

Incidence and Predictors of Obstructive Coronary Artery Disease

and the Role of Cardiac Troponin
Assays in Patients with Unstable Angina

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In a time when cardiac troponin assays are widely used to detect myocardial injury, data remain scarce concerning the incidence and predictors of substantial obstructive coronary artery disease that causes unstable angina.

This retrospective single-center study included consecutive patients hospitalized for unstable angina from January 2015 through January 2016. Patients with troponin I levels above the upper reference limit and those who did not undergo angiography were excluded. Multivariate logistic regression analysis was used to identify predictors of obstructive coronary artery disease that warranted revascularization and of major adverse cardiac events up to 6 months after discharge from the hospital.

Of the 114 patients who met the inclusion criteria, 46 (40%) had obstructive coronary artery disease. In the univariate analysis, male sex, white race, history of coronary artery disease, prior revascularization, hyperlipidemia, chronic kidney disease, aspirin use, long-acting nitrate use, and Thrombolysis in Myocardial Infarction score ≥ 3 were associated with obstructive coronary artery disease. History of coronary artery disease, prior revascularization, hyperlipidemia, and long-acting nitrate use were associated with major adverse cardiac events. Male sex was an independent predictor of obstructive coronary artery disease (adjusted odds ratio=4.82; 95% CI, 1.79–13; $P=0.002$) in the multivariate analysis.

Our results showed that coronary artery disease warranting revascularization is present in a considerable proportion of patients who have unstable angina. The association that we found between male sex and obstructive coronary artery disease suggests that the risk stratification of patients presenting with unstable angina may need to be refined to improve outcomes. (Tex Heart Inst J 2019;46(3):161-6)

Key words: Acute coronary syndrome/classification/diagnosis; angina, unstable/classification/diagnosis/physiopathology; biomarkers/blood; diagnosis, differential; hospitalization; logistic models; predictive value of tests; retrospective studies; sex factors; troponin I/blood

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The incidence of unstable angina (UA) has rapidly declined with the introduction of sensitive biomarkers of myocardial injury, which has resulted in the reclassification of a substantial proportion of UA patients as having non-ST-segment-elevation acute coronary syndrome (NSTEMI-ACS).¹ Even in this evolving clinical context, the treatment of patients who present with UA is largely guided by studies that were conducted before the widespread implementation of cardiac troponin assays, which have a higher sensitivity for myocardial injury than does creatine kinase.² The current guidelines do not differentiate between patients who present with biomarker-positive or -negative NSTEMI-ACS.³ Although previous research suggests that early invasive strategies improve outcomes in patients with biomarker-positive NSTEMI-ACS, such benefits may not apply to those with biomarker-negative UA.⁴ Our study was designed to determine the incidence of obstructive coronary artery disease (CAD) warranting revascularization in patients who present with UA, as well as the predictors and outcomes of revascularization in patients admitted with this diagnosis, areas that have been insufficiently explored in a clinical landscape that is being reshaped by the use of increasingly sensitive biomarkers.

Patients and Methods

This retrospective single-center study included consecutive patients admitted to our hospital with the diagnosis of UA and was approved by our institutional review board. We initially identified a list of patients with the International Classification of Diseases (ICD)-9 code 411.1 or ICD-10 code I20.0 who were hospitalized from January

2015 through January 2016 (n=467). Each chart was then manually reviewed to include patients whose history and physical examinations, as documented by the admitting physicians, revealed symptoms of exertional chest pain provoked by lower activity thresholds compared with the baseline thresholds, exertional chest pain with increased duration or intensity compared with those reported at baseline, or chest pain occurring at rest. We excluded patients in whom cardiac troponin I levels were elevated above the 99th percentile of the upper reference limit before revascularization (n=229), pre-revascularization troponin I levels or other laboratory values were unavailable (n=114), angiography was performed for stable angina (n=5), or angiography was not performed (n=5) (Fig. 1).

Demographic characteristics, comorbidities, cardiovascular medications, vital signs, laboratory values, electrocardiographic (ECG) findings, stress-testing methods and results, and angiographic results were documented. Presenting history and recorded variables were used to calculate Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scores. Obstructive CAD was defined as the presence of culprit coronary lesions warranting revascularization. The included patients underwent revascularization for left main coronary artery (LMCA) stenosis $\geq 50\%$, non-LMCA stenosis $\geq 70\%$, lesions deemed hemodynamically significant by fractional flow reserve measurement, or hazy lesions that suggested acute plaque rupture or thrombus formation. Patients with any degree of stenosis in distal small branches of the coronary arteries or with chronic occlusions of the arteries who did not undergo revas-

