Serial Assessment of Cardiac Biomarkers and Risk of Cardiovascular Death or Hospitalization for Heart Failure in DECLARE-TIMI 58

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DISCLOSURES

Dr. Berg has received consulting fees from AstraZeneca, Mobility Bio, Inc., and Youngene Therapeutics, honoraria from the Medical Education Speakers Network (MESN), and participates on clinical endpoint committees for studies sponsored by Kowa Pharmaceuticals. Dr. Berg is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women’s Hospital from Abbott, Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, Intarcia, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Softcell Medical Limited, The Medicines Company, Zora Biosciences.

DECLARE-TIMI 58 was sponsored by AstraZeneca.
BACKGROUND

• Heart failure (HF) is an impactful complication of type 2 diabetes (T2D), the risk of which can be reduced by treatment with SGLT2 inhibitors

• Circulating biomarkers reflecting subclinical myocardial structural changes provide an opportunity to detect the continuum of disease progression toward clinical HF in patients with T2D (“stage B HF”)

• Circulating natriuretic peptide (NP) and cardiac troponin (cTn) concentrations are strongly associated with risk of incident and recurrent HF events in patients with T2D
**TIMI Biomarker Score for Heart Failure in Diabetes**

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of HF</td>
<td>2</td>
</tr>
<tr>
<td>hsTnT</td>
<td></td>
</tr>
<tr>
<td>&lt;6 ng/L</td>
<td>0</td>
</tr>
<tr>
<td>6-10 ng/L</td>
<td>1</td>
</tr>
<tr>
<td>10-14 ng/L</td>
<td>2</td>
</tr>
<tr>
<td>≥14 ng/L</td>
<td>3</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
</tr>
<tr>
<td>&lt;50 ng/L</td>
<td>0</td>
</tr>
<tr>
<td>50-125 ng/L</td>
<td>2</td>
</tr>
<tr>
<td>125-450 ng/L</td>
<td>4</td>
</tr>
<tr>
<td>≥450 ng/L</td>
<td>6</td>
</tr>
</tbody>
</table>

**Risk Category**
- Low: 0-3 points
- Intermediate: 4-6 points
- High: 7-8 points
- Very High: 9-11 points

Biomarker-based score identifies patients with higher risk who derive greater absolute benefit from dapagliflozin in DECLARE-TIMI 58.

BACKGROUND

• Less is known about prognostic significance of changes in NPs and cTn over time or effect of SGLT2 inhibitors on these biomarkers

OBJECTIVES

• Assess prognostic significance of changes in NT-proBNP and hsTnT over 6 months in patients with T2D at elevated cardiovascular risk

• Assess the effect of dapagliflozin (SGLT2 inhibitor) on NT-proBNP and hsTnT in patients with T2D in the DECLARE-TIMI 58 trial
METHODS

DECLARE-TIMI 58

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

DAPAGLIFLOZIN
10 mg DAILY

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

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

NT-proBNP and hsTnT levels measured (Roche Diagnostics) in all
patients with available samples
(TIMI Clinical Trials Laboratory)

MEDICATIONS

David D. Berg, MD, MPH | Serial Assessment of CV Biomarkers in DECLARE-TIMI 58

Brigham and Women’s Hospital
Founding Member, Mass General Brigham
METHODS

- Analysis population = patients with serial NT-proBNP and hsTnT values
  - Patients with MI or HHF within 1 month prior to 6-month study visit
- Clinical outcome = cardiovascular death or hospitalization for HF
  - Centrally adjudicated by TIMI CEC using standard definitions
- Outcome analyses performed from landmark of 6-month study visit with patients categorized by change in biomarker over first 6 months
- Hazard ratios adjusted for baseline biomarker value, randomized therapy, age, sex, race, smoking, eGFR, prior HF, BMI, T2D duration, insulin use, CAD, prior MI, ischemic stroke, PAD, dyslipidemia, and hypertension
- Linear mixed models used to assess effect of dapagliflozin on log-transformed NT-proBNP and hsTnT levels
RESULTS

