Public health

Acute coronary syndrome without ST elevation: implementation of new guidelines

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Unstable angina and non-ST-segment-elevation myocardial infarction have in recent years been recognised as frequent and important clinical manifestations of coronary-artery disease. The European (ESC) and American (ACC/AHA) professional societies last year released guidelines on diagnosis, risk stratification, and treatment of these disorders. These guidelines summarise similarly the current evidence and translate them to clinical practice. Most important changes relate to the inclusion of troponins into the risk stratification algorithm, the addition of low-molecular-weight heparin and glycoprotein IIb/IIIa antagonists to medical treatment, and the role of invasive management for improved long-term outcome. Guidelines are constantly challenged by newly emerging study results. Recently, early invasive management and clopidogrel have been found to exert further benefit to this high-risk group of patients. Accordingly, the societies on both sides of the Atlantic will work together closely to update and implement these guidelines.

There have been more large-scale clinical trials in cardiology than in any other area of medicine, presenting physicians with the challenge of interpreting their results and applying them to clinical practice. National and international societies have formed expert panels to develop guidelines or recommendations on the diagnosis and treatment of various cardiovascular disorders and on the appropriate use of procedures and devices. These guidelines and recommendations are designed to set the standards for practice and have the potential to influence clinical behaviour.[1] The task of these expert groups is to review critically the results of clinical trials and to integrate them into a realistic management strategy.[2]

The levels of evidence to support any specific recommendation vary substantially, but they can be divided into three: the weight of evidence is highest (evidence level A) if the data are derived from several randomised trials involving large numbers of patients, intermediate (evidence level B) if the data are derived from a limited number of randomised trials involving small numbers of patients, and low (evidence level C) when the recommendation is based on observational studies or expert consensus. Additionally, the American College of Cardiology (ACC) and the American Heart Association (AHA) classify recommendations as those for which evidence indicates that a treatment is effective (class I), those for which there is conflicting evidence about effectiveness (class II), and those for which the evidence indicates that the treatment is ineffective or harmful (class III).

Coronary-artery disease is the leading cause of death in western countries. Unstable angina and myocardial infarction without ST-segment elevation are recognised as among the most frequent and important clinical manifestations of coronary-artery disease, bridging the gap between stable angina and ST-elevation myocardial infarction or sudden death. In 2000, in recognition of the very high frequency of unstable angina and myocardial infarction without ST-segment elevation, and the recent advances in the management of these disorders, professional societies in Europe and the USA released reports to guide practising physicians. The European Society of Cardiology (ESC) provided *Recommendations on acute coronary syndrome without persistent ST segment elevation*.[3] Simultaneously, the ACC/AHA published *Guidelines on UA/NSTEMI*,[4,5] which updated the US Agency for Health Care Policy and Research guidelines of 1994.[6] Additionally, some national cardiology societies have created their own guidelines tailored to account for local circumstances and preferences.[7,8] The purpose of this review is to summarise and compare the essentials of the European and US reports and to comment on the results of more recent trials.

A transatlantic difference?

The observations on which the recommendations are based, and their interpretation, are identical on both sides of the Atlantic, and one could question why separate guidelines are necessary. However, the two reports take somewhat different approaches, as reflected by the terms "guidelines" in the USA and "recommendations" in Europe. The US version is more comprehensive and guides the caregiver through many studies of unstable angina and myocardial infarction without ST-segment elevation. All aspects of diagnosis and treatment are discussed in detail over 92 pages (including 560 references)[4] and a 17-page executive summary.[5] By contrast, the ESC report leaves more room for individual decision making.[3] The report is shorter—27 pages including 190 references—and although easier to read, is less detailed than the ACC/AHA document.

