The SGLT2 Inhibitors: Heart Failure Drugs that Also Lower Glucose

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Diabetes and Heart Failure

• The two diseases entities are highly co-prevalent

• Diabetes contributes to disease progression in HF and is associated with substantially worse prognosis, even when conventional HF therapies are applied

• The relationship between HbA1c and outcome in patients with diabetes and heart failure is complex

• The choice of pharmacologic glycemic management can markedly impact heart failure outcomes
  – Certain therapies are neutral or associated with harm
  – Certain therapies markedly improve outcomes

• Pharmacologic glycemic management is a critical component of HF management
Diabetes and Incident Heart Failure in the US

- Framingham study (risk of HF in diabetics)
  - 2x diabetic males
  - 5x diabetic females
  - 4x young diabetic males
  - 8x young diabetic females

- US HMO prevalence study
  - With diabetes, incident HF developed at a rate of 3.3% per year

- Each 1% elevation in HbA$_{1c}$ leads to a 15% increase in frequency of HF

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD</td>
<td>25.8%</td>
</tr>
<tr>
<td>MERIT</td>
<td>24.5%</td>
</tr>
<tr>
<td>Val HEFT</td>
<td>25.4%</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>31.4%</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>34.7%</td>
</tr>
<tr>
<td>OPTIME (hospitalized)</td>
<td>44.2%</td>
</tr>
<tr>
<td>VMAC (hospitalized)</td>
<td>47.0%</td>
</tr>
</tbody>
</table>
Heart Failure Rates in Diabetes Glucose Control Trials

Risk of HF events with glucose-lowering drugs or strategies versus standard care

PPAR Agonists
DPP-4 Inhibitors
Intensive Control
Insulin
Weight loss

Lancet Diabetes Endocrinol 2015  March 17, 2015 http://dx.doi.org/10.1016/S2213-8587(15)00044-3
Effect of Glycemic Control in Type 2 DM on Cardiovascular Outcomes

### Impact of Glycemic Control

<table>
<thead>
<tr>
<th>Event</th>
<th>More Intensive</th>
<th>Less Intensive</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>378</td>
<td>370</td>
<td>0.96 (0.83, 1.10)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>730</td>
<td>745</td>
<td>0.85 (0.76, 0.94)</td>
</tr>
<tr>
<td>Hospitalization or Fatal heart failure</td>
<td>459</td>
<td>446</td>
<td>1.00 (0.86, 1.16)</td>
</tr>
<tr>
<td>CV Death</td>
<td>497</td>
<td>441</td>
<td>1.10 (0.84, 1.42)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>980</td>
<td>884</td>
<td>1.04 (0.90, 1.20)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CV, cardiovascular; CI, confidence interval

Turnbull FM et al. Diabetologia 2009;52:2288–2298
Major CV Outcome Trials in Type 2 Diabetes

- **SAVOR-TIMI 53** (n = 16,492) 1222 MACE3
- **EXAMINE** (n = 5380) 621 MACE3
- **TECOS** (n = 14,723) 1400 MACE4
- **CAROLINA** N = 6041 MACE4
- **Omarigliptin** (n = 4000) Q4 2017 ? MACE4
- **CARMELINA** N = 8300 MACE4

- **CAROLINA** N = 6041 MACE4
- **ELIXA* (n = 6000) 805 MACE4
- **LEADER† (n = 9341) 611 MACE3
- **EXSCEL§ (n = 14000) MACE3
- **SUSTAIN-6‡ (n = 3260) MACE3
- **CANVAS-R (n = 5700) Alb.uria
- **CANVAS (n = 4339) MACE3
- **DECLARE-TIMI 58 (n = 27,000) MACE3
- **SAVOR-TIMI 53 (n = 16,492) 1222 MACE3
- **EMPA-REG OUTCOME** N = 7034 MACE3
- **LEADER† (n = 9341) 611 MACE3
- **EXSCEL§ (n = 14000) MACE3
- **SUSTAIN-6‡ (n = 3260) MACE3
- **CANVAS-R (n = 5700) Alb.uria
- **CANVAS (n = 4339) MACE3
- **DECLARE-TIMI 58 (n = 27,000) MACE3


