Unanswered Questions for Management of Acute Coronary Syndrome

Risk Stratification of Patients With Minimal Disease or Normal Findings on Coronary Angiography

Raffaele Bugiardini, MD; Olivia Manfrini, MD; Gaetano M. De Ferrari, MD

Background: The prognostic implication of chest pain associated with normal or near-normal findings on angiography is still unknown. We explored outcomes and methods of risk stratification in patients with nonobstructive coronary artery disease in the setting of non–ST-segment elevation acute coronary syndromes.

Methods: Data were pooled from 3 Thrombolysis in Myocardial Infarction (TIMI) trials (TIMI 11B, TIMI 16, and TIMI 22). Angiographic data were available on 7656 patients with non–ST-segment elevation acute coronary syndromes. The primary end point of this analysis was the composite of the rates of death, myocardial infarction, unstable angina requiring rehospitalization, revascularization, and stroke at 1-year follow-up. Outcomes were evaluated by mean of the TIMI risk score for developing at least 1 component of the primary end point.

Results: Angiographic findings showed that 710 (9.1%) of 7656 patients had nonobstructive coronary artery disease; 48.7% of these had normal coronary arteries (0% stenosis), and 51.3% had mild coronary artery disease (>0% to <50% stenosis). A primary end-point event occurred in 101 patients (12.1%). It is noteworthy that a 2% event rate of deaths and myocardial infarctions had occurred in these patients at the 1-year follow-up. Event rates of death and myocardial infarction increased significantly as the TIMI risk score increased from 0.6% for a score of 1 to 4.0% for a score greater than 4.

Conclusions: Patients with non–ST-segment elevation acute coronary syndromes with nonobstructive coronary artery disease detected by angiography have a substantial risk of subsequent coronary events within 1 year. The risk is not univariately high, and the TIMI risk score helps to reveal patients at high risk.

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In clinical practice, chest pain in the presence of non-obstructive coronary artery disease (CAD) remains an unsolved problem.1,2 Thousands of patients are told that they have no significant heart disease following demonstration of normal or near-normal arteries on coronary angiography and often are offered no treatment beyond reassurance.3-5 Physicians agonize endlessly over the discrepancy between observed and expected angiographic findings in the subset of patients at greater risk, namely, those presenting with acute coronary syndromes (ACS). Their consternation is largely justified; ACS may result from disruption of modestly stenotic vulnerable plaques, is often not detectable by angiography, and may lead to thrombotic complication.7,8 However, available outcome data are limited to a few cohort studies that used special tests are not routinely employed, (ie, intravascular ultrasonography9 and intracoronary acetylcholine testing).10,11

The aims of this study were (1) to evaluate outcomes at the 1-year follow-up of patients without critical coronary stenosis as assessed by routine angiography in a large cohort of patients with non–ST-segment elevation (NSTE)–ACS drawn from international multicenter trials and (2) to evaluate the relative importance of simple clinical and biochemical variables in the risk stratification of these patients.

Methods

Data Sources

Because no published clinical trials on ACS provided outcome data sorted by angiographic groups (those with obstructive CAD vs those with nonobstructive CAD), we contacted 4 authors regarding 7 studies14-20 and received data from 3 studies: the Thrombolysis in Myocardial Infarction (TIMI) 11B, Orbofiban in Patients with Unstable coronary Syndromes (OPUS)-TIMI 16, and PRavastatin Or atorVasstatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trials.15,16,20

Study Population

The study design and the main results of the TIMI 11B, OPUS–TIMI 16, and PROVE IT–TIMI 22 trials have been previously reported.15,16,20 These
Patients with nonobstructive CAD were grouped as those with normal findings on angiography (\(0\%\) lumen stenosis in all vessels) and those with mild CAD (\(>0\%\) but \(<50\%\) lumen stenosis). We used adjusted baseline models to determine whether differences between groups were independent. Statistical testing was performed with the \(\chi^2\) test for categorical variables and the Wilcoxon rank sum test for continuous variables. Estimates of the hazard ratios and associated 95% confidence intervals were obtained with the use of the Cox proportional hazards model.

Data were analyzed by the TIMI Data Coordinating Center (Brigham and Women's Hospital and Harvard Medical School, Boston, Mass), which also handled our queries.

Angiographic data were available for 7656 patients with NSTE-ACS. A total of 6955 patients had obstructive CAD, and 701 (9.1%) had nonobstructive CAD (48.7% with normal coronary arteries and 51.3% with mild CAD).

