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Detectable Subclinical Myocardial Necrosis Is Associated With Cardiovascular Risk in Stable Patients With Diabetes

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OBJECTIVE—To investigate the relationship between different degrees of subclinical myocardial necrosis, glycemic control, and long term adverse clinical outcomes within a stable patient population with diabetes mellitus.

RESEARCH DESIGN AND METHODS—We examined 1,275 stable patients with diabetes mellitus undergoing elective diagnostic coronary angiography with cardiac troponin I (cTnI) levels below the diagnostic cut off for defining myocardial infarction (MI) (<0.03 ng/mL). The relationship of subclinical myocardial necrosis (cTnI 0.009–0.029 ng/mL) with incident major adverse cardiovascular events (MACE; defined as any death, MI, or stroke) over 3 years of follow up was examined.

RESULTS—Subclinical myocardial necrosis was observed in 22% of patients. A strong association was observed between the magnitude of subclinical myocardial necrosis and risk of 3 year incident MACE (hazard ratio, 1.98; 95% confidence interval, 1.48–2.65; \( P < 0.001 \)) and remained statistically significant even after adjustment for traditional risk factors, high sensitivity C reactive protein, and creatinine clearance. Only a weak correlation was observed between the presence of subclinical myocardial necrosis and either glycemic control (\( r = 0.06, P = 0.044 \) for hemoglobin A1c versus cTnI) or insulin resistance (\( r = 0.04, P = 0.044 \) for glucose to insulin ratio versus cTnI).

CONCLUSIONS—The presence of detectable subclinical myocardial necrosis in stable patients with diabetes mellitus is associated with heightened long term risk for MACE, independent of traditional risk factors and glycemic control.

Detection of systemic levels of cardiac troponin is associated with the presence of ongoing myocardial necrosis and fulfills the contemporary definition of myocardial infarction (MI) in the presence of ischemic symptoms (1). However, a minimal increase in cardiac troponin levels below the diagnostic range often presents clinical challenges, particularly in stable ambulatory patients without overt signs and symptoms suggestive of underlying ischemia and normal renal function (2). As biochemical assays become more and more sensitive, the ability to detect minimal myocardial damage may allow risk assessment in stable cardiac patients beyond the acute setting (3). We recently have demonstrated that such presence of subclinical myocardial necrosis was associated with adverse long term cardiovascular risks in stable patients undergoing elective coronary angiography (4). These findings were reported in diabetic and nondiabetic patients with and without coronary artery disease and heart failure. We sought to examine the prognostic significance of detectable subclinical myocardial necrosis in the setting of diabetes mellitus, particularly to examine its relationship with underlying glycemic control.

RESEARCH DESIGN AND METHODS The Cleveland Clinic GeneBank study is a large, prospective, cohort study that established a well characterized clinical repository with clinical data and longitudinal outcomes from consenting subjects undergoing elective diagnostic coronary angiography from 2001 to 2006. All GeneBank participants gave written informed consent approved by the Cleveland Clinic Institutional Review Board. All blood samples were collected at the time of cardiac catheterization procedure. This analysis included a cohort of 1,275 consecutive consenting subjects with a clinical diagnosis of diabetes mellitus without clinical evidence of acute coronary syndrome at the time of enrollment with 3 year follow up data. These patients underwent elective diagnostic coronary angiography within 1 year of attending outpatient appointments, scheduled coronary computed tomography angiogram scans, or computed tomography scans within 1 year of scheduled blood draws. The various reasons for the elective coronary angiography include (subjects could have more than one reason per person) the following: history of positive or indeterminate stress test (50%); evaluation for possible ischemic causes of symptoms (68%); preoperative evaluation (10%); and history of cardiomyopathy (3%). Subjects included were only those with cardiac troponin I (cTnI) <0.03 ng/mL, no history of revascularization within 30 days before enrollment, and at least 3 years of adjudicated follow up data. The diagnosis of diabetes mellitus was determined based on the latest guideline recommendations as clinical history of diabetes mellitus or fasting glucose ≥126 mg/dL or hemoglobin A1c (HbA1c) ≥6.5% at the time of enrollment (5).
Plasma levels of cTnI were measured using the 
STAT Troponin I assay (Abbott laboratories, 
Abbott Park, IL) in a research based immunoanalyzer 
that provides a three decimal point readout from 
venous blood samples collected by EDTA tubes. 
This assay provides highly sensitive analytical 
measurements of cTnI with a reported limit of detection 
reaching 0.009 ng/ml in the literature (4) and a 
diagnostic cut off of 0.03 ng/ml for MI defined by 
the upper limit of normal (99th percentile cut off 
with 10% coefficient of variation). Based 
the cTnI assay, we defined subclinical myocard 
ial necrosis as cTnI 0.009 0.029 ng/ml 
(above level of detection). High sensitivity 
C reactive protein (hsCRP), HbA1c, glu 
cose, insulin, creatinine, and fasting lipid 
profiles all were measured simultaneously 
with the cTnI assay using the same analysis 
platform. Treating physicians and adjudi 
cation committee were blinded to the re 
sults of cTnI.

