

Does unstable angina still exist?

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Abstract

The term unstable angina was popularized in the 1970s to describe angina-type symptoms and signs that did not fit into the category of either stable angina or acute myocardial infarction (AMI) and evolved from the term pre-infarction angina. Unstable angina was generally used for the sudden onset of severe chest pain (or change), which was longer in duration than stable angina, occurred without precipitating events, and was not associated with persistent electrocardiogram changes or cardiac biomarker elevation indicative of AMI. The incidence of unstable angina reached a peak in the 1990s, after which use of the term decreased progressively. Some of the factors that contributed to its decreasing incidence include more sensitive cardiac biomarkers, an increasing emphasis on preventative medicine, and the advent of early invasive therapy in high-risk patients. This article reviews the evolution of the term unstable angina, describes some reasons for the decrease in the prevalence of this condition in recent years, and forecasts for discontinuing its use. It appears that patients with ischemic heart disease are now best served by simply dividing them into only two groups, either stable angina or AMI. ■ *Heart Metab.* 2018;75:15-18

Keywords: myocardial infarction; troponin; unstable angina

Introduction

Although apparent for many decades, the seeming clear distinction between stable angina and myocardial infarction (MI) began to blur in the 1930s, when Sampson et al described the presence of “pre-infarction angina” or “crescendo angina.”^{1,2} These terms were used to categorize patients with spontaneous attacks of prolonged angina-type chest discomfort occurring at rest that was associated with coronary artery thrombus formation.² At that time, this symptom was thought to result from coronary blood flow that was not sufficient to supply the resting metabolic demands of the cardiomyocytes, but sufficient enough to prevent the development of

an acute MI (AMI).³ In the 1970s, a definition of the syndrome was formulated to describe patients who fell between stable angina and AMI. This syndrome was termed unstable angina.^{4,5} Unstable angina has been defined as the relatively sudden onset (or change) of one or more angina attacks per day from a previous background of reasonably good health; in other words, a dramatic change in the symptom pattern of a patient with previously identified coronary artery disease (CAD).⁴ These angina attacks could be longer in duration than the patient’s prior stable angina, may occur at rest or at a much lower level of activity or even without a precipitating activity, and they are not associated with persistent electrocardiogram changes or cardiac biomarker

Abbreviations

AMI: acute myocardial infarction; **CAD:** coronary artery disease; **CK-MB:** creatinine kinase–myoglobin isoenzyme; **cTnT:** cardiac troponin T; **cTnI:** cardiac troponin I; **IHD:** ischemic heart disease; **MI:** myocardial infarction; **NSTEMI:** non–ST-segment elevation myocardial infarction

elevation indicative of AMI.

In the decades following the popularization of the term “unstable angina,” there was an exponential increase in the diagnosis of this syndrome.⁶ However, with this increasing incidence, our understanding of the syndrome advanced. In a prospective study of patients with pre-infarction angina who were followed for 10 years, only about 1 in 5 actually developed an AMI within 8 months of the diagnosis.⁷ In another retrospective study of patients with an AMI, only a little more than a third described a pattern of unstable angina in the month prior to the AMI.⁸ Thus, it became clear that most patients with unstable angina did not develop an AMI later on, as has been the prevailing notion. Unstable angina may precede an AMI, may follow an AMI, or may neither precede nor follow an AMI and be the sole manifestation of ischemic heart disease (IHD).

Cardiac biomarker elevations, or lack thereof, played an essential role in the evaluation of the diagnosis of unstable angina. In the 1980s, the transition in practice to the use of the creatinine kinase–myoglobin isoenzyme (CK-MB), a more sensitive and specific cardiac biomarker when compared with lactate dehydrogenase and aspartate transaminase, led to an increase in the recognition of AMI.⁹ Similarly, in the 1990s, the development of cardiac-specific troponin T (cTnT) and I (cTnI) immunoassays for the detection of AMI showed improved sensitivity and specificity vs CK-MB, which, again, contributed to an increase in the diagnosis of AMI.¹⁰ Since then, high-sensitivity cTnT or cTnI assays have been developed that measure troponin values 10- to 100-fold lower than previous assays.¹¹ The remarkable development of cardiac biomarker assays for the detection of myocardial injury over the past 40 years has allowed for a more accurate diagnosis of non–ST-segment elevation myocardial infarction (NSTEMI), which would otherwise have been labeled as unstable angina.¹² This diagnosis capability is another important factor that has

contributed to an apparent decrease in the incidence of unstable angina.

However, while high-sensitivity troponin remains an appropriate test for individuals with suspected acute ischemic myocardial injury, the higher sensitivity of this test has resulted in decreased specificity in some situations, such as postprocedural AMI. The Third Universal definition of myocardial infarction emphasizes the routine monitoring of cardiac biomarkers in high-risk patients both prior to and 48 to 72 hours after major noncardiac surgery.¹³ However, it is worth noting that up to 45% of patients in this setting have elevated high-sensitivity troponin levels and up to 22% of patients have an elevated level with a rising pattern. In these patients, close clinical monitoring and judgment is warranted. It is also important to understand that, as with all markers of cardiomyocyte injury, cTnT and cTnI elevations do not necessarily indicate an ischemic mechanism. Other disorders may be associated with these elevations (eg, contusion, ablation, pacing, severe hypertension, heart failure, pulmonary embolism, myocarditis, renal failure, etc).

