The large prevalence at autopsy studies, as well as at coronary angiography, of obstructive coronary atherosclerosis in patients presenting cardiac ischemic pain led to the dominant concept, in the past century, that flow-limiting coronary artery stenoses were the only cause of ischemic heart disease (IHD). This notion was then supported by the observation that revascularization procedures improved symptoms and outcomes in several patient subsets. This also led to the paradigm that an ischemic cardiac origin of chest pain had to be excluded when significant coronary artery stenoses were not detected at angiography. Few research groups only, including ours, noticed, however, that obstructive coronary atherosclerosis did not explain all cases of IHD, and proved that dynamic changes in epicardial coronary artery tone and abnormalities of coronary microcirculation were responsible for IHD in a sizeable proportion of patients, even in the absence of significant coronary atherosclerosis. This view, initially considered with skepticism, has progressively been accepted by the scientific community. In particular, variant angina and primary stable microvascular angina, caused by epicardial spasm and coronary microvascular dysfunction respectively, have now been included in international guidelines.

The Issue of Ischemic Heart Syndromes Without Obstructive Atherosclerosis

In more recent years, particular interest has been raised by the causes and mechanisms of acute coronary syndromes (ACSs) that cannot be explained by the presence of obstructive coronary atherosclerosis. ACSs are usually caused by coronary thrombus formation at the site of a complicated atherothrombotic plaque. Accordingly, antithrombotic drugs and invasive strategies have substantially improved the clinical outcomes of these patients. Yet, several studies of patients with ACSs, in particular those presenting without persisting ST-segment–elevation (NSTE-ACS), have consistently shown that a sizeable proportion do not present obstructive stenoses nor coronary thrombosis is able to account for the occurrence of acute myocardial ischemia. The lack of obstructive atherosclerosis (usually defined as the presence of any stenosis ≥50% of the vessel lumen) among NSTE-ACS patients varies in different clinical studies, likely depending on the selection criteria utilized for its diagnosis and for the indication for coronary angiography.

In the large Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry, 8.6% of 38,301 patients with non–ST-segment–elevation acute myocardial infarction (NSTEMI) did not exhibit obstructive atherosclerosis at angiography, a proportion that rose to 10% in a second report of 55,514 patients. A sizeable proportion of patients with no obstructive atherosclerosis was also found among NSTE-ACS patients included in randomized clinical trials. In a retrospective analysis of 7656 patients enrolled in three large trials, 9.1% had no obstructive atherosclerosis, while a prevalence of 12% was found in other trials.

These studies have shown that, compared with those with obstructive stenoses, NSTE-ACS patients with no obstructive atherosclerosis are younger and have a lower prevalence of cardiovascular risk factors. Furthermore, no obstructive atherosclerosis is found more commonly in women (22% in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial versus 10% in men), and among patients with NSTEMI, compared with those with unstable angina (<20% versus 6%–10%, respectively).

Together with the consistent evidence that a sizeable proportion of patients with NSTE-ACS do not exhibit obstructive atherosclerosis, growing evidence suggests that the outcomes of these patients are not as good as could be expected because of the lack of obstructive atherosclerosis. In a retrospective analysis of clinical trials, major adverse events at 1 year occurred in 2.1% of patients, with death and acute myocardial infarction occurring in 1% and 1.2%, respectively, whereas the rate of adverse events reached 10% when including coronary revascularization and angina recurrence. In the CRUSADE registry, however, in-hospital death and reinfarction were significantly lower among NSTEMI patients with no obstructive atherosclerosis than among patients with obstructive atherosclerosis (0.7% versus 2.4% and 1.4% versus 2.9%, respectively). Similar data were shown in another study, in which death rates at 6-month follow-up, in patients without or with obstructive atherosclerosis, were 0.9% and 3.1%, whereas myocardial infarction rates were 0% and 5%, respectively.

The Present Study

In this issue of *Circulation: Cardiovascular Interventions*, Planer et al provide further important information on the
characteristics and outcomes of NSTE-ACS patients with no obstructive atherosclerosis. In their study they report data from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, which compared heparin (unfractionated or enoxaparin) plus glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus GPI, or bivalirudin monotherapy in NSTE-ACS patients. ACUITY enrolled patients who were admitted within 24 hours of symptom onset and showed ≥1 finding among new ST-segment changes, elevated troponin or creatine kinase-MB levels, a known history of IHD, and all 4 of the other variables of the Thrombolysis In Myocardial Infarction risk score for NSTE-ACS. In a planned substudy, a quantitative analysis of coronary angiography, performed within 72 hours from admission, was carried out in 6921 consecutive patients at an independent core laboratory by technicians blinded to clinical features and outcomes.