- **EMPA-REG OUTCOME** N = 7034 MACE3
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- **SUSTAIN-6‡ (n = 3260) MACE3
- **CANVAS-R (n = 5700) Alb.uria
- **CANVAS (n = 4339) MACE3
- **DECLARE-TIMI 58 (n = 27,000) MACE3
- **CREDENCE (n = 3627) Cardiorenal
- **REWIND# (n = 9622) MACE3
- **Ertugliflozin CVOT (n = 3900) MACE3

- **SGLT2i**
- **DPP4i**
- **GLP1**

---

DPP-4 Inhibitors are Neutral on MACE and HF Outcomes: No Improvement Compared to Placebo

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI 53¹</td>
<td>1.00 (0.89, 1.12)</td>
<td>0.99</td>
<td></td>
<td>1.27 (1.07, 1.51)</td>
<td>0.007</td>
</tr>
<tr>
<td>EXAMINE²,³</td>
<td>0.96 (≤1.16)ᵇ</td>
<td>0.32</td>
<td></td>
<td>1.19 (0.90, 1.58)</td>
<td>0.22</td>
</tr>
<tr>
<td>TECOS⁴,⁵</td>
<td>0.99 (0.89, 1.10)</td>
<td>0.84</td>
<td></td>
<td>1.00 (0.83, 1.20)</td>
<td>0.98</td>
</tr>
<tr>
<td>CARMELINA⁵</td>
<td>1.02 (0.89, 1.17)</td>
<td>0.74</td>
<td></td>
<td>0.90 (0.74, 1.08)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Favors DPP-4 inhibitor | Favors placebo

Favors DPP-4 inhibitor | Favors placebo

ᵃComposite of CV death, nonfatal myocardial infarction, and nonfatal stroke for SAVOR-TIMI 53, EXAMINE, and CARMELINA, with the addition of hospitalization for unstable angina in TECOS;ᵇParenthetical value is the upper boundary of one-sided repeated CI at an alpha level of 0.01;ᶜMACE reported HR, 95% CI, and P-value were for the secondary composite of CV death, nonfatal myocardial infarction, and nonfatal stroke.

Hospitalization for HF – GLP1 RA

**ELIXA**
- Primary + Heart Failure Hosp
  - HR = 0.97 (0.85, 1.10)
- Heart Failure Hospitalization
  - HR = 0.96 (0.75, 1.23)
- Primary + HF Hosp + Coronary Revasc
  - HR = 1.00 (0.90, 1.11)
- All-Cause Death
  - HR = 0.94 (0.78, 1.13)

**LEADER**
- Hazard ratio, 0.87 (95% CI, 0.73–1.05)
  - Placebo vs. Liraglutide
  - Patients with an Event (%)
  - Months since Randomization

**SUSTAIN-6**
- HR, 1.11 (95% CI, 0.77–1.61)
  - Events: 39 semaglutide; 4 placebo
  - p=0.57

**EXSCEL**
- Hazard ratio, 0.94 (95% CI, 0.78–1.13)
  - Placebo vs. Exenatide
  - Patients with Event (%)
  - Years since Randomization

References:
Liraglutide in Systolic Heart Failure: The FIGHT Trial

N=300: liraglutide (n = 154) vs. placebo (n = 146)

SGLT2 Inhibitors

• Virtually all glucose filtered by the kidney is reclaimed in the proximal tubule. Sodium glucose cotransporter 2 (SGLT2) is responsible for 90% of this reabsorption. ¹

• Selective inhibitors of SGLT2 have been developed. ²

• By reducing renal glucose reabsorption, SGLT2 inhibitors increases urinary glucose excretion. ³

• In patients with type 2 DM, SGLT2 inhibitors leads to: ⁴
  – Significant reductions in HbA1c
  – Weight loss
  – Reductions in BP without increases in heart rate

Potential CV and Renal Function Preservation Mechanisms of SGLT2i that May Benefit HF

