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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 A<sub>1c</sub> versus cTnI) or insulin resistance ( $r = 0.04$ ;  $P = 0.094$  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 provides 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  $\geq 126$  mg/dL or hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>)  $\geq 6.5\%$  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 measurement 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 on the analytical characteristics of the cTnI assay, we defined subclinical myocardial necrosis as cTnI 0.009–0.029 ng/mL (above level of detection). High sensitivity C reactive protein (hsCRP), HbA<sub>1c</sub>, glucose, insulin, creatinine, and fasting lipid profiles all were measured simultaneously with the cTnI assay using the same analysis platform. Treating physicians and adjudication committee were blinded to the results of cTnI.

We defined coronary angiography as any clinical history of MI, percutaneous coronary intervention, coronary artery 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 (eCrCl) 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 adverse cardiovascular event (MACE) was defined as death, nonfatal MI, or nonfatal stroke after enrollment. Nonfatal MI was defined as patients that remained 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 conjunction with evidence of myocardial ischemia (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 diagnosis 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 periodically after enrollment, official hospital record, or death certificate.

The Student *t* test or Wilcoxon rank sum test for continuous variables and  $\chi^2$  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 evaluated with the Cochran Armitage test using a time to event approach. Adjustments were made for individual traditional cardiac risk factor, Framingham risk factors (including age, sex, cigarette smoking, LDL cholesterol, HDL cholesterol, and systolic blood pressure) plus log transformed hsCRP, and CrCl to predict incident 3 year MACE risks. Kaplan Meier analysis with Cox proportional hazards regression was used for time to event analysis to determine hazard ratio (HR) and 95% confidence intervals (95% CIs) for MACE. Levels of cTnI then were adjusted for traditional

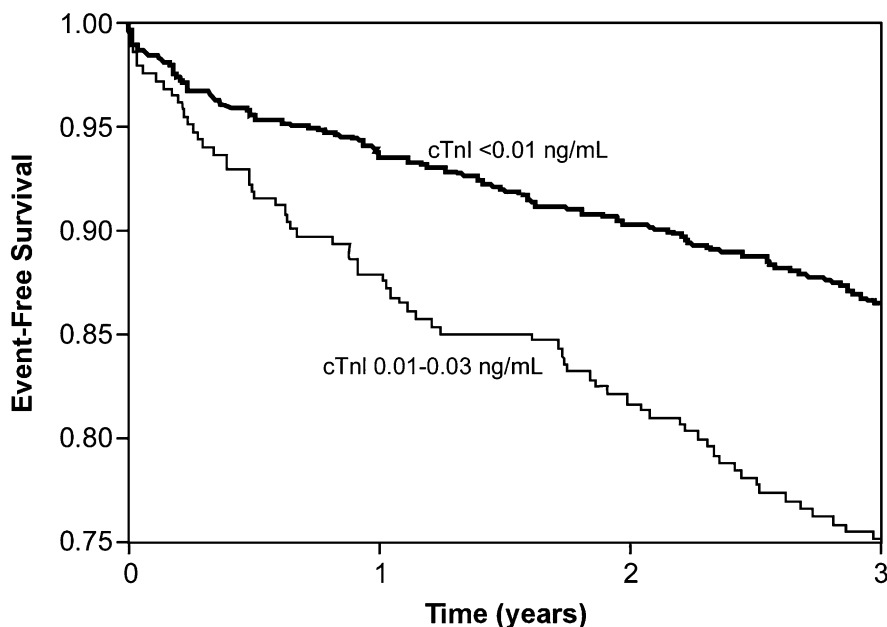
coronary angiography risk factors in a multivariable model including Framingham risk factors, log transformed hsCRP, and CrCl. We confirmed that both the proportionality hazards and linearity assumptions were met. All analyses were performed using R 2.10.1 (Vienna, Austria).  $P < 0.05$  was considered statistically significant. The authors had full access to all of the deidentified 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 necrosis (with 34% detectable but in the range of 0.001–0.008 ng/mL). The event numbers 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 1—Baseline characteristics**

