Special Article

Management Strategies for a Better Outcome in Unstable Coronary Artery Disease

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Summary: Unstable coronary artery disease is a term encompassing both unstable angina and non-Q-wave (non-ST-segment elevation) myocardial infarction. Patients with these conditions are at risk of early progression to acute myocardial infarction and death. Thus, management of these conditions must aim to reduce long-term mortality and morbidity. Risk stratification is crucial for the identification of patients whose risk of early progression is high; they may require coronary angiography and (if suitable) either percutaneous transluminal coronary angioplasty or coronary artery bypass surgery. No single variable can accurately predict risk, but considerable data are emerging to show that biochemical markers of myocardial injury, such as troponin-T and troponin-I, are valuable in combination with electrocardiographic findings and clinical features. Routine early invasive procedures (coronary angiography with or without revascularization) have not yet been shown to have any significant advantage over conservative regimens for the majority of patients. Antiplatelet, anticoagulant, and anti-ischemic agents remain the mainstay of treatment in the acute phase. New agents, such as glycoprotein IIb/IIIa receptor inhibitors and low-molecular-weight heparins,

as well as antithrombins and Factor Xa inhibitors add to the treatments currently available. Thrombolytic agents are contraindicated in the absence of ST-segment elevation. After clinical stabilization, ongoing assessment should include exercise testing for all patients who are able; other imaging techniques should be used for patients unable to exercise. A profile indicating a high risk of future events is an indication for elective angiography and consideration for revascularization.

Key words: unstable coronary artery disease, risk stratification, troponin-T, revascularization, anticoagulant, heparin

Introduction

The term unstable coronary artery disease (UCAD) describes the clinical syndromes of unstable angina (UA) and non-Q-wave myocardial infarction (NQMI), which lie between chronic stable angina and acute Q-wave myocardial infarction (MI) in the spectrum of coronary artery disease. The pathologic lesion found in the coronary arteries of patients with UCAD is commonly a platelet-rich, nonocclusive thrombus overlying fissured or “active” plaques, distinguishing it from acute MI where fibrin-rich “red” thrombus, occluding the vessel completely, is a more common finding.¹

Unstable coronary artery disease is one of the most frequent reasons for cardiovascular hospital admission and was responsible for 850,000 hospital admissions in the USA in 1990.² It is therefore a major public health concern, and as such has been the subject of much attention in recent years. The advent of new therapies for UCAD, such as percutaneous transluminal coronary angioplasty (PTCA),³ glycoprotein IIb/IIIa (GP IIb/IIIa) receptor inhibitors,^{4–7} and low-molecular-weight heparins (LMWHs),^{8–10} has also stimulated interest in this area, but has raised new questions about the optimum management of the disease.

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In many large centers, early cardiac catheterization (with or without revascularization) is now almost standard therapy; in the Global Utilization of Streptokinase and TPA Activator for Occluded Coronary Arteries (GUSTO)-IIb trial, 66% of patients with UCAD underwent catheterization within 48 h of admission.¹¹ However, the value of such a strategy has still not been properly established and further studies to evaluate the costs and benefits of such an approach are required. Many patients with UCAD will present to small local hospitals which may not have facilities for cardiac catheterization. Their physicians are required to make difficult decisions as to whether these patients should be transferred elsewhere for cardiac catheterization (and possible PTCA), or whether they should receive medical treatment in their local hospital.

Results from the few trials to compare invasive/conservative management have been inconclusive. In the TIMI-IIIB trial, there was no significant difference in the rates of death, MI, or an unsatisfactory symptom-limited exercise test at 6 weeks between patients treated under a routine invasive strategy (i.e., cardiac catheterization and revascularization if a suitable lesion was detected) and an early conservative strategy, under which cardiac catheterization was performed only if the patient did not respond adequately to medical therapy.¹² However, patients treated under the invasive strategy had a shorter total hospital stay and lower rates of rehospitalization within 6 weeks. By contrast, the Veterans' Affairs Non-Q-Wave Infarction Strategies in Hospitals (VANQWISH) study of patients with NQMI found a significantly higher early death rate among patients treated with a routine invasive strategy.¹³

