

A Classification of Unstable Angina Revisited

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Abstract—Unstable angina is a critical phase of coronary heart disease with widely variable symptoms and prognosis. A decade ago, a classification of unstable angina based on clinical symptoms was introduced. This system was then validated by prospective clinical studies to correlate with the prognosis and was linked to angiographic and histological findings. It has been used to categorize patients in many large clinical trials. In recent years, the pathophysiological roles of platelet activation and inflammation in unstable angina have been elucidated. Subsequently, improved markers of myocardial injury, acute-phase proteins, and hemostatic markers that may be associated with clinical outcomes have been identified. Particularly, cardiac-specific troponin T and troponin I have been shown to represent the best predictors of early risk in patients with angina at rest. Accordingly, it is suggested that the original classification be extended by subclassifying one large group of unstable angina patients, ie, those with angina at rest within the past 48 hours (class IIIB), into troponin-positive (T_{pos}) and troponin-negative (T_{neg}) patients. The 30-days risk for death and myocardial infarction is considered to be up to 20% in class IIIB- T_{pos} but <2% in class IIIB- T_{neg} patients. Initial results suggest that troponins may function as surrogate markers for thrombus formation and can effectively guide therapy with glycoprotein IIb/IIIa antagonists or low-molecular-weight heparins. These observations provide additional impetus for adding the measurement of these markers to the clinical classification and represent a novel concept of treating these high-risk patients. (*Circulation*. 2000;102:118-122.)

Key words: angina ■ atherosclerosis ■ coronary disease ■ myocardial infarction ■ prognosis

It has long been recognized that coronary artery disease comprises a wide spectrum of conditions, ranging from chronic stable angina to acute myocardial infarction. Unstable angina, in the middle of this spectrum is a heterogeneous syndrome with widely variable symptoms and prognosis. In 1989, a classification of unstable angina was introduced¹; this classification is based on the clinical history (accelerated exertional angina or rest pain, the timing of the latter in respect to presentation, and the clinical circumstances in which unstable angina developed), on the presence or absence of ECG changes, and on the intensity of anti-ischemic therapy.

Although the development of this classification was based on clinical experience, it has been validated in a number of prospective studies. For example, Calvin et al² studied 393 patients with unstable angina and reported that a history of a myocardial infarction within 14 days (class C) and ST-segment depression on the presenting ECG were both markers of increased risk. Miltenburg-van Zijl et al³ classified 417 patients with unstable angina and followed them up for 6 months. Death or myocardial infarction occurred more frequently in those with recent rest pain (class III) and in postinfarction patients (class C). The presence of ECG changes and the need for maximal antianginal therapy were also independent risk factors. A high unstable angina class (IIIB or IIIC) led to a high rate of coronary revascularization.⁴

A correlation between clinical class and coronary anatomy has also been described. Thus, Ahmed et al⁵ reported that an “unstable angina score” based on the clinical classification was the most important predictor of intracoronary thrombus and lesion complexity. Danges et al⁶ found that both classes III and C were associated with complex culprit artery lesions and reduced TIMI flow. De Servi et al⁷ reported that patients with recent onset or worsening angina without rest pain (class IB) had calcified lesions more frequently than did patients with angina at rest (classes IIB and IIIB), whereas the latter showed thrombus or intraplaque hemorrhage on angiography more frequently than did the former. In a histological study of arterial plaques obtained by directional atherectomy, a strong correlation was observed between unstable angina class and the histological structure of the culprit coronary lesion with high cellularity, thrombus, and abundant neovessels in patients with higher classes of unstable angina (IIC, IIIB, and IIIC).⁸ Rupprecht et al⁹ reported that the incidence of the angiographic evidence of complex lesions and/or thrombosis rose progressively with higher unstable angina classes. Owa et al¹⁰ found that unstable angina class III was associated with both a higher incidence of coronary thrombi on angiography and an increased risk of clinical progression to myocardial infarction.

The 1989 classification has been used extensively in major trials to describe patients with unstable angina undergoing a

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variety of diagnostic and therapeutic investigations and interventions.^{11–16} It also provided the definition used in the Unstable Angina Guidelines.¹⁷ Since the introduction of this classification, considerable progress has been made in understanding the pathophysiology of unstable angina and treatment of this condition. It therefore appears appropriate to “revisit” the original classification 1 decade after its initial presentation.

New Pathophysiological Insights

Five different although not mutually exclusive causes of unstable angina are now recognized.¹⁸ These are (1) a nonocclusive thrombus on a preexisting plaque, (2) dynamic obstruction, (3) progressive mechanical obstruction, (4) inflammation, and (5) secondary unstable angina. Most frequently, unstable angina is caused by coronary plaques that have undergone repeated phases of disruption and repair.⁸ Evidence is accumulating that thrombus formation and/or inflammatory mechanisms play key pathogenetic roles in these processes, and as pointed out above, the histological features of instability, ie, mononuclear cells infiltrating the plaque and thrombus, correlate with the clinical severity of unstable angina.⁷ The plaque morphology in patients with higher grades of unstable angina is similar to that in patients with myocardial infarction, whereas in patients with lower grades of unstable angina, the plaque morphology is similar to that in patients with stable angina.

