1. Background information

Guideline issue date: 2010
2 year review: 2012
National Collaborating Centre: National Clinical Guidelines Centre

2. Consideration of the evidence

Literature search

Through an assessment of abstracts from a high-level randomised control trial (RCT) search, new evidence was identified relating to the following clinical areas within the guideline:

- Assessing an individual's risk of adverse events
- Anti-platelet therapy (clopidogrel and glycoprotein IIb/IIIa inhibitors (GPIs))
- Anti-thrombin therapy (heparins, fondaparinux and bivalirudin)
- Management strategies:
  - Early invasive versus conservative management
  - Percutaneous Coronary Intervention (PCI) versus Coronary Artery Bypass Graft (CABG)
o Rehabilitation and discharge planning

Through this stage of the process, a sufficient number of studies relevant to the above clinical areas were identified to allow an assessment for a proposed review decision and are summarised in Table 1 below.

No additional clinical area was identified from initial intelligence gathering, qualitative feedback from other NICE departments, and the views expressed by the Guideline Development Group that required further focused literature searches.

All references identified through the high-level RCT search and the initial intelligence gathering can be viewed in Appendix 1.
Table 1: Summary of articles from the high level RCT search

<table>
<thead>
<tr>
<th>Clinical area 1: Assessing an individual’s risk of adverse events</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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</thead>
<tbody>
<tr>
<td>Clinical question</td>
<td>Through an assessment of abstracts from the high-level RCT search, 5 studies relevant to the clinical question were identified. Evaluations of different risk scores (2 studies)</td>
<td>No new evidence was identified which would invalidate current guideline recommendation(s).</td>
</tr>
<tr>
<td>Q: What tables, equations, engines or scoring systems for patient risk-stratification are most predictive of death, re-infarction or other vascular events in patients with UA/NSTEMI?</td>
<td>- A systematic review was identified which evaluated the use of risk scores in clinical decision making in acute coronary syndromes (ACS). The review indicated that the TIMI and GRACE risk scores have been most extensively investigated, however, further scores may also be potentially useful and should be investigated further. - One study was identified which investigated the accuracy of the SYNTAX score, CSS score, NERS score, ACEF score, GRACE score and the TIMI score for risk assessment of 1-</td>
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<tr>
<td>Relevant section of the guideline</td>
<td>Assessing an individual's risk of adverse events</td>
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<td>Recommendations</td>
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year mortality, cardiac mortality, myocardial infarction, target vessel revascularization and stent thrombosis in patients with non-ST elevation acute coronary syndromes (NSTE-ACS) undergoing percutaneous coronary intervention.\(^2\) The study concluded that risk scores incorporating clinical and angiographic variables had the highest predictive accuracy for a broad spectrum of ischaemic end points.

**Evaluations of individual risk scores (3 studies)**

- One study aimed to develop a practical risk score to predict the risk and implications of major bleeding in ACS.\(^3\) The study concluded that a simple risk score based on 6 baseline measures plus anticoagulation regimen identifies patients at increased risk for non-coronary artery bypass grafting-related bleeding and subsequent 1-year mortality.

- The development of a clinical risk algorithm to predict patient risk in patients undergoing percutaneous coronary intervention (PCI) was discussed in one study.\(^4\) The authors
concluded that further study is warranted to confirm the application of the algorithm in clinical practice.

- The predictive value of the SYNTAX score for risk assessment of 1-year clinical outcomes in patients with NSTE-ACS undergoing PCI was assessed in one study.\(^5\) The results of the study indicated that, in this population, the SYNTAX score was an independent predictor of the 1-year rates of death, cardiac death, myocardial infarction and target vessel revascularization.