<table>
<thead>
<tr>
<th>Effect</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis</td>
<td>Reduced filling pressures, pre/afterload reduction</td>
</tr>
<tr>
<td>Natriuresis</td>
<td>Reduced filling pressures, pre/afterload reduction</td>
</tr>
<tr>
<td>Blood pressure lowering</td>
<td>Reduced myocardial work, reduced filling pressures, pre/afterload reduction</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Improved CV risk profile, lower blood pressure</td>
</tr>
<tr>
<td>Reduction in/prevention of albuminuria, slowing of kidney function decline</td>
<td>Reduction in kidney risk profile, possibly lower incident CV events, including less HF</td>
</tr>
<tr>
<td>Effects on myocardial and kidney metabolism: shift to more efficient ketone-based metabolism</td>
<td>Improved metabolic efficiency, less myocardial workload</td>
</tr>
<tr>
<td>Blockade of kidney and myocardial sodium-hydrogen co-transporter</td>
<td>Tissue protection: reduction in kidney and myocardial injury</td>
</tr>
</tbody>
</table>
**EMPA-REG OUTCOME**
Trial design: SGLT2 Inhibitor

- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)
  - 10.2% of patients enrolled with pre-existing heart failure

EMPA-REG OUTCOME Trial: Key Results

**Primary Endpoint (3P MACE)**
- ↓ 14% (p=0.0382)

**CV DEATH**
- ↓ 38% (p<0.0001)

**All-Cause Mortality**
- ↓ 32% (p<0.0001)
  - Driven by ↓ CV Death

**Heart Failure**
- Hospitalization for Heart Failure ↓ 35% (p=0.0017)
- Hospitalization for Heart Failure or CV Death ↓ 34% (p<0.0001)
Empagliflozin is a highly selective inhibitor of Sodium-Glucose Cotransporter-2

7020 adults with type 2 diabetes and established CVD
BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)

Heart Failure Hospitalization or CV death

Cumulative incidence function. CV, cardiovascular; HR, hazard ratio; CI, confidence interval.

European Heart Journal doi:10.1093/eurheartj/ehv728
# Modes of Cardiovascular Death

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All CV Deaths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Events</td>
<td>172/4687 (3.7%)</td>
<td>137/2333 (5.9%)</td>
<td>0.62 (0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rate/100 PY</td>
<td>1.24</td>
<td>2.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fatal MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Events</td>
<td>15/4687 (0.3%)</td>
<td>11/2333 (0.5%)</td>
<td>0.68 (0.31, 1.48)</td>
<td>0.3271</td>
</tr>
<tr>
<td>Rate/100 PY</td>
<td>0.11</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fatal Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Events</td>
<td>16/4687 (0.3%)</td>
<td>11/2333 (0.5%)</td>
<td>0.72 (0.33, 1.55)</td>
<td>0.4015</td>
</tr>
<tr>
<td>Rate/100 PY</td>
<td>0.12</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death due to Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Events</td>
<td>14/4687 (0.3%)</td>
<td>22/2333 (0.9%)</td>
<td>0.32 (0.16, 0.62)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Rate/100 PY</td>
<td>0.10</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sudden death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Events</td>
<td>53/4687 (1.1%)</td>
<td>38/2333 (1.6%)</td>
<td>0.69 (0.45, 1.04)</td>
<td>0.0766</td>
</tr>
<tr>
<td>Rate/100 PY</td>
<td>0.38</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other CV Causes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Events</td>
<td>3/4687 (0.06%)</td>
<td>2/2333 (0.09%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rate/100 PY</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Presumed CV Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Events</td>
<td>71/4687 (1.5%)</td>
<td>53/2333 (2.3%)</td>
<td>0.66 (0.46, 0.94)</td>
<td>0.0218</td>
</tr>
<tr>
<td>Rate/100 PY</td>
<td>0.51</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Death due to worsening of heart failure or cardiogenic shock
*Due to CV causes other than MI, Stroke, HF or sudden death
CV, cardiovascular; MI, myocardial infarction
PY, patient years; CI, confidence interval; HR, hazard ratio

European Heart Journal doi:10.1093/eurheartj/ehv728
## Robustness of Heart Failure Results Across Multiple Outcomes