New terminology

A new term for the acute phases of coronary heart disease—viz, acute coronary syndrome—has emerged over the past decade and is used in both documents. This

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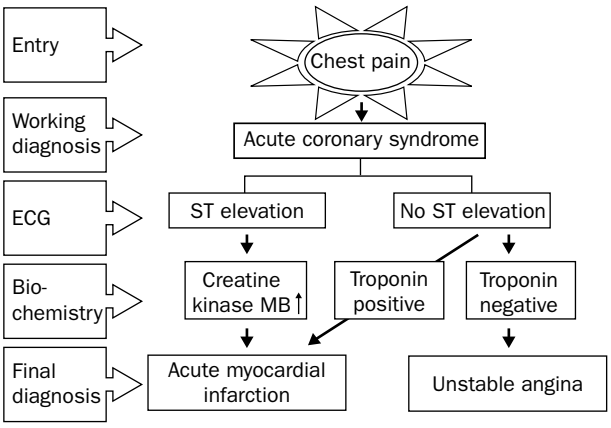

Figure 1: **Acute coronary syndrome terminology**
ECG=electrocardiography.

term is now widely accepted because it reflects the reality that, at first contact with the patient, only chest pain at rest or on minimal exertion might be present and no definite diagnosis is established (figure 1). This term is also consistent with the common pathophysiological mechanism believed to be responsible for most cases of unstable angina and myocardial infarction, with and without ST-segment elevations.[9]

An electrocardiogram is obtained as the first diagnostic step, allowing differentiation of patients with acute coronary syndrome into two large groups that require different therapeutic approaches (figure 2). If ST-segment elevation is present, the development of a myocardial infarction seems likely and immediate reperfusion therapy is usually indicated.[10,11] In the absence of ST elevation, biochemical markers are required for further categorisation. If concentrations of cardiac enzymes or troponins rise, irreversible cell damage will have occurred, and these patients must be regarded as having had myocardial infarctions, according to the new definition of the Consensus Conference that replaced the WHO criteria.[12] The ACC/AHA guidelines use the terms ST-segment elevation myocardial infarction and non-ST-segment-elevation myocardial infarction in place of Q-wave and non-Q-wave myocardial infarction; the latter terms are less useful in planning immediate management. Patients with acute coronary syndrome without raised concentrations of biomarkers can be regarded as having unstable angina.[13]

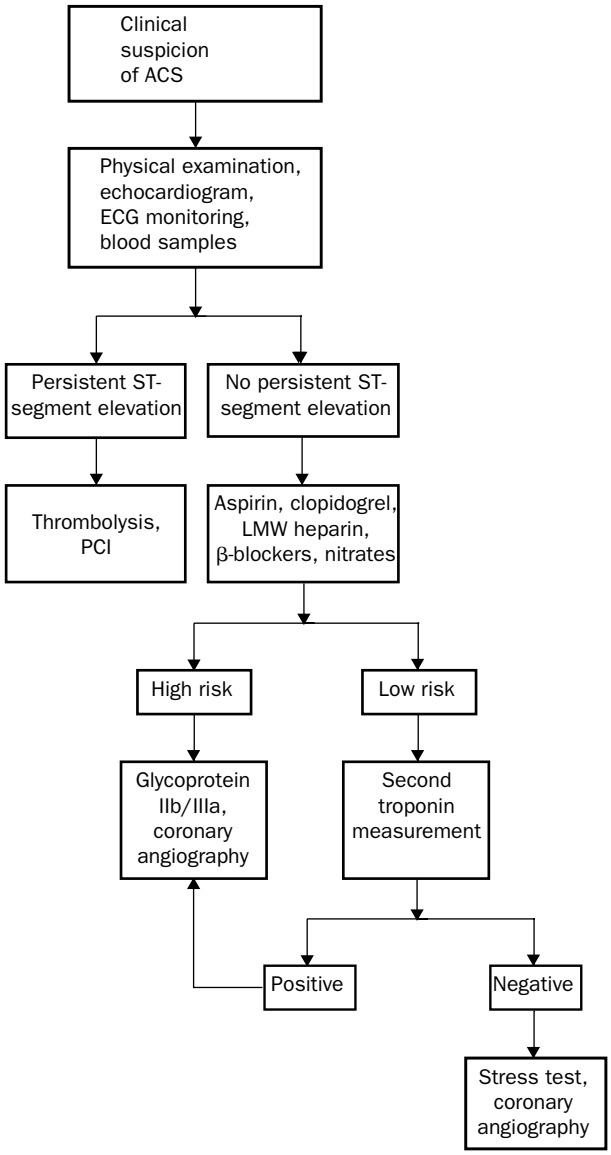

Figure 2: **Diagnostic and therapeutic pathway in patients with acute coronary syndrome with or without persistent ST elevation**
ACS=acute coronary syndrome. ECG=electrocardiography. PCI=percutaneous coronary intervention. LMW=low molecular weight.

