

Treatment of NSTEMI (Non-ST Elevation Myocardial Infarction)

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Published online: 24 January 2013
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Abstract Non-ST elevation myocardial infarction (NSTEMI) is a recognized diagnostic entity that has an unacceptable mortality rate when it goes unrecognized. Following diagnosis, initial treatment with analgesics, nitrates and anti-platelet agents forms the initial approach. New anti-platelet agents such as ticagrelor and prasugrel need to be clearly understood. Simultaneously, risk stratification for ischaemia and bleeding of each such patient into mild, moderate and severe helps determine the course of further treatment that will be provided to the patient. The major decision is the need for and timing of early coronary angiography to determine the anatomy of the culprit vasculature and the decision for coronary revascularization, either by the percutaneous approach or coronary artery bypass grafting. It is at this stage that the need for and type of anticoagulation will require decision making. Choices include fondaparinux, the heparins, bivalirudin and inhibitors of the coagulation cascade.

Keywords Non-ST elevation myocardial infarction · Cardiac biomarkers · Risk stratification · Clopidogrel · Ticagrelor · Percutaneous coronary intervention

Introduction

Coronary artery disease (CAD), by far the commonest variety of cardiovascular disease, includes a spectrum of conditions ranging from silent angina, stable and unstable

angina pectoris, acute myocardial infarction, heart failure and sudden death. The first four of these are referred to as “acute coronary syndromes” (ACS). Though chest pain is the commonest symptom in patients with ACS, the diagnosis is contingent on the electrocardiogram (ECG), which identifies two groups of people, viz. those with persistent ST-segment elevation of more than 20 min duration (ST-elevation myocardial infarction or STEMI), and without persistent ST-segment elevation (including patients with persistent or transient ST-segment depression, T wave inversions, flat T waves or pseudo-normalization of T waves or no ECG changes at all), after a diagnosis of non-cardiac chest pain has been excluded. This paper will focus on this latter group of patients, especially those with non-ST elevation myocardial infarction (NSTEMI). The annual incidence of NSTEMI varies significantly between countries, with a mean global annual incidence of about 3 per 1,000 population [1].

Pathophysiology of Acute Coronary Syndromes

The disease begins gradually with accumulation of atherosclerotic plaques in the coronary arteries until one of these either ruptures or erodes at the luminal surface. The acute thrombus formed over the diseased plaque may be associated with coronary vasoconstriction and critical reduction of blood flow to the distal myocardium. This may be accompanied by endothelial dysfunction, accelerated atherothrombosis and further myocardial injury. NSTEMI lesions have lesser coronary stenosis with a thin overlying fibroatheroma, a large plaque burden, small luminal cross-sectional area or some combination of these [2] than STEMI lesions.

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Diagnosis of NSTEMI

The diagnosis of NSTEMI requires the following:

1. *History*: Chest pain, the leading symptom, typically presents as retrosternal discomfort, heaviness or pressure sometimes radiating to the left arm, neck or jaw, and lasting several minutes or occasionally persistent. There may be accompanying dyspnea, diaphoresis, nausea or vomiting and occasionally palpitations and syncope. Atypical symptoms include epigastric discomfort, sharp chest pains, or increasing breathlessness and are more common in older patients (≥ 75 years age), women, diabetic patients, and those with uraemia or functional decline. Atypical symptoms can lead to under-diagnosis, hence requiring a high index of suspicion. The symptoms may be aggravated by exertion and anaemia and relieved by rest or taking of nitrates. Risk factors for NSTEMI are similar to that for STEMI.
2. *Physical Examination*: This involves looking for complications of CAD such as heart failure and arrhythmias, precipitating conditions such as anaemia or thyroid problems or identifying non-ischaemic cardiac or non-cardiac causes of chest pain, such as pulmonary embolism, aortic dissection, pneumothorax and others.
3. *Electrocardiogram*: Features on the ECG suggesting NSTEMI include ST-segment depression or transient elevation and/or T-wave changes. However, the presence of a normal or inconclusive ECG at presentation does not exclude NSTEMI. Diagnosis may be enhanced by comparing with previous ECGs, if available, or repeat ECGs at 3–9 h after presentation or even at 24 h, at discharge, or immediately on symptom recurrence. Occasionally changes may be picked up with additional chest leads at V₇–V₉ and V_{3R}–V_{6R}. Transient bundle branch block during occurrence of symptoms signals ongoing coronary ischaemia.
4. *Cardiac Biomarkers*: Elevation of cardiac markers is crucial for a diagnosis of NSTEMI, distinguishing this from unstable angina. They have a role in risk stratification. The range of cardiac biomarkers becoming available is growing. In addition to the traditional creatine kinase MB isoenzyme (CKMB) and myoglobins which are less specific for cardiac muscle damage, troponins (both Trop-T and Trop-I) have been used as standard biomarkers over the last few years. In NSTEMI patients, cardiac troponin elevation occurs from myocardial damage secondary to distal embolization of platelet-rich thrombi from the site of a ruptured or eroded plaque. Troponins, when released into the circulation, usually rise at least 3 h after symptom onset. Other life-threatening causes of chest pain, e.g. dissecting aortic aneurysms, pulmonary embolism and patients with renal