Acute phase mortality from UCAD is now low for patients treated in major units—2.4% in Thrombolysis in Myocardial Ischemia (TIMI)-IIIB.¹² Although most patients will survive the acute attack, the 1-year mortality ranges from 5 to 14%, with approximately half of these deaths occurring within 4 weeks of diagnosis.¹⁴ Consideration of both mortality and morbidity over the longer term is becoming increasingly important. This review will consider the evidence regarding the management of UCAD with a view to optimizing long-term outcomes. Unstable angina and NQMI are considered together because these two syndromes cannot be distinguished at the time of presentation at hospital. The nearly three-fold range of mortality at 1 year in different reports most likely reflects the different inclusion criteria associated with a variable baseline ischemic heart disease (IHD) mortality and a variable severity of the instability. Patients with impaired left ventricular function and elderly patients have an increased baseline risk. Patients with NQMI and unstable patients with positive troponin-T and troponin-I represent those with a documented, more severe form of instability, as they already show evidence of myocardial cell damage.¹⁵

Diagnosis and Early Management of Unstable Coronary Artery Disease

Unstable coronary artery disease is a clinical diagnosis made at the time of presentation on the basis of the history, ex-

amination, and electrocardiographic (ECG) findings, and supported by the analysis of biochemical markers of myocardial damage. It may present in any one of a number of ways: (1) Increased severity or frequency of pre-existing angina pectoris, (2) new onset of angina, (3) angina at rest, (4) angina following an established MI, and (5) MI not progressing to a full transmural infarction (NQMI, see below).

Non-Q-wave myocardial infarction is diagnosed on finding elevated serum levels of cardiac enzymes, principally creatine kinase (CK) or its isoform CK-MB, in a patient with a typical history who does not have the usual ECG changes seen in MI (i.e., persistent ST-segment elevation and Q waves). This diagnosis will therefore not be made immediately on admission, but will only become apparent later when the results of blood tests become available.

A diagnosis of UCAD implies that the immediate prognosis is uncertain and it should be revised once the patient's clinical condition has stabilized. Patients have a high risk of progression to full MI, with its attendant complications of cardiac failure or death from cardiac arrhythmias. Admission to a hospital unit with facilities for monitoring of the patient's ECG and clinical status is, therefore, appropriate. Table I shows a series of actions recommended at the time of admission.

Management of UCAD aims to stabilize the patient by relieving pain and preventing recurrent attacks of pain or ischemia, to prevent progression to MI or death, and to return the patient to a state of health that will permit resumption of all previous activities. Although the patient's clinical course and an assessment of future risk will guide management decisions during the acute phase, it is important to note that clinical stabilization does not imply stabilization of the underlying plaque. There is much evidence to suggest that a hypercoagulable (procoagulant) state, as evidenced by increased thrombin generation and platelet activation, may persist for many months after the acute attack.^{16, 17}

TABLE I Diagnosis and monitoring on admission of a patient with unstable coronary artery disease

Early management is driven by the patient's history and the initial ECG. Other factors (e.g., early hemodynamic instability or severe left ventricular dysfunction) are relevant both in the acute phase and later.

- Blood should be taken for measurement of
 - Hemoglobin and routine biochemistry
 - Troponin-T or -I (if available) and CK/CK-MB
 - Blood lipids (does not alter acute management, but is required for ongoing management)
- A second troponin-T or -I should be taken after 12–24 h
- Continuous ECG monitoring should be performed for the first 12–24 h whenever possible.

The combination of maximum troponin-T levels and ECG monitoring provides valuable prognostic information which may guide therapeutic decisions.

Abbreviations: ECG = electrocardiogram, CK = creatine kinase.

Risk Stratification

A full assessment of the patient's risk category forms a crucial part of management. The overall goal is to estimate the likelihood of the patient having (1) a fatal MI or sudden arrhythmic death, (2) progression of UA to MI, and (3) recurrence of symptoms after the initial episode has settled. This can be used to determine which patients require angiography as a matter of urgency, and in whom an uncomplicated initial clinical course may be anticipated. The overall risk of the patient is the combined result of two components:

1. The baseline risk related to the severity of pre-existing IHD (impairment of left ventricular function, heart failure, limitation of effort tolerance, and severity of coronary atherosclerosis). This baseline determinant of prognosis is greatly magnified by the severity of the instability because it influences the response of the heart to new ischemic insults.¹⁸

2. The severity of the instability [determined by the frequency, duration of ischemic attacks (painful or painless), and their lack of response to treatment]. Therefore, the acquisition of a thorough past and recent medical history is the foundation of risk stratification.

