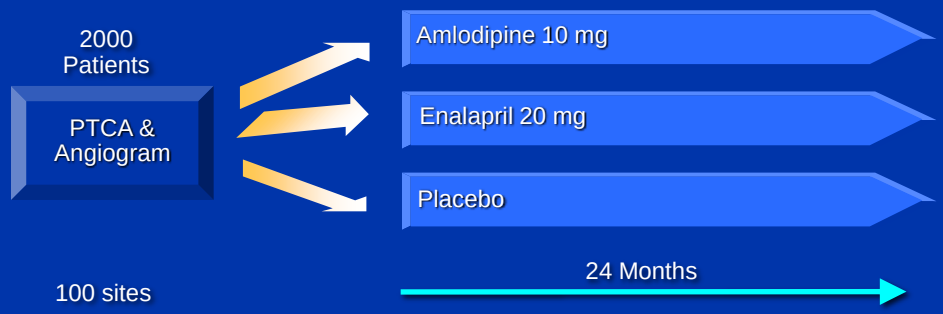
Adler AI, et al. *BMJ.* 2000;321:412-419.

Concept

- The benefits of blood pressure reduction are highly dependent of 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

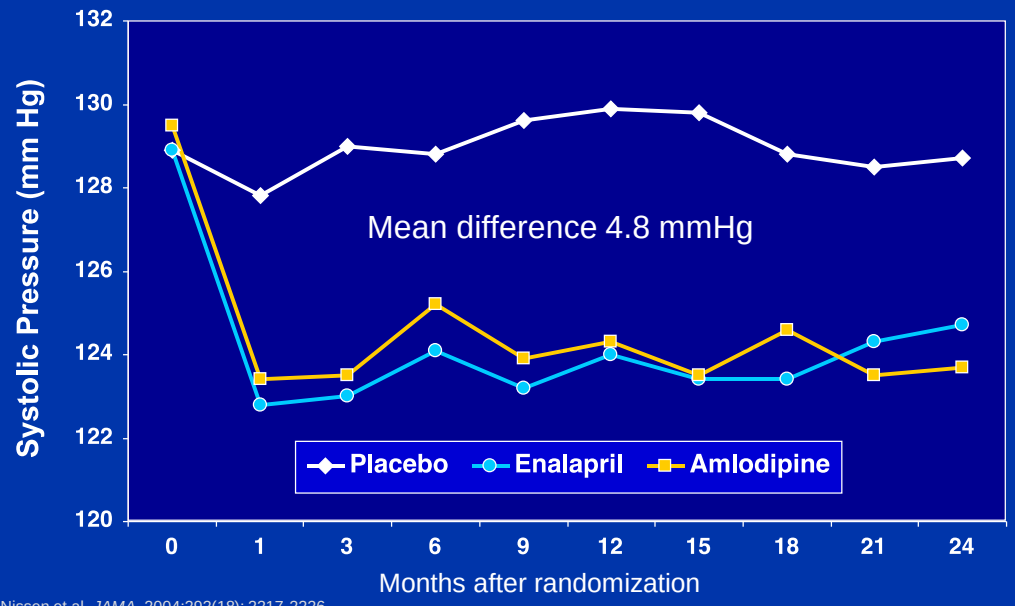


Prospective, Randomized, Double Blind, Multicenter

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

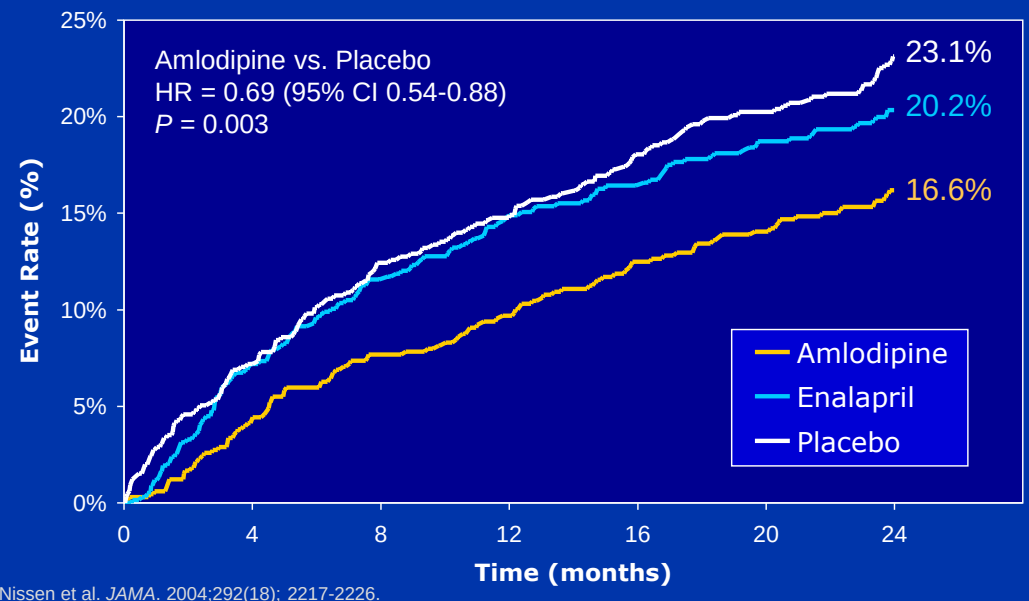
Nissen et al. *JAMA*. 2004;292(18); 2217-2226.

