Biomarker-Based Heart Failure Risk Stratification In Patients With Atherosclerotic Cardiovascular Disease: Observations From HPS3/TIMI-55-REVEAL

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Disclosures

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Background

• The prevalence of heart failure (HF) is increasing, including in patients with atherosclerotic cardiovascular disease (ASCVD)

• Cardiovascular disease guidelines have placed increasing emphasis on risk-guided HF prevention

• Circulating biomarkers reflecting pathways implicated in HF may improve HF risk assessment in patients with stable ASCVD
Methods

Study Population & Biomarker Testing

• **HPS3/TIMI 55-REVEAL** was a randomized, double-blind, placebo-controlled trial of the CETP inhibitor anacetrapib in patients with stable ASCVD

• We performed a nested prospective biomarker study using blood samples obtained at randomization (n=29,673)

• We measured the following biomarkers (Roche Diagnostics):
  • High-sensitivity troponin T (hsTnT)
  • N-terminal pro-B-type natriuretic peptide (NT-proBNP)
  • Growth differentiation factor-15 (GDF-15)
Methods

Statistical Methods

- We calculated KM event rates of hospitalization for heart failure (HHF) at 4 years post-randomization for each decile of baseline biomarker concentration.
- HRs adjusted for covariates of *a priori* clinical relevance to HHF risk (based on a prior analysis from TRA 2P-TIMI 50) → age, prior HF, hypertension, diabetes mellitus, eGFR <60, body-mass index, and polyvascular disease.
- Discrimination assessed using Harrell’s c-index.
Results
Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>hsTnT</th>
<th>NT-proBNP</th>
<th>GDF-15</th>
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<tr>
<td>p_trend &lt;0.001</td>
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Median concentration (IQR):
- hsTnT: 9.8 ng/L (6.9-14.2)
- NT-proBNP: 128 pg/ml (60-288)
- GDF-15: 1288 ng/L (935-1885)

Hospitalization for HF at 4 years
Results

Hospitalization for Heart Failure

**hsTnT**

- **Adj-HR**
  - Decile 10: 12.1 (7.65, 19.0)
  - Decile 9: 6.99 (4.41, 11.1)
  - Decile 8: 5.13 (3.22, 8.19)
  - Decile 7: 3.80 (2.36, 6.13)
  - Decile 6: 2.95 (1.80, 4.82)
  - Decile 5: 2.40 (1.45, 3.98)
  - Decile 4: 2.52 (1.53, 4.17)
  - Decile 3: 1.55 (0.90, 2.69)
  - Decile 2: 1.59 (0.92, 2.75)
  - Decile 1: Reference

- **p_{trend} < 0.001**

**NT-proBNP**

- **Adj-HR**
  - Decile 10: 40.9 (22.3, 75.1)
  - Decile 9: 16.2 (8.76, 29.8)
  - Decile 8: 9.23 (4.94, 17.2)
  - Decile 7: 5.11 (2.68, 9.76)
  - Decile 6: 4.21 (2.18, 8.13)
  - Decile 5: 4.21 (2.18, 8.13)
  - Decile 4: 2.46 (1.22, 4.96)
  - Decile 3: 2.19 (1.07, 4.47)
  - Decile 2: 1.53 (0.72, 3.27)
  - Decile 1: Reference

- **p_{trend} < 0.001**

**GDF-15**

- **Adj-HR**
  - Decile 10: 6.92 (4.33, 11.1)
  - Decile 9: 5.24 (3.28, 8.39)
  - Decile 8: 4.17 (2.60, 6.70)
  - Decile 7: 3.60 (2.24, 5.80)
  - Decile 6: 3.52 (2.18, 5.67)
  - Decile 5: 3.44 (2.13, 5.56)
  - Decile 4: 2.58 (1.57, 4.23)
  - Decile 3: 1.84 (1.09, 3.10)
  - Decile 2: 1.25 (0.71, 2.20)
  - Decile 1: Reference

- **p_{trend} < 0.001**

*Adjusted for age, h/o HF, DM, polyvascular disease, eGFR <60, BMI, HTN
Peripheral Arterial Disease (n=2,350)

Coronary Heart Disease (n=25,974)

Cerebrovascular Disease (n=6,615)

Peripheral Arterial Disease (n=2,350)
Results

• When added to a multivariable Cox regression model of clinical risk indicators,* these 3 biomarkers significantly improved the prognostic performance of the model:

\[ \text{C-index 0.74} \Rightarrow \text{C-index 0.85 (p<0.001)} \]

• The gradients of HHF risk were consistent in patients randomized to anacetrapib vs. placebo (no interaction)

*Clinical risk indicators: age, prior HF, hypertension, diabetes mellitus, eGFR <60, body-mass index, and polyvascular disease
Conclusions

• In patients with stable ASCVD, biomarkers of myocardial injury, hemodynamic stress, and oxidative stress provide incremental information for the prediction of HHF
  - Continuous graded relationship
  - Independent and additive to major clinical risk factors
  - Consistent across ASCVD subtypes

• Future studies should address whether these patients are more likely to benefit from emerging HF preventive therapies