We defined coronary angiography as 
any clinical history of MI, percutaneous 
coronary intervention, coronary artery 
h bypass graft, or angiographic evidence of 
significant stenosis (50%) in one or more 
major coronary arteries. Dyslipidemia was 
defined as LDL cholesterol > 130 mg/dL, 
HDL cholesterol <50 mg/dL, triglycerides 
> 150 mg/dL, or the use of lipid lowering 
agents. An estimate of creatinine clearance 
(eCRO) was calculated using the Cockcroft 
Gault equation, because a large majority of 
subjects had relatively preserved renal 
function. Adjudicated outcomes were 
prospectively ascertained over the ensuing 
3 years for all subjects after enrollment. 
Major or adverse cardiovascular event 
(MACE) was defined as death, nonfatal MI, 
or nonfatal stroke after enrollment. Nonf 
fatal MI was defined as patients that re 
mained alive over the follow up period of 
3 years and met the universal definition 
of MI, which is defined as a documented 
increase in cardiac biomarker in conjunc 
tion with evidence of myocardial ische 
mia (1). Nonfatal stroke in this cohort 
was defined as patients with a clinical 
diagnosis of rapid loss of brain function 
 attributable to blood flow disturbance to 
the brain with accompanying imaging 
techniques or records of confirmed diag 
osis who remained alive over the follow 
up period of 3 years. All cause death was 
ascertained by follow up (1 and 3 year) 
telephone interviews, Social Security 
Death Index that was assessed periodi 
cally after enrollment, official hospital 
record, or death certificate.

The Student ttest or Wilcoxon rank 
test for continuous variables and x2 
test for categorical variables were used to 
examine the difference between the 
groups. Unadjusted trends (adjusted for 
age and sex only) for all cause mortality 
rates as well as nonfatal MI/stroke rates 
with increasing tertiles of cTnI were eval 
uated with the Cochran Armitage test 
using a time to event approach. Adjust 
ments were made for individual tradi 
tional cardiac risk factor, Framingham 
风险 factors (including age, sex, cigarette 
smoking, LDL cholesterol, HDL choles 
terol, and systolic blood pressure) plus 
log transformed hsCRP, and CrCl to pre 
dict 3 year MACE risks. Kaplan 
Meier analysis with Cox proportional 
hazards regression was used for time 
to event analysis to determine hazard ra 	io (HR) and 95% confidence intervals 
(95% CIs) for MACE. Levels of cTnI 
then were adjusted for traditional 
coronary angiography risk factors in 
a multivariable model including Framing 
ham risk factors, log transformed hsCRP, 
and CrCl. We confirmed that both the 
proportionality hazards and linearity as 
sumptions were met. All analyses were 
performed using R 2.10.1 (Vienna, Aus 
tria). P < 0.05 was considered statistically 
significant. The authors had full access 
to all of the de identified data in the study 
and take responsibility for the integrity 
of the data and the accuracy of the data 
analysis.

RESULTS In our study cohort of 
1,275 subjects, 22% of subjects had 
evidence of subclinical myocardial necro 
sis (with 34% detectable but in the range 
of 0.001 0.008 ng/ml). The event num 
bers for MACE in our cohort over the 
3 year follow up were as follows: all 
cause death, 129/1,275; nonfatal MI, 62/ 
1,275; and nonfatal stroke, 31/1,275.

