The "Acute coronary syndromes: consensus recommendations for translating knowledge into action" position statement is based on a false premise

Brett H Forge

ABSTRACT

- Recent National Heart Foundation of Australia (NHFA) guidelines for management of acute coronary syndromes (ACS) recommend increasing the rates of early invasive management of ACS and providing equal access for all Australians to percutaneous coronary intervention (PCI) facilities.
- For patients with ACS managed in regional hospitals without PCI facilities, review of the evidence does not show unequivocal benefit of early routine PCI over selective PCI for patients with non-ST-segment-elevation ACS or ST-elevation myocardial infarction.
- The current pattern of transfer based on the NHFA guidelines is expensive and disruptive of patient care, as well as undermining regional health care services.
- Further increase in transfer rates and increases in PCI facilities would divert resources away from supporting the regional infrastructure needed to provide evidence-based therapies, without any evidence that lives would be saved.

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A recent position statement published in the Journal[1] asserts that it is time to implement the National Heart Foundation of Australia (NHFA) guidelines for management of acute coronary syndromes (ACS). These guidelines were published in 2006[2] and updated in 2007.[3]

The position statement states that rates of early invasive management for high-risk patients with non-ST-segment-elevation ACS (NSTEACS) should be increased, and that all Australians should have equal access to revascularisation facilities.

Such a policy would have profound economic and logistic implications, further increasing the existing trend towards transferring a high proportion of patients with ACS for percutaneous coronary intervention (PCI).

While the authors of the NHFA guidelines[2] state that the guidelines are evidence-based, I contend that this is not the case with respect to PCI, where the NHFA guidelines appear to be biased towards PCI.

Recommendations of the NHFA guidelines

The NHFA guidelines[2] recommend that all high-risk patients with NSTEACS and all patients who receive thrombolytic therapy for ST-segment-elevation ACS (STEACS) should be transferred early for angiography, with a view to performing PCI. These recommendations have already had a major effect on clinical practice in regional hospitals throughout Australia, resulting in large numbers of patients being transferred from regional hospitals to larger hospitals that provide PCI. Several Victorian regional hospitals that I contacted said they now routinely transfer all patients with any objective evidence of ischaemia directly to Melbourne. In some cases, the patient is assessed in the emergency department of the regional hospital and then transferred.

The guidelines define high-risk patients with NSTEACS as those with clinical features consistent with an acute coronary syndrome and any of: repetitive or prolonged (> 10 minutes) ongoing chest pain or discomfort; an elevated level of at least one cardiac biomarker (troponin or creatine kinase MB isoenzyme); or electrocardiographic changes of ST-segment depression $\geqslant 0.5$ mm or new T-wave inversion $\geqslant 2$ mm.

In other words, virtually all patients with objective evidence of ischaemia are defined as high-risk, and by virtue of inclusion of an elevated troponin level, this definition includes all patients with non-ST-elevation myocardial infarction (NSTEMI).

The evidence base: routine transfer of all patients with NSTEACS

The NHFA guidelines offer little evidence to suggest that all high-risk patients with NSTEACS benefit from routine early PCI and should therefore be transferred. This is despite recent urging that this aspect of the NHFA guidelines be more closely followed. In fact, although the document has over 100 references, I could not find any that relate to this issue.

A recent meta-analysis by O'Donoghue et al[4] of early invasive versus conservative treatment strategies for ACS showed a reduc-

Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndromes
AHA	American Heart Association
AMI	Acute myocardial infarction
FRISC	Fast Revascularisation during Instability in Coronary Artery Disease
ICTUS	Invasive versus Conservative Treatment in Unstable Coronary Syndromes
MI	Myocardial infarction
NHFA	National Heart Foundation of Australia
NSTEACS	Non-ST-segment-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
STEACS	ST-segment-elevation acute coronary syndrome
STEMI	ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
TIMI	Thrombolysis in Myocardial Ischemia
TRANSFER-AMI	Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction
UA	Unstable angina

tion in the composite end point of death, myocardial infarction (MI) or hospitalisation in the invasive arm. However, this was entirely due to the reduction in recurrent hospitalisation for ACS. There was no reduction in death or MI (Box 1).