It is now recognized that plaque disruption or erosion represents the final step in the pathogenetic cascade inducing tissue factor–mediated platelet activation.^{19,20} The resultant thrombus causes partial or transient total occlusion of the culprit artery. The severity, duration, and extent of the resultant myocardial ischemia determine the clinical presentation: Q-wave infarction, non-Q-wave infarction, or unstable angina.

Angioscopic studies have revealed that the thrombus responsible for unstable angina is more commonly white (platelet rich) and less likely red (fibrin rich), whereas the latter tends to be more prominent in acute myocardial infarction.²¹ Pathological studies in patients with unstable angina who died suddenly have demonstrated that the fatal event is often preceded by repetitive embolization of thrombi from an unstable atheroma.^{22,23} This results in focal myocardial necroses that are not large enough to be detected by creatine kinase or creatine kinase-MB measurements. The detection of this so called “minor myocardial injury”²⁴ in unstable angina may therefore reflect the presence of an unstable plaque containing platelet-rich thrombus in the proximal coronary artery and can be detected by measurement of serum cardiac troponin I or troponin T as surrogate markers for thrombus formation. Elevated troponins have been found in approximately one third of patients with unstable angina at rest (class IIIB)^{25,26} but in only 10% of patients in class I.²⁷ Differences between studies are explained by varying inclusion criteria, time, and frequency of blood sampling and the use of assays of different sensitivity.^{28–36}

The role of inflammation in patients with unstable angina and myocardial infarction is supported by the frequent pres-

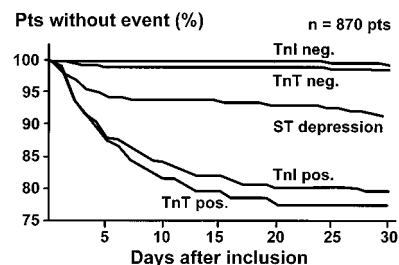


Figure 1. Risk of patients with acute chest pain according to troponin status and ECG (ST-segment depression) during 30 days of follow-up. Pts indicates patients; Tnl, troponin I; neg, negative; TnT, troponin; and pos, positive. Modified from Reference 31.

ence of elevations of circulating acute-phase reactants, such as C-reactive protein and fibrinogen.^{37–40} The presence of these acute-phase reactants in asymptomatic persons and in survivors of myocardial infarction has also been shown to be an independent long-term risk factor for adverse outcomes.⁴¹ These findings suggest that inflammation not only is an acute response to the underlying disease but is an integral component of it.

Risk Stratification

Major efforts in patients with unstable angina are directed at identifying patients at high risk of adverse outcome and subsequently to institute measures to improve the prognosis. ECG findings in unstable angina are quite variable. ST-segment depression was found to be present in one third of patients in the TIMI IIIB trial⁴² and the TIMI III Registry.⁴³ T-wave inversion was found in about one half, whereas one fourth of patients with unstable angina present with normal ECGs. However, only ST-segment depression (not T-wave inversion) has been found to be an independent risk factor for adverse outcome.⁴² Similarly, ST-segment alterations detected by continuous ST-segment monitoring have been found to be predictive of higher cardiac event rates.^{44–46} However, the fact that patients without ECG changes or T-wave inversions do have a considerable risk of $\approx 4\%$ mortality in 42 days demonstrates the limitations.⁴² Therefore, better prognostic markers are mandatory.

Cardiac-specific troponins were shown to be powerful independent predictors of future cardiac events in patients with unstable angina.^{25–36} Their superiority over the ECG as prognostic markers is confirmed by both prospective and retrospective analyses (Figure 1). The risk for myocardial infarction and death increases with increasing serum troponin concentrations and may be 20% in 30 days and 25% within 6 months in patients with the highest troponin levels.^{30,31}

In contrast to troponins, which are markers of cellular necrosis often secondary to plaque embolization, acute-phase reactants may function as indicators of risk by reflecting the underlying inflammatory process in patients with unstable angina. Among these, C-reactive protein and fibrinogen have attracted the greatest attention; the prognostic value of these markers with respect to mortality and ischemic cardiac events has been clearly established.^{37–41} Their prognostic value has been shown in retrospective analyses to be independent and probably additive to troponin T.^{37,40} C-reactive protein has

TABLE 1. Classification of Unstable Angina

Severity	Clinical Circumstances		
	A—Develops in Presence of Extracardiac Condition That Intensifies Myocardial Ischemia (Secondary UA)	B—Develops in Absence of Extracardiac Condition (Primary UA)	C—Develops Within 2 wk of AMI (Postinfarction UA)
I—New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II—Angina at rest within past month but not within preceding 48 h (angina at rest, subacute)	IIA	IIB	IIC
III—Angina at rest within 48 h (angina at rest, acute)	IIIA	IIIB-T _{neg} IIIB-T _{pos}	IIIC

