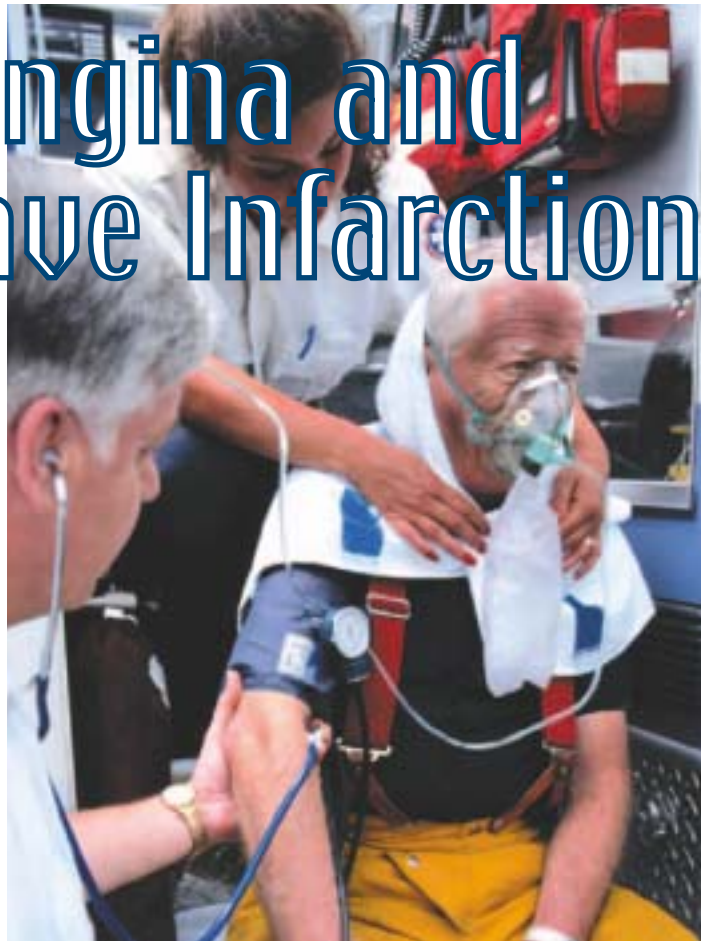
Unstable Angina and Non–Q-Wave Infarction



By Eric Demeule, MD, FRCPC

The treatment of unstable angina and non–Q-wave infarction (subendocardial infarction) has changed radically within the past two years. Even the nomenclature has changed. The term non-ST-segment elevation acute coronary syndrome (ACS) is now used to refer to unstable angina and non–Q-wave infarction, as the physiopathology (coronary thrombus) is identical. From a therapeutic perspective, we have seen the introduction of low-molecular-weight heparins (LMWHs), the use of glycoprotein IIb/IIIa inhibitors and a new antiplatelet drug, clopidogrel. Testing on selected target groups has demonstrated that all of these treatments have a clinical advantage over standard treatments. Even markers of myocardial lesions have become more precise with the widespread use of cardiac troponins. In this article, we will present a simple and rational way of implementing this new therapeutic arsenal in the emergency room (ER).

Standard Antithrombotic Treatment

The benefits of using acetylsalicylic acid (ASA) and heparin in the treatment of thrombosis in cases of unstable angina have been clearly established for more than a decade. The use of these agents results in a decrease of approximately 50% in mortality and infarction in the first few months. Such treatment is common practice and is included in the recommendations of various cardiology associations. It is evidently only beneficial, however, for patients with no apparent high risk of hemorrhaging. Considering the significance of the thrombotic process in the physiopathology of acute coronary syndrome, it is not surprising to see an increase in the use of antithrombotic agents.