Peters and colleagues, in a review of NSTEACS,[5] comment that the issue is "under debate". Referring to a meta-analysis by Mehta et al,[6] they state:

> In a meta-analysis published in 2005, including seven trials and 9212 patients, a routine invasive strategy exceeded a selective invasive strategy in reducing myocardial infarction, severe angina, and readmission to hospital over a mean follow-up of 17 months. Routine intervention was associated with a higher early mortality hazard and a trend towards a reduction in mortality during longer term follow-up. However, a subsequent randomised study [(the Invasive versus Conservative Treatment in Unstable Coronary Syndromes [ICTUS] study)] in 1200 high risk patients with non-ST segment elevation acute coronary syndrome who received optimal medical treatment according to current guidelines found no significant difference in the combined endpoint of death, myocardial infarction, or readmission to hospital at one year follow-up. This suggests that if medical treatment is optimised, a routine invasive approach may not be necessary.[5]

A 2007 report of the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction [UA/NSTEMI])[7] discusses the evidence relating to early invasive treatment in all high-risk patients and, in particular, the significance of the ICTUS study.[8] In concluding, it states: "Thus these guidelines recommend that in initially stabilized UA/NSTEMI patients, an initial conservative (selective invasive) strategy may be considered as a treatment option".[7]

Of the eight randomised controlled studies of early invasive versus conservative management of NSTEACS, the ICTUS study is the only one in which medical treatment was consistent with current standards in recommending clopidrogel and lipid-lowering therapy (as recommended in the NHFA guidelines[2]). The ICTUS study compared a routine invasive approach with a selective invasive approach. Aggressive medical therapy was recommended to both groups. The protocol recommended the use of clopidogrel in all medically treated patients, as well as aggressive lipid-lowering therapy. Both of these medical interventions have been proven to reduce adverse events in patients with ACS. Clopidogrel had been used in earlier trials, but only in patients who received early PCI, and aggressive lipid-lowering therapy was also not fully deployed. The ICTUS study only included patients with an elevated troponin level, so all patients were high-risk according to the NHFA guidelines. In the ICTUS study there was no reduction in death, Acute myocardial infection (AMI) or recurrent ischaemia with a routine invasive approach during a 12-month follow-up period. In fact, subgroup analysis failed to find any subgroup that was advantaged by routine PCI.

The ICTUS study raises two significant issues. The first is that, although it was recommended that all patients receive clopidogrel, only 49% in the selective management group and 61% in the early invasive group received it. Thus, it is likely that there is room for further improvement in a selective management strategy.

The other issue is that 53% of patients in the selective management group had angiography and 28% received an intervention during the index hospital admission. It was not clear from the article whether this was due to patients developing refractory angina or to clinicians' preference for an invasive approach, but either way, half the patients did not need angiography during that admission and there was no disadvantage to patients who were treated conservatively. It is quite possible that, with growing acceptance of the safety of a conservative approach, the intervention rate will fall further.

1 Summary of odds ratios and pooled event numbers for men and women after 12 months of follow-up*†

Events	Invasive treatment ($n = 5083$)	Conservative treatment ($n = 5067$)	OR (95% CI)
Death, MI or rehospitalisation	21.1%	25.9%	0.78 (0.61–0.98)
Death or MI	11.4%	12.3%	0.92 (0.69–1.23)
Death	4.3%	4.4%	0.97 (0.71–1.32)
Nonfatal MI	7.3%	8.5%	0.84 (0.63–1.12)
Rehospitalisation with ACS	12.8%	18.0%	0.68 (0.55–0.84)

ACS = acute coronary syndromes. MI = myocardial infarction. OR = odds ratio. * Data represent proportion of patients who experienced adverse events within 12 months after receiving either early invasive treatment or conservative treatment for ACS. † Source of data: O'Donoghue et al.[4] ◆

The difference in results between the ICTUS study and the earlier studies of a routine invasive versus selective invasive approach most likely relates to the greater use of clopidogrel and the more optimal use of statin therapy in the ICTUS study.

