

## CORONARY DISEASE

Acute coronary syndromes:  
risk stratification

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**R**isk stratification in acute coronary syndromes aims to identify those patients at greatest risk of recurrent ischaemic events who might benefit prognostically from further investigation and treatment. Unfortunately, however, none of the clinical or investigative markers currently available has sufficient diagnostic power to identify all high risk patients while excluding those at negligible risk. Moreover, for patients judged to be at high risk, the value of specific treatment may be poorly defined. Nevertheless, high event rates and finite facilities for invasive management emphasise the clinical and logistical importance of risk stratification which should play a central role in the management of acute coronary syndromes.

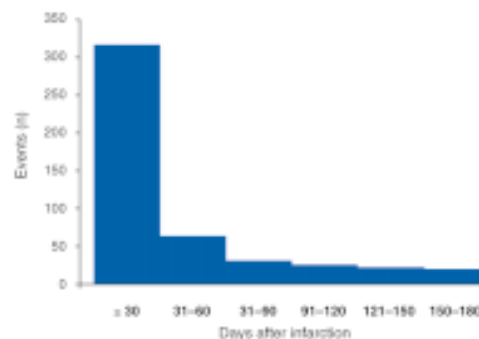
**What is the risk and when is it greatest?**

Our own database in east London shows that about 30% of patients with acute myocardial infarction and 20% with unstable angina experience a major event (death or non-fatal coronary syndrome) during the first year after hospital admission. Risk, however, is not a linear function of time, and as fig 1 shows, 66% of all major events during the first six months after myocardial infarction occur in the first 30 days. Moreover, the determinants of risk may change with time, acute phase arrhythmias and myocardial rupture in the first 48 hours giving way to reinfarction, heart failure, and secondary arrhythmias later after presentation. Thus assessment of risk, using strategies tailored to address its changing determinants, is an essential part of the management of acute coronary syndromes and must be applied at an early stage to identify successfully patients with most to benefit. Recognition of this fact has rendered obsolete old arguments about the appropriate timing of stress testing and other non-invasive tests which must be performed as early as possible (certainly before discharge) to be of significant value for risk stratification.

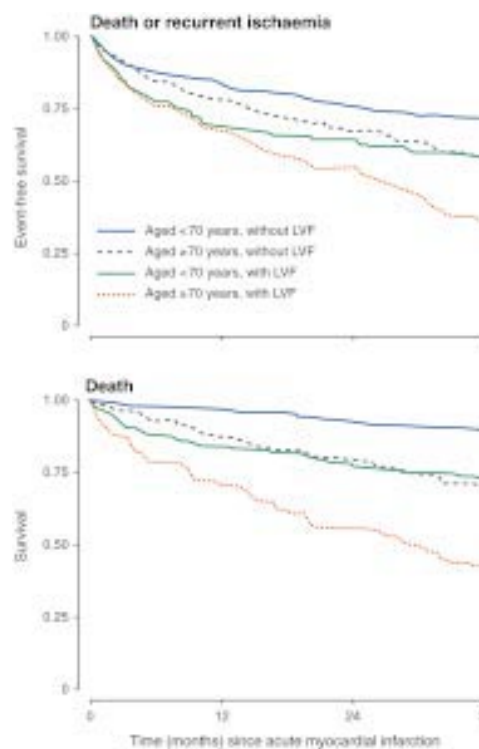
**Determinants of risk**

The major determinant of risk in the acute phase of ischaemic syndromes is ventricular fibrillation, which probably accounts for > 80% of out of hospital deaths. For hospital populations, risk is determined by the cumulative impact of a variety of clinical, pathophysiological, and coronary anatomical factors.

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**Figure 1:** Recurrent ischaemic events in the first six months after acute myocardial infarction (unpublished data of 1829 patients on Newham General Hospital database). Among 1829 patients with acute myocardial infarction, recurrent ischaemic events (death, non-fatal acute coronary syndromes) occurred in 481 patients during the first six months. Of these recurrent events, 66% occurred in the first 30 days.