Diagnosis and risk stratification

The recognition and risk stratification of acute coronary syndrome are closely linked, and, according to both reports, should be based on objective electrocardiographic and biochemical criteria (panel). The traditional risk factors for coronary-artery disease such as diabetes mellitus, hyperlipidaemia, smoking, and hypertension have only supportive roles in establishing the early recognition of acute coronary syndrome. The most valuable prognostic indicators are clinical presentation, presence and duration of angina at rest, and the response of angina to medical treatment. The US guidelines rank the five most important risk features derived from the initial history in the following order: (1) nature of anginal symptoms, (2) previous history of coronary-artery disease, (3) sex, (4) age, and (5) number of traditional risk factors present. The physical examination helps to exclude important differential diagnoses such as pleuritis, pericarditis, and pneumothorax, and allows detection of left-ventricular failure and haemodynamic instability.

Electrocardiograms are essential for excluding ST-segment-elevation myocardial infarction and must be obtained immediately. The ACC/AHA guidelines prescribe only 10 min from presentation until a 12-lead electrocardiogram is recorded. In patients with acute coronary syndrome but without ST elevations, the ESC Task Force regards an ST-segment depression of at least 0·1 mV and a T-wave inversion of more than 0·1 mV to signify ischaemia, whereas the ACC/AHA sets the cut-offs at 0·05 mV and 0·2 mV or more, respectively. Both reports point out that a normal electrocardiagram does not rule out myocardial infarction.

Creatine kinase and its MB isoenzyme have been the gold standard markers of myocardial necrosis for three decades. However, the ACC/AHA and ESC reports acknowledge the superiority of troponins T and I in detecting minor myocardial injury and for risk

Features of high risk in ACC/AHA Guidelines (USA) and European Society of Cardiology Task Force Report (EU)

• Increased troponin concentrations	EU/USA
• Recurrent ischaemia (ST depression, transient ST elevation)	EU/USA
• Haemodynamic instability	EU/USA
• Major arrhythmias (ventricular tachycardia, fibrillation)	EU/USA
• Early post-infarction angina	EU
• High-risk finding on non-invasive stress testing	USA
• Depressed left-ventricular function (<0·40)	USA
• PCI within 6 months	USA
• Previous CABG	USA

PCI=percutaneous coronary intervention. CABG=coronary-artery bypass surgery.

stratification. They refer to many studies that have shown that about 30% of patients with acute coronary syndrome but without persistent ST elevation have raised troponin concentrations.[14,15] Cardiac troponins are regarded as preferred markers and are rapidly gaining acceptance on both continents.

Troponins have assumed a central role in risk stratification and therapeutic decision-making in the ACC/AHA guidelines and in the ESC report. This focus on troponins has been criticised when it is misunderstood as the only tool for decision making. However, switching from creatine kinase MB to a troponin represents a major diagnostic step. Accordingly, the US guidelines allow a transition phase for caregivers and laboratories to become familiar with the use of troponins and they recommend continued measurement of creatine kinase MB mass (not activity) during this transition period.

Both guidelines leave the question of whether to measure troponins quantitatively in a central chemical laboratory or qualitatively by means of point-of-care or bedside tests to the discretion of the individual. The decision can be made according to the local circumstances and the time necessary to deliver the result. In the ACC/AHA guidelines, a turnaround time of 30–60 min is required. The US National Academy of Clinical Biochemistry advises implementation of point-of-care test systems if the hospital logistics cannot consistently deliver cardiac marker results within 1 h.[16] Although troponins T and I are regarded as equivalent, several troponin I assays have still not been adequately validated or standardised.[15] Other confounders of assay performance such as heparin are still under investigation. If qualitative point-of-care tests are used, potential reading errors by inadequately trained personnel should be addressed. The analytic cut-off for the troponin T assay has been lowered to 0·03 mg/L, identifying an increasing number of patients with acute coronary syndrome who are regarded as at high risk. Even more sensitive and accurate assays are expected in the next few years.