The Kaplan-Meier estimates of 1-year event rates for patients with obstructive lesions were 3.9% for deaths, 6.9% for nonfatal myocardial infarction, 11.2% for either myocardial infarction or death, 12.8% for revascularization, 18.8% for unstable angina requiring rehospitalization, 1.1% for stroke, and 32.7% for composite cardiovascular events.

### OUTCOME OF PATIENTS WITH NONOBSTRUCTIVE CAD

The Kaplan-Meier event rates for the primary end points are shown in Table 1. In the overall population with nonobstructive CAD, recurrent ischemia was the most frequent end point (10.1%). Death and myocardial infarction occurred in 2.1% of patients. In angiographic subgroups, the primary end points occurred in 15.1% of patients with mild CAD and in 9.4% of those with normal findings on angiography (\(P<.05\)). Patients with mild CAD were more likely to have undergone revascularization during 1-year follow-up (1.6% vs 0%, \(P=.02\)). Death, nonfatal myocardial infarction, and unstable angina requiring rehospitalization occurred less frequently in the group with normal findings on angiography than in the group with mild CAD (Table 1).

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Patients With Nonobstructive CAD, %</th>
<th>Patients With Obstructive CAD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>(n = 355)</td>
<td>(n = 3300)</td>
</tr>
<tr>
<td>MI</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Death or MI</td>
<td>9.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8.4</td>
<td>12.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Primary end point†</td>
<td>1.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Abbreviations: MI, myocardial infarction; OPUS, Orbofiban in Patients with Unstable coronary Syndromes; NA, not applicable; PROVE IT, PRavastatin Or atorVastatin Evaluation and Infection Therapy; TIMI, thrombolysis in myocardial infarction.*

†Death, MI, revascularization, unstable angina, or stroke.

### TIMI RISK SCORE

The TIMI risk score for patients with NSTE-ACS is a risk assessment tool comprised of 7 independent clinical risk indicators that are evaluated at presentation. The 7 predictor variables are age older than 65 years, 3 cardiovascular risk factors (family history of coronary disease, diabetes mellitus, hypertension, hypercholesterolemia, or current smoking), previous CAD (\(>50\%\) stenosis at angiography), severe anginal symptoms (2 episodes in preceding 24 hours), use of aspirin in the last 7 days, ST-segment deviation greater than 0.05 mV, and elevated concentrations of serum cardiac markers of necrosis. For each patient, the score is calculated as the simple sum of the number of risk indicators that are present (range, 0–7). Cutoff points for positive biomarkers were 0.01 ng/mL for cardiac troponin T and 0.1 ng/mL for troponin I.19

In our study, the highest TIMI risk score was only 6, because 1 component (stenosis >50% at angiography) was 0 by definition in patients without obstructive lesions.

### STATISTICAL ANALYSIS

Data were analyzed by the TIMI Data Coordinating Center (Brigham and Women's Hospital and Harvard Medical School, Boston, Mass), which also handled our queries.

### RESULTS

Angiographic data were available for 7656 patients with NSTE-ACS. A total of 6955 patients had obstructive CAD, and 701 (9.1%) had nonobstructive CAD (48.7% with normal coronary arteries and 51.3% with mild CAD).
with mild CAD, but the differences were not statistically significant. The Figure shows the primary end-point event rate in patients with normal findings on angiography and those with mild CAD at 7, 30, and 180 days and at 1-year follow-up.

**CLINICAL CHARACTERISTICS VS OUTCOME**

A primary end-point event at 1-year follow-up occurred in 75 patients. Patients with and without a primary end-point event matched well with regard to age, sex, risk factors, and treatment of the index event (Table 2). Presence of ST-segment deviation and biochemical markers for death and myocardial infarction ranged from 0.6% for a score of 0 to 14.7% for a score of 4 or higher than 4 (P < .05). Patients in whom the primary end point did not subsequently develop were more likely to have a TIMI risk score of 0 to 2 (P = .003).

**DISCRIMINATION OF TIMI RISK SCORE FOR THE COMBINED END POINT**

The analysis excluded patients with missing values for assessing the TIMI risk score. Of the 710 patients with NSTE-ACS, 665 were eligible for TIMI risk score evaluation.