**Figure 2:** Kaplan-Meier overall and event free survival by age for 1225 patients with acute myocardial infarction surviving to hospital discharge. LVF, left ventricular failure. Reproduced from Barakat et al<sup>2</sup> with permission of The Lancet.

Most important are advanced age and ventricular dysfunction (fig 2), with residual myocardial ischaemia and cardiac arrhythmias also contributing significantly.<sup>1</sup> Thus, the mortality risk within one year of acute myocardial infarction is 14.8 times greater in men aged  $\geq 70$  years with heart failure than in men aged  $< 60$  years without heart failure.<sup>2</sup> Clinical factors variably related to advanced ventricular dysfunction include diabetes, heart failure, Q wave development, and bundle branch block, while ongoing chest pain and fluctuating ST segment change usually reflect important residual ischaemia.

### Major determinants of risk in acute coronary syndrome

- Electrical instability
- Advanced age
- Left ventricular dysfunction
- Residual ischaemia

### Making risk assessments

Faced with these multiple determinants of risk, the clinician must decide which to measure and which to apply in the stratification process. Clinical determinants are, of course, readily available and are often sufficient to define risk and management options without the need for additional tests. Cardiac chest pain that fails to settle, for example, indicates that the risk of further ventricular injury is high and provides clear indication for angiography with a view to revascularisation. Similarly, intractable heart failure confirms a high level of risk, and additional tests aimed merely at refining risk status will not always provide significant incremental information. In many patients, however, particularly those who make an uncomplicated initial recovery, risk status is difficult to define based solely on clinical criteria and in this group further tests are necessary. These will usually include an evaluation of left ventricular function, or residual myocardial ischaemia, or both. Interpretation of these tests should take account of clinical, electrocardiographic, and biochemical data already available, recognising that risk stratification is an incremental process and the predictive value of non-invasive investigation is influenced importantly by the pretest assessment of risk.

### Risk stratification in the acute phase of coronary syndromes

Ventricular fibrillation, the major determinant of risk in the acute phase, requires immediate electrical cardioversion to avoid death. Because it is largely unpredictable, electrocardiographic monitoring and ready access to a defibrillator are the most important management strategies for saving lives in acute coronary syndromes. Also important is antithrombotic treatment which should be given to all patients acutely, with daily aspirin continuing thereafter. In other respects, management in the acute phase of coronary syndromes is largely determined by the perceived risk as judged by clinical, electrocardiographic, metabolic, and biochemical factors.

#### Clinical factors

Severe hypertension in the acute phase that does not respond promptly to opiate analgesia, heightens risk by intensifying ischaemia and predisposing to myocardial rupture. Intravenous  $\beta$  blockade may protect against rupture

and should be used in acute infarction if systolic blood pressure is  $> 160$  mm Hg. Heart failure also heightens risk and identifies a group that may benefit prognostically from angiotensin converting enzyme inhibition and  $\beta$  blockade. The risk is particularly high in cardiogenic shock which remains the leading cause of hospital death despite reperfusion treatment; primary angioplasty does not appear to offer any short term benefit but may improve survival in the longer term. For most patients, emergency cardiac catheterisation is reserved for patients with ongoing or recurrent chest pain, although this policy is largely pragmatic and may be overly conservative, particularly for patients with unstable angina.<sup>3</sup>