failure may also demonstrate elevated troponin levels. The recent introduction of highly-sensitive or ultrasensitive troponin assays [3, 4, 5•, 6•, 7, 8, 9•] has allowed earlier detection of myocardial damage in patients presenting with chest pain. The addition of a second sample of these newer assays 2–3 h after the first further increases their sensitivity.

Newer cardiac biomarkers [10••] are being tested in clinical trials for their incremental value and cost-effectiveness. One promising example is Copeptin (C-terminal pro-vasopressin) which is released very early soon after onset of symptoms [11–13, 14••, 15] and has demonstrated myocardial damage within an hour of symptom onset. Combinations of biomarkers may provide greater sensitivity for earlier diagnosis of NSTEMI.

Relief of Ischaemic Pain

Pain relief is one of the most pressing needs of the patient. In acute coronary ischaemia, the increased heart rate, higher blood pressure or high preload result in decreased myocardial oxygen supply and increased myocardial oxygen demand. This oxygen imbalance results in ischaemic pain. The objective of anti-ischaemic drugs is to reverse these processes and secure pain relief. Drugs that have been demonstrated to benefit symptoms and promote good outcomes are:

Nitrates: Their venodilator effects decrease myocardial oxygen demand by lowering myocardial preload and left ventricular end-diastolic volume, and at the same time increase myocardial oxygen supply by dilating coronary arteries and increasing coronary collateral blood flow. Nitrate use favours lesser increase in cardiac biomarker levels [16•]. When given intravenously, nitroglycerine allows titration of dose until symptom relief or occurrence of side effects. Caution is needed when administering nitrates to patients on phosphodiesterase-5 inhibitors (e.g., sildenafil) because of likely severe vasodilatation and hypotension.

β -Blockers: While the CRUSADE registry [17] registered a significant 34 % reduction (3.9 vs 6.9 %, $p < 0.001$) in in-hospital mortality with acute β -blocker administration, a systematic review conducted some years later [18•] did not demonstrate any such benefit if given within the first 8 h of presentation. Current recommendation [19•] includes introducing β -blockers within 24-h of diagnosis in those without signs of low-output heart failure or major risk factors for cardiogenic shock.

Calcium Channel Blockers: These are for patients already on nitrates/ β -blockers, those for whom β -blockers are contraindicated [20], and those with coronary vasospasm.

Angiotensin Converting Enzyme (ACE) Inhibitors: Oral ACE inhibitors (if not contraindicated) may be given within 24 h of presentation for NSTEMI patients with pulmonary venous congestion or left ventricular ejection fraction (LVEF) $\leq 40\%$ or in the absence of hypotension. If ACE inhibitors are contraindicated, an angiotensin receptor blocker (such as losartan, telmisartan or valsartan) may be used [21].

Morphine: Data from the CRUSADE registry [22] demonstrated higher mortality in patients requiring morphine. While this may have been owing to a higher level of pain in such patients, the use of intravenous morphine in NSTEMI would be mainly for those with chest pain refractory to nitrates and presuming other anti-anginal therapy is also underway.

Risk Stratification in NSTEMI

The objective of risk stratification in patients with NSTEMI is to identify those at high risk for further ischemic events or adverse outcomes. The initial assessment is to detect patients at immediate high risk. Subsequent evaluation is to identifying patients who will benefit from an early invasive strategy at 4–48 h and, finally, at predicting who are at increased risk after discharge [23••].