**Summary**

In summary, the identified new evidence evaluated a range of risk scoring systems. As such, it reveals that there is currently insufficient consistent new evidence in this area of the guideline and is therefore unlikely to invalidate the current guideline recommendation which states:

- As soon as the diagnosis of unstable angina or NSTEMI is made, and aspirin and antithrombin therapy have been
offered, formally assess individual risk of future adverse cardiovascular events using an established risk scoring system that predicts 6-month mortality (for example, GRACE)

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<th>Clinical area 2: Anti-platelet therapy</th>
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<tr>
<td><strong>Clinical question</strong></td>
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<tr>
<td>Q: What is the efficacy and safety of aspirin, clopidogrel or glycoprotein IIb/IIIa inhibitors in the medical management of patients with UA/NSTEMI compared to other antiplatelets or placebo?</td>
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<tr>
<td><strong>Relevant section of the guideline</strong></td>
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<tr>
<td>Anti-platelet therapy</td>
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<tr>
<td>Recommendations</td>
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<td>R6 – R8</td>
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<td>R9 – R13</td>
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<td>R14 – R16</td>
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or lower dose aspirin in 25,086 patients with ACS. The study concluded that there was no significant difference in primary outcomes for the treatment regimens tested.

- A subgroup analysis of the CURRENT-OASIS 7 trial investigated the effect of various clopidogrel and aspirin regimens in prevention of major cardiovascular events in patients with ACS undergoing PCI. The results of the study indicated that a double-dose clopidogrel regimen was associated with a reduction in cardiovascular events compared with the standard dose.

- A meta-analysis evaluated the risk of CABG in patients with ACS continuing clopidogrel therapy. The study concluded that further multinational trials are required to fully determine the balance of ischaemia and bleeding.

- A systematic review was identified which assessed the use of clopidogrel in combination with aspirin for patients with NSTE-ACS. Clopidogrel was found to be effective in reducing adverse cardiovascular events in patients with
NSTE-ACS at intermediate and high risk of ischaemic events.

- A meta-analysis was identified which concluded that new oral antiplatelet regimens are associated with a reduction in mortality, reinfarction and in-stent thrombosis in patients with ACS without an overall increase in major bleeding.\(^{12}\)

In summary, several studies were identified comparing different doses of clopidogrel however, they reported conflicting results. At the time of guideline publication a 600mg loading dose of clopidogrel did not have UK marketing authorisation and this is still the case (at August 2012). In addition, a systematic review concluded that clopidogrel was found to be effective in reducing adverse cardiovascular events in patients with NSTE-ACS at intermediate and high risk of ischaemic events. As such, the identified new evidence is unlikely to change the direction of the current guideline recommendations which state:

- As soon as the risk of adverse cardiovascular events has
been assessed, offer a loading dose of 300mg clopidogrel in addition to aspirin to patients with a predicted 6-month mortality of more than 1.5% and no contraindications (for example, an excessive bleeding risk)

- Offer a 300mg loading dose of clopidogrel to all patients with no contraindications who may undergo PCI within 24 hours of admission to hospital.

**Clopidogrel versus ticagrelor (4 studies)**

- In the PLATO trial, 18, 624 patients with acute ST elevation (STEMI) and NSTE-ACS were randomised to either ticagrelor or clopidogrel in addition to aspirin. Total major bleeding was similar between both groups although ticagrelor was associated with increased non-procedure-related major bleeding after 30 days of treatment. Furthermore, sub-studies of the PLATO trial reported the following:
  - Ticagrelor is a preferred option compared with clopidogrel for patients with ACS in whom an early
Invasive strategy is planned.\textsuperscript{14}

- A pre-specified analysis in 5216 patients admitted to hospital for ACS who were specified as planned for non-invasive management benefited from ticagrelor treatment with results consistent with those from the overall PLATO results.\textsuperscript{15}

- Treatment with ticagrelor compared with clopidogrel significantly reduced the rate of death from vascular causes or myocardial infarction without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.\textsuperscript{16}

In summary, new evidence was identified comparing clopidogrel with ticagrelor in patients with NSTE-ACS. However, a related Technology Appraisal has been published (TA236: Ticagrelor for the treatment of acute coronary syndromes, 2011) which provides recommendations for use of ticagrelor in patients with STEMI, NSTEMI and unstable angina. As such, cross-referral to this
Technology Appraisal should be considered.