Most (65%) of the patients with nonobstructive CAD had a score ranging from 1 to 3. Because of the small number of patients with very high risk scores, those with a score of 4 or higher were combined. Event rates (Table 3) of patients with nonobstructive CAD increased significantly as the TIMI risk score increased from 4.9% for a score of 0 to 14.7% for a score of 4 or higher than 4 (P < .01). Rates for death and myocardial infarction ranged from 0.6% for a score of 1 to 4.1% for a score of 4 or higher than 4 (P < .05).

**COMMENT**

The assumption that nonobstructive CAD carries a good prognosis is not based on hard data, and, to our knowledge, this is the first examination of it in a large study. The study described herein demonstrates that the assumption turns out to be incorrect, at least in those patients presenting with an ACS.

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**Table 2. Baseline Characteristics According to Presence or Absence of a Primary End Point in Patients With Nonobstructive Coronary Artery Disease in the PROVE IT–TIMI 22, OPUS–TIMI 16, and TIMI 11B Trials**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Primary End Point (n = 75)*</th>
<th>Patients Without a Primary End Point† (n = 625)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>38.7 vs 47.9</td>
<td></td>
<td>.13</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>58.2 (11.1) vs 57.1 (11.8)</td>
<td></td>
<td>.42</td>
</tr>
<tr>
<td>White race</td>
<td>94.2 vs 96.9</td>
<td></td>
<td>.24</td>
</tr>
<tr>
<td>History of MI</td>
<td>69.6 vs 63.9</td>
<td></td>
<td>.36</td>
</tr>
<tr>
<td>ACE-I</td>
<td>26.1 vs 26.3</td>
<td></td>
<td>.97</td>
</tr>
<tr>
<td>Current smoker</td>
<td>26.7 vs 30.9</td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>8.0 vs 9.0</td>
<td></td>
<td>.79</td>
</tr>
<tr>
<td>History of PAD</td>
<td>4.0 vs 2.7</td>
<td></td>
<td>.46</td>
</tr>
<tr>
<td>Drug for management of qualifying event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>94.2 vs 96.9</td>
<td></td>
<td>.24</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>69.6 vs 63.9</td>
<td></td>
<td>.36</td>
</tr>
<tr>
<td>ACE-I</td>
<td>26.1 vs 26.3</td>
<td></td>
<td>.97</td>
</tr>
<tr>
<td>TIMI risk score†</td>
<td>0-2</td>
<td></td>
<td>.003</td>
</tr>
<tr>
<td>≥3</td>
<td>50.0 vs 67.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>29.7 vs 41.0</td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>ST-deviation</td>
<td>68.9 vs 57.8</td>
<td></td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; ACS, acute coronary syndromes; MI, myocardial infarction; NSTE, non–ST-segment elevation; OPUS, Orbiblain in Patients With Unstable Coronary Syndromes; PAD, peripheral artery disease; PROVE IT, Pravastatin Or AspirinVastatin Evaluation and Infection Therapy; TIMI, thrombolysis in myocardial infarction; UA, unstable angina.

*Data are given as percentages except where noted.
†Of the 710 patients with unstable angina and NSTE-MI, 665 were eligible for TIMI risk score evaluation.

We performed a post hoc analysis of 3 published randomized clinical trials (TIMI 11B, OPUS–TIMI 16, and PROVE IT–TIMI 22), involving 7656 patients with NSTE-ACS for whom angiographic data were available.

The prevalence of nonobstructive CAD in this population with ACS was 9.1%. Slightly more than half of the 701 affected patients had mild CAD (defined as those with less than 50% stenosis), whereas the remainder had normal, smooth coronary arteries found on angiography. The primary outcome measure was the combined 1-year rates of death, myocardial infarction, unstable angina requiring rehospitalization, revascularization, and stroke. The incidence rate of events was 9.4% in patients withACS and with normal arteries found on angiography and 15.3% in those with less than 50% stenosis. Even more disturbing, however, were the rates of the most serious outcomes, death and myocardial infarction. The overall incidence was 2.1% at 1 year, with a 1.2% rate among patients with normal coronary arteries found on angiography and 3.3% in those with mild CAD. These findings are not in agreement with the notion that chest pain with normal or near-normal findings on coronary angiography implies benign prognosis, at least in those patients presenting with ACS.

