# New Strategies for Cardiovascular Risk reduction in Diabetes


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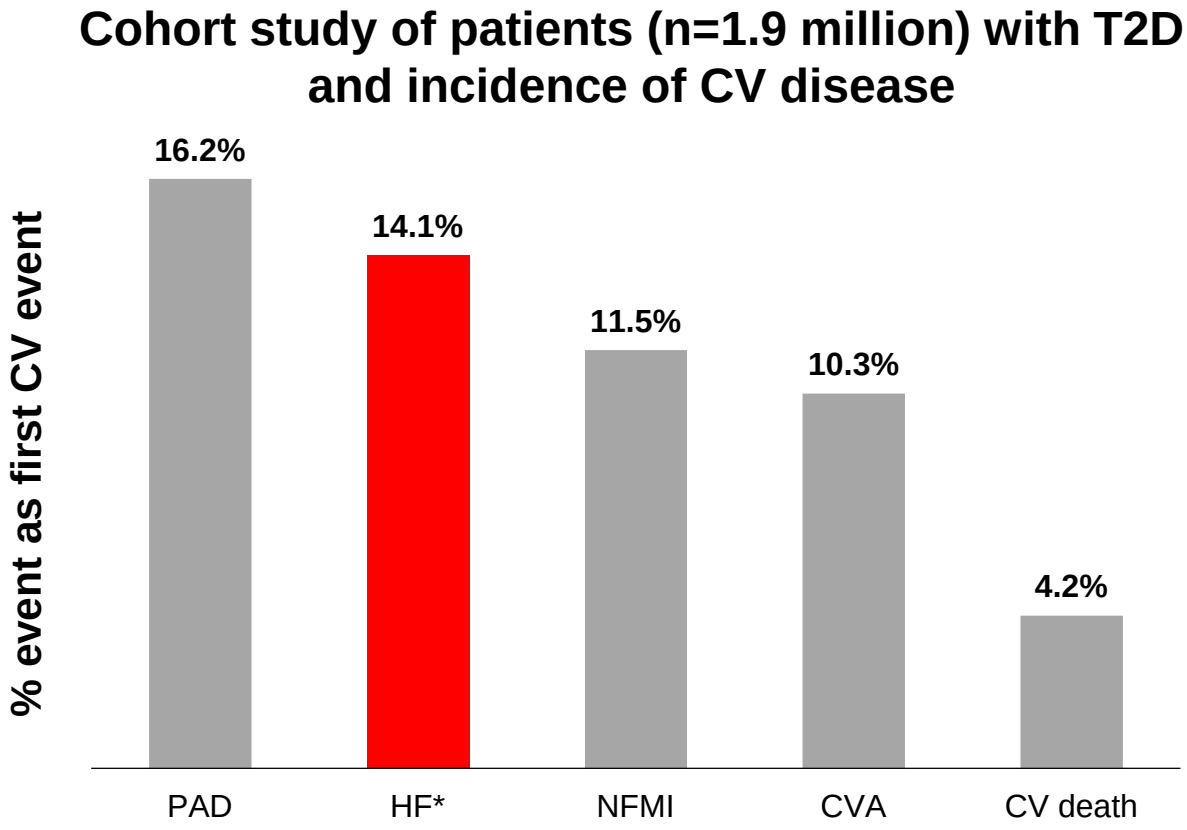
# HF was the one of the first manifestation of T2D-related CV disease



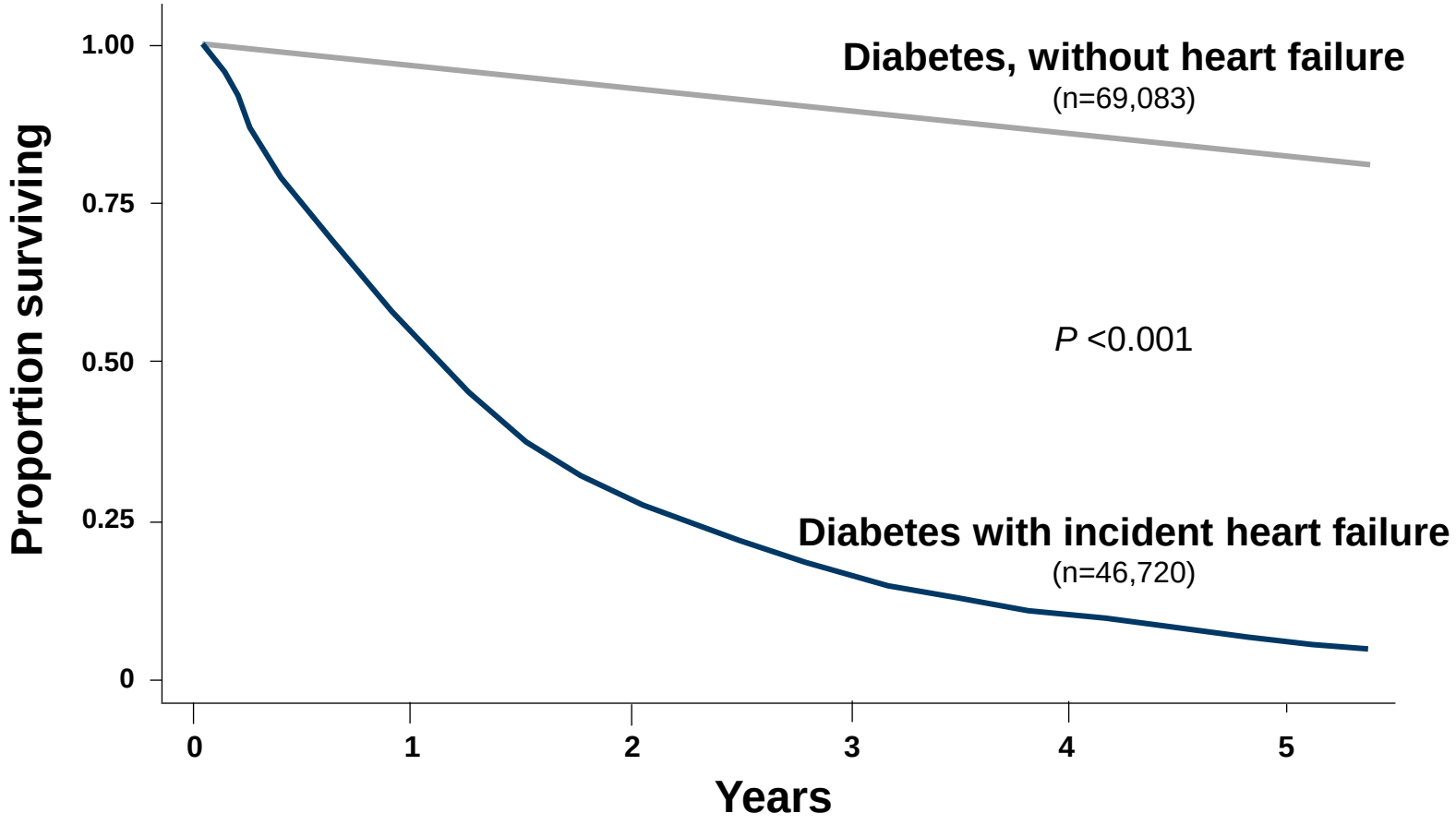

*Heart failure post MI was not included in this definition of HF

- In this large cohort, PAD and HF were the two most common first presentations of T2D-related CV disease
- Yet, myocardial infarction and stroke continue to be chosen as primary outcomes of major type 2 diabetes trials, as part of the MACE endpoint
- This suggests that future studies should assess CV events that occur earlier in patients with T2D such as HF and PAD

CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; NFMI, nonfatal myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.

Shah AD, et al. *Lancet Diabetes Endocrinol.* 2015;3:105-113, Appendix.

# The presence of HF in patients with diabetes is associated with an increased risk of death



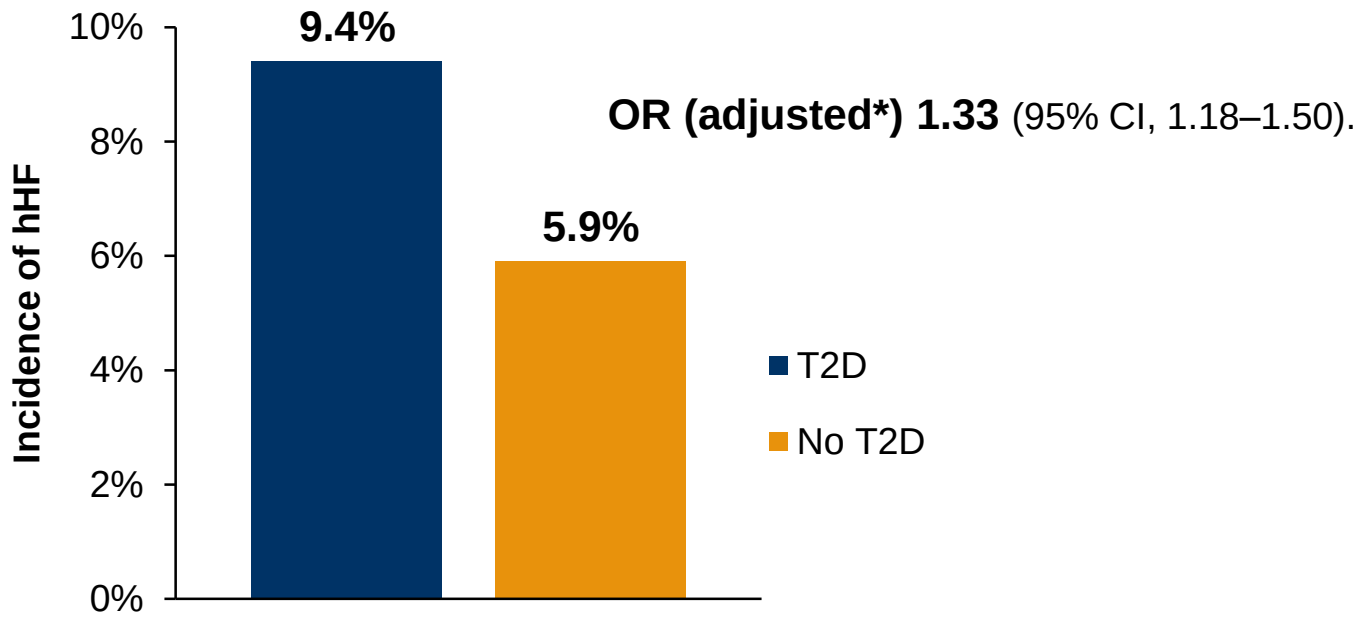

- 115,803 adults 65 years and older in fee-for-service Medicare without a prior HF claim were followed for 5 years
- Incident HF was determined using DRG codes
- Survival was significantly lower in those who developed HF compared with those without HF

HF, heart failure; DRG, diagnosis related group

Bertoni AG, et al. *Diabetes Care.* 2004;27:699–703.

# Type 2 diabetes is a potent, independent risk factor for heart failure

**Four year follow up of a cohort with and without T2D (n=45,227) and either established CVD or CV risk factors**




**OR (adjusted*) 1.33** (95% CI, 1.18–1.50).

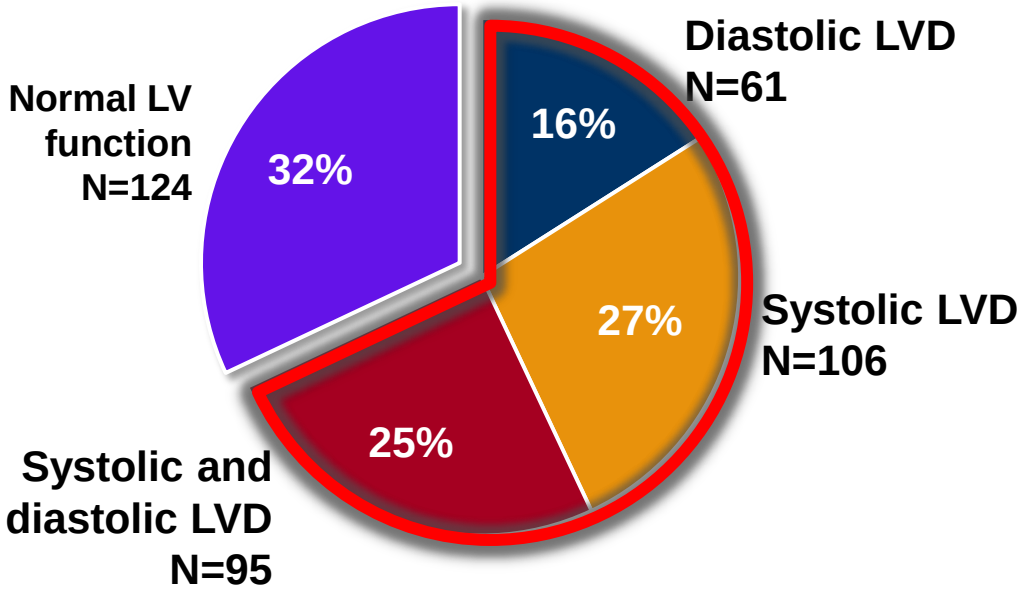
**Diabetes mellitus was associated with a 33% greater risk of hospitalization for heart failure**

hHF, hospitalization for heart failure
Cavender *Circulation*. 2015;132:923-931.

* sex, age, geographic region , cardiovascular risk factors; ischemic event, renal dysfunction, known vascular disease, congestive heart failure, atrial fibrillation, and medications (statins, aspirin, blood pressure treatment, antihyperglycemic agent).

# Left ventricular dysfunction is an early complication of T2 diabetes

**68% of patients with T2D had evidence of LV dysfunction 5 years after T2D diagnosis**




**This suggests the earliest defect in the diabetic heart is diastolic dysfunction**

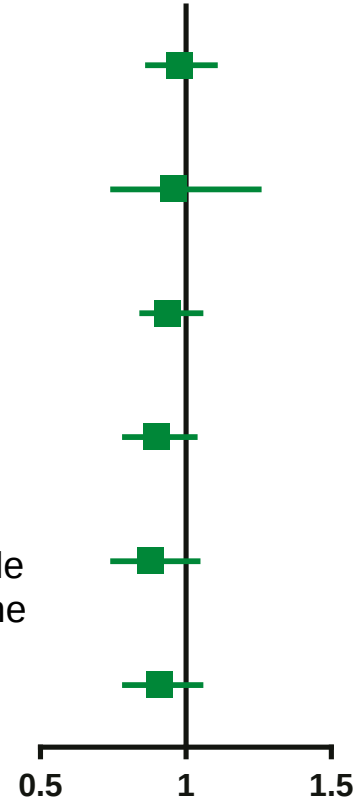
**Patients had no evidence of inducible ischemia by stress testing at baseline**

LV, left ventricular; LVD, LV dysfunction

Faden Diabetes and Clinical Research 2013; Seferović PM, Paulus WJ. *Eur Heart J*. 2015;36:1718-27, 1727a-1727c

# ‘Older’ glucose-lowering agents have not definitively shown positive effects on major CV events …

| Trial | Outcome | HR (95% CI) |
|---|---|---|
| ACE (N=6522)[1]<br>**Acarbose versus placebo + CV prevention therapy** | 5P-MACE: CV death, NF-MI, NF-stroke, hUA, hHF | 0.98 (0.86, 1.11) |
| TOSCA.IT (N=3,028)[2]<br>**PIO versus SU as add-on to MET** | All-cause death, NF-MI, silent MI, NF-stroke, urgent coronary revascularization | 0.96 (0.74, 1.26) |
| ADVANCE (N=11,140)[3]<br>**$HbA_{1c}$ ≤6.5% versus $HbA_{1c}$ >6.5% (gliclazide + any other agent)** | 3P-MACE: CV death, NF-MI, NF-stroke | 0.94 (0.84, 1.06) |
| ACCORD (N=10,251)[4]<br>**$HbA_{1c}$ <6.0% versus $HbA_{1c}$ 7.0–7.9% (MET, SU, TZD, insulin)** | 3P-MACE: CV death, NF-MI, NF-stroke | 0.90 (0.78, 1.04) |
| VADT (N=1791)[5]<br>**$HbA_{1c}$ –1.5% versus the standard group (MET or GLIM, ROSI, insulin)** | 7P-MACE: CV death, MI, stroke, HF, surgery for vascular disease, inoperable CHD, amputation for ischemic gangrene | 0.88 (0.74, 1.05) |
| DEVOTE (N=7367)[6]<br>**IGlar versus IDeg** | 3P-MACE: CV death, NF-MI, NF-stroke | 0.91 (0.78, 1.06) |