On diagnosis of NSTEMI, a decision is required on the level of acute ischaemic and bleeding risk for the patient (high, intermediate or low). Such risk determinations aid decision making on available treatment options. Some common or promising risk stratification scoring systems [24] are:

- Thrombolysis in Myocardial Infarction (TIMI) score [25, 26] includes age ≥ 65 years, ≥ 3 CAD risk factors (high cholesterol, family history, hypertension, diabetes mellitus, smoking), prior CAD, aspirin in the past 7 days, at least two angina-related events in the previous 24 h, ST-segment deviation and elevated cardiac biomarkers (CKMB or troponin).
- Global Registry of Acute Coronary Events (GRACE) Score [27], which uses age, heart rate, systolic blood pressure, creatinine level, Killip class, cardiac arrest at admission, elevated cardiac markers and ST segment deviation.
- Platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) [28, 29] scoring uses age (as a decade), gender, symptomatic class within the last 6 weeks, presence of heart failure symptoms, and ST depression on ECG.
- History, ECG, age, risk factors and troponin (HEART) [30] scores begin with zero, one or two points, depending

on the extent of the abnormality. The HEART score is the sum of these five factors.

Some scoring systems for bleeding risk that may be used in the early assessment of NSTEMI include:

- Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early (CRUSADE implementation of the ACC/AHA guidelines) bleeding score [31] which considers baseline patient characteristics (female sex, history of diabetes, peripheral vascular disease), admission clinical variables (heart rate, systolic blood pressure, signs of CHF), and admission laboratory values (hematocrit, calculated creatinine clearance) to estimate the patient's likelihood of having an in-hospital major bleed event.
- Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) [32], an integer-based risk score that includes age, gender, serum creatinine levels, white cell count, anaemia, clinical presentation and use of antithrombotic medications, with weightage given to different levels of these seven variables.

With such available stratification systems, risks may be categorized into one of three groups with predicted six-monthly mortality, viz. low (0–3.0%), intermediate (3.0–6.0%) and high-risk (9.0% and above) [33••]. Primary criteria for high-risk categorization includes relevant rise or fall in cardiac biomarker levels, and/or dynamic ST- or T-wave changes. Secondary criteria include diabetes mellitus, renal insufficiency (with eGFR of less than 60 mL/min/1.73 m²), left ventricular ejection fraction $\leq 40\%$, early post-infarction angina, recent percutaneous coronary intervention (PCI) procedures, prior coronary artery bypass grafting and intermediate to high risk stratification scores.

Early Management of NSTEMI

Risk-level determination allows one to offer advice regarding a variety of treatment procedures, viz. need for a variety of anti-platelet agents, glycoprotein IIb/IIIa inhibitors (GP23I) and anticoagulants, and allow rational discussion of a choice of early invasive versus conservative management. Figure 1 below outlines a schema for such decision making.

Antiplatelet Therapy

Measures to reduce the dominant role of platelet activation and aggregation in the formation and propagation of an arterial thrombus, form a major therapeutic objective in the management of these patients. Antiplatelet agents should be administered once the diagnosis of NSTEMI is likely

or definite. Three classes of antiplatelet agents will be discussed, viz. aspirin, P2Y₁₂ receptor antagonists and glycoprotein IIb/IIIa receptor antagonists.

Aspirin

Aspirin (between 150 and 325 mg per oral) should be administered [34–41] as soon as possible after presentation, provided no contraindications (e.g., allergy, active bleeding, current peptic ulceration, recent neurosurgery or haemorrhagic stroke) [42] exist to its use. Aspirin should be continued indefinitely at a daily maintenance dose of 75–150 mg. Aspirin therapy reduces the risk of a vascular event. Efficacy is not increased with higher maintenance doses, which carry a greater risk of gastrointestinal intolerance. The drug should be offered to all patients with NSTEMI, unless contraindicated.

P2Y₁₂ Receptor Inhibitors

The thienopyridines were the first group of P2Y₁₂ receptor inhibitors used in NSTEMI.