Low-Molecular-Weight Heparins

Two low-molecular-weight heparins (LMWHs) are currently available in Canada for the treat-

ment of unstable angina: dalteparin and enoxaparin. Dalteparin has been demonstrated to be an effective unfractionated heparin in the treatment of unstable angina. As for enoxaparin, various ACS studies have shown that it consistently tends to reduce infarctions and refractory ischemia. A meta-analysis of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial and the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) trial, which studied more than 7,000 patients, showed an 18% reduction (1.5% in absolute terms) in the combined outcome of infarction and death at one month.[1] This is an advantage over standard treatment (heparin IV), even in the treatment of coronary patients with no increase in troponins. Considering the therapeutic advantage, ease of administration and pharmacodynamic benefits, enoxaparin is now recognized as superior to unfractionated heparin in the treatment of patients with unstable angina. Moreover, there is a body of evidence supporting the safety of enoxaparin used in combination with glycoprotein IIb/IIIa inhibitors.

Summary

Angina & Non-Q-Wave Infarction

- Glycoprotein IIb/IIIa inhibitors are the most potent antiplatelet agents, as they intervene in the final common pathway for platelet aggregation.
- Risk stratification should be used to determine the appropriate antithrombotic treatment.
- Since it is essential to treat not only the ACS patient's thrombosis, but also ischemia, it is important to administer anti-ischemic agents, such as beta-blockers and nitrates, along with the antithrombotic treatment.

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CURE: A Landmark Study

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial compared clopidogrel plus ASA to ASA alone in 12,562 ACS patients with ECG changes or positive troponin results.[2] This combination of antiplatelet drugs, which inhibit platelet activation by two different mechanisms and are administered orally for nine months, has shown an approximately 20% reduction (2.1% in absolute terms) in the risk of mortality, infarction and stroke, as compared with standard treatment with ASA. This benefit became apparent as quickly as two hours after treatment was initiated. With the combined use of ASA and clopidogrel, however, an increase in major hemorrhaging occurred in approximately 1% of the patients. A significant increase in hemorrhaging following cardiac surgery was noted if clopidogrel was not discontinued five days prior to surgery.

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors are the most potent antiplatelet agents, as they intervene in the final common pathway for platelet aggregation. It has been demonstrated that glycoprotein IIb/IIIa inhibitors administered intravenously reduce complications in ACS patients undergoing coronary angioplasty.[3,4] The benefits in terms of reduced mortality and risk of infarction in those patients is between 20% and 30% (an

Table 1

Variables in the TIMI Risk Score

• Age ≥ 65 years
• ≥ 3 cardiovascular risk factors
• (Documented coronary stenosis > 50%) Known CAD
• ASA use in the previous seven days
• Two or more episodes of angina in 24 hours
• ST-segment deviation > 0.5 mm
• Elevated cardiac markers (troponins)

Table 2

Additional High-Risk Markers

• Heart failure
• Hypotension
• ST-segment depression ≥ 2 mm
• Significant T-wave inversion in five or more ECG leads.

absolute difference of 3%). The benefits of using glycoprotein IIb/IIIa inhibitors in non-angioplasty patients are less significant, however, with respect to reducing infarction and mortality, the benefits are less than 5% (under 1% in absolute terms). The use of glycoprotein IIb/IIIa inhibitors is, therefore, appropriate for high-risk patients and patients who are about to undergo coronary angioplasty. The use of oral glycoprotein IIb/IIIa inhibitors has no proven benefits.[5]

The Use Of Risk Stratification In Determining Appropriate Treatment

In light of the therapeutic arsenal we have at our disposal, it is important that we make appropriate choices in treating ER patients. We must consider the risk of hemorrhaging, as well as the benefits and costs involved in each treatment. High-risk

