Non-ST segment elevation acute coronary syndromes: A simplified risk-oriented algorithm

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Non-ST segment elevation acute coronary syndromes (NSTEMI) include a clinical spectrum that ranges from unstable angina to NSTEMI myocardial infarction. Management goals aim to prevent recurrent ACS and improve long-term outcomes by choosing a treatment strategy according to an estimate of the risk of an adverse outcome. Recent registry data suggest that patients with NSTEMI ACS frequently do not receive recommended treatment, and that risk stratification is not used to determine either the choice of treatment or the speed of access to coronary angiography.

The present article evaluates the evidence for recommended treatment using information from recent trials and guidelines published by the major cardiac organizations in Europe and North America. Using this information, a multidisciplinary group developed a simplified algorithm that uses risk stratification to select an optimal early management strategy. Long-term outcomes are improved by a multifaceted vascular protection strategy that is initiated at the time of hospitalization for NSTEMI ACS.

Key Words: Anticoagulants; Coronary disease; Myocardial infarction; Platelet aggregation inhibitors; Thrombosis

Non-ST segment elevation acute coronary syndromes (NSTEMI) include a clinical spectrum that ranges from unstable angina to NSTEMI myocardial infarction (MI). Nevertheless, it is recognized that this broad spectrum of clinical presentations and outcomes results from a common underlying pathophysiology, with atherosclerotic plaque disruption and differing degrees of associated thrombosis and distal embolization (1,2). While patients with NSTEMI ACSs, in comparison with those with ST segment elevation MI (STEMI), have a greater prevalence of early culprit coronary artery patency (3), they are also at higher risk of recurrent ischemic events (4). The goals of the early management of NSTEMI ACSs are the prevention of recurrent ischemic

Les syndromes coronariens aigus sans surélévation du segment ST : Un algorithme simplifié orienté sur le risque

Les syndromes coronariens aigus sans surélévation du segment ST (SCA SSST) incluent un spectre clinique qui varie de l'angine instable à l'infarctus du myocarde SSST. La prise en charge vise à prévenir une récurrence des SCA et à améliorer les issues à long terme par une stratégie thérapeutique fondée sur une évaluation du risque d'issue négative. D'après les données récentes contenues dans les registres, il n'est pas rare que les patients atteints d'un SCA SSST ne reçoivent pas le traitement recommandé et que la stratification du risque ne soit pas utilisée pour déterminer le choix de traitement ou la vitesse d'accès à une angiographie coronaire.

Le présent article vise à évaluer les données probantes quant aux traitements recommandés au moyen de l'information tirée de récents essais et de récentes lignes directrices publiées par les principaux organismes de cardiologie d'Europe et d'Amérique du Nord. À l'aide de cette information, un groupe multidisciplinaire a mis au point un algorithme simplifié qui fait appel à la stratification du risque pour sélectionner une stratégie optimale de prise en charge précoce. Les issues à long terme s'améliorent grâce à une stratégie de protection vasculaire polyvalente entreprise au moment de l'hospitalisation secondaire à un SCA SSST.

coronary events and adverse remodelling of the damaged myocardium.

A Toronto-based group, with representation from community and tertiary cardiac centres, has previously published guidelines for the early management of NSTEMI ACSs (5), with a subsequent update in 2002 (6). The present document was developed using additional information from recent trials, and focuses on measures aimed at preventing recurrent ACS and improving long-term outcomes in patients presenting with NSTEMI ACSs. In addition, a simplified algorithm and a structured order set to encourage more consistent care that is in line with consensus conferences of the major North American and European associations, societies and colleges of cardiology is presented.

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The conference discussed evidence to support management and considered the consensus conference recommendations for individual treatments of the American Heart Association/American College of Cardiology (AHA/ACC) (7) and the European Society of Cardiology (8). The application of individual management strategies, an algorithm, and structured orders were developed, which were considered applicable in Canada and especially for use in the local Ontario context.

Rationale for an updated algorithm in the management of NSTEMI ACSs

Several issues drive the need for regular updates to management strategies in suspected NSTEMI ACSs. First, this patient group is more heterogeneous than STEMI patient groups, ranging from patients with high-risk non-STEMI to patients with unstable angina, as well as a proportion that are eventually shown to have final diagnoses other than an ACS. Second, the treatment strategy is not as well defined, and there exists a wider range of therapeutic options. Third, recent clinical trials have added new treatments and provided new information about older options.

With the wide range of risks for adverse events in NSTEMI ACSs, it is important to select management strategies that result in the greatest benefit and an optimal benefit-to-risk ratio. The early recognition of patients at highest risk of cardiovascular events allows for the selection of patients that will benefit most and avoids exposing those at low risk to treatments with minimal net benefit despite the risk of significant bleeding. Recent trials and registries have emphasized the need to minimize the risk of major bleeding, because hemorrhage is associated with an important increase in later mortality and recurrent myocardial ischemic events (9-11).

Rationale for structured orders in the management of NSTEMI ACSs

In the management of NSTEMI ACSs, treatment consistent with guidelines is associated with better outcomes (12,13). Registries in Europe and North America have shown that treatment is frequently neither consistently based on current guidelines (14-17) nor tailored to indicators of risk. For example, lower risk patients undergo cardiac catheterization more often and at an earlier point in time than higher risk patients (18).

Due to the complexities in the management of NSTEMI ACSs and the associated high risk for death and recurrent MI, it is important to apply treatment based on evidence-based strategies. Individualization of treatment should be confined to a careful assessment for contraindications to therapy that could increase risk. Furthermore, because most ACS patients in Canada are managed by physicians without specialist expertise in cardiology, it is important that treatment guidelines in the

form of a care map or structured standing orders be in place to facilitate consistent and optimal treatment.

For optimal care, it is recommended that individual institutions develop a process committee to review documents such as the present paper and tailor their application at the local level. To put the recommendations into practice, it is suggested that the process committee develop structured standing orders and a care map that streamlines the assessment of a patient's risk for cardiac events with a management strategy. To facilitate quality assurance, we suggest that physicians caring for patients with NSTEMI ACS be asked to provide justification on standing orders when they choose not to follow recommended strategies. Although physician choice in the selection of therapies must always be respected, it is also important to understand why recommended therapies have not been used.

RISK EVALUATION

Clinical trials and registries demonstrate a wide range of outcomes in patients with NSTEMI ACSs. Worse outcomes are observed in 'real world' registries (19) compared with better outcomes in clinical trials that generally include younger subjects and those with fewer comorbidities. Early risk stratification aims to identify patients who are at a high risk of early mortality or (re)infarction using information available during the first 6 h to 12 h after presentation. The principles of risk stratification in ACSs are to quickly identify patients with a severe ischemic episode, extensive and/or severe proximal coronary artery stenoses, and important left ventricular dysfunction. A recurrent ACS results from rethrombosis at the site of the culprit plaque disruption or plaque rupture at another site. Multiple and simultaneous plaque rupture across several coronary arteries has been documented to occur commonly in the setting of ACSs (20). Finally, the outcome from a recurrent ischemic event is likely to be worse in patients with higher risk features.

