INTRODUCTION

The term “acute coronary syndrome” encompasses unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) and ST-segment elevation myocardial infarction (STEMI). UA/NSTEMI is the combination of two closely related clinical entities (i.e., a syndrome), whereas STEMI is a distinct clinical entity. UA/NSTEMI is characterized by an imbalance between myocardial oxygen supply and demand. Most often, the syndrome develops because of decreased myocardial perfusion resulting from coronary narrowing caused by nonocclusive thrombus formation subsequent to disruption of an atherosclerotic plaque. In contrast, STEMI results from an occlusive thrombus.

DEFINITION

The presence of one or more of the following may define UA: (i) angina at rest; (ii) angina that increases in severity or duration or frequency; (iii) new-onset angina at least Canadian Cardiovascular Society Grade III severity. Non-Q-wave MI may be defined as an increase in cardiac enzymes in the absence of Q-wave in the ECG. Subendocardial MI or Non-ST-elevation MI are other terms usually used synonymously with NQMI.

CLASSIFICATION

Braunwald’s classification of UA published in 1989 is not only clinically useful but also has been validated by prospective trials. UA class: Class I, new-onset or accelerated angina; Class II, angina at rest during the preceding 1 month but not within the previous 48 h; Class III, Angina at rest within the preceding 48 h. Clinical circumstances: secondary UA (e.g. exacerbated by anaemia, thyrotoxicosis etc.); primary UA; post-infarction UA (within 2 weeks of a documented MI). Among such unstable patients, there are high-risk groups with poorer outcomes. Indicators of high risk in unstable angina are: raised troponin concentration (troponin I>1.0 mcg/l; troponin T>0.1 mcg/l); ST segment depression in ECG.

PATHOPHYSIOLOGY

Usually a fissure or rupture of a coronary atherosclerotic plaque triggers new thrombus formation with increased platelet adhesiveness and aggregation. This progresses to partial occlusion of the coronary lumen. Rapid thrombosis and subtotal coronary occlusion remains the main cause of the ACS despite the recognition of other causative factors, e.g. inflammation. Since 1983, the main target of UA treatment has therefore been the platelets.

RISK STRATIFICATION

Biomarkers

Recent studies have examined the role of nontraditional biomarkers in the risk stratification of patients with acute coronary syndrome. High-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, has been shown to provide prognostic information in patients with acute coronary syndromes, independent of clinical factors and traditional markers of necrosis. B-type natriuretic peptide (BNP) has been associated with heart failure, as well as adverse clinical outcomes (predominantly mortality), in patients with acute coronary syndromes. The study findings suggest that future risk stratification in patients with acute coronary syndrome may involve a panel of biomarkers.

One investigative team has proposed a simplified method of combining the information provided by biomarkers. From zero to three points are assigned, depending on the number of elevated biomarkers (cardiac-specific troponin, hs-CRP, BNP). The risk of death, recurrent myocardial infarction, or congestive heart failure has been found to be 4.5 times higher when all three biomarkers are elevated than when no biomarker is elevated. However, more data are needed before use of hs-CRP and BNP can be recommended for risk stratification in UA/NSTEMI.

TIMI Risk Score

This represents a simple, convenient method of risk stratification, in which the number of independent risk factors on presentation is determined. The incidence of an adverse outcome (death, myocardial reinfarction, or recurrent severe ischemia) at 14 days...
Table 1: Likelihood of Acute Coronary Syndrome Secondary to Coronary Artery Disease Based on Clinical Features

<table>
<thead>
<tr>
<th>Area of assessment</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Chest or left arm pain or discomfort reproducing previously documented angina</td>
<td>Chest or left arm pain or discomfort</td>
<td>Symptoms with features other than those indicating intermediate or high likelihood</td>
</tr>
<tr>
<td>History</td>
<td>Known history of coronary artery disease or myocardial infarction</td>
<td>Patient age &gt; 70 years, male sex, diabetes mellitus</td>
<td>Recent cocaine use</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Transient mitral regurgitation, hypotension, diaphoresis, rales</td>
<td>Manifestations of extracardiac vascular disease</td>
<td>Chest pain reproduced by palpation</td>
</tr>
<tr>
<td>ECG</td>
<td>New transient ST-segment deviation or T-wave inversions with symptoms</td>
<td>Q waves; abnormal ST segments or T waves not documented to be new</td>
<td>Normal ECG</td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td>Elevated cardiac-specific troponin level or elevated MB isoenzyme of creatine kinase level</td>
<td>Cardiac biomarker levels not elevated</td>
<td>Cardiac biomarker levels not elevated</td>
</tr>
</tbody>
</table>