#### Electrocardiographic factors

When regional ischaemia is sufficiently severe to produce ST segment depression or elevation, risk increases significantly.<sup>4</sup> Thus, in unstable angina ST depression, particularly when recurrent, identifies a group at risk of infarction and provides indication for urgent cardiac catheterisation.<sup>5</sup> In myocardial infarction, ST elevation increases risk substantially but its prompt resolution, either spontaneously or in response to thrombolytic treatment and aspirin (fig 3), may reflect successful reperfusion and is a good prognostic sign, particularly if Q waves do not develop.<sup>6</sup> Failure of ST resolution, on the other hand, or recurrent episodes of ST elevation indicate failed reperfusion or coronary reocclusion, which increase risk and may provide indication for urgent angiography with a view to rescue angioplasty. Risk also increases progressively with increasing degrees of atrioventricular block, and is particularly high when advanced bundle branch block complicates anterior infarction, probably reflecting the adverse consequences of extensive myocardial injury. Primary ventricular arrhythmias in the first 48 hours of acute coronary syndromes do increase the risk of hospital death although there is no evidence that prophylactic antiarrhythmic treatment is helpful. Secondary arrhythmias later after admission are commonly associated with advanced left ventricular dysfunction and identify a group at high risk of death in the first year. If secondary arrhythmias fail to respond to treatment cardiac catheterisation is recommended to define revascularisation options, with electrophysiological investigation in reserve for tailored antiarrhythmic treatment or deployment of an implantable defibrillator.

#### Metabolic factors

The heightened risk associated with diabetes requires measurement of blood glucose concentration. Patients known to be diabetic or with a blood glucose concentration  $> 11$  mmol/l should receive insulin and glucose infusion during the acute phase which improves prognosis in acute myocardial infarction, although whether similar benefit occurs in unstable angina is not known. Hypercholesterolaemia also increases long term risk and lipid profiles should be measured at the time of admission, patients with a total cholesterol

### Electrocardiographic determinants of risk in acute coronary syndromes

- ST elevation or depression
- Failure of prompt ST resolution in response to treatment
- Q wave development
- Intraventricular conduction defects
- Secondary arrhythmias

≥ 5.0 mmol/l benefiting from treatment with statins.

### Biochemical factors

Enzymes released from cardiac myocytes have long been used as markers of injury to confirm myocardial infarction in patients presenting with acute coronary syndromes (fig 3). Creatine kinase and its more specific MB fraction remain widely used, but in recent years a number of novel biochemical markers (myoglobin, troponin I and T) have been developed that are more sensitive and appear in the blood earlier after the onset of symptoms. Almost regardless of which biochemical marker is used, increased concentrations are associated with an increased risk of recurrent ischaemic events. Myoglobin peaks particularly early and is reliably detected within four hours of injury, making it potentially useful for very early diagnosis. However, myoglobin is relatively non-specific and it is troponin I and T (regulatory proteins with isoforms found only in cardiac myocytes) that have emerged as the most useful biochemical markers for diagnostic and prognostic purposes. Raised concentrations of troponins are reliably detected within 12 hours of injury, and are highly specific for myocardial infarction and for the “minimal myocardial damage” that may occur following transient or subocclusive thrombus formation in unstable angina.

Minimal damage of this type is now recognised as a powerful predictor of subsequent ischaemic events. Troponins are there-

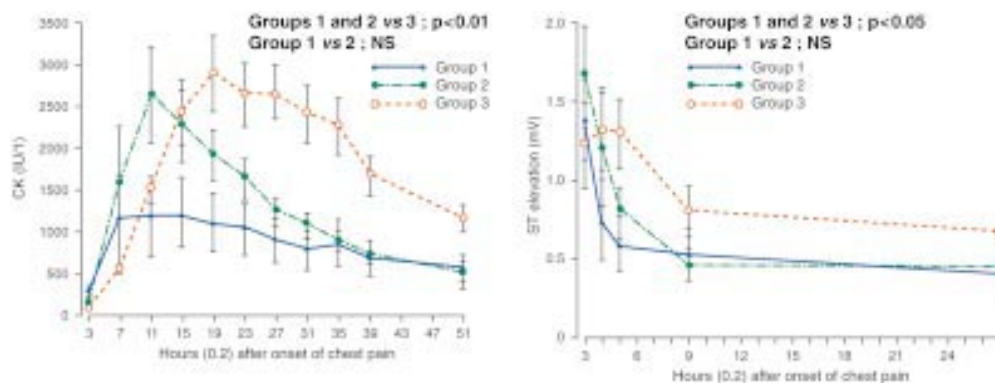
fore finding special application for risk stratification in unstable angina.<sup>7</sup> A recent study found that troponin T ≥ 0.10 µg/l in patients with acute coronary syndromes was associated with a 30 day mortality rate of 10.4% compared with only 3.2% in troponin negative patients.<sup>8</sup> Similarly, troponin positivity in acute myocardial infarction is associated with a substantially higher risk of future events. These findings are consistent with those of other investigators and have led to recommendations for troponin based risk management in acute coronary syndromes, with troponin positive patients a target for more aggressive strategies.

