DAPAGLIFLOZIN IN MYOCARDIAL INFARCTION
WITHOUT DIABETES OR HEART FAILURE

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DAPA-MI TRIAL

Dapagliflozin in myocardial infarction without diabetes or heart failure

Conflicts of interest

Institutional research grants/support from AstraZeneca, Novartis, Jansen and Amgen.

The DAPA-MI trial is sponsored by AstraZeneca (AZ)
**RATIONALE FOR DAPA-MI TRIAL**

**What we want to achieve with secondary prevention after a myocardial infarction**

- Reduce recurrent myocardial infarction
- Reduce heart failure
- Reduce mortality
- Optimize blood pressure
- Improve kidney function
- Optimize glucose levels
- Weight reduction
- Improve lipid profile
- Promote exercise
- Promote smoking cessation

**Effects of SGLT2i**

- Reduce myocardial infarction
- Reduce heart failure
- Reduce mortality
- Reduce blood pressure
- Improve kidney-related outcomes
- Reduce glucose levels
- Weight reduction
- Slightly lower triglycerides

- *SGLT2i have positive effects on almost all cardiometabolic parameters*
- *It could be an effective secondary prevention medication*
BENEFITS OF SGLT2- INHIBITION

Diabetes & Cardiovascular Risk$^1$
Heart Failure irrespective of LVEF$^{2,3}$
Chronic Kidney Disease$^4$
Post-myocardial Infarction$^5$

**DAPA-MI objective:** To evaluate the effect of dapagliflozin on cardiometabolic outcomes in patients with acute myocardial infarction without diabetes or chronic heart failure


LVEF: left ventricular ejection fraction
REGISTRY-BASED RANDOMIZED CLINICAL TRIAL – R-RCT


DAPA-MI: Digital technologies underpin world’s first indication-seeking registry-based randomised controlled outcomes trial.

Innovative approaches enhance patient experience and drive 50% per patient cost reduction without impacting timelines.

Accelerating and expanding patient recruitment.

Use of quality registers from clinical routine through scientific leadership with UCR and NICOR.

Reduced patient and investigator burden.

Streamlined trial design with automated data transfer from routine clinical practice.

Advancing Drug Adherence.

Use of SmartCap adherence monitoring technology.

Remote patient monitoring.

Patient app for information sharing and signalling of events.

Evaluating dapagliflozin for prevention of heart failure and CV death following myocardial infarction in 6400 patients in only 2 countries.

Dapagliflozin 10 mg once daily on top of SoC.

Placebo once daily on top of SoC.
TRIAL DESIGN

Main Inclusion Criteria
- MI (NSTEMI or STEMI) < 10 days
- Impaired LV systolic function or Q-wave MI
- Hemodynamically stable

Main Exclusion Criteria
- Type 1 or type 2 diabetes
- Chronic symptomatic HF with a prior HHF within the last year and known reduced EF (LVEF ≤ 40 %)
- eGFR <20 mL/min/1.73 m²

Key assumptions
- 4000 patients
- Minimum follow up 3 months
- Assumed true win ratio 1.2
- Total trial duration 2.5 years
- Power 80%, $P<0.05$

Dapagliflozin 10 mg + standard of care
Placebo + standard of care

Screening and randomization
1:1 Double-blind

ENDPOINTS

The composite of CV death and hospitalization for heart failure was initially chosen as the primary outcome. During the trial, it became evident that the number primary composite outcomes was substantially lower than anticipated. Thus, in Feb 2023, the trial was modified to a hierarchical composite outcome approach with cardiometabolic outcomes.¹

### Primary

The hierarchical (win ratio) composite outcomes:

- Death (first cardiovascular death, followed by non-cardiovascular death)
- Hospitalization due to heart failure (first adjudicated, followed by investigator reported)
- Non-fatal myocardial infarction
- Atrial fibrillation/flutter event
- New diagnosis of type 2 diabetes
- NYHA functional class at last visit
- Body weight decrease at least 5% at last visit

### Key secondary

- Primary outcome excluding body weight component

### Other secondary

- Time to the first occurrence of any of the components of the composite:
  - Hospitalization for heart failure
  - Cardiovascular death