Table 2: Clinical Features Associated with Risk of Death or Nonfatal Myocardial Infarction in Patients with NSTEMI

<table>
<thead>
<tr>
<th>Area of assessment</th>
<th>Risk of death or nonfatal myocardial infarction based on clinical features</th>
<th>High*</th>
<th>Intermediate†</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Accelerating tempo of ischemic symptoms in preceding 48 hours</td>
<td>Previous myocardial infarction, peripheral vascular disease, cerebrovascular disease, coronary artery bypass grafting, or aspirin use</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Character of pain</td>
<td>Prolonged, ongoing (&gt; 20 minutes) angina at rest</td>
<td>Prolonged angina at rest (&gt; 20 minutes), now resolved</td>
<td>New-onset or progressive anginal symptoms, not occurring at rest</td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Ischemic pulmonary edema, new or worsening mitral regurgitation, S3 gallop, hypotension, bradycardia, tachycardia, patient age &gt; 75 years</td>
<td>Angina at rest (&lt; 20 minutes) or relieved with rest or sublingual nitroglycerin</td>
<td>Patient age &gt; 70 years</td>
<td>-</td>
</tr>
<tr>
<td>ECG</td>
<td>Angina at rest, with new transient ST-segment deviation; bundle-branch block or sustained ventricular tachycardia</td>
<td>T-wave inversions, Q waves</td>
<td>Normal ECG, or no changes in ECG during pain episode</td>
<td></td>
</tr>
<tr>
<td>Cardiac biomarker</td>
<td>Cardiac-specific troponin level elevated above “necrosis limit”</td>
<td>Cardiac-specific troponin level elevated but below “necrosis limit”</td>
<td>Cardiac-specific troponin level not elevated</td>
<td></td>
</tr>
</tbody>
</table>

ranged from 5% with a risk score of 0–1 to 41% with a risk score of 6–7. This risk score was derived from an analysis of patients in the TIMI IIB trial and has been validated in four additional trials and one registry. With an increasing risk score, progressively greater benefits of treatment with LMWH versus UFH, of the platelet GP IIb/IIIa receptor blocker tirofiban versus placebo, and of an invasive versus a conservative strategy were observed. However, patients across all levels of the TIMI risk score showed similar relative reductions in adverse outcomes with clopidogrel. The risk score was effective also in predicting postdischarge adverse outcomes. This ability of a risk assessment scheme to detect differences in treatment benefit specific to particular therapies greatly enhances the imperative to use the score in practice.

Multiple Biomarker Risk Assessment

Two approaches have been employed. Newby et al. demonstrated that a bedside strategy using myoglobin, creatine kinase-MB, and troponin I provides more accurate risk stratification than a single-marker, laboratory-based approach. MANAGEMENT

Antiplatelet Therapy

Aspirin

The important role played by this cyclooxygenase-1 inhibitor is well established from multiple clinical trials and several meta-analyses and based on these, aspirin has become a cornerstone in the management of UA/NSTEMI. A syndrome of “aspirin-resistance” has emerged recently. This syndrome has been variously described as relative failure to inhibit platelet aggregation and/or failure of prolongation of the bleeding time, or the development of a clinical event while on aspirin therapy. Patients with aspirin resistance appear to be at higher risk of recurrent events, and although prospective randomized trials have not yet been reported in these patients, it is logical to treat them with clopidogrel, although aspirin should not be discontinued. Furthermore, Alexander et al. demonstrated both a high event rate and a large treatment effect of eptifibatide in patients with an acute coronary syndrome (ACS) despite prior aspirin therapy.
Current Management Strategies for Non-ST Segment Elevation Myocardial Infarction

Fig. 1: TIMI risk score for UA/NSTEMI. The risk factors are shown on the right and the risk of death (D), myocardial infarction (MI), or urgent revascularization (UR) is shown along the vertical axis.