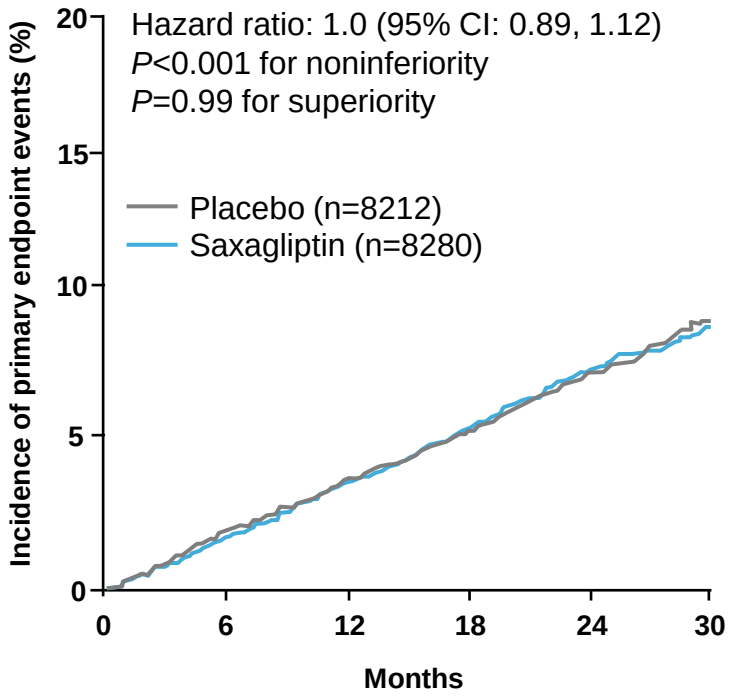

CI, confidence interval; CV, cardiovascular; GLIM, glimepiride; HR, hazard ratio; MACE, major adverse cardiovascular event; hHF, hospitalization for heart failure; HF, heart failure; hUA, hospitalization for unstable angina; MET, metformin; NF, non-fatal; PIO, pioglitazone; ROSI, rosiglitazone; SU, sulfonylurea; TZD, thiazolidinedione

1. Holman RR, et al. *Lancet Diabetes Endocrinol* 2017; doi: 10.1016/S2213-8587(17)30318-2; 2. Vaccaro O, et al. *Lancet Diabetes Endocrinol* 2017;5:887–897;
3. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572; 4. The ACCORD Study Group. *N Engl J Med* 2008;358:2545–2559;
5. Duckworth W, et al. *N Engl J Med* 2009;360:129–139; 6. Marso SP, et al. *N Engl J Med* 2017;377:723–732

# … while DPP-4 inhibitors were largely CV neutral

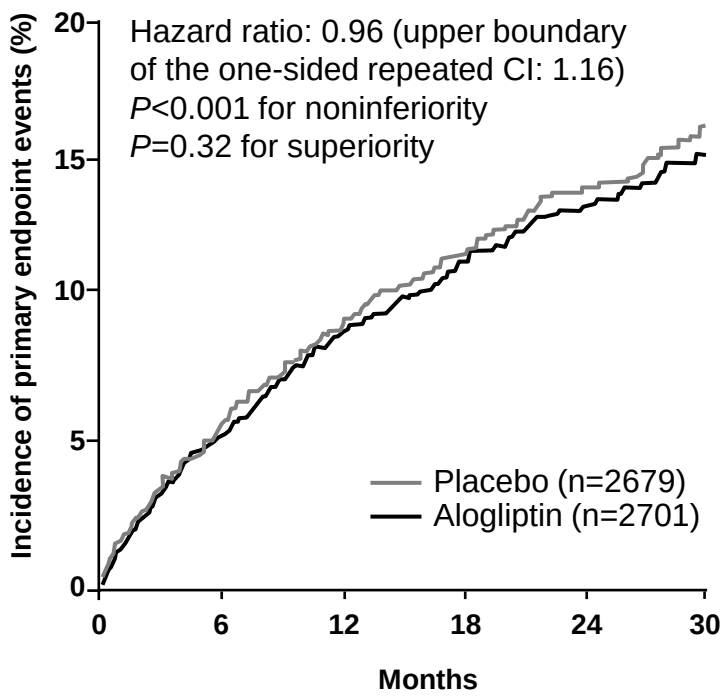
## Saxagliptin (SAVOR trial)[1]

**Primary endpoint:** Composite of CV death, myocardial infarction, or ischemic stroke



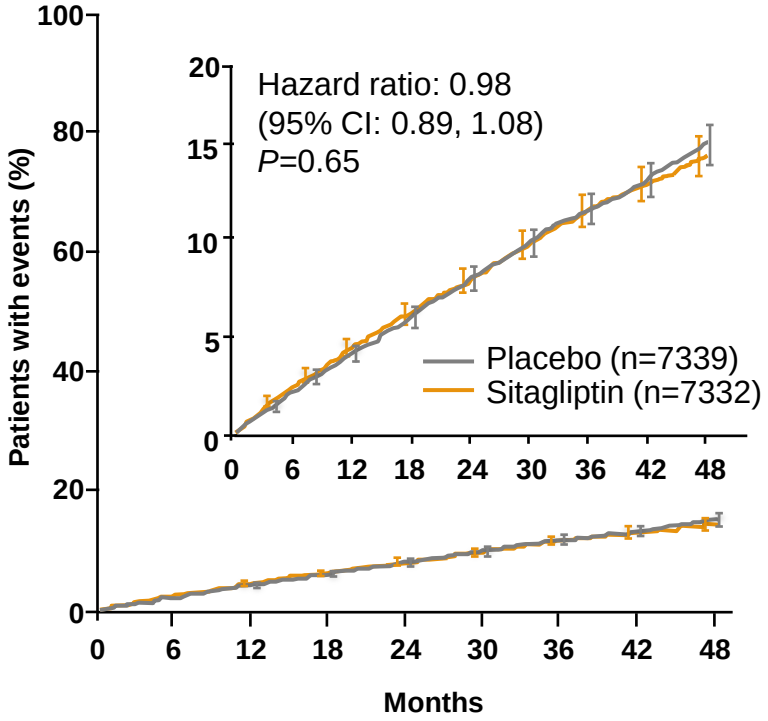

## Alogliptin (EXAMINE trial)[2]

**Primary endpoint:** Composite of CV death, nonfatal myocardial infarction, or nonfatal stroke




## Sitagliptin (TECOS trial)[3]

**Primary endpoint:** Composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina

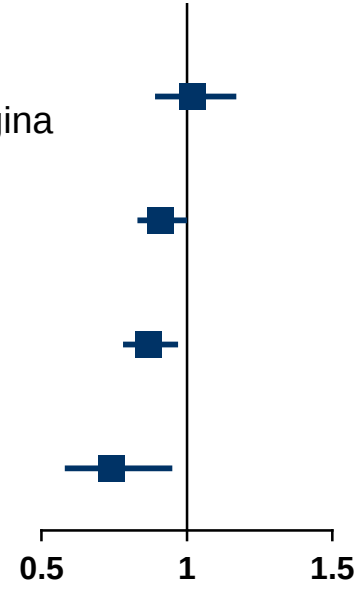



CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Adapted from Scirica B, et al. *N Engl J Med* 2013;369:1317–1326; 2. Adapted from White W, et al. *N Engl J Med* 2013;369:1327−1335;
3. Adapted from Green JB, et al. *N Engl J Med* 2015;373:232–242

# CVOTs with GLP-1 RAs in patients with type 2 diabetes demonstrated heterogeneous results

| Trial | Outcome | HR (95% CI) |
|---|---|---|
| **ELIXA (N=6068)**[1] Lixisenatide vs placebo | Time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina | 1.02 (0.89, 1.17) |
| **EXSCEL (N=14,752)**[2] Exenatide vs placebo | 3P-MACE: CV death, NF-MI, NF-stroke | 0.91 (0.83, 1.00) |
| **LEADER (N=9340)**[3] Liraglutide vs placebo | 3P-MACE: CV death, NF-MI, NF-stroke | 0.87 (0.78, 0.97) |
| **SUSTAIN-6 (N=3297)**[4] Semaglutide vs placebo | 3P-MACE: CV death, NF-MI, NF-stroke | 0.74 (0.58, 0.95) |




CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MI, myocardial infarction; NF, nonfatal; 3P-MACE. 3 point major adverse cardiac event

1. Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; 2. Holman RR, et al. N Engl J Med 2017;377:1228–1239; 3. Marso SP, et al. *N Engl J Med* 2016;375:311–322; 4. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844

# The impact of GLDs on heart failure has also been heterogeneous and may depend on the class

| Class | Study | Impact on HF | |
|---|---|---|---|
| Insulin | Review of diabetes registry from Kaiser Permanente Northwest Registry (n=8063) [1] | ↑ | 2 fold increase* |
| SU (2nd generation) | Analysis of UK General Practice Research Database (n=91,521) [2] | ↑ | HR 1.18 – 1.30 (p=0.01 and p< 0.001)** |
| TZD | Meta-analysis of patients with prediabetes and diabetes (n=20,191) [3] | ↑ | RR 1.72 [1.21-2.42] (p=0.002) |
| DPP4 | Meta-analysis of RCT with DPP4s [4] | ↑ | OR 1.19 [1.03-1.37] (p=0.015) |
| GLP-1 | Meta-analysis of four CV outcome studies with GLP-1 receptor antagonists[5] | ↔ | HR 0.93 [0.83-1.04] (p=0.20) |

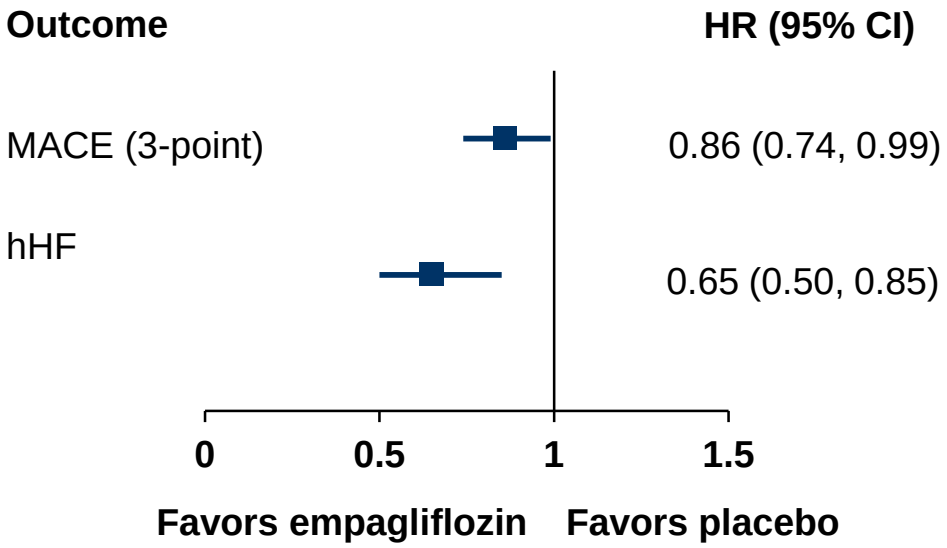
GLD, glucose lowering drugs; HR, hazard ratio; RR relative risk; RCT randomized clinical trials; HF, heart failure; SU, sulfonylurea; TZD, thiazolidinedione *when insulin was added; ** compared to metformin monotherapy

1. Nichols Diabetes Metab Res Rev. 2005;21:51-57; 2.Tzoulaki et al. BMJ2009;339:b4731; 3. Lago et al. Lancet 2007; 370:1129-36; 4. Monami et al. Nutr Meta Cardiovasc Dis 2014;24:689-697; 5. Bethel et al, Lancet Diabetes Endocrinology 2018;6:105-13