### Predischarge risk stratification

Many high risk patients with coronary syndromes can be clearly identified in the acute phase, but there remains a group that makes a largely uncomplicated early recovery, some of whom remain at high risk. This group, therefore, should be a target for predischarge risk stratification, although identification of high risk individuals may not be easy. Strategies for predischarge risk stratification include non-invasive evaluation of left ventricular function, tests for ongoing myocardial ischaemia (silent or stress induced), and tests for electrical instability.

### Left ventricular function

Left ventricular function is one of the major determinants of long term risk. There is now clear evidence that specific treatment with angiotensin converting enzyme (ACE) inhibitors (probably also β blockers) can reduce that risk, and coronary bypass surgery may be particularly beneficial when left ventricular dysfunction is associated with multivessel coronary artery disease. For many patients clinical criteria are sufficient to exclude significant left ventricular dysfunction, and an analysis of data from the GUSTO 1 trial confirmed that in patients presenting with a first infarct, absence of anterior infarction, left bundle branch block, or acute phase pulmonary oedema accurately



**Figure 3:** Kinetics of creatine kinase (CK) release (left) and ST resolution (right) in response to coronary reperfusion. Sequential coronary arteriograms 90 minutes apart in 41 patients presenting with acute coronary syndromes and ST elevation permitted identification of three groups: group 1—patency of infarct related artery at first arteriogram before thrombolytic treatment (n = 12); group 2—early recanalisation of the infarct related artery within 90 minutes of thrombolytic treatment (n = 10); group 3—persistent occlusion of infarct related artery (n = 19). Serial CK analysis showed early peaking in groups with coronary recanalisation (groups 1 and 2). Cumulative CK release was considerably greater in patients with failed recanalisation (group 3). Serial ECGs showed rapid resolution of ST segment elevation in patients in groups 1 and 2, while in those patients with persistent coronary occlusion (group 3), ST elevation persisted considerably longer. Reproduced from Timmis et al<sup>6</sup> with permission of BMJ Publishing Group.

### Clinical criteria associated with an ejection fraction $\geq 40\%$ in acute myocardial infarction

- First myocardial infarction in the absence of:
  - anterior infarction
  - left bundle branch block
  - acute phase pulmonary oedema

identified 94% of all patients with an ejection fraction  $\geq 40\%$ .<sup>9</sup> For the remainder, non-invasive evaluation of left ventricular function by echocardiography or radionuclide angiography is recommended in order to determine appropriate risk management.