<table>
<thead>
<tr>
<th>Table 1-Baseline characteristics</th>
<th>Subclinical myocardial necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 989)</td>
</tr>
<tr>
<td>cTnI range (ng/ml)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Demographics and clinical data</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Male (%)</td>
<td>59</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>136 ± 21</td>
</tr>
<tr>
<td>History of H type nerosis (%)</td>
<td>77</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>16</td>
</tr>
<tr>
<td>Cigarette smoking (former/current %)</td>
<td>63</td>
</tr>
<tr>
<td>Previous myocardial infarction(%)</td>
<td>31</td>
</tr>
<tr>
<td>Previous revascularization (%)</td>
<td>31</td>
</tr>
<tr>
<td>Maximal stenosis 50% (%)</td>
<td>77</td>
</tr>
<tr>
<td>Number of coronary vessel disease</td>
<td></td>
</tr>
<tr>
<td>None(%)</td>
<td>23</td>
</tr>
<tr>
<td>One(%)</td>
<td>19</td>
</tr>
<tr>
<td>Two(%)</td>
<td>20</td>
</tr>
<tr>
<td>Three(%)</td>
<td>38</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.7 (6.1 7.7)</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
</tr>
<tr>
<td>Fasting LDL cholesterol (mg/dL)</td>
<td>94 (76 114)</td>
</tr>
<tr>
<td>Fasting HDL cholesterol (mg/dL)</td>
<td>32.9 (27.5 40.1)</td>
</tr>
<tr>
<td>Fasting triglycerides (mg/dL)</td>
<td>128 (90 187)</td>
</tr>
<tr>
<td>hsCRP (mg/ml)</td>
<td>2.4 (1.1 5.9)</td>
</tr>
<tr>
<td>CrCl (ml/min/1.73m²)</td>
<td>104 (78 132)</td>
</tr>
<tr>
<td>Baseline medications</td>
<td></td>
</tr>
<tr>
<td>Aspirin(%)</td>
<td>75</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>64</td>
</tr>
<tr>
<td>ACE inhibitors (%)</td>
<td>57</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>64</td>
</tr>
<tr>
<td>Insulin(%)</td>
<td>19</td>
</tr>
<tr>
<td>Oral glucose lowering drugs(%)</td>
<td>42</td>
</tr>
</tbody>
</table>

Values expressed in mean ± SD or median (interquartile range).
Baseline characteristics of the study population are shown in Table 1 and are stratified according to presence or absence of subclinical myocardial necrosis. Patients with evidence of subclinical myocardial necrosis were more likely to be older, with more cardiovascular risk factors and history of heart failure, and with slightly lower renal function at baseline. Subjects with evidence of subclinical myocardial necrosis were associated with an increased 3 year risk of death (HR, 2.39; 95% CI, 1.68 3.40; $P = 0.001$), nonfatal MI or stroke (HR, 1.70; 1.09 2.66; $P = 0.019$), and MACE (HR, 1.98; 1.48 2.65; $P < 0.001$) (Fig. 1). The risk prediction appeared to be log linear as detectable cTnI levels increased (Fig. 2).

After adjusting for traditional risk factors, including Framingham risk factors, hsCRP, and eCrCl, evidence of subclinical myocardial necrosis within stable diabetic patients remained a significant risk of incident MACE over the ensuing 3 years (HR, 1.48; 1.08 2.01; $P = 0.013$; Table 2).

A weak correlation was observed between the presence of subclinical myocardial necrosis and either glycemic control ($r = 0.06$ and $P = 0.044$ for HbA1c versus cTnI) or insulin resistance ($r = 0.04$ and $P = 0.094$ for glucose to insulin ratio versus cTnI). Adjustments with either metabolic parameters had little impact on the prognostic value of detectable subclinical myocardial necrosis within the study cohort. Figure 3 illustrates similar risk prediction for major adverse clinical events at 3 years according to subclinical myocardial necrosis status stratified by on treatment HbA1c using a cut off of 6.5%. The cTnI levels demonstrated no significant interaction with ation use or HbA1c, levels ($P$ for interaction $\geq 0.20$).

**CONCLUSIONS** The major finding of our study is the demonstration that the presence of subclinical myocardial necrosis in a respectable proportion of stable patients with diabetes mellitus has heightened long term adverse cardiovascular event risk. We further demonstrated that such risk may be independent of underlying glycemic control. These findings would appear to imply that any detectable cTnI level should warrant consideration for more globally aggressive risk reduction efforts, including closer evaluation and long term monitoring, and such intervention efforts may focus beyond glycemic control measures. The concept of diabetes mellitus being a “coronary artery disease risk equivalent” has been suggested in several important studies (6 8) and even for those subjects with suspected acute coronary syndrome but with “normal” cardiac troponin levels (9). Guideline recommendations for routine aspirin prescription and secondary prevention therefore have been proposed (10 12). However, recent analyses have directly challenged such assertions (13,14). It is therefore conceivable that differences in risk profiles of patients with diabetes mellitus may warrant different indications of preventive interventions (5). Using the latest guideline recommendations for the definition and classification of diabetes mellitus including HbA1c assessments (15), the current study provides
Table 2—Unadjusted and adjusted HR for major adverse cardiac events at 3 year follow up