Ticlopidine

Ticlopidine, the first of this group to be used is an adenosine diphosphate (ADP) receptor antagonist. Originally used in patients not tolerating aspirin and later tried in patients requiring dual antiplatelet therapy, reports of increased risk of thrombotic thrombocytopenic purpura (TTP) and neutropenia led to its relative non-use and replacement by clopidogrel. Ticlopidine is usually given orally in 250 mg doses twice daily. It is contraindicated in patients with bleeding disorders, active bleeding and severe liver disease, and needs to be reviewed in those with renal or hepatic impairment, geriatric patients (increased sensitivity), pregnancy, lactation, children, neutropenia and TTP. It may be used in patients allergic to clopidogrel.

Clopidogrel

Clopidogrel, a pro-drug activated in the liver by the CYP2C19 isoenzyme of cytochrome P450, irreversibly inhibits the P2Y₁₂ subtype of ADP receptor and also blocks activation of the glycoprotein IIb/IIIa pathway. Platelet

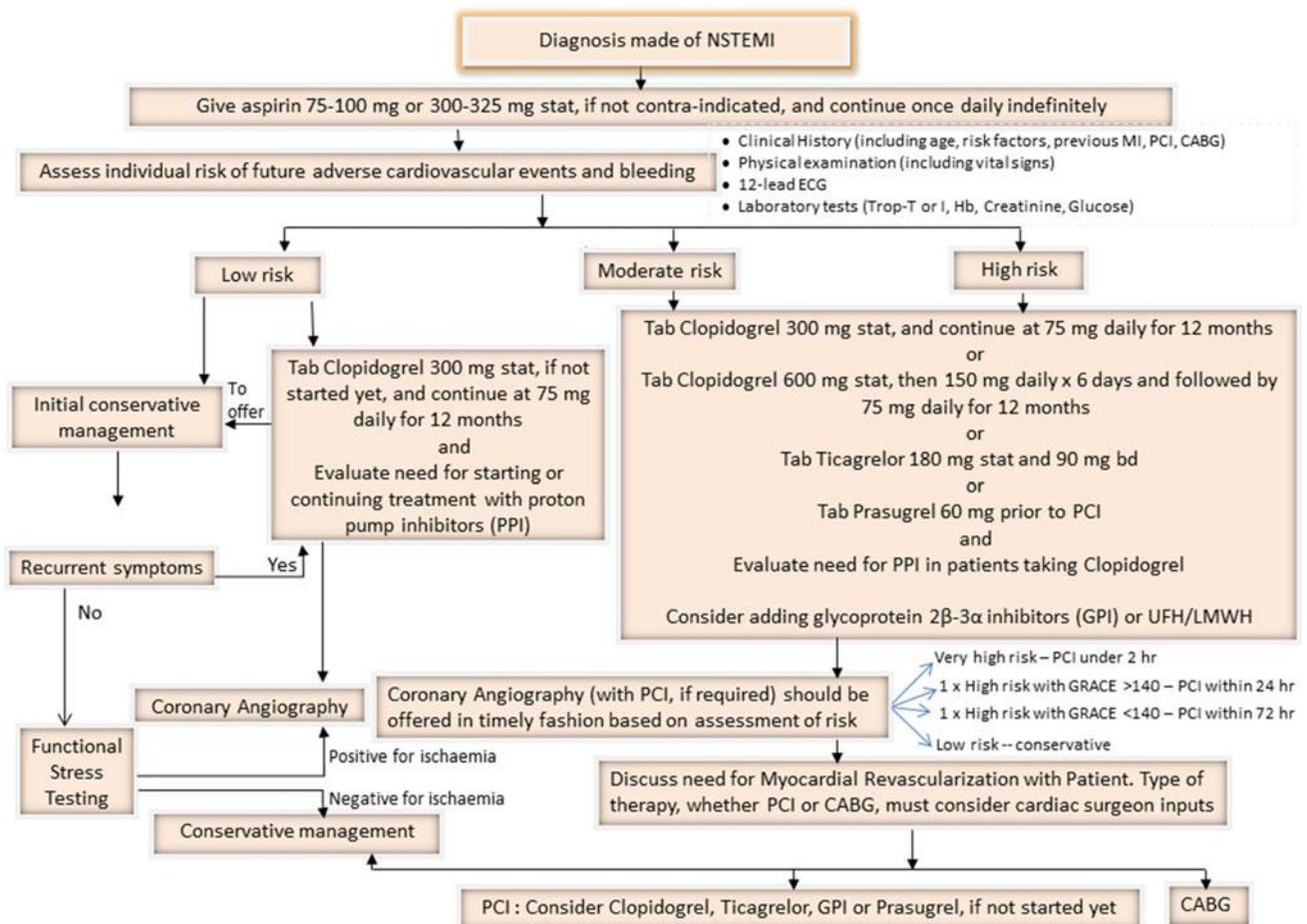


Fig. 1 Schema for early management of NSTEMI

inhibition is evident 2 h after a single dose of oral clopidogrel. Patients with a variant allele for the CYP2C19 isoenzyme have lower levels of active metabolite and are 1.5–3.5 times more likely to die or have complications than those with the high-functioning allele [43–45]. Poor metabolizers apparently make up to about 14 % of the patients and are at high risk of treatment failure. The Food and Drug Administration (FDA) [46] has placed a warning on clopidogrel to make doctors and patients aware of this.

Serious adverse drug reactions associated with clopidogrel include severe neutropenia, TTP and hemorrhage (gastrointestinal and cerebral). Use of NSAIDs is discouraged in those taking clopidogrel, owing to increased risk of gastrointestinal bleeding. Other side effects include diarrhea and rash.

Clopidogrel interacts with many drugs, especially proton pump inhibitors (PPIs) (except possibly pantoprazole), phenytoin, tamoxifen, tolbutamide, warfarin, heparin, enoxaparin, anistreplase, dipyridamole, streptokinase, ticlopidine and urokinase. In November 2009, the FDA announced that clopidogrel should be used with caution in patients on PPIs such as omeprazole and esomeprazole [47].