Clopidogrel

This thienopyridine blocks the P2Y<sub>12</sub> adenosine diphosphate receptor on the platelet surface and thereby inhibits platelet activation. Its use in UA/NSTEMI is based primarily on the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) and Clopidogrel for the Reduction of Events During Observation (CREDO) trials. The former randomized 12,562 patients with UA/NSTEMI (all of whom were receiving aspirin) to clopidogrel (300-mg loading dose followed by 75 mg daily) or placebo. After a follow-up averaging 9 months, the primary prespecified "hard" endpoints of cardiovascular death, MI, and stroke were reduced significantly by 20% from 11.5% in the placebo group to 9.3% in the clopidogrel group. A reduction of recurrent ischemia was already present within 6 h of randomization. The salutary effects were noted across all of the subgroups, including those without ST-segment deviation or troponin release and those with a low TIMI risk score. The major benefit was a reduction in MI; although death and stroke trended in favor of clopidogrel, the reduction in these events did not achieve statistical significance. However, clopidogrel was associated with significant increases in major bleeding (3.7% versus 2.7%) and minor bleeding, as well as with a trend toward increases in life-threatening bleeding. Excess bleeding was greater in patients on higher doses of aspirin or who underwent CABG within 5 days of discontinuing clopidogrel. The increased risk of bleeding with the combination of aspirin and clopidogrel in patients undergoing CA in an observational substudy in CURE in 2658 patients undergoing PCI a median of 10 days after randomization (the PCI-CURE Study), most of the patients received open-label thienopyridine for about 4 weeks after the procedure. Pretreatment with clopidogrel was associated with a 30% lower relative risk of cardiovascular death, MI, or revascularization within 30 days (6.4% versus 4.5%). Continuing benefit of clopidogrel was observed during the 8 months after blinded study medication (clopidogrel or placebo) was resumed 1 month after PCI. The benefit of pretreatment and long-term follow-up treatment with clopidogrel was also observed in CREDO, a trial in 2116 patients, 55% of whom had UA/NSTEMI and were to undergo PCI.

Based on these trial results, it is recommended that clopidogrel be considered a first-line drug in UA/NSTEMI and added to aspirin in patients with UA/NSTEMI, except those at high risk for bleeding and those in whom the need for urgent CABG cannot be excluded. Thus, clopidogrel should be administered to patients with UA/NSTEMI: (1) in whom an early noninvasive approach is planned; (2) who are known not to be candidates for urgent coronary bypass surgery based on previous knowledge of the coronary anatomy or who have contraindications to surgery; and (3) in whom catheterization will be deferred for >24–36 h. In patients in whom a diagnostic catheterization is planned within 24–36 h after presentation, it is reasonable to withhold clopidogrel until the findings on a coronary angiogram exclude the need for urgent bypass surgery. The loading dose of clopidogrel can then be administered in the catheterization laboratory prior to PCI or it may be started immediately after the catheterization. Because clopidogrel (like aspirin) is an irreversible inhibitor of platelet function, it is recommended that the drug be discontinued for 5 or preferably 7 days before elective surgery, including CABG.

An alternative view is that the extra risk of bleeding is tolerable in patients in whom angiography has not yet been performed because of the prevention of ischemic events during the waiting period. This view is bolstered by the observations within CREDO that pretreatment >6 h before PCI tended to enhance the benefit of the drug and that the combination of clopidogrel and GP IIb/IIIa inhibition appeared to be at least additive for benefit without enhancing the risk of bleeding.

Platelet GP IIb/IIIa Antagonists

There is strong evidence from multiple trials that GP IIb/IIIa antagonists reduce the incidence of death or MI in patients with UA/NSTEMI undergoing PCI, and that their use in this setting is indicated clearly. However, little data are available from trials in which the strategy of purposefully not undergoing PCI was employed. One notable exception is the GUSTO IV-ACSTrial, which was designed specifically to examine the potential benefit of abciximab in patients with UA/NSTEMI in whom PCI was not intended. No benefit was observed; indeed a secondary endpoint, i.e., death within 48 h, favored placebo. The situation is less clear for the small-molecule GP IIb/IIIa antagonists eptifibatide or tirofiban.
A retrospective analysis of the PRISM-PLUS trial showed that tirofiban reduced the incidence of adverse outcomes in patients at high risk (TIMI risk score ≥4) who did not undergo PCI. 

