High-sensitivity Cardiac Troponin at Any Detectable Concentration Identifies Higher Risk of Major Cardiovascular Events in Patients with Stable Ischemic Heart Disease

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An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School
Disclosures

▪ Presenter Disclosure: None

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▪ Biomarker testing received reagent support from Abbott Laboratories
Stable patients with a history of MI (SIHD) have a heterogeneous risk of recurrent major CV events

- hsTn is an emerging tool to better risk-stratify these patients

**PROVE IT-TIMI 22**

- Subset of 4,162 patients
- 30 days out from ACS

**TRA 2P - TIMI 50**

- 15,833 patients
- Prior MI, stroke, or PAD


Objective: To further explore this relationship in the stable ischemic heart disease population
Methods

- Nested prospective cohort study (n= 8,635) from PEGASUS-TIMI 54
  - Randomized, double-blinded, placebo controlled trial of ticagrelor vs. placebo
  - ≥55 years old
  - SIHD with a MI 1-3 years prior to enrollment
  - ≥1 high-risk feature: ≥65 yo, DM, ≥2 MIs, multivessel CAD, CKD
  - Median F/U 33 months

- Primary endpoint (PEP): CV death, MI, or stroke
  - All elements of PEP centrally adjudicated
Serum hsTnI (Abbott ARCHITECT) drawn at enrollment
- Limit-of-detection 2 ng/L
- MI cut-point 26 ng/L (99th percentile)

hsTnI was analyzed as categorical variable using *a priori* categories within the normal reference range, defined as:
- Undetectable (<2 ng/L)
- Low (2-6 ng/L)
- High (>6 ng/L)

**Population studies with risk thresholds between 5-7 ng/L**
- CAPS (Patterson, et al. *IJC*. 2015)
- BiomarCare (Blankenberg, et al. *EHJ*. 2016)
**hsTn Distribution**

- **Median hsTnI (ng/L)**
  - Overall: 4.2 [2.7, 7.2]
  - Female: 3.6 [2.3, 6.5]
  - Male: 4.3 [2.8, 7.3]

- **Total N**: 8,635
- **Undetectable**: 920 (10.7%)
- **Detectable**: 7,715 (89.3%)
- **<2 ng/L**: 920 (10.7%)
- **2-6 ng/L**: 5,028 (58.2%)
- **>6 ng/L**: 2,687 (31.1%)
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics by hsTnI Level</th>
<th>&lt;2 (N=920) %</th>
<th>2-6 (N=5028) %</th>
<th>&gt;6 (N=2687) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs) (median, IQR)</td>
<td>61 (55,66)</td>
<td>65 (58,70)</td>
<td>67 (60,73)</td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>77</td>
<td>79</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>70</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>29</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>History of CABG</td>
<td>1</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>History of 2&lt;sup&gt;nd&lt;/sup&gt; prior MI</td>
<td>9</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>7</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>12</td>
<td>20</td>
<td>33</td>
</tr>
</tbody>
</table>

*All p-values <0.001*
Results: Unadjusted Analysis

CV Death, MI, Stroke by hsTnI Level (ng/L)

hsTnI Level
- >6 (n=2,687)
- 2-6 (n=5,028)
- <2 (n=920)

CV Death, MI, Stroke (%) vs. Days

- 13.5%*
- 6.0%^p=0.0002 vs. undetectable
- 2.8%

* p<0.0001 vs. undetectable
^p=0.0002 vs. undetectable
Results: Unadjusted Analysis

CV Death, MI, Stroke by hsTnI Level (ng/L)

<table>
<thead>
<tr>
<th>hsTnI Level</th>
<th>CV Death, MI, Stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥26 (n=433, 5.0%)</td>
<td>18.6% #</td>
</tr>
<tr>
<td>&gt;6-&lt;26 (n=2,254)</td>
<td>12.5% *</td>
</tr>
<tr>
<td>2-6 (n=5,028)</td>
<td>6.0% ^</td>
</tr>
<tr>
<td>&lt;2 (n=920)</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

# p<0.0001 vs. undetectable
* p<0.0001 vs. undetectable
^ p=0.0002 vs. undetectable
Components of PEP

Cardiovascular and Coronary Death, MI and Stroke by hsTnI Level (ng/L)  

- <2  
- 2-6  
- >6

<table>
<thead>
<tr>
<th>Component</th>
<th>hsTnI Level</th>
<th>3 Year KM Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Death</td>
<td>&lt;2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-6</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>4.1</td>
</tr>
<tr>
<td>Coronary Heart Death</td>
<td>&lt;2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-6</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>2.3</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>&lt;2</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>2-6</td>
<td>4.3</td>
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<tr>
<td></td>
<td>&gt;6</td>
<td>8.7</td>
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<tr>
<td>Stroke</td>
<td>&lt;2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>2-6</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Significance Levels:  
- *P<0.0001*  
- ^P-Trend

Notes:  
- >6 vs 2-6  

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PEP, Mortality, MI, and Stroke

Adjusted Hazard Ratios by hsTnI Level

Adjusted for congestive heart failure, hypertension, age >=75, diabetes mellitus, history of stroke, history of CABG, PAD, eGFR <60, current smoker
hsTnI and TRS 2ºP Score

Incidence of Primary Endpoint at 3 Years by TRS 2ºP score and hsTnI

KM Rate (%)

High* 9.1 (n=1094)
Int* 6.1 (n=769)
Low* 4.1 (n=806)

hsTnI (ng/L)

High* 2.3 (n=1218)
Int* 2.4 (n=1660)
Low* 2.9 (n=2107)

nP-Trend <0.0001

*P-Trend <0.0001
Ticagrelor by hsTnI

Trial Population

0.84

P=0.001

Ticagrelor Better

Hazard Ratio

Placebo Better
Conclusion

hsTn is a strong independent predictor of recurrent major CV events in SIHD

- Gradient of risk is present at any detectable level
  - As low as 2-6 ng/L

- hsTnI >6 ng/L present in nearly 1/3 of patients
  - >10% 3-year risk of MACE
  - Extrapolated 10-year risk of MACE = 45%

- In combination with TRS 2ºP, hsTnI provides complementary information
THANK YOU
99th Percentile by Sex

Women

Men

Sex-specific 99th %ile URL:
34 ng/L in men and 16 ng/L in women
Adjusted Hazard Ratios by hsTnI Level

Adjusted for congestive heart failure, hypertension, age >=75, diabetes mellitus, history of stroke, history of CABG, PAD, eGFR <60, current smoker