Systolic Pressure: All Three Treatment Groups



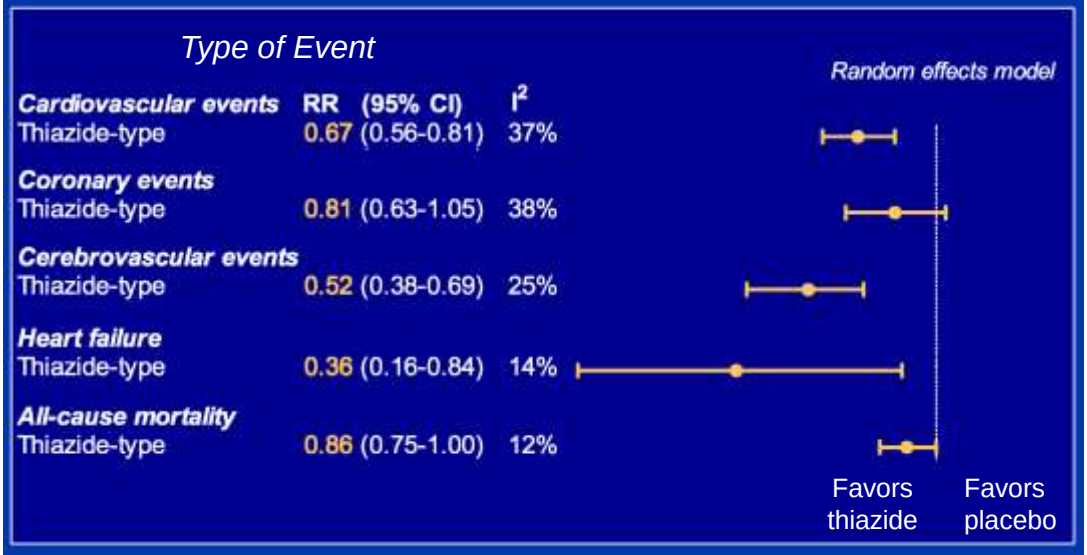
Nissen et al. *JAMA*. 2004;292(18); 2217-2226.

CAMELOT: Time to Major Cardiovascular Event



Nissen et al. *JAMA*. 2004;292(18); 2217-2226.