	Subclinical myocardial necrosis		
	No ( <i>n</i> = 989)	Yes ( <i>n</i> = 286)	<i>p</i>
cTnI range (ng/mL)	<0.01	0.01–0.03	
Demographics and clinical data			
Age (years)	64 ± 10	67 ± 10	<0.001
Male (%)	59	70	0.002
Systolic blood pressure	136 ± 21	138 ± 24	0.205
History of hypertension (%)	77	82	0.111
History of heart failure (%)	16	38	<0.001
Cigarette smoking (former/current %)	63	68	0.17
Previous myocardial infarction (%)	31	53	<0.001
Previous revascularization (%)	31	40	0.003
Maximal stenosis 50% (%)	77	87	<0.001
Number of coronary vessel disease			
None (%)	23	14	0.001
One (%)	19	13	0.017
Two (%)	20	21	0.606
Three (%)	38	52	<0.001
HbA <sub>1c</sub> (%)	6.7 (6.1–7.7)	7.0 (6.4–8)	0.006
Laboratory data			
Fasting LDL cholesterol (mg/dL)	94 (76–114)	92 (75–112)	0.387
Fasting HDL cholesterol (mg/dL)	32.9 (27.5–40.1)	31.4 (25.7–38.1)	0.002
Fasting triglycerides (mg/dL)	128 (90–187)	126 (90–172)	0.508
hsCRP (mg/L)	2.4 (1.1–5.9)	3.6 (1.5–7.0)	<0.001
CrCl (mL/min/1.73m <sup>2</sup> )	104 (78–132)	84 (61–112)	<0.001
Baseline medications			
Aspirin (%)	75	72	0.442
Statin (%)	64	62	0.58
ACE inhibitors (%)	57	70	<0.001
Beta blockers (%)	64	67	0.358
Insulin (%)	19	23	0.085
Oral glucose lowering drugs (%)	42	44	0.466

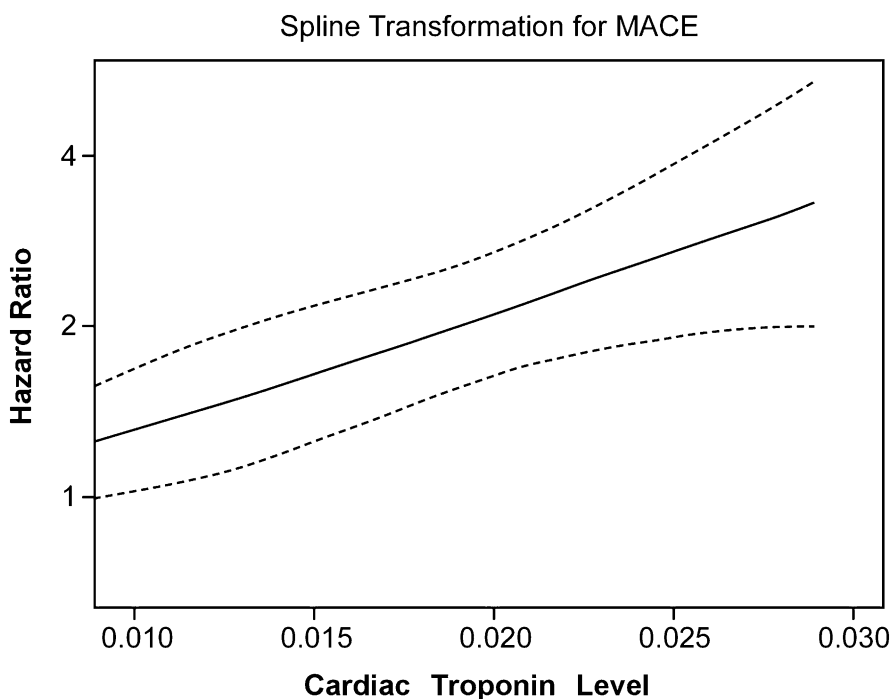
Values expressed in mean ± SD or median (interquartile range).



**Figure 1**—Kaplan Meier analysis for 3 year major adverse clinical events, stratified according to subclinical myocardial necrosis status (rounded to the nearest 0.001 ng/mL).

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).



**Figure 2**—Cubic spline curve of HRs for major adverse clinical events at 3 years with cTnI levels.

After adjusting for traditional risk factors, including Framingham risk factors, hsCRP, and eCrCl, evidence of subclinical myocardial necrosis within stable cardiac 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 HbA<sub>1c</sub> 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 HbA<sub>1c</sub> using a cut off of 6.5%. The cTnI levels demonstrated no significant interaction with statin use or HbA<sub>1c</sub> 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 HbA<sub>1c</sub> assessments (15), the current study provides