# CV outcomes data for SGLT2 inhibitors are building

**Two SGLT2 studies demonstrate a reduction in both MACE and heart failure endpoints**

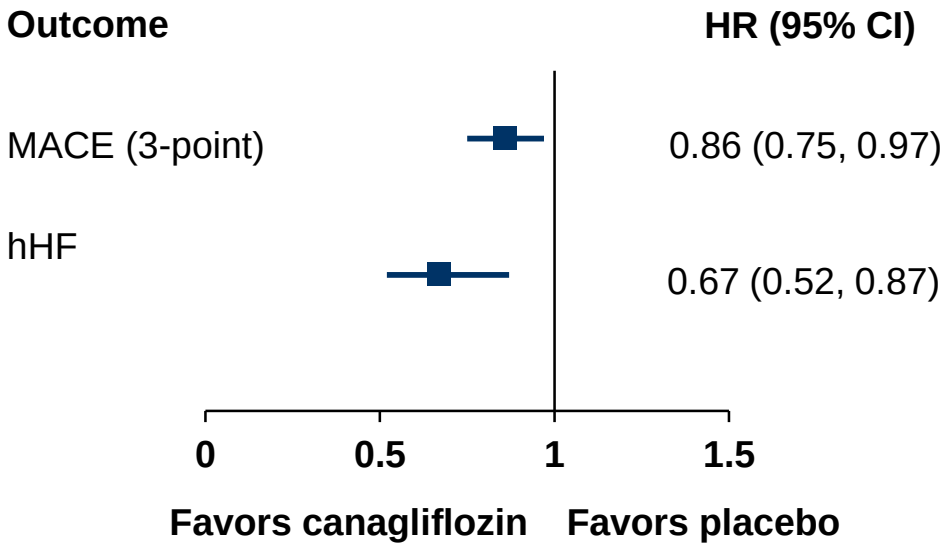
## EMPA-REG OUTCOME




**Demonstrated a significant reduction in CV events in patients receiving empagliflozin**

**Established CVD: 99%**

## CANVAS



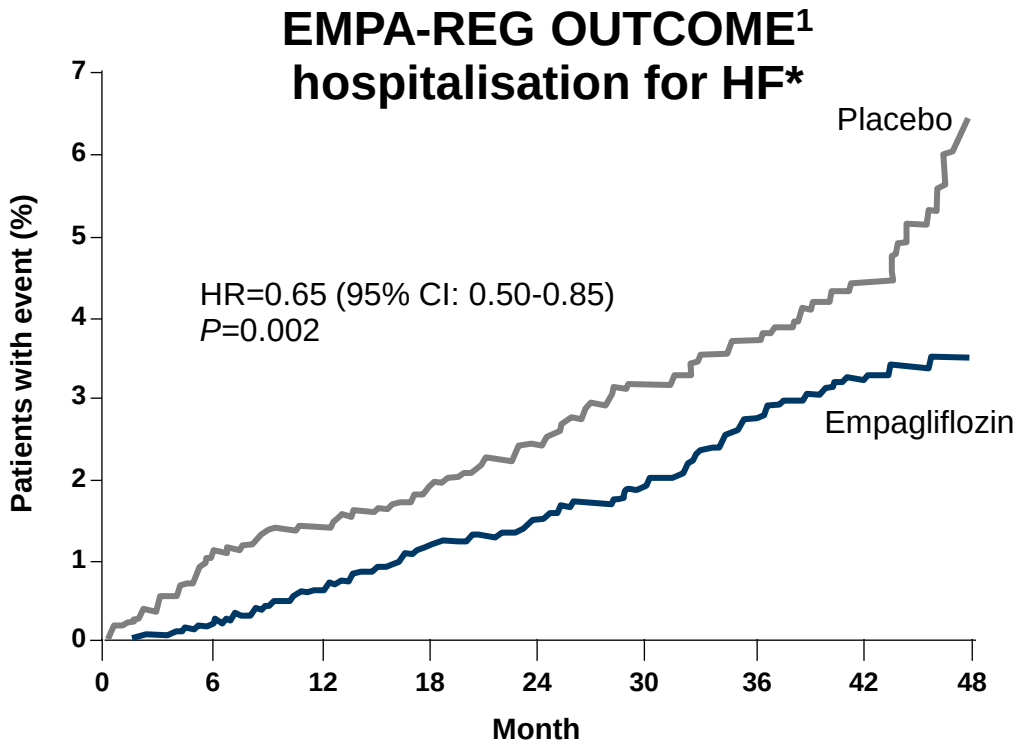

**Demonstrated a significant reduction in CV events in patients receiving canagliflozin**

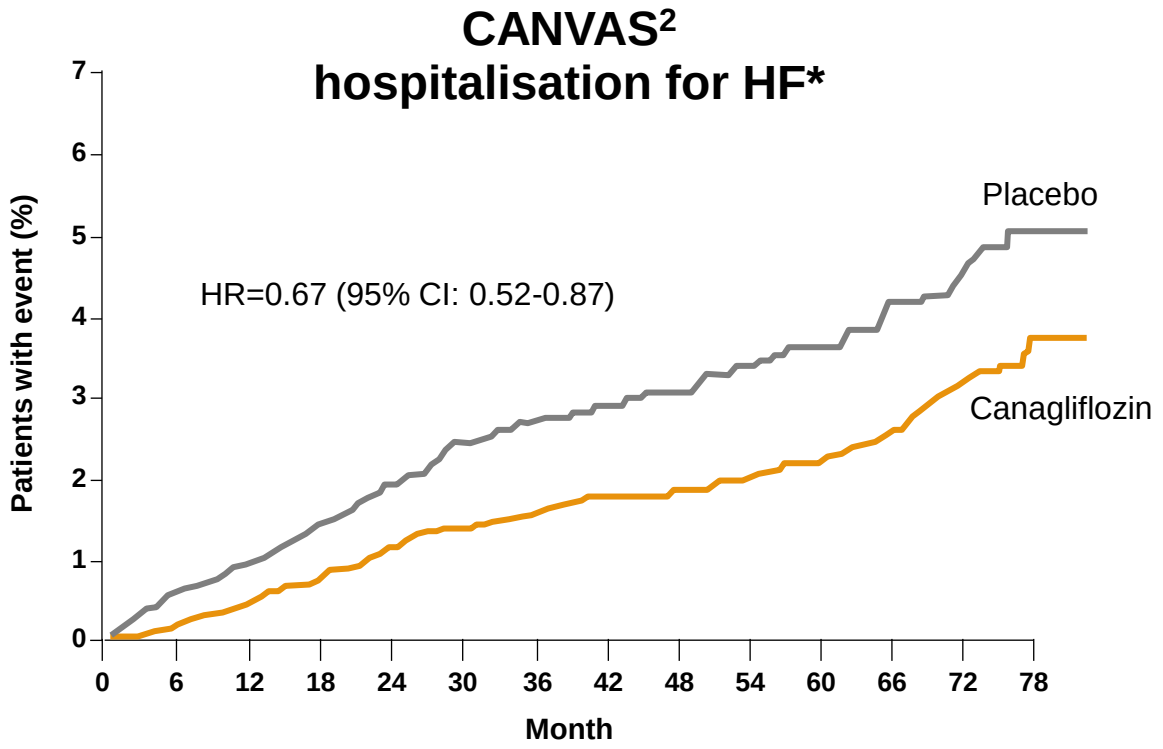
**Established CVD: 66%**

MACE, major adverse cardiovascular event (CV death, nonfatal MI and nonfatal stroke); MI, myocardial infarction; hHF hospitalization for heart failure.

Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; Neal B, et al. *N Engl J Med* 2017 377:644-57

# Hypothesis about HF prevention have emerged from SGLT2i trials




**These hypothesis generating exploratory analyses* will need to be confirmed in future trials**

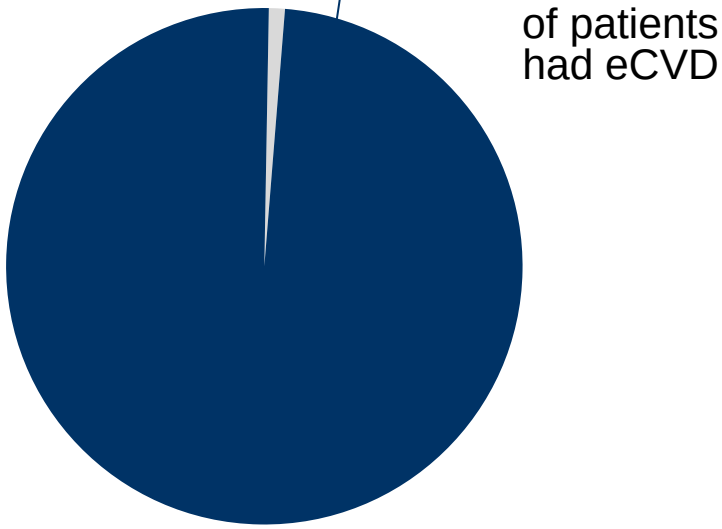
***hHF is an exploratory end point in both studies.** In the EMPA-REG OUTCOME protocol it was considered an exploratory end point. In CANVAS, after the MACE end point, the hierarchical testing started with all-cause mortality. This did not meet statistical significance thus no additional testing was done. Therefore the HF end point is considered exploratory.

CI, confidence interval; CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

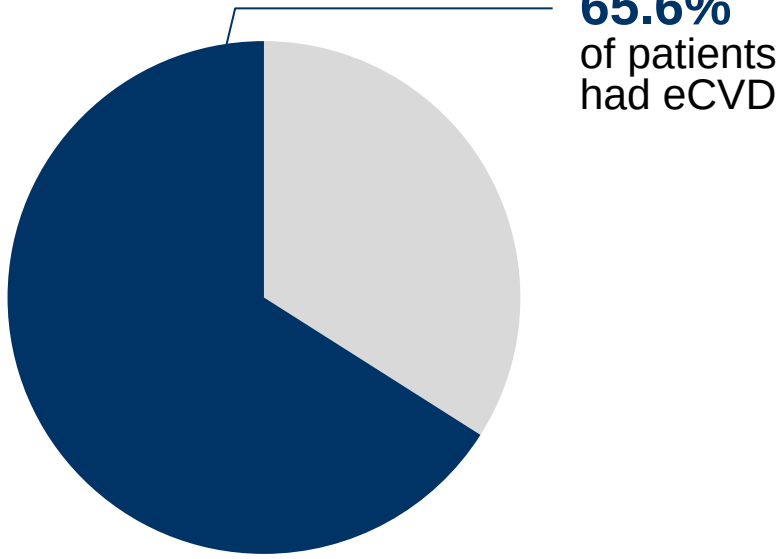
**1.** Zinman B, et al. *N Engl J Med.* 2015;373:2117–2128. **2.** Neal B, et al. *N Engl J Med.* 2017;377:644-657.

# While EMPA-REG and CANVAS suggest CV risk can be reduced, these results were seen in T2D patients who predominantly had established CV disease

**EMPA-REG OUTCOME[1]**
**(N=7,020)**




**CANVAS[2]**
**(N=10,142)**




>99% of T2D patients in the EMPA-REG OUTCOME trial and 65.6% of the T2D patients in the CANVAS trials already had established CV disease i.e. had a previous CV event (MI, stroke) or documented atherosclerosis (coronary artery stenosis, peripheral arterial stenosis)[1,2]

CV, cardiovascular; eCVD, established CV disease; MI, myocardial infarction; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes.

1. Zinman B, et al. N Engl J Med 2015;373:2117–2128; 2. Neal B, et al. N Engl J Med 2017;377:644–657

CVDREAL

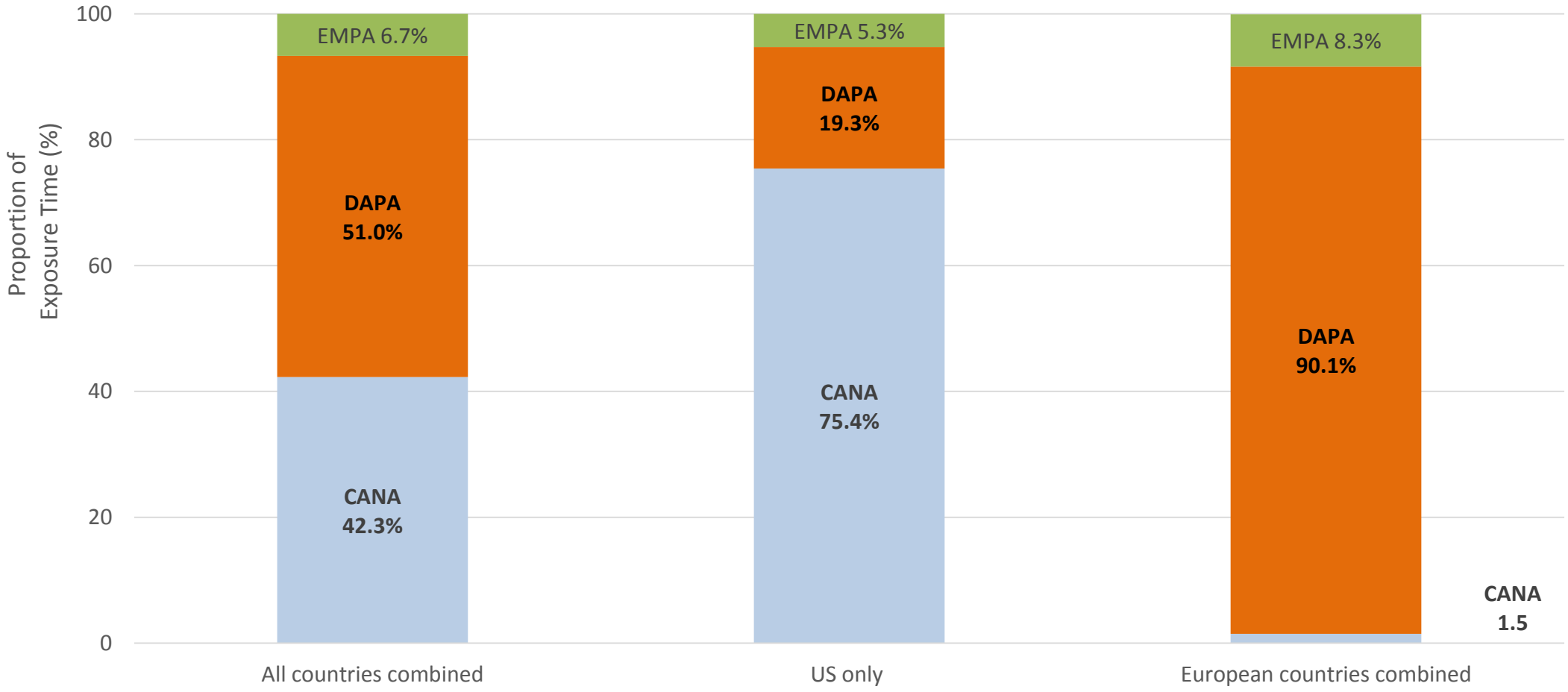
ACC.17

# The CVD-REAL Study

## Lower Rates of Hospitalization for Heart Failure and All-Cause Death in New Users of SGLT-2 Inhibitors versus Other Glucose Lowering Drugs: The CVD-REAL Study

- Real World Data from 6 Countries
  (US, UK, Germany, Sweden, Denmark, Norway)
- > 300,000 patients

# CONTRIBUTION OF SGLT-2 INHIBITORS TO ALL-CAUSE DEATH AND HHF IN CVD REAL

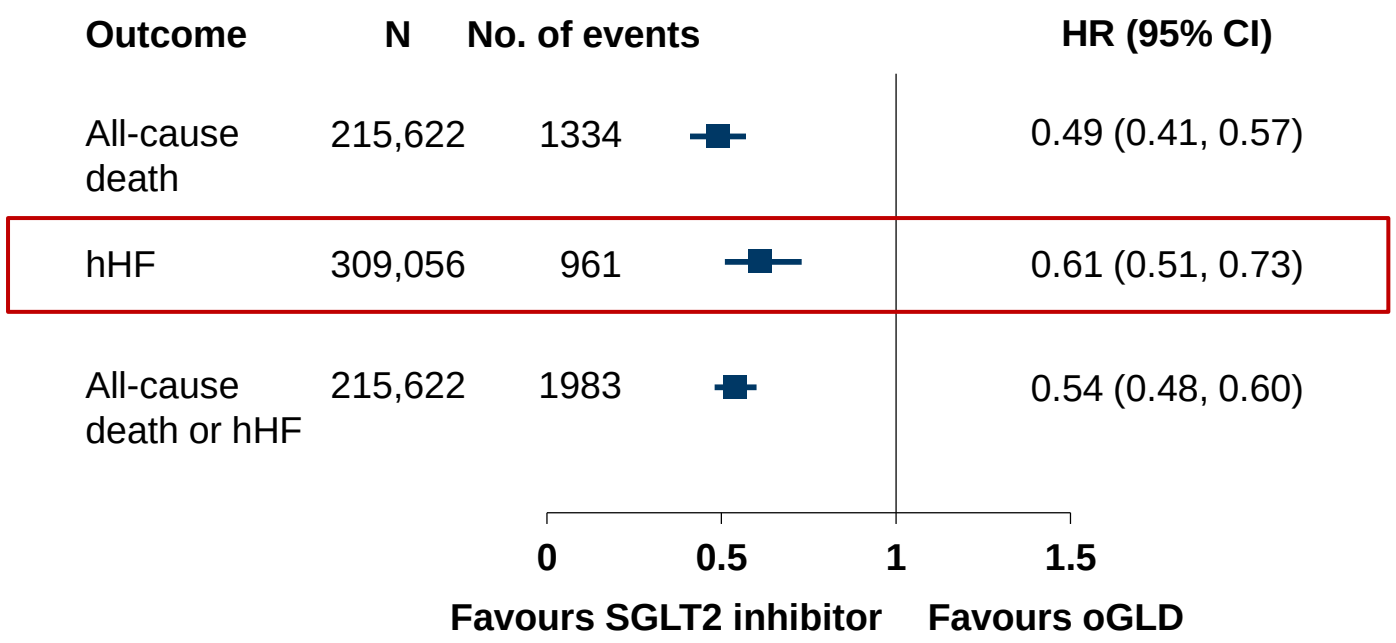



*Toulis et al, JCEM, Feb 2017*

US, Norway, Sweden, Denmark, UK, Germany

# In CVD-REAL, a real-world study, SGLT2 inhibitors were associated with reductions in CV outcomes as well as hHF compared to oGLDs

## All-cause death and hHF for SGLT2 inhibitors vs oGLDs[1]

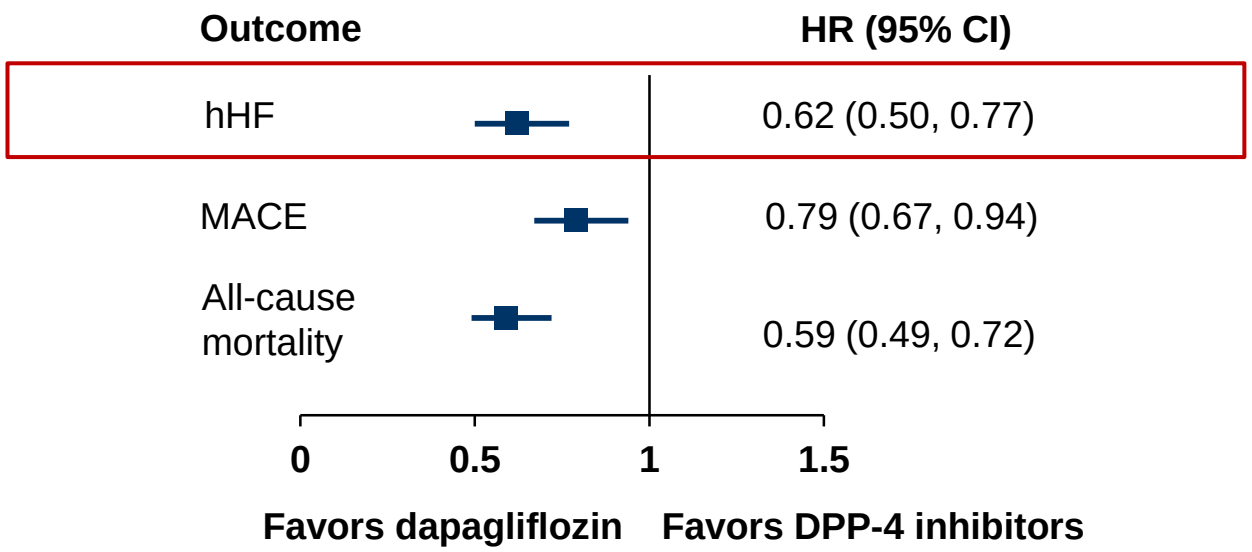



- **13% of patients had established CVD***
- **Compared to oGLDs, SGLT2 inhibitors were associated with a 39% reduction in hHF**

*Previous event of myocardial infarction, stroke, unstable angina, heart failure or atrial fibrillation.
CI, confidence interval; CVD, cardiovascular disease; hHF, hospitalisation for heart failure; HR, hazard ratio; oGLD, other glucose-lowering drug.
SGLT2, sodium-glucose cotransporter-2.
Kosiborod M, et al. *Circulation.* 2017;136:249–259.