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

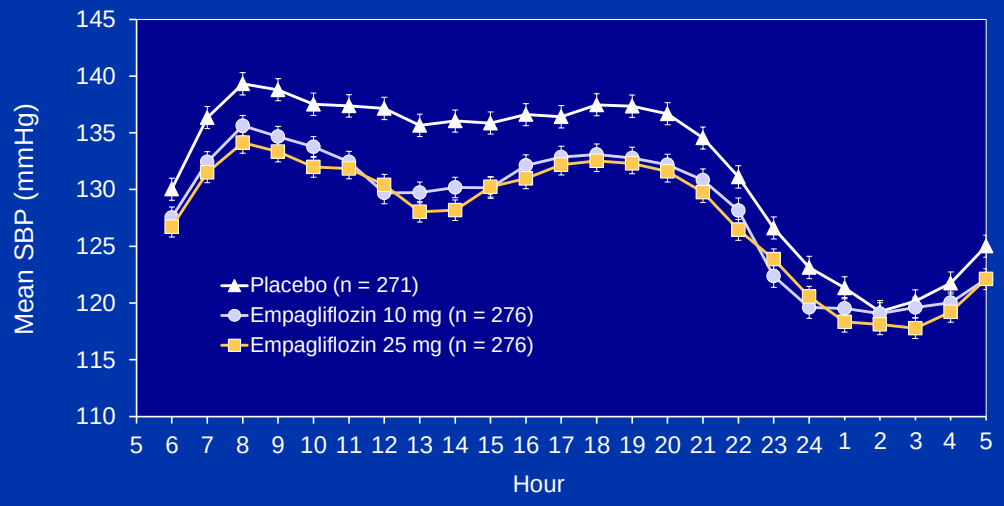


Rik et al. Hypertension. 2015;65:1033-1040

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

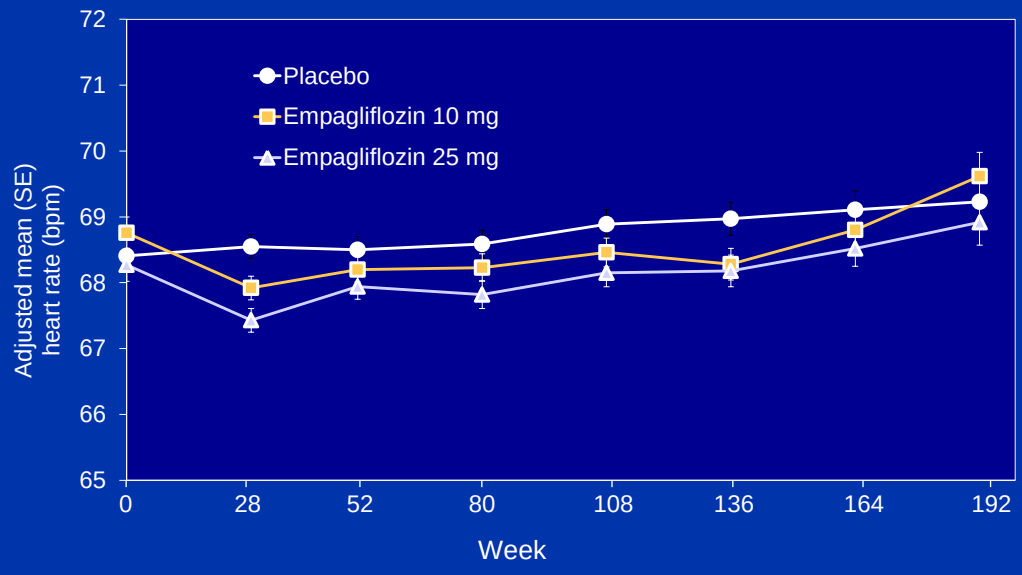


Tikkanen I *et al*. *Diabetes Care* 2015;38:420–428.

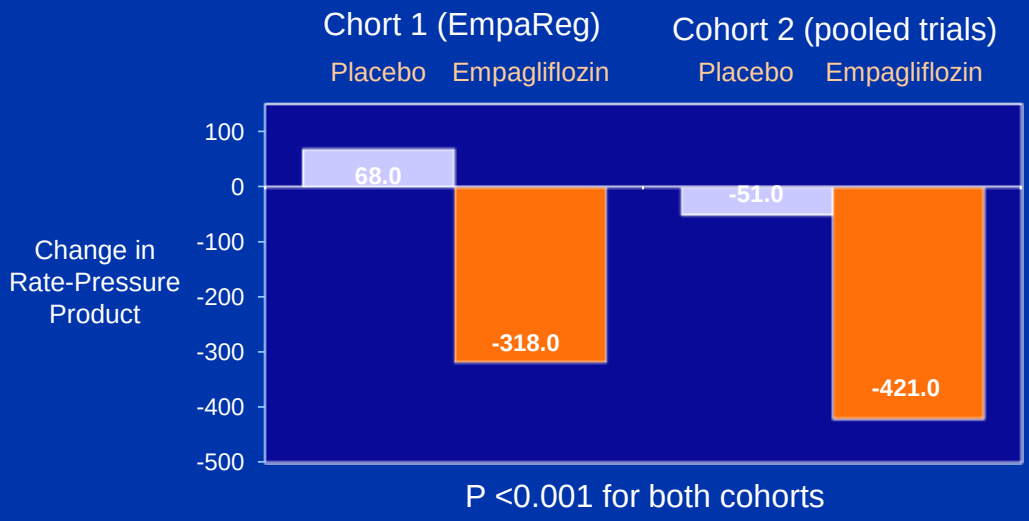
Absence of Sympathetic Activation

The blood pressure reduction in the EmpaReg Trial was not accompanied by reflex increases in sympathetic activity

Effect of Empagliflozin on Heart Rate



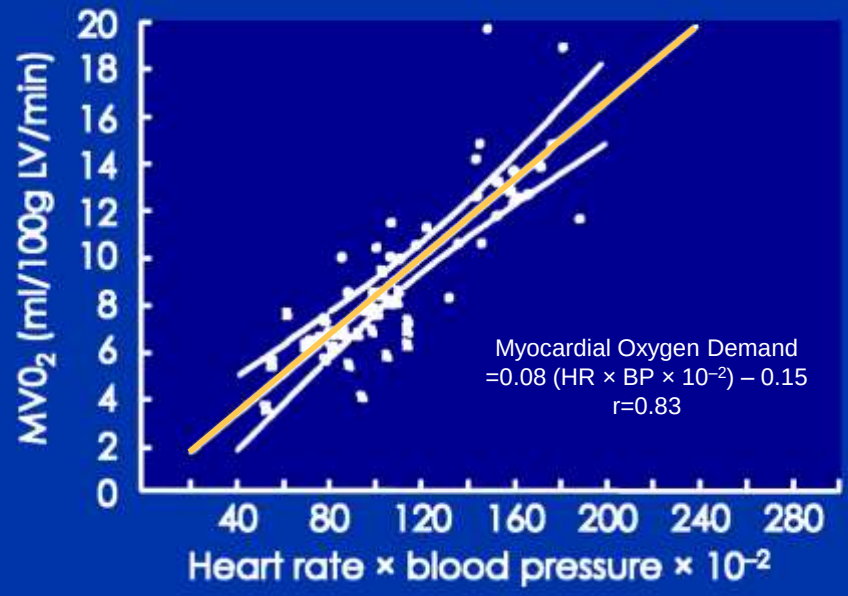
Effect of Empagliflozin on Rate-Pressure Product in Two Treatment Cohorts