**Clopidogrel versus prasugrel (1 study)**

- A sub-group analysis of the TRITON-TIMI 38 trial evaluated treatment with aspirin plus clopidogrel or prasugrel in patients with ACS undergoing PCI without stent implantation. The study concluded that prasugrel reduced ischaemic events and increased bleeding events to a similar magnitude as among patients who received stents.

Prasugrel is the subject of a separate Technology Appraisal and was not considered in CG94: Unstable angina and NSTEMI:


**Glycoprotein IIb/IIIa inhibitors (16 studies)**

*General systematic reviews*

- A Cochrane systematic review was identified which assessed
the effects and safety of glycoprotein IIb/IIIa inhibitors (GPIs) when administered during PCI and as an initial medical treatment for patients with NSTE-ACS. The review concluded that when administered as initial medical treatment glycoprotein IIb/IIIa inhibitors do not reduce mortality. However, when administered during PCI, intravenous GPIs reduce the risk of death at 30 days and at six months although the risk of severe bleeding is increased.

- A second systematic review found that triple antiplatelet therapy based on intravenous GPIs was more effective than aspirin-based dual therapy in reducing vascular events in patients with NSTEMI.

- A systematic review was identified which evaluated whether intracoronary administration of GPIs was superior to intravenous administration for patients with ACS undergoing PCI. The review concluded that intracoronary administration of GPIs in patients with ACS undergoing PCI can significantly increase target coronary flow and
myocardial reperfusion without increasing the risk of bleeding complication, but cannot improve clinical outcome compared with intravenous administration. Similar results were reported in a meta-analysis.\textsuperscript{21}

- One systematic review evaluated the use of GPIs as part of early medical management in patients with NSTE-ACS.\textsuperscript{22} Three additional systematic reviews were identified and reported conflicting results with one study concluding that upstream administration of GPIs did not improve clinical outcomes compared to downstream selective administration\textsuperscript{23} whilst two other systematic reviews indicated that in NSTE-ACS treatment with upstream GPIs provided ischaemic benefit.\textsuperscript{24,25}

In summary, several systematic reviews and meta-analyses were identified focusing on the use of GPIs. However, as timings of treatments, patient populations, use of adjunctive therapies and invasive strategies differ across the literature it is difficult to make...
comparisons between the studies.

*Tirofiban*

- An RCT assessed immediate and early outcomes in patients with NSTE-ACS who received tirofiban with conventional therapy compared with those who received conventional therapy (combination of aspirin, clopidogrel, heparin with or without beta-blockers and angiotensin-converting enzyme inhibitors) only.\(^{26}\) The study concluded that tirofiban improved the outcome of patients with high-risk NSTE-ACS.
- A systematic review was identified which assessed the efficacy of tirofiban compared with usual care or other GPIs.\(^{27}\) Tirofiban was found to be more effective than usual care for NSTE-ACS patients receiving planned PCI and medical management.
- One RCT was identified which evaluated the efficacy and safety of tirofiban in high-risk patients with NSTE-ACS after PCI.\(^{28}\) The study concluded that tirofiban administration is
safe and effective in this population.

In summary, despite the heterogeneity between the studies on tirofiban, it was found to be a beneficial treatment. Therefore, the identified new literature is unlikely to change the direction of the current guideline recommendation which states:

- Consider intravenous eptifibatide or tirofiban as part of the early management for patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%), and who are scheduled to undergo angiography within 96 hours of hospital admission.

**Eptifibatide**

- One RCT was identified which compared a strategy of early, routine administration of eptifibatide with delayed, provisional administration in patients with NSTE-ACS assigned to an invasive strategy. The results of the study indicated that, in this population, the use of eptifibatide 12 hours or more
before angiography was not superior to the provisional use of eptifibatide after angiography and was associated with an increased risk of non-life threatening bleeding.

- A post-hoc analysis of an RCT examined efficacy and safety of early eptifibatide in the setting of concurrent upstream clopidogrel use in patients with NSTE-ACS.\textsuperscript{30} The results of the study indicated that early eptifibatide use reduced 30-day death/myocardial infarction among patients with intended upstream clopidogrel but not among those without intended upstream clopidogrel use.