The additional prognostic value of tests, above that provided by the clinical presentation, should be assessed in homogeneous subgroups of unstable patients, classified according to a history of chronic stable angina or previous MI and the impairment of left ventricular ejection fraction (which indicate their pre-existing baseline determinants of prognosis), and to the waxing and waning of anginal attacks (which indicate the acute determinants of prognosis).

Risk stratification is an ongoing process, starting at the time of presentation and continuing until hospital discharge. A patient's risk category may be revised at any time in the light of further events, or as the results of investigations becoming available. No single factor has yet been identified that can adequately assess the total risk,¹⁹ and a combination of all the relevant risk factors is likely to produce the best overall picture.

Patient's Age

The risk of progression to acute MI or death in UCAD increases with the patient's age^{3, 20} and forms part of the background risk upon which all other factors must be considered. The importance of age increases substantially with advancing years; although it is relatively unimportant as a predictor of progression of UA to MI or death for patients under 65 years of age,³ it assumes much greater significance in patients above the age of 70.²¹

Severity of Ischemia at Presentation

ST-segment deviation on the ECG (either depression or transient elevation) may be used as a marker of myocardial ischemia. The greater the number and duration of ischemic

attacks, the greater the risk of early progression to MI or death.²²⁻²⁴ Continued attacks of ischemia (which may or may not be associated with pain), despite adequate medical therapy, give particular cause for concern.

Refractory angina (see below) has been used as a marker of disease progression for several years.²⁵ Continuing pain is associated with a higher risk of progression than pain that has been controlled; there is an inverse relationship between the length of time since the pain settled and the risk of progression (i.e., the risk falls with increasing time since the last episode of pain).¹² A cumulative duration of pain of more than 60 min, particularly if it persists after treatment has been initiated, is associated with a high risk of progression to MI.²⁶ An initial diagnosis of NQMI carries a greater risk of progression to full MI than does an initial diagnosis of UA.

Regardless of the severity of the present attack, pre-existing left ventricular damage will increase the risk of an adverse outcome.²⁷ Should MI develop, the risk of death, both in the long and the short term, becomes much higher than it is in UA.

Electrocardiogram on Admission

Electrocardiographic findings in UCAD are variable and may change over time in the same patient. In a patient with a typical history, T-wave inversion (deep/symmetric inversion in multiple leads) or ST-segment depression strongly support the diagnosis.³ A normal 12-lead ECG recorded during an episode of pain is associated with an excellent prognosis and suggests a noncardiac origin for the patient's pain.

New persistent ST-segment elevation on the 12-lead ECG, which does not respond promptly to high doses of intravenous nitrates, indicates that the patient is developing a full thickness MI. Immediate reperfusion therapy with either thrombolytic agents or PTCA is indicated.

Isolated T-wave inversion on the initial ECG was found to be associated with a low risk of future MI or death. Many of these patients have normal coronary arteries and the prognosis is better than for those patients who have ST-segment shifts (either depression or transient elevation).²⁰ However, T-wave inversion represents only part of the overall clinical picture, and deep negative T waves in an elderly man, particularly in the presence of other risk factors, give rise to greater concern than minor negative T waves in a young woman.

Biochemical Markers of Cardiac Injury

Creatine kinase and its isoform CK-MB, as well as troponin-T and troponin-I, have all been identified as biochemical markers of cardiac damage. Elevated levels can identify patients who remain at high risk despite apparent stabilization of their clinical condition. A small rise in the serum levels of these cardiac enzymes probably reflects the development of small foci of myocardial necrosis, but there is a lag period of several hours before these elevated levels become detectable. A more pronounced elevation indicates a definite MI, although the level at which MI is diagnosed is arbitrary and varies between and within countries. Measurement of these markers may provide valuable information for determining

the most appropriate ongoing management, particularly in patients whose clinical condition appears to have stabilized, but the delay before a rise in levels becomes apparent means that the levels of these markers do not influence the initial management at presentation.

