ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

# What Can SGLT-2 Inhibitors Do For the Cardiovascular Patient?

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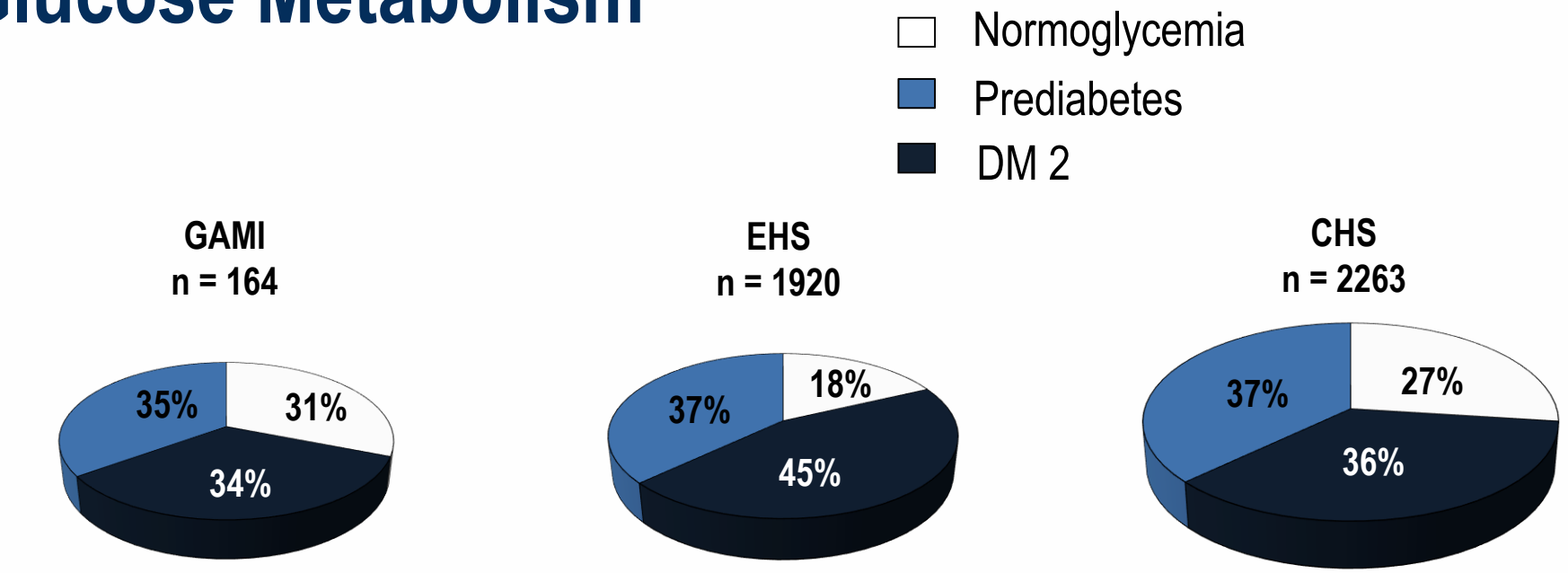
# Objectives

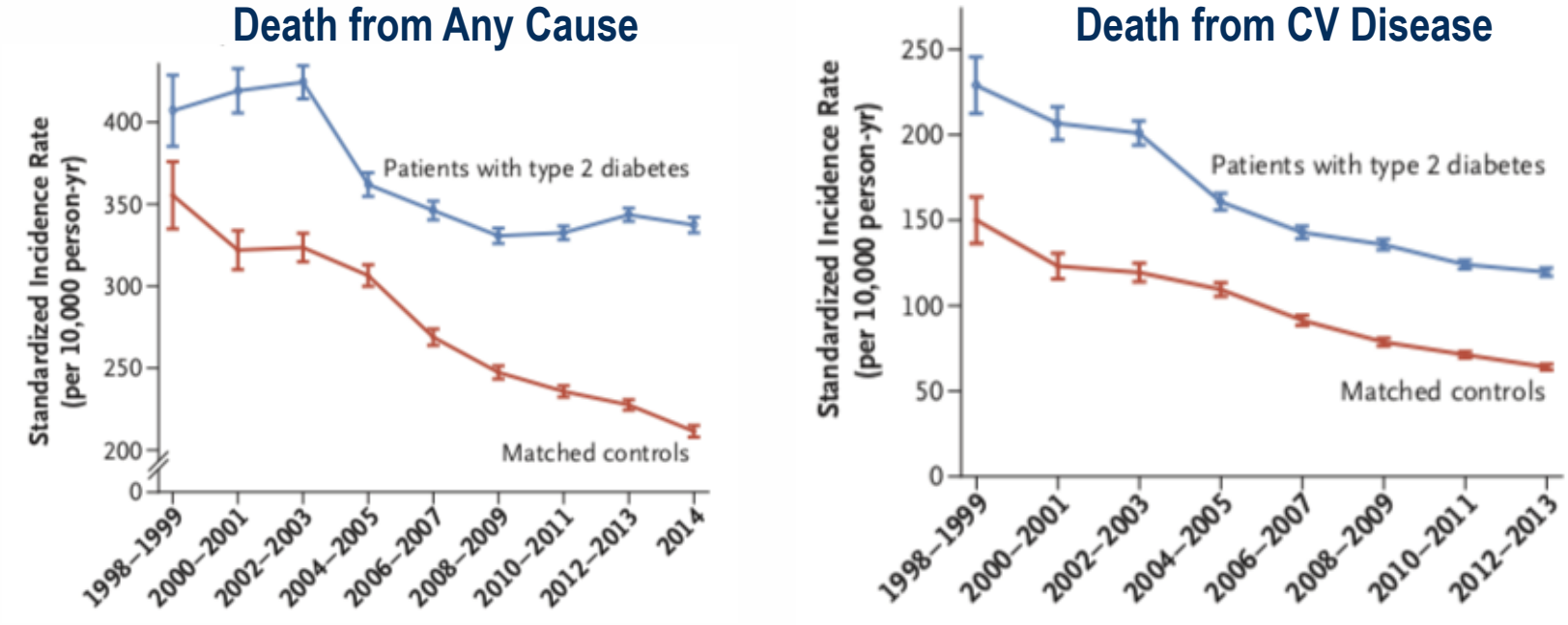
- Review the increased CV risk in patients with DM 2
- Describe the role of sodium–glucose cotransporter 2 (SGLT2) in health
- Discuss the clinical trial data for SGLT2 Inhibitors

# Most Cardiovascular Patients Have Abnormal Glucose Metabolism



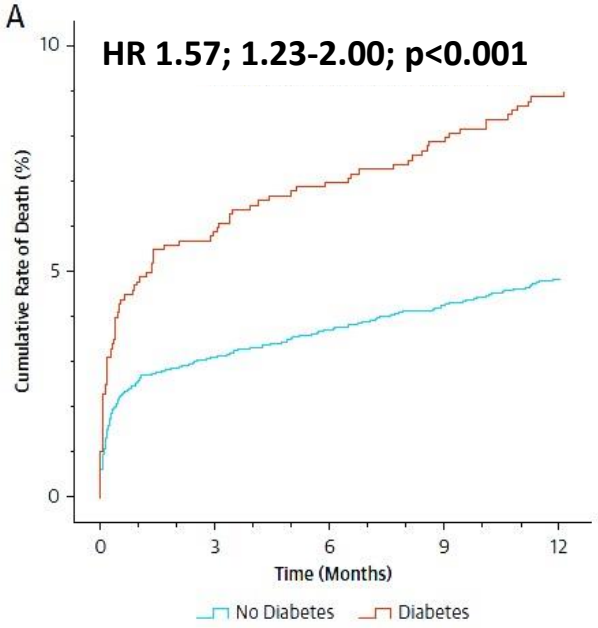

Anselmino M, *Diabetes Vasc Dis Res* 2008

# Increased Mortality in DM 2



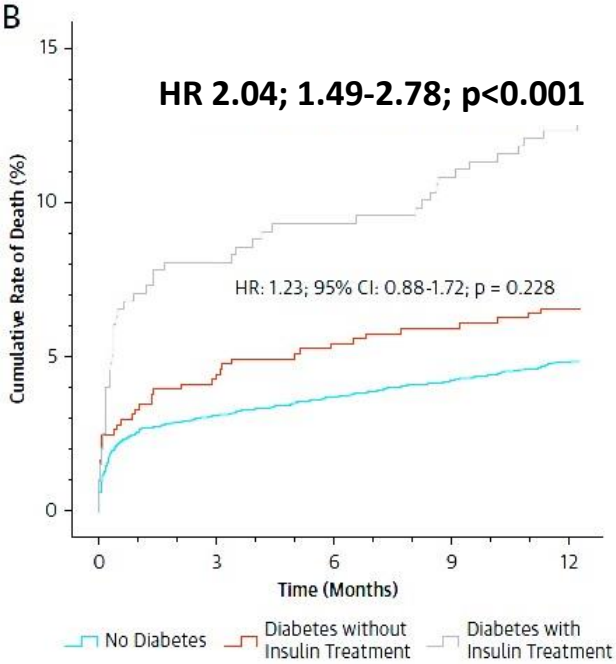

Rawshani A. *N Engl J Med* 2017

# Mortality after ACS Higher in Diabetics




DM

No DM



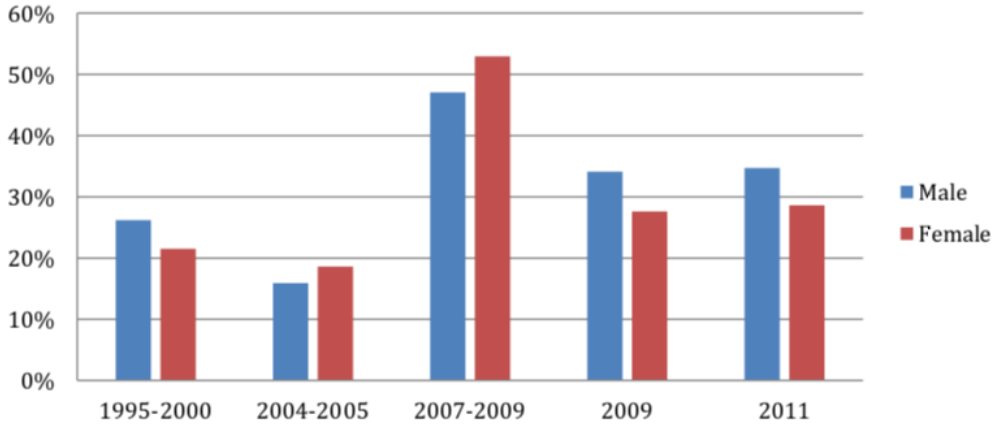

DM--Insulin

DM—No Insulin

No DM

Karayiannides S, *J Am Coll Cardiol* 2018

# Prevalance of DM 2 in Saudi Arabia




**Patient demographics in the Saudi Project for Assessment of Coronary Events (SPACE) registry: Overall, SPACE-own* and SPACE-referral† cohorts**