P <0.001 for both cohorts

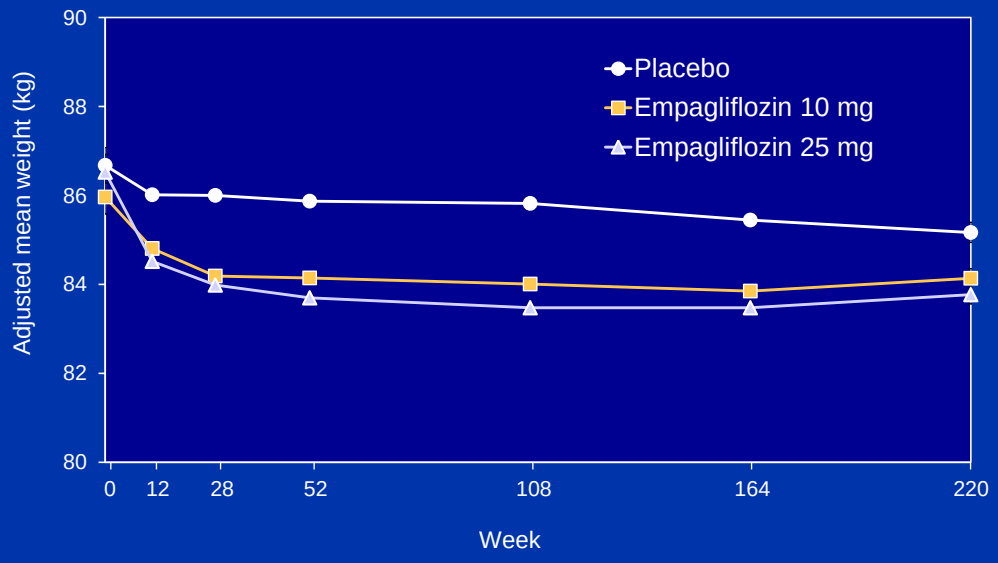
Diabetes, Obesity and Metabolism 17: 1180–1193, 2015