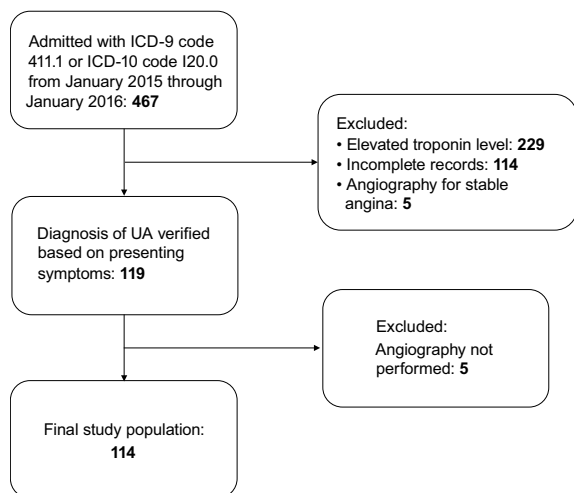


Fig. 1 Flow chart shows selection of patients for the study. ICD = International Classification of Diseases; UA = unstable angina

cularization were not categorized as having obstructive CAD. Major adverse cardiac events (MACE), defined as readmission for cardiovascular causes, myocardial infarction (MI), stroke, or cardiac death during the index hospitalization and within 6 months of discharge from the hospital, were recorded. Readmissions within the timeframe of the study were considered to be new admissions if they occurred more than 6 months after the date of discharge of the index admission.

The ARCHITECT® STAT Troponin-I system (Abbott) was used to measure troponin I levels. The 99th percentile upper reference limit was 0.028 ng/mL; the intra-assay coefficient of variation, 10% at 0.2 ng/mL. The limit of detection was 0.01 ng/mL.

Statistical Analysis

Clinical characteristics were compared between patients with obstructive CAD warranting revascularization and those without obstructive CAD. The Student *t* test was used to compare continuous variables, and the Pearson χ^2 test was used for categorical variables. Multivariate logistic regression analysis was performed to identify independent predictors of obstructive CAD warranting revascularization and those of MACE in patients admitted with UA. Variables known to be associated with risk for CAD were used in the multivariate model for obstructive CAD. These included TIMI scores ≥ 2 or GRACE scores ≥ 110 , male sex, new ST-segment depression ≥ 0.5 mV in at least 2 contiguous leads, prior revascularization, and history of diabetes mellitus. The cutoffs for risk scores were chosen on the basis of values above those considered low-risk in the current guidelines for the management of patients with NSTEMI-ACS.³ All *P* values were 2-sided, with a significance threshold of *P* < 0.05. Analyses were performed by using the R programming environment for statistical computing and graphics, version 3.1.1 (R Foundation for Statistical Computing).

Results

During the study period, 467 patients with UA were admitted to our hospital. Of those, we excluded 229 who had elevated troponin levels, 114 who had incomplete records, and 5 who underwent angiography for stable angina. Of the remaining 119 patients with a verified diagnosis of UA, 5 did not undergo angiography. Of the 114 patients included in the analysis, 75 (66%) were men and 92 (81%) were white; the patients' mean age was 61 ± 10.5 years. Obstructive CAD warranting revascularization was identified in 46 patients (40%).

Predictors of Significant Obstructive CAD

In the univariate analysis, male sex, white race, history of CAD, prior revascularization, hyperlipidemia, chronic kidney disease, aspirin use, long-acting nitrate use,

and TIMI score ≥ 3 were associated with obstructive CAD (Table I). In the multivariate analysis, male sex (adjusted odds ratio=4.82; 95% CI, 1.79–13; $P=0.002$) was an independent predictor of obstructive CAD in patients admitted with UA (Table II). Of those found to have obstructive CAD, 37 patients (81%) underwent percutaneous coronary intervention (PCI), 8 patients (17%) underwent coronary artery bypass grafting (CABG), and one patient (2%) chose not to undergo revascularization. Of the patients who underwent PCI, 35 patients (95%) had single-vessel disease, and 2 patients (5%) had 2-vessel disease. Thirty-one patients (84%) received drug-eluting stents, 5 (13%) received bare-metal stents, and one (3%) underwent angioplasty

without stent placement. Of the patients who underwent CABG, 4 (50%) had 3-vessel disease, 3 (38%) had 2-vessel disease with involvement of the left anterior descending coronary artery, and one (12%) had single-vessel disease that affected the LMCA.