Risk assessment is a dynamic and ongoing process that aims to detect new higher risk features during the early hours after presentation that may require changes in the management strategy. Although the risk of an adverse outcome does decrease with time, it is not acceptable today to wait to see whether a high-risk patient stabilizes with conservative therapy. High-risk patients, by their very nature, have a high chance of failing conservative therapy, leading to an adverse outcome. Furthermore, clinical trial data (summarized below) show that the high-risk patient benefits to a greater extent from a more aggressive antiplatelet and antithrombotic regimen, and an early invasive strategy than does the lower risk patient.

Early and accurate recognition of patients with an ACS, followed by careful clinical risk stratification, provides the first steps in identifying the optimal treatment strategy.

ACS recognition

The majority of patients with an ACS have chest pain that has characteristic features of myocardial ischemic pain. However, a significant proportion of individuals (particularly older patients, women, and patients with diabetes) may have other symptoms (ie, syncope, dyspnea and malaise) as their predominant complaint. Patients with atypical symptoms during an ACS are less likely to receive optimal treatment and more likely to have worse outcomes (21). Using the clinical data available, it is important that the patient be allocated to one of three groups (Figure 1). Patients with symptoms highly

Figure 1) Management of the patient with chest pain or atypical symptoms. ACS Acute coronary syndrome

compatible with an ACS (likely ACS) or a possible ACS (often with atypical features) should be managed according to their risk assessment.

Diagnostic techniques and skills need to be optimized. Electrocardiogram (ECG) interpretation is physician-dependent, varies widely and appears to be in need of improvement (22). It was our opinion that ECG computer interpretation cannot be trusted in patients with chest pain because subtle abnormalities, such as terminal T wave inversion and minor degrees of ST segment depression, are often not identified by the computer algorithm. Elevation of cardiac troponin (cTn) I or T above the normal reference level has important prognostic implications (23), which are additive to that indicated by ECG abnormalities (24). While mortality after an ACS relates to both the presenting level and the maximum level of cTn I or T, low-level cTn elevation is predictive of recurrent ischemic events and (re)infarction (25). However, cTn levels close to the normal reference level are reliable only if the assay has a low variability in this range. Choice of an assay with a variability of less than 10% at the reference level is important for the accurate diagnosis of an ACS. It is also essential to recognize that many medical conditions (eg, pulmonary embolism, heart failure and sepsis) may have myocardial damage and elevated troponin that has not resulted from atherosclerotic plaque rupture (26). In these non-ACS conditions, troponin elevation also predicts a higher risk of adverse outcome.

Predictors of high risk

Multivariable analyses of clinical trials (27) and registries (28) have shown that high-risk patients with a clear diagnosis of an ACS are identified by the following features: hypotension, tachycardia, frequent episodes of ischemia, elevated troponin, ST segment shift and refractory myocardial ischemia. Other factors that are included in risk stratification algorithms include increasing age, diabetes, renal dysfunction, the presence of known coronary artery disease, prior acetylsalicylic acid (ASA) usage and multiple risk factors for coronary artery disease. These latter indicators are useful to more precisely define risk in patients with a clear diagnosis of ACSs (eg, those with ST depression or elevated troponin). Furthermore, they provide help in determining the likelihood of ACSs and in the risk stratification of patients without objective evidence.

Risk scores

Models of risk evaluation have been derived from clinical trials, such as the Thrombolysis in Myocardial Infarction (TIMI) trial (29) and the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PUR-SUIT) trial (30), and from registries, such as the Global

TABLE 1
Features of a stress electrocardiogram (ECG) or a myocardial perfusion scan that suggest a high risk for death or nonfatal myocardial infarction in patients with recent (possible) acute coronary syndromes

Exercise ECG*	Myocardial perfusion scan
Low exercise tolerance – maximal exercise capacity <6 METs	Multiple, reversible myocardial perfusion defects
BP fall >10 mmHg or failure to rise >10 mmHg	Large territory of reversible myocardial perfusion
Ischemic response at low exercise level – ST depression >1 mm at <5 METs	Large, fixed defect Lung uptake of tracer
Sustained ST depression >3 min after exercise	LVEF <35%
Ventricular tachycardia induced by stress	

*Data from reference 129. BP Blood pressure; LVEF Left ventricular ejection fraction; MET Metabolic equivalent

Registry of Acute Coronary Events (GRACE) (31,32). These models identify high-risk populations of patients but may be of limited value in the recognition of individual patients at high risk. For example, a previously healthy, young patient with chest pain, 2 mm ST segment depression and no elevation in cardiac biomarkers may have a low TIMI risk score despite the high-risk electrocardiographic findings. Risk scores may be of value in establishing the risk in patients with no high-risk features (such as heart failure, hypotension, ST depression or elevated troponin). Risk scores derived from registries (such as GRACE) that include patients with a wide risk spectrum are preferable for the assessment of these indeterminate risk patients, rather than risk scores derived from clinical trials (such as TIMI) that largely include high-risk patients with either ST depression or elevated biomarkers troponin or creatine kinase (CK) MB.

'Low-risk' ACS patients

The patient with symptoms compatible with an ACS but with no high-risk features requires careful observation and further testing before it can be decided that the risk of early adverse events is not high. The risk should be considered to be indeterminate until serial ECG and troponin level tests have been performed and found to be unchanged or normal over a 6 h to 8 h period. However, it should be recognized that patients with negative serial biomarkers and no ECG ST segment shift, albeit at lower risk, are not necessarily at low risk (33). Furthermore, although it is current practice to make triage decisions based on negative troponin testing after an observation period of 6 h, the sensitivity of both troponin I and T for the diagnosis of an ACS is only 60% at this point in time and does not maximize until 14 h to 18 h (34). In patients stratified as indeterminate risk, either an early stress ECG or a stress myocardial perfusion scan has been shown to be helpful in identifying a higher risk subset that requires coronary angiography (Table 1). Ideally, the test should be performed within 24 h after presentation. However, in most Canadian hospitals, it is not currently possible to obtain a stress ECG or perfusion scan within this time frame. Consequently, a decision has to be made based on the likelihood of an ACS and the outcome, if indeed an ACS had occurred. Patients with a 'background risk' (eg, known coronary artery disease, diabetes or renal insufficiency) or with very typical ischemic cardiac symptoms, but with no high-risk ECG abnormalities and troponin levels

below the normal reference range, should be considered for admission for further observation, especially if noninvasive testing is not immediately available. The Chest Pain Evaluation in the Emergency Room (CHEER) study (35) showed that patients with increased background risk but no high-risk ECG features or troponin elevation could be safely discharged from a chest pain unit after observation for 9 h and after passing a stress test with no high-risk features.