Troponin-T and troponin-I are both used as indicators of increased risk in UCAD, although most of the published data and clinical experience relate to troponin-T. Troponin-T is more sensitive as a marker of myocardial damage than CK-MB.²⁸ It is an independent prognostic marker, adding to the information from other sources, but on its own it is a better predictor of mortality than either the ECG category or the CK-MB level.²⁸

Elevated levels of troponin-T >0.1 $\mu\text{g/l}$ have a linear relationship with an increased risk of cardiac events and are associated with a significantly higher mortality at 30 days.²⁸ By contrast, a maximum level <0.1 $\mu\text{g/l}$ indicates a very low risk of subsequent MI or death. At least two assays, separated by a 12–24 h interval, should always be performed, and additional information may be gained from a third test. Serum levels of cardiac troponin-I, which is undetectable in healthy persons, can also be used to predict future MI or mortality after UA or NQMI.²⁹ Cut-off levels for the prediction of risk depend on the assay system used.

Markedly elevated levels of CK-MB (more than 100% above the reference level) may be taken as diagnostic of acute MI.³⁰ Smaller elevations of CK-MB, not diagnostic of Q-wave MI or NQMI, also indicate an increased risk of future events. Troponin-T will usually be elevated in these circumstances.

Coagulation Activity and Indices of Inflammation

The fibrinogen level in peripheral blood is a nonspecific indicator of inflammatory activity, influencing blood viscosity and contributing to the substrate for platelet aggregation and clot formation. It is an independent indicator of future episodes of ischemia in UA¹⁹ and may be useful in conjunction with other prognostic indicators (e.g., troponin-T or ECG).

Raised levels of cross-linked fibrin degradation products (measured as D-dimer) also identify those patients at a higher risk of thrombotic complications,³¹ although it should be noted that D-dimer is not specific and is also raised in patients with heart failure even of nonischemic origin.³²

C-reactive protein (CRP) is raised in inflammatory conditions and is related to an increased risk of future events.³³ As a nonspecific marker, its place in the management of UCAD has not yet been fully defined in large-scale studies.

Electrocardiographic Monitoring

Single-lead ECG monitoring systems probably underestimate ischemic activity in a large proportion of patients in the coronary care unit (CCU). Although not proven to be superior, multilead ECG monitoring, using an inferior lead and V₅, is generally considered to be better than standard monitoring in terms of ischemia detection, and it should therefore be used when the lead showing ischemic changes is unknown.

ST-segment monitoring should ideally be used for all patients with UCAD. Holter monitoring, although widely available, is limited by the need for off-line analysis, meaning that medical and nursing staff are not alerted to ischemic episodes until some time after they have happened. Continuous, real-time ST-monitoring with a hard copy printout is preferable for providing immediate prognostic information.

As previously stated, normal findings on the 12-lead ECG during an episode of pain are associated with an excellent prognosis and probably indicate pain of noncardiac origin.³ The absence of ischemic events during 12–24 h of monitoring indicates a good prognosis, whereas prolonged or repeated episodes of ischemia, as indicated by ST-monitoring, are indicative of an increased risk of future events.²⁶

Acute Management

Antiplatelet Treatment

Antiplatelet agents form the mainstay of treatment in UCAD, and, unless contraindicated, aspirin should be given to all patients on presentation. Patients who have not previously been taking aspirin therapy regularly will require an initial loading dose of 160–325 mg, followed by ongoing maintenance treatment at a daily dose of 75–160 mg. Recent studies such as RISC suggest that very low-dose aspirin may be as effective as the higher doses previously used.³⁴

Absolute contraindications to aspirin, such as allergy, are rare; however, in those patients who are known to be allergic or unresponsive to aspirin, ticlopidine may be used as an alternative.³ It is considerably more expensive than aspirin and carries a known risk of adverse effects. Clopidogrel has a better safety profile than ticlopidine and, although it is not yet licensed for use, it may eventually be preferred to ticlopidine in aspirin-intolerant patients. Clopidogrel has been shown to be as effective as aspirin in post-MI patients,³⁵ although there are as yet no trial data regarding its efficacy in UCAD.

Glycoprotein IIb/IIIa receptor inhibitors, used in addition to aspirin and heparin, have been the subject of intensive clinical trials programs. It is now well established that these agents are of value in UCAD when used in conjunction with PTCA,^{4, 5} and, more recently, evidence has become available that they may also improve prognosis, when used in addition to aspirin and heparin, in patients who do not undergo angioplasty. In the CAPTURE trial, abciximab (c7E3) reduced the event rate in patients with refractory UA in the period before PTCA was performed from 2.1% with placebo to 0.6% ($p = 0.029$),⁶ and in the PRISM study, tirofiban, used as part of a conservative strategy, was reported to reduce the event rate by 25% in low-risk patients with UA or NQMI.⁷

Anticoagulation

The value of intravenous heparin (in addition to aspirin) in protecting patients with UCAD from recurrence of symptoms and progression to MI or death is well established.^{24, 34, 36} Heparin should be considered for use in all patients, but must

be carefully monitored with frequent measurement of the activated partial thromboplastin time (APTT) because of the variability in patient response, complex pharmacokinetics, and the acknowledged risk of hemorrhage.