Both reports agree that a single test for troponins on arrival of the patient in hospital is insufficient. The ACC/AHA guidelines ask for a repeat measurement 8–12 h after the onset of symptoms (evidence level B). The ESC task force recommends a second test 6–12 h after admission (evidence level C).

The ACC/AHA guidelines define, in addition to high-risk and low-risk groups of patients, a group at intermediate risk of death and myocardial infarction (or reinfarction). These intermediate-risk patients have a moderate to high likelihood of coronary-artery disease according to history, age, electrocardiographic T-wave inversion, or borderline increases in troponin concentration. This intermediate-risk group has been introduced because of the evidence that risk increases continuously, depending on the numbers of risk factors present. By contrast, the ESC risk stratification is binary, and focuses on thrombotic risk. In addition to electrocardiographic findings and troponin concentration, the recurrence of chest pain and the presence of thrombus on angiography are considered. Furthermore, the ESC report distinguishes explicitly between short-term and long-term risk. Long-term risk is based on the underlying disease such as age, history of coronary-artery disease, traditional coronary risk factors, angiographic findings, and C-reactive protein concentrations. The ACC/AHA guidelines currently see only a supportive role for C-reactive protein that can be incorporated into the overall assessment scheme.

Medical management

The recommendations for antianginal treatment do not differ between the two reports. The ACC/AHA guidelines comment on general measures such as oxygen and morphine. The evidence levels are rated similarly for nitrates (level C) and β-blockers (level B), and both reports view calcium antagonists with some reservation. Detailed lists of drugs and dosages are presented in the US guidelines.

Antiplatelet therapy with aspirin and antithrombotic therapy with heparin are well established measures in unstable angina and myocardial infarction without ST-segment elevation. Low-molecular-weight heparins have more consistent antithrombin potential and less platelet stimulating effects than unfractionated heparin, and are easier to apply and need no monitoring. In acute coronary syndrome, low-molecular-weight heparins have been shown to be superior to placebo (evidence level A). However, there are inconsistencies in the results in the four large studies comparing low-molecular-weight heparins with unfractionated heparin, which are discussed in both reports. A moderate benefit with respect to adverse ischaemic outcome has been shown for enoxaparin, but not for other compounds. Therefore, the choice between unfractionated heparin and low-molecular-weight heparins (and the specific form of the latter) is left to the physician's discretion. A prolonged treatment beyond the sixth day could be of benefit only in selected patients who are managed medically or in whom angiography is delayed (evidence level C).

Results of trials with the glycoprotein IIb/IIIa antagonists—the most potent antiplatelet drugs available—are presented in detail in both reports. The consistent benefit seen with these drugs led to recommendations of their use, in addition to standard treatment (aspirin and unfractionated heparin or low-molecular-weight heparins) for patients with high-risk features such as increased troponin concentrations, ST-segment changes, or recurrent ischaemia. Small molecules such as tirofiban and eptifibatide have been approved for this indication (evidence level A), whereas the evidence for abciximab is limited to patients scheduled for, or undergoing, percutaneous coronary interventions. In patients with acute coronary syndrome, such interventions should be carried out in the presence of a glycoprotein IIb/IIIa inhibitor.

Conservative versus invasive approach

Both reports discuss the current evidence for an early invasive strategy (ie, coronary angiography followed by

revascularisation if feasible) or an early conservative strategy (ie, initial intensive medical management with coronary angiography limited to patients who fail therapy). Although no explicit across-the-board recommendation for invasive management is made in either report, both advise this strategy in those who fail medical therapy as well as in high-risk patients. High-risk patients are defined on the basis of their clinical picture and non-invasive testing. The list of the high-risk features of the ESC includes recurrent ischaemia by clinical or electrocardiographic criteria, increased troponin concentrations, haemodynamic or electrical instability, and post-infarction angina (panel). Coronary angiography should be done as soon as possible during hospital admission in these patients, as well as in those with a history of coronary-artery bypass grafting. In the US guidelines, the list of indications for the invasive strategy also includes a strongly positive stress test, impaired left-ventricular function (ejection fraction <0·40), or clinical evidence of heart failure and haemodynamic instability.