Perhaps the most light that has been shed on this question comes from a meta-analysis of GP IIb/IIIa antagonists of six large trials involving 31,402 UA/NSTEMI patients who were not scheduled to undergo PCI conducted by Boersma et al. 22 A significant, albeit small (-9% relative, -1% absolute), reduction in the odds for the combined endpoint of death or MI was observed in the GP IIb/IIIa antagonist group, while bleeding was increased significantly from 1.4% in the placebo group to 2.4% in the GP IIb/IIIa antagonist group. On additional analysis, it was found that 5847 of the 31,402 (19%) patients actually underwent early (within 5 days) revascularization, and the observed benefit of GP IIb/IIIa antagonists, i.e., reduction of death or MI, was largely confined to this subgroup (-21%). These findings include and are bolstered by detailed analyses of the PURSUIT trial within the United States, in which the early invasive strategy was used frequently. In this United States subgroup, 35 events/1000 patients treated were averted. 37 On the other hand, the majority of patients, 25,555 (81%), in the Boersma meta-analysis did not undergo early revascularization and the reduction in death or MI (-3%) was not significant. Baseline troponin measurements were available in 16,151 patients, albeit not from all of the trials. As anticipated, adverse outcomes in this subgroup were substantially more frequent in those with troponin elevation (10.9%) than in those without (6.6%). Assignment to a GP IIb/IIIa antagonist was associated with a relative reduction of death or MI in the former (-14%) but not in the latter (+11%) group.

Although caution must be exercised in the interpretation of results obtained from such nonrandomized subgroups, based on the totality of evidence, it was concluded by the ACC/AHA Guideline Committee 4 that high-risk patients, especially troponin-positive patients who are likely to undergo angiography, should receive a GP IIb/IIIa antagonist. The two small-molecule agents, eptifibatide and tirofiban, may be started “upstream,” i.e., 1 or 2 days before, and continued during the procedure. Any of the three available GP IIb/IIIa antagonists may be started immediately before or in the course of the procedure. However, in accord with the findings of GUSTO-IV ACS, abciximab is not indicated in patients in whom PCI is not planned. 24 None of the GP IIb/IIIa antagonists appear to be effective or indicated in the routine management of low-risk, troponin-negative patients in whom early angiography is not intended. It would now be useful to compare prospectively “upstream” early treatment with a small-molecule GP IIb/IIIa antagonist in patients with UA/NSTEMI with the commencement of therapy just before PCI.

Based on observations in PCI-CURE 23 and CREDO, 24 clopidogrel does not appear to add to the bleeding risk of GP IIb/IIIa antagonists; however, additional observations on the interaction between these drugs is warranted. The efficacies of thienopyridine and GP IIb/IIIa antagonists appear to be additive, and triple antiplatelet therapy (aspirin, clopidogrel, and a GP IIb/IIIa antagonist) are indicated in high-risk patients in whom PCI is planned and who do not have an excessive risk of bleeding.

**ANTICOAGULANT THERAPY**

**UFH**

The benefit of UFH when added to aspirin has been established in seven randomized trials, and the combination of UFH and aspirin has been used in the management of UA/NSTEMI for >15 years. Moreover, the aforementioned trials demonstrating the benefits of clopidogrel and the GP IIb/IIIa inhibitors have all been carried out on a background of aspirin and UFH. Nonetheless, there are many disadvantages of UFH. These include its nonspecific binding to and resulting inactivation by platelets, vascular endothelium, fibrin, platelet factor 4, and a variety of circulating proteins. The production of antiheparin antibodies may be associated with heparin-induced thrombocytopenia. This binding leads to an uncertain and erratic anticoagulant effect, requiring frequent monitoring of the activated partial thromboplastin time, dose adjustments, and requirement for continuous intravenous infusion. 25

**LMWH**

Given these problems with UFH, attention has focused on the LMWHs in which these disadvantages have largely been overcome. Importantly, monitoring of the anticoagulant effect is not necessary, and the incidence of heparin-induced thrombocytopenia is reduced. LMWHs are potent inhibitors not only of circulating thrombin but also of factor Xa. Therefore, these agents interfere not only with the action of circulating thrombin (their anti-factor IIa effect), as does UFH, but they also reduce the formation of thrombin (their anti-factor Xa effect). Another practical advantage of LMWHs is their rapid and predictable absorption after subcutaneous administration. Their prolonged elimination makes twice-daily administration feasible. Two double-blind, randomized trials, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and TIMI 11B, comprising a total of 7081 patients, showed a significant benefit of enoxaparin over UFH, and a prespecified meta-analysis showed a significant reduction of death or MI. 24