Evidence is now accumulating that LMWHs, given by subcutaneous injection twice daily, can offer an equally effective alternative to intravenous heparin in the treatment of UCAD. Compared with placebo, the LMWH dalteparin sodium reduced the risk of death or MI in the first 6 days after an attack of UCAD by 63%,⁸ and other studies have shown that these agents, given by subcutaneous injection, are as effective as intravenous heparin in UCAD.^{9,10} Low-molecular-weight heparins have a highly predictable dose-response curve, which means that they can be used without the need for APTT monitoring.

The current recommendations from the American College of Cardiology/American Heart Association Task Force state that heparin should be given for 3–4 days;³⁷ slightly longer treatment periods (3–5 days) have been used in many trials. Longer periods of anticoagulation (e.g., by subcutaneous LMWH) are advisable in patients who are awaiting cardiac catheterization and possible PTCA, in whom it should continue until the procedure has taken place.

There are several reasons for believing that long-term anticoagulation might further improve outcomes in UCAD. These patients remain in a hypercoagulable state for several months after the acute attack.^{16,17} Recent findings suggest that patients with elevated levels of CRP at discharge have a significantly greater incidence of MI and recurrent admissions for unstable angina at 3 months and 1 year.³⁸ They continue to be at high risk of recurrent ischemic episodes for up to 12 weeks,³⁴ and the period immediately after heparin is withdrawn is a time of particularly high risk.³⁹ Low-molecular-weight heparins are more suitable for long-term use than standard heparin; subcutaneous administration allows for outpatient use, and the risk of thrombocytopenia is very much lower than that with standard heparin. It has already been shown that continuing treatment with the LMWH dalteparin sodium for a total of 6 weeks further reduces the rate of death or MI from 10.9 to 7.4% (RR 0.67, confidence index 0.31–1.44) in high-risk patients who have elevated levels of troponin-T during the acute phase;⁴⁰ no other interventions have yet been shown to offer similar benefits to these patients.

Hirudin and other direct thrombin inhibitors have similar levels of efficacy to intravenous heparin in UCAD, but carry the risk of major hemorrhage. These agents are currently undergoing investigation in several Phase III clinical trials, but as yet there is no evidence that they are more effective than heparin or LMWH.

Anti-Ischemic Therapy

It is customary to treat all patients presenting with UCAD with intravenous or sublingual nitrates. Although this may provide symptomatic relief of pain, there is no evidence that the prognosis is affected. Similarly, it is generally accepted that beta blockers should be given to all patients in whom they are

not contraindicated, although not all studies support this practice.^{41,42} However, reduction of the heart rate to <60 beats/min to reduce myocardial oxygen consumption, and normalization of the blood pressure by titrating doses of beta blockers, is a widely accepted clinical practice.

Patients who do not stabilize on beta blockers may benefit from the addition of a calcium-channel antagonist. Because of the evidence that short-acting dihydropyridine agents may increase mortality when used without beta blockade,⁴¹ long-acting calcium-channel agents are preferred in UCAD. Long-acting calcium-channel antagonists (e.g., verapamil or diltiazem) may be used in patients in whom beta blockers are contraindicated, such as those with chronic obstructive pulmonary disease.^{43,44}

Thrombolytic Therapy

Thrombolytic treatment may worsen prognosis in UA.^{12,45–48} It is therefore contraindicated in the routine management of patients without ST-segment elevation (with the exception of patients with true posterior wall infarction presenting with horizontal ST-segment depression in the precordial leads). Intracoronary thrombolytics have been used when a large clot burden is documented at angiography,^{49,50} but the benefits of antiplatelet therapy with a GP IIb/IIIa inhibitor have been conclusively demonstrated in a number of studies.^{4,51–53}

Cardiac Catheterization/Revascularization

Cardiac catheterization may be undertaken in patients with UCAD for the following reasons: (1) to assist with risk stratification in cases of uncertainty or where the patient has a complex medical history, (2) as a prelude to revascularization, and (3) to exclude obvious coronary atherosclerotic disease as a cause of symptoms (except for patients with variant angina and normal coronary angiograms and those with selected microvascular angina). A negative coronary angiogram may allow early hospital discharge.