| | SPACE overall (n=435) | SPACE-own (n=319) | SPACE-referral (n=116) | P |
|---|---|---|---|---|
| Age, mean ± SD, years | 57.1±13.6 | 56.7±13.9 | 58.1±12.6 | 0.7 |
| Male sex | 332 (77) | 243 (77) | 89 (77) | 1.0 |
| Saudi nationality | 345 (80) | 240 (76) | 105 (91) | 0.005 |
| DM on insulin | 69 (16) | 44 (14) | 25 (22) | 0.044 |
| DM not on insulin | 161 (37) | 124 (39) | 37 (32) | 0.18 |

>50% of ACS patients

Alotaibi A. *J Epidemiol Glob Health* 2017
Al Habib KF. *Can J Cardiol* 2009

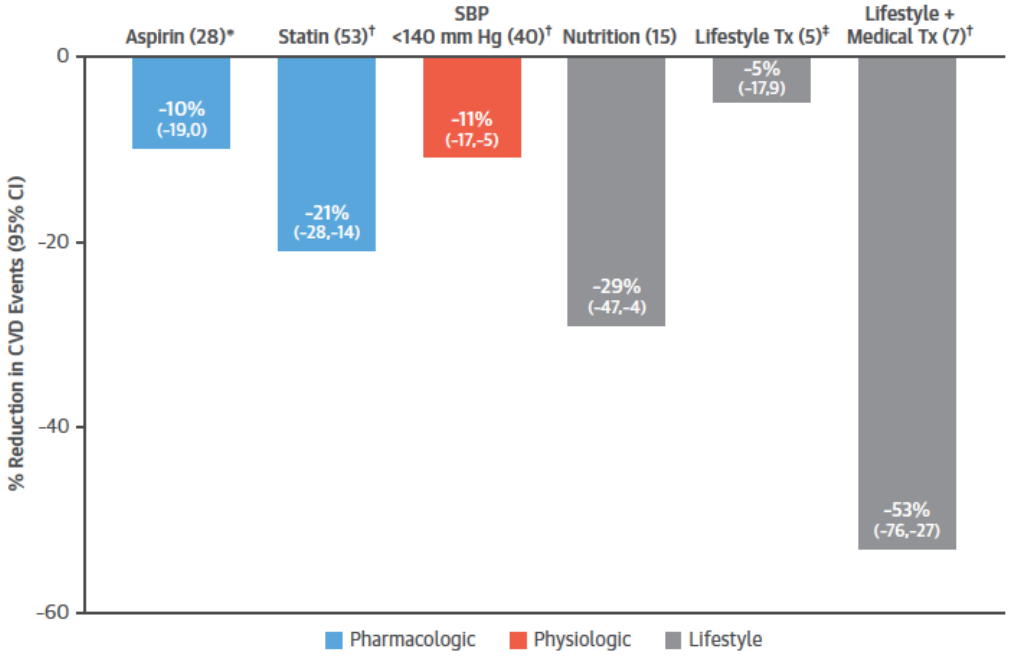
# Control of DM 2 in Saudi Arabia

**Table 1** Demographic and lifestyle characteristics by level of glycaemic control

| Variable | Glycaemic control | | |
|---|---|---|---|
| | Good (HbA1c < 7.0%) *n* = 263 | Partial (HbA1c 7.0% - 7.9) *n* = 237 | Poor (HbA1c ≥ 8%) *n* = 592 |
| Age % (n) | | | |
| > 60 years | 28.4 (109) | 22.4 (86) | 49.2 (189) |
| 46–60 years | 21.4 (123) | 21.6 (124) | 57.0 (327) |
| < 46 years | 23.1 (31) | 20.2 (27) | 56.7 (76) |

Alramadan MJ. *BMC Endocrine Disorders* 2018

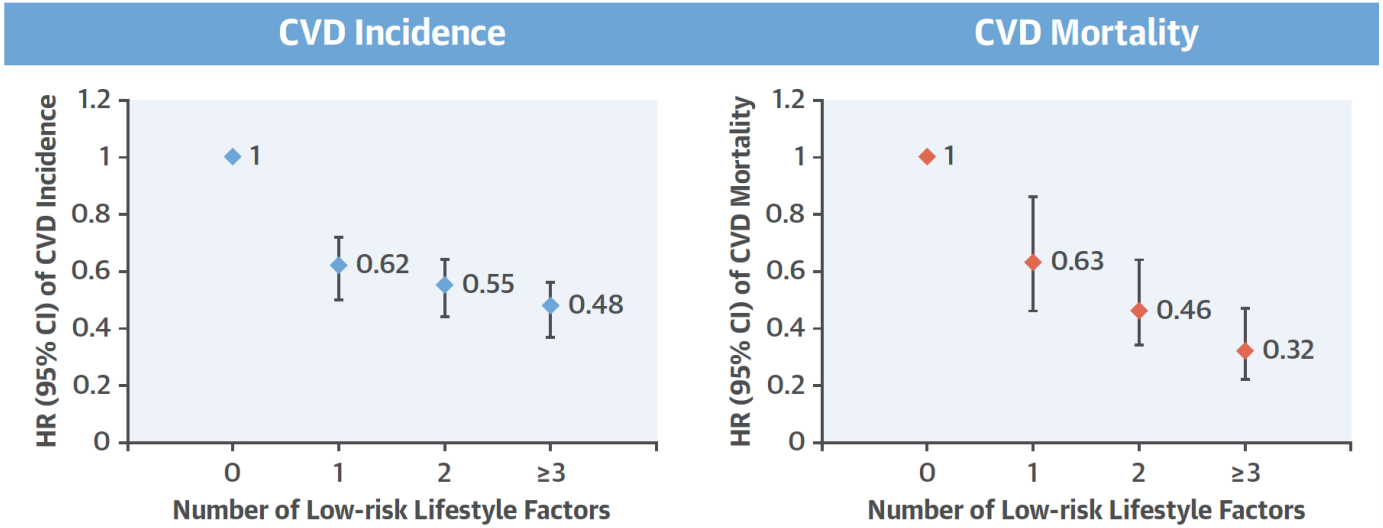
# Primary Prevention of CV Events in DM 2




*all-cause mortality; †revascularization or amputation; ‡hospitalization for angina.

Newman JD. *J Am Coll Cardiol* 2017

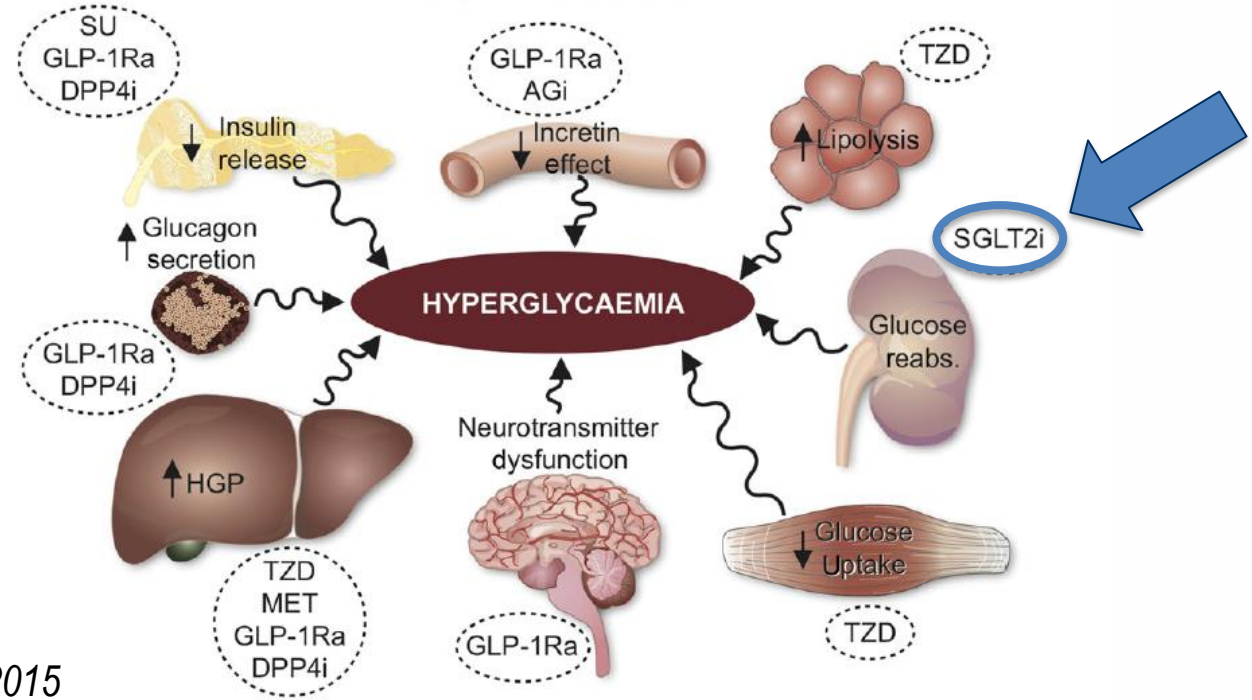
# Healthy Lifestyle Factors* and CVD in DM 2