# Dapagliflozin versus DPP-4 inhibitors was associated with reductions in CV endpoints and death in a population with a broad cardiovascular risk profile

**MACE and all-cause mortality for dapagliflozin vs DPP-4 inhibitors[2]**




- **23% of patients had established CVD**
- **Compared to DPP4i, Dapagliflozin was associated with a 38% reduction in hHF**

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; hHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiac event; SGLT2, sodium–glucose co-transporter 2; oGLD, other glucose-lowering drug.

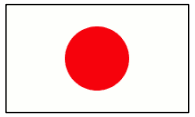
1. Persson F, et al. *Diabetes Obes Metab* 2018;20:344-351

# The CVD-REAL 2 Study (Asia Data)

## Lower Risk of Cardiovascular Events and Death Associated with Initiation of SGLT-2 Inhibitors versus Other Glucose Lowering Drugs

- Real World Data from 6 Countries
  (S. Korea, Japan, Singapore, Australia, Canada, Israel)

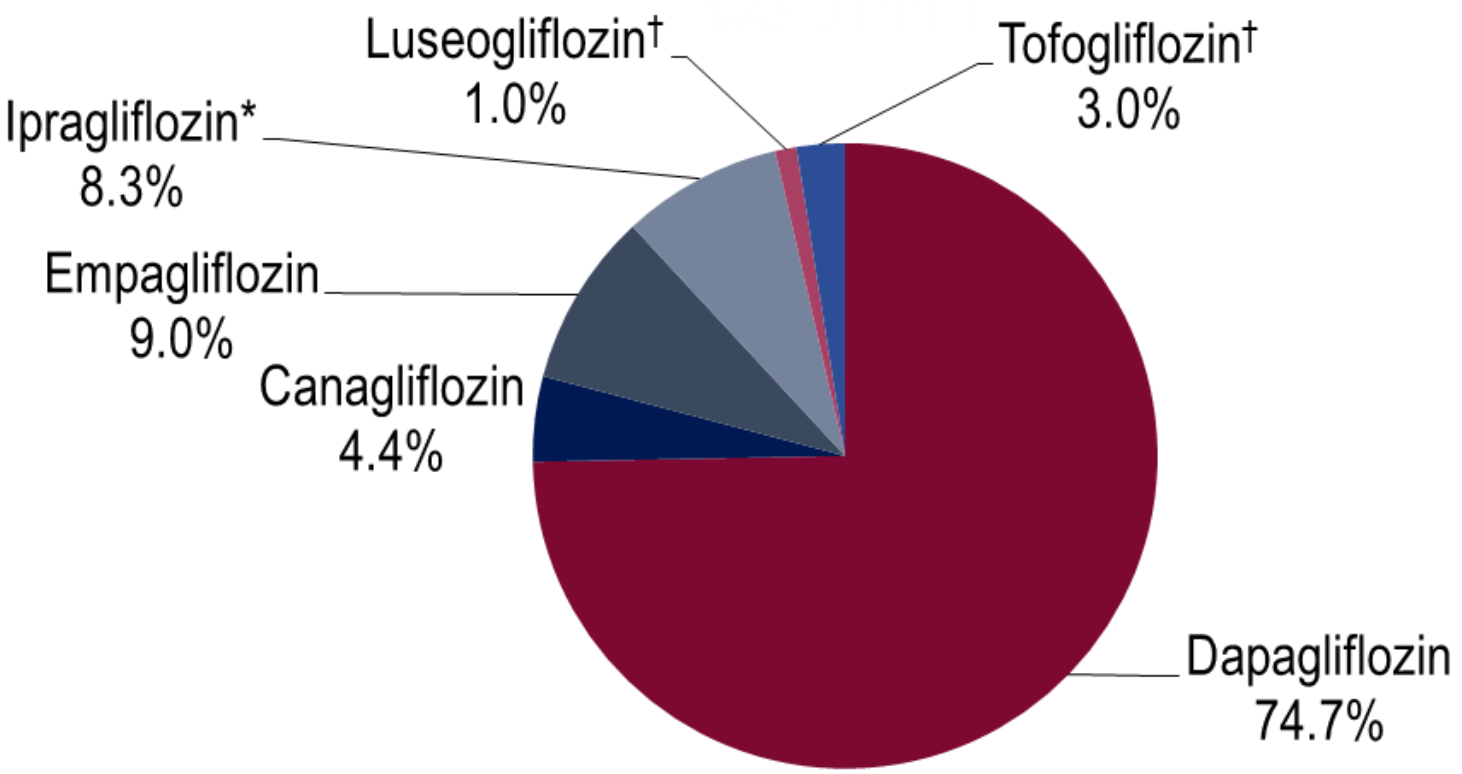
- > 400,000 Patients




CVDREAL 2

# Use of SGLT-2i: Proportion of Exposure Time

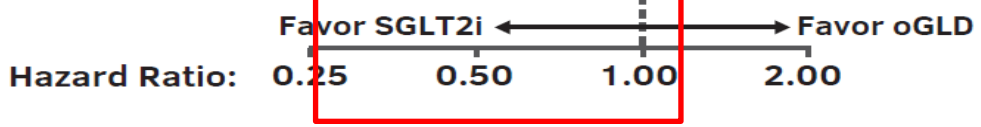



*In South Korea and Japan; †In Japan only.

# Subgroup Analyses – Outcomes With and Without CVD at Baseline

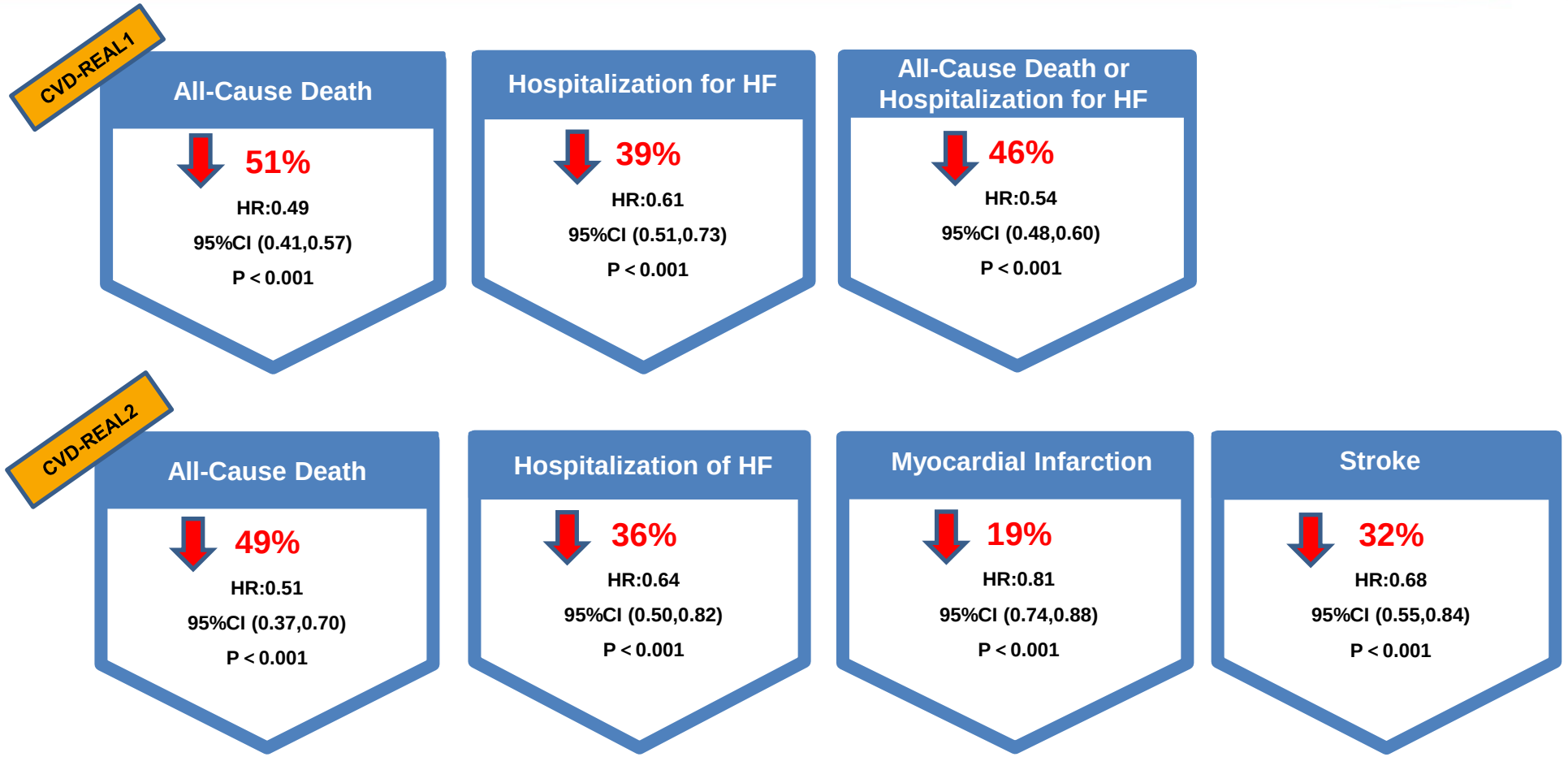
CVDREAL 2

| Event | | Event rate | HR (95% CI) | P-value interaction |
|---|---|---|---|---|
| All-cause death | Prior CVD | 1.98 | | 0.198 |
| | No Prior CVD | 0.70 | | |
| Heart Failure | Prior CVD | 3.73 | | 0.738 |
| | No Prior CVD | 0.60 | | |
| HHF or ACD | Prior CVD | 5.31 | | 0.303 |
| | No Prior CVD | 1.23 | | |
| MI | Prior CVD | 1.15 | | 0.595 |
| | No Prior CVD | 0.30 | | |
| Stroke | Prior CVD | 3.73 | | 0.299 |
| | No Prior CVD | 0.74 | | |




ITT, adjusted analysis

# Summary of CVD-REAL 1 & CVD-REAL 2 results




Kosiborod M et al. Circulation. 2017 Jul 18;136(3):249-259

# DECLARE-TIMI58 TRIAL: THE LARGEST (N=17,160) OUTCOME TRIAL IN SGLT-2 INHIBITORS

**Established CV disease n=~7,000 (40%):**

Age ≥40 years

**AND** ≥1 additional diagnoses:

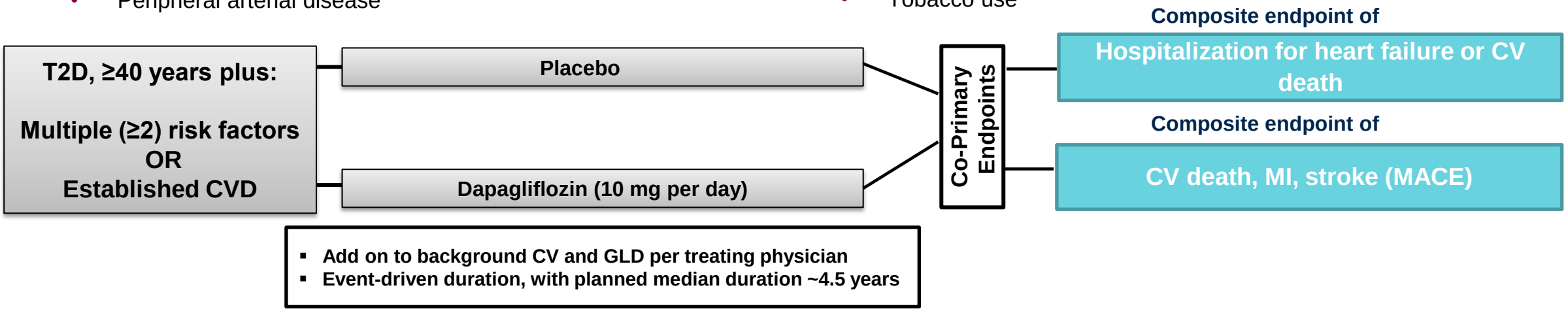
- Ischemic heart disease
- Cerebrovascular disease
- Peripheral arterial disease

**Multiple risk factors n=~10,000 (60%):**

Age ≥55 years (men), ≥60 years (women)

**AND** ≥1 additional risk factors:

- Dyslipidemia
- Hypertension
- Tobacco use



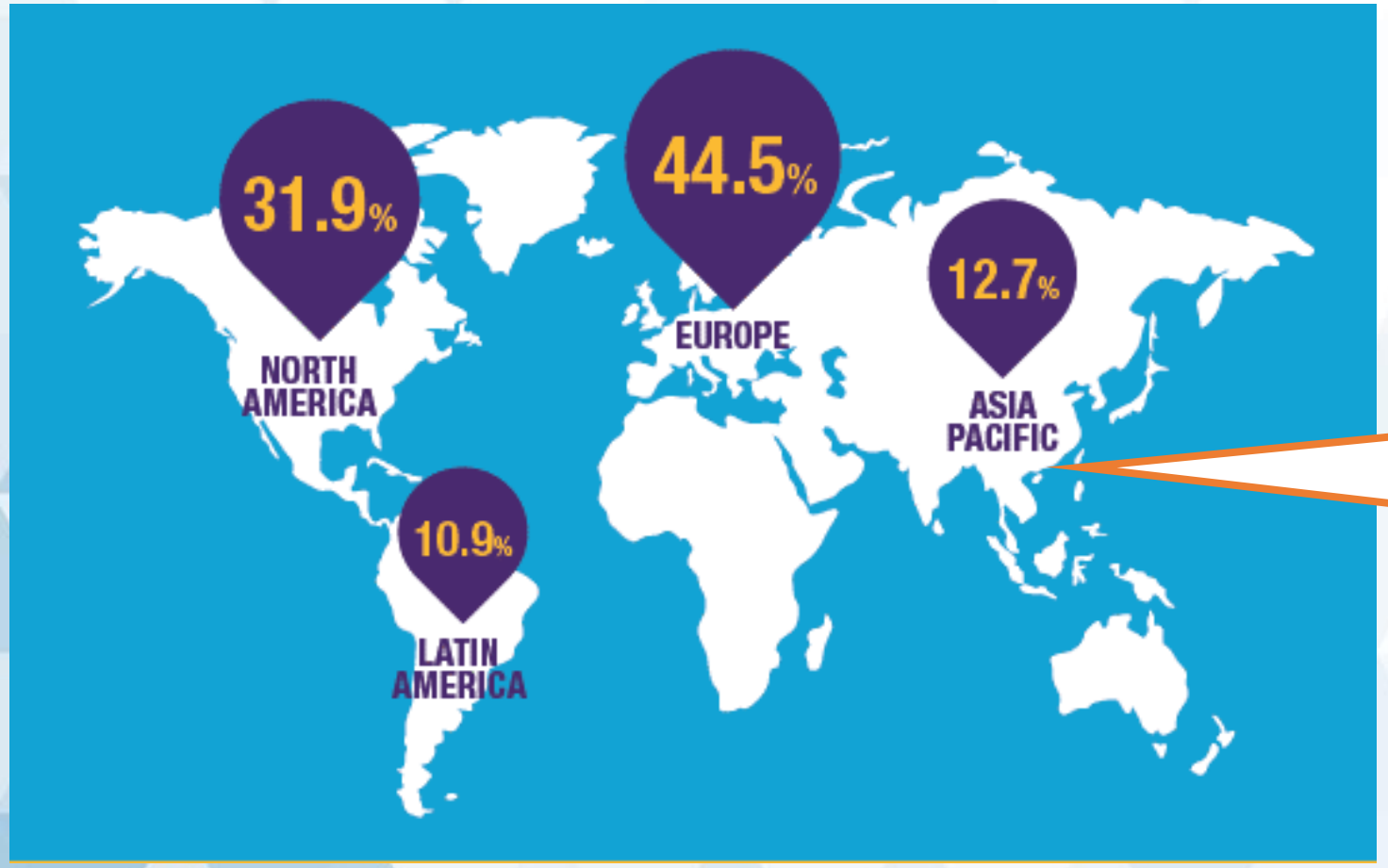

- **Prior to the first interim analysis, the secondary endpoint of hHF was elevated to a composite primary endpoint of hHF and CV death**
- **Therefore DECLARE will provide a comprehensive assessment of the impact of dapagliflozin on common and important diabetes-related CV events**

