

Viewpoints

Increasing burden of treatment in the acute coronary syndromes: is it justified?

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A striking change has occurred in the management of myocardial infarction (MI) and unstable angina (UA), collectively referred to as the acute coronary syndromes (ACS). Recent trials and guidelines have resulted in a substantial increase in use of invasive cardiac procedures and new pharmacological treatments. Without necessarily being at high risk, previously well patients in hospital with a first ACS are increasingly likely to undergo invasive coronary procedures with implantation of one or more stents, and to receive intravenous IIb/IIIa platelet receptor blockers, in addition to heparin, aspirin, clopidogrel, β blockers, angiotensin-converting-enzyme (ACE) inhibitors, and lipid-lowering agents. A prescription for indefinite long-term use of these latter oral agents is likely. Such practices are in accord with guidelines based on results of randomised trials published in peer-reviewed journals, and are strongly promoted by non-peer-review publications, consensus roundtables, expert forums, workshops, and key-note invited-speaker conferences, usually subsidised by industry. The clinical, economic, and ideological consequences of routine recourse to expensive drugs and technology are profound. We present an alternative perspective, which we hope will help to refine clinical decision-making, promote more rational use of our limited resources, and improve overall patient care in ACS.

Randomised clinical trials are rightly regarded as the epitome of methodological excellence for the determination of clinical efficacy. Too often, however, the term randomised confers a sanctity in the minds of physicians, which obviates the need for critical examination of trial methodology. Some concerns about the limitations of contemporary clinical trials should be considered.

- Combined endpoints are frequently used to determine outcomes¹⁻⁸ because death is a rare outcome in ACS, and to demonstrate differences in mortality would need trials with tens of thousands of patients. Therefore, death is usually combined with less serious endpoints, such as MI.^{1,3,4} However, most MIs have a good prognosis,⁹ and investigators have not attempted to triage the gravity of this outcome. Furthermore, soft outcomes like recurrent angina, rehospitalisation, or revascularisation for recurrent ischaemia, which can depend more on clinical practice than on clinical need, often dominate composite endpoints.^{2,5,8,10} The nature of endpoints should certainly affect the decision to incorporate new drugs or procedures into clinical practice, but such issues are rarely discussed.

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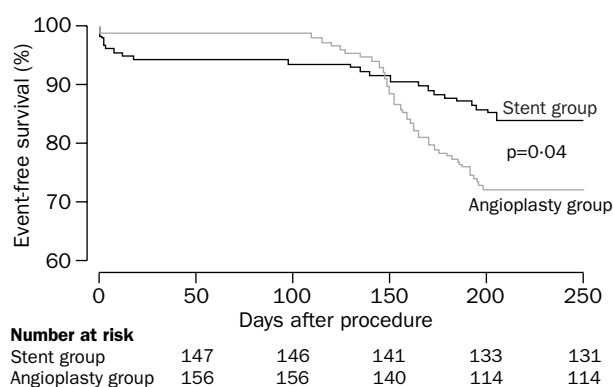


Figure 1: Event-free survival in angioplasty and stent groups in a trial comparing coronary balloon angioplasty with stenting for the treatment of restenosis after balloon angioplasty¹²

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- When blinding is impossible—eg, in comparisons of invasive with conservative strategies—there is a clear potential for bias that might affect such endpoints as length of hospital stay, recurrent ischaemia, or the need for repeat angioplasty with a consistent overestimation of any true effect.¹¹ Figure 1 shows an example of how the unblinded nature of a randomised study might affect outcomes. Since there were no significant differences in death and MI between groups, event-free rates refer essentially to differences in repeat angioplasty. Although the angioplasty group did better initially compared with the stent group, hazard ratios between the two groups changed markedly at about 150 days. The driving force behind this change might well have been the protocol that mandated a control angiogram at that time. Although the angioplasty group had more angiographic restenosis than the stent group, and consequently the number of repeat angioplasties increased, the clinical importance may be questioned since angiography is not routinely done during follow-up. Also, repeat angioplasty might have been undertaken more readily in the angioplasty group than in the stent group since it is easier to do in patients without stents.

Moreover, the way in which patient preferences could profoundly bias outcomes in unblinded trials is not generally recognised.¹³

- The period of study for the primary endpoint is usually quite short (48 h to 30 days).^{1-3,7} When longer follow-up data are available, they generally show an attenuation of the beneficial treatment effect, even to non-significance.^{2,7} However, such findings rarely receive the same publicity as the initial report in high profile journals.