Predictors of Major Adverse Cardiac Events

No patients experienced MACE at the index hospitalization, regardless of whether obstructive CAD was present. By the 30-day follow-up, 4 MACE (5.9%) occurred in patients without obstructive CAD, all of which were readmissions for cardiovascular causes, and 3 MACE (6.5%) occurred in patients with obstructive CAD (one readmission and 2 MI; $P=0.889$). Between

TABLE I. Univariate Analysis of Predictors of Obstructive Coronary Artery Disease

| Variable | No Obstructive CAD (n=68) | Obstructive CAD (n=46) | P Value |
|--------------------------------------|------------------------------|---------------------------|---------|
| Age (yr) | 60 \pm 9.9 | 62 \pm 11.4 | 0.222 |
| Male sex | 36 (53) | 39 (85) | 0.001 |
| White | 49 (72) | 43 (93) | 0.004 |
| History | | | |
| CAD | 38 (56) | 36 (78) | 0.014 |
| Prior revascularization | 32 (47) | 32 (70) | 0.018 |
| Congestive heart failure | 2 (3) | 4 (9) | 0.177 |
| Hypertension | 51 (75) | 34 (74) | 0.896 |
| Hyperlipidemia | 38 (56) | 37 (80) | 0.007 |
| Diabetes mellitus | 19 (28) | 16 (35) | 0.437 |
| Chronic kidney disease | 0 | 7 (15) | <0.001 |
| Peripheral artery disease | 4 (6) | 3 (7) | 0.889 |
| Familial CAD | 44 (65) | 31 (67) | 0.767 |
| Tobacco use | 34 (50) | 30 (65) | 0.108 |
| Aspirin therapy | 38 (56) | 35 (76) | 0.027 |
| Statin therapy | 43 (63) | 33 (72) | 0.345 |
| Long-acting nitrate therapy | 6 (9) | 11 (24) | 0.026 |
| Body mass index (kg/m ²) | 30 \pm 6.3 | 31 \pm 7.7 | 0.686 |
| Baseline creatinine (mg/dL) | 0.95 \pm 0.26 | 1.16 \pm 0.64 | 0.087 |
| New ST depression on ECG | 3 (4) | 3 (7) | 0.621 |
| Stress testing before angiography | 12 (18) | 9 (20) | 0.795 |
| Positive before angiography | 11 (92) | 8 (89) | 0.83 |
| TIMI score | 2.26 \pm 1.44 | 3.09 \pm 1.24 | 0.002 |
| GRACE score | 108.6 \pm 14.9 | 110.8 \pm 18.8 | 0.609 |

CAD = coronary artery disease; ECG = electrocardiogram; GRACE = Global Registry of Acute Coronary Events; TIMI = Thrombolysis in Myocardial Infarction

Data are expressed as mean \pm SD or as number and percentage. $P < 0.05$ was considered statistically significant.

TABLE II. Multivariate Analysis of Predictors of Obstructive Coronary Artery Disease

| Variable | Odds Ratio (95% CI) | P Value |
|----------------------------------|---------------------|---------|
| Male sex | 4.82 (1.79–13) | 0.002 |
| Prior revascularization | 1.42 (0.53–3.81) | 0.482 |
| Diabetes mellitus | 1.41 (0.54–3.63) | 0.482 |
| New ST depression | 1.49 (0.23–9.83) | 0.676 |
| High risk by TIMI or GRACE score | 2.01 (0.57–7.15) | 0.281 |

GRACE = Global Registry of Acute Coronary Events; TIMI = Thrombolysis in Myocardial Infarction

P < 0.05 was considered statistically significant.

one month and 6 months, 9 additional MACE (13.2%) occurred in patients without obstructive CAD (7 re-admissions and 2 MI), and 5 (10.9%) in patients with obstructive CAD, all readmissions (*P*=0.706). The univariate analysis revealed that history of CAD, prior revascularization, hyperlipidemia, and long-acting nitrate use were associated with MACE (Table III).

Discussion

Our results showed that obstructive CAD warranting revascularization is present in 40% of patients admitted with a diagnosis of UA. Male sex was an independent predictor of obstructive CAD. To our knowledge, this is the largest single-center study to analyze the incidence of angiographically significant UA since increasingly sensitive biomarkers have become widely used tools for detecting myocardial injury.

Current guidelines recommend an early invasive strategy, in the form of coronary angiography within 24 hours of presentation, for patients with biomarker-positive NSTE-ACS and for high-risk biomarker-negative patients who meet GRACE score or ECG criteria.³ Such recommendations, however, are based on results of studies that did not differentiate between biomarker-positive and -negative presentations.⁵ Moreover, subanalyses indicate that the survival benefits of early invasive strategies are limited to biomarker-positive patients.^{4,6} Researchers have also reported a trend toward higher rates of death and MI associated with an early invasive strategy than with a conservative strategy among women who present with biomarker-negative UA.⁴ Indications for an early invasive strategy specific to the UA population need to be clarified to improve risk-benefit evaluation.