The recommended techniques of revascularisation in both reports are similar to those established for patients with chronic stable angina. The ACC/AHA guidelines stress that interventions should be done by experienced operators, whereas the ESC version provides suggestions on how to do coronary angiography in high-risk patients. The use of stents is recommended on both sides of the Atlantic. The safety of percutaneous interventions is thought to be improved by the addition of a glycoprotein IIb/IIIa antagonist. In Europe, percutaneous intervention on the "culprit" lesion as a bridge to coronary-artery bypass grafting is also recommended in circumstances when early surgery poses an extremely high risk. Also, patients with severe co-morbidity, which precludes surgery, could undergo staged percutaneous treatment or angioplasty of main-stem lesions.

Long-term management

Post-hospital care is addressed in both reports. The ACC/AHA guidelines are more explicit in defining the goals and use of lipid lowering and antihypertensive therapy. There is agreement with respect to drugs with proven benefit in patients with post acute coronary syndrome—ie, aspirin, β-blockers, statins, and angiotensin-converting-enzyme inhibitors (level A). The potential role of statins in stabilising the plaque independent of cholesterol lowering is also presented.

The special mechanisms in Prinzmetal's angina is addressed in both reports. The ACC/AHA guidelines also consider in detail other, non-atherosclerotic causes of unstable angina such as syndrome X and cocaine abuse. They also discuss special groups, which constitute increasing proportions of patients with unstable angina and myocardial infarction without ST-segment elevation—ie, women, the elderly, patients with diabetes mellitus, and patients who have had coronary-artery bypass grafting.

Newer studies

Guidelines and recommendations are always challenged by new observations. After the release of the two reports in September, 2000, several major studies in patients with acute coronary syndrome or post acute coronary syndrome have been released and must now be considered.

Most puzzling were the results of the GUSTO IV ACS trial,[17] in which the researchers studied abciximab in patients with unstable angina and myocardial infarction without ST-segment elevation in whom coronary intervention was not planned. This large study (7800 patients at 458 hospitals) failed to show a benefit of abciximab even in high-risk patients with raised troponin concentrations and electrocardiographic changes. Many possible explanations for this unexpected result have been offered, such as the selection of patients, the short duration of pain required for eligibility (>5 min), the unusually low intervention rate, and the possible loss of inhibition of platelet aggregation or prothrombotic effects with prolonged infusions of abciximab. The guidelines seem not to be directly affected by the outcome of this trial. However, although abciximab currently has no place outside of the catheterisation laboratory, the results of GUSTO IV ACS are also causing reassessment of the role of the other glycoprotein IIb/IIIa inhibitors in patients managed conservatively.

The TACTICS-TIMI 18 trial[18] compared an early invasive (within 48 h) strategy with a conservative approach in patients with acute coronary syndrome, all of whom received aspirin, heparin, and tirofiban. The 30-day and 6-month outcome in the invasive group was significantly better than in the conservative group, which was driven by a 33% reduction in myocardial infarctions, even though 51% of patients in the conservative group also underwent catheterisation during their hospital stay. By contrast with the FRISC II trial,[19] there was no early hazard—a finding related to the upstream use of tirofiban in all patients and the early invasiveness with a high rate of stenting with percutaneous coronary intervention (86%). The superiority of the invasive approach, however, was limited to high-risk patients, especially those with increased troponin concentrations or ST depressions. By contrast, in lower-risk patients, a more conservative concept might be acceptable. Accordingly, updates of the guidelines will more strongly favour an invasive strategy (<48 h) with upstream use of glycoprotein IIb/IIIa antagonists by raising the evidence to level A.