- Even when we consider combined endpoints, event rates tend not to exceed 15%, with typical relative risk reductions of 15–25%.^{1,4-6,8,10} Thus, absolute risk

reductions with treatment are small—usually 3–4% or less.^{1,4-6,10,14} Although results are often only marginally significant, investigators tend to be enthusiastic in their interpretation of data, and these views are reinforced by favourable endorsements in accompanying editorials.

Results are often presented such that differences between study drug and placebo seem magnified. Figure 2 shows the published graph from a typical contemporary clinical trial in ACS and beside it the same data plotted on a Y axis of 100%. The reader's impression of the findings can be affected by such data framing, as well as by overemphasis of relative risk reductions and insufficient appreciation of the limits of p values as a measure of the strength of evidence.¹⁵ Use of NNT—ie, numbers of patients needing treatment to avoid one event—is an improvement, but this value is not usually stated. When NNT is reported, it is most often without confidence intervals, belying any associated uncertainty.

● The external validity of randomised studies is problematic. In ACS trials, the patient population is typically younger and has fewer comorbidities than encountered in clinical practice. Extrapolation of the results of trials with potent therapies to patients who are older and more fragile than those who took part in the trials, and who are often on several drugs, could be hazardous. The validity of the aphorism “greater risk but greater benefit”—which is frequently invoked to justify more aggressive approaches—should not be lightly presumed.

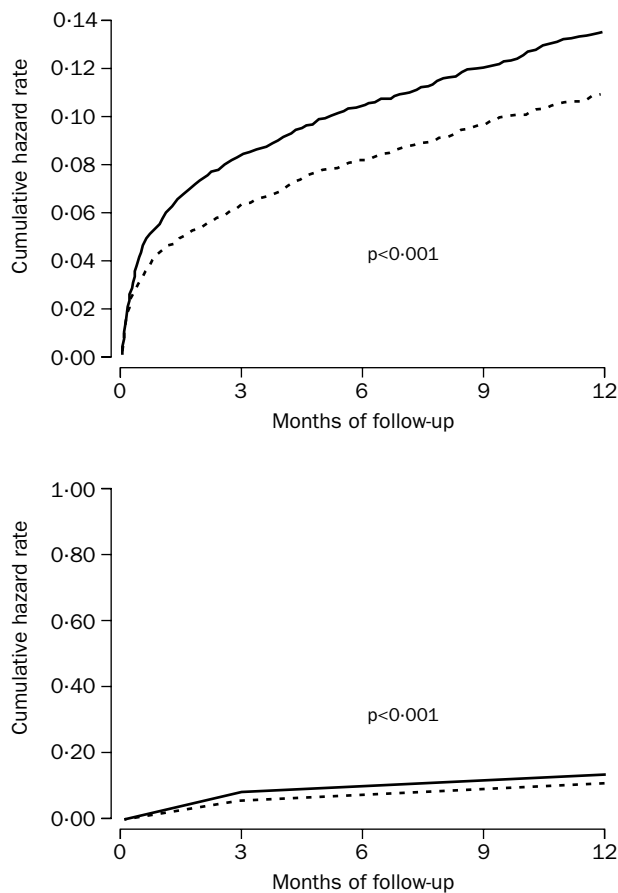


Figure 2: Example of how visual effect of findings can differ according to presentation

Top: cumulative first primary outcome rates in a typical contemporary placebo-controlled study in ACS with limited Y axis. Bottom: the same data plotted on a Y axis scaled from 0 to 1.

● Conflicts of interest of clinical researchers and writers of editorials should be considered.¹⁶ The authors of guidelines are often the principal investigators of the studies on which recommendations are based. Stock equity, consulting fees, and investigators' wish for continued support from industry are sources of potential conflict of interest. Although most clinical investigators feel they are impartial to industry pressures, they are uncertain about their peers.¹⁶ Positive research findings increase citation impact factors that raise prestige and favour academic promotion. Such influences on data interpretation can be entirely unconscious.

With these elements in mind, consider two pioneering studies comparing aspirin with placebo in ACS, undertaken in the 1980s. Each showed that the endpoints of both death and death or MI were reduced with aspirin by 50%, with absolute risk reductions of 5.1% and 8.4%.^{17,18} Aspirin is inexpensive and well tolerated, and its incorporation into the standard of care for patients with ACS came naturally. By contrast, trials assessing far more expensive treatments have found only modest benefit even in much larger study populations. In the table, we summarise data from these trials in ACE inhibitors, clopidogrel, platelet IIB/IIIa inhibitors, the invasive strategy, and lipid-lowering drugs in ACS.