**Table 2—Unadjusted and adjusted HR for major adverse cardiac events at 3 year follow up**

Subclinical myocardial necrosis (n)	No (cTnI <0.01 ng/mL) (n = 989)	Yes (cTnI 0.01–0.03 ng/mL) (n = 286)
Death/nonfatal MI/stroke		
Unadjusted HR	1	1.98 (1.48–2.65)†
Adjusted HR (model 1)	1	1.48 (1.08–2.01)*
Adjusted HR (model 2)	1	1.56 (1.14–2.14)†
Adjusted HR (model 3)	1	1.54 (1.13–2.12)†
Adjusted HR (model 4)	1	1.49 (1.06–2.09)*

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

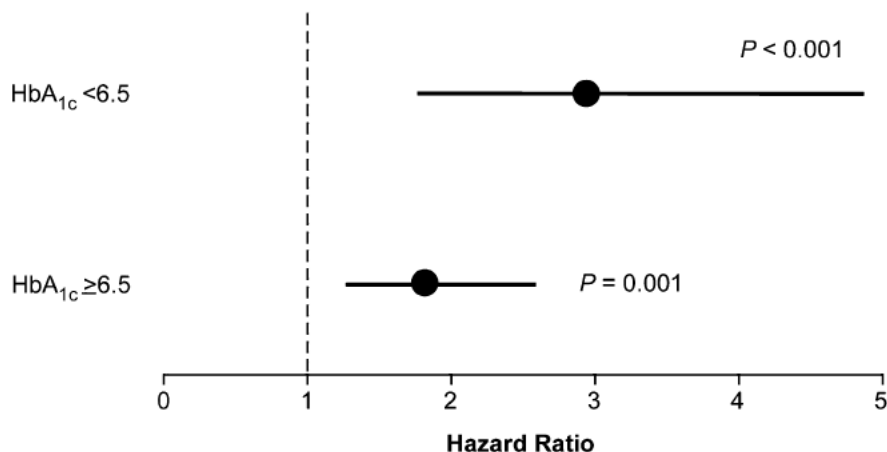
some novel insight into the utility of detecting subclinical myocardial necrosis as a potential way to help identify those subjects with high versus low risks for the development of future major adverse cardiac events. The implications of these findings and whether the detection of subclinical myocardial 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).

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 adjustments 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 myonecrosis 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,

biochemical detection of subclinical myocardial necrosis may occur without overt clinical presentation (18) and may portend further disease progression (19). Finally, there is a potential for increasing oxidative and nitrate stress in parallel with the metabolic derangements, leading to continuing decline in myocardial reserve (4). Regardless of these speculated underlying mechanisms, our findings provided evidence to support the measurement of cTnI levels using contemporary and more sensitive immunoassays in a stable but relatively vulnerable patient population. This appears to represent a novel strategy to detect underlying cardiac vulnerability that is beyond traditional risk factors and metabolic indices that would benefit from further investigations.

This analysis extends our previous findings by providing valuable insights into the incremental prognostic value of cTnI measurements in patients within the cohort of patients with diabetes mellitus, specifically by adjusting for glycemic control as well as established metabolic parameters. The discordance between the prognostic value of subclinical myocardial dysfunction and glycemic control or glucose to insulin ratio is perhaps not unexpected but is worth discussion. The majority of epidemiologic data indicate the utility of adequate glycemic control in reducing microvascular rather than macrovascular disease progression (20). There have been data regarding differential long term cardiovascular outcomes with different glucose lowering drugs that targeted to the same HbA<sub>1c</sub> (21), and there have been observations of tighter glycemic control and paradoxically higher rates of future MACE (22,23). Therefore, it would be intriguing to hypothesize that development of subclinical myocardial necrosis in some patients with diabetes mellitus may, in part, contribute to these discrepant findings. It is conceivable that a tiered approach to ward cardiovascular prevention should be considered with the use of more sensitive contemporary cardiac troponin assays in a vulnerable population in which current practice guidelines have not considered utilizing these cardiac specific biomarkers for risk prediction. By identifying those with subclinical myocardial necrosis, this “risk equivalent” strategy of applying the most aggressive modifiable risk reduction strategies (both pharmacologically and nonpharmacologically) should be considered.



**Figure 3—Forest plot of risk prediction for major adverse clinical events at 3 years according to subclinical myocardial necrosis status stratified by HbA<sub>1c</sub> 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.

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W.H.W.T. wrote the manuscript and researched data. Y.W. and E.B.B. researched data. N.I. researched data and contributed to discussion. S.L.H. researched data, reviewed and edited manuscript, and contributed to discussion. W.H.W.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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