Because of the difficulty in determining therapeutic anticoagulant levels, there has been concern about the appropriate dose of LMWH in patients undergoing PCI, and the safety of LMWH in patients receiving GP IIb/IIIa inhibitors has been questioned. These concerns are being allayed by a number of observational studies and registries using enoxaparin. 27 Importantly, enoxaparin was compared with UFH in 746 patients with UA/NSTEMI receiving aspirin and eptifibatide in the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial. 28 The primary endpoint, non-CABG-associated major bleeding, was significantly lower in the enoxaparin compared to the UFH groups (1.8% versus 4.6%), although the relative incidence of minor bleeding was reversed. Also, the rate of death or nonfatal MI at 30 days and of ischemia on a continuous Holter monitor were each reduced almost by half in the enoxaparin
Thus, based on the available evidence it is advisable to use enoxaparin in place of UFH in patients with UA/NSTEMI. There are two caveats. First, the results of two large trials are awaited. In Superior Yield of New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY), UFH and enoxaparin are being compared in patients in whom an invasive strategy is planned, whereas in Aggrastat to Zocor (A to Z) they are being compared in patients who are routinely receiving a GP IIb/IIIa inhibitor. The information available on the relative efficacies of different LMWHs is relatively scant. However, in the Enoxaparin versus Tinzaparin in the Management of Unstable Coronary Artery Disease (EVET) trial, a head-to-head comparison of two agents in which 438 patients with UA/NSTEMI were randomized to two LMWHs, enoxaparin and tinzaparin, the former was found to be superior to the latter in reducing the recurrence of UA and the need for revascularization.

**EARLY CONSERVATIVE AND EARLY INVASIVE STRATEGY**

There are 2 different treatment strategies, termed “early conservative” and “early invasive,” may be used in patients...
with UA/NSTEMI. In the early conservative strategy, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest or with minimal activity or dynamic ST-segment changes) or a strongly positive stress test despite vigorous medical therapy. In the early invasive strategy, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and angiographically directed revascularization, if possible.

Several trials comparing these 2 strategies were reviewed, but greatest attention was paid to the then-most-recent trial, FRISC II (Fragmin and Fast Revascularization during InStability in Coronary artery disease II). At 1 year, the mortality rate in the invasive strategy group was 2.2% compared with 3.9% in the noninvasive strategy group (P=0.016). However, in FRISC II, the invasive strategy involved treatment for an average of 6 days in the hospital with LMWH, ASA, nitrates, and beta-blockers before coronary angiography, an approach that would be difficult to adopt in US hospitals.

In the interim, the TACTICS-TIMI 18 trial was reported. In this trial, 2220 patients with UA or NSTEMI were treated with ASA, heparin, and the GP IIb/IIIa antagonist tirofiban. They were then randomized to an early invasive strategy with routine coronary angiography within 48 hours followed by revascularization if the coronary anatomy was deemed suitable, or to a more conservative strategy. In the latter, catheterization was performed only if the patient had recurrent ischemia or a strongly positive stress test. Death, myocardial (re)infarction, or rehospitalization for an acute coronary syndrome at 6 months occurred in 19.4% of patients assigned to the conservative strategy versus 15.9% assigned to the invasive strategy (OR 0.78; 95% CI 0.62 to 0.97; P=0.025). Occurrence of death or MI was also reduced at 6 months (9.5% versus 7.3%; P < 0.05). The beneficial effects on outcome were particularly evident in medium- and high-risk patients, as defined by an elevation of troponin T greater than 0.01 ng/mL or of troponin I greater than 0.1 ng/mL, the presence of ST-segment deviation, or a TIMI risk score greater than or equal to 3. In the absence of these high-risk features, outcomes in patients assigned to the 2 strategies were similar. Rates of major bleeding were similar, and lengths of hospital stay were reduced in patients assigned to the invasive strategy. The benefits of the invasive strategy were achieved at no significant increase in the cost of care over the 6-month follow-up period.

Thus, both the FRISC II and TACTICS-TIMI 18 trials, the 2 most recent trials comparing invasive versus conservative strategies in patients with UA/NSTEMI, showed a benefit in patients assigned to the invasive strategy. In contrast to earlier trials, a large majority of patients undergoing PCI in these 2 trials received coronary stents as opposed to balloon angioplasty alone. In TACTICS-TIMI 18, treatment included the GP IIb/IIIa antagonist tirofiban, which was administered for an average of 22 hours before coronary angiography. The routine use of the GP IIb/IIIa antagonist in this trial may have eliminated the excess risk of early (within 7 days) acute MI in the invasive arm, an excess risk that was observed in FRISC II and other trials in which there was no routine “upstream” use of a GP IIb/IIIa antagonist. Therefore, an invasive strategy is associated with a better outcome in UA/NSTEMI patients at high risk who receive a GP IIb/IIIa antagonist. Although the benefit of GP IIb/IIIa antagonists is well established for patients with UA/NSTEMI who undergo PCI, the optimum time of commencing these drugs—as early as possible after presentation, ie, “upstream,” as in TACTICS-TIMI 18, or just before the PCI—has not been established.