In addition to the improvement in cardiac biomarkers, there has been an increasing emphasis on preventative medicine over the past 40 years. This emphasis has resulted in progressive reductions in blood pressure, tobacco use, and cholesterol levels, which have contributed to the reduced incidence of IHD-related adverse outcomes via risk factor modification. Considerable emphasis has been placed on the improved management of hypertension, diabetes, cholesterol, and smoking.¹⁴ For example, in the 4S trial (Scandinavian Simvastatin Survival Study), patients with angina pectoris or a previous myocardial infarction and elevated cholesterol levels were randomized to either simvastatin or placebo.¹⁵ At 5.4 years, patients who were assigned to simvastatin had a 30% lower relative risk of death ($P=0.003$), a 34% lower relative risk of major coronary events ($P=0.00001$), and a 37% reduction in the risk of myocardial revascularization ($P=0.00001$). Likewise, in the ASCOT-LLA trial (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm), in hypertensive patients, atorvastatin 10 mg daily resulted in a 36% reduction in the risk of fatal and nonfatal MI at a median of only 3.3 years.¹⁶ Similarly, additional studies have confirmed the reduction in AMI and mortality associated with smoking cessation.¹⁷⁻¹⁹ One mechanism by which these preventative measures have been pro-

posed to lead to decreased ischemic events is via the transformation of vulnerable atherosclerotic plaques to more stable plaques.¹² Major plaque ruptures appear to have been replaced by only minor erosions. This mechanism has been proposed, at least in part, for the reduction in STEMI, with an increase in NSTEMI.²⁰ Parallel to these changes, there has also been a reduction in the incidence of unstable angina.

Furthermore, many, if not most, patients with unstable angina and high-risk features are now likely to undergo early invasive therapy, which has the potential to reduce the incidence of ischemia-related adverse outcomes, such as death or MI.²¹⁻²⁴ In an updated meta-analysis of 12 trials with almost 10 000 patients treated with stents and adenosine diphosphate antagonists, a routine invasive strategy was associated with a reduction in the risk of death or MI (predominantly due to a reduction in the risk of MI) at 39 months.²⁴ This benefit has been noted even in the subgroups in which an early invasive strategy has been previously thought to be harmful, such as in women.²⁵ Additionally, with the development of improved noninvasive methods for detecting high-risk CAD, such as pharmacological stress tests, computed tomography of coronary arteries, and cardiac magnetic resonance angiography, there has been a rise in the earlier diagnosis and management of CAD with the potential to reduce ischemia-related outcomes.²⁶

Given the expected continued decrease in unstable angina over the next several years, and its lack of significant association with AMI, its inclusion as an “event” in trials as a 4-item outcome (death, AMI, stroke, or hospitalization for unstable angina) has recently been questioned.²⁷ Inclusion of unstable

angina in such a composite outcome could lower the prognostic relevance and potentially favor a shift in the hazard ratio toward the null.

Conclusions

In summary, the diagnosis of unstable angina reached its peak in the 1990s. Advances in the detection of previously subclinical AMI with more sensitive cardiac biomarkers, an increased emphasis on preventative medicine, and perhaps the adoption of an early invasive strategy for the management of patients with acute IHD at a high risk of adverse outcomes have contributed to this marked reduction in the prevalence of unstable angina. Over the next several years, some might argue that this syndrome might need to be renamed as an intermediate syndrome between stable angina and AMI. Our group and others have opined that the taxonomy for IHD needs a major revision (*Figure 1*).²⁸ ■

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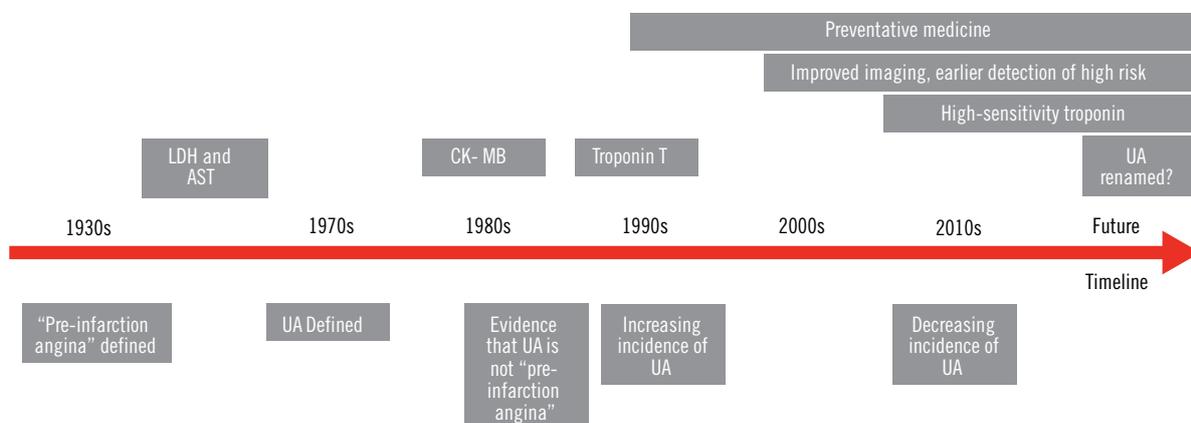


Fig. 1 Evolution of unstable angina.

Abbreviations: LDH, lactate dehydrogenase; AST, aspartate aminotransferase; CK-MB, creatinine kinase-myoglobin isoenzyme; UA, unstable angina.

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