There is currently no evidence that early revascularization offers any advantage over medical therapy in reducing the rates of death or MI when it is used as routine treatment for all patients,^{12,13} although it may reduce the need for hospital admission for recurrent ischemia. It is clearly necessary for patients with refractory ischemia who do not settle on maximal medical therapy. Selected patients, such as those with poor left ventricular function or triple-vessel disease, may prolong their life expectancy if treated with revascularization in addition to medical therapy.

Patients who are candidates for cardiac catheterization and possible revascularization should continue antiplatelet and anticoagulant treatment (with or without a GP IIb/IIIa receptor inhibitor) until after the planned procedure has taken place.

Assessment after Stabilization on Medical Therapy

Stabilization of the patient's clinic condition does not imply that the underlying pathologic process has stabilized. Correc-

tion of hyperlipidemia should therefore be considered in all cases with a proven diagnosis.⁵⁴

A symptom-limited exercise test should be performed in patients at indeterminate risk. It offers much valuable prognostic information⁵⁵ that can be used to determine continuing management such as intense medication or an elective revascularization procedure. If facilities for further investigations are not available locally, patients should be transferred to another unit with suitable facilities.

The risks of performing an exercise test are very low once the patient has been pain free for 24–48 h and the ECG is stable,⁵⁶ and it should be regarded as a minimum requirement undertaken before or soon after discharge of a stabilized patient. Combining exercise with radionuclide or echocardiographic imaging increases the predictive accuracy of testing and should be considered as an alternative where resources allow.

Severe ischemia or low exercise tolerance in a patient who has had either UA or NQMI are associated with a poor short-term prognosis. If combined with elevated troponin-T, there is a substantial risk of further events and immediate angiography and consideration for revascularization is warranted.⁵⁵

Treated chronic heart failure is not a contraindication to exercise testing, although patients who are in severe heart failure because of a previous MI warrant careful assessment for the possible presence of viable, noncontractile myocardium. Patients who are unsuitable or otherwise unable to exercise may undergo radionuclide myocardial perfusion imaging (e.g., thallium or technetium scan) or dobutamine/dipyridamole stress echo if clinically indicated.⁵⁷ A good effort tolerance is associated with an excellent prognosis.⁵⁵

Left ventricular function should be evaluated in all patients. In patients undergoing invasive testing, this may be done by contrast ventriculography. In patients who are not scheduled for invasive procedures, echocardiography is indicated. Although clinical algorithms have been developed to attempt the prediction of major ventricular dysfunction,⁵⁸ these appear to be predictive only in certain subsets of patients. Measurement of ventricular function should only be omitted when the clinician is confident that no major impairment exists.

Refractory Unstable Angina

Refractory unstable angina may be defined as ongoing ischemia with ongoing signs (dynamic ST-segment deviation) or symptoms (chest pain) despite 24 h maximal anti-ischemic and anticoagulant therapy (Table II). Patients who satisfy this definition should undergo urgent angiography and revascularization if a suitable lesion can be detected.

Non-Q-Wave Myocardial Infarction

Non-Q-wave myocardial infarction is a syndrome which shares many clinical features with UA and may present in the same way, but it is a separate pathologic entity. It may be de-

fined as MI not progressing to a transmural infarction, and it is usually associated with a subtotal coronary artery occlusion.⁵⁹ The diagnosis is made on finding the CK or CK-MB elevated to more than twice normal levels in a patient without the ECG findings typical of an acute MI (i.e., ST-segment elevation and the development of Q waves).²²

Differentiating UA and NQMI may be difficult at the time of initial presentation, before the results of enzyme assays are available. In the TIMI-IIIIB trial, the following characteristics were found to increase the likelihood of NQMI:²² (1) Pain persisting for longer than 60 min, (2) new ST-segment deviation, (3) no history of PTCA, (4) recent onset of angina (< 1 month). The prevalence of NQMI increased from 7% when none of these characteristics was present, to over 70% when all four were present.