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NYHA, New York Heart Association
### Summary of key demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dapa 10 mg (N=2019)</th>
<th>Placebo (N=1998)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean 63.0</td>
<td>62.8</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Female 388 (19.2)</td>
<td>419 (21.0)</td>
</tr>
<tr>
<td>Country, n (%)</td>
<td>Sweden / United Kingdom 584 (28.9) / 1435 (71.1)</td>
<td>594 (29.7) / 1404 (70.3)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>Mean 28.2</td>
<td>28.3</td>
</tr>
<tr>
<td>Baseline LVEF, n (%)</td>
<td>&lt;30 130 (6.4)</td>
<td>137 (6.9)</td>
</tr>
<tr>
<td></td>
<td>30-49 1363 (67.5)</td>
<td>1311 (65.6)</td>
</tr>
<tr>
<td></td>
<td>≥50 416 (20.6)</td>
<td>432 (21.6)</td>
</tr>
<tr>
<td>Myocardial Infarction Index Event, n (%)</td>
<td>STEMI 1465 (72.6)</td>
<td>1428 (71.5)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m³)</td>
<td>Mean 83.5</td>
<td>83.4</td>
</tr>
<tr>
<td>Co-morbidities, n (%)</td>
<td>Hypertension 766 (37.9)</td>
<td>716 (35.8)</td>
</tr>
<tr>
<td></td>
<td>Prior myocardial infarction 178 (8.8)</td>
<td>189 (9.5)</td>
</tr>
<tr>
<td></td>
<td>Prior stroke 46 (2.3)</td>
<td>50 (2.5)</td>
</tr>
<tr>
<td>Key medications, n (%)</td>
<td>Acetylsalicylic acid 1873 (92.8)</td>
<td>1854 (92.8)</td>
</tr>
<tr>
<td></td>
<td>Thienopyridine/Ticagrelor 1857 (92.0)</td>
<td>1819 (91.0)</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor/ARB 1868 (92.5)</td>
<td>1835 (91.8)</td>
</tr>
<tr>
<td></td>
<td>Aldosterone receptor blocker 459 (22.7)</td>
<td>464 (23.2)</td>
</tr>
<tr>
<td></td>
<td>Beta blockers 1805 (89.4)</td>
<td>1797 (89.9)</td>
</tr>
<tr>
<td></td>
<td>Statins 1938 (96.0)</td>
<td>1897 (94.9)</td>
</tr>
</tbody>
</table>

N: Number of subjects in the treatment group, Dapa: Dapagliflozin, ACE: Angiotensin-converting enzyme, ARB: angiotensin receptor blocker
The components in hierarchical order are:
1. Death, 2. Hospitalization for heart failure, 3. MI event, 4. Atrial fibrillation/flutter,
5. Type 2 diabetes, 6. NYHA class, and 7. Weight decrease ≥ 5%

Primary outcome
All 7 components

Ties 42.5%

Win ratio (95% CI)
1.34 (1.20, 1.50) p < 0.001

Win ratio
Placebo better
Dapagliflozin better
The components in hierarchical order are:
1. Death, 2. Hospitalization for heart failure, 3. MI event, 4. Atrial fibrillation/flutter,
5. Type 2 diabetes, and 6. NYHA class

**Primary outcome**
- **All 7 components:**
  - Ties: 42.5%
  - Win: 32.9%
  - Win ratio (95% CI): 1.34 (1.20, 1.50) \( p < 0.001 \)

**Key secondary outcome**
- **Components 1-6**
  - Ties: 62.8%
  - Win: 20.3%
  - Win ratio (95% CI): 1.20 (1.04, 1.40) \( p = 0.015 \)
The components in hierarchical order are:
### PRIMARY OUTCOME BY SUBGROUPS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>N</th>
<th>WR [95% CI]</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Sweden</td>
<td>1178</td>
<td>1.28 [1.12, 1.47]</td>
<td>0.240</td>
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<tr>
<td></td>
<td>United Kingdom</td>
<td>2839</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td>≤65</td>
<td>2387</td>
<td>1.39 [1.19, 1.63]</td>
<td>0.477</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>1630</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>807</td>
<td>1.35 [1.10, 1.65]</td>
<td>0.760</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>No</td>
<td>314</td>
<td>1.43 [1.09, 1.90]</td>
<td>0.720</td>
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<tr>
<td></td>
<td>Yes</td>
<td>3703</td>
<td></td>
<td></td>
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<tr>
<td>BMI</td>
<td>&lt;30</td>
<td>2727</td>
<td>1.37 [1.20, 1.59]</td>
<td>0.216</td>
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<td></td>
<td>≥30</td>
<td>1264</td>
<td></td>
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<tr>
<td>eGFR by CKD–EPI</td>
<td>&lt;60</td>
<td>385</td>
<td>1.39 [1.21, 1.62]</td>
<td>0.228</td>
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<tr>
<td></td>
<td>≥60</td>
<td>3630</td>
<td></td>
<td></td>
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<tr>
<td>Diastolic BP</td>
<td>&lt;80</td>
<td>2986</td>
<td>1.23 [1.13, 1.34]</td>
<td>0.057</td>
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<tr>
<td></td>
<td>≥80</td>
<td>1031</td>
<td></td>
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<tr>
<td>Systolic BP</td>
<td>&lt;130</td>
<td>3056</td>
<td>1.25 [1.09, 1.43]</td>
<td>0.750</td>
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<tr>
<td></td>
<td>≥130</td>
<td>961</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LVEF</td>
<td>&lt;30</td>
<td>2674</td>
<td>1.40 [1.23, 1.60]</td>
<td>0.804</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>828</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI index event</td>
<td>STEMI</td>
<td>1106</td>
<td>1.39 [0.96, 1.59]</td>
<td>0.273</td>
</tr>
<tr>
<td></td>
<td>NSTEMI</td>
<td>2893</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c</td>
<td>&lt;Median</td>
<td>1571</td>
<td>1.39 [1.09, 1.80]</td>
<td>0.679</td>
</tr>
<tr>
<td></td>
<td>≥Median</td>
<td>2020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Creatinine</td>
<td>&lt;Median</td>
<td>1953</td>
<td>1.25 [1.05, 1.48]</td>
<td>0.181</td>
</tr>
<tr>
<td></td>
<td>≥Median</td>
<td>2062</td>
<td></td>
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</tbody>
</table>
## SECONDARY AND EXPLORATORY OUTCOMES