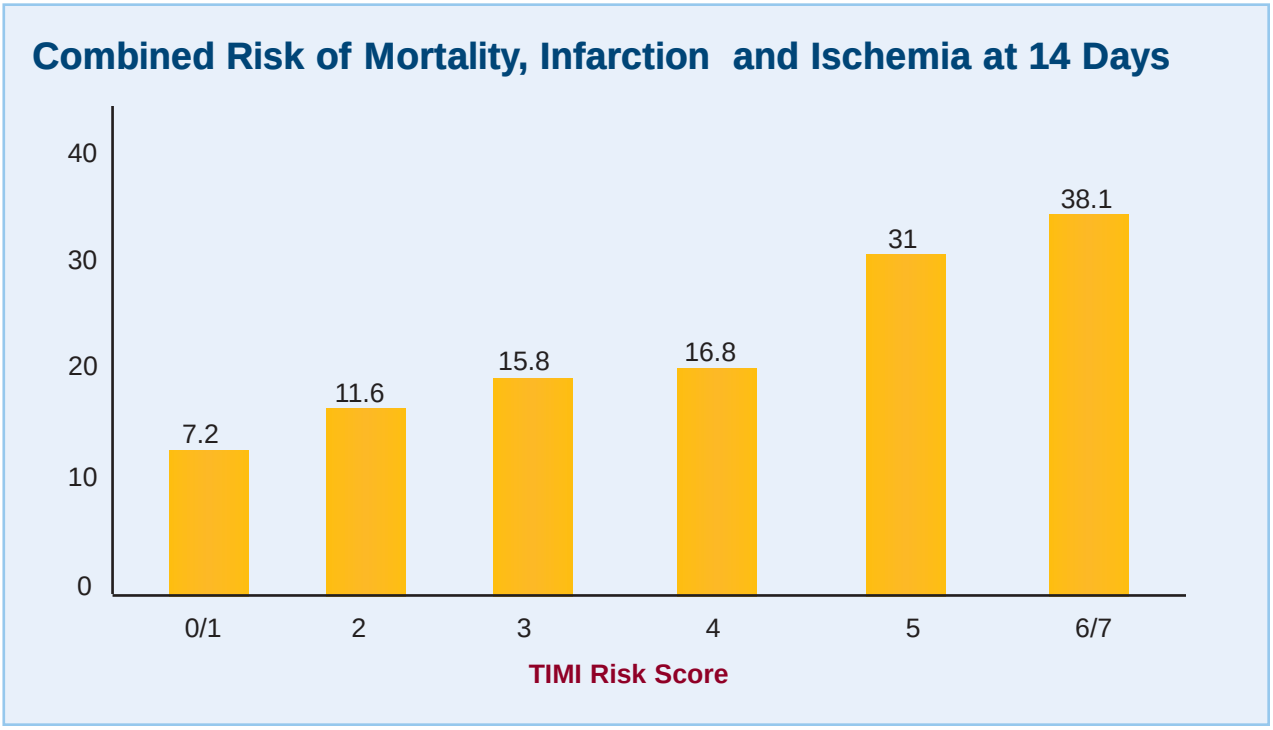

Figure 1. Combined risk of mortality, infarction and refractory ischemia at 14 days according to the TIMI risk score in patients who underwent standard treatment in the ESSENCE trial.
Adapted from Antman ME: The TIMI risk score for unstable angina/non ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000; 284:835-42.

patients are clearly those who stand to benefit the most from such treatments.

With this perspective in mind, various authors have proposed risk-stratification tools. We shall examine two that allow for easy risk assessment of emergency patients.

Antman and the TIMI group developed a risk score made up of seven variables that are easily assessed in the ER.[6] It is valid for patients with unstable angina and can be used to determine the combined risk of mortality, infarction and refractory ischemia at 14 days. The seven variables that make up the TIMI risk score are listed in Table 1. Scoring simply involves adding up the number of TIMI risk factors present. The total will be in the range of 0 to 7, serving as a proportional indicator of the risk of mortality, infarction and refractory ischemia. Figure 1 illustrates the correlation between the number of TIMI risk factors and the combined risk of death, infarction and refractory ischemia at 14 days in patients who underwent standard treatment (heparin IV) in the ESSENCE trial.[6]

The TIMI risk score is very useful. It provides a simple means of assessing patient risk in the ER, however, it overlooks some significant high-risk markers.

Fitchett also published a risk-stratification scale for patients with unstable angina.[7] It specifically outlines high risk in connection with heart failure or hypotension in ACS patients. It also identifies severe changes in ECG results as

prognosis indicators (*i.e.*, an ST-segment depression of 2 mm or more or a clear T-wave inversion in five or more ECG leads). It would be important, therefore, to add these risk-stratification factors to the TIMI risk indicators. Table 2 lists the additional high-risk markers proposed by Fitchett.