Importance of Rate Pressure Product

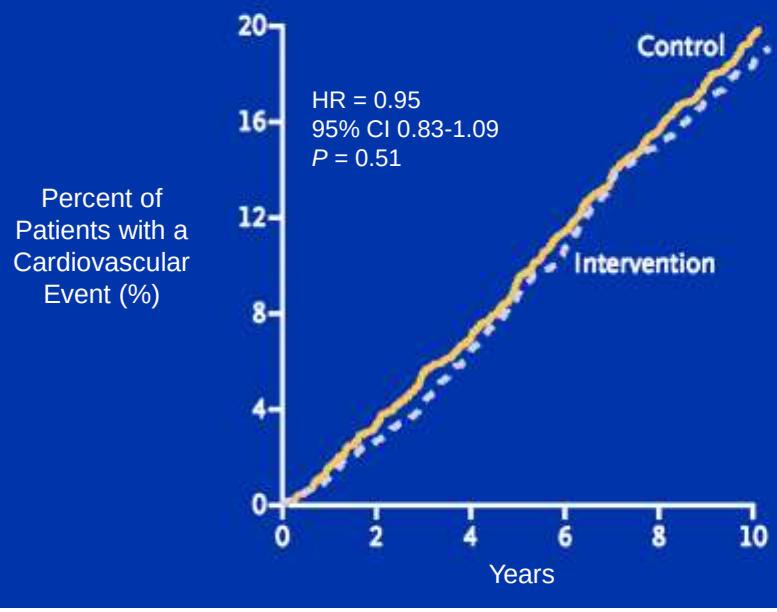


Gobel *et al*. *Circulation* 1978;57:549–556

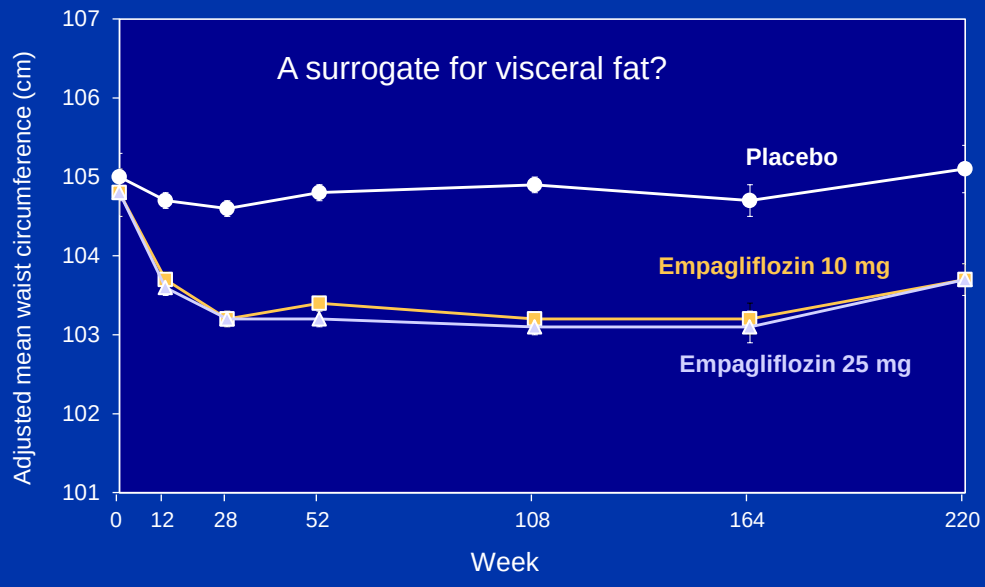
Effect of Empagliflozin on Body Weight



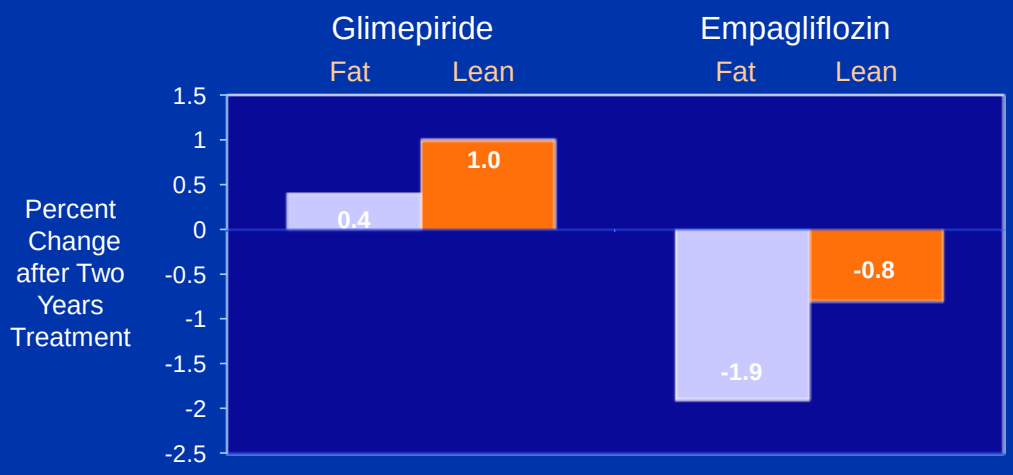
Cardiovascular Outcomes: Look Ahead



Effect of Empagliflozin on Waist Circumference

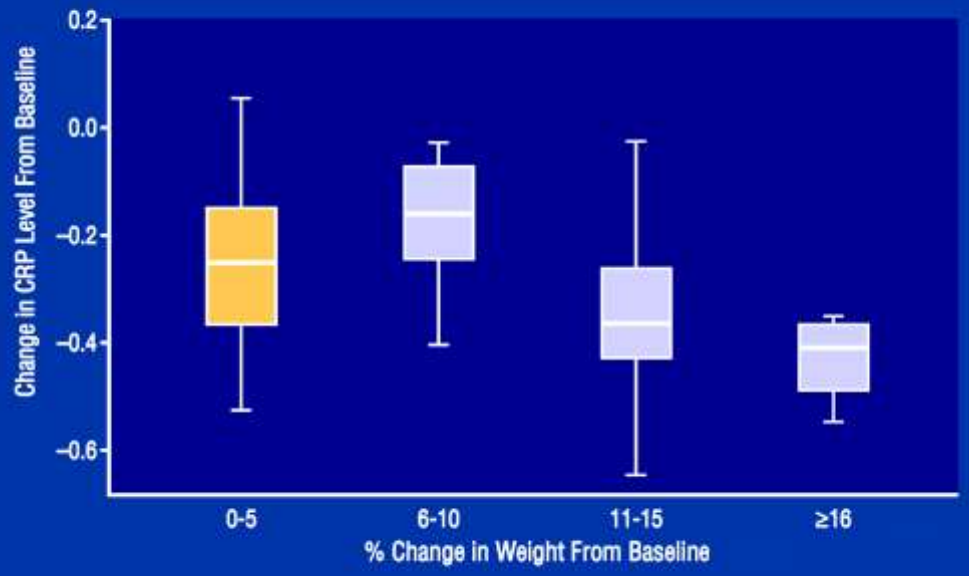


Change in Fat and Lean Mass over Two Years Glimepiride vs. Empagliflozin with Metformin