Clopidogrel is currently the commonest used P2Y₁₂ receptor inhibitor in patients presenting with NSTEMI. The recommended loading dose is uncertain, especially in those undergoing PCI. The benefit of higher-dose clopidogrel loading is offset by an increase in major bleeding [48]. Current United States guidelines recommend higher-dose (600 mg loading, 150 mg daily for 6 days and then 75 mg daily for 12 months) than the lower dose of 300 mg loading and 75 mg daily thereafter for those undergoing PCI, because of reduction in myocardial (re)infarction and cardiovascular death at these higher doses in the CURRENT–OASIS 7 Trial [48, 49] and in stent thrombosis. For those who had a prior loading dose of 300 mg, a supplementary dose of 300 mg is suggested. Doses for patients aged 75 years and above has not been established.

Clopidogrel therapy may be initiated early, such as at the emergency department or even earlier, or delayed until just after cardiac catheterisation when coronary anatomy can be defined and a decision made on whether revascularisation is appropriate. The advantage of early treatment is the potential to reduce ischaemic events. The disadvantage is the potential for increased bleeding in patients who subsequently may require early CABG [50]. The delayed approach avoids the increased bleeding risk. Current consensus is to go for early initiation of higher-dose clopidogrel.

Prasugrel

Prasugrel is chemically similar to and produces more rapid and consistent platelet inhibition than clopidogrel [51]. Response to prasugrel is not affected significantly by CYP

inhibitors, including PPIs, or loss-of-function variants of the CYP2C19 gene; nor by reduced ABCB1 function [52]. The recommended loading dose is 60 mg orally administered not later than 1 h once coronary anatomy is defined and a decision made to proceed with PCI. Maintenance therapy is 10 mg daily for at least 12 months. Prasugrel has a lower incidence of cardiovascular death, non-fatal myocardial infarction and stroke when compared to clopidogrel [53] owing to a significant risk reduction for myocardial infarction and lesser stent thrombosis. However, life-threatening bleeding has been noted, especially in patients with a history of cerebrovascular accidents. Greater benefit without increased risk of bleeding is observed in diabetic patients. There is no apparent net clinical benefit in patients >75 years of age and in those with body weight <60 kg.

Ticagrelor

This is a cyclopentyl-triazolo-pyrimidine and reversibly binds to the P2Y₁₂ inhibitor with a plasma half-life of 12 h. The degree of P2Y₁₂ inhibition depends mainly on the plasma ticagrelor level. The onset of action is rapid compared with clopidogrel. Offset of action is also quicker with faster recovery of platelet function and shorter duration of effect. Ticagrelor increases levels of drugs metabolized through CYP3A, such as simvastatin. Moderate CYP3A inhibitors such as diltiazem increase levels and lengthen duration of ticagrelor effect.