In our study, male sex was a predictor of obstructive CAD, a finding that suggests that the current guidelines for the risk stratification of patients who present with UA need to be refined. Previous investigators have

TABLE III. Univariate Analysis of Predictors of MACE up to 6 Months

| Variable | No MACE (n=96) | MACE (n=18) | P Value |
|--------------------------------------|----------------|--------------|---------|
| Age (yr) | 62 ± 9.8 | 58 ± 14.9 | 0.105 |
| Male sex | 62 (65) | 13 (72) | 0.531 |
| White | 76 (79) | 16 (89) | 0.337 |
| History | | | |
| CAD | 58 (60) | 16 (89) | 0.02 |
| Prior revascularization | 49 (51) | 15 (83) | 0.011 |
| Congestive heart failure | 5 (5) | 1 (6) | 0.952 |
| Hypertension | 70 (73) | 15 (83) | 0.352 |
| Hyperlipidemia | 59 (61) | 16 (89) | 0.024 |
| Diabetes mellitus | 30 (31) | 5 (28) | 0.769 |
| Chronic kidney disease | 6 (6) | 1 (6) | 0.91 |
| Peripheral artery disease | 5 (5) | 2 (11) | 0.338 |
| Familial CAD | 60 (63) | 15 (83) | 0.087 |
| Tobacco use | 53 (55) | 11 (61) | 0.643 |
| Aspirin therapy | 59 (61) | 14 (78) | 0.186 |
| Statin therapy | 62 (65) | 14 (78) | 0.276 |
| Long-acting nitrate therapy | 11 (12) | 6 (33) | 0.017 |
| Body mass index (kg/m ²) | 31 ± 7.2 | 30 ± 5.5 | 0.902 |
| Baseline creatinine (mg/dL) | 1.04 ± 0.48 | 1 ± 0.31 | 0.929 |
| New ST depression on ECG | 5 (5) | 1 (6) | 0.952 |
| Stress testing before angiography | 17 (18) | 4 (22) | 0.65 |
| Positive before angiography | 15 (88) | 4 (100) | 0.471 |
| TIMI score | 2.52 ± 1.47 | 3 ± 1.08 | 0.288 |
| GRACE score | 109.8 ± 16.5 | 107.6 ± 17.1 | 0.463 |
| Obstructive CAD | 39 (41) | 7 (39) | 0.89 |

CAD = coronary artery disease; ECG = electrocardiogram; GRACE = Global Registry of Acute Coronary Events; MACE = major adverse cardiac events; TIMI = Thrombolysis in Myocardial Infarction

Data are expressed as mean ± SD or as number and percentage. *P* < 0.05 was considered statistically significant.

also found that, despite a higher incidence of symptoms and ECG findings that suggest ischemia, women were less likely than men to have obstructive CAD; such findings were reported in UA populations,⁷ as well as in studies that included both biomarker-positive and -negative presentations of unstable ischemic heart disease.^{8,9} This outcome has been attributed to a higher rate of endothelial dysfunction caused by a relative estrogen deficiency and a higher rate of metabolic syndrome

among postmenopausal women, which correlate with symptoms and findings of ischemia in the absence of obstructive CAD.¹⁰

Although the combined use of TIMI and GRACE scores for risk stratification did not predict obstructive CAD in our study, Trivi and colleagues¹¹ found that the TIMI score was an independent predictor of CAD with $\geq 70\%$ stenosis. Other predictors observed in small studies include a history of CAD, ischemia detected during stress testing, and ECG changes.^{11,12} The differences in sample sizes and definitions of obstructive CAD between studies may explain why our results differ from previous findings. In previous studies, obstructive CAD was defined according to the degree of stenosis, without consideration for revascularization procedures.

Our univariate analysis showed that, in addition to conditions that are known to be associated with ACS—including a history of CAD, prior revascularization, hyperlipidemia, and chronic kidney disease—white race was also a predictor of obstructive CAD warranting revascularization. Racial differences in the incidence of obstructive CAD have been described. In the TIMI and Global Unstable Angina Registry and Treatment Evaluation (GUARANTEE) cohorts, which included biomarker-positive and -negative patients who presented with ACS, white patients were more likely to have obstructive CAD than were other racial groups.^{13,14} Such discrepancies have been attributed to the differences in risk-factor profiles, because nonwhite racial groups tend to have higher rates of diabetes mellitus and hypertension and lower rates of hyperlipidemia than do white populations. It is also possible, however, that we observed an association between white race and obstructive CAD because our study population was predominantly white.