<table>
<thead>
<tr>
<th>Time to First:</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator reported:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>340 (8.6)</td>
<td>262 (13.3)</td>
<td>0.62 (0.53, 0.73)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Edema AE</td>
<td>251 (5.4)</td>
<td>235 (10.1)</td>
<td>0.51 (0.43, 0.61)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>HF* AE</td>
<td>204 (4.4)</td>
<td>143 (6.1)</td>
<td>0.70 (0.56, 0.87)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>HF† Serious AE</td>
<td>192 (4.1)</td>
<td>136 (5.8)</td>
<td>0.69 (0.55, 0.86)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>HHF</td>
<td>151 (3.2)</td>
<td>98 (4.2)</td>
<td>0.76 (0.59, 0.98)</td>
<td>p=0.035</td>
</tr>
<tr>
<td>Central Adjudication Committee confirmed:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHF</td>
<td>126 (2.7)</td>
<td>95 (4.1)</td>
<td>0.65 (0.50, 0.85)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Death Due to HF</td>
<td>14 (0.3)</td>
<td>22 (0.9)</td>
<td>0.32 (0.16, 0.62)</td>
<td>p=0.0008</td>
</tr>
<tr>
<td>CV Death</td>
<td>172 (3.7)</td>
<td>137 (5.9)</td>
<td>0.62 (0.49, 0.77)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>HHF or CV Death</td>
<td>265 (5.7)</td>
<td>198 (8.5)</td>
<td>0.66 (0.55, 0.79)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Cox regression analysis, ITT population.
HR, hazard ratio; CI, confidence interval; AE, adverse event; HF, heart failure; HHF, hospitalization for HF; CV, cardiovascular; Death Due to HF, clinical event committee confirmed death due to worsening of HF or cardiogenic shock.
*Based on narrow HF Standard MedRA query (SMQ) of adverse events.
Heart Failure Hospitalization or CV Death in Patients with vs without HF at Baseline

Patients with heart failure hospitalization or CV death (%)

- **Placebo:** HR 0.63 (95% CI 0.51, 0.78)
- **Empagliflozin:** HR 0.72 (95% CI 0.50, 1.04)

# SGLT2 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Dapagliflozin&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Canagliflozin&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Launch year</strong></td>
<td>2014 (EU/US)</td>
<td>2012 (EU) 2014 (US)</td>
<td>2013 (EU/US)</td>
</tr>
<tr>
<td><strong>MoA</strong></td>
<td>Molecular class</td>
<td>C-glycoside</td>
<td>C-glycoside</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Dual renal and hepatic</td>
<td>Mainly hepatic 97:3</td>
<td>Mainly hepatic, no details reported</td>
</tr>
<tr>
<td></td>
<td>50:50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>10 mg and 25 mg</td>
<td>5 mg and 10 mg</td>
<td>100 mg and 300 mg</td>
</tr>
</tbody>
</table>
CANVAS Program
Hospitalization for Heart Failure

Number of participants
Placebo  4347  4198  3011  1274  1236  1180  829
Canagliflozin  5795  5653  4437  2643  2572  2498  1782

HR 0.67
(95% CI 0.52, 0.87)
ARR=1.6% at 5 y;
NNT3y=105; NNT5y=63
33% RRR
NNT = 63
Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

17,160 patients with type II diabetes, including 10,186 without ASCVD randomized to dapagliflozin 10 mg daily vs placebo, who were followed for a median of 4.2 years.

NEJM 2018 DOI: 10.1056/NEJMoa1812389
Hospitalization for HF in Patients with T2DM Treated with SGL2i

- **EMPA-REG OUTCOME**
  - Empagliflozin
  - 9.4 vs 14.5 events/1000 p-y
  - HR 0.65 (0.50-0.85)

- **CANVAS/CANVAS-R**
  - Canagliflozin
  - 5.5 vs 8.7 events/1000 p-y
  - HR 0.67 (0.52-0.87)

- **DECLARE-TIMI 58**
  - Dapagliflozin
  - 6.2 vs 8.5 events/1000 p-y
  - HR 0.73 (0.61-0.88)

*P < .05; p-y, patient-years; NR, not reported. Not currently indicated by the US FDA for reducing hospitalization in patients with HF.
Meta-Analysis: SGLT2 Inhibitors and Heart Failure Hospitalizations

Lancet. 2019 Jan 5;393(10166):31-39
The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P = 0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001).

There were no significant differences in rates of amputation or fracture.

