failure compared to placebo, but when this is seen
with no demonstrable dose response it calls the
reliability of this finding into question. Of most
striking impact was a significantly lower all-cause
mortality over the 14 day observation period after
starting the treatment period in the four active
groups compared to placebo (11.7% compared to
19.6%, \( P=0.031 \)). Yet again no dose response was seen.

There were borderline effects on symptomatic status
and patient self-assessments. No consistent effect was
seen for objective signs of worsening cardiac function,
however.

Perhaps the most convincing effect was a significant
reduction in the need for additional heart failure
therapy, as would be expected for an effective therapy
for the acutely failing heart. Does this study alone
require us to consider this a proven therapy for acute
heart failure complicating myocardial infarction? The
answer is definitely no. It does, however, give valu-
able information on the safety and tolerability of an
effective positive inotropic therapy that appears at
least unlikely in the short term to increase mortality.

The benefits were seen with an increase in hypoten-
sion and ischaemia only in the highest dose group.
Does this make us revisit the possibility of acute
pharmacological inotropic support in acute transient
heart failure with the calcium sensitizers? Here more
of an argument can be made. Particularly in the
modern era of beta-blockade in heart failure the
risk/benefit ratio of positive inotropic agents may be
different if the myocardium is protected by beta-
blockers, a situation we are much more likely to see
in the future.\(^ \text{[10]} \). One must be careful, of course,
given the evidence for selection bias in reporting
positive as opposed to negative trials in heart fail-
ure\(^ \text{[11]} \) that we do not exaggerate the significance of
these findings. It does tell us, however, that more
rather than fewer clinical trials of acute heart failure
are needed, and that the positive inotropes may still
earn their evidence-based credentials in certain
circumstances.

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More histological information in acute coronary death

See doi:10.1053/euhj.2002.3159 for the article to which
this Editorial refers

Just as art historians dissect the colours, the pigments
and the brushstrokes in paintings, the best histo-
pathologists avoid an immediate diagnosis, ana-
lysing the nature of the tissue types in the section
and the appearance of the cellular infiltrates before
reaching a conclusion. In this way, the provenance
of paintings is established and new histological
diagnoses evolve. For several decades, pathologists failed to recognize Helicobacter pylori in gastric biopsies and until the advent of immunohistology, overlooked the obvious lymphocytic infiltrates in atheromatous plaques. We had probably recognized that rupture of the cap of an atheromatous plaque was the stimulus to coronary thrombosis but detailed descriptions of this important change only appeared in the 1980s[1,2]. Plaque rupture usually occurs when the atheromatous lesion is eccentric and contains a large core of lipid. The concept of plaque rupture is now widely accepted and has been incorporated into the so-called 'Starry system' of classifying atheromatous lesions[3] and its more recent modification by Virmani et al.[4].

Recent histological studies suggest that multiple subclinical episodes of plaque rupture, followed by healing, are an important mechanism for the growth of atheromatous lesions. Burke and his colleagues studied men who died of sudden coronary death and looked specifically for evidence of healed rupture sites and multilayering of the collagenous cap within lesions[5]. Thirty-three of 44 patients who died suddenly[7] had died suddenly[7]. An acute coronary thrombus in the hearts of 113 men with coronary disease who had died suddenly[7] was the stimulus to coronary thrombosis but detailed sectioned in 298 patients who had sustained an acute myocardial infarction but had not received any form of thrombolytic treatment or myocardial revascularization. Acute coronary thrombi were identified in 98% of these patients and in 10% multiple thrombi were present. This careful histological study has set a standard for all practising pathologists and, if it is needed, has provided clear justification for current management strategies in acute myocardial infarction. Seventy-five percent of thrombi occurred over ruptured plaques, whereas 25% were in patients with acute erosions. Plaque erosion was more common in women. Infarct size, the specific artery affected and the multiplicity of thrombi were distributed similarly amongst the two types of lesion. The patients in these studies were largely middle-aged and elderly and there was no clear relationship between age and the nature of the culprit lesion. In this context, a particularly interesting report from the Amsterdam group appears in the current issue[10]. Henriques de Gouveia and her colleagues studied four women and seven men between 24 and 35 years of age who died suddenly of coronary artery disease. In contrast to previous studies, the majority of these (9 out of 11) had plaque erosions whilst only two had ruptures. The authors use a strict definition of sudden cardiac death and there was no evidence of previous symptoms of note in any patient. This group has particular expertise in arterial histology and immunohistochemistry. Their findings and illustrations demonstrate that in only three cases was the thrombus completely fresh, two in ruptured and one in an eroded plaque. In the remaining eight, all erosions, there was histological evidence that pathological changes had occurred days, or even weeks, before the time of death. So just as the Washington group has demonstrated that subclinical rupture has a role in plaque progression, it appears that the same story may be true for plaque erosion.

