Relationship between baseline cardiac biomarkers and cardiovascular death or hospitalization for heart failure with and without SGLT2 inhibitor therapy in DECLARE-TIMI 58

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On behalf of the DECLARE-TIMI 58 Investigators

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Conflicts of Interests

• Grants from AstraZeneca and Bristol-Myers Squibb and reagent support from Roche Diagnostics to Brigham and Women’s Hospital.

• Research grant from the Deutsche Forschungsgemeinschaft

• Lecture fees from AstraZeneca
Background

- Dapagliflozin is a selective SGLT2 inhibitor that blocks glucose and Na\(^+\) reabsorption in the kidneys and thereby lowers HbA1c in patients with T2DM.
- In DECLARE-TIMI 58, dapagliflozin has been shown to significantly reduce the risk of CV death/HHF in T2DM, driven by a reduction in HHF, and was non-inferior with regard to MACE.

Zelniker TA, Braunwald E; JACC 2018
Wiviott SD et al.; NEJM 2018
Background

• Biomarkers can be helpful tools and provide diagnostic and/or prognostic information & give insight in pathobiological mechanisms.

• NT-proBNP and hsTnT are established markers that reflect hemodynamic stress and myocardial injury and have been shown to predict HF events and death.

• We hypothesized that baseline hsTnT and NT-proBNP levels would help identify patients who are at higher baseline risk and thus benefit more from treatment with dapagliflozin.
Objective

- To evaluate the association of baseline hsTnT and NT-proBNP levels with CV death/HHF in patients with and without prior HF and with the magnitude of benefit with dapagliflozin.

Methods

- Prespecified biomarker study from DECLARE-TIMI 58.
- NT-proBNP and hsTnT levels were measured (Roche Diagnostics) in all patients with available blood samples at randomization (n=14,565) in the TIMI Clinical Trials Laboratory.
DECLARE-TIMI 58

17,160 with Type 2 DM
Established CV Disease (6974) or
Multiple Risk Factors (10186)

RANDOMIZE 1:1 DOUBLE BLIND
All other DM Rx per treating MD

DAPAGLIFLOZIN
10 mg DAILY

PLACEBO

Follow-up visits
In Person Q 6 mo/ telephone Q 3 mo

Primary EPs
Safety: MACE (CVD/MI/Ischemic Stroke)
Dual Efficacy: CVD/HHF, MACE

DURATION
EVENT DRIVEN
≥1390 MACE

Median follow up –
4.2 years

Wiviott SD, et al., AHJ 2018; Wiviott SD et al., NEJM 2019
## Baseline Biomarker Concentrations

<table>
<thead>
<tr>
<th></th>
<th>NT-proBNP</th>
<th></th>
<th>hsTnT</th>
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<tbody>
<tr>
<td></td>
<td>Median,</td>
<td>IQR</td>
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</tr>
<tr>
<td></td>
<td>≥125 pg/ml</td>
<td>≥450 pg/ml</td>
<td>≥6 ng/L</td>
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<tr>
<td>≥14 ng/L</td>
<td></td>
<td></td>
<td>≥14 ng/L</td>
</tr>
<tr>
<td>Total Population</td>
<td>75</td>
<td>33%</td>
<td>10.2 (6.9-15.5)</td>
</tr>
<tr>
<td>N = 14,565</td>
<td>(35 - 165)</td>
<td>8%</td>
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<td></td>
</tr>
<tr>
<td><strong>History of HF</strong></td>
<td>208 (91-541)</td>
<td>65%</td>
<td>29%</td>
<td>14.1 (9.1-21.3)</td>
</tr>
<tr>
<td>N = 1,464</td>
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<td></td>
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<td>30%</td>
</tr>
<tr>
<td><strong>History of HF</strong></td>
<td>208</td>
<td>65%</td>
<td>14.1</td>
<td>90%</td>
</tr>
<tr>
<td>N = 1,464</td>
<td>(91-541)</td>
<td></td>
<td>(9.1 - 21.3)</td>
<td>50%</td>
</tr>
<tr>
<td><strong>No History of HF</strong></td>
<td>68</td>
<td>29%</td>
<td>9.9</td>
<td>81%</td>
</tr>
<tr>
<td>N = 13,101</td>
<td>(33-142)</td>
<td></td>
<td>(6.7 - 14.8)</td>
<td>28%</td>
</tr>
</tbody>
</table>
## Baseline Characteristics by Biomarker Quartiles