Raz I, et al. Presented at the 77th Scientific Sessions of the American Diabetes Association, June 9-13, 2017, San Diego, CA

## Outcomes

- Primary safety outcome
  - Non inferiority for 3-pt MACE (CV death, MI or ischaemic stroke)
- Co-primary efficacy outcomes
  - Composite of CV death or hospitalization for heart failure
  - 3-pt MACE
- Secondary outcomes
  - Renal composite (40% fall in eGFR, ESRD or renal or CV death)
  - All-cause mortality

# DECLARE Study Population




China + HONG KONG
~300 subjects

# Baseline Characteristics

| | Full Trial Cohort<br>N = 17160 |
|---|---|
| Age, yrs, Mean (SD) | 64 (7) |
| Female Sex (%) | 37 |
| BMI, Mean (SD) | 32 (6) |
| Duration of T2DM, yrs, Median (IQR) | 11 (6, 16) |
| HbA1c (%), Mean (SD) | 8.3 (1.2) |
| eGFR (CKD-EPI), Mean (SD) | 85 (16) |
| Region (%): North America | 32 |
| Europe | 44 |
| Latin America | 11 |
| Asia Pacific | 13 |
| Established CV Disease (%) | 41 |
| History of Heart Failure (%) | 10 |

P=NS for all between treatment arm comparisons

# Baseline Characteristics: Medication Use

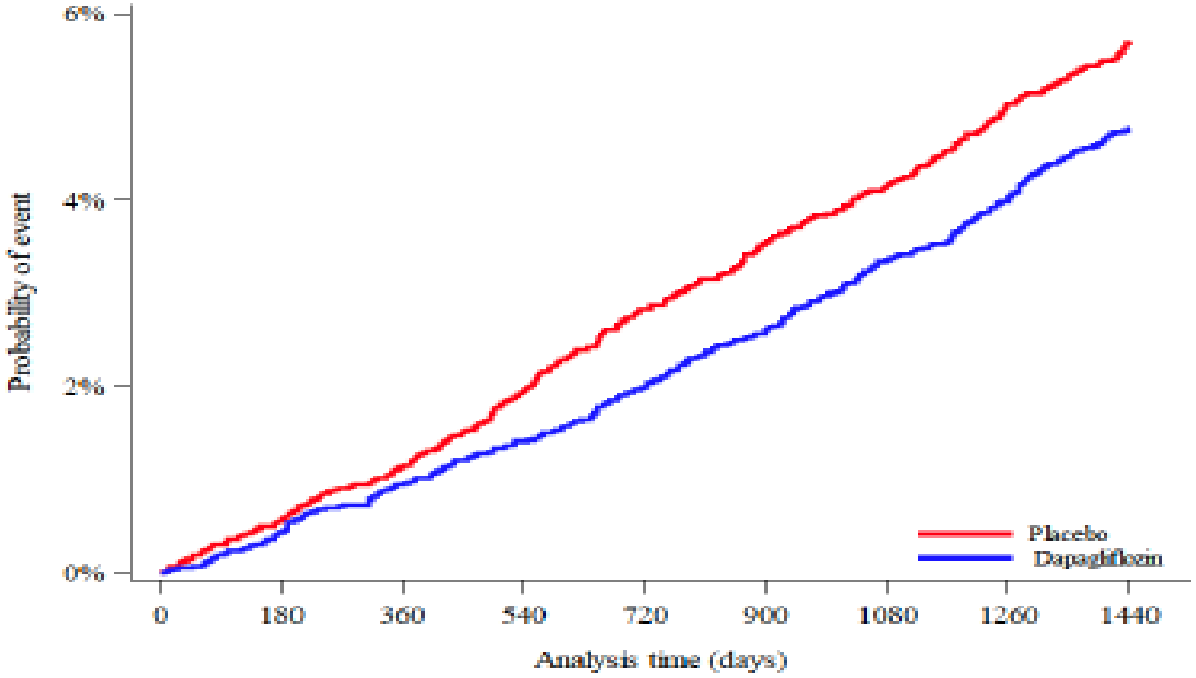
| | Full Trial Cohort N = 17160 |
|---|---|
| Glucose lowering therapies (%) | |
| Metformin | 82 |
| Insulin | 41 |
| Sulfonylurea | 43 |
| DPP4i | 17 |
| GLP-1 RA | 4 |
| Cardiovascular therapies (%) | |
| Antiplatelet | 61 |
| ACEI/ARB | 81 |
| Beta-blocker | 53 |
| Statin or Ezetimibe | 75 |

P=NS for all between treatment arm comparisons

# Primary Endpoints

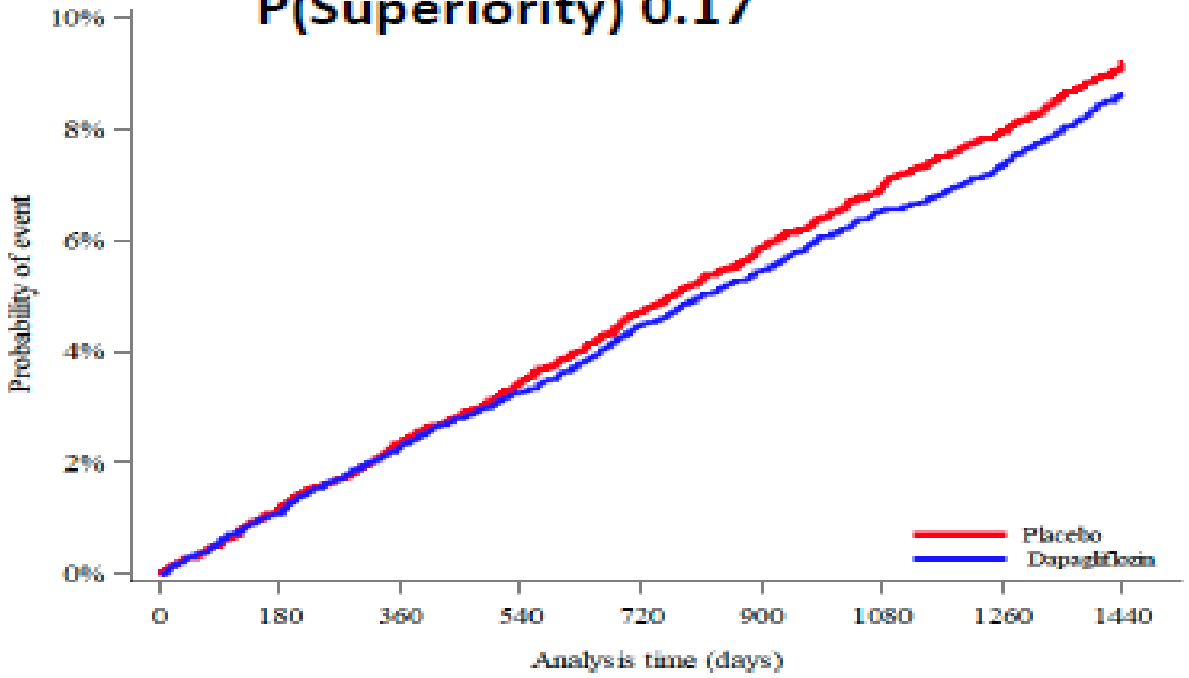
## CVD/HHF

**4.9% vs 5.8%**
**HR 0.83 (0.73-0.95)**
**P(Superiority) 0.005**




## MACE

**8.8% vs 9.4%**
**HR 0.93 (0.84-1.03)**
**P(Noninferiority) <0.001**
**P(Superiority) 0.17**



# Secondary Endpoints

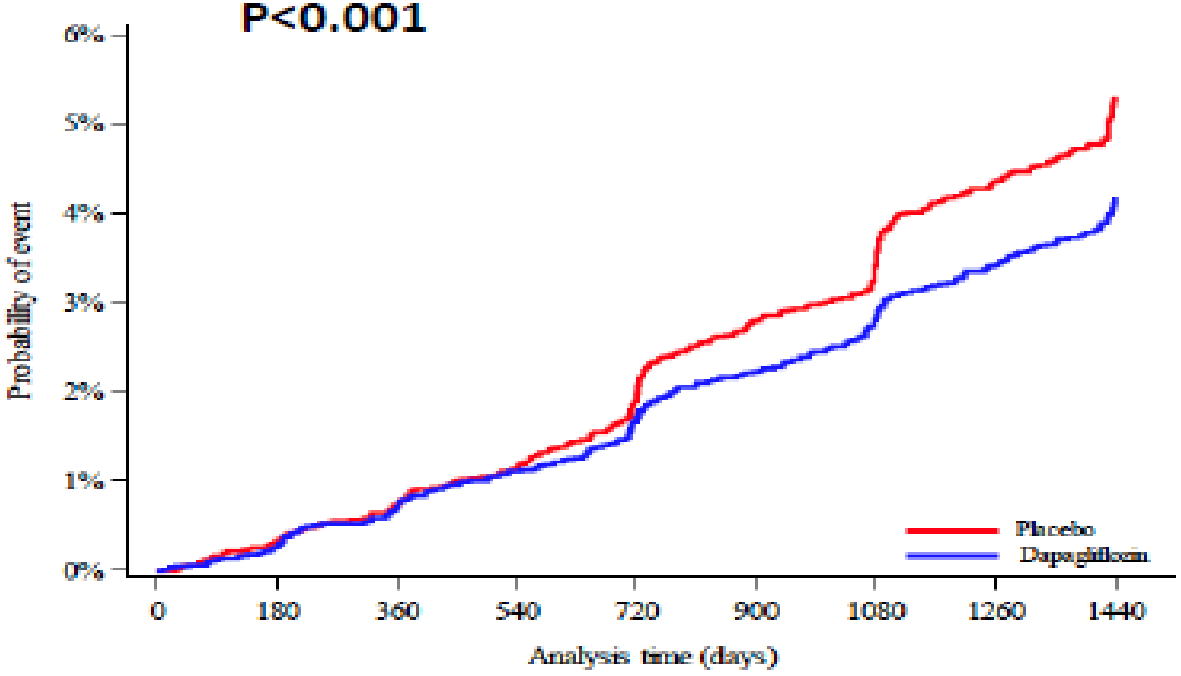
## Renal Composite EP

40%↓ eGFR, ESRD, Renal or CV death

4.3% vs. 5.6%

HR 0.76 (0.67-0.87)

P<0.001

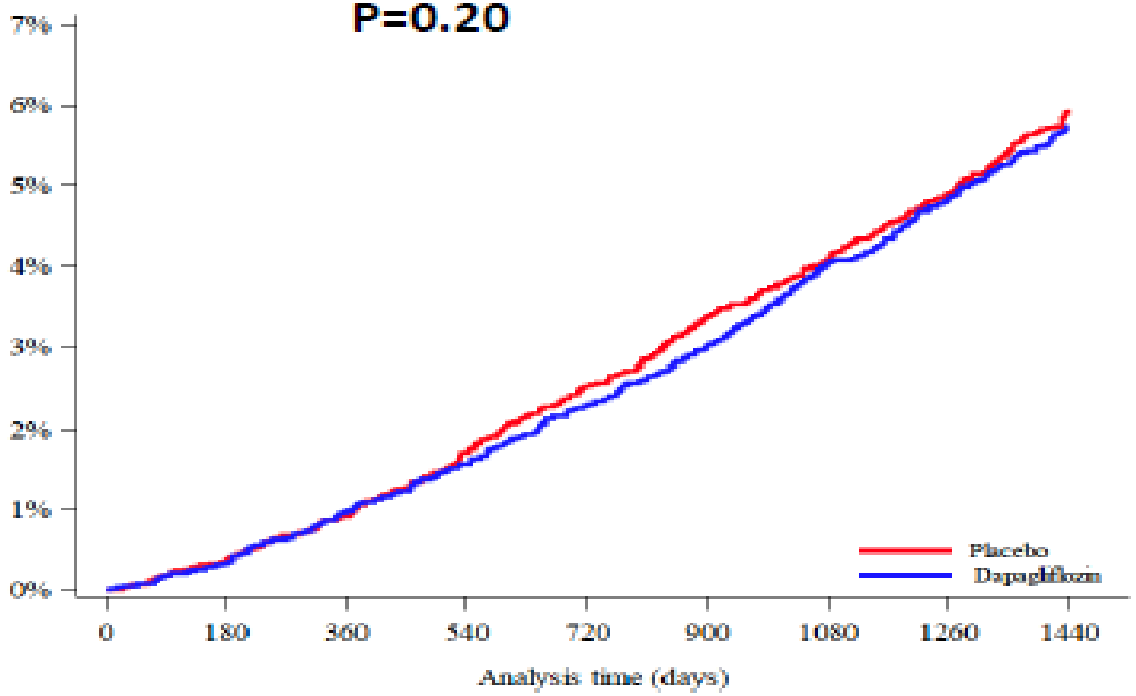



## All-Cause Mortality

6.2% vs 6.6%

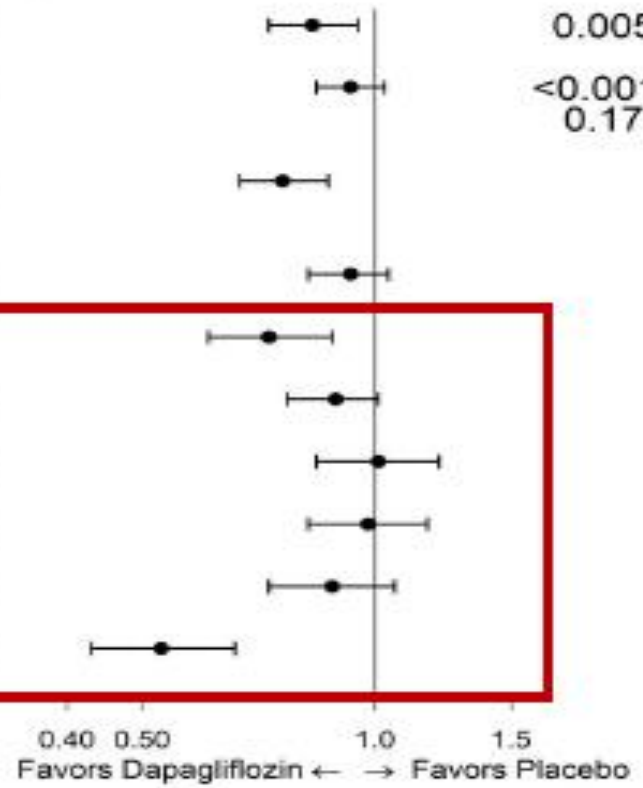
HR 0.93 (0.82-1.04)