In summary, due to heterogeneity between the identified new evidence, no conclusive new literature was identified which would change the direction of current guideline recommendations.

\textit{Abciximab}

- One RCT evaluated the efficacy and safety of abciximab in Japanese patients undergoing PCI for unstable angina.\textsuperscript{31} The
results of the study indicated that there was no significant difference in the incidence of coronary events between placebo and abciximab groups.

- One RCT was identified which concluded that although abciximab reduced the 30-day and 1-year incidence of major adverse cardiac events in patients with NSTE-ACS undergoing PCI, treatment did not improve the impact of left ventricular ejection fraction over 6-8 months of follow-up.\(^{32}\)

- An RCT evaluated the long-term efficacy of abciximab bolus-only with aspirin and clopidogrel pretreatment and systematic coronary stenting.\(^{33}\) The results of the study indicated that similar efficacy, up to 3 years after PCI, was observed in subgroup analysis including patients with unstable angina and NSTEMI.

In summary, due to heterogeneity between the identified new evidence, no conclusive new literature was identified which would change the direction of current guideline recommendations on
Summary
In summary, as timings of treatments, patient populations, use of adjunctive therapies and invasive strategies differ across the literature it is difficult to make comparisons between the studies. As such, no new evidence that would contradict current guideline recommends was identified. However, the guideline needs to cross refer to a new technology appraisal that was previously not mentioned in the guideline - TA236: Ticagrelor for the treatment of acute coronary syndromes, 2011.

Clinical area 3: Anti-thrombin therapy

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<tr>
<th>Clinical question</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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<tbody>
<tr>
<td>Clinical questions in the guideline:</td>
<td>Through an assessment of abstracts from the high-level RCT search, 27 studies relevant to the clinical question were identified. As the review included an assessment of abstracts only it was not always possible to determine whether more than 60% of the study</td>
<td>No new evidence was identified which would invalidate current guideline</td>
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<tr>
<td>Q: What is the efficacy and safety of adding a low</td>
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molecular weight heparin (LMWH) compound to aspirin (with or without clopidogrel) in the medical management of patients with UA or NSTEMI compared to the combination of unfractionated heparin and aspirin (with or without clopidogrel)?

Q: What is the efficacy and safety of adding a GPI (tirofiban, eptifibatide and abciximab) to aspirin and heparin therapy in the medical management of patients with UA or NSTEMI compared to the combination of aspirin and

population included people with NSTE-ACS, the criteria used for the guideline.

Anti-thrombin therapy (1 study)

- One study was identified which evaluated the cost-effectiveness of anticoagulants in patients with ACS. The results of the analysis indicated that fondaparinux is cost effective compared with enoxaparin whilst bivalirudin in patients with ACS treated invasively is cost effective compared with heparin plus a GPI.

Heparins (4 studies)

- An RCT was identified which compared the efficacy and safety of dalteparin, a low molecular weight heparin, with a standard unfractionated heparin in patients with unstable angina. The study concluded that dalteparin is as effective and safe as unfractionated heparin in the treatment of unstable angina.
Q: What is the efficacy and safety of adding a GPI (tirofiban, eptifibatide and abciximab) to aspirin and heparin therapy as adjunct therapy to patients with UA/NSTEMI undergoing PCI compared to the combination of aspirin and LMWH?

Q: What is the efficacy and safety of adding Thrombin inhibitor (Bivalirudin) to the combination of aspirin, with or without a GPI, in the medical

- A subgroup analysis from the ACUITY trial was unable to demonstrate an association between adverse ischaemic outcomes with the timing of antithrombin administration in patients with NSTE-ACS undergoing an early invasive management strategy.36

- An RCT compared the safety of two unfractionated heparin regimens during PCI in high-risk patients with NSTE-ACS initially treated with fondaparinux.37 The results of the study indicated that low-dose compared with standard-dose unfractionated heparin did not reduce major peri-percutaneous coronary intervention bleeding.