Type 2 diabetes and albuminuric CKD, eGFR of 30 to <90 ml per minute per 1.73 m2 of BSA and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. DOI: 10.1056/NEJMoa1811744
DAPA-HF Trial in HFrEF with or with Type 2 Diabetes

- Informed consent
- Inclusion/exclusion
- Clinical assessment
- ECG
- NT-proBNP
- Laboratory assessments

Enrolment

N=2371
Placebo

N=2373
Dapagliflozin 10 mg once daily

Visit 1
Day -14

Visit 2
Day 0

Visit 3
Day 14

Visit 4
Day 60

Visit 5
Day 120

Visit 6 etc.
Every 120 days

≥844 Primary endpoints
Composite of:
- CV death
- HF hospitalization
- Urgent HF visit

DOI: 10.1056/NEJMoa1911303
## Key baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Male (%)</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>NYHA class II/III/IV (%)</td>
<td>68/31/1</td>
<td>67/32/1</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Median NT pro BNP (pg/ml)</td>
<td>1428</td>
<td>1446</td>
</tr>
<tr>
<td>Mean systolic BP (mmHg)</td>
<td>122</td>
<td>122</td>
</tr>
<tr>
<td>Ischaemic aetiology (%)</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Mean eGFR (ml/min/1.73m²)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Prior diagnosis T2D (%)</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Any baseline T2D (%)*</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)
# Baseline treatment

<table>
<thead>
<tr>
<th>Treatment (%)</th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>ACE-inhibitor/ARB/ARNI*</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>ARB</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>MRA</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>ICD*</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>CRT**</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

*ARNI = angiotensin receptor neprilysin inhibitor  
*ICD or CRT-D  **CRT-P or CRT-D

For full details see McMurray JJV et al  
Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548
DAPA-HF Primary Composite Outcome

HR 0.74 (0.65, 0.85)
p=0.00001
NNT=21
Components of primary outcome

Worsening HF event
HR 0.70 (0.59, 0.83); p=0.00003

Cardiovascular death
HR 0.82 (0.69, 0.98); p=0.029
All-cause death

HR 0.83 (0.71, 0.97)  
p=0.022*

Number at Risk

<table>
<thead>
<tr>
<th>Dapagliflozin</th>
<th>2373</th>
<th>2342</th>
<th>2296</th>
<th>2251</th>
<th>2130</th>
<th>1666</th>
<th>1243</th>
<th>672</th>
<th>233</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2371</td>
<td>2330</td>
<td>2279</td>
<td>2231</td>
<td>2092</td>
<td>1638</td>
<td>1221</td>
<td>665</td>
<td>235</td>
</tr>
</tbody>
</table>

*Nominal p value
DAPA-HF Primary Composite Outcome

CV Death/HF hospitalization/Urgent HF visit

Diabetes

HR 0.75 (0.63, 0.90)

Placebo

Dapagliflozin

No Diabetes

HR 0.73 (0.60, 0.88)

Placebo

Dapagliflozin

P interaction 0.80
DAPA-HF: Treatment Effect by Diabetes Status and HbA1c

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>Type 2 diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63, 0.90)</td>
</tr>
<tr>
<td>No</td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60, 0.88)</td>
</tr>
<tr>
<td>HbA1c tertiles in patients without T2D at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5.6%</td>
<td>65/521</td>
<td>77/485</td>
<td>0.74 (0.53,1.04)</td>
</tr>
<tr>
<td>5.7-5.9%</td>
<td>44/365</td>
<td>66/388</td>
<td>0.71 (0.48,1.04)</td>
</tr>
<tr>
<td>≥6.0%</td>
<td>62/408</td>
<td>87/432</td>
<td>0.72 (0.52,1.00)</td>
</tr>
</tbody>
</table>
Treatment Effect According to Baseline HbA1c (All patients)

Primary Endpoint

Cardiovascular Death

Continuous HR

HR=1 (unity)

Placebo better

Dapa better

95% CI
## ARNI/no ARNI post hoc subgroup: Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>386/2373</td>
<td>502/2371</td>
<td><strong>0.74 (0.65, 0.85)</strong></td>
</tr>
<tr>
<td><strong>Angiotensin Receptor Neprilysin Inhibitor (ARNI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41/250</td>
<td>56/258</td>
<td><strong>0.75 (0.50, 1.13)</strong></td>
</tr>
<tr>
<td>No</td>
<td>345/2123</td>
<td>446/2113</td>
<td><strong>0.74 (0.65, 0.86)</strong></td>
</tr>
</tbody>
</table>