P=0.20



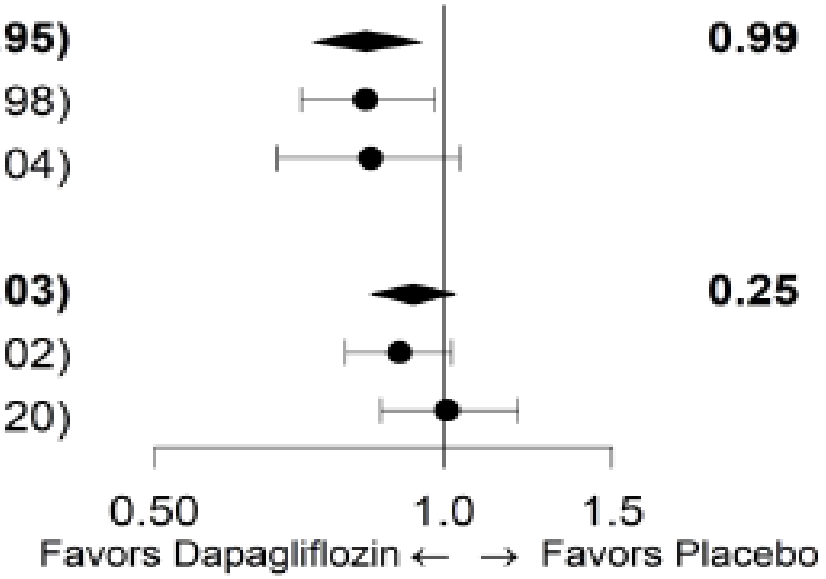
# Endpoints and Components

| | Dapagliflozin rate/1000 patient-yr | Placebo rate/1000 patient-yr | Hazard Ratio (95% CI) | P value |
|---|---|---|---|---|
| **CV death/HHF** | 12.2 | 14.7 | 0.83 (0.73-0.95) | 0.005* |
| **MACE** | 22.6 | 24.2 | 0.93 (0.84-1.03) | <0.001** 0.17* |
| **40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal or CV death** | 10.8 | 14.1 | 0.76 (0.67-0.87) | |
| **All-cause death** | 15.1 | 16.4 | 0.93 (0.82-1.04) | |
| **HHF** | 6.2 | 8.5 | 0.73 (0.61-0.88) | |
| **Myocardial infarction** | 11.7 | 13.2 | 0.89 (0.77-1.01) | |
| **Ischemic Stroke** | 6.9 | 6.8 | 1.01 (0.84-1.21) | |
| **CV death** | 7.0 | 7.1 | 0.98 (0.82-1.17) | |
| **Non-CV death** | 6.0 | 6.8 | 0.88 (0.73-1.06) | |
| **40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal death** | 3.7 | 7.0 | 0.53 (0.43-0.66) | |



# Primary Efficacy Endpoints by Presence of ASCVD vs MRF

| Outcomes | Dapagliflozin Events per 1000 pt years | Placebo Events per 1000 pt years | Hazard Ratio (95% CI) | P value for interaction |
|---|---|---|---|---|
| **CV death/HHF** | **12.2** | **14.7** | **0.83 (0.73-0.95)** | **0.99** |
| ASCVD | 19.9 | 23.9 | 0.83 (0.71-0.98) | |
| MRF | 7.0 | 8.4 | 0.84 (0.67-1.04) | |
| **MACE** | **22.6** | **24.2** | **0.93 (0.84-1.03)** | **0.25** |
| ASCVD | 36.8 | 41.0 | 0.90 (0.79-1.02) | |
| MRF | 13.4 | 13.3 | 1.01 (0.86-1.20) | |



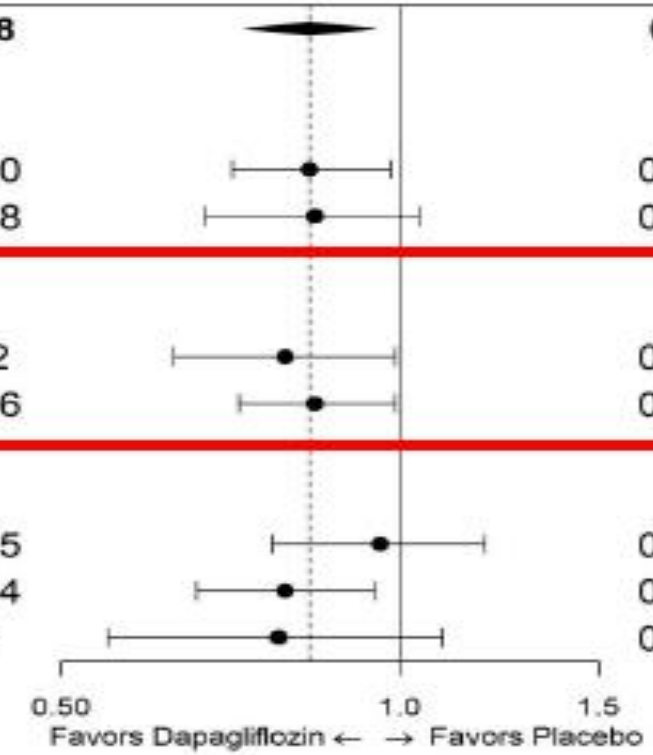
# Effect on CVD/HHF in Key Subgroups

DECLARE TIMI-58 Dapagliflozin Effect on Cardiovascular Events

TIMI

## CVD/HHF

| | Dapagliflozin n\N | Placebo n\N | HR (95%-CI) | P Value for Interaction |
|---|---|---|---|---|
| **Total Cohort** | **417/8582** | **496/8578** | **0.83 (0.73-0.95)** | |
| **Risk Group** | | | | **0.99** |
| ASCVD | 272/3474 | 325/3500 | 0.83 (0.71-0.98) | |
| MRF | 145/5108 | 171/5078 | 0.84 (0.67-1.04) | |
| **History of HF** | | | | **0.60** |
| Yes | 142/852 | 172/872 | 0.79 (0.63-0.99) | |
| No | 275/7730 | 324/7706 | 0.84 (0.72-0.99) | |
| **eGFR** | | | | **0.37** |
| >=90 mL/min/1.73m2 | 163/4137 | 163/4025 | 0.96 (0.77-1.19) | |
| 60 - <90 mL/min/1.73m2 | 199/3838 | 252/3894 | 0.79 (0.66-0.95) | |
| <60 mL/min/1.73m2 | 55/606 | 81/659 | 0.78 (0.55-1.09) | |



# Key Safety Events

| | Dapagliflozin (%) | Placebo (%) | Between Group Comparison |
|---|---|---|---|
| Treatment emergent SAE | 34.1 | 36.2 | P<0.001 |
| Treatment emergent AE leading to drug D/C | 8.1 | 6.9 | P=0.01 |
| Major Hypoglycemia | 0.7 | 1.0 | P=0.02 |
| Diabetic Ketoacidosis* (DKA) | 0.3 | 0.1 | P=0.02 |
| Amputation | 1.4 | 1.3 | NS |
| Fracture | 5.3 | 5.1 | NS |
| Acute Kidney Injury | 1.5 | 2.0 | P=0.002 |
| Symptoms of volume depletion | 2.5 | 2.4 | NS |
| Genital infection (SAE, DAE) | 0.9 | 0.1 | P<0.001 |
| Urinary tract infection (SAE, DAE) | 1.5 | 1.6 | NS |
| Fournier's Gangrene | 0.01 | 0.08 | NS |
| Cancer of Bladder* | 0.3 | 0.5 | P=0.02 |

DECLARE
TIMI-58
Dapagliflozin Effect on Cardiovascular Events

TIMI

# In DECLARE – TIMI 58, the largest SGLT-2i trial, which included a broad representation of 1° and 2° prevention patients:

- **Dapagliflozin reduced CVD/HHF and was safe with regard to MACE and appeared to reduce renal events**
  - Reduction in CVD/HHF was consistent regardless of baseline ASCVD or HF
- **Dapagliflozin was safe and generally well-tolerated**
  - ↑ Genital infections & DKA
  - No difference in: amputation, fracture, or stroke
  - ↓ Hypoglycemia, AKI, bladder Ca

DECLARE
TIMI-58
Dapagliflozin Effect on Cardiovascular Events

TIMI

# Now with the context of 3 large CVOTs:

- *SGLT2i have moderate benefits on atherosclerotic MACE that appear confined to those with established ASCVD*

- *SGLT2i have robust effects on reducing the risk of heart failure and renal outcomes which do not appear dependent on baseline atherosclerotic risk, prior HF*

**These data with dapagliflozin from DECLARE - TIMI 58 extend the benefit of SGLT2i to a broader population of patients for primary and secondary prevention**

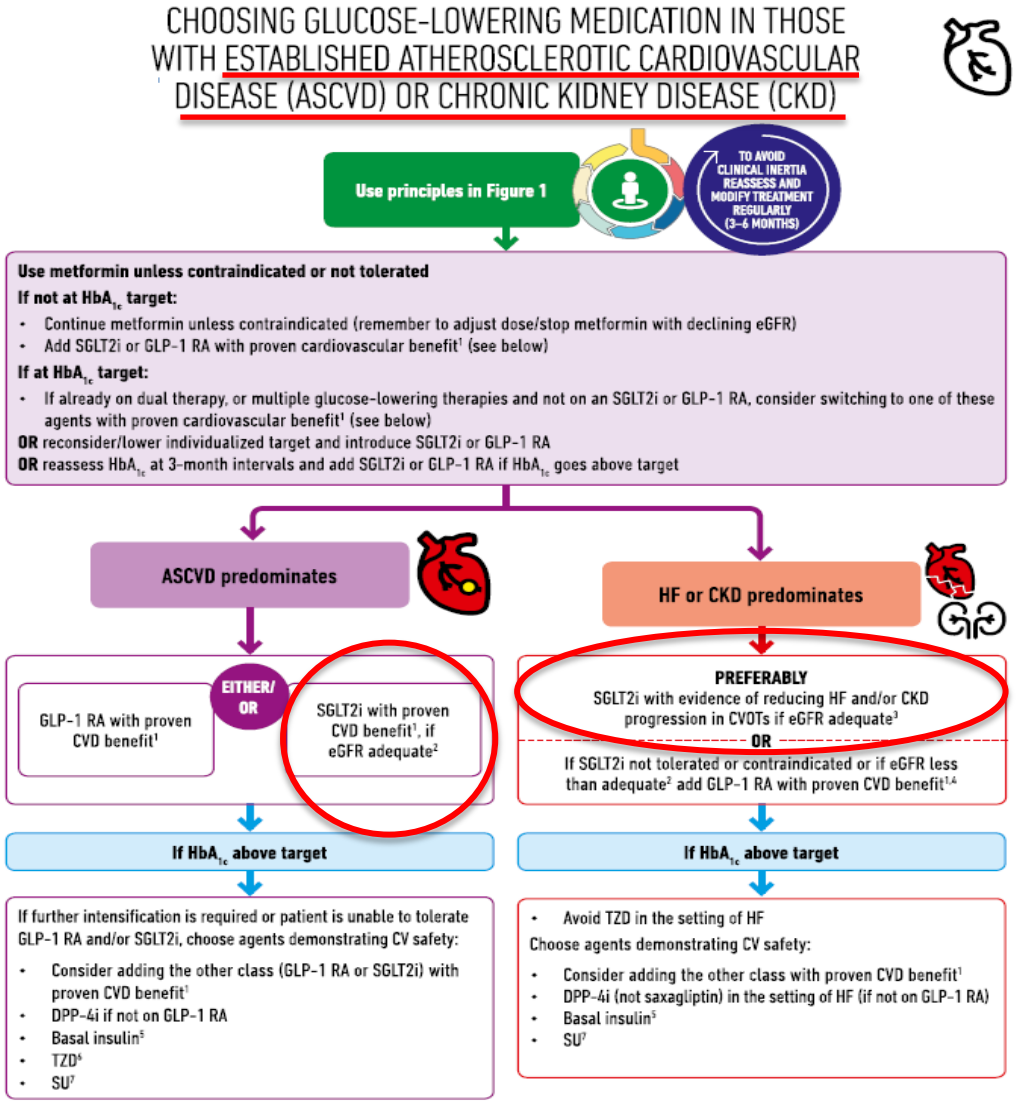
# Additional Information

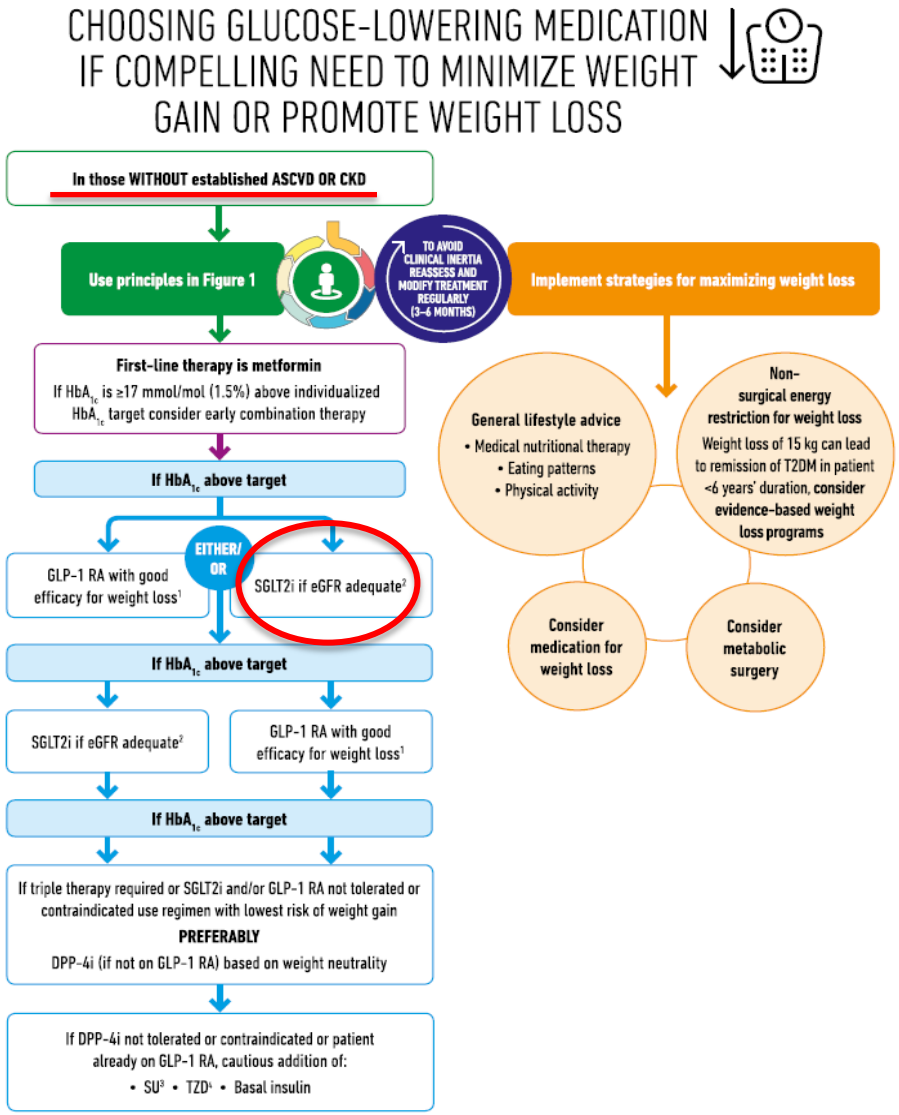
LBCT slides available:
www.timi.org


# Differences and similarities between SGLT2 inhibitor CVOT

| | DECLARE-TIMI 58 | EMPA-REG | CANVAS |
|---|---|---|---|
| Intervention | Dapaglifloxin / PBO | Empagliflozin / PBO | Canagliflozin / PBO |
| Patient number | 17,160 | 7,020 | 10,142 |
| | | | |
| HbA1c | 6.5 - <12.0% | 7.0%-10.0% | 7.0%-10.5% |
| Established CVD | Yes | Yes | Yes |
| Multiple risk factors without established CVD | Yes | No | Yes |
| Renal function | CrCl >60 ml/min | eGFR ≥30 ml/min/1.73m$^2$ | eGFR ≥30 ml/min/1.73m$^2$ |
| Primary endpoint(s) | Co-primary:<br>• MACE<br>• hHF or CV death | MACE | MACE |
| Target number of events | 1,390 | 772 | 688 |
| Estimated follow-up | ~4.5 years | 3.1 years | 5.7 years |