In the present study, Planer et al10 have assessed patients included in the angiographic study who presented with NSTEMI, ie, with abnormally elevated troponin I or troponin T levels. The clinical outcomes of patients with or without obstructive atherosclerosis were compared in the whole population and in 2 matched subgroups selected according to a propensity score technique.

Of the 6921 patients of the angiographic study, 2422 (32.8%) had elevated troponin levels. Of these, 197 patients (8.1%) had no obstructive atherosclerosis on coronary angiography. Compared with patients with significant coronary stenoses, those with no obstructive atherosclerosis were younger, more often female, had less cardiovascular risk factors, less prior evidence of IHD, and less frequently presented with ST-segment deviation ≥1 mm. Left ventricular function was similar in the 2 groups, whereas creatine kinase-MB levels were higher in patients with obstructive atherosclerosis, who also showed a trend toward higher troponin levels.

In the entire cohort, 30-day and 1-year all-cause and cardiac mortality rates were similar in patients with and those without obstructive atherosclerosis. At 1 year, all-cause mortality was 3.6% versus 4.7%, respectively, whereas cardiac deaths were 2.4% versus 2.6%, respectively. Of note, patients with no obstructive atherosclerosis showed a tendency toward a higher rate of noncardiac deaths (2.1% versus 1.2% at 1 year, \( P = 0.23 \)), but a lower rate of recurrent myocardial infarction (1.5% versus 4.0%) and of unplanned revascularization (0.5% versus 8.1%); no differences were observed in the rates of major bleeding or cerebrovascular events.

Remarkably, in the propensity score-matched patients, all-cause mortality was significantly higher among patients without obstructive atherosclerosis (5.2% versus 1.6%, \( P = 0.04 \)), a difference driven by a greater noncardiac mortality rate (4.0% versus 0%), whereas recurrent MI and unplanned revascularization rates were, again, higher among patients with obstructive atherosclerosis.

**NSTE-ACS With No Obstructive Atherosclerosis: Not a Single Disease**

The study by Planer et al10 lends further support to the notion that patients admitted with a diagnosis of NSTE-ACS, but showing no obstructive atherosclerosis, present a relevant incidence of adverse clinical events during follow-up. Mortality, in particular, was even higher in this study than in a previous report of patients with a similar follow-up length1 and was similar to that of patients with obstructive atherosclerosis. This finding can, at least in part, be explained by the inclusion of NSTEMI patients (ie, with increased troponin levels) only, a subset previously shown to be at higher risk compared with patients without troponin rise.9

Data from the ACUITY and previous studies, therefore, clearly show that NSTE-ACS patients with no obstructive atherosclerosis represent a clinically relevant and challenging subset that should not be overlooked simply because of the lack of critical stenoses. It is obvious, however, that this subset is heterogeneous, likely including patients with different mechanisms of acute myocardial ischemia. Thus, a careful diagnostic workup is needed to establish the specific cause of the syndrome in each individual patient, which can then allow reliable risk stratification and appropriate treatment.

A first possible cause of NSTE-ACS with no obstructive atherosclerosis that deserves careful attention is epicardial coronary artery spasm, in particular, in patients who present with transient ST-segment–elevation, an accepted hallmark of variant angina.11 Untreated, recurrent spasm may result in arrhythmic sudden death, myocardial infarction, or recurrent angina, which can usually be fully prevented by appropriate calcium-antagonist therapy.12 In the majority of patients, clinical and ECG findings allow establishment of the diagnosis of coronary spasm, while provocative tests (by ergonovine or acetylcholine) can be utilized in doubtful cases. Unfortunately, the proportion of patients presenting with transient ST-segment–elevation in Planer’s studies is not reported.10