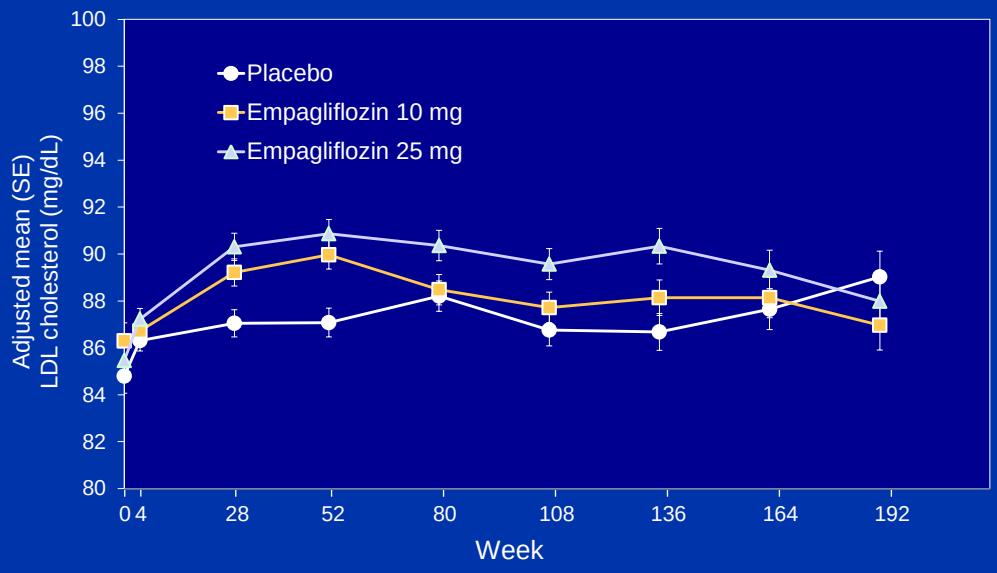
Ridderstråle *et al*. *Lancet Diabetes Endocrinol* 2014

