2007 addendum to the National Heart Foundation of Australia/ Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006

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Results from recently published clinical trials provide additional information to be considered in the choice of therapies in the management of acute coronary syndromes. This addendum summarises the important findings and their implications for recommended practice. ***(MJA 2008; 188: 302-303)***

This addendum supplements the recommendations outlined in the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand "Guidelines for the management of acute coronary syndromes 2006".[1]

Results from recently published clinical trials provide additional information to be considered in the choice of therapies in the management of acute coronary syndromes. This new evidence provides additional information that strengthens the recommendations in the guidelines or provides alternatives to current recommended practice that should be considered based on the circumstances of the individual patient and setting. The specific implications of this new evidence on recommended practice are highlighted in the "Implications of the findings" sections of this addendum.

Reperfusion and revascularisation for ST-segment-elevation myocardial infarction

Important findings

- The REACT (Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis) study,[2] MERLIN (Middlesbrough Early Revascularisation to Limit Infarction) study and a recent meta-analysis[3] have demonstrated a decrease in the composite endpoints of death, re-infarction, stroke and heart failure with rescue percutaneous coronary intervention (PCI).
- The OAT (Occluded Artery Trial)[4] trial showed no reduction in death, re-infarction or heart failure during 4 years of follow-up in stable patients with occlusion of the infarct-related artery 3 to 28 days after myocardial infarction who underwent routine PCI.

Implications of the findings *(Guidelines page S19)*

Rescue PCI

- The evidence for rescue PCI has strengthened since the development of the 2006 guidelines.
- Patients who receive fibrinolytic therapy and have not reperfused by 90 minutes should be considered for rescue PCI, which optimally should be performed within 12 hours. Transfer between facilities may be necessary to achieve this, and systems need to be in place to facilitate transfer of appropriate patients. If it is not possible for transfer within the 12-hour window, then transfer can be delayed if the patient is asymptomatic.

Revascularisation

- Patients in whom the infarct-related artery is completely occluded do not benefit from re-opening the artery routinely if this occurs more than 24 hours after the initial event. If patients are symptomatic, revascularisation may be considered.

Antiplatelet and antithrombin therapy

Recent evidence, while providing additional information on outcomes for individual agents, does not provide conclusive evidence of the superiority of one agent over another, nor of one combination of therapies over another. The risks and benefits of these therapies and strategies should be evaluated individually in each patient.

Important findings

- The EXTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment) trial[5] demonstrated that, in patients receiving fibrinolysis for ST-segment-elevation myocardial infarction (STEMI), the use of enoxaparin (a low molecular weight heparin; 30 mg intravenous bolus followed by 1 mg/kg every 12 hours in patients younger than 75 years, omission of the bolus but 0.75 mg/kg every 12 hours in patients aged 75 years or older) results in less re-infarction than the use of unfractionated heparin, but is associated with an increase in episodes of major bleeding.
- The OASIS-6 (Sixth Organization for the Assessment of Strategies for Ischemic Syndromes) trial[6] demonstrated that fondaparinux in comparison to no heparin or unfractionated heparin reduces mortality and produces less bleeding in patients with STEMI. Patients treated with fondaparinux who went on to PCI required additional heparin to reduce catheter thrombosis.
- The OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) study[7] and the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) study[8] on the treatment of non-ST-segment-elevation acute coronary syndromes (NSTEACS) demonstrated non-inferiority of two new agents, fondaparinux and bivalirudin, in the treatment of patients with NSTEACS when compared with "standard" antithrombin therapy, but with a significant reduction in major bleeding.
- The OASIS-5 study demonstrated non-inferiority of fondaparinux (2.5 mg daily) compared with enoxaparin (1 mg/kg twice daily) at the composite clinical endpoint, but reduced the rate of major bleeding at 9 days and reduced total mortality at 30 days and at 6 months.
- The ACUITY study demonstrated non-inferiority at a composite ischaemic endpoint, but a reduction in the rate of major bleeding and an improvement in the net clinical outcome endpoint when comparing bivalirudin with a glycoprotein IIb/IIIa (GP IIb/IIIa)

inhibitor with standard treatment with unfractionated heparin or enoxaparin.

- The ISAR-REACT 2 (Second Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) study[9] demonstrated that GP IIb/IIIa inhibition with abciximab administered among heparin-treated NSTEACS patients undergoing PCI and being pretreated with clopidogrel 600 mg, at least 2 hours before intervention, reduces rates of death, myocardial infarction or urgent target vessel revascularisation at 30 days, driven largely by the reduction in myocardial infarction. Following further analysis, it appeared that all of this benefit was evident among the troponin-positive patients.
- The ACUITY Timing trial[10] demonstrated that "in-lab" initiation use of GP IIb/IIIa inhibitors (abciximab or eptifibatide) just before PCI compared with routine "upstream" use (for a median time of 4 hours before intervention with tirofiban or eptifibatide) in high-risk NSTEACS patients could be associated with a 25% increase in ischaemic events, but is associated with a reduced rate of major bleeding.

Implications of the findings

Antithrombin therapy for acute STEMI (Guidelines page S14)

- Enoxaparin and fondaparinux are appropriate antithrombin agents and may be considered for use in patients with STEMI.

Antithrombin therapy for NSTEACS (Guidelines page S22)

- Fondaparinux and bivalirudin, both currently not licensed for upstream therapy of NSTEACS, may be preferable alternatives to standard therapy with unfractionated heparin or low molecular weight heparin with a GP IIb/IIIa inhibitor for patients with high-risk NSTEACS, particularly where there is an increased risk of bleeding. The selection of the most appropriate upstream therapy may best be determined for any individual patient from their risk of ischaemia versus bleeding.
- Fondaparinux may be particularly useful in patients for whom invasive management is significantly delayed or those not suitable for invasive management.
- Bivalirudin has the advantage of monotherapy for both upstream and procedural administration at the time of PCI, and therefore may be particularly useful in patients planning to have an early invasive intervention.

Antiplatelet therapy for NSTEACS (Guidelines pages S21–S22)

- GP IIb/IIIa inhibition with abciximab reduces adverse cardiac events in biomarker-positive NSTEACS patients undergoing PCI who have been pretreated with clopidogrel. Pretreatment with high-dose clopidogrel is not an adequate alternative to abciximab among biomarker-positive NSTEACS patients.
- A deferred in-lab initiation approach to the use of intravenous GP IIb/IIIa inhibitors (particularly with abciximab) may be preferable to short-term (median 4 hours) upstream administration in patients presenting with high-risk NSTEACS.

Competing interests

Constantine Aroney has received speaker fees from CSL. Philip Aylward has received research honoraria, speaker fees or travel assistance from TIMI Group (Harvard University), VIGOUR Group (Duke University), Pfizer, AstraZeneca, Eli Lilly, Boehringer Ingelheim and Sanofi-Aventis, and is a member of advisory boards to AstraZeneca, Sanofi-Aventis, Eli Lilly, CSL, Boehringer Ingelheim, and Pfizer. Derek Chew has received speaker fees from CSL and Sanofi-Aventis. Anne-Maree Kelly is a member of an advisory board to Sanofi-Aventis. Harvey White has received research grants, consulting fees or speaker fees from Sanofi-Aventis, Eli Lilly, Medicines Company, NIH, GlaxoSmithKline, Pfizer, Roche, Johnson & Johnson, Schering-Plough, Merck Sharpe & Dohme, Novartis, AstraZeneca, Boehringer Ingelheim, Servier Laboratories, Wyeth Ayerst, and Bayer.

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