- A systematic review was identified which assessed the efficacy and safety of unfractionated heparin plus GPs compared with controls during revascularization for an ACS.38 Minor bleeding was increased in the groups taking unfractionated heparin plus GPs although no difference in mortality between the two groups was observed.
management of patients with UA or NSTEMI compared to the combination of LMWH/UFH, aspirin, with or without a GPI?

Q: What is the efficacy and safety of adding a Thrombin inhibitor (Hirudin and Bivalirudin) to the combination of aspirin and a GPI as adjunct therapy to patients with UA/NSTEMI undergoing PCI compared to the combination of LMWH/UFH, aspirin, and a GPI?

Q: What is the efficacy and safety of adding a factor Xa

In summary, the identified new literature on heparins included different comparator groups and reported different outcomes. As such, no conclusive new evidence was identified which would change the direction of the current guideline recommendations on heparins.

Factor Xa inhibitors (fondaparinux and enoxaparin) (8 studies)

- A cost-effectiveness analysis was identified which aimed to compare the short-term costs and long-term cost-effectiveness of fondaparinux and enoxaparin for NSTE-ACS.\(^{39}\) The study concluded that fondaparinux is a more cost-effective antithrombotic agent in NSTE-ACS.

- Several studies were identified which indicated a benefit of fondaparinux treatment in patients with ACS.\(^{40,41,42,43,44}\)

- A subgroup analysis of the synergy trial reported that patients who received enoxaparin before PCI had improved outcomes compared with those who did not.\(^{45}\)
inhibitor (fondaparinux) to aspirin in the medical management of patients with UA or NSTEMI compared to the combination of LMWH/ UFH and aspirin therapy?

Q: What is the efficacy and safety of adding a synthetic pentasaccharide (fondaparinux and enoxaparin) to aspirin as adjunct therapy to patients with UA/ NSTEMI undergoing PCI compared to the combination of LMWH/UFH and aspirin therapy?

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<tr>
<th>Relevant section of the</th>
<th>• One RCT was identified which compared the incidence of adverse cardiac outcomes of enoxaparin versus unfractionated heparin in the management of NSTE-ACS. The results of the study indicated that enoxaparin use led to a decrease in the incidence of ischaemic events.</th>
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</table>

In summary, the identified new evidence indicated a beneficial effect of treatment with fondaparinux and therefore is unlikely to invalidate the current guideline recommendation which states:

- Offer fondaparinux to patients who do not have a high bleeding risk, unless coronary angiography is planned within 24 hours of admission

**Bivalirudin (6 studies)**

- Several studies were identified which compared bivalirudin with heparins in patients with NSTE-ACS. The results of one study (which compared heparin plus GPIs versus bivalirudin in ACS patients pre-treated with 600mg

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<th>guideline</th>
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<tr>
<td><strong>Recommendations</strong></td>
<td>R17 – R23</td>
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clopidogrel) indicated that there were no differences between the groups for the outcomes measured although, in one study\(^48\), treatment with bivalirudin led to a significant decrease in the risk of bleeding complications.  
- Sub-group analyses of the ACUITY trial concluded that bivalirudin is an effective anticoagulant in percutaneous coronary intervention for ACS\(^49\) and that bivalirudin significantly reduced bleeding complications compared with heparin without any negative impact on ischaemic outcomes at 1 year.\(^50\)  
- One study was identified which examined the impact of gender and antithrombotic therapy for NSTE-ACS.\(^51\) The results of the study indicated that, in women, bivalirudin therapy compared with a GPI-based strategy resulted in significantly decreased bleeding but similar rates of ischaemia and mortality.

From an assessment of the abstracts it was not possible to
determine the risk score of the study population and the background therapy used. In addition, interpretation of bivalirudin trial data is complicated by differences in dosages, duration of therapy, adjunctive therapies and study populations. The current guideline indicates that trials comparing bivalirudin with heparin and GPIs suggest that bivalirudin may offer equivalent ischaemic protection with reduced bleeding and no new literature was identified which would change this conclusion.