# 2018 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report



# Heart failure: Preventable and Treatable CV complication of Diabetes

- Diabetes is an independent risk factor for heart failure (HF)
- HF is an early complication of T2D with significant morbidity and mortality
- When choosing an antidiabetic therapy, the impact on HF merits consideration
- Exploratory analyses of RCTs suggest that SGLT2 inhibitors reduce hHF in those with prior CVD
- DECLARE-TIMI 58 results and CVD REAL 1 & 2 suggest that this extends to those without prior CVD (mainly for dapagliflozin)

## Summary

- The pattern of complications of diabetes is changing
  - Improvements in some classical complications; emergence of newer complications
- RCTs show CVD benefits for SGLT2i and GLP1 agonists
  - Findings predominantly in secondary prevention
- Real world evidence for SGLT2i suggests:
  - Benefits are seen outside clinical trials
  - Benefits extend to primary prevention
  - Benefits extend to Asian populations
- DECLARE extends SGLT2i RCT benefits to primary prevention

# Recent evidence on individualizing cardio-protective therapy in DM

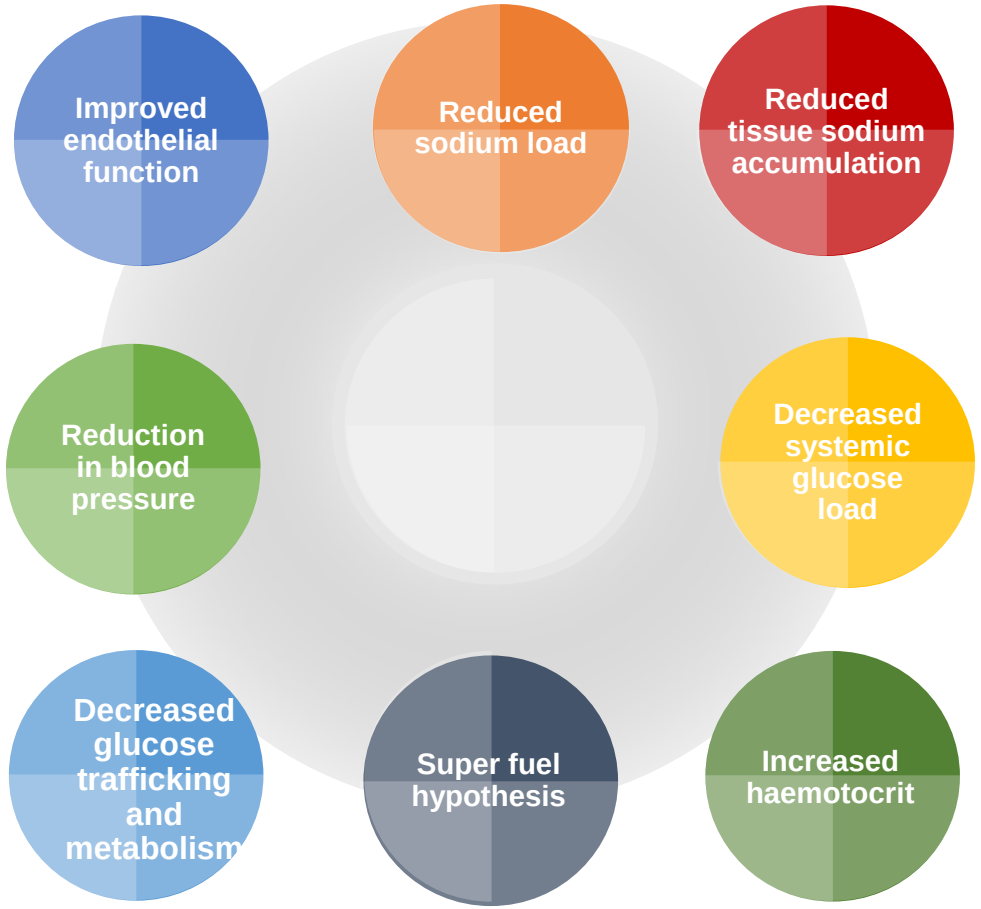
- For people with prior CVD
  - Strong evidence of benefit for SGLT2i
  - Evidence of modest benefit for liraglutide
  - Suggestive evidence of benefit of exenatide

**All people with T2DM & prior CVD should be considered for an SGLT2i or GLP1 agonist**

- For people without prior CVD
  - DECLARE and CVD REAL indicate benefit of SGLT2i (mainly dapagliflozin)
  - SGLT2i becoming the preferred second line agent

# Thank You

# A number of possible mechanisms of CV benefit with SGTL2 inhibitors have been put forward




**Evidence supporting potential mechanisms is sparse**

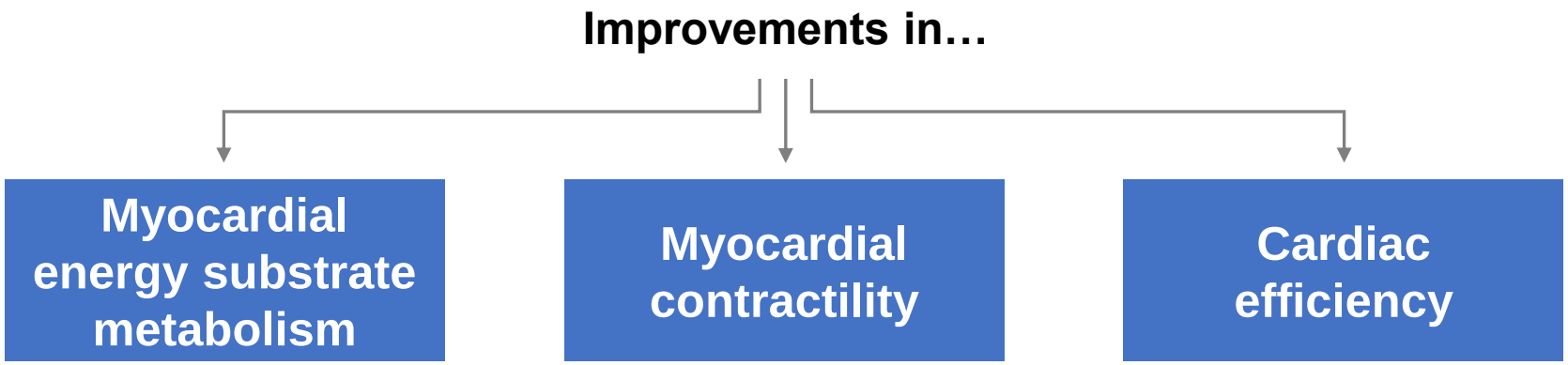
**There has been considerable discussion about three potential mechanisms**

- **Improvements in hemodynamics**
- **Super-fuel hypothesis**
- **Improved oxygen delivery**

CV, cardiovascular; SGLT2, sodium-glucose cotransporter-2.

Mudaliar S, et al. *Diabetes Care.* 2016;39:1115–1122.

# The super-fuel hypothesis suggests that SGLT2 inhibitors shift fuel metabolism to a more efficient source




**…by shifting to a more energy-efficient fuel: ketone bodies instead of fatty acids/glucose**

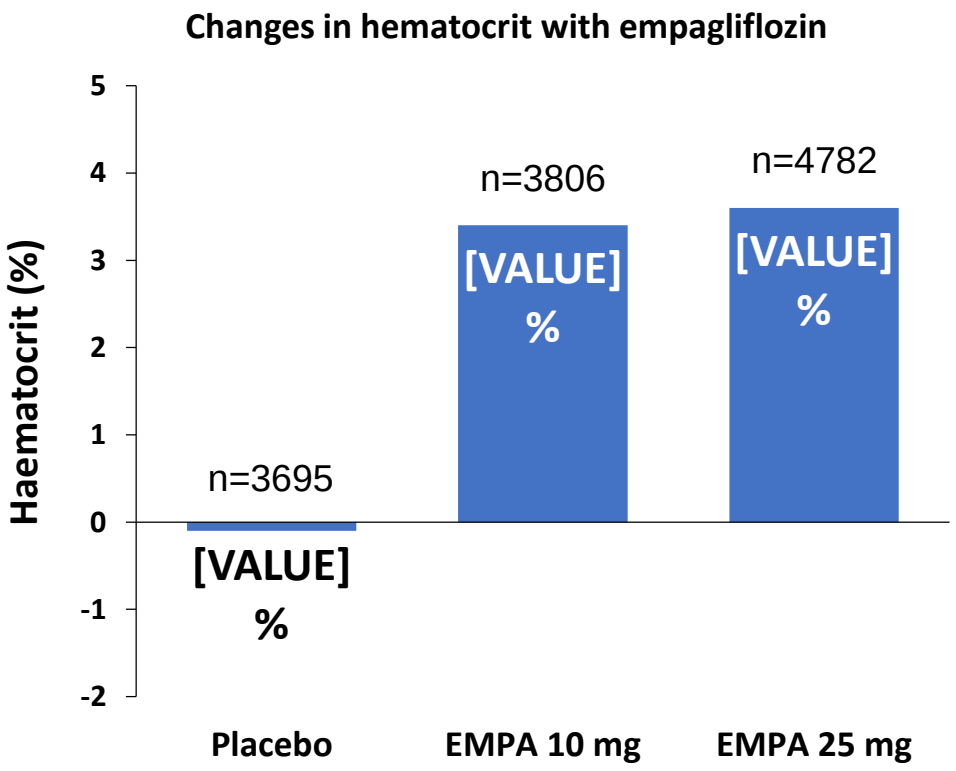
**By shifting fuel utilisation away from lipids and glucose (which are less energy efficient) toward ketone bodies that produce ATP energy more efficiently than glucose or FFA, SGLT2 inhibitors improve myocardial fuel metabolism, myocardial contractility, and cardiac efficiency**

SGLT2, sodium-glucose cotransporter-2.

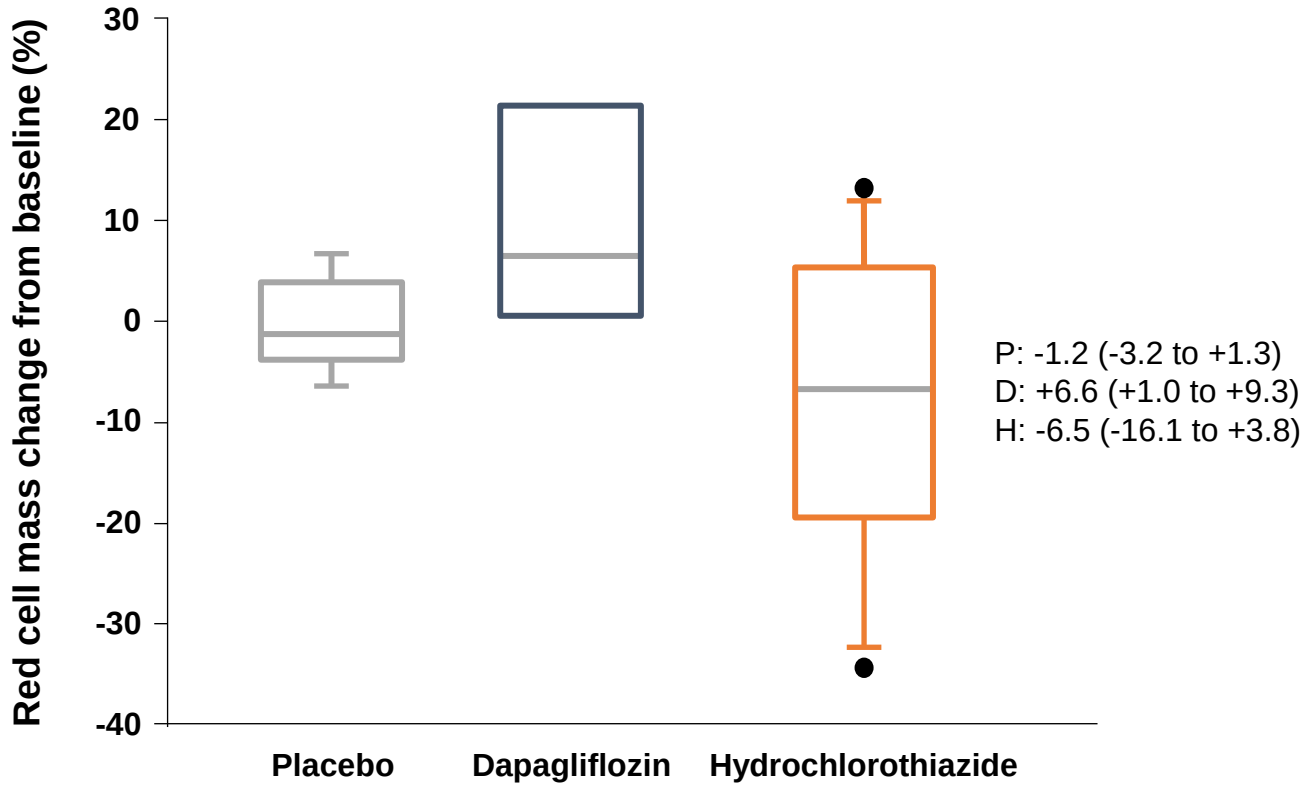
Mudaliar S, et al. *Diabetes Care.* 2016;39:1115–1122.

# SGLT2 inhibitor-associated increased haematocrit and red blood cell mass may increase tissue oxygen delivery

**Pooled data from 17 randomised trials in patients with T2DM[1]**




**Increased red blood cell mass (~6%) was observed following treatment with dapagliflozin[2]**

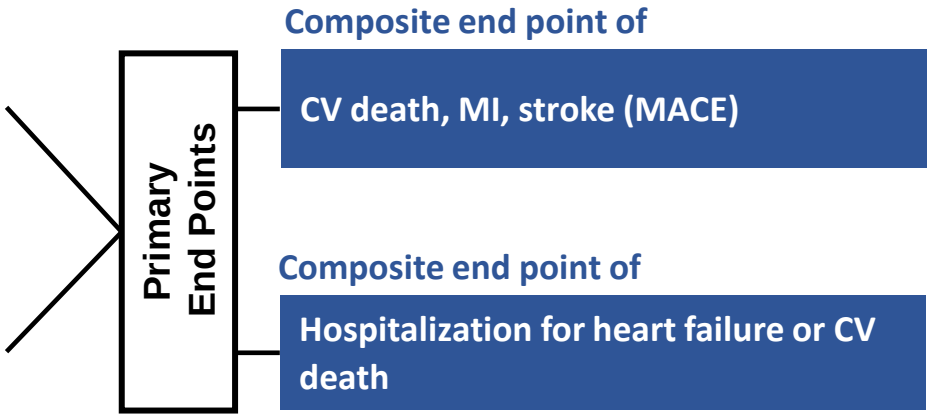



EMPA, empagliflozin; SGLT2, sodium-glucose cotransporter-2.