In the PLATO trial [54], ticagrelor (180 mg loading dose and 90 mg twice daily for up to 12 months) reduced death from vascular causes, MI, or stroke to 9.8 % from 11.7 % in the clopidogrel group (HR 0.84; 95 % CI 0.77–0.92; $p = 0.001$). Stent thrombosis was reduced from 1.9 to 1.3 % ($p = 0.01$) and total mortality from 5.9 to 4.5 % ($p = 0.001$). Ticagrelor also reduced early and late mortality following CABG from 9.7 to 4.7 % (HR 0.49; CI 0.32–0.77; $p = 0.01$). Adverse effects include dyspnea (usually transient, occurring within the first week and occasionally persisting until cessation of treatment [54, 55, 56, 57]) without any deterioration in cardiac or pulmonary function, increased frequency of ventricular pauses, and asymptomatic increases in uric acid [54, 58, 59]. Caution is advised in patients with either advanced sinoatrial disease or second- or third-degree atrioventricular block, unless already treated by permanent pacemaker. The mechanism for the dyspnoea and ventricular pauses remains uncertain.

Glycoprotein IIb/IIIa Inhibitors

GP23I have not demonstrated any reduction in MI or death rates when used in purely medically managed patients

not subjected to coronary revascularization procedures. In patients who had undergone PCI [60••], if GP23Is were maintained during the procedure, significant cardiovascular benefit was observed. There was generally an increase in bleeding complications, though not intracranial haemorrhage. The recommendations for use of these agents would be as follows:

1. Not routinely before coronary angiography if the decision is for an invasive treatment strategy [61].
2. Not for patients on dual anti-platelet therapy if for conservative management, unless the risk of bleeding is low [60••, 61].
3. In high-risk patients eptifibatid or tirofiban may be added to those on aspirin alone or on dual anti-platelet therapy prior to angiography if there is ongoing ischaemia and the risk of bleeding is low [61, 62].
4. They may be withheld until after angiography, when the procedure demonstrates the presence of thrombi and the extent of the disease is clear, biomarker levels are elevated, and there has already been concurrent treatment with a P2Y₁₂ inhibitor and a relative lack of factors that contribute to serious bleeding [63, 64].

Anti-coagulant Therapy

Since the initiating event in a myocardial infarction is the formation of a thrombus, reducing pro-thrombotic events would assist in minimizing propagation of the clot formed. In addition to platelet inhibition, processes that counteract conversion of prothrombin to thrombin would naturally decrease the conversion of fibrinogen to fibrin [65, 66]. Together, these two processes may be expected to further inhibit thrombus formation in a coronary vessel. Therefore, anticoagulation is recommended for all patients presenting with NSTEMI, in addition to dual anti-platelet therapy. Selection of anticoagulants should be based on subsequent ischaemic bleeding risk profile. Such anticoagulation should be maintained at least until hospital discharge. Discontinuation of anticoagulant should be considered after completion of an invasive procedure, unless otherwise contra-indicated. During anticoagulation, gastric protection should be considered, especially with PPIs, since the commonest spontaneous bleed in such patients is gastrointestinal. Anti-platelet agents, on the other hand, need to be continued for at least a further 12 months, even without PCI.

Anti-coagulants can be divided into a few groups depending on their mode of action:

- a. Heparins, such as unfractionated heparin (UFH) and low-molecular weight heparins (LMWH) have been used in patients with NSTEMI for more than a decade.

UFH is proven to reduce the rate of death and MI in multiple trials [65], especially when given in combination with aspirin, though with some increased risk of bleeding. When invasive procedures such as PCI are performed the usual dose given is 70–100 IU/kg body weight, or 50–60 IU/kg if used in combination with a GP IIB/IIIa inhibitor [66]. Dosing should be guided by measurements of activated clotting times (ACT). UFH use should be terminated after removal of the arterial sheath. LMWHs, however, can be administered subcutaneously at a dose of 1 mg/kg every 12 h for at least 2 days until clinical stabilization. The arterial sheath should be removed at least 8 h following a dose of enoxaparin with the subsequent dose another 8 h after sheath removal. Treatment may be continued for up to 8 days. LMWH can be administered without the use of anti-factor Xa monitoring, except in patients with renal failure or obesity. Efficacy rates have generally been similar with both UFH and LMWH while lower bleeding rates have been noted with the LMWHs [67, 68]. Crossover of heparins in the same patient is usually not recommended.