<table>
<thead>
<tr>
<th>Subclinical myocardial necrosis (n)</th>
<th>No (cTnI &lt;0.01 ng/mL) (n = 989)</th>
<th>Yes (cTnI 0.01–0.03 ng/mL) (n = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/nonfatal MI/stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1</td>
<td>1.98 (1.48–2.63)†</td>
</tr>
<tr>
<td>Adjusted HR (model 1)</td>
<td>1</td>
<td>1.48 (1.08–2.01)*</td>
</tr>
<tr>
<td>Adjusted HR (model 2)</td>
<td>1</td>
<td>1.56 (1.14–2.14)†</td>
</tr>
<tr>
<td>Adjusted HR (model 3)</td>
<td>1</td>
<td>1.54 (1.13–2.12)†</td>
</tr>
<tr>
<td>Adjusted HR (model 4)</td>
<td>1</td>
<td>1.49 (1.06–2.09)*</td>
</tr>
</tbody>
</table>

Model 1: Traditional risk factors (including age, sex, LDL, HDL cholesterol, systolic blood pressure, smoking, diabetes, CrCl, hsCRP); Model 2: Traditional risk factors + HbA1c; Model 3: Traditional risk factors + HbA1c + insulin-to-glucose ratio; Model 4: Traditional risk factors + HbA1c + insulin-to-glucose ratio + ACE inhibitor/angiotensin receptor blocker + history of MI/coronary angiography/vascularization/heart failure/number of vessels with >50% stenosis. Values presented as HR and 95% CI. *P < 0.05; †P < 0.01.

Although we cannot definitely refute this potential explanation, our findings still indicate that the prognostic value of detectable subclinical myocardial necrosis remained robust after statistical adjustment for eCrCl. We also note that analysis of only the subset of diabetic subjects with normal eCrCl at time of study entry still showed subclinical myocardial necrosis to be an excellent independent predictor of incident MACE risk over the ensuing 3 year period (adjusted HR, 1.47; 95% CI, 1.01–2.14). Second, the presence of microvascular diseases commonly present in patients with diabetes mellitus may contribute to progressive microvascular ischemia or microembolization that can be readily detectable by highly sensitive cTnI assay. Such a phenomenon has been observed in the setting of acute coronary syndrome setting and has been demonstrated in animal models (17). Because silent ischemia commonly occurs in patients with diabetes mellitus, some novel insight into the utility of detecting subclinical myocardial necrosis as a potential way to help identify those subjects with high versus low risks for the development of future major adverse cardiac events. The implications of these findings and whether the detection of subclinical myocardial necrosis truly represents ongoing myocardial damage that can be averted by more globally aggressive preventive efforts reducing future MACE risk comprise a hypothesis that needs further testing by a biomarker guided therapeutic approach.

There are several potential explanations for our findings. First, there was noticeable reduction in renal function (estimated by CrCl) associated with the cohort with definite subclinical myocardial necrosis, which may suggest that the presence of underlying subclinical nephropathy may have some influence on the reduced renal clearance of cTnI (16).

![Figure 3](image-url)

**Figure 3**—Forest plot of risk prediction for major adverse clinical events at 3 years according to subclinical myocardial necrosis status stratified by HbA1c at cut off of 6.5%.
The strength of the current study is the ability to determine the future cardiac risk in a broad clinical population of patients with contemporary definition and management of diabetes mellitus in which cardiac troponin measurements are not routinely performed or clinically indicated at this time. However, the fact that all subjects were referred for coronary angiography, albeit electively, and that many had relatively preserved renal function, also may represent some degree of selection bias and may not be fully representative of the broad population of patients with diabetes mellitus in clinical practices. Nevertheless, the fact that we only included those with no revascularization performed within 30 days after enrollment ensured a population deemed “medically managed” for their cardiac conditions. It also should be noted that our study was limited to a single measurement and further work with serial measurements is needed to substantiate the variability of the marker for risk stratification. Moreover, serial measures will be useful because it is unclear what impact various interventions have on cTnI levels in the subclinical range in these subjects (24). It also is worth noting that limitations of our assays cannot precisely define subclinical myocardial necrosis in the lower range of 0.001 0.008 ng/mL, although the diagnostic accuracies of those with current definition of subclinical myocardial necrosis are certain. Most importantly, further studies are needed to determine if the presence of subclinical myocardial necrosis represents an underlying process that can be targeted for interventions. The presence of detectable subclinical myocardial necrosis in stable patients with diabetes mellitus is associated with heightened long term risk for MACE, independent of traditional risk factors and glycemic control.

References
2. Francis GS, Tang WH. Cardiac troponins in renal insufficiency and other non ischemic cardiac conditions. Prog Cardiovasc Dis 2004;47:196 206