Medications currently not indicated for use in ACS (8 studies)

**Apixaban (oral, direct factor Xa inhibitor)**
- Three studies were identified which compared apixaban with placebo, in addition to standard antiplatelet therapy in patients with NSTE-ACS.\(^{52,53,54}\) In all the studies a dose-related increase in bleeding was observed with the studies concluding that further testing of apixaban is required.

**Rivaroxaban (oral, direct factor Xa inhibitor)**
One RCT compared rivaroxaban with placebo in patients with a recent ACS.\textsuperscript{55} The results of the study indicated that rivaroxaban reduced the risk of death from myocardial infarction or stroke however an increased risk of major bleeding was observed.

\textit{Otamixaban (intravenous, direct factor Xa inhibitor)}

- One RCT was identified which evaluated the efficacy and safety of otamixaban in patients with NSTE-ACS.\textsuperscript{56} Preliminary data indicated otamixaban may reduce ischaemic events however further study is required.

\textit{Darexaban (oral, direct factor Xa inhibitor)}

- One RCT assessed the safety and tolerability of darexaban for the prevention of ischaemic events in patients with ST-elevation acute coronary syndrome or NSTE-ACS.\textsuperscript{57} Preliminary results demonstrated higher bleeding rates in the darexaban arm. Further study is warranted to evaluate
<table>
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<tr>
<th>Vorapaxar (oral protease-activated receptor 1 (PAR-1) antagonist)</th>
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<tr>
<td>• One RCT was identified which compared vorapaxar with placebo in patients with NSTE-ACS.(^5)(^8) Follow-up in the trial was terminated early after a safety review. The results of the study indicated that vorapaxar did not significantly reduce the primary end point but significantly increased the risk of major bleeding.</td>
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<tr>
<td>Atopaxar (reversible protease-activated receptor 1 (PAR-1) antagonist)</td>
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<td>• The efficacy of atopaxar compared with placebo in patients with NSTE-ACS was evaluated in an RCT.(^5)(^9) Early ischaemia was reduced in the atopaxar group, however the authors concluded that further trials to fully establish the efficacy and safety of atopaxar are warranted.</td>
</tr>
</tbody>
</table>
New evidence was identified relating to new pharmacological treatments which are currently licensed but not indicated for use in NSTE-ACS (except for vorapaxar which currently does not have UK marketing authorisation). However, it would be pertinent to await further evidence, particularly on the benefits, harms and cost-effectiveness of these treatments, before an update is warranted. This area will be factored into the future reviews of this guideline.

**Summary**

In summary, no consistent new evidence was identified which would invalidate the current guideline recommendations on anti-thrombin therapy. Although new evidence was identified relating to new pharmacological treatments for NSTE-ACS, it would be pertinent to await further evidence, particularly on the benefits, harms and cost-effectiveness of these treatments, before an update is warranted.

### Clinical area 4: Management strategies

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Summary of evidence</th>
<th>Relevance to guideline</th>
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Clinical questions in the guideline:
Q: In adults with UA or non-ST elevation MI does early invasive investigation (i.e. angiography) with intent to assess for (and in those patients deemed suitable, to perform) revascularization improve outcomes in comparison with initial conservative treatment, with or without later angiography?

Q: In adults with UA or non-ST elevation MI does CABG improve outcomes in comparison with PCI?

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<th>recommendations</th>
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<tbody>
<tr>
<td>Through an assessment of abstracts from the high-level RCT search, 20 studies relevant to the clinical question were identified. As the review included an assessment of abstracts only it was not always possible to determine whether more than 60% of the study population included people with NSTE-ACS.</td>
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Management strategies (19 studies)
- Eleven studies were identified which concluded that an early invasive strategy is not superior to a selective or delayed invasive strategy in patients with NSTE-ACS. However, one RCT indicated that an immediate strategy was associated with an increased rate of myocardial infarction compared with a 24-48 hr delayed strategy. In addition, a sub-group analysis of the ACUITY trial indicated that delaying revascularization with PCI by 24 hours in patients with NSTE-ACS was an independent predictor of early and late mortality and adverse