The risk of progression to full thickness MI is greater in NQMI than in UA.^{12, 14} Older patients are at greatest risk: over the age of 70, mortality 1 year after NQMI is significantly higher than in younger patients.²¹ Despite the increased overall risk in NQMI, management should be similar to that for patients with UA. There is no evidence that patients with NQMI benefit from routine early revascularization; indeed, such a policy may be associated with a higher early death rate.¹³ Revascularization may reduce the rate of subsequent ischemia. Thrombolytic treatment does not alter the rate of death or MI in patients with NQMI.¹²

Comment

Despite the acknowledged risks of UCAD progressing to acute MI, it is clear both from pathologic studies and clinical experience that these are very different conditions that require different management.

TABLE II Maximal anti-ischemic and anticoagulant therapy

Anti-ischemic therapy
Oral beta blockers (up to maximum tolerated dose, to cause fall in heart rate to <60 beats/min) ^a
Plus
Oral calcium-channel blocker to maximum tolerated or prescribable dose (dihydropyridines only to be used with a beta blocker) ^a
Plus
Intravenous nitroglycerin to maximum tolerable dose ^a
Anticoagulant therapy
Oral aspirin (loading dose 160–325 mg, then 75–160 mg o.d.)
Plus
Either intravenous heparin (bolus of 70 U/kg, then continuous infusion titrated to give APTT 1.5–2 times control) or subcutaneous LMWH 100–120 U/kg b.d.—no monitoring required

^aDose should be reduced if hypotension develops in hypertensive patients. Reducing the mean arterial pressure by more than 30 mmHg may compromise the perfusion pressure.

Abbreviations: APTT = activated partial thromboplastin time, LMWH = low-molecular-weight heparin.

FIG. 1 Algorithm for the management of unstable coronary artery disease. IHD = ischemic heart disease, ECG = electrocardiogram, CK-MB = creatine kinase-MB, ETT = exercise treadmill test, LV = left ventricular, +ve = positive, -ve = negative.

Although thrombolysis and PTCA are now established as highly effective in the management of acute ST-elevation MI, this is not the case in UCAD. Thrombolytic agents currently have no place in the management of UCAD; they do not improve the prognosis in NQMI and they make it worse in UA. However, the question of whether or not patients with UCAD should routinely undergo cardiac catheterization and possible PTCA remains more controversial. These interventions have a clear role to play in the management of patients not responding to medical therapy or otherwise at very high risk. The investment in resources required to make these interventions a routine part of treatment for all patients must be weighed against the absence of data showing a clear clinical advantage.

Risk stratification is an essential part of management strategies for the individual patient. Maximum values of biochemical markers such as troponin-T (or troponin-I) and CK or CK-MB are valuable prognostic indicators, and their value may be enhanced by considering, in addition, the serum levels of D-dimer, fibrinogen, and CRP. Electrocardiographic findings, both at presentation and over time, can also offer much information. In the longer term, exercise testing should

also form part of the assessment process for all patients. Figure 1 shows how these may be used in the clinical setting.

With the advent of effective new medical therapies, it may be that fewer patients will undergo revascularization procedures in the future. Recent data from trials of GP IIb/IIIa receptor inhibitors suggest that these agents will have an exciting role to play in restoring and maintaining the coronary circulation in UCAD in their own right, without the need for mechanical intervention. The results of further trials in this area are eagerly awaited.

The use of heparin in the acute phase of UCAD is not disputed, but it is now becoming apparent that it may also have a part in ongoing therapy. The finding that continued anticoagulation for 6 weeks reduced the event rate in high-risk patients with elevated troponin-T may point the way to much longer treatment periods than those currently used.⁴⁰ Intravenous heparin may be replaced by subcutaneous LMWH; it is as effective as standard heparin but is also more predictable in effect and easier to use. The Fragmin during Instability in Coronary Artery Disease II (FRISC-II) trial is now underway and will not only compare the results of routine intervention and conservative treatment in the acute phase, but also long-term LMWH and placebo in ongoing management. Should long-term heparin therapy become established as part of management, LMWH will enable patients to be discharged from hospital to continue treatment at home.

Unstable coronary artery disease is a dynamic condition which may either settle spontaneously or progress to a full-blown acute MI. Management is directed at preventing progression because of the much poorer prognosis such patients carry. The strategies presented here can serve only as a guide; in the clinical situation, management will always be guided by the patient's progress and response to previous treatment.

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