1. Kohler S. *Clin Ther.* 2016;38:1299–1313. 2. Lambers-Heerspink HJ, et al. *Diabetes Obes Metab.* 2013;15:853–862.

# Heart failure hospitalization is well characterized in DECLARE TIMI-58

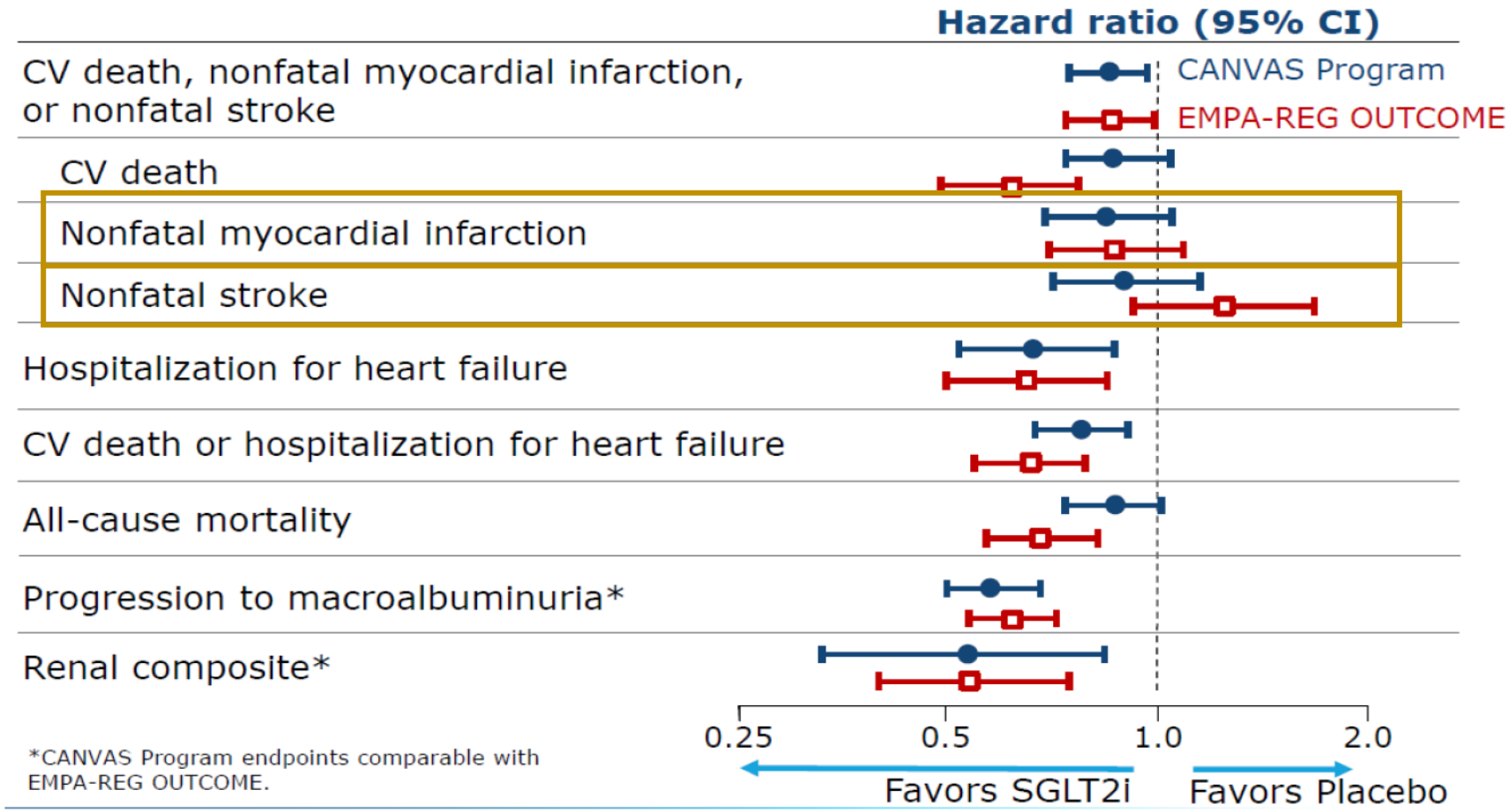
- Hospitalization for HF is prespecified in a primary endpoint as part of a composite with CV death
- Adjudication criteria for hHF are defined from study start
- Baseline LV-function data are collected where available and blood samples for biomarkers like NT-proBNP are collected




CV, cardiovascular; hHF, hospitalization for heart failure; LV, left ventricular; NT-proBNP, N-terminal pro b-type natriuretic peptide.

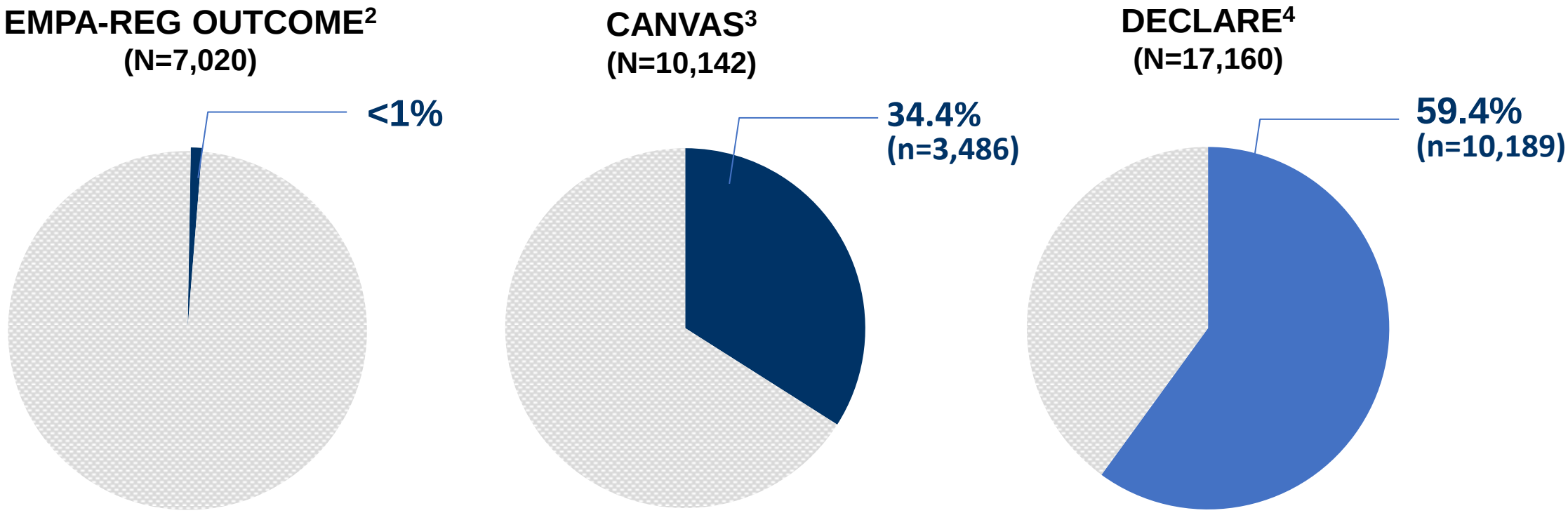
1. Raz I, et al. *Diabetes Obes Metab.* 2018. http://dx.doi.org/10.1111/dom.13217. 2. Wiviott SD, et al. *Am Heart J.* 2018. http://dx.doi.org/10.1016/j.ahj.2018.01.012.

# CANVAS vs EMPAR-REG OUTCOME
# - Effect on MI and stroke??



# DECLARE has the largest number of T2D patients without prior CVD among the SGLT2i CV outcomes studies to date

**In the T2D patient population, most patients do not have established CV disease[1]**



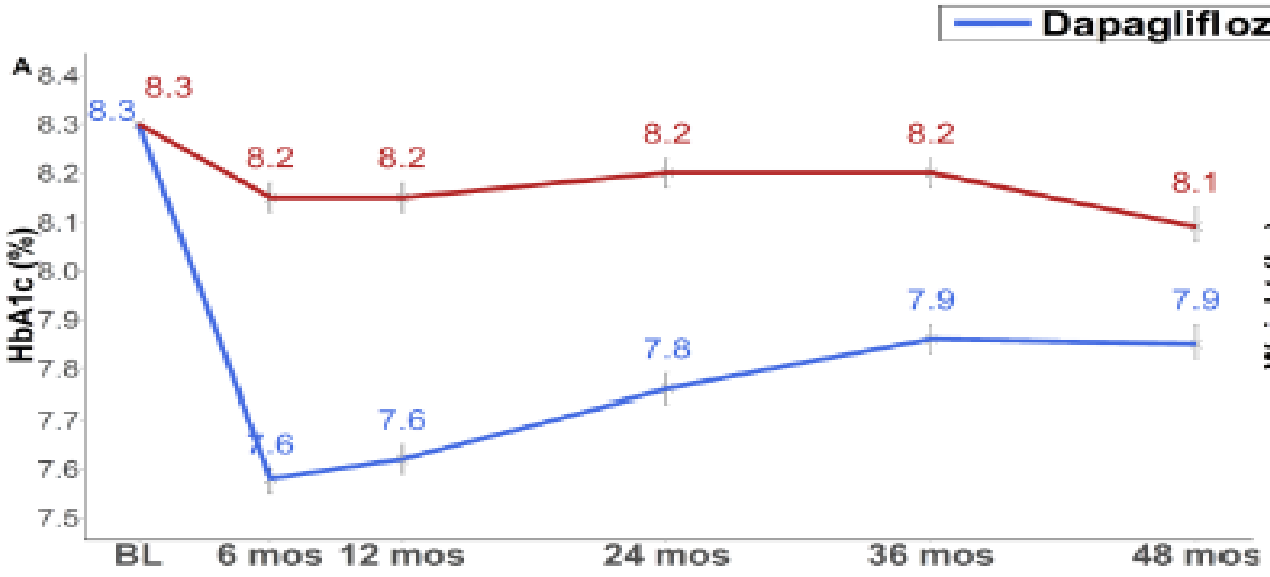

CV, cardiovascular; CVD, CV disease; SGLT2i, sodium glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1. Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83; 2. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 3. Neal B, et al. *N Engl J Med* 2017;377:644–657;
4. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110

# Cardiovascular Risk Factors

## HbA1c

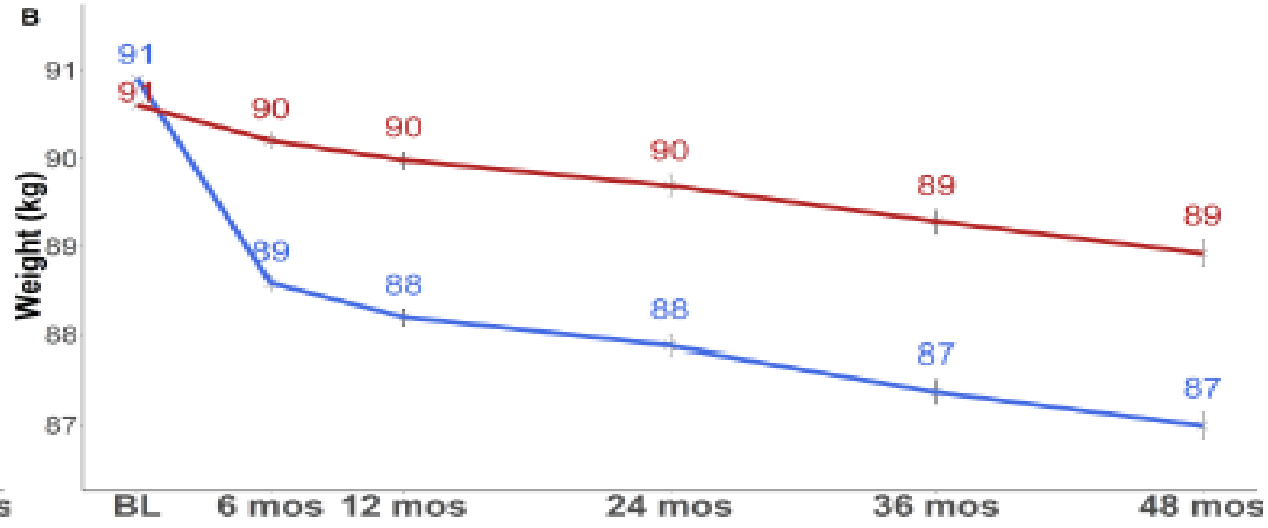
LSM Difference 0.42% (95% CI 0.40-0.45)




All P-values (except BL) <0.001

## Weight

LSM Difference 1.8 kg (95% CI 1.7-2.0)

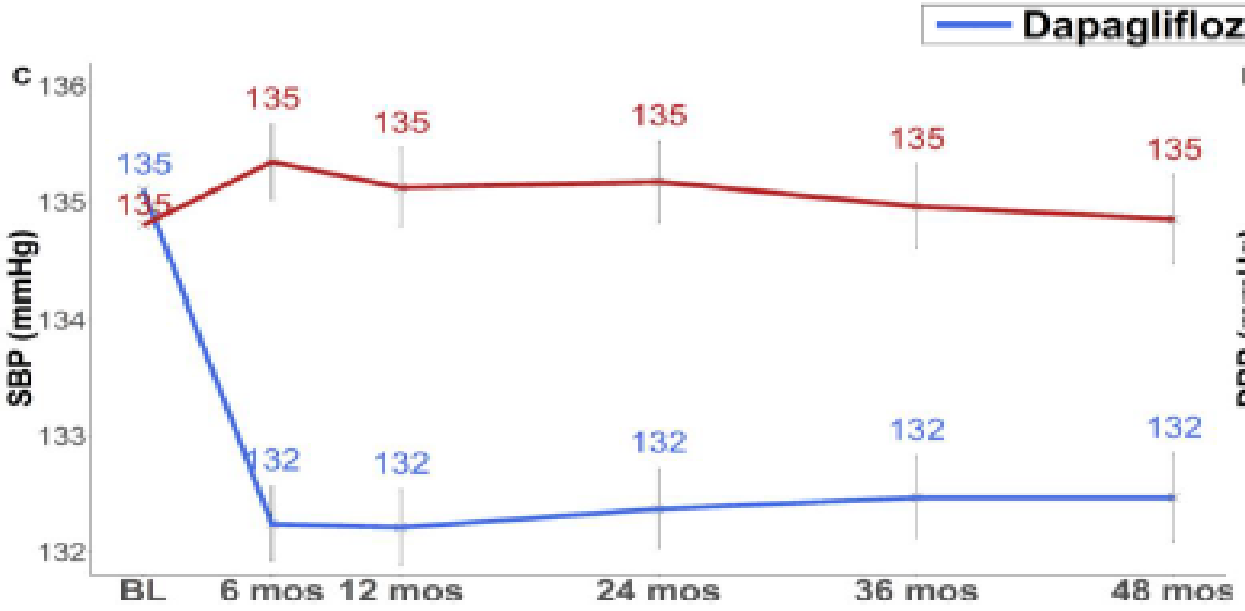



All P-values (except BL) <0.001

# Cardiovascular Risk Factors

## SBP

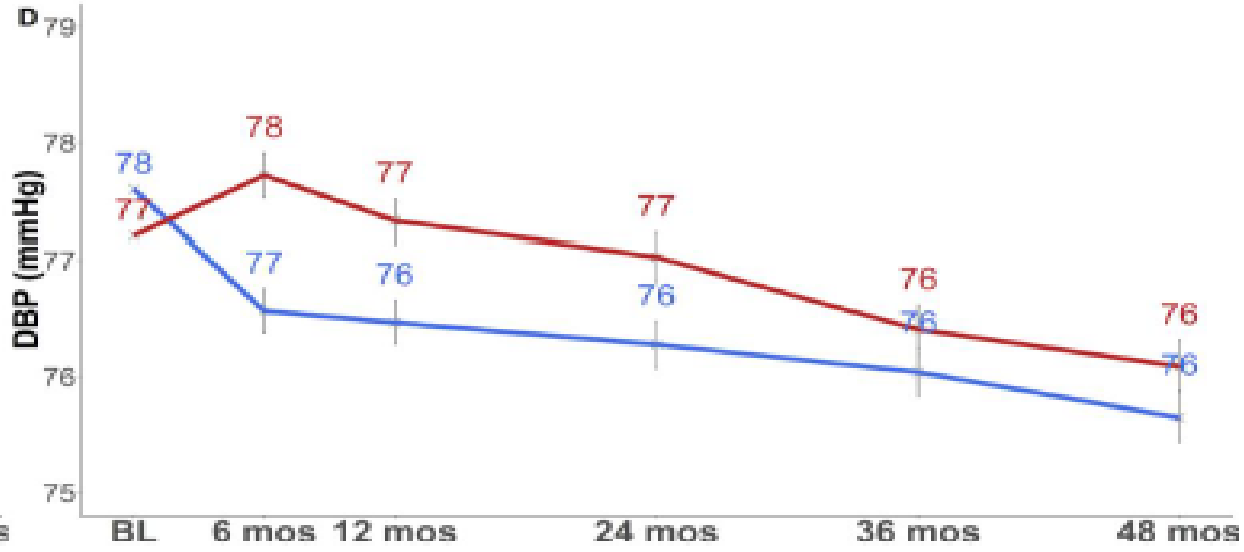
**LSM Difference 2.7 mmHg (95% CI 2.4-3.0)**




**All P-values (except BL) <0.001**

## DBP

**LSM Difference 0.7mmHg (95% CI 0.6-0.9)**




**All P-values (except BL) <0.001**