*High-quality diet; nonsmoking; 150 min/week moderate- to vigorous-intensity physical activity; and drinking alcohol in moderation (5 -15 g/day ♀and 5 to 30 g/day♂)

Liu G. *J Am Coll Cardiol* 2018

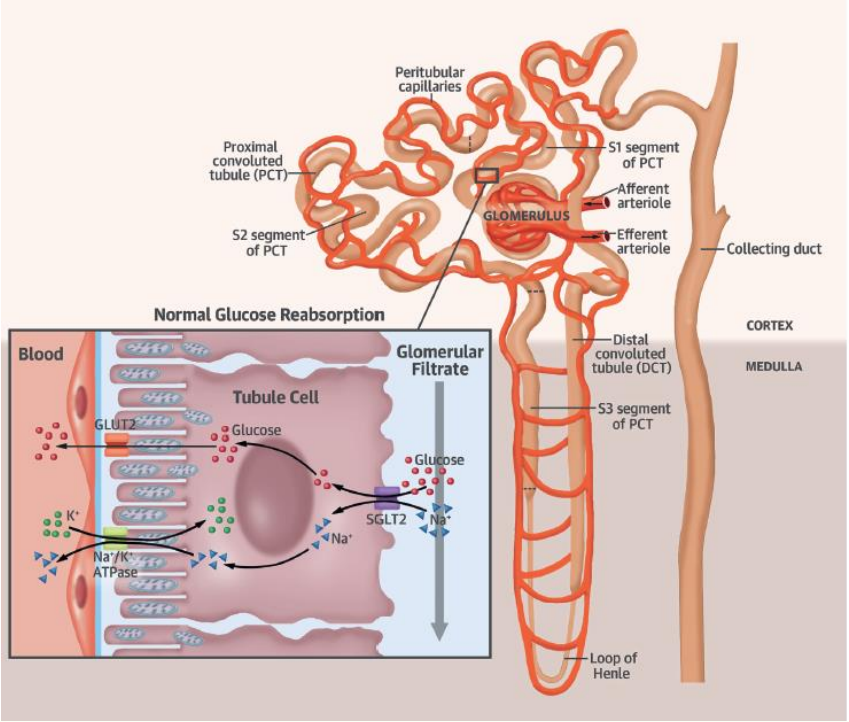
# Mechanisms of Hyperglycemia




Ferrannini E. *Eur Heart J 2015*

# Sodium–glucose co-transporter 2 (SGLT2)

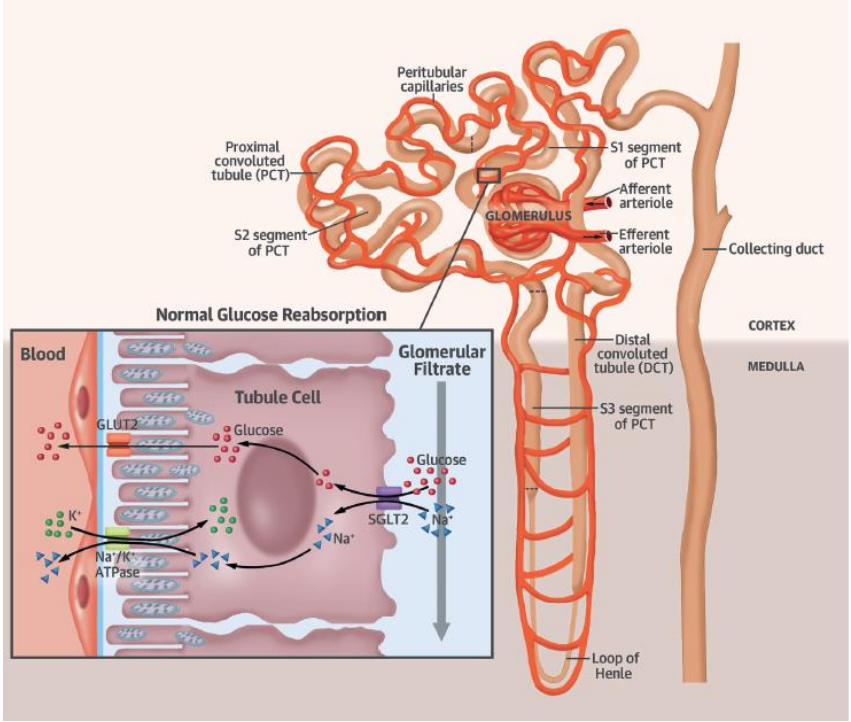
- Located in the proximal tubule
- Patients with DM2 express a significantly higher number of SGLT2s in the proximal tubule




Zelniker TA. *J Am Coll Cardiol* 2018

# Sodium–glucose co-transporter 2 (SGLT2)

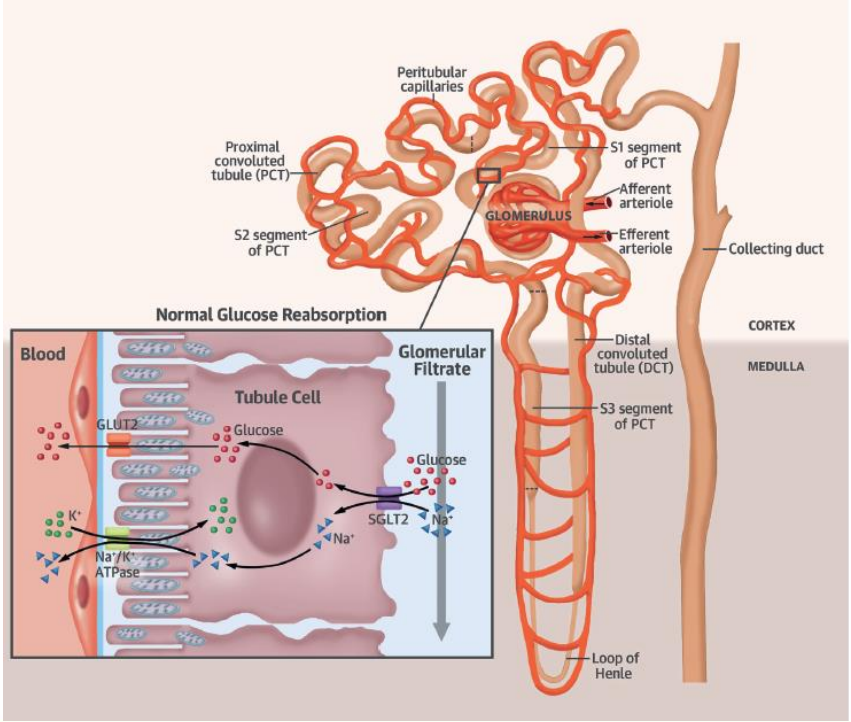
- SGLTs move glucose from the urine into the cell via an energy-dependent $Na^+$-coupled pump
- $Na^+$ moves out of the cell into blood as $K^+$ is pumped into the cell
- Glucose leaves the cell down its concentration gradient into the blood




Zelniker TA. *J Am Coll Cardiol* 2018

# Sodium–glucose co-transporter 2 (SGLT2)

- Inhibiting this transporter forces glucose to be excreted into the urine
- Insulin-independent improvements in glycemic control due to glycosuria of ~70 to 80 g/day




Zelniker TA. *J Am Coll Cardiol* 2018

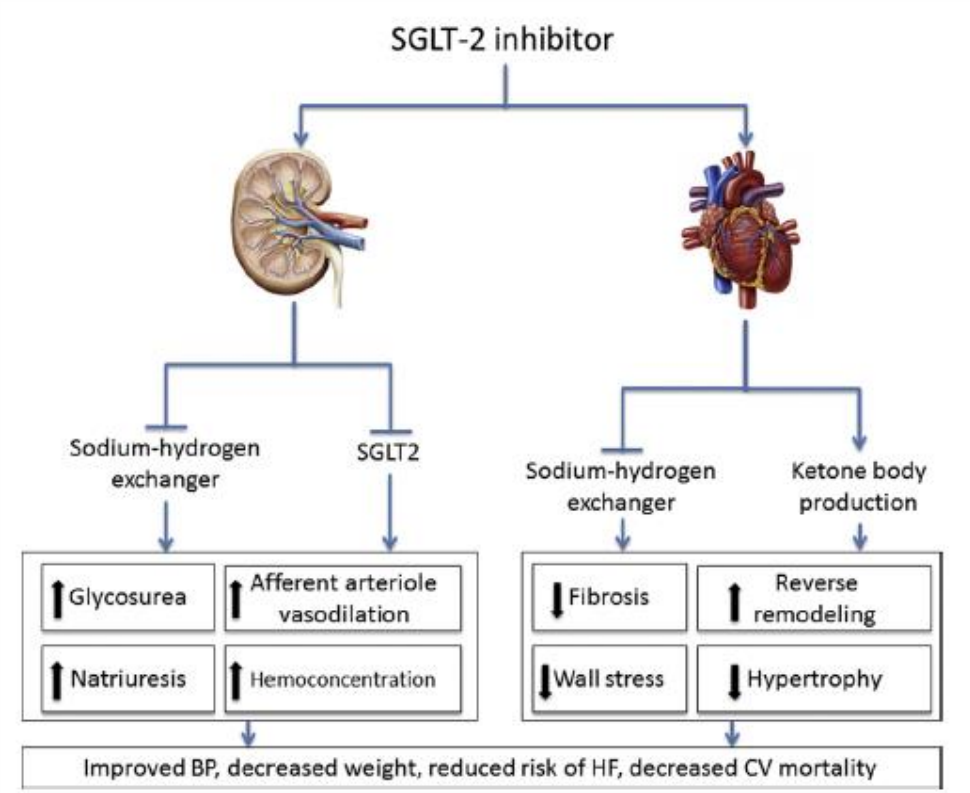
# Sodium–glucose co-transporter 2 (SGLT2)