Specific recommendations for the use of an invasive strategy in the revised guidelines are as follows:

Class I

1. An early invasive strategy in patients with UA/NSTEMI without serious comorbidity and who have any of the following high-risk indicators: (Level of Evidence: A)
   a. Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy.
   b. Elevated TnT or Tnl
   c. New or presumably new ST-segment depression
   d. Recurrent angina/ischemia with CHF symptoms, an S3 gallop, pulmonary edema, worsening rales, or new or worsening MR
   e. High-risk findings on noninvasive stress testing
   f. Depressed LV systolic function (eg, EF less than 0.40 on noninvasive study)
   g. Hemodynamic instability
   h. Sustained ventricular tachycardia
   i. PCI within 6 months
   j. Prior CABG

2. In the absence of any of these findings, either an early conservative or an early invasive strategy may be offered in hospitalized patients without contraindications for revascularization. (Level of Evidence: B)

INHOSPITAL MANAGEMENT AND SECONDARY PREVENTION

The diagnosis of an ACS should serve as a “wake-up call” to patients with UA/NSTEMI and to their caregivers, and the latter should commence a vigorous, meticulous program of secondary prevention, including achievement of optimal weight, dietary advice, cessation of smoking, exercise, control of hypertension, intensive management of established diabetes, and detection of previously unrecognized diabetes. One area that is not settled is the timing and intensity of statin therapy. The results of observational studies of the early (predischARGE) commencement of statins are mixed. The only large double-blind, placebo-controlled trial, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, while showing a benefit of early statin...
use, achieved just nominal statistical significance (P=0.048), without any benefit in the “hard” prespecified endpoints of death or MI.44 Two large prospective statin trials in post-ACS patients have completed enrollment, are now in a follow-up phase, and will be reported within the next year. In the A to Z trial,45 patients with ACS are assigned to commence simvastatin 40 mg/day or placebo before hospital discharge, and at 4 months these two treatment arms are advanced to simvastatin 80 mg/day and 20 mg/day, respectively. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial37 is comparing marked cholesterol lowering using atorvastatin 80 mg/day with modest cholesterol lowering using pravastatin 40 mg/day, and thereby addresses the question of “how low is low enough” with respect to low-density lipoprotein (LDL) cholesterol. This trial also compares, in a second randomization, gatifloxacin, an oral fluoroquinolone that has potent antichlamydial properties, with placebo.

While awaiting the results of these two trials, there is agreement on several points. First, patients with UA/NSTEMI should be treated, at the very least, in accord with the third report of the National Cholesterol Education Program (NCEP III), and their LDL cholesterol concentrations should be reduced to <100 mg/dL.38 The Heart Protection Study indicates that the outcome of stable patients with even lower baseline levels can be improved with a statin. Second, early, i.e., predischargel commence ment of a statin is well tolerated. Third, observational studies have shown that patients who commence statin therapy before hospital discharge are much more likely to be taking a statin and to have achieved NCEP III established target levels (<100 mg/dL) of LDL cholesterol than patients who are not treated in this manner.39 Fourth, in patients with UA/NSTEMI already receiving a statin at the time of presentation, the drug should not be withdrawn.40 Fifth, the Lescol Intervention Prevention Study (LIPS) compared fluvastatin 80 mg/day with placebo, commencing 2 days after PCI in patients, many with UA/NSTEMI.41 The clinical event rate in the statin-treated group was reduced significantly by 20%. Therefore, it is logical to include UA/NSTEMI patients who have undergone PCI in early cholesterol reduction program.

Last, patients with low high-density lipoprotein cholesterol (<40 mg/dL) should be considered for additional therapy with a fibrate or niacin.11

**LONG TERM LIFESTYLE MODIFICATIONS**

An acute event, like a heart attack, is an opportunity to re-evaluate your lifestyle, including aggressive risk factor modification that can greatly reduce the risk of additional cardiovascular events. Patients with coronary artery disease are at increased risk of other blood vessel problems such as stroke. Therefore, patients who have suffered a heart attack and their families should learn how to manage their cholesterol, blood pressure, and diabetes. Physicians and their staff can provide valuable information on diet, weight control, physical activity, tobacco cessation, and other appropriate lifestyle modifications. Diabetes greatly increases risk of future events, which means lifestyle changes are especially important if diabetes is present or there is a family history of diabetes.