Twenty-one separate MACE were reported in 18 patients (some patients had more than one event) at 6 months. Most of the events were readmissions for cardiovascular causes, with only 4 cases of MI. Traditional cardiovascular risk factors correlated with MACE in the univariate analysis. Although a meaningful multivariate analysis was not possible because of our low event rate, Trivi and colleagues¹¹ found that TIMI score independently predicted MACE at 6 months. We found that the incidence of MACE was similar among patients regardless of whether they had obstructive CAD; however, it is possible that revascularization improved outcomes in patients with obstructive disease to the extent that their MACE incidence was comparable with that of patients without disease. Therefore, the risks of early invasive therapy in the UA population may be balanced by the benefits of revascularization.

As cardiac troponin assays have become increasingly sensitive for myocardial injury, a proportion of the patients who were once diagnosed with UA are being reclassified as having NSTEMI-ACS.¹ However, our findings suggest that CAD warranting revasculariza-

tion still exists among UA patients. One pathogenetic mechanism of UA, identified by means of coronary angiography, is the formation of a partial thrombus on a fissured atherosclerotic plaque.¹⁵⁻¹⁸ Such thrombi undergo rapid lysis, which may lead to negative cardiac biomarker results and the absence of angiographically significant lesions, while the resultant healed lesion contributes to further luminal narrowing. Thus, although sensitive assays have helped to refine ACS classification, resulting in fewer diagnoses of UA, patients with negative troponin findings may still be at risk of developing severe coronary lesions that lead to infarction. Patients with biomarker-negative UA are often considered to have a lower risk of myocardial injury than do biomarker-positive patients.^{19,20} However, further multicenter prospective studies are necessary to improve the risk stratification and management of patients hospitalized with the diagnosis of UA.

Study Limitations

The major limitation of our study is the small size of the cohort from a single center. However, extensive chart review enabled accurate evaluations of diagnoses, risk factors, and outcomes, leading to comprehensive analyses of the patients hospitalized with UA. Moreover, we intended the study to be hypothesis-generating and to pave the way for larger, multicenter studies. Other limitations include the retrospective nature of the study and the use of ICD codes for the preliminary identification of patients who presented with UA. Unstable angina can be a subjective diagnosis because it is highly dependent on the presenting history. Information relevant to the presentation may be misrepresented or omitted when using different documentation styles, and, therefore, ICD codes may not accurately capture the diagnosis. However, each chart was manually reviewed and standardized inclusion criteria were used to ensure that the included cases most accurately reflected the diagnosis of UA. In addition, selection bias may have been introduced when we excluded patients with incomplete records, many of whom were transferred from other institutions for higher levels of care, suggesting that they were high-risk patients. However, by including only patients who had complete records, we ensured that the study population was limited to patients with biomarker-negative UA and that all risk factors for CAD were included. Our study cohort may represent a high-risk population of UA patients because we included only those who underwent angiography, but this selection criterion enabled us to confirm the presence of obstructive CAD. Only 5 patients diagnosed with UA did not undergo angiography, which may suggest alternative coding of most patients in whom angiography was not performed. Patients whose presenting history suggested UA but whose stress tests had negative results may also have been coded differently, although

such patients most likely did not undergo subsequent angiography and would have been ultimately excluded. Our low MACE rate limited the ability to perform a multivariate analysis; however, this finding highlights the low event rate among a high-risk group of patients who underwent angiography. Finally, the identification of MACE at follow-up was restricted to patients readmitted to our institution. However, event rates were low and similar in patients with and in those without obstructive CAD, suggesting that inclusion of events at other hospitals would have contributed little to the overall analysis.

Conclusions

Although sensitive cardiac biomarkers have improved discrimination between UA and NSTEMI presentations, resulting in the classification of higher numbers of patients with CAD as having NSTEMI, a substantial proportion of patients who present with UA have underlying obstructive CAD warranting revascularization. In our study, male sex was an independent predictor of significant obstructive CAD. In addition, the incidence of MACE was low in this group of high-risk UA patients who were selected to undergo angiography. Our findings suggest that the risk factors for obstructive CAD warranting revascularization in patients with biomarker-negative UA may differ from those that drive disease in patients with biomarker-positive NSTEMI-ACS, and that the benefits of revascularization may balance the risks of angiography in patients who present with UA. Larger multicenter studies are necessary to improve the risk stratification and management of patients with this clinical presentation.

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