- Mechanisms of action of SGLT2is other than their hypoglycemic effects are not fully understood

Zelniker TA. *J Am Coll Cardiol* 2018

# SGLT2 Inhibitors

- SGLT2i-mediated natriuresis and glycosuria reduce plasma volume and lower cardiac preload
- Induces an increase in FFA oxidation that stimulates ketogenesis and shifts substrate use toward fat
- Reduces epicardial fat




Scheen AJ. *Circ Res* 2018

# SGLT2 Inhibitors

- 4 SGLT2is (empagliflozin, canagliflozin, dapagliflozin and ertugliflozin) approved by the FDA for treatment of DM 2

- Empagliflozin has the highest (~2,500-fold) selectivity for SGLT2 over SGLT1 compared with
  - Ertugliflozin (~2,000-fold)
  - Dapagliflozin (~1,200-fold)
  - Canagliflozin (~250-fold)

Zelniker TA. *J Am Coll Cardiol* 2018

# SGLT2 Inhibitors

- Administered orally once daily because of their half-life of >10 h
- Drug-induced urinary glucose excretion requires at least moderately preserved renal function
- SGLT2is are contraindicated in patients with an estimated glomerular filtration rate (GFR)<30 ml/min/1.73

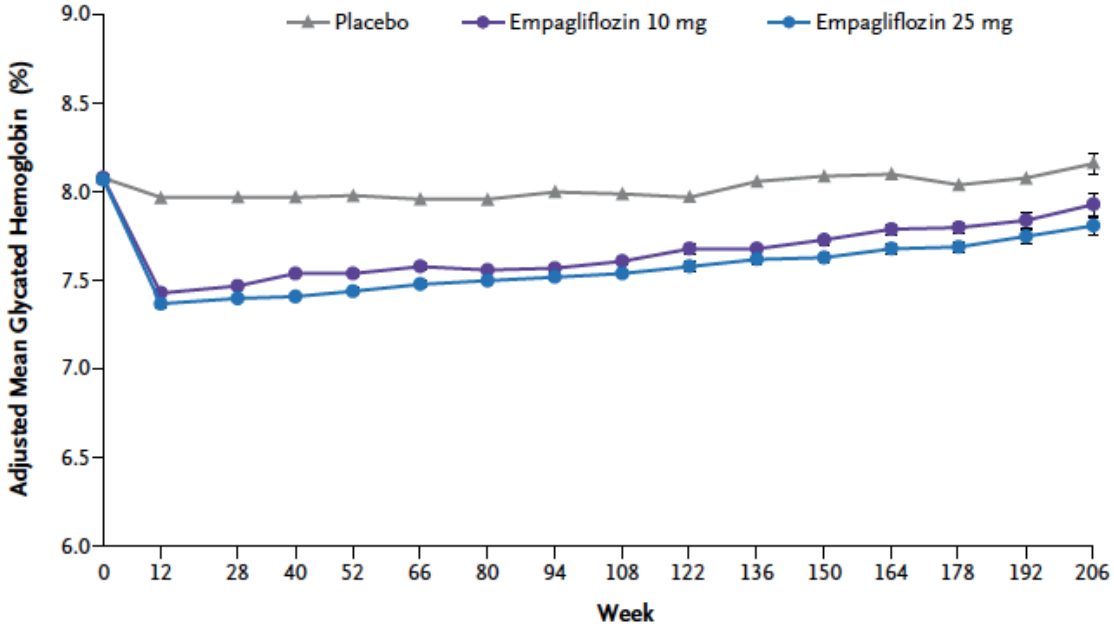
Zelniker TA. *J Am Coll Cardiol* 2018

# EMPA-Reg: Trial Overview

- 7020 patients
- Established CVD
- Randomized, double-blind, placebo-controlled
- Empaglifozin 10 mg or 25 mg versus placebo

