Biomarkers, Cardiovascular Outcomes & Effect of Ezetimibe after ACS in the IMPROVE-IT Trial

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On behalf of the IMPROVE IT Investigators

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Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125 mg/dL (or 50–100 mg/dL if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (Median f/u 6 yrs)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke
Addition of ezetimibe to statin therapy reduces the risk of recurrent CV events in patients with prior ACS

- HR 0.90 CI (0.84, 0.97)
- p=0.003

Background

Biomarkers improve risk stratification of patients with CAD

hsTnT

NT-pro-BNP

Omland T, et al. NEJM, 2009

Kragelund C, et al. NEJM, 2005
Objectives

To assess the application of available cardiac biomarkers for:

1. Long-term risk stratification
2. Therapeutic decision-making with ezetimibe
Methods

• Prespecified biomarker analysis (hsTnT, NT-proBNP, GDF-15 & hsCRP [Roche Diagnostics]) in stable phase after ACS (1 month after randomization; N=7,327 pts)

• Pts with recurrent CV events prior to biomarker analyses were excluded

• Outcomes of interest: CVD/MI/Stroke; CVD/HF at 7 yrs
High % of established CAD pts have elevated biomarkers

- hsTnT
  - <14 ng/L: 36.2%
  - ≥14 ng/L: 63.8%

- NT-proBNP
  - <450 pg/mL: 33.5%
  - ≥450 pg/mL: 66.5%

- GDF-15
  - <1800 pg/mL: 25.9%
  - >1800 pg/mL: 74.1%

- hsCRP
  - <2 mg/L: 45.6%
  - ≥2 mg/L: 54.4%

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Results

Significant correlation between biomarkers representing different pathobiological axes

<table>
<thead>
<tr>
<th></th>
<th>NT-proBNP</th>
<th>hsTnT</th>
<th>GDF-15</th>
<th>hsCRP</th>
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</thead>
<tbody>
<tr>
<td>NT-proBNP</td>
<td>-</td>
<td>0.65*</td>
<td>0.60*</td>
<td>0.24</td>
</tr>
<tr>
<td>hsTnT</td>
<td>-</td>
<td></td>
<td>0.91*</td>
<td>0.48*</td>
</tr>
<tr>
<td>GDF-15</td>
<td></td>
<td>-</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>hsCRP</td>
<td></td>
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*= p<0.05

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Biomarkers & Risk of MACE

Graded ↑ in risk of MACE across levels of each biomarker

KM Rate (%) of CVD/MI/Stroke at 7 yr

Q1 Q2 Q3 Q4 P-trend <0.001*

- hsTnT
- NT-proBNP
- GDF-15
- hsCRP

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Biomarkers & Risk of CV Death/HF

Graded ↑ in risk of CV Death/HF across biomarker levels

KM Rate (%) of CV Death/HF at 7 yr

Graded in risk of CV Death/HF across biomarker levels

P-trend <0.001*

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Biomarkers and Adjusted Risk of CV Events

Biomarkers were independently associated with ↑ risk of CV death, MI, stroke

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<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Adjusted HR* (95% CI) for MACE (Q4 vs. Q1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsTnT</td>
<td>2.64 (2.17-3.20)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2.27 (1.88-2.73)</td>
</tr>
<tr>
<td>GDF-15</td>
<td>1.66 (1.36-2.03)</td>
</tr>
<tr>
<td>hsCRP</td>
<td>1.41 (1.25-1.58)</td>
</tr>
</tbody>
</table>
Multimarker Strategy for Risk Stratification

Incremental increase in the risk of CV events across biomarker risk categories

Multimarker Score
Assign pts 1 point for the presence of each elevated biomarker

- hsTnT>14 ng/L
- NT-proBNP>450 pg/mL
- GDF-15>1800 pg/mL
- hsCRP>2 mg/L


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Biomarker-Predicted Risk & Absolute Benefit of Ezetimibe

High absolute benefit from the addition of ezetimibe to statin therapy in high risk pts

- High Risk (Score 3-4) 7.3% ARR NNT 14
- Intermediate Risk (Score 1-2) 2.5% ARR NNT 40
- Low Risk (Score 0) HR 1.1

High Risk (Score 3-4)
Intermediate Risk (Score 1-2)
Low Risk (Score 0)
Conclusions

• A substantial % of pts with established CAD in the stable phase have evidence of ongoing (chronic) myocardial injury, hemodynamic stress, or systemic inflammation

• A biomarker based strategy identifies a gradient of risk among those with established CAD offering the potential to further personalize therapy

• A multimarker approach identified high risk pts with a correspondingly high absolute benefit from the addition of ezetimibe to statin therapy