McMurray J. ESC Presentation Sept 1, 2019, Paris, France
## Safety/Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Patients exposed to at least one dose of study drug*</th>
<th>Placebo</th>
<th>Dapa</th>
<th>(P)-value</th>
<th>Placebo</th>
<th>Dapa</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE of interest (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume depletion</td>
<td>7.8</td>
<td>7.8</td>
<td>1.00</td>
<td>6.1</td>
<td>7.3</td>
<td>0.24</td>
</tr>
<tr>
<td>Renal AE</td>
<td>8.7</td>
<td>8.5</td>
<td>0.94</td>
<td>6.0</td>
<td>4.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Fracture</td>
<td>2.4</td>
<td>2.1</td>
<td>0.66</td>
<td>1.9</td>
<td>2.1</td>
<td>0.78</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.8</td>
<td>1.1</td>
<td>0.66</td>
<td>0.2</td>
<td>0.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Major hypoglycaemia(^+)</td>
<td>0.4</td>
<td>0.4</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>0</td>
<td>0.3</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>AE leading to treatment discontinuation (%)</strong></td>
<td>5.4</td>
<td>4.0</td>
<td>0.15</td>
<td>4.5</td>
<td>5.3</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Any serious AE (incl. death) (%)</strong></td>
<td>48.3</td>
<td>41.7</td>
<td>0.002</td>
<td>36.9</td>
<td>34.6</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*The safety population included patients receiving ≥1 dose of trial medication: dapagliflozin n= 2368 and placebo n=2368. \(^+\)Major hypoglycemia defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates, glucagon, or take other corrective action.
The Metabolodiuretic Promise of SGLT2 Inhibition

- Increased myocardial energetics
- Increased ATP
- Increased β-hydroxybutyrate (ketone body)

- Reduced preload
- Reduced LV wall stress

- Reduced afterload

- Increased diuresis
- Increased natriuresis
- Reduced glycosuria
- Reduced proteinuria

Afferent arteriolar dilatation:
- Increased intraglomerular pressure
- Increased Na⁺/glucose cotransport

SGLT2 inhibitors cause afferent arteriolar constriction

JAMA Cardiol. 2017;2(9):939-940
How Does Empagliflozin Reduce Cardiovascular Mortality?
Mediation Analysis of the EMPA-REG OUTCOME Trial

In this exploratory investigation into potential mediators of the reduction in risk of CV death with empagliflozin versus placebo, found that changes in hematocrit and hemoglobin, markers of the effects of the drug on volume, appeared to be important mediators of the reduction in mortality risk in univariable and multivariable models. Obesity, blood pressure, lipids, and renal function made negligible contribution.

Diabetes Care 2018;41:356–363
**Inclusion Criteria and Primary Endpoints**

**Major Trials of SGLT2 Inhibitors in HF**

**EMPEROR-Preserved**
- N = 6000 ± T2DM
- LVEF > 40%
- eGFR ≥ 20 mL/min/1.73 m²
- CV death or HHF

**SOLOIST-WHF**
- N = 4000 (T2DM only)
- Worsening HF, any LVEF
- eGFR ≥ 30 mL/min/1.73 m²
- CV death or HHF

**DELIVER**
- N = 4700 ± T2DM
- LVEF > 40%
- eGFR ≥ 25 mL/min/1.73 m²
- CV death or HHF or urgent HF visit

**Dapa-HF**
- N = 4744 ± T2DM
- LVEF ≤ 40%
- eGFR ≥ 30 mL/min/1.73 m²
- CV death or HHF or urgent HF visit

**EMPEROR-Reduced**
- N = 2850 ± T2DM
- LVEF ≤ 40%
- eGFR ≥ 20 mL/min/1.73 m²
- CV death or HHF

### 2016 ESC Guidelines for the Diagnosis and Treatment of Acute & Chronic HF

#### Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>126, 129, 150, 151</td>
</tr>
<tr>
<td>Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>137-140, 152</td>
</tr>
<tr>
<td>Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>C</td>
<td>131-134</td>
</tr>
<tr>
<td>Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.</td>
<td>IIa</td>
<td>C</td>
<td>130, 141, 153-155</td>
</tr>
<tr>
<td>Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.</td>
<td>IIa</td>
<td>B</td>
<td>130</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>5, 144, 145</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>B</td>
<td>5</td>
</tr>
<tr>
<td>ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.</td>
<td>IIa</td>
<td>A</td>
<td>142</td>
</tr>
<tr>
<td>Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.</td>
<td>I</td>
<td>B</td>
<td>146</td>
</tr>
</tbody>
</table>
Practical Guide to Prescribing Sodium-Glucose Cotransporter 2 Inhibitors for Cardiologists