No new evidence was identified which would invalidate current guideline recommendation(s).
Q: Do early psychosocial and educational interventions, mobilisation and discharge planning (cardiac rehabilitation – Phase 1) improve emotional and physical wellbeing and long-term outcomes in people with unstable angina or NSTEMI compared to deferred (cardiac rehabilitation Phase 2) 

Relevant section of the guideline
Management strategies

Recommendations
R24 – R27

ischaemic outcomes.\textsuperscript{72} One study which included an economic analysis demonstrated slightly increased costs associated with an early invasive strategy.\textsuperscript{61}

- A meta-analysis evaluated whether a routine invasive strategy reduces the long-term frequency of cardiovascular death or nonfatal myocardial infarction in patients with NSTE-ACS.\textsuperscript{73} The results indicated that a routine invasive strategy reduces the long-term rates of cardiovascular deaths or myocardial infarction with the largest absolute effect seen in higher-risk patients.

- A Cochrane systematic review was identified which investigated the benefits of an invasive compared with a conservative strategy for treating UA/NSTEMI.\textsuperscript{74} The review concluded that an invasive strategy is associated with reduced rates of refractory angina and rehospitalisation in the short term and decreased myocardial infarction in the long term plus an increased risk of bleeding in patients with UA/NSTEMI, compared with a conservative strategy. The
review concluded that an invasive strategy may be particularly useful in those at high risk for recurrent events.

- A meta-analysis was identified which evaluated the effect of age on long-term outcomes after a routine invasive or selective invasive strategy in patients with NSTE-ACS. The study concluded that the long-term benefit of a routine invasive strategy over a selective invasive strategy is attenuated in patients aged <65 years and in women by the increased risk of early events.

- A post-hoc analysis of the ICTUS trial investigated the association between actual in-hospital revascularization and long-term outcome in patients with NSTE-ACS. The study concluded that in-hospital revascularization was independently associated with a reduction in 4 year mortality however, no differences in cumulative event rates were observed between the early invasive and selective invasive strategies.

- A sub-group analysis of the ACUITY trial evaluated the
impact of arterial access site on bleeding and ischaemic outcomes in patients with ACS managed with an early invasive strategy. 

In summary, several studies compared an early invasive strategy with a delayed invasive strategy in patients with NSTE-ACS. However, as the studies considered different time frames for early and delayed invasive strategies, further evidence is required to assess the choice of an early invasive versus a delayed invasive approach. In addition, from an assessment of the abstracts it was not possible to determine the risk score of the study population which may have an impact on whether to use an early invasive or delayed invasive strategy. As such, there is currently insufficient consistent new evidence which would change the direction of the current guideline recommendations.

Furthermore, a Cochrane systematic review compared a conservative strategy with an invasive strategy. The review
concluded that an invasive strategy may be particularly useful in those at high risk for recurrent events. As such, this identified new evidence supports the current guideline recommendation which states:

- Offer coronary angiography (with follow-on PCI if indicated) within 96 hours of first admission to hospital to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%) if they have no contraindications to angiography (such as active bleeding or comorbidity). Perform angiography as soon as possible for patients who are clinically unstable or at high ischaemic risk.

### Coronary artery bypass grafting versus percutaneous coronary intervention (1 study)

- A subgroup analysis of the ACUITY trial evaluated outcomes in patients with ACS and multivessel coronary artery disease managed with PCI versus CABG.\(^7\) The results of the study indicated that 1-month and 1-year rates of mortality were...
comparable whilst patients treated with PCI more frequently developed recurrent ischaemia requiring repeat revascularization procedures during follow-up.