Zinman B. *N Engl Med* 2015

# EMPA-Reg: Mean HbA1c Levels



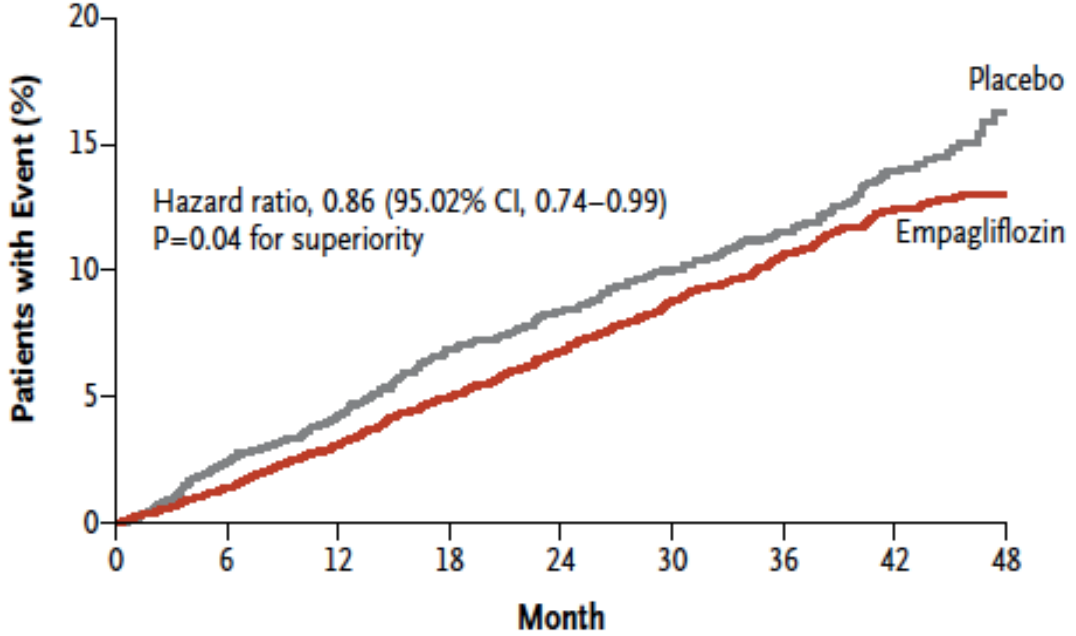

10 mg: −0.54%

25 mg: −0.60%

Zinman B. *N Engl Med* 2015

# EMPA-Reg: Primary Outcome

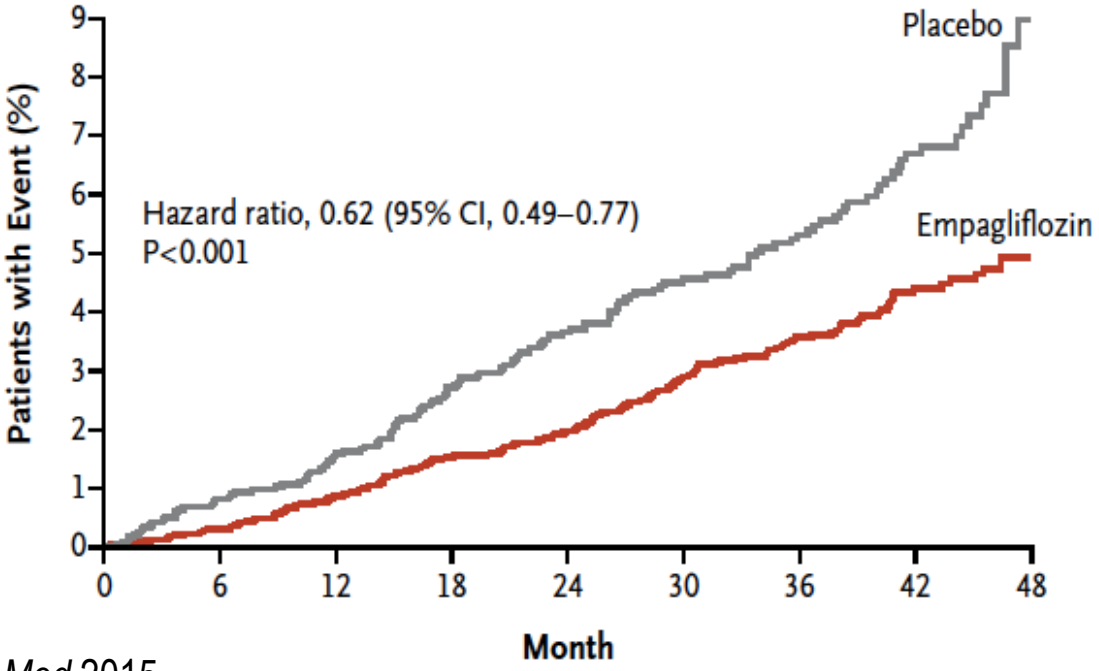
## CV Death, Nonfatal MI, Nonfatal CVA




↓14% in Composite Endpoint

Zinman B. *N Engl Med* 2015

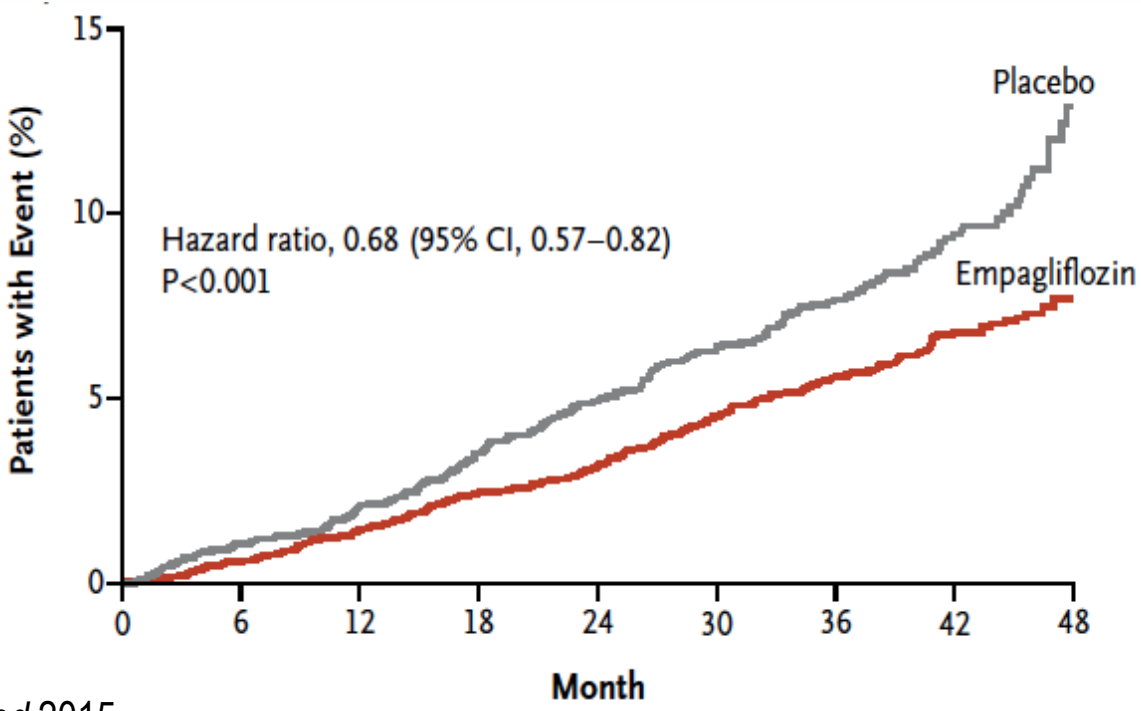
# EMPA-Reg: CV Death*




↓38% in CV death

Zinman B. *N Engl Med* 2015

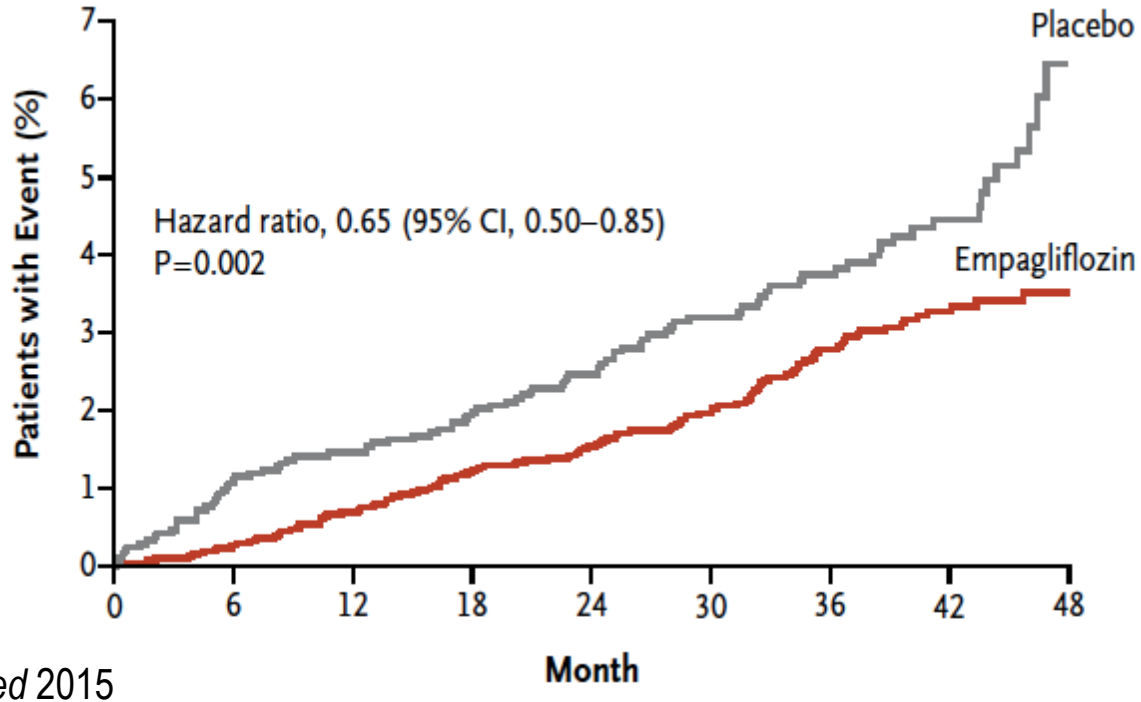
# EMPA-Reg: Death from Any Cause*




↓32% in All-Cause death

Zinman B. *N Engl Med* 2015

# EMPA-Reg: Hospitalization for HF




↓35% in HF Hospitalization

Zinman B. *N Engl Med* 2015

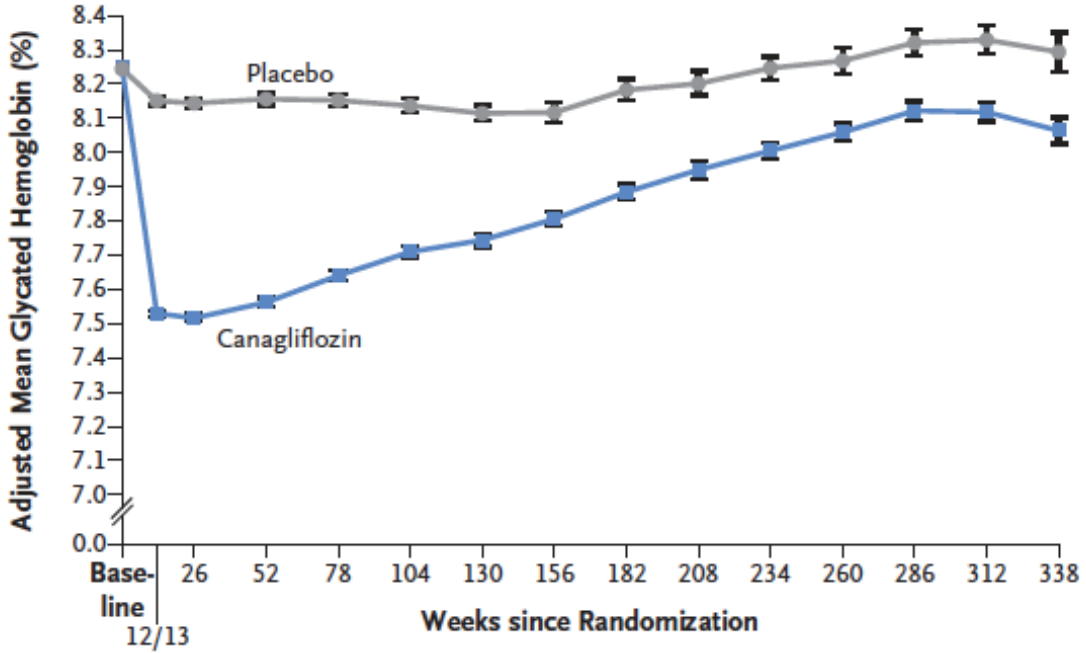
# CANVAS: Trial Overview

- CANVAS program: 10,142 participants
  - 4330 in CANVAS
  - 5812 in CANVAS-R
- Randomized, double-blind, placebo-controlled
- ≥30 yo with DM and symptomatic CVD
- ≥50 you with DM and ≥2 RF
- 65.6% had CVD
  - 22.6% had microalbuminuria
  - 7.6% had macroalbuminuria