Antithrombotic Agents and Patient Risk

Patients with unstable angina, but without any high-risk factors, will likely benefit from ASA. High-risk patients, as identified by a TIMI risk score of 5 to 7, or those who show hemodynamic instability (hypotension/heart failure) would benefit, however, from aggressive treatment with a combination of ASA, enoxaparin, clopidogrel, a glycoprotein IIb/IIIa inhibitor and early cardiac catheterization.[8]

Intermediate-risk patients, such as those with a history of coronary disease, but with no other high-risk factors, would benefit from treatment with ASA in conjunction with enoxaparin. Patients with positive troponin results or moderate changes in ECG results, but with no other high-risk factors, would benefit from a combination of ASA, enoxaparin and clopidogrel.

Table 3 provides simple guidelines for the use of antithrombotic agents in treating ACS patients. The table takes into account the available risk scales. A cumulative approach is suggested as patient risk increases. Patients are stratified in four risk groups, with a suggested treatment strategy for each.

Table 4 lists the recommended dosage for each of the commonly used antithrombotic agents.

Discussion

The proposed therapeutic guidelines are intended to be straightforward and easily applied in an emergency situation. A cumulative (pyramid) approach is favoured, therefore, according to the level of risk. Clinicians must adjust their approach according to the comorbidity factors presented by each patient, especially those at risk of hemorrhaging.

Clopidogrel must be discontinued at least five days before surgery in order to avoid an elevated risk of hemorrhaging.

Since it is essential to treat not only the ACS patient's thrombosis, but also ischemia, it is important to administer anti-

Table 3

Therapeutic Guidelines for Antithrombotic Agents

	ASA	Enoxaparin	Clopidogrel	Glycoprotein IIb/IIIa inhibitors and catheterization**
Possible unstable angina	+*			
History of heart disease	+	+		
Positive troponin or ECG change	+	+	+	
5 to 7 TIMI risk factors or high-risk markers	+	+	+‡	+

* +/- Unfractionated heparin or enoxaparin.
** Early cardiac catheterization recommended in combination with treatment.
‡ Discontinuation of clopidogrel recommended at least five days before surgery.

Table 4

Recommended Dosage of Antithrombotic Agents

Agent	Loading Dose	Maintenance Dose
ASA	160 mg to 325 mg po	80 mg to 160 mg po daily
Clopidogrel	300 mg po	75 mg po daily
Enoxaparin	30 mg IV (optional)	1 mg/kg sc q 12 hours
Tirofiban0.4 µg/kg/min. IV x 30 min Glycoprotein IIb/IIIa inhibitor		0.1 µg/kg/min. IV for 48 to 72 hours
Eptibatide Glycoprotein IIb/IIIa inhibitor	180 µg/kg bolus IV	2.0 µg/kg/min. IV for 72 to 96 hours

po = by mouth; IV = intravenous; sc = subcutaneous; q = every

ischemic agents, such as beta-blockers and nitrates, along with the antithrombotic treatment.

Treatment also must be adapted as the patient's condition evolves. Consider that a patient who presents with refractory ischemia at the time of treatment is also a high-risk patient.

Unfortunately, despite all our efforts, certain patients with unstable angina may suffer a transmural infarction (with ST-segment elevation) while undergoing treatment. If the patient is on glycoprotein IIb/IIIa inhibitors, it is suggested that the clinician proceed with reperfusion using an emergency catheter (if available) or a half-

dose of a thrombolytic, such as r-TPA or tenecteplase, in order to reduce the risk of hemorrhaging. If the patient is simply being treated with enoxaparin, however, standard thrombolysis, while pursuing treatment with enoxaparin, would be a very safe option.

Conclusion

While treatment options are increasing and improving constantly, each patient is unique, and the treatment of unstable angina continues to be a challenge for the clinician. We are now able to better target our interventions using risk-stratification tools and, indeed, we must use the means at our disposal. CME

References

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