1. Smoking dramatically increases the risk of fatal and non-fatal heart attacks in both men and women. Women who smoke and use oral contraception have an even greater risk of heart attacks and strokes. One year after you quit smoking, your risk of a heart attack drops to about half that of current smokers and gradually returns to normal if there is no established heart disease. Even among people with heart disease, the risk drops sharply 1 year after quitting and continues to decline over time. Nicotine replacement therapies include gum, lozenges, inhalers, nasal spray, and nicotine patches. There is also a non-nicotine prescription drug, called bupropion, which reduces the severity of nicotine cravings and withdrawal symptoms. The likelihood that you will successfully quit smoking is increased further with participation in stop smoking programs that are offered at many local hospitals and health centers. Besides stopping smoking, individuals who have had heart attacks should avoid secondhand smoke, too.

2. There are a number of important lifestyle modifications that are recommended for anyone with a blood pressure of 120/80 mm Hg or greater. These recommendations include: weight reduction if overweight or obese; a daily diet rich in fruits, vegetables, and low-fat dairy products, as well as an overall diet low in total fat and saturated fat; and a reduction of sodium (salt) to no more than 2.4 grams per day.

3. Unless you have specific contraindications to aspirin, anyone who has experienced STEMI should take aspirin indefinitely. Aspirin therapy reduces the risk of a second heart attack by about one-third. Aspirin and medications known as nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly consumed drugs in the world. However, one aspirin alternative known as ibuprofen may limit the protective effects of aspirin, so ibuprofen should not be taken on a regular basis if you are on long-term aspirin therapy. If you need both indefinite aspirin therapy to reduce your risk of a heart attack as well as the regular use...
of aspirin alternatives for pain or other medical conditions, talk to your doctor about which over-the-counter drugs are best for you. Also, if you can’t take aspirin, there are other drugs that your doctor may consider to reduce your risk of another heart attack.

4. Body mass index (BMI) is a measure of a person’s weight in relationship to their height. BMI should be assessed regularly. Weight maintenance or weight reduction should be attained through an appropriate balance of increased physical activity, a reduction in calories consumed every day, and if necessary, formal weight loss programs.

5. Waist circumference is another important measurement, and can point to the presence of metabolic syndrome (a group of several risk factors that greatly increases the risk of future heart problems). If your waist circumference is 35 inches (89 cm) in women or 40 inches (102 cm) in men, initiate lifestyle changes that will help you lose weight and start strategies that will reduce your risk of metabolic syndrome. Waist circumference should be assessed regularly.

In addition to those recommendations listed above, you should reduce your intake of saturated fats (found mostly in animal products) to less than 7% of total calories, greatly reduce intake of trans fats (also in animal products and most snack foods), and limit cholesterol intake to less than 200 mg per day. (Note: 3.5 ounces of beef has 70 mg of cholesterol; 3.5 ounces of chicken has 60 mg of cholesterol; and one boiled egg has 225 mg of cholesterol.) Also, all patients are encouraged to increase their consumption of omega-3 fatty acids, found in fish and in supplement form. At a minimum, low-density lipoprotein cholesterol (LDL) should be reduced to below 100 mg/dl. Indeed, it is reasonable to attempt to reduce LDL-C to less than 70 mg/dl. There is a wealth of evidence that cholesterol-lowering therapy reduces the risk of future cardiovascular events.

Hemoglobin A1c is a blood test which reflects the average blood sugar (properly called blood glucose) level over a 3-month period. In patients with diabetes who have had a heart attack, lifestyle changes (e.g., increased physical activity and management of weight, cholesterol, and blood pressure) are strongly recommended, as are medications necessary to achieve a normal or near-normal HbA1c (less than 7%).

OTHER

Every year in the United States, influenza (“the flu”) causes more than 36,000 deaths and 225,000 hospitalizations. Individuals with chronic conditions, such as cardiovascular disease or diabetes, are particularly vulnerable to complications of the flu. Vaccination during the flu season has a critical but under-appreciated role in the prevention of death or hospitalization. That’s why the guidelines now suggest that any child or adult with cardiovascular disease should have an annual flu shot.

Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) have NOT been shown to be beneficial in reducing risk following a heart attack. Nor is there evidence supporting the use of folic acid, with or without B6 and B12, for secondary prevention. However, it is reasonable to increase consumption of omega-3 fatty acids in the form of fish or in capsule form (1 gram per day) for risk reduction. For treatment of elevated triglycerides, the guidelines suggest that higher doses of omega-3 fatty acids (2 to 4 grams per day) may be used for risk reduction.