UA indicates unstable angina; AMI, acute myocardial infarction.

been shown to be a good long-term prognostic marker in coronary heart disease, but its value in the acute phase is controversial.⁴⁷

A New Subclassification

The major goals of developing the clinical classification¹ in 1989 were to assess risk and to select patients for therapy and clinical trials. At that time, assays for the cardiac-specific troponins were not yet available. During the past decade, it has become apparent that unstable angina with rest pain occurring within 48 hours without a recent myocardial infarction (class IIIB) is a very frequent condition and is, in turn, made up of subgroups of patients at various risks. Within class IIIB, cardiac-specific troponins T and I, C-reactive protein, and fibrinogen allow differentiation between high-risk and low-risk patients. Although a combination of markers may represent the optimal risk assessment, in daily practice, this process must be simple, rapid, and reliable. An assessment of serum troponin can be made quantitatively with tests based on monoclonal antibodies or qualitatively within 15 to 20 minutes at the bedside with a “point of care” handheld device^{48–50} with no laboratory facilities needed.

We suggest that unstable angina class IIIB patients now be subdivided into troponin-positive (T_{pos}) and troponin-negative (T_{neg}) subgroups (Table 1). The risk of cardiac death or myocardial infarction within 1 month in class IIIB T_{pos} patients is estimated to be 15% to 20%. Class IIIB T_{neg} patients have a far better prognosis, with cardiac death or myocardial infarction within 1 month of <2% (Table 2). It should be noted that a single negative determination of troponin at the time of presentation is inadequate for risk stratification (Figure 2). A minimum of 2 measurements with the last obtained at least 6 hours after the episode of pain is

TABLE 2. Risk of Death and Myocardial Infarction

Braunwald Class IIIB	Risk, %		
	24 h, %	30 Days, %	6 mo, %
T _{pos}	5	15–20	25
T _{neg}	<1	<2	<5

necessary to rule out minor myocardial damage.³¹ Tests may be repeated when the clinical presentation remains highly suspect for an acute coronary syndrome. Negative test results do not exclude coronary heart disease but rule out a high-risk state. ECG-documented ST-segment depression, C-reactive protein, and a positive stress test can provide additive information.^{29,40,51} After acute myocardial infarction, troponins may be elevated for >10 days, which precludes their use in postinfarction angina (class C).⁵²

Troponins T and I have similar prognostic power. Differences between these markers relate largely to the analytical performances of the assays used. Only 1 troponin T assay is available, whereas several different troponin I assays with different analytical characteristics have been introduced,^{53–57} making comparisons between the 2 troponins difficult. False-positive elevations of troponins are only very rarely observed in patients with chronic renal failure; elevation of troponin in the absence of coronary heart disease may occur in patients with myocarditis, pulmonary embolism, and acute heart failure.^{58–60}

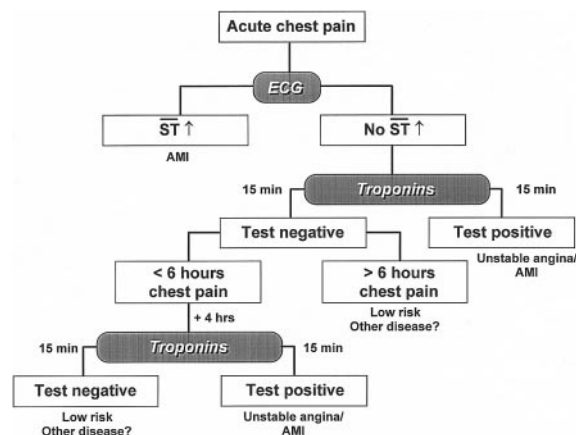


Figure 2. Algorithm to risk stratify patients with unstable angina based on ECG and repeated troponin measurements. If ST-segment elevation is excluded, serial testing for troponin allows identification of subgroups with different risk. AMI indicates acute myocardial infarction.

Implications

Therapeutic options in unstable coronary syndromes other than acute myocardial infarction with ST-segment elevation have not been satisfactory.¹⁷ Troponins may serve as surrogate markers for unstable atherosclerotic plaques and consequent microembolization, causing minor myocardial damage. The availability of new antithrombotic drugs, such as low-molecular-weight heparin and glycoprotein IIb/IIIa receptor antagonists, provides new therapeutic opportunities. It has been demonstrated that these agents improve clinical outcome in troponin-positive patients with unstable angina, with little if any effect in troponin-negative patients.^{26,61,62} These observations provide additional impetus for adding the measurement of these markers to the clinical classification and provide a novel concept of treating these high-risk patients in the future.

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