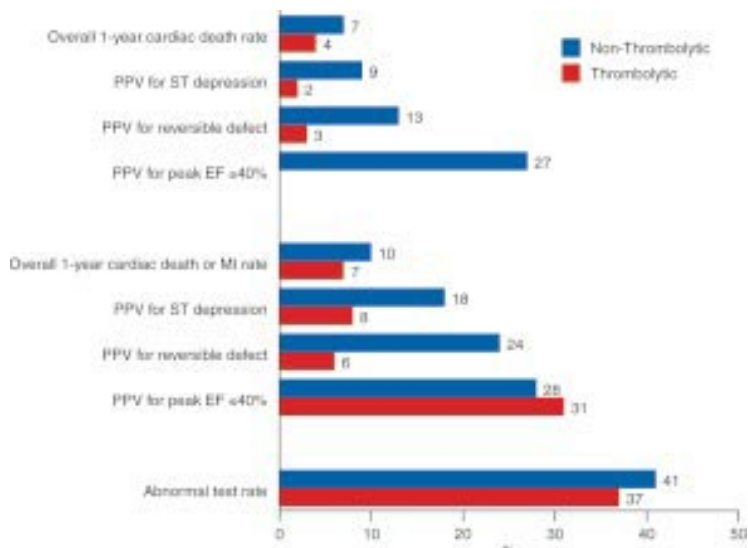
### Myocardial ischaemia

#### Stress testing

Patients with ongoing symptomatic ischaemia early after acute coronary syndromes are usually regarded as a high risk group requiring urgent angiographic investigation. However, many patients who make an uncomplicated early recovery have inducible ischaemia (with or without symptoms) that is variably predictive of recurrent ischaemic events. Thus stress testing has a time honoured role for predischarge risk stratification, particularly in uncomplicated myocardial infarction. A symptom limited test using the Bruce protocol is recommended for most patients although for some, particularly the elderly, modified protocols may be more suitable. An abnormal stress test with ST depression may be predictive of recurrent ischaemic events and provides grounds for coronary arteriography with a view to revascularisation. Other markers of risk include low exercise tolerance ( $< 7$  mets), failure of the blood pressure to rise normally during exercise, and exertional arrhythmias. Unfortunately, recent meta-analysis has shown that inducible ischaemia during treadmill testing has a low positive predictive value for death and myocardial infarction in the first year (fig 4), falling below 10% in patients who have received thrombolytic treatment.<sup>10</sup> Nevertheless, when “non-ischaemic” risk criteria are considered, the treadmill may provide added clinical value, inability to perform a stress test and low exercise tolerance both being independently predictive of recurrent events.<sup>11</sup> Moreover, the negative predictive accuracy of predischarge stress testing is high, those with a normal test usually having a good prognosis without the need for additional investigation. Finally, it should be noted that the diagnostic value of exertional ST depression and reversible thallium perfusion defects is equivalent, making the treadmill a more cost effective strategy for risk stratification after myocardial infarction than the gamma camera.<sup>10</sup> Predischarge stress testing has also been recommended in unstable angina, but although an ischaemic response at low work load has been associated with an increased risk, the positive predictive value of an abnormal test is low.

#### Holter ST monitoring

Ambulatory ischaemia during predischarge Holter monitoring also identifies patients at



**Figure 4:** Positive predictive value (PPV) of non-invasive tests in non-thrombolytic and thrombolytic treated patients for cardiac death or reinfarction rates, and rates of abnormal tests. EF, ejection fraction. Reproduced from Shaw *et al*<sup>10</sup> with permission.

### Treadmill stress testing for predischarge risk stratification

- Positive predictive accuracy of ST depression  $< 10\%$  after thrombolytic treatment
- Inability to perform a stress test and low exercise tolerance are most useful predictors of recurrent events
- Negative predictive accuracy is high
- Diagnostic value of exertional ST depression and thallium perfusion defects are equivalent, making the treadmill more cost effective than the gamma camera

risk of recurrent ischaemic events. In unstable angina its use is well documented; although it provides prognostic information additional to that available from the admission ECG, its incremental value relative to stress testing is not clear. In myocardial infarction ischaemic ST shift during predischarge Holter monitoring has a positive predictive value for recurrent infarction and death of 20%, and provides prognostic information that is additional to and independent of that obtained from stress testing and clinical assessment.<sup>12</sup> Preliminary evidence suggests therefore that ambulatory ischaemia during Holter monitoring may be more useful than stress testing for risk stratification in acute coronary syndromes. It can certainly be applied earlier after admission when risk is greatest, but it is unlikely to become more widely used until further studies are available defining its role.