Future Directions

Despite the substantial improvement in every aspect of the assessment and care of patients with UA/NSTEMI, this condition remains associated with an unacceptably high incidence of both short- and long-term adverse outcomes. Three current areas of research appear to be quite promising.

The first promising area is the detection of arterial inflammation, using a combination of systemic biomarkers (such as C-reactive protein) and noninvasive imaging (such as high resolution magnetic resonance), in the identification of patients with vulnerable plaques who are at high risk of future development or recurrence of UA/NSTEMI.

The second area is the treatment not only of the culprit lesion but of other vulnerable plaques with multiple drug-eluting stents in patients who have already developed UA/NSTEMI as well as those who have not yet developed a clinical manifestation, but are at high risk, as in the first area, above.

The third area is the use of novel, potent systemic anti-inflammatory drugs (in addition to statins, aspirin, and clopidogrel) in patients with vulnerable plaques.

As important as these future approaches are likely to be, it is of the highest priority to apply the wealth of available information to patient care at this time. Registry-based data suggest that the gap between available knowledge and its application remains unacceptably high.

SUMMARY

Current strategy for medical management of UA/NSTEMI

Patients with UA and negative troponin (low-risk group) should continue to be treated initially with ‘conventional therapy’ with LMWH plus aspirin and anti-anginal drugs. There is no advantage of GP IIb/IIIa receptor antagonist (tirofiban) over conventional heparin therapy in the treatment of UA with negative troponin. During stabilization, LMWH is usually continued for 2 to 8 days. A stress test may then be considered pre-discharge to stratify further risks. Those patients who do not improve with conservative therapy or who have a positive pre-discharge stress test should be promptly considered for coronary angiography and PCI or coronary artery bypass graft surgery (CABG). Patients with negative stress test are at low risk of cardiac events and can be followed-up medically.

Patients of UA with raised serum troponin (high-risk UA) and/
or persistent ST segment depression should be treated with intravenous infusion of a platelet GP IIb/IIIa receptor antagonist plus intravenous UFH and aspirin within 12–24 h of onset of symptoms. One third of all UA patients the regimen is to be continued for at least 48 h or on average, for 72 h. Those who have improved on this regimen can mobilize and undertake a pre-discharge stress test. Patients with negative tests are at low risk of cardiac events and can be followed up medically. Patients who do not respond to the initial GP IIb/IIIa antagonist and heparin combination therapy and who have positive pre-discharge stress test should undergo urgent coronary angiogram and, if necessary PCI/CABG.

More than 80–90% of patients of UA will usually improve with optimal medical therapy. Where cardiac catheterization and PCI/CABG facilities are available on site or within easy reach, all high-risk patients should preferably undergo early coronary angiogram and PCI/CABG if necessary. The combination of GP IIb/IIIa antagonist (tirofiban) and LMWH (enoxaparin) was used in a pilot study consisting of 53 patients. There was better inhibition of platelet aggregation with this combination in comparison to that of tirofiban and UFH. Minor and major bleeding complications were the same on both sides. Whether LMWH is superior to UFH in this regard requires large clinical trials such as the ACUTE II to determine. There is usually no benefit from thrombolytic therapy in the management of UA, including acute NQMI.

CONCLUSION

Risk stratification using troponin level and ST segment deviation in the ECG can help to identify high-risk patients with unstable angina. Low-risk UA should be treated with the conventional regimen of LMWH plus aspirin and anti-anginal drugs. Intravenous platelet GP IIb/IIIa receptor antagonist when given with intravenous unfractionated heparin plus aspirin further improves the outcome of high-risk UA without increasing intra-cranial bleeding complications. The ischaemia-guided conservative approach should remain the initial treatment of choice for UA/NQMI, in the district general hospitals where there is no invasive facility or it is not within easy reach. Patients who are unresponsive to initial medical treatment should be urgently considered for coronary angiogram and further intervention. Early treatment with intravenous GP IIb/IIIa receptor antagonists followed by early coronary angiogram and PCI/CABG if necessary may be considered where readily available. More large randomized controlled trials such as the TACTICS-TIMI 18 and RITA 3 will provide further information on whether the invasive treatment of all patients of UA or the ischaemia-guided initial conservative approach is superior, practicable or cost-effective.

REFERENCES


40. 2007 focused update of the ACC/AHA 2002 guideline for the management of patients with Non ST-elevation myocardial infarction.