Neal B. *N Engl Med* 2017

# CANVAS: Mean HbA1c ↓ 0.58%

- ↓ Body weight –1.60 kg
- ↓ SBP–3.93 mm Hg
- ↓ DBP –1.39 mm Hg

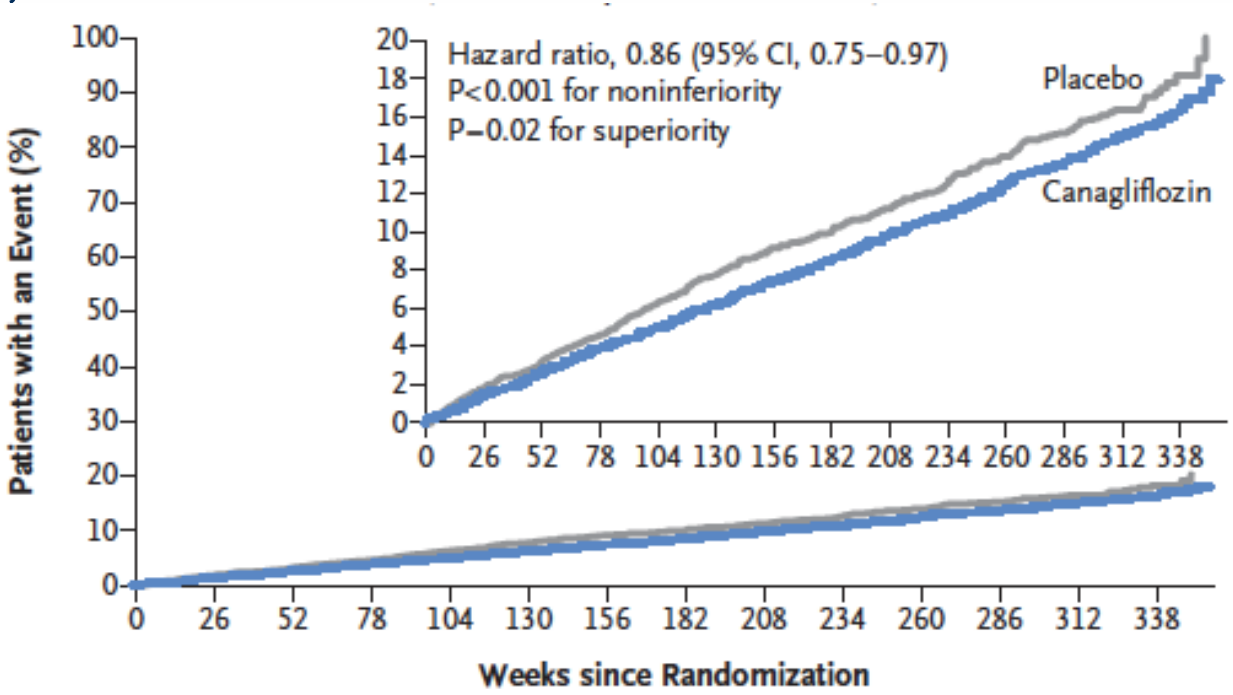



Neal B. *N Engl Med* 2017

# CANVAS: Primary Outcome

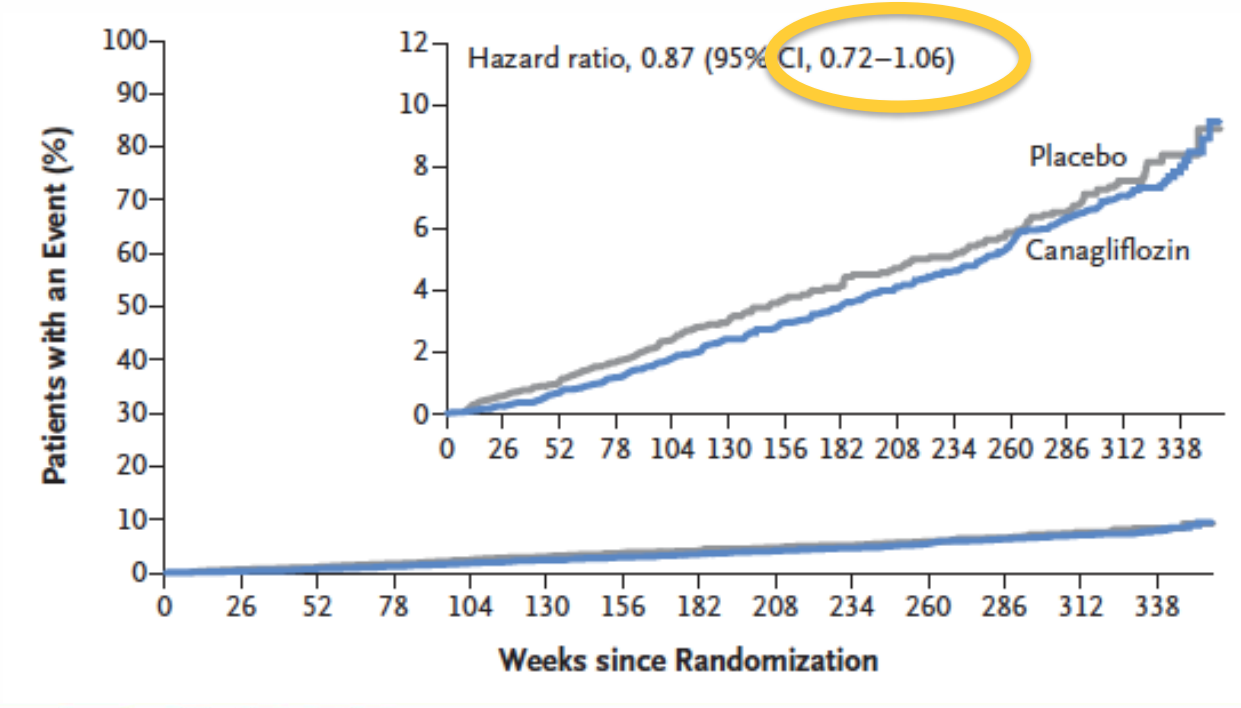
## CV Death, Nonfatal MI, Nonfatal CVA

⬇14% in Composite Endpoint



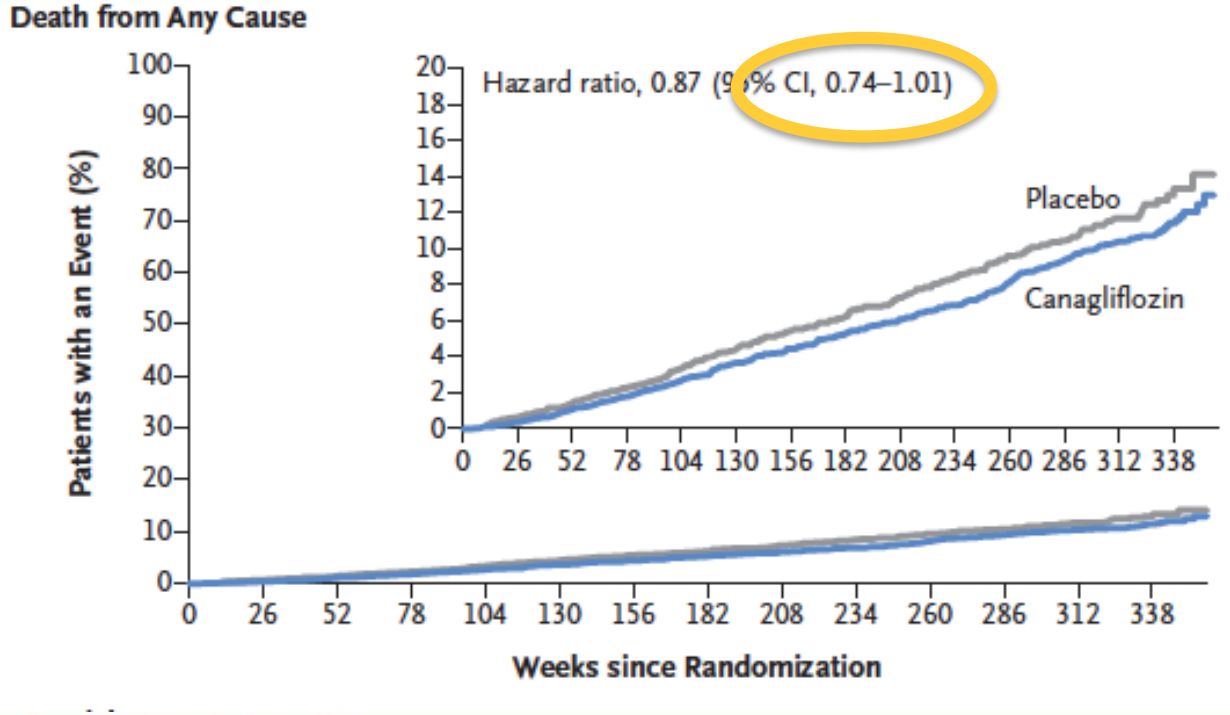

Neal B. *N Engl Med* 2017

# CANVAS: CV Death




Neal B. *N Engl Med* 2017

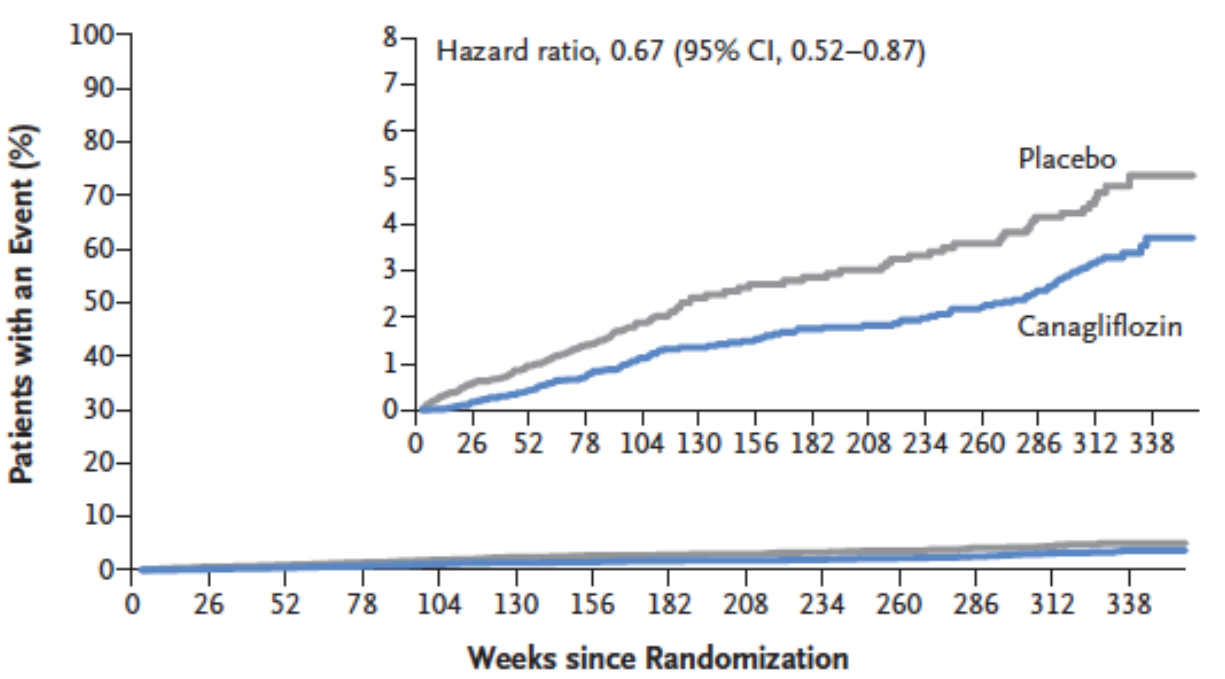
# CANVAS: All-Cause Death




Neal B. *N Engl Med* 2017

# CANVAS: Hospitalization for HF

↓33% in HF Hospitalization




Neal B. *N Engl Med* 2017

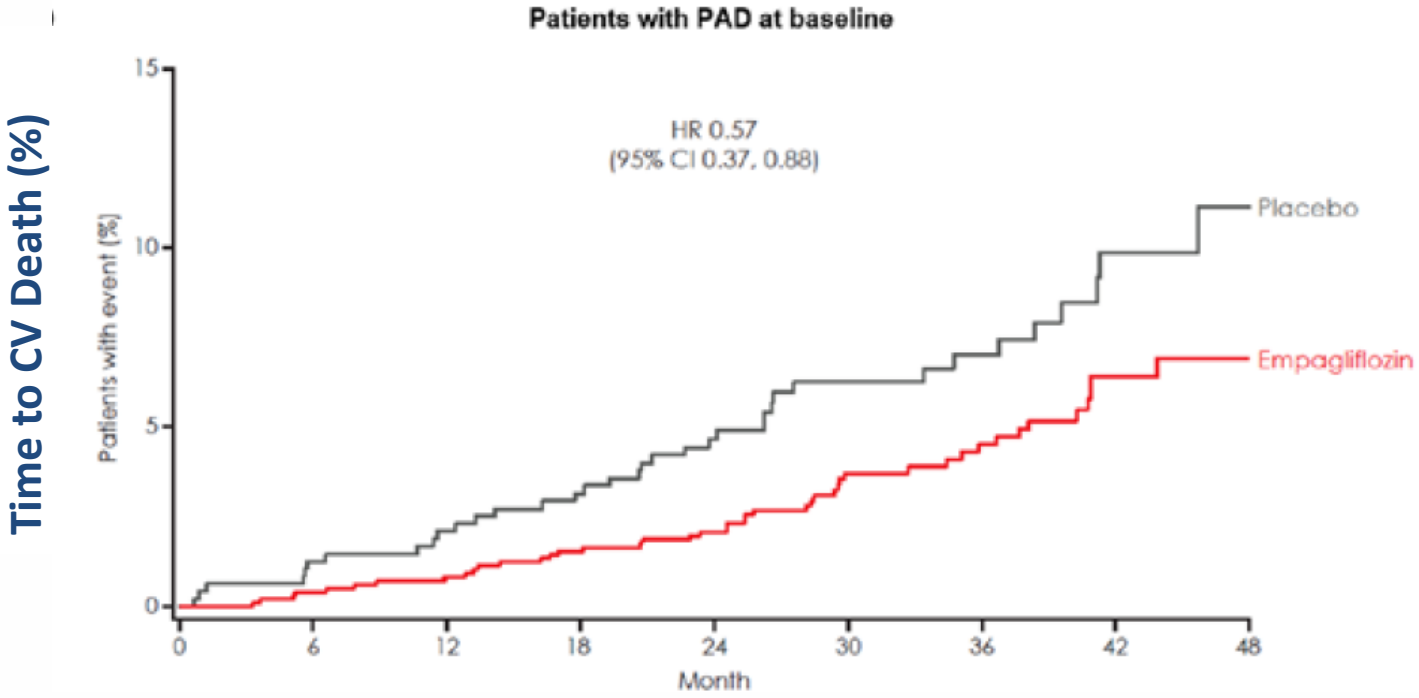
# CANVAS: 2X Increased risk of Amputation

- There was an ***↑↑ risk of lower extremity amputation***:
  - 
  - 
  - 
- An rsal

**FDA issued a black box warning for lower limb amputation in May 2017**

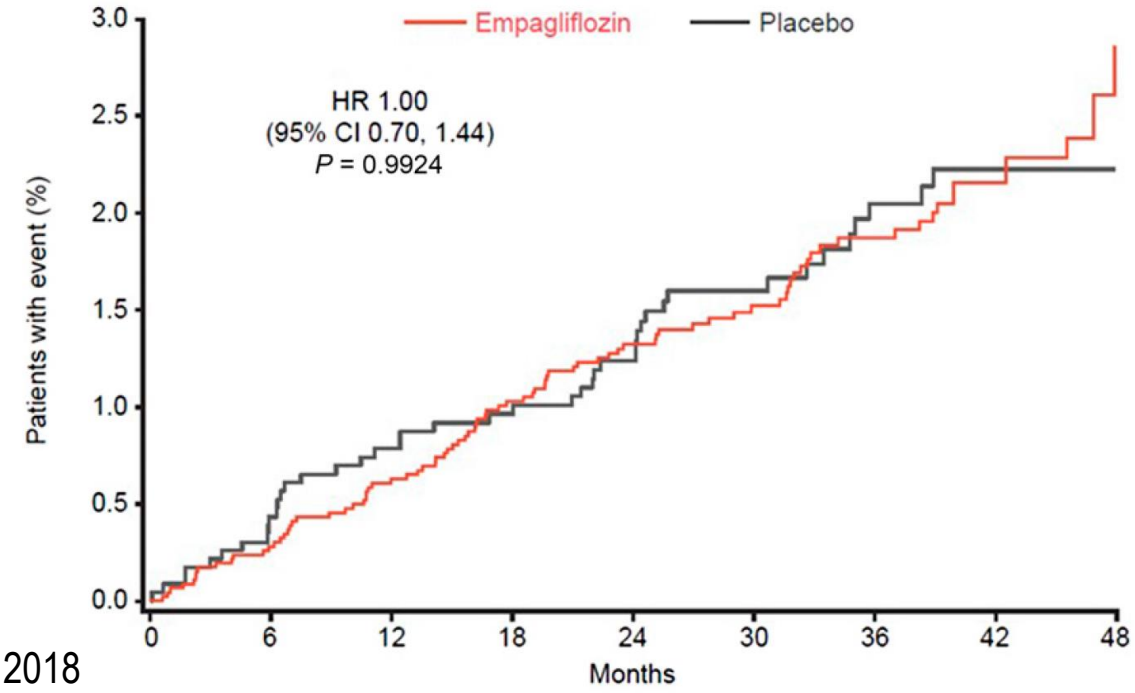
Neal B. *N Engl Med* 2017

# EMPA-Reg: PAD Subgroup




Verma S. *Circulation* 2018

# EMPA-Reg: Lower Limb Amputation




Inzucchi SE. *Diabetes Care* 2018

# CANVAS: Increased fracture risk

**FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture**

**Canagliflozin use has been associated with increased fracture risk**

edicine

information about decreased bone mineral density. Bone mineral density relates to the strength of a person's bones. To address these safety concerns, we added a new *Warning and Precaution* and revised the *Adverse Reactions* section of the Invokana and Invokamet drug labels.

Health care professionals should consider factors that contribute to fracture risk prior to starting patients on canagliflozin. Patients should talk to their health care professionals about factors that may increase their risk for bone fracture. Patients should not stop or change their diabetes medicines without first talking to their health care professional.

https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm

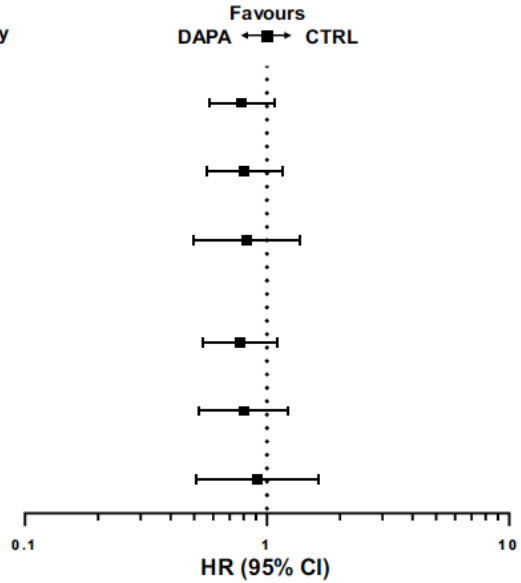
# Dapaglifozin: DECLARE-TIMI 18

- 17295 pts in 33 countries with DM 2 and elevated CV risk