Effect of Weight Reduction on C-reactive Protein

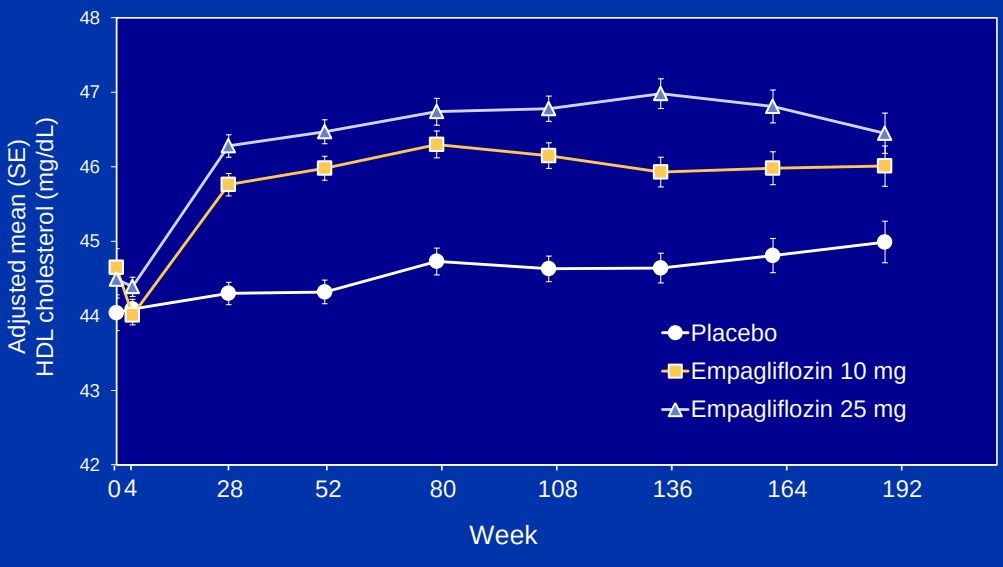


Arch Intern Med. 2007;167:31-39

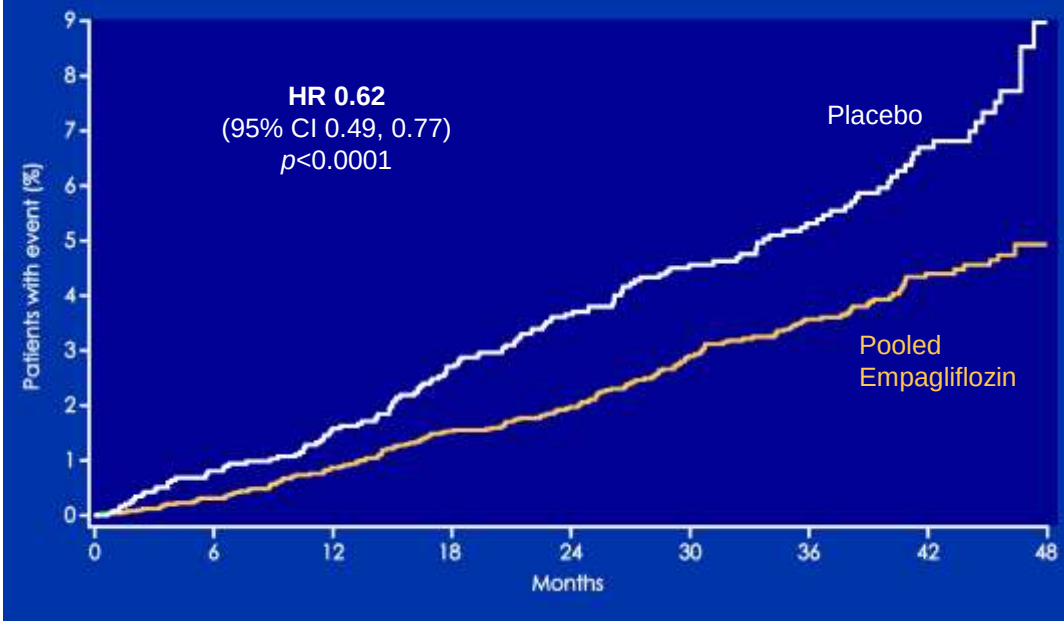
Effect of Empagliflozin on LDL-Cholesterol



Effect of Empagliflozin on HDL-cholesterol

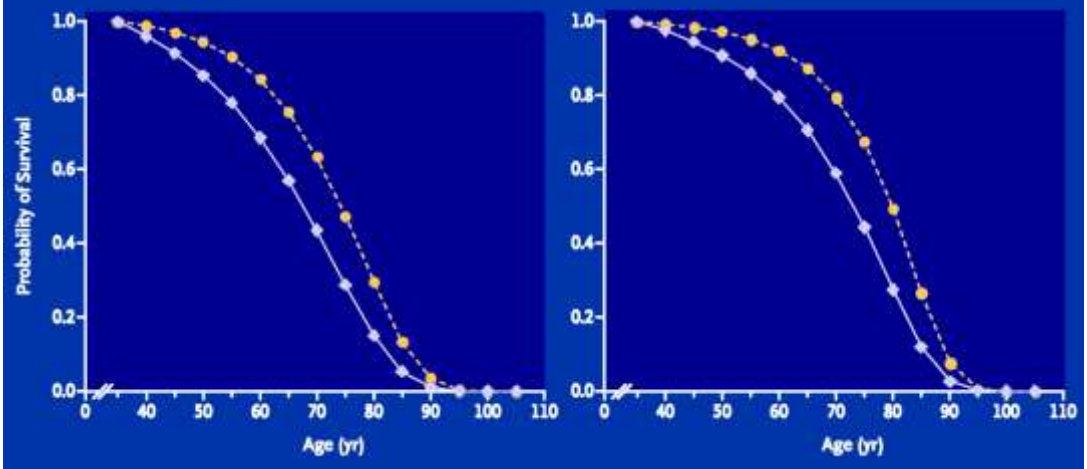


Effect of Empagliflozin on Cardiovascular Death



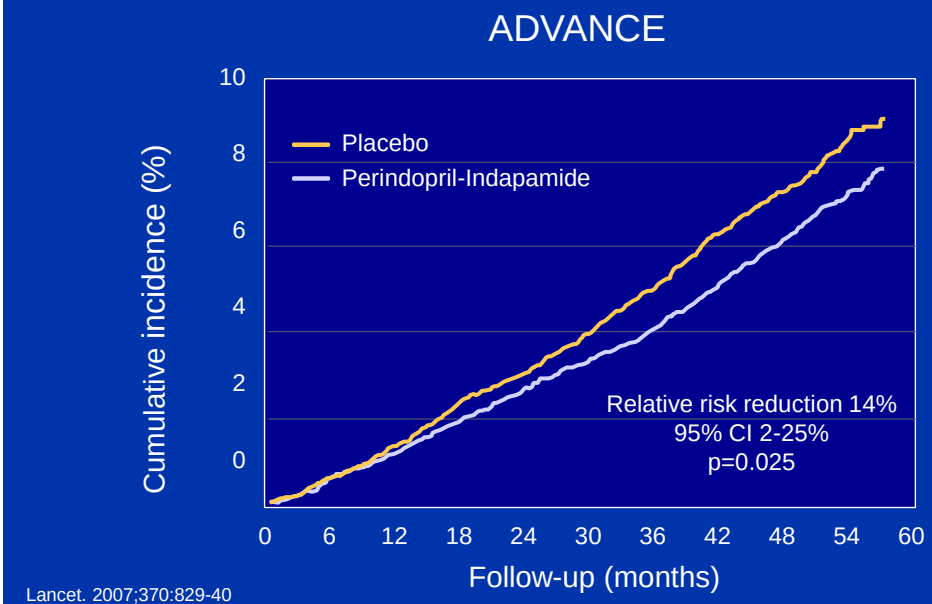
Emerging Risk Factor Collaborative: Years of Life Lost Due to Diabetes

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



N Engl J Med 2011;364:829-41.