Orly Vardeny, PharmD, MS,a Muthiah Vaduganathan, MD, MPHb

ABSTRACT

The sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of glucose-lowering therapies that have been shown to reduce risks of heart failure (HF) events in patients with type 2 diabetes mellitus (T2DM) at high-risk for or with cardiovascular disease. The United States Food and Drug Administration has expanded the regulatory label for empagliflozin and canagliflozin for use to lower cardiovascular risk in patients with T2DM and cardiovascular disease. SGLT2 inhibitors are being actively studied in the treatment of patients with HF, including in those without diabetes mellitus. Despite the accumulating data supporting this class of therapies in HF prevention, cardiologists infrequently prescribe SGLT2 inhibitors, potentially due to lack of familiarity with their use. We provide an up-to-date practical guide highlighting important elements for treatment initiation, dosing, anticipated adverse effects, and barriers to uptake. (J Am Coll Cardiol HF 2019;7:169-72) © 2019 by the American College of Cardiology Foundation.

CENTRAL ILLUSTRATION Stepwise Approach to Prescription of SGLT2 inhibitors by Cardiologists

Patients with T2DM with or at High Risk for CV Disease, Already on Metformin

Below Individualized HbA1c Target: Switch non-metformin oral therapies (e.g., sulfonylureas) to a SGLT2i

Above Individualized HbA1c Target: Consider SGLT2i initiation

Drug Type
- Canagliflozin, dapagliflozin, & empagliflozin with similar efficacy profile in reducing HF events

Starting Dose (once daily in AM)
- Canagliflozin (100mg)
- Dapagliflozin (5mg)
- Empagliflozin (10mg)
- Ertrigliflozin (5mg)

Metformin±SGLT2i Combination Therapies
Consider to limit non-adherence and pill burden

Stable Hemodynamic and Clinical Status
Pre-initiation eGFR must be above:
- 60 mL/min/1.73 m² (dapagliflozin, ertrigliflozin)
- 45 mL/min/1.73 m² (canagliflozin, empagliflozin)

Anticipatory Guidance
Consider diuretic dose reduction

Patient Counseling
- Genital/perineal hygiene
- Orthostatic hypotension
- Regular foot exams
- Symptoms of DKA
- Avoid excessive alcohol

Multidisciplinary Care
Close communication with other providers, including PCPs and endocrinologists

Follow-up and Monitoring
- Serial assessment of renal function, body weights, blood pressure, and symptoms
- Dose up titration guided by need for glycemic control
- Ensure adherence to SGLT2i, other therapies, and therapeutic lifestyle
- Multidisciplinary care team follow-up

Cumulative Impact of Evidence-Based Heart Failure with Reduced EF Medical Therapies on All Cause Mortality (Quadruple Rx)

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Relative Risk</th>
<th>2 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- -</td>
<td>35.0%</td>
</tr>
<tr>
<td>ARNI (vs imputed placebo)</td>
<td>↓ 28%</td>
<td>25.2%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓ 35%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>↓ 30%</td>
<td>11.5%</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>↓ 17%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction in mortality if all evidence-based medical therapies are used: Relative risk reduction 72.9%, Absolute risk reduction: 25.5%, NNT = 3.9

Conclusions

- Until 2015, no known diabetes therapy demonstrated in RTCs to improve CV outcomes in general or for HF
- Most diabetes medications were neutral in ASCVD and worsened outcomes in HF or at best were neutral
- EMPA-REG Outcome, CANVAS, DECLARE trial data
  - SGLT2 inhibitors are a new option to reduce CV events, CV death and HF in patients with diabetes with and without HF
  - Compelling data
- DAPA-HF establishes SGLT2i therapy as part of standard of care GDMT for HFrEF patients
- It is critical for cardiologists and HF specialists to play an active role in this management as choice of therapy is key determinate of outcomes, including survival