Perspective

For the Patient with "Low-risk Chest Pain"—How Low Is Low?

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Patients who present to the emergency department (ED) with chest pain or other anginal-equivalent symptoms and have negative cardiac enzymes and nonischemic electrocardiograms (ECGs) are at low risk for having an acute coronary syndrome (ACS) and subsequent cardiovascular events (1). But how low is low? The answer to this question has important implications for patient safety and health policy. Here we will review the literature pertaining to this topic and highlight gaps in the current understanding.

ACS is characterized by an abrupt reduction in coronary blood flow that is most often caused by atherosclerotic plaque rupture or erosion (2,3). It is an umbrella term that now includes the conditions unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). ACS meets the criteria for myocardial infarction (MI) when there is a rise or fall in cardiac troponin (I or T), with one value exceeding the 99th percentile upper reference limit of a normal population (4). Much confusion exists regarding the possibility of missing MI, but because it is defined by abnormal troponin it cannot be missed *if* suspected and if troponin is checked at least twice over a 6-hour period after the onset of symptoms (2). Based strictly on the current definition, the risk of MI in patients with suspected ACS and negative serial troponins is 0%; however, a miss rate of 2%–5% is frequently cited (5).

More than two decades ago, Pope et al. published the most influential paper on ED miss rates for ACS (6). Using prospective registry data from 10,689 patients enrolled in the multicenter Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) trial, investigators found that 4% of patients ultimately diagnosed with ACS were missed (2% MI, 2% UA) and inappropriately discharged. Level of evidence (LOE) 2 The results of this 1993 vintage study do not apply to contemporary practice because the definition of MI has changed. Furthermore, at the time of the ACI-TIPI trial, troponin testing was not routinely performed; instead, Creatinine kinase myocardial b fraction (CKMB) was primarily used, which is far less sensitive for detecting myocardial necrosis.

In the Thrombolysis in myocardial infarction (TIMI) 3 trial, 25% of patients classified as having UA on the basis of negative serial CKMB levels had troponin I levels ≥0.4 ng/mL (the relatively insensitive cut point used in the mid-1990s), and could therefore be reclassified as having an NSTEMI (7). (LOE 2) Similarly, Hamm et al. prospectively studied a cohort of 773 patients with acute chest pain but no ST segment elevation (8). They found that in 47 patients diagnosed with NSTEMI, CKMB was elevated in only 91% 4 hours after arrival, whereas troponin I was elevated in all (8). (LOE 2) And in 315 patients diagnosed with UA, troponin I was elevated in 36% (8). These classical studies used first-generation troponin assays. Since then, the definition of MI has changed to reflect a troponin-based definition, and troponin assays have become far more sensitive.

In the TIMI 3 trial, which was performed in 1996, the cut point for defining MI was 0.4 ng/mL, whereas in the TIMI 11B trial, performed in 2000, it was 0.10 ng/mL (7,9). In 2010, the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndrome (MERLIN)-TIMI 36 trial used a cut point of 0.04 ng/mL (10). As troponin assays become more sensitive, lowered cut points for detecting myocardial necrosis have resulted in reclassifying a substantial percentage of patients previously diagnosed with UA as NSTEMI. Mills et al. reported that reducing the cut point from 0.2 to 0.05 ng/mL (the widely used current-generation assay cut point is 0.04 ng/mL) increased NSTEMI diagnoses by 27% (11) (LOE 1).

Occurring in parallel with the rise in NSTEMI diagnoses was the development of chest pain observation units, and increased use of stress tests and coronary computed tomography angiography (12). From 1999 through 2008, advanced testing in ED patients with chest pain increased by 368% (12). Initially, this practice was important for the detection of patients with UA—the kind initially described as "preinfarctional" angina in the 1970s (13). However, as troponin assay sensitivity increased and UA became increasingly reclassified as NSTEMI, a new class of UA developed. This new class of disease is defined by stress test positivity or the presence of obstructive atherosclerotic disease on coronary computed to-

