SGLT-2 INHIBITORS: CVD REDUCTION THROUGH DIURESIS

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MP Shah Hospital

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Sarova Whitesands, Mombasa
I have received honoraria from the following pharmaceutical companies for lectures and participation on advisory boards:

- Novartis
- Eli Lilly
- Sanofi
- Zawadi Healthcare
- Servier
- Astra Zeneca
- Novo Nordisk
- Merck
The Epidemiological impact

Global prevalence of diabetes (2015 and 2040)

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20–79 years)

- **North America and Caribbean**
  - 2015: 44.3 million
  - 2040: 60.5 million

- **Europe**
  - 2015: 59.8 million
  - 2040: 71.1 million

- **Middle East and North Africa**
  - 2015: 35.4 million
  - 2040: 72.1 million

- **Western Pacific**
  - 2015: 153.2 million
  - 2040: 214.8 million

- **South-East Asia**
  - 2015: 78.3 million
  - 2040: 140.2 million

- **Africa**
  - 2015: 14.2 million
  - 2040: 34.2 million

- **World**
  - 2015: 415 million
  - 2040: 642 million

No data were collected from Greenland or Svalbard

CVD is the leading cause of death in people with T2D

Years of life lost in people with diabetes* compared with non-diabetes peers

Mortality risk associated with diabetes (n=820,900)

*Information on diabetes type (i.e., type 1 or 2) was generally not available, though the age of the participants suggests that the large majority with diabetes would have type 2. In high income countries, up to 91% of adults with diabetes have type 2.1

CVD, cardiovascular disease; CI, confidence interval; T2D, type 2 diabetes.

Higher HbA\textsubscript{1c} predicts higher CV risk

**Fatal & non-fatal MI**

Hazard ratio

\begin{align*}
\text{Hazard ratio} & = 1 + 0.14 \times (\text{Updated mean HbA}\textsubscript{1c} - 6) \\
p & < 0.0001
\end{align*}

14% decrease per 1% reduction in HbA\textsubscript{1c}

**Fatal & non-fatal stroke**

Hazard ratio

\begin{align*}
\text{Hazard ratio} & = 1 + 0.12 \times (\text{Updated mean HbA}\textsubscript{1c} - 6) \\
p & = 0.035
\end{align*}

12% decrease per 1% reduction in HbA\textsubscript{1c}

**Amputation/death from PVD**

Hazard ratio

\begin{align*}
\text{Hazard ratio} & = 1 + 0.43 \times (\text{Updated mean HbA}\textsubscript{1c} - 6) \\
p & < 0.0001
\end{align*}

43% decrease per 1% reduction in HbA\textsubscript{1c}

**Heart failure**

Hazard ratio

\begin{align*}
\text{Hazard ratio} & = 1 + 0.16 \times (\text{Updated mean HbA}\textsubscript{1c} - 6) \\
p & = 0.021
\end{align*}

16% decrease per 1% reduction in HbA\textsubscript{1c}

Reference category (hazard ratio 1.0) is HbA\textsubscript{1c} < 6% with log linear scales.

CV, cardiovascular; HbA\textsubscript{1c}, glycosylated haemoglobin; MI, myocardial infarction; PVD, peripheral vascular disease.

Cardiovascular risk in type 2 diabetes

- Type 2 diabetes is estimated to affect 415 million people globally in 2015, with this number expected to rise to 642 million by 2040\textsuperscript{1}
- Cardiovascular disease is responsible for approximately half of deaths in people with type 2 diabetes\textsuperscript{2}
- Higher HbA\textsubscript{1c} predicts higher cardiovascular risk\textsuperscript{3}
- Intensive glucose-lowering regimens led to reduction of MI risk after 10 years of therapy\textsuperscript{4}

MI, myocardial infarction
Multiple drugs in combination may be required to improve glucose homeostasis
- Treatment should target underlying pathophysiology

Dysfunctions outlined in orange are the three core pathophysiologies of type 2 diabetes, known as the triumvirate. DeFronzo RA. Diabetes. 2009;58:773-795.
Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors

• SGLT are a family of glucose transporters
  – SGLT1: found in the mucosa of the small intestine
  – SGLT2: found in proximal tube of the nephron

• SGLT2 inhibitors prevent reabsorption of glucose from the kidney and reduce blood glucose levels