Key messages

For patients presenting with symptoms compatible with an ACS:

- Make a clear provisional diagnosis.
- Assess the risk of an adverse outcome.

High risk

Chest pain at rest and one or more of the following:

- Heart failure;
- Hypotension;
- ECG ST shift (depression more than 0.5 mm or transient elevation);
- Elevated cTn I or T; or,
- Refractory pain with ECG change despite medical treatment.

Indeterminate risk

- Patients with chest pain compatible with an ACS and no high-risk features until further risk stratification is completed.

Lower risk

- Indeterminate risk at the initial assessment and no high-risk features at the reassessment 6 h to 8 h later; and,
- Stress ECG or perfusion scan not high risk (Table 1).

EARLY CARDIAC CATHETERIZATION AND CORONARY REVASCULARIZATION

Current evidence supports a strategy of early cardiac catheterization in most patients with NSTEMI ACSs who are considered to be at high risk for an adverse outcome. Four meta-analyses (36-39) have concluded that an early (during the index hospitalization), routine invasive strategy is superior to a selectively invasive approach. A recent analysis of seven trials that included 9212 patients showed that the rate of death or MI was reduced by 18% (OR 0.82, 95% CI 0.72 to 0.93) at a mean follow-up period of 17 months (range six to 24 months) with routine, early coronary angiography and revascularization when appropriate, compared with a selective approach (37). This early benefit was largely related to a reduction of MI. The meta-analysis showed that higher risk patients with elevated cardiac biomarkers benefited from the routine invasive strategy, whereas patients without troponin or CK MB elevation had little benefit. The Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) TIMI 18 study (40) and the TIMI 3B study (41) showed that high-risk patients stratified by risk factors in addition to markers of myocardial necrosis benefited most from an early invasive strategy. In the TACTICS-TIMI 18 study (40), patients with intermediate risk classified by a TIMI risk score

of 3 or 4 also had a smaller but still significant benefit. It should be noted that the patients with TIMI intermediate risk scores of 3 or 4 had a six-month death, nonfatal MI or rehospitalization for ACS rate of 20.3% and would likely have presented with ECG ST segment depression and/or positive troponin or CK MB. Consequently, such patients cannot be considered to be intermediate risk by the usual standards of risk stratification (no high-risk features, but prior history of coronary artery disease or diabetes).

The long-term benefit of the routine invasive strategy versus a conservative management strategy is tempered by an early hazard, with a significant increase in death or MI during the initial hospitalization (3.8% versus 5.2%; OR 1.36, 95% CI 1.12 to 1.66; $P=0.002$) (37). However, after discharge, the routine invasive strategy is associated with fewer deaths (3.8% versus 4.9%; OR 0.76, 95% CI 0.62 to 0.94) and reduced death or MI rates (7.4% versus 11.0%; OR 0.64, 95% CI 0.56 to 0.75). Both severe angina and the need for rehospitalization are reduced by the routine invasive strategy. Trials performed since 1999 (FRagmin and fast revascularisation during InStability in Coronary artery disease II [FRISC II] [42], TACTICS-TIMI 18 [40], Value of first day angiography/angioplasty In evolving non-ST segment elevation myocardial infarction: An open multicentre randomized trial [VINO] [43], and Randomized Intervention Trial of unstable Angina 3 [RITA 3] [44]) show a clear reduction of death or MI compared with trials performed earlier than 1999 (TIMI 3 [45], Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital [VAN-QWISH] [46], and Medicine versus Angiography in Thrombolytic Exclusion [MATE] [47]). A recent metaregression analysis (38) indicated that these benefits from an early invasive strategy (including reduced mortality) were only achieved when coronary stenting and an aggressive antiplatelet strategy was employed.

The recently reported Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial (48) compared a routine early invasive strategy with a more selective invasive strategy in NSTEMI ACS patients with elevated troponin, and either ECG abnormalities or a documented history of coronary artery disease. Both strategies resulted in a similar outcome based on a combined end point of death, nonfatal MI or rehospitalization for anginal symptoms within one year after randomization. One-year mortality was very low at 2.5% in both groups, suggesting that these patients constituted a lower risk group than originally intended. In this study, the conservative group was aggressively managed, with 40% of the selective invasive group undergoing revascularization during the index hospitalization, compared with 76% in the early invasive group. This difference in early revascularization may have not been large enough for the study to show the benefit of one strategy over the other. Myocardial infarction, defined by any increase in CK MB above the reference level, was increased in the early invasive strategy group. However, when the analysis was repeated using a CK MB level of threefold above the normal range for patients undergoing percutaneous coronary intervention (PCI), which was the threshold for the diagnosis of peri-PCI infarction in the TACTICS-TIMI 18 study (49), the difference in the incidence of MI between the two management strategies was no longer statistically significant. Furthermore, the follow-up period of the ICTUS study may have been insufficient to observe differences in mortality between the two groups.

The longer term benefit of an early revascularization strategy was observed in the FRISC II trial (42), which found a 30% reduction in one-year mortality for patients treated with an early strategy compared with patients managed conservatively. Although the one-year data from RITA 3 (44) showed no reduction of death and MI, after a median follow-up of five years (50), there was a 22% reduction in death or nonfatal MI and a 26% reduction in cardiovascular death in patients treated with an early invasive strategy compared with those managed conservatively.

Higher risk patients receive the greatest benefit from an early and routine invasive strategy compared with a selective and delayed invasive strategy (51). Patients with the greatest benefit had an elevated troponin level, ST segment depression or a high-risk TIMI risk score. The long-term benefit of an early invasive strategy in the RITA 3 trial (50) was also observed in the highest risk group.

The increased incidence of MI during the first 24 h to 48 h in patients randomly assigned to an early invasive strategy in the FRISC II trial was not observed in the TACTICS-TIMI 18 study. These early ischemic events may have been avoided in the TACTICS-TIMI 18 study by the earlier time to PCI and by pretreatment with the glycoprotein (GP) IIb/IIIa inhibitor tirofiban. The optimal timing of early cardiac catheterization remains controversial. There is an increasing trend toward NSTEMI ACS patients being taken to the catheterization laboratory within the first 24 h after symptom onset. Early revascularization within 48 h in patients in the Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) registry (52) was associated with significant reductions in death and MI. The TACTICS-TIMI 18 study indicated that the best results were obtained when the procedure was performed within the first 48 h. The Intracoronary Stenting with Antithrombotic Regimen Cooling-Off (ISAR COOL) trial (53) suggested that there was no benefit from a 72 h period of medical stabilization compared with immediate cardiac catheterization within 6 h, as ischemic events occurred more frequently, despite an aggressive protocol of heparin, ASA, clopidogrel and GP IIb/IIIa inhibitors for up to 72 h before PCI in the medical stabilization group. However, the difficulty of diagnosing early reinfarction in patients undergoing very early PCI prejudices the results against the medical stabilization group. Hence, the current evidence supports early angiography within the first 48 h in the majority of patients identified as high risk. This time frame is supported by a report by the Canadian Cardiovascular Society Access to Care working group that emphasized the need to prioritize access to cardiac catheterization and revascularization according to risk (54). For patients with frequent episodes of ischemia or hemodynamic disturbance, even more urgent coronary angiography may be necessary.

