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.

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 = 0.094 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.

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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), HbA1c, 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 (CrCl) 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 5 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-squared 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.

**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 (n = 989) | Yes (n = 286) | P |
|---------------------------------|-------------|--------------|---|
| 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 |
| HbA1c (%)                      | 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/1.73m²)           | 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).
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, 1.90; 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 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 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 statin 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...
in 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 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 cTnl 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 nitrative 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 cTnl 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 cTnl 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 Hba1c (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 toward 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.

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

| Subclinical myocardial necrosis (%) | No (cTnl <0.01 ng/mL) | Yes (cTnl 0.01–0.03 ng/mL) |
|-----------------------------------|----------------------|--------------------------|
| 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 + Hba1c; Model 3: Traditional risk factors + Hba1c + 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.

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 cTnl 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,
The strength of the current study is the ability to determine the future cardiac risk in a broad clinical population of patients with subtype 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 practice. 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 cTnl 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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