• Dapagliflozin
• Canagliflozin
• Empagliflozin
• Ipragliflozin

Renal Handling of Glucose

(180 L/day) (900 mg/L) = 162 g/day

SGLT1

Glucose

SGLT2

S1

90%

S2

10%

S3

No Glucose
SGLT2 Mediates Glucose Reabsorption in the Kidney

Major transporter of glucose in the kidney
- Low affinity, high capacity for glucose
- Nearly exclusively expressed in the kidney
- Responsible for ~90% of renal glucose reabsorption in the proximal tubule

If plasma glucose levels get too high the glucose transporters cannot reabsorb all the glucose, leading to glucosuria.

Adapted from Nair S & Wilding JPH. J Clin Endocrinol Metab 2010;95:34–42.
SGLT2 inhibitors: Benefits and potential concerns

• Potential advantages
  – Durable glucose lowering at all stages of disease
  – Can be used with wide range of oral glucose-lowering drugs and insulin
  – Weight loss
  – Blood pressure lowering
  – Low risk of hypoglycaemia

• Questions
  – Increase in urinary tract infections
  – Increase in genital infections
  – Potential for volume depletion
  – Ketoacidosis
  – Renal safety
  – Effects on bone health
  – Risk of CV disease (LDL increase; diuretic effect / volume depletion; BP lowering)
Dapagliflozin’s multiple benefits on HbA$_{1c}$, weight and BP are consistent in RWE

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Baseline ≤6 months before ID</th>
<th>Baseline ≤6 months before ID</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>82 6</td>
<td>8.5 (1.5)</td>
<td>7.8 (1.2)</td>
<td>-0.8 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>26 8</td>
<td>102.7 (22.1)</td>
<td>100.4 (21.6)</td>
<td>-2.3 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>47 1</td>
<td>137.0 (14.5)</td>
<td>134.8 (17.3)</td>
<td>-2.2 (17.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Baseline ≤6 months before ID</th>
<th>6 months after ID</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>64 5</td>
<td>8.5 (1.6)</td>
<td>7.8 (1.2)</td>
<td>-0.8 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>23 9</td>
<td>102.3 (22.5)</td>
<td>99.8 (22.1)</td>
<td>-2.5 (7.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>38 8</td>
<td>137.7 (16.7)</td>
<td>135.4 (16.2)</td>
<td>-2.3 (16.7)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Relationship between change in HbA$_{1c}$ (%) and body weight (kg) after 3 months in patients with T2DM initiating dapagliflozin treatment.
Dapagliflozin CV meta-analysis showed no increase in CV risk

- Meta-analysis of 21 Phase 2b/3 trials, n=9339 (dapagliflozin n=5936; control n=3403)

<table>
<thead>
<tr>
<th>n/N</th>
<th>DAPA meta-analysis*</th>
<th>Event rate/ 100 p–y</th>
<th>Event rate/ 100 p–y</th>
<th>Favours DAPA ↔ Control</th>
<th>DAPA HR vs Control (95% CI)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE plus UA</td>
<td>95/5699</td>
<td>1.46</td>
<td>81/3240</td>
<td></td>
<td>0.79 (0.58, 1.1)</td>
</tr>
<tr>
<td>MACE</td>
<td>72/5418</td>
<td>1.15</td>
<td>62/3101</td>
<td></td>
<td>0.77 (0.54, 1.1)</td>
</tr>
<tr>
<td>CV death</td>
<td>20/3825</td>
<td>0.37</td>
<td>18/2200</td>
<td></td>
<td>0.70 (0.36, 1.36)</td>
</tr>
<tr>
<td>MI</td>
<td>30/5244</td>
<td>0.48</td>
<td>33/3014</td>
<td></td>
<td>0.57 (0.34, 0.95)</td>
</tr>
<tr>
<td>Stroke</td>
<td>25/4227</td>
<td>0.45</td>
<td>18/2412</td>
<td></td>
<td>1.00 (0.54, 1.86)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>10/2576</td>
<td>0.15</td>
<td>16/1780</td>
<td>0.41</td>
<td>0.36 (0.16, 0.84)</td>
</tr>
</tbody>
</table>