ACE inhibitors confer no mortality benefit at 30 days in 99.5% of patients after MI.¹⁴ The HOPE trial¹⁹ is frequently cited to support broad prescription of ACE inhibitors for patients with ACS, even though stable patients without ACS were investigated in this study, and more than 96% of patients taking the ACE inhibitor ramipril for at least 4 years did not benefit in terms of the primary endpoint (cardiovascular death, MI, or stroke). Instead of the blanket use favoured by guidelines,²⁰ could we not be selective, by considering ACE inhibition in patients with coronary artery disease who also have hypertension, diabetes, repetitive vascular events, or moderate to severe cardiac dysfunction? Consistently higher absolute benefits have been shown with ACE inhibitors in such high-risk patients.²¹

The lukewarm findings in favour of clopidogrel in the CURE study⁶ should also invite caution rather than the broad prescription currently recommended.²⁰ Nearly 98% of patients showed no apparent benefit, and clopidogrel added to aspirin did not reduce mortality. Perhaps clopidogrel should be considered only for patients who remain unstable, or who have recurrent acute vascular events despite treatment with aspirin.

Platelet glycoprotein IIB/IIIa receptor blockers are increasingly used as first-line treatment in ACS, and are recommended in guidelines for high-risk patients with ACS.¹⁹ The list of suggested high-risk features is very broad and unequal; it includes some factors that portend a grave prognosis, others that do not, and still others that have not been properly assessed. These drugs have not been proven to reduce mortality, and their benefit remains uncertain even in patients at higher risk because of raised troponin (table). Moreover, women treated with these drugs had a significant 15% increase in adverse outcomes.²² Most of the slender benefit of platelet IIB/IIIa inhibition was confined to the group that underwent percutaneous coronary intervention (PCI; odds ratio for death or MI 0.77, 95% CI 0.64–0.92), whereas the nearly 16 000 non-PCI patients did not benefit (0.95, 0.87–1.02).²² The weak efficacy data, increased risk of bleeding, and cost make it difficult to justify the broad-based algorithms for platelet IIB/IIIa inhibitors recommended in guidelines and so strongly promoted by industry. A selective approach, reserving these agents for

Study	Follow-up for primary outcome (days)	Primary outcome	Relative reduction outcome primary (95% CI)	Absolute mortality reduction (95% CI)	Number needed to treat (save one life) (95% CI)	Number needed to harm (lose one life) (95% CI)	Comments
Study							
ACE (meta-analysis) ¹³ n=96 712	30	M	6.6% (2 to 11)	0.5% (0.1 to 0.7)	200 (143 to 1000)	NA	
CURE ⁵ (clopidogrel vs placebo) n=12 500	90*	Composite (M, MI, S)	18.4% (10 to 28)	0.45% (-0.39 to 1.30)	222 (83 to ∞)	250 to ∞	Severity of strokes and MIs not fully characterised
Platelet IIb/IIIa inhibitors (meta-analysis) ²¹ n=31 405	30	Composite (M, MI)	9% (2 to 15)	0.07% (-0.18 to 0.32)	1428 (333 to ∞)	555 to ∞	Significant 15% increase in adverse outcome in women; benefit uncertain even in men and women with raised troponin
FRISC-2 ⁴ (invasive vs non-invasive strategy) n=2457	180	Composite (M, MI)	22% (2 to 38)	1.00% (-0.27 to 2.30)	100 (43 to ∞)	370 to ∞	Clinical threshold to allow invasive procedures in the non-invasive arm was high (incapacitating symptoms or a very poor exercise test [≥ 3 mm ST-segment depression or limiting angina at low workload]), which might have unduly disadvantaged the non-invasive arm
TACTICS ⁵ (early invasive vs conservative strategy) n=2220	180	Composite (M, MI, R)	22% (3 to 38)	0.2% (-1.3 to 1.8)	500 (56 to ∞)	76 to ∞	Troponin+invasive subset: reduced death/MI at 6 months not significant; higher threshold enzyme definition of MI, if PCI-related, favoured invasive arm; greater use of IIb/IIIa blockers during PCI in invasive vs conservative arm favoured invasive arm
RITA 3 ⁸ (invasive vs conservative strategy) n=1810	120	Composite (M, MI, RA)	34% (15 to 49)	-0.49% (-1.9 to 1.2)	83 to ∞	200 (53 to ∞)	Similar death/MI in 2 groups at 1 year; difference between groups driven by soft endpoint of RA (5% absolute difference)
MIRACL ¹⁰ (atorvastatin 80 mg vs placebo) n=3 086	120	Composite (M, MI, R, CA)	16% (0 to 30)	0.2% (-1.2 to 1.7)	500 (59 to ∞)	83 to ∞	Similar death/MI in 2 groups; modest difference driven by soft endpoint of unstable angina