The underlying wall has concentric atheromatous disease with little evidence of the lipid pool that is characteristic of plaque rupture. Pathologists at the Armed Forces Institute in Washington D.C. examined the hearts of 113 men with coronary disease who had died suddenly[7]. An acute coronary thrombus was identified in 59 (54%), very much what would be expected from other studies[8]. Forty-one of the 59 thromboses resulted from rupture of a lipid-rich atheromatous plaque and 18 from the erosion of a fibrous plaque. An unusually large amount of clinical information was available in this study. Multivariate analyses demonstrated that abnormal lipid profiles were associated with plaque rupture, whereas cigarette smoking was a strong risk factor for erosion with thrombosis. This group then collaborated with pathologists in Pavia, Italy, in a study that has produced some unique information[9]. The entire epicardial coronary artery tree was retained and serially sectioned in 298 patients who had sustained an acute myocardial infarction but had not received any form of thrombolytic treatment or myocardial revascularization. Acute coronary thrombi were identified in 98% of these patients and in 10% multiple thrombi were present. This careful histological study has set a standard for all practising pathologists and, if it is needed, has provided clear justification for current management strategies in acute myocardial infarction. Seventy-five percent of thrombi occurred over ruptured plaques, whereas 25% were in patients with acute erosions. Plaque erosion was more common in women. Infarct size, the specific artery affected and the multiplicity of thrombi were distributed similarly amongst the two types of lesion. The patients in these studies were largely middle-aged and elderly and there was no clear relationship between age and the nature of the culprit lesion. In this context, a particularly interesting report from the Amsterdam group appears in the current issue[10]. Henriques de Gouveia and her colleagues studied four women and seven men between 24 and 35 years of age who died suddenly of coronary artery disease. In contrast to previous studies, the majority of these (9 out of 11) had plaque erosions whilst only two had ruptures. The authors use a strict definition of sudden cardiac death and there was no evidence of previous symptoms of note in any patient. This group has particular expertise in arterial histology and immunohistochemistry. Their findings and illustrations demonstrate that in only three cases was the thrombus completely fresh, two in ruptured and one in an eroded plaque. In the remaining eight, all erosions, there was histological evidence that pathological changes had occurred days, or even weeks, before the time of death. So just as the Washington group has demonstrated that subclinical rupture has a role in plaque progression, it appears that the same story may be true for plaque erosion.

Do these careful histological studies have any immediate clinical relevance? Plaque erosion and plaque rupture appear to be distinct pathological processes but as yet they have not been shown to produce different patterns of clinical disease[9]. The very least that should be done in the future is to determine how they may be distinguished by imaging methods and how they respond to emergency or routine angioplasty and lipid lowering strategies.

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‘I can see clearly now’: a new view on the use of IV GP IIb/IIIa inhibitors in acute coronary syndromes

See doi:10.1053/euhj.2001.3160 for the article to which this Editorial refers

‘I can see clearly now the rain is gone
I can see all obstacles in my way . . .’
Johnny Nash

It has been several decades since the popular singer Johnny Nash used the above words in the opening lines of the popular song ‘I can see clearly now’. How apt they seem today as one reads the latest analysis of the use of intravenous glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors in patients presenting with an acute coronary syndrome (ACS)[1]. In this issue, Roffi et al. analyse the data from the PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IV ACS trials with two goals in mind: (1) to characterize the overall benefit of GP IIb/IIIa inhibitors and (2) to assess whether the reduction in ischemic endpoints varied with the revascularization strategy used[2–7].

The first objective of the Roffi analysis is not particularly novel and in one way or another has been touched on in prior publications. It is generally agreed that GP IIb/IIIa inhibitors represent an important advance in the management of patients with an ACS. In fact, reports on the effects of GP IIb/IIIa inhibitors have ‘rained down’ on the cardiology literature at such a rate that many practitioners find the data overload an ‘obstacle’ to a proper interpretation of how to use such agents. Clinicians ‘cannot see clearly’ what to do.

Trials such as those listed above as well as ‘pure’ trials of percutaneous coronary intervention (PCI) such as EPIC, EPILOG, CAPTURE, IMPACT II, RESTORE, and EPISTENT collectively form a database of about 40 000 patients[8–12]. From that database it has been reported that there is a significant 15–20% reduction in the proportion of patients who die or experience a myocardial infarction (MI) when they are treated with a GP IIb/IIIa inhibitor compared to placebo[13]. When we focus on just the PCI trials, we see a 30–40% reduction in death/MI, significantly favouring the use of GP IIb/IIIa inhibitors[13].

The strength of the evidence in favour of GP IIb/IIIa inhibitors, especially in patients undergoing PCI, formed the basis for the Class I recommendation (Level of Evidence A) in the current version of the ACC/AHA Guidelines for the Management of Patients with UA/NSTEMI that states: ‘A platelet GP IIb/IIIa antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterization and

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