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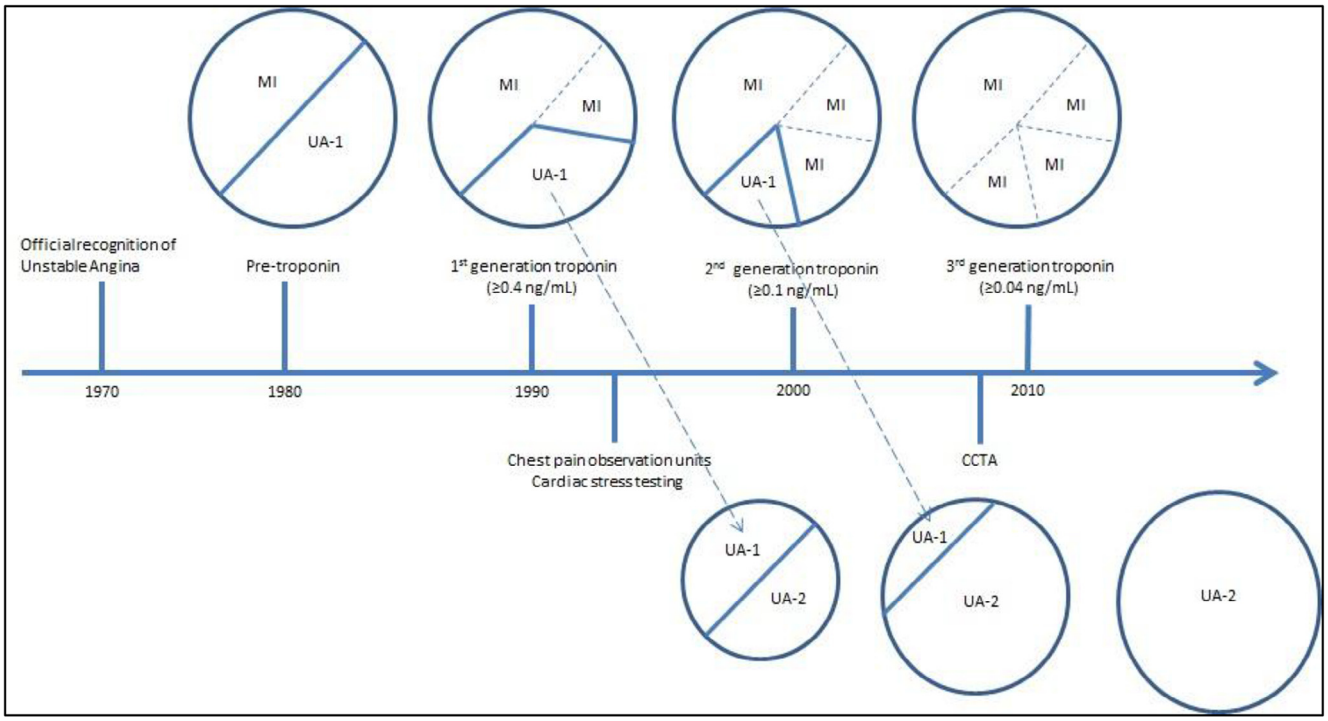

Figure 1. Evolution of the diagnosis of acute coronary syndrome.

mography angiography (CCTA). Most of these patients have atypical symptoms, nonischemic ECGs, and would *not* have been classified as UA based on its original description. Figure 1 depicts this transition graphically, with UA-1 denoting the condition as originally described and UA-2 denoting this new condition defined by cardiac imaging.

The question in EDs has now become: "For patients with negative troponins and nonischemic ECGs, how low is the risk of ACS?" As always—it depends. For MI and UA as originally defined in the 1970s, the chance is either 0% or very close to it. Using the new definition of UA, it is about 3% (LOE 1), but importantly will depend on the imaging modality used. CCTA will detect more UA than functional testing (14). The key unknown is the importance of this diagnosis. UA is no longer the "preinfarctional" angina originally described in the 1970s, and in our opinion does not represent ACS at all. And if it does not represent ACS, it is not an emergent condition. Instead there are two possibilities: One is that the diagnosis represents coronary atherosclerosis and stable angina (yearly rate of MI is 4%), or it is coronary atherosclerosis unrelated to the presenting symptom also known as overdiagnosis (15,16).

Leaders in the field of cardiovascular medicine who were responsible for developing the original definition and classification scheme for UA agree with this sentiment (17,18). In 2013, Eugene Braunwald and David Morrow called for a requiem on the diagnosis of UA and suggested ACS be composed *only* of patients with MI who meet the universal definition; everything else, they said, was stable disease (19). The caveat of course is that this does not imply that the rate of death or MI following an ED visit for suspected ACS, negative troponins, and nonischemic ECGs is 0%. In a population of asymptomatic individuals, there will be a monthly rate of spontaneous MI that is greater than 0%, and this small but finite risk will increase with age and accumulating risk factors. Using the atherosclerotic cardiovascular disease risk calculator for any 65-year-old man with high cholesterol, diabetes, hypertension that is controlled with medication, and who does not smoke, the 10-year risk of a major adverse cardiovascular event (MACE) is >40% or roughly 0.3% per month (20).

To precisely estimate the risk of MACEs following an ED or hospital admission with suspected ACS, negative troponins, and nonischemic ECGs, there would need to be either a prospective registry where patients were followed without testing for a prespecified period or a randomized controlled trial comparing stress testing or CCTA to no testing. These do not exist. That leaves making nuanced estimates from observational data and randomized trials that compared advanced testing modalities. We have chosen to divide these studies into first-generation (data acquired circa 2000), second-generation (mid-2000s), and third-generation (performed after 2010) studies to reflect the increasing sensitivity of troponin assays. The main limitations to interpreting these studies are nonuniform cohort selection and heterogeneous patient populations. For this review, we focused on patients with negative serial troponins and nonischemic ECGs. However, this criterion is not strictly met in all the studies discussed hereafter. Finally, selection bias limits interpretation of comparative studies.