*38% had 365 days follow-up. ACE=angiotensin-converting-enzyme. n=number. M=total mortality. MI=non-fatal myocardial infarction. R=rehospitalisation for cardiac cause (usually ischaemic). CA=cardiac arrest. RA=refractory angina. S=stroke. PCI=percutaneous coronary intervention. N/A=not applicable.

Summary of recent studies in acute coronary syndromes

patients refractory to standard treatment or undergoing high-risk PCI, seems more appropriate.

In the persistent controversy over conservative or invasive strategy in patients with non-ST-segment elevation ACS, results of early trials^{23,24} suggested that a systematic invasive strategy was ineffective or could even be deleterious.²⁴ The prevailing aggressive attitude stems from more recent studies than these^{4,5,8} (table). Despite the modest findings and methodological limitations that we have noted, guidelines now strongly endorse an early invasive strategy in patients with ACS who have any high-risk indicators.²⁰ Again, these indicators are broad and uneven, and the rationale for grouping them is unclear. Why cannot an initially conservative approach, particularly in uncomplicated patients, be as acceptable? Most patients with new ST-segment depression and raised cardiac troponins, although at higher risk than patients without

these features, do well. The positive predictive value of troponin is quite low since 85–90% of such patients do not reach the endpoint of death or MI.²⁵ Therefore, the systematic use of invasive interventions and expensive drugs for such patients should be questioned. We are surprised that the medical establishment uncritically accepts that a major management decision should be driven by the result of one biological test, dissociated from other specific and dynamic clinical features.

Statins are recommended if LDL cholesterol exceeds 2.6 mmol/L in patients in hospital with ACS.²⁰ Findings of the MIRACL study¹⁰ (table) are often cited, but are too soft to justify a major change in clinical practice, as confirmed by a recent negative trial.²⁶ If the rationale for acute institution of treatment is concern that it will be otherwise forgotten, the quality of follow-up will probably be such that sustained compliance should not be

expected. Patients can and should assume responsibility for control of their risk factors for coronary artery disease. In the absence of any clear benefit of acute pharmacological treatment, should we not instigate dietary measures first, and reserve the option of treatment for follow-up? This approach would reduce unnecessary side-effects during treatment in hospital, alleviate the substantial drug burden imposed on patients in hospital, and encourage empowerment of patients.

New options for clinical management and treatment in ACS do have the potential to better control pathogenic mechanisms, leading to reduced morbidity and improved survival. The pitfall lies in the imposition of an increasing burden on many patients who will not derive benefit. This situation is the result of complex relations between a powerful pharmaceutical and device industry, medical researchers who are keen to publish positive new findings, clinicians who are overly dependent on simple indiscriminant recipes, and opinion leaders who are often the same medical researchers who strengthen the conclusions of their studies by revising guidelines and recommendations. The interplay of these elements, added to a need for consensus and conformity, have reduced the scope for healthy controversy. By robotic application of the findings of clinical trials, we risk transforming evidence-based medicine from a creative methodology to a clumsy and sterile orthodoxy. Paradoxically, the advent of novel and powerful treatment options in ACS, which should normally reinforce clinical finesse, has favoured a dogmatic, shotgun approach to patient care. The contemporary challenge in the management and treatment of coronary artery disease is to reverse this tendency and to seize the terrific opportunities offered by the findings of new studies to better identify patients who will especially benefit from specific treatments and interventions, and to reduce the large numbers of patients now being treated unnecessarily. Such initiatives have to depend on the medical profession; they are unlikely to come from industry. Finally, medical education should shift emphasis from the ability to cite the acronyms and facile conclusions of the latest clinical trials, and instead reinforce the analytical skills necessary for critical assessment of an ever-expanding stock of published work.

Conflict of interest statement
None declared.

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