*All Phase 2b and 3 Pool, ST + LT -30MU; Stratified by study; Only trials with at least one positively adjudicated event included in analysis; Cox Proportional Hazards model.
Meta-analysis data suggest a net protection against cardiovascular events with SGLT-2 inhibitors

Study objectives

Primary
• To compare the risk of HHF in patients with T2DM newly initiated on SGLT2 inhibitors versus other glucose-lowering drugs

Secondary
• To compare the risk of all-cause death between the two treatment groups
• To compare the risk of the composite of HHF or all-cause death between the two treatment groups
Inclusion/exclusion criteria

Inclusion criteria

• New users receiving SGLT2 inhibitors or other glucose-lowering drugs
  • Established T2DM on or prior to the index date
  • ≥18 years old
  • >1 year* historical data available prior to the index date

Exclusion criteria

• Patients with type 1 diabetes
• Patients with gestational diabetes

*In Germany, >6 months
Patient population for all countries/databases combined

- 1,392,254 new users of SGLT2 inhibitor or other glucose-lowering drug fulfilling the eligibility criteria

- 166,033 SGLT2 inhibitor
- 1,226,221 other glucose-lowering drug

- 1,071,693 (87%) excluded during 1:1 match process
- 11,505 (7%) excluded during 1:1 match process

- 1:1 propensity match
- 154,528 SGLT2 inhibitor
- 154,528 other glucose-lowering drug
Baseline characteristics for the full propensity matched cohort

<table>
<thead>
<tr>
<th></th>
<th>SGLT2 inhibitor* N=154,528</th>
<th>Other glucose-lowering drug* N=154,528</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>56.9 (10.0)</td>
<td>57.0 (10.6)</td>
</tr>
<tr>
<td>Women</td>
<td>68,420 (44.3)</td>
<td>68,772 (44.5)</td>
</tr>
<tr>
<td>Established cardiovascular disease†</td>
<td>20,044 (13.0)</td>
<td>20,302 (13.1)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>3793 (2.5)</td>
<td>3882 (2.5)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>2529 (1.6)</td>
<td>2568 (1.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4714 (3.1)</td>
<td>4759 (3.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5632 (3.6)</td>
<td>5698 (3.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6337 (4.1)</td>
<td>6394 (4.1)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>5239 (3.4)</td>
<td>5229 (3.4)</td>
</tr>
<tr>
<td>Frailty (yes)‡</td>
<td>11,982 (7.8)</td>
<td>12,731 (8.2)</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>42,217 (27.3)</td>
<td>42,215 (27.3)</td>
</tr>
</tbody>
</table>
Baseline characteristics for the full propensity matched cohort (continued)

<table>
<thead>
<tr>
<th></th>
<th>SGLT2 inhibitor* N=154,528</th>
<th>Other glucose-lowering drug* N=154,528</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy†</td>
<td>123,696 (80.0)</td>
<td>123,563 (80.0)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>14,280 (9.2)</td>
<td>14,314 (9.3)</td>
</tr>
<tr>
<td>Thiazides</td>
<td>42,446 (27.5)</td>
<td>42,510 (27.5)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>66,812 (43.2)</td>
<td>67,067 (43.4)</td>
</tr>
<tr>
<td>ARBs</td>
<td>48,718 (31.5)</td>
<td>48,443 (31.4)</td>
</tr>
<tr>
<td>Statins</td>
<td>103,968 (67.3)</td>
<td>104,128 (67.4)</td>
</tr>
<tr>
<td><strong>Diabetes therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>121,500 (78.6)</td>
<td>123,432 (79.9)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>59,406 (38.4)</td>
<td>59,788 (38.7)</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>51,400 (33.3)</td>
<td>50,088 (32.4)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>13,650 (8.8)</td>
<td>12,970 (8.4)</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>31,355 (20.3)</td>
<td>27,088 (17.5)</td>
</tr>
<tr>
<td>Insulin</td>
<td>45,573 (29.5)</td>
<td>45,097 (29.2)</td>
</tr>
</tbody>
</table>

*Data are n (%); †Includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Ca²⁺ channel blockers, β-blockers, thiazides.
Contribution of SGLT2 inhibitor: All countries combined