Earlier important trials such as the FRISC II (Fast Revascularisation during Instability in Coronary Artery Disease II)[9] and TIMI IIIB (Thrombolysis in Myocardial Ischemia IIIB)[10] trials failed to show a reduction in mortality with a routine invasive approach, but did show a reduction in non-fatal AMI. However, the reduction in non-fatal AMI was based on measurement of biomarker levels, and less stringent criteria were required to define AMI if it occurred after PCI. The biological significance of this is doubtful, and certainly not sufficient to justify major policy decisions.

Clearly, the NHFA guideline recommendation that all high-risk patients with NSTEACS be transferred for early PCI is controversial, is not supported by the only randomised controlled trial that recommended acceptable medical treatment, and is not in agreement with the ACC/AHA recommendations.

The evidence base: routine transfer of all patients with STEACS

With respect to patients who have received thrombolytic therapy, the NHFA guidelines recommend the following:

> Patients who have had STEMI should be considered for early transfer to a tertiary cardiac centre with PCI facilities and links to cardiac surgical facilities. If immediate transfer is not possible, patients should be transferred or referred as soon as is practicable for assessment of need for revascularisation (through PCI or coronary artery bypass grafting).[2]

The recent TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myo-

2 Clinical endpoints in the TRANSFER-AMI study[11]

	Standard treatment ($n = 522$)	Routine early PCI ($n = 537$)	RR with routine early PCI (95% CI)	*P*
Cardiac catheterisation	88.7%	98.5%		
Median time from administration of tenecteplase to first balloon inflation (hours)	22.7	3.9		
Efficacy end points at 30 days				
Primary endpoint*	17.2%	11.0%	0.64 (0.47–0.87)	0.004
Death	3.4%	4.5%	1.30 (0.71–2.36)	0.39
Reinfarction	5.7%	3.4%	0.57 (0.33–1.04)	0.06
Recurrent ischaemia	2.1%	0.2%	0.09 (0.01–0.68)	0.003
New or worsening congestive heart failure	5.6%	3.0%	0.54 (0.30–0.98)	0.04
Cardiogenic shock	3.1%	4.5%	1.46 (0.79–2.72)	0.23
Efficacy end points at 6 months				
Death	4.5%	5.7%	1.27 (0.77–2.23)	0.39
Reinfarction	6.5%	4.0%	0.60 (0.34–1.05)	0.07
Death or reinfarction	10.6%	8.9%	0.83 (0.55–1.25)	0.36

PCI = percutaneous coronary intervention. RR = relative risk. TRANSFER-AMI = Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction. * Death, reinfarction, recurrent ischaemia, new or worsening congestive heart failure, or cardiogenic shock. ◆

cardial Infarction) study[11] assessed the role of early routine transfer of patients from hospitals without PCI facilities after receiving thrombolytic therapy for STEMI.[11] In the TRANSFER-AMI study, patients who had received thrombolytic therapy were randomly allocated to either be immediately transferred for PCI or selectively transferred as required. Early transfer for PCI was not associated with any reduction in death or AMI at 6 months (Box 2). Although there was a reduction in recurrent ischaemia, the authors stated:

> It could be argued that a reduction in the rate of recurrent ischemia alone does not necessarily justify the strategy of routine early PCI after successful fibrinolysis, since presumably a patient can be transferred for elective or urgent PCI if ischemia recurs.[11]

Implications of following the NHFA guidelines

Hospitals who follow the NHFA recommendations to transfer all high-risk patients with NSTEACS for early angiography and consider all patients with STEMI for early transfer now transfer most, if not all, of their patients with ACS who have any evidence of ischaemia (electrocardiographic or biomarker changes). This policy has already had a major effect on regional hospitals throughout Australia.

The resulting reduction in patient workload has placed some units in jeopardy. All of them have become deskilled, as most of their sicker patients are transferred. Failure of these units to maintain a critical throughput makes it even more difficult to attract medical and nursing specialists to regional areas. The loss of skills further reduces the ability of these units to provide the non-interventional treatment that makes the greatest contribution to reducing cardiac death rates.

Another major problem is that the centralised PCI facilities are now so deluged with the additional workload that they are frequently unable to accept the sicker patients who need urgent treatment. One of the commonest complaints of regional physicians who manage patients with ACS is the amount of time they have to spend finding a bed in a PCI unit.