#### Electrical instability

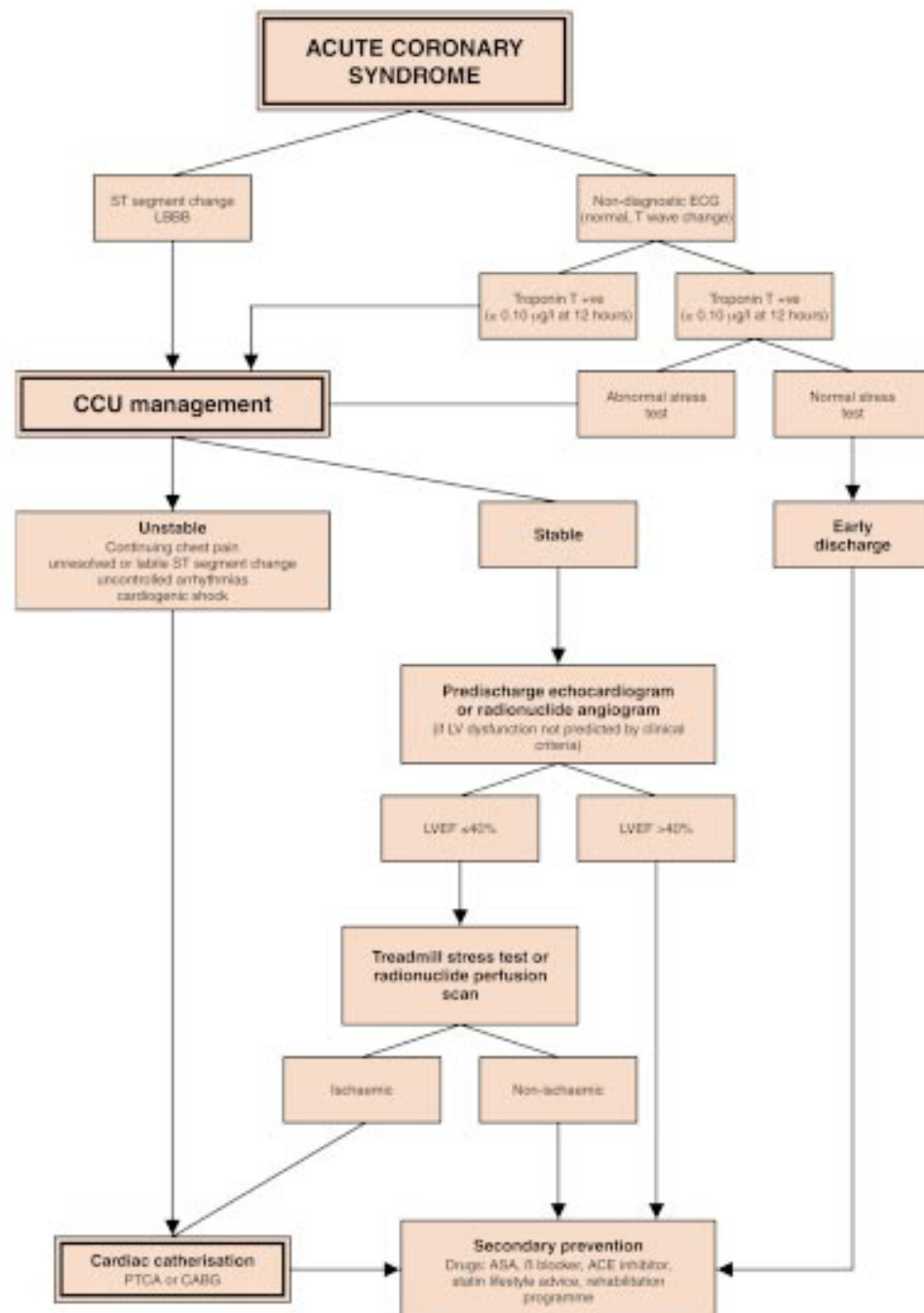
Patients at greatest risk of arrhythmic death in the first year are those with extensive myocardial injury evidenced by Q waves, anterior infarction, left bundle branch block, or heart failure. Risk is further increased if late ventricular arrhythmias (frequent ectopy, ventricular