  - Multiple CV Risk Factors or CVD
- Demonstrated a reduction in a composite of CV death or hospitalization for HF
- Failed to show a significant difference in MACE (CV death, MI, CVA)
- Will be presented at AHA 11/2018

www.tctmd.com

# Dapaglifozin

| Subgroup | DAPA n/N | DAPA Event rate/ 100 p-y | Control n/N | Control Event rate/ 100 p-y | HR (95% CI) |
|---|---|---|---|---|---|
| **MACE+UA** | | | | | |
| Overall | 95/5699 | 1.46 | 81/3240 | 2.15 | 0.787 (0.579, 1.070) |
| CVD History | 67/1826 | 2.94 | 61/1333 | 3.76 | 0.806 (0.562, 1.156) |
| Elderly patients with CVD risk | 33/653 | 4.19 | 32/535 | 5.06 | 0.824 (0.497, 1.365) |
| **MACE** | | | | | |
| Overall | 72/5418 | 1.15 | 62/3101 | 1.69 | 0.772 (0.543, 1.097) |
| CVD History | 50/1799 | 2.21 | 45/1325 | 2.76 | 0.802 (0.527, 1.221) |
| Elderly patients with CVD risk | 26/653 | 3.28 | 23/535 | 3.61 | 0.916 (0.512, 1.640) |




MACE = CV death, MI, CVA

MACE + UA = MACE + unstable angina

Sonesson C. Cardiovasc Diabetol 2016

# SGLT2 Inhibitors: Additional Thoughts

- ***Hypoglycemia risk ↑↑*** when an insulin secretagogue or insulin is given with an SGLT2i, so it may be necessary to reduce the dose of insulin
- ***SGLT2i's may ↓↓ BP***, so it will be important to monitor for signs and symptoms of hypotension
- *The patient may **lose weight** with the use of an SGLT2i*
- *SGLT2i-triggered **diabetic ketoacidosis** may occur in euglycemic patients who may have delayed diagnosis and therapy*

Zelniker TA. *J Am Coll Cardiol* 2018

# SGLT2 Inhibitors

| Favorable effects |
| --- |
| Reduction of pre-load (diuretic effects) |
| Reduction of afterload (blood pressure, arterial stiffness) |
| Improvement of mitochondrial efficiency |
| Delay of decline in eGFR |
| Delay of micro- and macroalbuminuria |
| Weight loss |
| Reduction in epicardial adipose tissue |
| Improvement in glycemia |
| Reduction in uric acid |

| Unfavorable effects |
| --- |
| Amputations (in particular toe, metatarsal) |
| Volume depletion/Hypotension |
| Diabetic ketoacidosis |
| Fractures |
| Urinary and genital infections |