Early cardiac catheterization not only identifies patients that may benefit from revascularization but also provides useful prognostic information. Approximately 20% of patients have minimal disease or even normal angiographic coronary arteries. In addition, 10% to 15% have significant left main coronary artery disease. Patients undergoing 'routine' early coronary angiography do not all require early revascularization. In the TACTICS-TIMI 18 trial, revascularization was performed for suitable coronary anatomy (49) and in the FRISC II trial for lesions greater than 70% in severity (42). There may

be danger of excessive revascularization of borderline lesions or attempting PCI in lesions that are not anatomically suitable. Discrimination is required to select patients who may benefit from early revascularization.

Key messages

- Patients with NSTEMI ACSs and high-risk features benefit from an early invasive strategy (prevention of MI and improved long-term survival).
- High-risk NSTEMI ACS patients should ideally undergo cardiac catheterization during the initial 48 h after presentation; the referral process should be initiated immediately upon identification of the patient as belonging to a high-risk group.
- Hemodynamically unstable patients or those with frequent ischemic episodes should be referred for emergency catheterization.

ANTIPLATELET THERAPY

ASA

Clinical trials completed more than 20 years ago confirmed the benefit of ASA use in patients with unstable angina, and showed a 50% to 70% reduction in both early and late cardiovascular event rates (55,56). More recent analyses (57) have shown that this benefit can be achieved with ASA doses of 75 mg to 100 mg daily (these doses are associated with less gastrointestinal intolerance and bleeding). Patients that are allergic to ASA can be successfully desensitized, although they must then continue with ASA without interruption to prevent re-sensitization (58,59). 'Aspirin resistance' is reported in 8% to 56% of individuals (60). However, the mechanisms of this variability and the clinical significance are unclear.

Clopidogrel

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial (61) confirmed the value of clopidogrel added to ASA treatment in patients with NSTEMI ACSs. Over the nine-month period of follow-up, the composite primary end point of death, MI or stroke was reduced by 20% with clopidogrel therapy initiated within 24 h of symptom onset (RR 0.8, 95% CI 0.72 to 0.90; $P < 0.001$). Recurrent ischemic events were reduced within several hours following administration of the clopidogrel 300 mg loading dose given at the time of randomization. Similar benefits were observed from clopidogrel across a wide range of subgroups and risk classes (62). An excess of major bleeding events occurred in 1% of the patients receiving clopidogrel and ASA compared with those who received ASA alone. Those receiving under 100 mg of ASA plus clopidogrel had lower bleeding rates than subjects receiving 325 mg of ASA alone, with similar recurrent ischemic event rates across the range of ASA doses.

Increased perioperative bleeding in patients receiving clopidogrel within five days before coronary artery bypass graft (CABG) surgery was observed in the CURE trial and in subsequent observational reports (63). In the CURE trial, the 50% increase in perioperative major bleeding in the group that continued clopidogrel treatment to within five days of surgery was not associated with an increase in either death or MI. Furthermore, patients randomly assigned to clopidogrel and CABG surgery had an important benefit from early and

postoperative clopidogrel therapy, which translated into an improvement in long-term outcomes (64). Most of this benefit was obtained during the preoperative waiting period.

Prior iterations of NSTEMI ACS algorithms (5,6) and the AHA/ACC guidelines (7) have recommended that clopidogrel not be given initially to ACS patients with a high likelihood of requiring early bypass surgery. However, recent Canadian registry data show that only 1.6% of NSTEMI ACS patients underwent CABG within five days of presentation (SG Goodman, ACS Registry II, personal communication). It is difficult at the time of the initial clinical risk assessment to predict which patient may require early surgical revascularization. Furthermore, risk stratification tools to identify patients that may need coronary bypass surgery have a poor predictive accuracy (65). Consequently, patients in whom clopidogrel has not been initiated for fear of requiring early CABG may forego the early benefits of clopidogrel. A high proportion of these patients are subsequently found to be candidates for medical or PCI therapy rather than CABG surgery. Thus, the potential for perioperative bleeding in a very small number of patients is outweighed by the early benefits of clopidogrel in high-risk patients. In cases in which clopidogrel therapy is followed by early bypass surgery, recent clinical trials indicate that the excess surgical bleeding associated with clopidogrel can be reduced using antifibrinolytic agents such as aprotinin (66,67). One trial (68) compared the strategy of continuing ASA and clopidogrel treatment until surgery with the strategy of dual placebo treatment for five preoperative days. Patients receiving clopidogrel and ASA also received aprotinin at the time of surgery. The clopidogrel/ASA/aprotinin group had significantly fewer bleeding complications than the placebo group. Recent uncontrolled data (69) suggest that aprotinin use at the time of cardiac surgery may be associated with an increased incidence of renal failure and perioperative MI. However, this study was observational, and the randomized data comparing aprotinin and placebo do not indicate harm with aprotinin. Given the absence of good randomized, controlled data showing harm with aprotinin, the known excessive bleeding risk with recent clopidogrel administration and controlled evidence showing the benefit of aprotinin in these patients, aprotinin should remain an option for the prevention of excessive bleeding in these high-risk patients.

For high-risk patients receiving an intravenous GP IIb/IIIa agent, the combination with ASA and clopidogrel is probably not associated with excessive bleeding provided that the duration of patient exposure to all three agents is short (48). Because GP IIb/IIIa inhibitor therapy is likely only used for very high-risk patients, including those with refractory ischemia, the duration of triple antiplatelet treatment before cardiac catheterization and revascularization is likely to be short (eg, less than 24 h to 48 h).

In vitro testing of platelet function has suggested that over one-third of patients with a recent ACS have a diminished response to clopidogrel (70). It is uncertain whether this in vitro failure to inhibit platelet aggregation translates into diminished clinical effectiveness. One study of patients undergoing primary PCI for STEMI (71) indicated that a reduced platelet response to clopidogrel was associated with an adverse outcome. Diminished in vitro responsiveness is reduced by increasing the loading dose and with longer periods of administration (72). Recent studies suggest that an increased loading dose of clopidogrel 600 mg (73) or 900 mg (72) before elective

PCI reduces periprocedural adverse events and appears to be safe compared with the standard 300 mg dose.