Proportion of exposure time (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHF</td>
<td>52.7%</td>
<td>41.8%</td>
<td>5.5%</td>
</tr>
<tr>
<td>All-cause death</td>
<td>51.0%</td>
<td>42.3%</td>
<td>6.7%</td>
</tr>
<tr>
<td>HHF + all-cause death</td>
<td>45.3%</td>
<td>49.1%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>
Hospitalization for heart failure or all-cause death primary analysis

<table>
<thead>
<tr>
<th>Database</th>
<th>N</th>
<th># of events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>143,264</td>
<td>424</td>
<td>0.44 (0.36, 0.54)</td>
</tr>
<tr>
<td>Norway</td>
<td>25,050</td>
<td>622</td>
<td>0.58 (0.50, 0.69)</td>
</tr>
<tr>
<td>Denmark</td>
<td>18,468</td>
<td>477</td>
<td>0.57 (0.48, 0.67)</td>
</tr>
<tr>
<td>Sweden</td>
<td>18,378</td>
<td>364</td>
<td>0.50 (0.41, 0.63)</td>
</tr>
<tr>
<td>UK</td>
<td>10,462</td>
<td>96</td>
<td>0.66 (0.44, 1.00)</td>
</tr>
<tr>
<td>Total</td>
<td>215,622</td>
<td>1983</td>
<td>0.54 (0.48, 0.60)</td>
</tr>
</tbody>
</table>

P-value for SGLT2i vs other glucose-lowering drug: <0.001
Heterogeneity p-value: 0.166

Data are on treatment, unadjusted.
CVD-REAL Nordic: Dapagliflozin compared to DPP4i

- Norhammar A, Bodegard J, Nystrom, T et al. Dapagliflozin is associated with lower risk of hospitalization for heart failure, major adverse cardiovascular events and all-cause death compared to DPP-4i in T2D patients: CVD-REAL Nordic. [poster] Presented at European Society of Cardiology - Heart Failure meeting; April 29 – May 2, 2017; Paris, France.

Study outcomes

- MACE
- All-cause death (ACD)
- Hospital events for heart failure (HHF; acute, chronic or unspecified)
- Hospital events for kidney disease (HKD; acute, chronic or unspecified)
- A combination of HKD or HHF
Study design and statistical analysis

• Patients were divided by index drug into two groups
  – New users of dapagliflozin
  – New users DPP-4 inhibitors

• The groups were matched 1:3 by propensity score, calculated by using variables covering patient characteristics, co-morbidities and drug treatment

• Patients were followed from the index date until the index drug discontinuation, death or end of register

• Cox survival models estimated hazard ratio per country separately and presented by weighted averages
Patient flow chart

642,558
T2D patients during 2013-2016

77,074
New users of dapagliflozin or DPP-4 inhibitor

19,662
Dapagliflozin

57,452
DPP-4 inhibitor

8582
Dapagliflozin

25,746
DPP-4 inhibitor

56%

55%
Data source: The Health Improvement Network (THIN) Database (UK)
• Anonymized electronic patient records contributed by over 640 general practices
• Study period: January 1, 2013 – September 1, 2015

Patients
• Registered at least 1 year at current practice
• Exposed group
  • 18+ years at index
  • Diagnosis of diabetes any time prior to index
  • Initiated dapagliflozin
  • Remained at their practice ≥3 months after dapagliflozin initiation (index date: 3 months post-initiation)
• Up to 4 unexposed controls were matched to each exposed patient based on sex, age at index, BMI, duration of diabetes, and smoking status

Outcomes
• Primary: all-cause mortality
• Secondary: composite cardiovascular disease outcome (consisting of myocardial infarction, ischemic heart disease, stroke, TIA, heart failure, or left ventricular dysfunction)
  • The composite analysis was restricted to the low-risk population
UK THIN database study: All-cause mortality

- Real-world evidence from an open cohort study of the THIN database suggests that dapagliflozin may be associated with a decrease in all-cause mortality irrespective of baseline CVD status

**Total study population**
Control, n = 17,680  
DAPA, n = 4,444

**Low risk population**
Control, n = 14,118  
DAPA, n = 3,656

Touli KA, et al. J Clin Endocrinol Metab 2017;[Epub ahead of print]
EMPA-REG: Empagliflozin reduced secondary endpoints of all-cause death and hospitalization for heart failure