The past year has seen completion of two other large trials that included subgroups of patients with acute coronary syndrome and which investigated the role of glycoprotein IIb/IIIa inhibitors in the frame of percutaneous coronary intervention with stents. In the ESPRIT trial, a significant reduction of ischaemic complications by eptifibatide was most evident in the subgroup of patients with acute coronary syndrome.[20] The TARGET study compared tirofiban with abciximab and found that, in patients with acute coronary syndrome, abciximab was better over 30 days[21] as well as 6 months (unpublished data) of follow-up. In this context, the finding that abciximab plus enoxaparin is safe and provides effective anticoagulation during percutaneous coronary intervention is of interest. Whether the combination of abciximab and unfractionated heparin is better remains uncertain.[22]

Still unresolved in the guidelines is the question of the difference in strategy in hospitals with and without cardiac catheterisation facilities. A subanalysis of the PURSUIT study addressed this issue and revealed that, in patients with acute coronary syndrome admitted to community hospitals, eptifibatide treatment resulted in a reduced need for transfer and improved clinical outcomes.[23] Further studies are needed to provide well based evidence for this common problem.

The CURE trial[24] investigated the effect of adding the thienopyridine clopidogrel to standard treatment including aspirin in patients with unstable angina or

myocardial infarction without ST-segment elevation. This trial included 12 562 patients and showed that a loading dose followed by long-term administration of clopidogrel was associated with an early benefit and continued efficacy during 9 months of follow-up. The risk of myocardial infarction was reduced by 23%, cardiovascular death by 7%, and stroke by 14%. The effect was noted in all subgroups of patients, independent of the elevation of cardiac markers, electrocardiographic findings, or revascularisation. This benefit was accompanied by an increase in the risk of major, non-life-threatening bleedings. Whether patients undergoing emergency surgery are exposed to an extra risk by this potent antiplatelet treatment remains to be analysed in detail.

The subgroup of patients undergoing percutaneous coronary intervention was presented in a separate publication.[25] By contrast with the TACTICS study, patients were recruited at hospitals not pursuing a policy of early invasive management, and treatment with glycoprotein IIb/IIIa antagonists was discouraged. Accordingly, the delay to percutaneous coronary intervention was 10 days. Pretreatment resulted in a 31% overall reduction of cardiovascular death and myocardial infarction, although 30 days after percutaneous coronary intervention, open-label clopidogrel was given to more than 80% of all patients. Beyond 30 days after percutaneous coronary intervention, however, no significant benefit could be shown. Therefore revision of the guidelines will need a consensus agreement by the experts with respect to timing of percutaneous coronary intervention, length of clopidogrel treatment, and combination with glycoprotein IIb/IIIa antagonists.

Evidence is accumulating to support the anti-inflammatory and plaque-stabilising actions of statins.[26] These processes result in improved outcome, especially in patients with increased concentrations of C-reactive protein, and use of these drugs deserves consideration in future versions of the guidelines. The MIRACL trial[27] was designed to determine whether early treatment with high-dose atorvastatin is associated with a reduction of ischaemic events (death, acute myocardial infarction, or recurrent unstable angina) in patients with unstable angina and myocardial infarction without ST-segment elevation. The nominal level of significance (p=0·048) was just reached at 4 months follow-up. Future versions of the guidelines could recommend the early use of statins independent of LDL cholesterol concentrations. However, additional trials are needed to reach a level A recommendation.

Clinical guidelines will undoubtedly have an increasingly important role as quality control of clinical practice is emphasised. In turn, the guidelines will be based more on evidence derived from rigorously conducted trials, than on expert opinions or registries.[28] However, the usefulness of guidelines will also be measured by how well they can be implemented into clinical practice, particularly by non-cardiologists.[29,30] Therefore, they should be adaptable to local settings. Implementation programmes by the professional societies could help to disseminate the evidence.[31,32] This approach was followed in the ESC report, which was designed to be applicable to many countries with differing health systems, while the ACC/AHA guidelines are designed for a somewhat more uniform health system. These variations could account for the different emphasis in the two reports. The two sponsoring organisations—ie, the ESC and the ACC/AHA—intend to work closely together on the revisions.

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