All high-risk patients should receive clopidogrel 300 mg and ASA 160 mg at the time of presentation, followed by clopidogrel 75 mg daily and ASA 81 mg daily. Lower risk patients with an important comorbidity, such as pre-existing coronary artery disease, diabetes and/or renal disease, and no ECG high-risk features, can be considered for clopidogrel as well. Evidence from the CURE trial (62) is supportive of clopidogrel use in these patients.

Key messages

- ASA for all patients:
 - Except those with ASA allergy (consider desensitization).
 - Use a low dose (eg, 81 mg daily).
- Clopidogrel 300 mg loading dose followed by 75 mg daily:
 - For all high-risk patients without bleeding contraindications.
 - Consider clopidogrel for indeterminate risk patients with high-risk comorbidity (eg, diabetes and/or renal disease) but with no high-risk features.
 - In place of ASA for true ASA allergy.
- Consider clopidogrel and the risk of CABG bleeding in the context of:
 - The early benefits associated with clopidogrel therapy;
 - The benefit of clopidogrel in patients undergoing CABG surgery;
 - The small number of patients requiring urgent CABG surgery within five days of presentation; and,
 - Bleeding, which can be controlled and/or reduced.
- Clopidogrel resistance is of uncertain clinical importance.

GP IIb/IIIa inhibitors

Intravenous platelet GP IIb/IIIa inhibitors have been studied in several large-scale clinical trials that included over 31,000 patients, with findings suggesting a modest but statistically significant benefit (one fewer death or MI at 30 days per 100 patients treated) over placebo (74). While trials of abciximab administered during or for a short period before PCI showed clear benefit, there was no advantage with a more prolonged (24 h to 48 h) infusion in a wider range of patients with NSTEMI ACSs (75). In contrast, tirofiban (76,77) and eptifibatide (78) infusions for periods of up to 96 h reduced early death and nonfatal MI when used in the initial medical management of patients with NSTEMI ACSs. Although it has been suggested that the benefit of GP IIb/IIIa inhibition in NSTEMI ACSs is limited to patients undergoing PCI, it is important to acknowledge that this is an improper (postrandomization) subgroup comparison (79). The relative treatment benefit has been found to be similar in subgroups of patients according to important clinical (prerandomization) baseline characteristics (eg, patients with troponin elevation [80,81] and diabetes mellitus [82]); hence, the absolute treatment benefit is largest in

high-risk patients. Consistent with the randomized clinical trial experience, registry data, including patients with NSTEMI ACSs in the CRUSADE experience (83) and the National Registry of Myocardial Infarction 4 (NORMI 4) experience (84), show an association between improved outcomes and early GP IIb/IIIa inhibition use.

The AHA/ACC guidelines (7) recommend the early use of either tirofiban or eptifibatide in high-risk patients if cardiac catheterization or PCI is planned. Because most high-risk NSTEMI ACS patients currently undergo early cardiac catheterization and revascularization when feasible, it is possible to predict which patients will proceed to coronary angiography. Canadian clinical registries show that GP IIb/IIIa use in patients with high-risk NSTEMI ACSs is less than 15% (85). Multiple reasons are likely for such low utilization and include the modest, overall short-term benefit, the neutral outcome for abciximab in the Global Use of Strategies To Open occluded arteries trial IV (GUSTO IV) trial (75), cost, substitution with clopidogrel and failure to appreciate the high-risk patient profile.

Although GP IIb/IIIa inhibitors are frequently reserved for patients that have refractory and/or recurrent ischemia despite ASA, clopidogrel and a heparin, there is no randomized clinical trial evidence to support benefit in this situation. Platelet aggregation studies suggest that GP IIb/IIIa inhibitors have powerful antiaggregatory properties in addition to those achieved with clopidogrel (86). The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) study (87) compared outcomes in patients with recent NSTEMI ACSs who had been pretreated with clopidogrel and were randomly assigned to receive either abciximab or placebo at the time of PCI. The patients receiving both clopidogrel and the GP IIb/IIIa inhibitor had a 25% reduction in the combined end point of death, nonfatal MI or urgent target vessel revascularization. The added benefit from a GP IIb/IIIa inhibitor in addition to clopidogrel was seen in patients with elevated troponin, with no added benefit in those without troponin elevation.

The AHA/ACC guidelines (7) recommend that a GP IIb/IIIa inhibitor be administered either at the time of presentation or delayed until the patient undergoes PCI. A sub-randomization of the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial allocated patients with a recent moderate- to high-risk NSTEMI ACS to administration of an early 'upfront' GP IIb/IIIa inhibitor or to later administration at the time of early PCI. The early administration of the GP IIb/IIIa inhibitor was associated with no decrease in ischemic events, although bleeding was increased in patients receiving 'upfront' GP IIb/IIIa inhibitors. However, the very brief time from randomization to PCI (median 5 h to 6 h) makes it difficult to detect a potential difference in the 'upstream' versus 'downstream' use of GP IIb/IIIa inhibition. Thus, in the ACUITY trial, patients receiving upstream therapy would be exposed to the bleeding risk but would not likely have enough time to experience the potential benefits of initial GP IIb/IIIa inhibition. Further, post hoc analyses of GP IIb/IIIa inhibitor trials in NSTEMI ACS have demonstrated important benefits (eg, lower reinfarction rates) of upstream use before PCI.

Thus, for many patients with NSTEMI ACSs, the administration of a GP IIb/IIIa inhibitor has been delayed until the patient is to undergo PCI. For patients with refractory ischemia

or very unstable ischemia, a GP IIb/IIIa inhibitor before urgent cardiac catheterization is likely beneficial. The ongoing Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial (88) will better address the issue of early eptifibatide compared with placebo in patients with high-risk NSTEMI ACSs in whom an invasive strategy is planned, on a background of ASA, heparin, clopidogrel and other evidence-based therapies.

Key messages

- The GP IIb/IIIa inhibitors eptifibatide and tirofiban reduce ischemic coronary events in high-risk NSTEMI ACS patients before and during PCI. However, with current early revascularization strategies and the use of clopidogrel, GP IIb/IIIa inhibitor use could probably be reserved for higher risk patients.
- A GP IIb/IIIa inhibitor has added benefit in patients pretreated with clopidogrel and undergoing PCI. Administration of a GP IIb/IIIa inhibitor should be strongly considered at the time of PCI in patients with elevated troponin if not already administered as initial medical management.
- Tirofiban or eptifibatide should be considered for acutely ill patients in urgent need of coronary angiography and revascularization. Such patients include those with:
 - frequent ischemic episodes with ST segment changes;
 - hypotension or heart failure in association with ischemic episode;
 - refractory ischemia despite ASA/clopidogrel/heparin;
 - very high-risk ECG features (eg, transient ST elevation).