BP Reduction and All-Cause Mortality

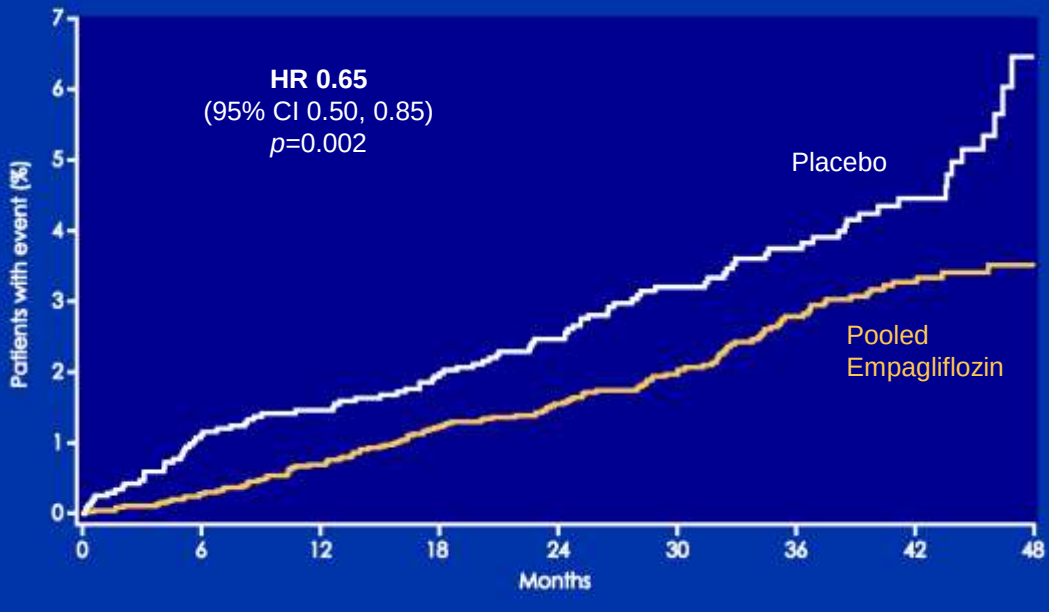


Lancet. 2007;370:829-40

Effect of Empagliflozin on Death by Cause

	Placebo (N = 2333)	Pooled Empagliflozin N= 4687)
All cardiovascular deaths	5.9%	3.7%
Sudden death	1.6%	1.1%
Worsening of heart failure	0.8%	0.2%
Acute myocardial infarction	0.5%	0.3%
Stroke	0.5%	0.3%
Cardiogenic shock	0.1%	0.1%
Other cardiovascular death	2.4%	1.6%

Effect of Empagliflozin on CHF Hospitalization

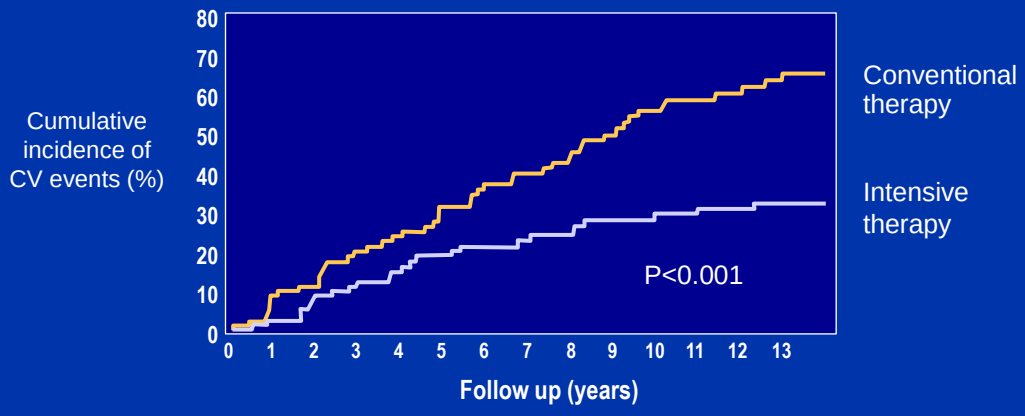


Many Unanswered Questions

- 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



Gaede et al New Engl J Med 2008; 358: 580

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, an 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 form cardiovascular morbidity.