tachyarrhythmia, ventricular fibrillation) occur before discharge.<sup>13</sup> Because there are no well defined strategies for reducing the risk of arrhythmic death, routine electrocardiographic monitoring (Holter, telemetry) before discharge is not recommended although patients who declare themselves clinically with sustained ventricular arrhythmias require investigation to identify provocative factors (ischaemia, hypoxaemia, metabolic derangement). Where possible  $\beta$  blockers should be prescribed, based on evidence of efficacy in

protecting against sudden death, but resistant life threatening arrhythmias require cardiac catheterisation to examine the potential for revascularisation. Electrophysiological investigation using programmed stimulation, though recommended by certain investigators, has proved unreliable for guiding treatment and predicting mortality.

#### Heart rate variability analysis

Holter monitoring after myocardial infarction permits analysis of autonomic function by



**Figure 5:** Algorithm for risk management in acute coronary syndromes. CCU, coronary care unit; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ASA, acetylsalicylic acid (aspirin); ACE, angiotensin converting enzyme.

measurement of heart rate variability. Sympathovagal balance is usually reduced in the postinfarction period, and the severity of the derangement is predictive of outcome, particularly arrhythmic and sudden death, but also all cause mortality.<sup>14</sup> At present, however, it is not clear if heart rate variability analysis provides incremental data for risk stratification, or what the therapeutic implications of reduced heart rate variability should be. Similar considerations apply to unstable angina.

#### Signal averaged ECG

Ventricular late potentials detected by signal averaging are predictive of arrhythmic events late after myocardial infarction. Again, however, the therapeutic implications of ventricular late potentials are not well defined and the role, if any, in unstable angina is unknown.

#### Practical recommendations

In patients with acute coronary syndromes, management should be risk based from the time of arrival in the emergency room (fig 5). An ECG and troponin assay should be obtained immediately with repeat troponin assay at 12 hours.<sup>15</sup> Patients with regional ST change (elevation or depression) or left bundle branch block are a high risk group requiring admission to the coronary care unit and appropriate antithrombotic treatment. Patients with an ECG that is normal, or shows non-diagnostic T wave changes, should be treated similarly if troponin assay is positive, but if troponins are negative at 12 hours further management should be guided by the results of a stress test. An abnormal stress test requires further cardiac investigation and treatment, but if the stress test is normal then risk is very low, permitting early discharge pending review of the diagnosis.

If ST elevation or depression fails to respond promptly to treatment or recurs after early resolution, the risk of ongoing myocardial injury is considerable and urgent cardiac catheterisation is recommended with a view to revascularisation. Similar considerations apply to patients with unrelieved or recurrent cardiac chest pain. Invasive management may also be required for heart failure and late ventricular arrhythmias, particularly if responses to initial treatment are unsatisfactory or there is evidence of residual ischaemia or stunning.

For patients in whom the hospital course is uncomplicated, discharge at five days is usually possible. If clinical criteria are insufficient to exclude significant left ventricular dysfunction, a predischARGE echocardiogram should be obtained, those with an ejection fraction  $\leq 40\%$  representing a high risk group requiring ACE inhibition and also cardiac catheterisation if there is residual ischaemia on stress testing. Those with well preserved left ventricular function are a low risk group in whom stress testing is not usually helpful for risk assess-

ment. Nevertheless, for troponin positive patients with unstable angina or non-Q wave infarction, risk is high and a predischARGE stress test is recommended.

Regardless of the hospital course, all patients should receive secondary prevention with aspirin and, when possible,  $\beta$  blockers. Aggressive management of diabetes and dyslipidaemia is essential and ACE inhibitors should be given to patients who have had clinical evidence of heart failure. A cardiac rehabilitation course should be available for all patients recovering from acute coronary syndromes.

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