ANTITHROMBINS

The addition of a heparin to ASA in patients with NSTEMI ACSs reduces the incidence of death or nonfatal MI by 33% (89). A recent meta-analysis (90) showed that the low-molecular-weight heparin enoxaparin has a modest 9% relative reduction of 30-day death/MI (OR 0.91, 95% CI 0.83 to 0.99) compared with unfractionated heparin (UFH). The benefit of enoxaparin over UFH is greatest in higher risk patients. For patients managed aggressively with cardiac catheterization in the first 24 h, the Superior Yield of the New strategy of Enoxaparin, Revascularization and GLYCOPROTEIN IIb/IIIa inhibitors (SYNERGY) trial (91) showed no benefit of enoxaparin over UFH, with major bleeding increased by enoxaparin in this setting. In the Canadian context, where NSTEMI ACS patients usually undergo coronary angiography beyond the first 24 h, enoxaparin has the benefits of enhanced efficacy, practical convenience and no increased bleeding compared with UFH (92). The SYNERGY trial (91) indicated that recurrent ischemic events and major bleeding were more frequent when antithrombotic therapy was switched from enoxaparin to UFH or vice versa. Ideally, patients should remain on the heparin initiated in the emergency department. Enoxaparin is safe to use during cardiac catheterization and PCI (91,93), and most Canadian interventional cardiologists perform PCI on patients receiving enoxaparin without mandating a switch to UFH (94).

Fondaparinux

The recently published Organization to Assess Strategies for Ischemia Syndromes 5 (OASIS 5) study (95) randomly assigned the factor Xa inhibitor fondaparinux or enoxaparin to 20,078 patients with NSTEMI/ACSs in a noninferiority design. As hypothesized, early outcomes were similar with the two agents, but the rate of major bleeding in patients receiving fondaparinux was almost one-half of that observed in patients receiving enoxaparin. Furthermore, 30-day and six-month mortality was significantly lower in the patients treated with fondaparinux. The lower mortality in the fondaparinux-treated patients was almost entirely explained by the reduction in major bleeding observed with fondaparinux. The OASIS 5 study reinforces earlier observations that early major bleeding in the setting of NSTEMI/ACSs is associated with adverse outcomes (96). Fondaparinux-treated patients had less bleeding in a wide range of subgroups that included PCI, renal dysfunction and the use of concomitant UFH.

Catheter-related thrombi occurred rarely but significantly more frequently in the fondaparinux-treated group. However, many patients underwent PCI after receiving a single dose of fondaparinux, and most of the catheter-related thrombi occurred in fondaparinux-treated patients who had not routinely received UFH peri-PCI. When open-label UFH was used before PCI, only one case of catheter thrombus was reported, without any apparent increase in bleeding risk. Thus, fondaparinux should be considered as an initial antithrombin therapy; it has an efficacy similar to that of enoxaparin, but with superior safety and associated mortality benefits. It is important that centres considering the routine use of fondaparinux in NSTEMI/ACS patients work collaboratively with interventional cardiologists to develop a protocol to effectively and safely transition patients who subsequently undergo PCI.

Bivalirudin

A recent meta-analysis (97) has suggested that direct thrombin inhibitors such as bivalirudin are more effective than heparin in reducing death or reinfarction in patients with ACSs undergoing early PCI. Furthermore, for patients undergoing either elective or urgent PCI, bivalirudin was shown in the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events 2 (REPLACE 2) trial (98) to be as effective as the combination of heparin with a GP IIb/IIIa inhibitor, but with reduced bleeding. The ACUITY trial (99), presented at the Scientific Sessions of the 2006 Annual Meeting of the ACC, compared the use of the following: enoxaparin or UFH in combination with a GP IIb/IIIa inhibitor; bivalirudin with a GP IIb/IIIa inhibitor; and, bivalirudin alone in patients with moderate- to high-risk NSTEMI/ACSs undergoing an aggressive, early invasive strategy. Although there was no difference in the ischemic end point among the three strategies, patients receiving bivalirudin alone had less major bleeding than the patients in the other two groups. Bivalirudin is an attractive antithrombin in patients with moderate- to high-risk NSTEMI/ACSs who will undergo very early cardiac catheterization within 12 h to 24 h. It is unlikely to be used for a longer duration, in part due to the cost of the medication.

Conclusions

The AHA/ACC guidelines currently recommend that all high-risk patients receive a form of heparin. However, enoxaparin is considered preferable to UFH unless the patient requires urgent

coronary artery surgery or will likely undergo coronary angiography within 24 h. Indeterminate risk patients, especially those with a prior history of coronary artery disease or with diabetes, may also receive enoxaparin until further risk stratification with noninvasive testing is completed. Because enoxaparin is renally excreted, creatinine clearance must be estimated in all patients before starting enoxaparin. The current labelling recommendation for enoxaparin administration in patients with an estimated glomerular filtration rate of less than 30 mL/min is to halve the dose to 1 mg/kg subcutaneously once daily. This recommendation was based on pharmacodynamic studies. However, little safety data are available in patients with renal insufficiency (especially with end-stage renal disease) receiving enoxaparin in the setting of NSTEMI/ACSs. Consequently, it is preferable to use UFH for patients with renal insufficiency and an estimated creatinine clearance of less than 30 mL/min.

Fondaparinux is a very attractive alternative to enoxaparin because it has similar short-term efficacy, as well as an improved safety profile, lower medium-term mortality and lower cost. Fondaparinux should therefore emerge as the preferred antithrombin therapy. For patients undergoing PCI, catheter-related thrombosis appears to be mitigated by peri-PCI UFH administration. Consequently, it is important that protocols be developed collaboratively with interventional centres for patients receiving fondaparinux who are likely to undergo PCI.

Key messages

- All high-risk patients should receive an antithrombin – one of UFH to achieve an activated partial thromboplastin time (aPTT) target 1.5 to 2.0 times control aPTT, low-molecular-weight heparin (preferably enoxaparin at a dose of 1 mg/kg subcutaneously twice daily) or fondaparinux (2.5 mg subcutaneously once daily).
- Enoxaparin is preferable to UFH in patients managed conservatively or those unlikely to undergo cardiac catheterization in the next 24 h.
- Switching from enoxaparin to UFH or from UFH to enoxaparin is associated with increased adverse outcomes and bleeding.
- In patients with renal dysfunction (estimated glomerular filtration rate less than 30 mL/min) should be given UFH rather than enoxaparin.
- Fondaparinux should be considered the preferred antithrombotic agent based on an enhanced safety profile, a lower mortality and a similar anti-ischemic benefit compared with enoxaparin.
- Bivalirudin is a potential alternative antithrombotic agent in patients undergoing very early coronary angiography.
- Each institution should choose an antithrombin strategy (enoxaparin, UFH or fondaparinux) in the majority of patients and use it consistently.