- 14,565 patients (85%) participated in nested biomarker substudy
  - Serial NT-proBNP and hsTnT levels available in 13,459 patients (78%)

**DISTRIBUTION OF CHANGE IN BIOMARKER CONCENTRATIONS (PLACEBO ARM ONLY)**

<table>
<thead>
<tr>
<th>NT-proBNP</th>
<th>hsTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL median (IQR) = 75 (35-165) pg/ml</td>
<td>BL median (IQR) = 10 (7-15) ng/L</td>
</tr>
<tr>
<td>≥20% change = 70%</td>
<td>≥20% change = 33%</td>
</tr>
<tr>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>30%</td>
<td>9%</td>
</tr>
<tr>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- NT-proBNP more dynamic than hsTnT (among patients allocated to placebo)
RESULTS

ADJUSTED SUBSEQUENT RISK OF CV DEATH OR HOSPITALIZATION FOR HF BY CHANGE IN BIOMARKER

**Relative Change in Biomarker from Baseline to 6M**

- ≥50% Increase (N=1696)
- 20%-<50% Increase (N=931)
- No Change (N=1989)
- 20%-<50% Decrease (N=1406)
- ≥50% Decrease (N=641)

**NT-proBNP**

P-trend <0.01

**Relative Change in Biomarker from Baseline to 6M**

- ≥50% Increase (N=502)
- 20%-<50% Increase (N=580)
- No Change (N=4493)
- 20%-<50% Decrease (N=764)
- ≥50% Decrease (N=321)

**hsTnT**

P-trend <0.01

HRs adjusted for baseline biomarker value, randomized therapy, age, sex, race, smoking, eGFR, prior HF, BMI, T2D duration, insulin use, CAD, prior MI, ischemic stroke, PAD, dyslipidemia, and hypertension.
RESULTS

ADJUSTED SUBSEQUENT RISK OF CV DEATH OR HOSPITALIZATION FOR HEART FAILURE BY CHANGE IN BOTH NT-PROBNP AND HSTNT OVER 6 MONTHS

<table>
<thead>
<tr>
<th>Change in NT-proBNP</th>
<th>Change in hSTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20% Increase</td>
<td>2.39 (1.79-3.19)</td>
</tr>
<tr>
<td>No Change</td>
<td>1.31 (0.91-1.89)</td>
</tr>
<tr>
<td>≥20% Decrease</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td></td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td></td>
<td>0.75 (0.58-0.95)</td>
</tr>
<tr>
<td></td>
<td>1.16 (0.80-1.68)</td>
</tr>
</tbody>
</table>

HRs adjusted for baseline biomarker value, randomized Rx, age, sex, race, smoking, eGFR, prior HF, BMI, T2D duration, insulin use, CAD, prior MI, ischemic stroke, PAD, dyslipidemia, & HTN
RESULTS

Effect of Dapagliflozin on NT-proBNP and hsTnT over 6 Months

**NT-PROBNP**
- Relative LS mean change with dapagliflozin: -6% (-4% to -8%)
- p<0.001

**HS TROTONIN T**
- Relative LS mean change with dapagliflozin: 0% (-1% to +1%)
- p=0.92

Geometric means with 95% CIs are plotted
CONCLUSIONS

• Among patients with T2D randomly allocated to placebo in DECLARE-TIMI 58, NT-proBNP was more dynamic than hsTnT over 6 months

• Short-term (6-month) changes in hsTnT and NT-proBNP are associated with subsequent risk of CV death or hospitalization for HF in patients with T2D
  • Increases in either biomarker associated with higher subsequent risk
  • Decreases in either biomarker associated with lower subsequent risk

• Considered together, changes in the two CV biomarkers are complementary

• Dapagliflozin significantly (albeit modestly) reduced NT-proBNP but did not affect hsTnT over 6 months in DECLARE-TIMI 58

• Serial measurement of NT-proBNP and hsTnT may provide objective assessment of clinical trajectory, which might in turn be used to inform clinical decision-making
THANK YOU