In another subset of patients, NSTEMI might be related to coronary microvascular constriction or spasm.13 This diagnosis can be suggested by the evidence of slow coronary flow at angiography14 and proved by the induction of typical angina and ST-segment changes, together with impaired coronary blood flow, in the absence of epicardial spasm, after intracoronary administration of acetylcholine or other vasoconstrictor stimuli.15 Outcome data in this specific subset of patients are lacking, whereas vasodilator therapy might prevent ACS recurrence. Importantly, intense coronary microvascular constriction is the likely cause of tako-tsubo (apical ballooning) syndrome,16 a clinical syndrome with a usual good prognosis.17 Of note, in Planer’s study, 16 patients (8.1%) among those with no obstructive atherosclerosis were eventually diagnosed with a tako-tsubo syndrome, and none had adverse clinical events during follow-up.10 The diagnosis of tako-tsubo syndrome can easily be achieved by performing left ventriculography at the time of coronary angiography.

Transient thrombosis associated with distal embolism is another possible cause of ACS without obstructive atherosclerosis. This is more likely to occur in patients with nonsignificant stenoses, rather than in those with angiographically normal coronary arteries. Acute thrombosis can indeed occur at the level of subcritical complicated stenosis,17 whereas this is less likely in normal coronary arteries. Remarkably, in a revision of data from clinical trials of NSTE-ACS patients,7 1-year mortality was 1.6% in patients with subcritical stenosis, but 0.6% only in those with angiographically normal coronary arteries, and similar rates were observed for acute
myocardial infarction. Unfortunately, Planer et al10 do not provide data on the prevalence of patients with nonsignificant stenoses or angiographically normal coronary arteries in their study. Patients with a thromboembolic cause of NSTE-ACS can efficiently be identified by intracoronary vascular ultrasound or, better, optical coherence tomography at the time of coronary angiography.17,18 Importantly, an appropriate anti-thrombotic therapy is likely to improve clinical outcomes in this subset of patients.

An NSTE-ACS presentation in the absence of obstructive atherosclerosis can also be related to a considerable sustained increase of myocardial oxygen consumption, which cannot be fully met by coronary blood flow increase. Thus, atrial fibrillation with high ventricular rate can be associated with chest pain and troponin rise in patients with no obstructive atherosclerosis,19 an event that may occur, in particular, in patients with subclinical cardiomyopathy, left ventricular hypertrophy, or diabetes mellitus, all conditions characterized by coronary microvascular dysfunction. Atrial fibrillation by itself can present an ominous prognosis, in particular, when occurring in patients with cardiovascular or systemic disease.

A nonischemic cardiac cause of acute chest pain should also carefully be considered in patients presenting with NSTE-ACS but showing no obstructive atherosclerosis. Indeed, myocarditis may have an infarction-like presentation.20 Of note, myocardial ischemia can also be present in some cases of myocarditis as a result of coronary microvascular involvement, as in the case of parvovirus B19 myocarditis.21 Unrecognized myocarditis might evolve toward heart failure or be complicated by life-threatening arrhythmias. Cardiac magnetic resonance allows its diagnosis, while specific therapies remain questionable.

A final important point to be considered when assessing outcomes of NSTE-ACS patients with no obstructive atherosclerosis emerges from the study by Planer et al10 and concerns the high proportion of noncardiac death found among these patients. Of note, most of these deaths occurred within 2 months of clinical presentation. Renal failure, pulmonary failure, hematologic diseases, subclinical cancer, and noncoronary vascular disease may all contribute to clinical outcomes, and therefore their presence needs to be carefully addressed and managed to improve the outcomes of these patients. Importantly, most of these clinical conditions might favor ACSs by resulting in increased prothrombotic state or impairment of myocardial oxygen supply (eg, for severe anemia or respiratory failure) or both.

Conclusions

In conclusion, Planer et al10 have to be congratulated for this excellent study. Indeed, this is by far the largest report to date of the characteristics and prognosis of patients admitted with acute cardiac ischemic symptoms, troponin elevation, but no obstructive coronary atherosclerosis, as quantitatively evaluated by a central angiographic core laboratory. The challenge for researchers and clinicians is now to define the optimal workup for the identification of the specific cause of NSTE-ACS in the individual patient, an essential premise for an appropriate risk stratification and clinical management.

Disclosures

None.

References


Key Words: Editorials • acute coronary syndrome • non obstructive coronary artery disease • outcome
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Gaetano A. Lanza and Filippo Crea

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