Zelniker TA. *J Am Coll Cardiol* 2018

# SGLT2 Inhibitors Summary

| | Empagliflozin | Canaglifozin | Daptaglifozin |
|---|---|---|---|
| Patients | CVD | CVD or CV RF | CVD or CV RF |
| Mortality | **Reduces** | Neutral | ? |
| MACE | Reduces | Reduces | ? |
| HF | Reduces | Reduces | ? |

# Addition of SGLT-2 Vs Other DM drugs

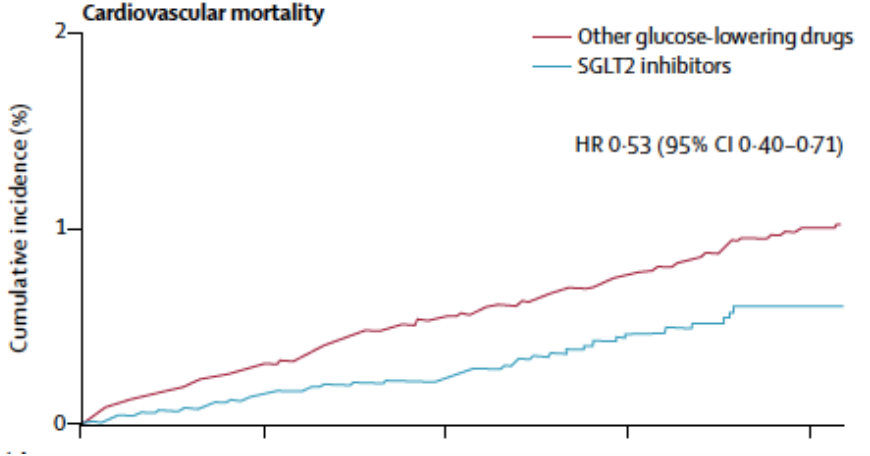
## Denmark, Norway and Sweden

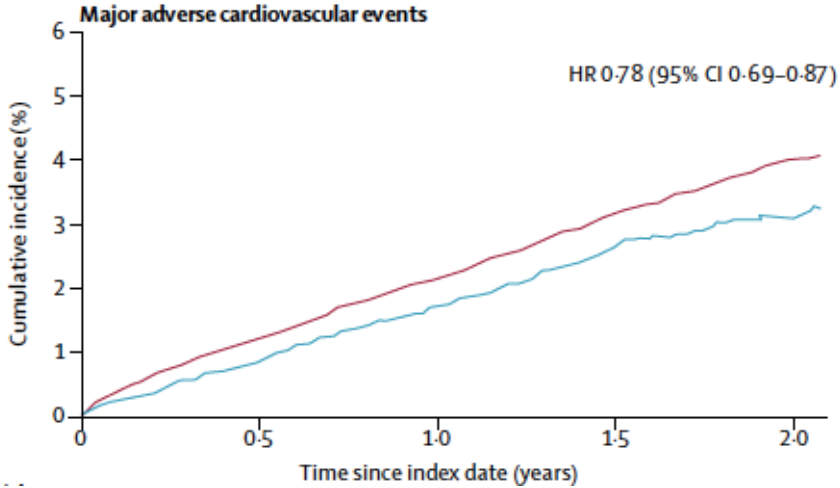
| | SGLT2 inhibitors (n=22 830) | Other glucose-lowering drugs (n=68 490) | Standardised difference* |
|---|---|---|---|
| Metformin | 16 935 (74·2%) | 53 006 (77·4%) | 0·061 |
| Sulfonylureas | 6044 (26·5%) | 18 623 (27·2%) | 0·013 |
| DPP4 inhibitors | 4398 (19·3%) | 12 566 (18·3%) | 0·019 |
| GLP-1 receptor agonists | 3888 (17·0%) | 10 105 (14·8%) | 0·050 |
| Thiazolidinediones | 343 (1·5%) | 948 (1·4%) | 0·008 |
| Insulin | 6822 (29·9%) | 20 634 (30·1%) | 0·004 |
| Short-acting | 2452 (10·7%) | 7257 (10·6%) | 0·004 |
| Intermediate-acting | 3143 (13·8%) | 9345 (13·6%) | 0·003 |
| Premixed | 1630 (7·1%) | 4809 (7·0%) | 0·004 |
| Long-acting | 2585 (11·3%) | 7650 (11·2%) | 0·004 |

Birkeland KI. *Lancet Diabetes Endocrinol* 2018

# Addition of SGLT-2 Vs Other DM drugs

## Denmark, Norway and Sweden

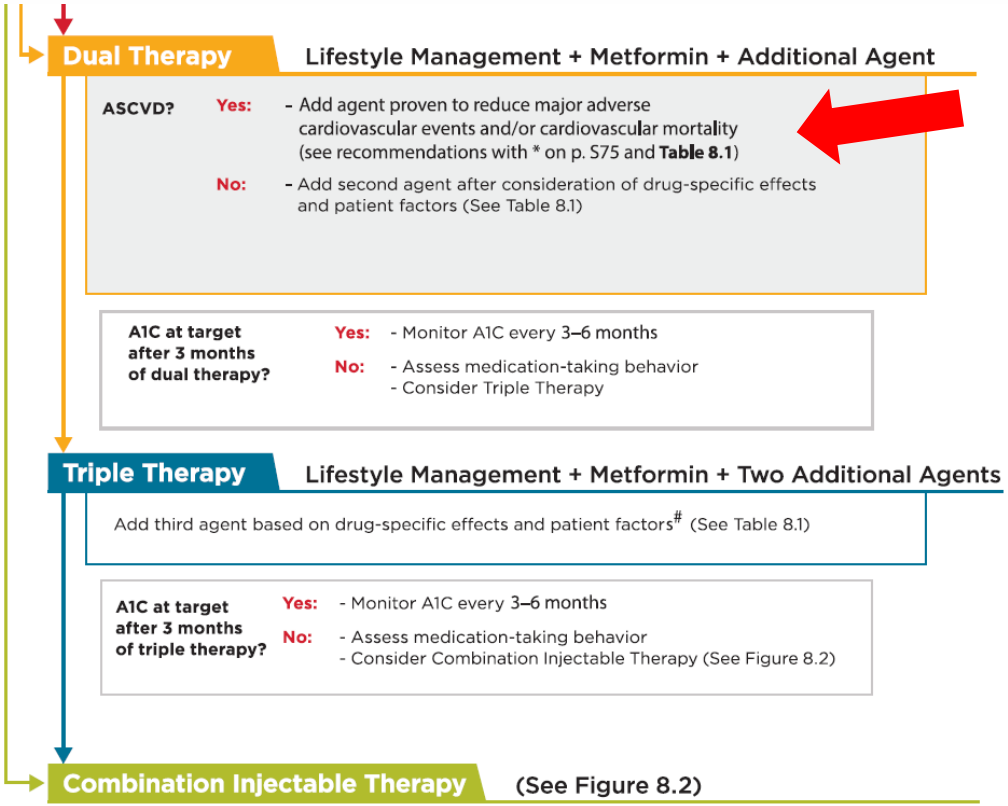



Birkeland KI. *Lancet Diabetes Endocrinol* 2018

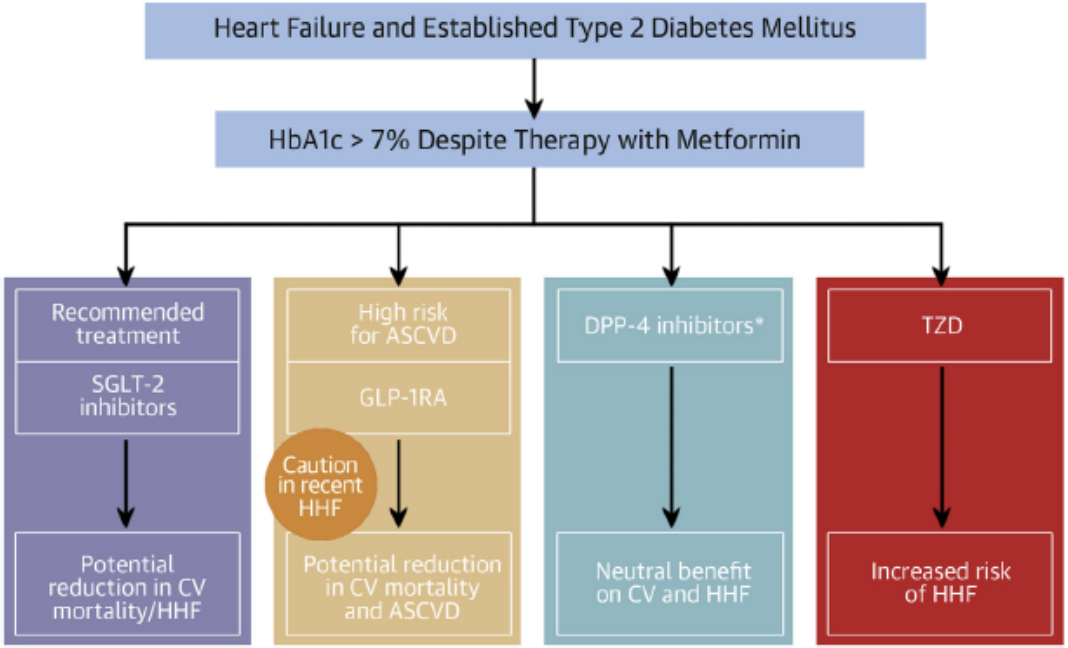
# Antihyperglycemic Therapy in Adults with T2DM

- European guidelines CVD prevention and the European Society of Cardiology recommended empagliflozin “to prevent or delay the onsetof HF in patients with diabetes and to prolong life”




ADA. *Diabetes Care* 2018

# Antihyperglycemic Therapy in Adults with DM2 & HF




Sharma A. *J Am Coll Cardiol HF* 2018

# Conclusions

- DM increases CV risk and risk of death
- Lifestyle changes are crucial for management
- Empagaflozin is FDA-approved for CVD benefit
- Canaglifozin offers CV benefit in select populations
- Dapaglifozin is currently being investigated for CV outcomes