In summary, the results of this subgroup analysis indicated that mortality rates between PCI and CABG were comparable for people with ACS. As such, this identified new evidence is unlikely to invalidate the current guideline recommendation which states:

- When advising patients about the choice of revascularization strategy (PCI or CABG), take account of coronary angiographic findings, comorbidities, and the benefits and risks of each intervention

**Summary**

In summary, new evidence was identified on invasive management strategies, and CABG versus PCI. No conclusive new literature was identified which would change the direction of current guideline recommendations.
Thirty six clinical trials (publication dates unknown) were identified focusing on anti-platelet therapy; anti-thrombin therapy; early invasive versus conservative management; angiography and PCI.

**Guideline Development Group and National Collaborating Centre perspective**

A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. Five responses were received with some respondents highlighting new trials on risk stratification, anti-thrombotic therapy and new studies on the timing of the invasive approach. In terms of risk stratification, one respondent stated that there has been concern that the emphasis on 6 month mortality for risk stratification potentially disadvantages young patients with low predicted mortality but high predicted risk of recurrent myocardial infarction.

In relation to drug treatment, respondents stated that clopidogrel is now available in generic form whilst enoxaparin goes off patent in 2013, which may have an impact on the cost-effectiveness analyses. In addition, newly available therapies were highlighted including the anti-thrombin therapy, rivaroxaban.

Four respondents felt that there is sufficient variation in current practice supported by adequate evidence at this time to warrant an update of the current guideline.

**Implementation and post publication feedback**

In total 20 enquiries were received from post-publication feedback, most of which were routine. Post-publication enquiries were generally requests for clinical advice on a range of cardiovascular issues.
Feedback from the NICE implementation team indicated that since publication of the guideline a Technology Appraisal (TA236 published 2011) has been published on ticagrelor for the treatment of acute coronary syndromes (including unstable angina and NSTEMI).

**Relationship to other NICE guidance**

The following NICE guidance is related to CG94:

<table>
<thead>
<tr>
<th>Guidance</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA182: Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention, 2009.</td>
<td>Review decision date: June 2012. The Institute’s Guidance Executive decided that a review of the guidance should be scheduled into the appraisal work programme.</td>
</tr>
<tr>
<td>TA80: Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome, 2004.</td>
<td>TA80 was updated by CG94.</td>
</tr>
<tr>
<td>IPG36: Off-pump coronary artery bypass (OPCAB), 2004.</td>
<td>IPG36 was updated by IPG377: Off-pump coronary artery bypass grafting, 2011.</td>
</tr>
<tr>
<td>TA73: Myocardial perfusion scintigraphy for the diagnosis of angina and myocardial infarction, 2003.</td>
<td>TA73 has been partially updated by ‘Chest pain of recent onset’ (NICE clinical guideline 95, 2010) and ‘Management of stable angina’ (NICE clinical guideline 126, 2011).</td>
</tr>
<tr>
<td>TA52: Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction, 2002.</td>
<td>In January 2006, following consultation, the Institute decided to make this guidance 'static.' This means that the guidance remains in force and has no scheduled review date.</td>
</tr>
</tbody>
</table>

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Anti-discrimination and equalities considerations

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope is inclusive of adults (18 years and older) with a diagnosis of unstable angina or NSTEMI.

Conclusion

The evidence and intelligence identified through the update review process indicate that there are no additional areas which would indicate a significant change in clinical practice. In addition, there are no factors described above which would invalidate or change the direction of current guideline recommendations. However, there needs to be consideration of cross-referral to a new Technology Appraisal that was previously not mentioned in the guideline - TA236: Ticagrelor for the treatment of acute coronary syndromes, 2011.

3. Review recommendation

The guideline should not be considered for an update at this time.

The guideline should cross refer to new Technology Appraisal (TA236) that was previously not mentioned in the guideline.

Centre for Clinical Practice
20 Aug 2012
Appendix I


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45. Cohen M, Levine GN, Pieper KS et al. (2010) Enoxaparin 0.3 mg/kg IV supplement for patients transitioning to PCI after subcutaneous enoxaparin therapy for NSTE ACS: a subgroup analysis from the SYNERGY trial. Catheterization & Cardiovascular Interventions 75:928-935.


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73. Fox KA, Clayton TC, Damman P et al. (2010) Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-

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