DIABETES, PRE-DIABETES AND INCIDENCE OF SUBCLINICAL MYOCARDIAL DAMAGE

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Disclosures

• The high sensitivity assay for cardiac troponin T discussed in this presentation is for investigational use only and is not cleared for clinical use in the USA.

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• Reagents for the high sensitivity troponin assays were donated by the Roche Diagnostics Corporation.
Diabetes, pre-diabetes and myocardial damage

• Persons with pre-diabetes and diabetes are at high risk for cardiovascular events

• Elevated glucose is thought to contribute to microvascular dysfunction and may lead to myocardial damage

• Little is known about the relationships of pre-diabetes and diabetes with the development of subclinical myocardial damage
Cardiac troponin measured with novel highly sensitive assay (hs-cTnT)

- Cardiac troponins are elevated in acute myocardial infarction (MI) and are a standard measure used for diagnosis of MI
- There have been several generations of increasingly sensitive tests for cardiac troponin
  - Novel (pre-commercial) assays measure troponin far below detection limits of current assays in clinical practice
- Elevations of troponin detected with new highly sensitive assays (hs-cTnT) strongly predict future cardiovascular events
  - In ARIC participants with no history of cardiovascular disease (HRs for hs-cTnT ≥14 ng/L vs undetectable)*:
    - Heart failure incidence: HR=6.0 (95%CI 4.5, 7.9)
    - Death from any cause: HR=4.0 (95%CI 3.2, 4.9)
    - Coronary heart disease incidence: HR=2.3 (95%CI 1.8, 2.9)

*Source: Saunders et al, Circulation 2011
**Hs-cTnT as a biomarker of chronic myocardial damage**

- Elevations in hs-cTnT in asymptomatic persons are thought to reflect *chronic* subclinical myocardial damage.

- There is some suggestion that hs-cTnT may reflect cardiac disease of a *non-atherosclerotic* origin (vs early atherosclerosis):
  - Hs-cTnT is strongly associated with typical microvascular disease risk factors such as diabetes and hypertension and is not highly related to LDL-cholesterol.
  - Hs-cTnT is more strongly associated with heart failure and total mortality as compared to coronary heart disease.
Study Objective

- To characterize the associations of diabetes and prediabetes with incidence of subclinical myocardial damage, as assessed by hs-cTnT, in a community-based population without clinically evident cardiovascular disease.
Study Population: The Atherosclerosis Risk in Communities (ARIC) Study

• On-going community-based prospective cohort of over 15,000 middle-aged adults from four U.S. communities
• Prospective cohort analysis
• Participants with two measurements of hs-cTnT 6 years apart and no clinical cardiovascular disease (including silent MI) at visits 2 and 4

Visit 2
1990-92

Visit 4
1996-98

N=8,692

- Hs-cTnT
- Diabetes status
  - Fasting glucose, HbA1c
- Covariates

ARIC
Exposures

- **Diagnosed diabetes**
  - Self-reported history of physician diagnosis
  - Current diabetes medication use

- **Undiagnosed diabetes**
  - No history of diabetes
    - HbA1c ≥6.5%
    - Fasting glucose ≥126 mg/dL

- **Pre-diabetes**
  - No history of diabetes
    - HbA1c 5.7-6.4%
    - Fasting glucose 100-125 mg/dL
Outcome: Incident Elevated hs-cTnT

• Cardiac troponin T
  – highly sensitive (pre-commercial) assay (Roche Elecsys T; Roche Diagnostics)

• “Incident elevated” hs-cTnT
  – ≥14 ng/L at visit 4 (1996-1998, 6 years after baseline) among persons with hs-cTnT <14 ng/L at baseline (1990-1992)
  – 14 ng/L used by convention to define “elevation”

• Poisson regression to estimate relative risk (cumulative incidence ratios) of elevated hs-cTnT at the follow-up visit after adjustment for covariates
  – Age, race, sex, BMI, CRP, smoking, mean systolic blood pressure (BP), current BP med use, alcohol use, LVH
## Baseline Characteristics by Incident 6-year Elevation in hs-cTnT, N=8,692

<table>
<thead>
<tr>
<th></th>
<th>Hs-cTnT &lt;14 ng/L at baseline, N=8,692</th>
<th>Incident elevation, N=496†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No elevation at follow-up, N=8196</td>
<td></td>
</tr>
<tr>
<td>Age (yrs), mean</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td>Male</td>
<td>38%</td>
<td>74%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29%</td>
<td>51%</td>
</tr>
<tr>
<td>Obesity</td>
<td>27%</td>
<td>37%</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>High LDL-cholesterol</td>
<td>21%</td>
<td>19%*</td>
</tr>
</tbody>
</table>

Bolded values: p<0.001
*Not statistically significant

† hs-cTnT median [p25, p75]: 17 [14, 22] ng/L
Cumulative incidence of elevated (≥14 ng/L) hs-cTnT according to diabetes status

- HbA1c < 5.7% (No Diabetes): 4.1%
- HbA1c 5.7 - 6.4% (Pre-diabetes): 7.6%
- HbA1c ≥ 6.5% (Undiagnosed Diabetes): 10.2%
- Diagnosed Diabetes: 16.9%
## Adjusted* risk ratios for elevated hs-cTnT at 6 years of follow-up

<table>
<thead>
<tr>
<th>Baseline Diabetes Categories</th>
<th>Incident elevated hs-cTnT (≥14 ng/L)</th>
<th>N Events/Total</th>
<th>Adjusted* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c Criteria</strong></td>
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<tr>
<td>&lt;5.7% (no diabetes)</td>
<td>245 / 5,989</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>5.7-6.4% (pre-diabetes)</td>
<td>151 / 1,997</td>
<td>1.40 (1.13, 1.73)</td>
<td></td>
</tr>
<tr>
<td>≥6.5% (undiagnosed diabetes)</td>
<td>29 / 285</td>
<td>1.85 (1.24, 2.75)</td>
<td></td>
</tr>
<tr>
<td>Diagnosed diabetes</td>
<td>71 / 421</td>
<td>2.83 (2.14, 3.75)</td>
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</tr>
<tr>
<td><strong>Fasting Glucose Criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 mg/dL (no diabetes)</td>
<td>124 / 3,540</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>100-125 mg/dL (pre-diabetes)</td>
<td>255 / 4,245</td>
<td>1.09 (0.87, 1.36)</td>
<td></td>
</tr>
<tr>
<td>≥126 mg/dL (undiagnosed)</td>
<td>46 / 486</td>
<td>1.46 (1.03, 2.07)</td>
<td></td>
</tr>
<tr>
<td>Diagnosed diabetes</td>
<td>71 / 421</td>
<td>2.61 (1.92, 3.55)</td>
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</tr>
</tbody>
</table>

*Adjusted for age, race, sex, BMI, CRP, smoking, mean systolic blood pressure (BP), BP meds, LDL-c, alcohol, LVH
Conclusions

- Diabetes and pre-diabetes were significantly associated with 6-year incidence of subclinical myocardial damage, as assessed by elevated hs-cTnT.

- Supports the contention that hyperglycemia may contribute to subclinical myocardial damage.

- Cardiac damage in diabetes may be occurring through non-atherosclerotic mechanisms; possibly mediated via microvascular ischemia and microvascular damage.
Implications

• Hyperglycemia-induced injury to the myocardium may be an important contributor to epidemic of heart failure and cardiovascular disease in diabetes

• Primary and secondary prevention of atherosclerotic disease (e.g. statins) may be insufficient to address the cardiovascular risk associated with diabetes and pre-diabetes

• Underscores the importance of preventing progression to early hyperglycemic states and the development of diabetes
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