Because the event rate of patients with nonobstructive CAD was very high, physicians should classify virtually every patient admitted with a clinical diagnosis of...
patients, the associated 1-year risk rate of death or nonfatal myocardial infarction climbed from 0.6% (in those with a TIMI score of 1) to 4.1% (in those with a score of 4 or higher). The 0.6% rate in death or myocardial infarction seen in patients with a TIMI score of 1 is the expected rate in the general population of low-risk asymptomatic subjects. An event rate of 2.8% (TIMI score of 3) to 4.1% (TIMI score of 4) for death and myocardial infarction at 1-year follow-up is unacceptably high for this supposedly low-risk population.

Although elevated concentrations of serum cardiac markers and the presence of electrocardiographic changes are considered to be excellent risk stratification tools in the appropriate clinical setting, little is known about their prognostic value for patients without obstructive CAD. Previous studies on this issue were small (fewer than 110 patients) and had low statistical power (fewer than 5 end points). In our study, a large percentage (40% [278 of 701]) of patients showed elevated cardiac biomarkers. As well, many patients (412 [59%] of 701) showed electrocardiographic changes. Comparing patients who did have vs those who did not have subsequent coronary events, the former were more likely to have electrocardiographic changes (68.8 vs 57.8%) but not to have more elevated serum cardiac markers.

The present analysis, therefore, highlights the principle that no single variable can accurately predict the risk for nonobstructive CAD in patients with NSTE-ACS. In this subset of patients, biochemical markers of myocardial injury, such as troponin T, and troponin I, are valuable only in combination with electrocardiographic findings and clinical features. Accordingly, the TIMI risk score has a greater statistical power in discriminating patients who are having vs those who are not having subsequent coronary events.

Although we have described angiographically occult CAD as a potential mechanism for coronary events in patients with ACS and normal or near-normal findings on cardiac angiography, consideration also should be given to other causes such as angiograms that are inadequate or misinterpreted by visual analysis, myocardial infarction caused by coronary spasm, microembolization, and a misdiag-

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**Table 3. Clinical Events at 1-Year Follow-up and TIMI Risk Scores in Patients With Angiography Findings of NSTE-ACS in the PROVE IT–TIMI 22, OPUS–TIMI 16, and TIMI 11B Trials**

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>TIMI Risk Score (Range, 0-6), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n = 42)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
</tr>
<tr>
<td>Death and MI</td>
<td>0</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>4.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Primary end point‡</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Abbreviation: MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; OPUS, Orbofabin in Patients with Unstable coronary Syndromes; PROVE IT, PRavastatin Or atorVastatin Evaluation and Infection Therapy; TIMI, thrombolysis in myocardial infarction.

*Kaplan-Meier rates.
†P value for trend.
‡Death, MI, revascularization, unstable angina, or stroke.
nosis of ACS in patients with a variety of different clinical entities, such as myocarditis and Takotsubo cardiopathy, among others. Obviously, the same diagnostic uncertainties may affect those patients diagnosed as having obstructive CAD and the overall populations of the ACS trials. We do not have data to quantify the relative contribution of these factors. However, queries about the use of angiography by visual estimation seem to be clinically irrel­evant. No matter how precisely measured, the angiogram of a complex lesion poorly represents the real lumen size. Accordingly, interpretation of angiography by visual analysis is still considered by most catheter laborato­ries to be the gold standard for defining coronary anatomy and represents, therefore, the real clinical world.

Some limitations must be noted. First, clinical trials usually select high-risk patients. The 3 TIMI trials enrolled a population of patients presenting with classic, typical, ischemic discomfort at rest. Patients are more likely to experience subsequent coronary events if they present typically. Therefore it could be asked whether the rate of events would be the same in an unselected population of patients who are representative of general clinical practice. Most patients in the general population are different. Admissions are often related to atypical symp­toms of chest pain and continued seeking of medical care. Second, the decision to perform coronary angiography was performed at the local level. It is not known whether there was any bias in the referral pattern.

In conclusion, patients presenting with typical symp­toms of ACS but without critical obstruction on visual angiography have a prognosis that is not as benign as previ­ously thought. Although the mean risk was high even for death and myocardial infarction (2.1% after 1 year), most events were driven by repeated admission for un­stable angina (10.1%). The risk is not univariately high, and thus the TIMI risk score helps to predict the likeli­hood of patients to develop coronary events.

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Correspondence: Raffaele Bugiardini, MD, Diparti­mento di Medicina Interna, Cardioangiologia, Epatolo­gia (Padiglione 11), University Alma Mater of Bologna, Via Massarenti 9, 40138 Bologna, Italy (raffaele.bugiardini@unibo.it).

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REFERENCES