**Death from any cause**

- Placebo: HR=0.68 (95% CI: 0.57, 0.82)
- Empagliflozin: HR=0.75 (95% CI: 0.63, 0.89)
- Placebo: $P<0.001$
- Empagliflozin: $P=0.001$

**Hospitalization for heart failure**

- Placebo: HR=0.65 (95% CI: 0.50, 0.85)
- Empagliflozin: HR=0.65 (95% CI: 0.50, 0.85)
- Placebo: $P=0.002$
- Empagliflozin: $P<0.001$

SGLT-2 INHIBITORS

• Weight loss: 1-4.5 kg observed
• 1. Loss of calories from glycosuria and osmotic diuresis
• 2. Potential for reduced insulin requirements
• 3. Maintained past initial therapy period
• Reduction in uric acid5,6,11,20
  • 1. Increased levels associated with HTN, CVD and renal disease
  • 2. 10-15% reduction in plasma uric acid levels
    a. Clinical relevance unclear Cardiovascular Effect4,11,17,18,20-23
• 1. Modest reduction in blood pressure
  a. 2014 Meta-analysis by Baker and colleagues
    i. 27 unique RCT including 12,960 patients
    ii. SBP: 4 mmHg drop consistent between SGLT-2 inhibitors
    iii. DBP: 1.6 mmHg drop consistent between SGLT-2 inhibitors
• b. No increase in orthostatic hypotension
• c. Reduces BP even in “non-dippers” i. Patients without nocturnal BP drop (“dip”) have an increased risk of CVD
• d. BP reduction observed even in patients with CKD
• 2. Reduction in arterial stiffness
  • a. Well established surrogate marker for CVD
  • b. 8-week open label prospective trial (n=42): T1DM with empagliflozin 25 mg vs placebo
    • i. Decreased carotid-radial pulse wave velocity (measure of arterial stiffness) under euglycemic and hyperglycemic conditions
    • ii. Vagal tone and SNS activity not significantly changed
  • c. T2DM: Improved markers of arterial stiffness
    • i. Pulse pressure, myocardial oxygen consumption
• 3. Proposed pathophysiology behind cardiovascular benefits: multifactorial
  • a. Proposed pathophysiology
    • i. Volume contraction 1. Unclear if volume contraction persists through treatment
    • ii. Weight loss correlation 1. Conflicting data between studies a. BP lowering independent of weight loss in patients with CKD
      • iii. Neurohormonal changes-most are unlikely to play a significant role
        • 1. Increased plasma aldosterone, renin and angiotensin II and urinary angiotensinogen (vasoconstriction)
        • 2. Increased urinary ACE2 (vasodilation) a. Possible: requires further study
        • 3. SNS activity unchanged
      • iv. Reduced arterial stiffness b. Metabolic effects: weight loss, Increased fat oxidation, increased glucagon secretion i. Unlikely to support reduction in CV death
Similarities and differences between SGLT2 inhibitor CVOTs (1)

- In addition to the EMPA-REG OUTCOME trial, two other SGLT2 inhibitors, canagliflozin and dapagliflozin, are investigating the same endpoints but in different (CANVAS in 2017) and also broader populations (DECLARE in 2019)

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG(^1)</th>
<th>(CANVAS+CANVAS-R)(^2)</th>
<th>DECLARE(^3)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>7020 (EMPA, 4687; PBO, 2333)</td>
<td>10,143 (CANA, 5794; PBO, 4349)</td>
<td>17,276</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>EMPA/PBO (1:1:1)</td>
<td>CANA/PBO (1:1:1)</td>
<td>DAPA/PBO (1:1)</td>
</tr>
<tr>
<td></td>
<td>(10 mg, 25 mg, PBO)</td>
<td>(100mg, 300mg, PBO)</td>
<td>(10mg, PBO)</td>
</tr>
<tr>
<td><strong>Key inclusion criteria</strong></td>
<td>• HbA(_{1c}) ≥7% and ≤10%</td>
<td>• HbA(_{1c}) ≥7% and ≤10.5%</td>
<td>• T2DM uncontrolled</td>
</tr>
<tr>
<td></td>
<td>• eGFR &gt;30 mL/min</td>
<td>• eGFR &gt;30 ml/min</td>
<td>• Primary prevention</td>
</tr>
<tr>
<td></td>
<td>• Age ≥18 years</td>
<td>• Primary prevention: ~35%</td>
<td>○ Multiple risk factors</td>
</tr>
<tr>
<td></td>
<td>• Secondary prevention (99%)</td>
<td>• Secondary prevention: ~65%</td>
<td>• Secondary prevention</td>
</tr>
<tr>
<td></td>
<td>○ Previous CV event</td>
<td>• Established vascular complications</td>
<td>○ Established vascular complications</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>MACE (CV death, non-fatal MI, non-fatal stroke)</td>
<td>Pooled MACE (CV death, non-fatal MI, non-fatal stroke) from CANVAS &amp; CANVAS-R</td>
<td>MACE (CV death, non-fatal MI, non-fatal ischemic stroke)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Co-primary: HHF + CV mortality</td>
<td></td>
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Similarities and differences between SGLT2 inhibitor CVOTs (2)