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<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q4</td>
<td>Q1</td>
<td>Q4</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61</td>
<td>66</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>70</td>
<td>62</td>
<td>37</td>
<td>83</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
<td>31.9</td>
<td>32.6</td>
<td>31.2</td>
<td>33.1</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>10</td>
<td>12</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>ASCVD (%)</td>
<td>28</td>
<td>58</td>
<td>32</td>
<td>52</td>
</tr>
<tr>
<td>Prior HF (%)</td>
<td>3</td>
<td>23</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min/1.73m²)</td>
<td>90</td>
<td>80</td>
<td>92</td>
<td>78</td>
</tr>
</tbody>
</table>

All P-trend <0.001
Event Rates in the **Placebo** Arm

**NT-proBNP**

- **≤35 pg/ml**: 1.0%
- **35-75 pg/ml**: 1.9%
- **75-165 pg/ml**: 4.7%
- **>165 pg/ml**: 15.1%

**hsTnT**

- **≤6.9 ng/L**: 1.6%
- **6.9-10.2 ng/L**: 2.4%
- **10.2-15.5 ng/L**: 6.1%
- **>15.5 ng/L**: 13.0%
Event Rates in the Placebo Arm

Prior HF

No Prior HF
CV death/HHF
Cut at Median of NT-proBNP

**KM Event Rates**

**P**\textsubscript{Interaction} for HR 0.27

**P**\textsubscript{Interaction} for ARR 0.010

**HR 0.81**

(0.70-0.95)

**ARR 1.9**

**HR 1.01**

(0.70-1.44)

**ARR 0**
CV death/HHF
Cut at Median of hsTnT

P_{Interaction} for HR 0.68
P_{Interaction} for ARR 0.026

HR 0.83 (0.71-0.97)
ARR 1.8

HR 0.89 (0.64-1.24)
ARR 0.1
Combined Biomarker Approach

ARR

CV death/HHF

-0.5 (-1.1 to 0.1) 0.9 (0.0 to 1.8) 2.5 (0.5 to 4.5)

P interaction for ARR 0.002

KM Event Rates (%)

NT-proBNP & hsTnT <=Median

NT-proBNP or hsTnT >Median

NT-proBNP & hsTnT >Median

31%

38%

31%

0 5 10 15 20

0 10 20

0.8 1.3 3.2 2.3 13.8 11.3
History of HF

CV death/HHF

ARR -6.0 (-11.1 to -0.9)  2.1 (-3.0 to 7.2)  6.9 (1.1 to 12.6)

P interaction for ARR 0.004

KM Event Rates (%)

0 5 10 15 20 25 30 35 40 45

0.0 6.0 8.2 6.1 28.6 21.8

NT-proBNP & hsTnT <=Median  NT-proBNP or hsTnT >Median  NT-proBNP & hsTnT >Median

11% 28% 61%
No History of HF

CV death/HHF

ARR: -0.3 (-0.9 to 0.3)
Placebo: 0.8 (-0.0 to 1.7)
Dapaglisofzin: 1.3 (-0.6 to 3.3)

P interaction for ARR 0.059

KM Event Rates (%)

NT-proBNP & hsTnT ≤ Median: 0.8
NT-proBNP or hsTnT > Median: 2.8
NT-proBNP & hsTnT > Median: 10.0

33% 39% 28%
1. Patients with higher NT-proBNP or hsTnT levels are at increased risk of CV death and HHF.

2. Dapagliflozin consistently reduced the relative risk of CV death/HHF regardless of baseline NT-proBNP or hsTnT quartiles.

3. The magnitude of the absolute risk reduction was larger in patients with higher biomarker levels reflecting their higher baseline risk.

4. A combined biomarker approach including two widely available biomarkers, NT-proBNP and hsTnT, may assist in identifying patients at highest risk and with the greatest potential benefit from the administration of dapagliflozin.
Conclusion

Dapagliflozin reduced the relative risk of CV death/HHF irrespective of NT-proBNP and hsTnT levels, with greater absolute risk reductions seen in patients with higher baseline NT-proBNP and hsTnT levels.

Slides available at www.timi.org