OTHER THERAPY

Intravenous beta-blockers have been shown to have a modest benefit on short-term mortality and reinfarction. Two meta-analyses of 28 (100) and 52 (101) trials showed an absolute

benefit of approximately seven lives saved per 1000 patients treated. However, the recent Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trial (102), which included over 45,000 patients (most of whom had STEMI), showed no overall benefit with early beta-blocker use. Although intravenous metoprolol reduced reinfarction and ventricular fibrillation, these benefits were counteracted by an increased incidence of cardiogenic shock, particularly in patients with a Killip class greater than 1. As a result of this trial, the early use of intravenous beta-blockade in patients with acute MI (AMI) is only recommended when the hemodynamic situation has stabilized. In patients with NSTEMI ACSs in the absence of infarction, there is little evidence to support the use of early intravenous beta-blockade, except as a measure to relieve symptoms in the patient with persistent chest pain.

Angiotensin-converting enzyme (ACE) inhibitors (with enalapril, captopril or lisinopril) started in the early phase of MI (within 36 h) reduce mortality by 7% (95% CI 2% to 11%) after a few weeks or months of treatment (103). For patients with heart failure or impaired left ventricular function (left ventricular ejection fraction [LVEF] less than 35% to 40%), ACE inhibition with lisinopril, ramipril, captopril ortrandolapril begun during the first three to 28 days and continued for 15 to 42 months reduces mortality by 26% (OR 0.74, 95% CI 0.66 to 0.83), readmission for heart failure by 27% (OR 0.73, 95% CI 0.63 to 0.85; $P < 0.0001$) and reinfarction by 20% (OR 0.8, 95% CI 0.69 to 0.94). The Valsartan in Acute Myocardial Infarction (VALIANT) trial (104) showed that the angiotensin receptor blocker valsartan is an alternative medication for patients with AMI and either heart failure or impaired left ventricular function, especially if they are intolerant of an ACE inhibitor.

Key messages

- Intravenous beta-blockade has a modest benefit for patients with AMI but should not be administered until the patient is hemodynamically stable.
- Oral ACE inhibition started within a few days after an NSTEMI AMI should be considered in all patients with heart failure or an LVEF less than 40%.

HIGH-RISK SUBGROUPS

Patients with chronic kidney disease (105), advanced age (106) and heart failure (107) have a high risk for adverse outcomes after an ACS. Unfortunately, these patients are less likely to receive optimal treatment as recommended by current guidelines (108). Although it is recognized that clinical trials have rarely included these high-risk patients, it is generally accepted that the net benefit of treatment remains favourable. Because the risk for death and nonfatal MI is very high, the larger absolute benefit from treatment exceeds any increased risk of hemorrhage. Consequently, aggressive treatment according to guidelines devised for younger patients and those with normal renal function should be applied to these high-risk patients. Aggressive treatment in the highest risk patients should be considered an opportunity, not a threat, because the absolute treatment benefits can be quite large. However, dose adjustments and choice of medications both for older patients and for those with renal insufficiency are necessary to optimize outcomes (109). Long exposures to antiplatelet and antithrombotic agents increase the risk of bleeding.

Consequently, the duration of treatment with agents such as heparin and GP IIb/IIIa inhibitors should be minimized by providing rapid, early access to coronary angiography and PCI in these high-risk groups.

For patients with renal insufficiency, an early invasive treatment strategy may precipitate contrast nephropathy, renal failure and dialysis. This risk needs to be considered when determining the timing of coronary angiography. Patients with renal insufficiency who undergo cardiac catheterization should receive measures to minimize the risk of contrast nephropathy (especially hydration pre- and postprocedure, and minimization of the volume of contrast media).

Key messages

- High-risk groups of patients, such as those with advanced age, renal insufficiency, diabetes and heart failure, who stand to benefit the most from proven therapies, are less likely to receive them than patients at lower risk.
- The net benefit of antithrombotic, antiplatelet agents and early cardiac catheterization in these patients with higher risk NSTEMI ACSs features favours treatment, despite a greater incidence of hemorrhagic complications.

LONG-TERM TREATMENT: THE DISCHARGE PRESCRIPTION

The greatest impact on long-term outcomes is achieved by optimizing measures to prevent recurrent cardiovascular events. Patient education to encourage lifestyle changes must be initiated early. Efforts to promote smoking cessation after an acute coronary event are likely to be more successful than at any other time. However, it is recognized that for implementation of lifestyle modification, ongoing support in a cardiac rehabilitation centre is most likely to result in long-term success.

Over two-thirds of patients with ACS have abnormal glucose metabolism: 30% have known diabetes, 15% have newly diagnosed diabetes, 22% have impaired glucose tolerance and 5% have impaired fasting glucose (110,111). The identification of undiagnosed diabetes provides an opportunity to improve outcomes by initiating glycemic control. For patients with impaired glucose tolerance and impaired fasting glucose, weight loss and increased physical activity are most likely to prevent the progression to diabetes.

Long-term treatment with statins results in a substantial reduction of death, MI and stroke in patients with stable coronary artery disease, even when low-density lipoprotein (LDL) cholesterol levels are not elevated. Additionally, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study (112) and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) TIMI 22 (PROVE IT-TIMI 22) study (113) have shown that high-dose atorvastatin, when started early after an ACS, reduces cardiovascular events, with event curves beginning to diverge within 30 days of initiating treatment (114). The PROVE IT-TIMI 22 study showed that atorvastatin 80 mg, compared with treatment with pravastatin 40 mg, reduced the combined end point of death, nonfatal MI, unstable angina, late revascularization and stroke by 16% ($P < 0.005$). These benefits were seen despite the fact that pravastatin-treated

patients achieved a target LDL of 2.5 mmol/L. Neither the Pravastatin in Acute Coronary Treatment (PACT) trial (with pravastatin 20 mg versus 40 mg versus placebo) nor phase Z of the Aggrastat to Zocor (A to Z) study (with simvastatin 40 mg for one month followed by 80 mg daily) (115) showed clinical benefit within the first four months of treatment. The recently published Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) study (116) compared high-dose atorvastatin with lower dose simvastatin in patients with a history of MI and showed a trend to enhanced benefit with the more aggressive therapy. However, nearly all of the patients were entered into the study more than two months after their acute coronary event. Thus, current evidence supports treatment early after an ACS with an intensive statin regimen, such as atorvastatin 80 mg daily.