<table>
<thead>
<tr>
<th>Secondary and exploratory outcomes</th>
<th>Dapagliflozin 10 mg (N = 2019)</th>
<th>Placebo (N = 1998)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/hospitalization for HF, n (%)</td>
<td>50 (2.5)</td>
<td>52 (2.6)</td>
<td>0.95 (0.64–1.40)</td>
</tr>
<tr>
<td>CV death/hospitalization for HF/MI, n (%)</td>
<td>82 (4.1)</td>
<td>85 (4.3)</td>
<td>0.95 (0.70–1.29)</td>
</tr>
<tr>
<td>MACE (MI, stroke or CV death), n (%)</td>
<td>68 (3.4)</td>
<td>72 (3.6)</td>
<td>0.94 (0.67–1.31)</td>
</tr>
<tr>
<td>All-cause death, n (%)</td>
<td>41 (2.0)</td>
<td>33 (1.7)</td>
<td>1.22 (0.77–1.92)</td>
</tr>
<tr>
<td>CV death, n (%)</td>
<td>27 (1.3)</td>
<td>23 (1.2)</td>
<td>1.15 (0.66–2.01)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>44 (2.2)</td>
<td>39 (2.0)</td>
<td>1.11 (0.72–1.71)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>10 (0.5)</td>
<td>17 (0.9)</td>
<td>0.61 (0.28–1.34)</td>
</tr>
<tr>
<td>New diagnosis of type 2 diabetes, n (%)</td>
<td>42 (2.1)</td>
<td>78 (3.9)</td>
<td>0.53 (0.36–0.77)</td>
</tr>
<tr>
<td>Hospitalization due to AF/flutter, n (%)*</td>
<td>16 (0.8)</td>
<td>18 (0.9)</td>
<td>0.88 (0.45–1.73)</td>
</tr>
<tr>
<td>All cause hospitalization, n (%)</td>
<td>418 (20.7)</td>
<td>372 (18.6)</td>
<td>1.12 (0.97–1.29)</td>
</tr>
<tr>
<td>Adjudicated hospitalization for HF, n (%)*</td>
<td>27 (1.3)</td>
<td>32 (1.6)</td>
<td>0.83 (0.50–1.39)</td>
</tr>
</tbody>
</table>

No unexpected safety concerns were reported during the trial. Serious adverse events leading to death on treatment** occurred in 30/1995 (1.5%) in the dapagliflozin group and in 29/1997 (1.5%) in the placebo group.

*Exploratory outcome. **On-treatment period will include events with an onset date on or after the first dose of randomized study drug and on or before 30 days after the last dose of the study drug. CI: confidence interval, CV: cardiovascular, HF: heart failure, MACE: major adverse cardiovascular event, AF: atrial fibrillation.
NEW DIAGNOSIS OF TYPE 2 DIABETES
Overall treatment effect on change in body weight (kg) for dapagliflozin vs placebo
-1.65 (95% CI, -2.12 to -1.18)
CONCLUSIONS

• In patients with acute MI and impaired left ventricular systolic function, without prior diabetes or chronic heart failure, dapagliflozin demonstrated significant benefit with regards to improvement in cardiometabolic outcomes compared with placebo.

• The cardiometabolic benefit was consistent across all pre-specified subgroups and there were no new safety concerns.

• Clinical event rates were low with no significant difference between randomized groups.

• The innovative registry-based clinical trial (R-RCT) design, incorporating national clinical registry data, facilitated efficient patient recruitment and outcome ascertainment.
Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure

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All participating patients