- To complement current and future CVOTs, CVD-REAL results suggest a class effect of SGLT2 inhibitors, including dapagliflozin, on associated reductions in risk of HHF and ACD applicable to a broad population of T2DM patients in the real clinical setting.

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG(^1)</th>
<th>(CANVAS+CANVAS-R)(^2)</th>
<th>DECLARE(^3)*</th>
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<tbody>
<tr>
<td><strong>Primary endpoint power</strong></td>
<td>Powered 80% (2-sided 95.02%) for 21.5% relative risk reduction</td>
<td>CANVAS: Powered 80% for 25% risk reduction CANVAS-R: Powered &gt;90% (2-sided ( P = 0.05 )) for 22% risk reduction</td>
<td>Powered for non-inferiority Powered 5% for 15% risk reduction</td>
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<td><strong>Important secondary endpoints</strong></td>
<td>4P-MACE (3P-MACE with hospitalization for unstable angina), HHF, microvascular composite, micro- and macroalbuminuria</td>
<td>Fasting insulin secretion (HOMA-B, pro-insulin:insulin ratio), regression of albuminuria, urinary albumin/creatinine ratio</td>
<td>Renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR&lt;50 mL/min/1.73m(^2) and/or ESKD and/or renal or CV death), all cause mortality</td>
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<tr>
<td><strong>Estimated median follow-up</strong></td>
<td>~3.1 years</td>
<td>CANVAS: 6–7 years CANVAS-R: 3 years</td>
<td>~4.5 years</td>
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Summary

• Dapagliflozin has demonstrated in RCTs to result in HbA$_{1c}$ lowering efficacy, weight loss and blood pressure reduction
  — This has been consistently confirmed in the real-world clinical setting

• The CVD-REAL study was the first large, multinational, retrospective, observational study of CV outcomes in new users of SGLT-2 inhibitors compared with new users of other glucose-lowering drugs in a broad population of patients with T2DM, only 13% of whom had CVD

• The CVD-REAL primary analysis showed that in the real-world clinical setting, patients initiated on SGLT-2 inhibitors, including dapagliflozin, were associated with a 39% reduction risk of HHF and a 51% reduction in all-cause death compared with patients initiated on other glucose-lowering drugs
  — The effect was consistent across countries, various sensitivity analyses and in patients with or without CVD

• Data from CVD-REAL Nordics demonstrated that new users of dapagliflozin were associated with risk reductions in hHF, MACE, ACD and HKD compared to new users of DPP-4 inhibitors

• In a secondary analysis of CVD-REAL, patients initiated on SGLT2 inhibitors, including dapagliflozin, were associated with a significant risk reduction in total hHF (new and recurrent) compared with those initiated on other glucose-lowering drugs

• The multiple benefits and CV profile of dapagliflozin are reinforced by data in the real-world clinical setting, further supporting the earlier use of SGLT-2 inhibitors in the treatment paradigm for T2DM
SGLT-2 inhibitors: My experience

- 95 patients at MP Shah hospital (hospital clinic and private) since August 2016
- 89 on Dapagliflozin (87 on 10mg 2 on 5mg) and 6 on Canagliflozin 100mg
- Excellent glycaemic control
- Weight loss in all patients (average 3kg)
- No UTI/ genital infections or DKA
- 1 patient discontinued due to weight loss but restarted this year after weight gain!
- Good patient satisfaction
- Patient education important