Early administration (starting day from day 2) of an ACE inhibitor should be considered in all patients with an ACS and heart failure or impaired LVEF (LVEF less than 40%). Clinical trials (Heart Outcomes Prevention Evaluation [HOPE] [117], EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease [EUROPA] [118], and Prevention of Events with Angiotensin Converting Enzyme Inhibition [PEACE] [119]) that specifically examined the benefits of ACE inhibition for the reduction of recurrent vascular events (eg, cardiovascular death, MI and stroke) have not included patients during the first one to three months after an AMI. But the Survival and Ventricular Enlargement (SAVE) trial (120) showed a reduction of recurrent MI with captopril administered three to 16 days after the acute event. Hence, it is likely that ACE inhibitors started early after an AMI exert vascular protective benefits as observed in the HOPE and EUROPA trials.

Dual antiplatelet therapy with ASA and clopidogrel, initiated early after admission, should be continued after discharge from hospital for a minimum of nine months. However, there was no evidence of benefit from continuing dual antiplatelet therapy beyond the nine-month treatment period in the CURE trial. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial (121) showed no overall advantage of dual antiplatelet therapy with ASA and clopidogrel beyond ASA alone in 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors. The study suggested benefit with clopidogrel treatment in patients with symptomatic atherothrombosis, as well as harm in patients with multiple risk factors. It is possible that patients with prior ACS could benefit from long-term dual antiplatelet therapy, but the CHARISMA trial did not directly address this issue.

Beta-adrenergic blockers were shown in clinical trials more than 20 years ago to reduce mortality by approximately 25% in patients with an MI during treatment for two years or more after the acute event (122). Patients with non-Q wave infarction were included in these studies.

Key messages

- Long-term vascular protective measures are an essential component of the management of all patients with ACSs.
- Lifestyle modification (smoking cessation, weight loss and increased physical activity) teaching should be initiated during hospitalization for an ACS.
- Glycemic control in patients with diabetes and in previously undiagnosed diabetes is an important component of the long-term management of patients with an ACS.
- The use of an intensive statin therapy such as atorvastatin 80 mg daily should be considered in all patients with NSTEMI ACSs, irrespective of LDL cholesterol levels.
- Beta-blockers should be considered in all patients with a diagnosis of MI.
- ACE inhibition should be considered in most ACS patients for vascular protection. Patients with left ventricular dysfunction (LVEF less than 40%) or heart failure should be treated with optimal doses of an ACE inhibitor; in the case of intolerance to an ACE inhibitor, an angiotensin receptor blocker can be used.
- Dual antiplatelet therapy with ASA and clopidogrel should be continued for nine to 12 months after an NSTEMI ACS. ASA at a dose of under 100 mg should be continued indefinitely.

CLOSING THE GAP

Registries from the United States (108), Canada (85,123) and Europe (124) show that a substantial proportion of patients with ACSs are not receiving optimal treatment either at the time of presentation or discharge. In the CRUSADE registry, a wide range of care is observed in hospitals that lead and lag in providing optimal treatment (108). Adherence to guidelines is associated with better patient outcomes (13,125,126). Hospitals with higher adherence rates have mortality rates that are significantly lower than institutions with lower adherence (127). High-risk patients who would benefit most, such as the elderly, women, patients with diabetes, patients with congestive heart failure and those with elevated troponin, are paradoxically less likely to receive recommended treatments (128). Furthermore, high-risk patients with NSTEMI ACSs are referred less frequently and later for coronary angiography than lower risk individuals (123).

The first step for implementing management change is the education of all health care professionals that participate in the care of NSTEMI ACS patients. It is important to identify a local physician champion within each institution who will pursue the necessary steps towards successful implementation. The emergency department team needs to be involved early in the development of standardized orders that are suitable for the individual institution. The standardized orders should be simple and provide the start of a care map for patient management. An example of a structured order set can be found at <www.chrc.net/ACSguidelines>.

MANAGEMENT ALGORITHM

A management algorithm based on the above discussion is shown in Figure 2. After deciding that the patient's symptoms are compatible with an ACS, risk assessment separates patients into 'high risk' and 'indeterminate risk'. High-risk patients have any one of the individual high-risk features that clearly identify the presence of an ACS. In the absence of high-risk features, patients with symptoms compatible with an ACS are classified as 'indeterminate risk'. These patients require further

Figure 2) Algorithm for the management of non-ST segment elevation acute coronary syndromes (ACS)

NOTES:

1. Very unstable patients with one of:

- Frequent ischemic episodes with or without pain and electrocardiogram (ECG) ST segment shift;
- Very high-risk ECG changes (eg, transient ST elevation or deep ST depression across many leads);
- Hemodynamic instability (heart failure or hypotension); or,
- Refractory ischemia with ECG ST shift despite acetylsalicylic acid (ASA), clopidogrel and heparin.

Need intensive management with:

- Very urgent or immediate cardiac catheterization.
 - Consider adding intravenous glycoprotein IIb/IIIa inhibitor (tirofiban or eptifibatide) to ASA, clopidogrel and unfractionated heparin (UFH). (if low-molecular-weight heparin has been started, it should be continued and not switched).
 - Consider use of intra-aortic balloon pump to stabilize the patient before transfer for coronary angiography.
- For patients in hospitals where cardiac catheterization will occur within 24 h, UFH should be used.
 - The stress ECG/perfusion scan ideally should be performed before hospital discharge. This is usually not practical. In patients with a higher probability of more extensive coronary artery disease (prior known coronary disease, multiterritory vascular disease, diabetes and chronic renal insufficiency), short-term admission may be necessary to facilitate early noninvasive testing. In other patients, arrangements should be made for testing in the following few days.
 - For low-risk patients with a normal stress test, the decision to use long-term vascular protective medication will depend on the patient's risk factor profile and the clinical history of the acute event. Other causes of chest pain should be considered in many of these patients.

evaluation to decide whether they are high risk and, hence, require aggressive antithrombotic or antiplatelet therapy, as well as early coronary angiography. Observation for recurrent ischemia, repeated ECG and biomarkers provide the initial assessment. If no high-risk features are identified, then noninvasive testing is recommended. For patients with a higher risk for an ACS (ie, known coronary artery disease, diabetes, chronic renal disease) or those with symptoms highly suggestive of myocardial ischemia, it is suggested that hospital admission to a nonintensive care unit or coronary care unit bed is desirable to expedite further testing. For the patient with no high background risk for coronary artery disease, noninvasive stress testing is suggested within 48 h to 72 h of discharge from the emergency department.

A patient with a high-risk stress ECG or myocardial perfusion scan (Table 1) has a high risk of either three-vessel or left main coronary artery disease, and should be considered for coronary angiography and revascularization when appropriate.

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APPENDIX

DISCLOSURES

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