In most regional hospitals, patients with ACS are managed in emergency departments that are overstretched and underfunded. It is in this environment that time-critical and evidence-based interventions such as treatment with aspirin, clopidogrel, thrombolytics, tirofiban, heparin, β-blockers and lipid-lowering drugs should be initiated after diagnosis. It is in this difficult and under-resourced environment that the greatest gains in cardiac care can be made. Our hospital, in regional Victoria, is not exceptional in having patients who are sometimes managed in chairs in corridors and sometimes cannot even be unloaded from an ambulance until corridor space can be found to accommodate them.

As Scott stated in his authoritative article in the Journal:

> Of all AMI-related deaths that are prevented by therapeutic interventions, both acutely and as secondary prevention, medical treatments account for 80% of these (35% acutely, 45% secondarily) compared with only 6% for early invasive management. If all indicated drugs are prescribed to eligible patients, risk-adjusted mortality at 6 months is reduced by 90% compared with patients who receive none of these drugs. Routine use of more costly invasive care is not associated with population survival benefit beyond that seen with optimal medical management.[12]

The position statement[1] recommends equal access to PCI services for all Australians. This would necessitate more PCI units. The costing for such a proposal was not discussed in the position statement.

The cost of ambulance transport has become a significant component of hospital budgets, and vital ambulance services are frequently unavailable for acute local services, as they are so often deployed in transferring patients to and from major cities.

All of this would be a sacrifice that might be worthwhile if there were proof that developing more PCI facilities would save lives. However, as discussed above, there is no evidence that continuing

the current policy of routine transfer of all high-risk patients with NSTEACS and all patients with STEMI saves any lives at all compared with a selective regime.

The NHFA guidelines[2] do not reflect the current evidence, and certainly provide no clue as to the controversial nature of some of their conclusions, especially those relating to care of patients who attend hospitals without PCI facilities.

Increasing PCI rates, as recommended in the position statement, would result in a further shift in health care services towards expensive centralised intervention services and a weakening of regionally located services without any proven benefit.

Towards a better guideline development process

One wonders how the guideline authors could simply ignore the ICTUS study.[8] The ICTUS study was published several months before the original NHFA guidelines were published, and if time constraints meant that the ICTUS study was not considered in the 2006 guidelines, then it surely should have been reviewed in the 2007 update to the guidelines.

The NHFA is a not-for-profit organisation whose members give generously of their time and resources. Clinical guidelines are increasingly fundamental to the way in which we practise medicine. The process and funding of these functions needs to be recognised and supported by government agencies. Furthermore, if a particular craft group has a pecuniary interest in the development of guidelines and thus a potential conflict of interest exists, it is essential that members of that craft group be confined to an advisory role rather than being the principal authors of the guidelines. For this reason, the composition of the expert panel that is responsible for writing and updating the guidelines for managing ACS should be managed so that non-interventionists with extensive knowledge of the relevant literature predominate.

Conflict of interest issues are vigorously pursed by journals when the conflict involves possible payment from third parties such as drug companies. However, in the vast majority of cases, the actual amounts involved are very small relative to the authors' total income. Ironically, when the conflict relates to a pecuniary interest in a procedure or operation, it is rarely reported as a conflict of interest, even when the pecuniary benefit represents a large proportion of the authors' income.

Obviously, guidelines recommending that all patients with STEMI or NSTEMI be referred for PCI will have a substantial impact on the income of interventional cardiologists.

As recommended in the position statement,[1] national standards for data collection and clinical outcomes with performance monitoring should be established as soon as possible to ensure that evidence-based interventions are being applied according to the highest standards.

The NHFA guidelines[2] should be revised. If they reflected current evidence, we might see a dramatic change back towards regional facilities managing most patients with ACS and referring only those who are unstable or at particularly high risk. This would redirect ambulance services back towards local acute services and support the infrastructure needed to manage coronary patients locally. Hospitals with PCI facilities would then have the resources to treat urgent cases immediately, and resources could be directed towards supporting emergency departments and local coronary care units where the most important interventions for ACS are applied.

Competing interests

None identified.

Author details

Brett H Forge, MB BS, FRACP, Non-interventional Cardiologist
West Gippsland Hospital, Warragul, VIC.
Correspondence: bforge@absoluterisk.com

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