- b. Direct inhibitors of thrombin, e.g., bivalirudin. Bivalirudin directly inhibits thrombin by specifically binding both to the catalytic site and the anion-binding exosite of circulating and clot-bound thrombin [69]. It is to be administered at a dose of 0.1 mg/kg IV bolus followed by an infusion at 0.25 mg/kg/h until the PCI procedure is completed. Trials have demonstrated a similar efficacy endpoint when compared to heparins, both given with GP IIB/IIIa inhibitors [32, 70–72] with significant reduction in major bleeding [73].
- c. Direct inhibitors of factor Xa such as apixaban, rivaroxaban and otamixaban: while apixaban and rivaroxaban have been used mainly for management of deep vein thrombosis, otamixaban, an investigational anti-factor Xa compound, in intermediate dosages, has been found, in initial studies [74] to offer substantial reduction in major coronary complications such as death and myocardial infarction in patients presenting with NSTEMI, with similar bleeding rate when compared to a combination of UFH and eptifibatid.
- d. Indirect inhibitors of factor Xa such as fondaparinux: this is a synthetic, highly sulfated pentasaccharide, with a sequence derived from the minimal antithrombin (AT) binding region of heparin. Fondaparinux binds to AT with a higher affinity than the native pentasaccharide of UFH or low molecular weight heparin, and causes a conformational change in AT that significantly increases the ability of AT to inactivate factor Xa. Fondaparinux is licensed in Europe for treatment of NSTEMI in patients for whom invasive management is not indicated within 2 h of diagnosis. Administration of

the drug is recommended [75, 76, 77•] as soon as possible following diagnosis and continued for up to 8 days or hospital discharge, whichever occurs earlier. Fondaparinux is not yet recommended in patients for whom urgent PCI is indicated.

Coronary Revascularization in NSTEMI

The primary mechanism for occurrence of symptoms is coronary artery blockage. Various grades of patients constitute the spectrum that is NSTEMI. Those with low risk benefit from conservative management, while those at high risk may require an invasive approach. Whichever is taken would depend on the patient's clinical condition, presence of co-morbidities and risk factors, severity of lesions seen on coronary angiography, and a clear understanding of the risks and benefits of invasive versus conservative strategies.

Though routine invasive management has shown reduced overall rates of adverse outcomes compared with selective invasive strategy, it has also demonstrated an early hazard of death and/or MI during the initial hospitalization for the procedure [78–80]. Two-year survivals and coronary ischaemia rates are significantly better with an early invasive approach [81, 82•] in both men and women. The reductions in cardiovascular death and MI are greater in high-risk groups than in those with low or intermediate risk [60••].

The best timing for invasive evaluation in NSTEMI patients at extremely high risk and who are haemodynamically unstable (those with ongoing chest pain in spite of optimal medical therapy, severe heart failure or life-threatening arrhythmias) is generally immediately after presentation (i.e., less than 2 h) [83••]. For patients with at least one primary high-risk criterion and a GRACE risk score >140, an early invasive strategy within 24 h of presentation would be advisable [84, 85•]. In patients with at least one primary high-risk criterion and a GRACE risk score <140, an invasive strategy is recommended within 72 h after first presentation [60••]. In those at low-risk and without recurrent symptoms, there needs to be non-invasive documentation of inducible ischaemia before a decision is made for invasive evaluation of the patient [60••, 86, 87]. For such patients, routine invasive evaluation is not recommended [60••, 81]. Where angiography is carried out, PCI of non-significant lesions is also not recommended.

Conclusion

Management of patients with NSTEMI is contingent on diagnosis, followed by stratification of risk for adverse

cardiac events and major bleeding. Following initial relief of symptoms and haemodynamic optimization, further management revolves around measures to decrease thrombus propagation and re-open significantly blocked coronary vessels, if any. Future areas of NSTEMI management will include more aggressive imaging modalities to define coronary anatomy safely for earlier definitive treatment options.

Disclosure No potential conflict of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Fox KAA, Eagle KA, Gore JM, Steg PG, Anderson FA. The Global Registry of Acute Coronary Events, 1999 to 2009—GRACE. *Heart*. 2010;96(14):1095–101.
2. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364(3):226–35.
3. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Frohlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Munzel TF, Blankenberg S. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med*. 2009;361(9):868–77.
4. Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus HA. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clin Chem*. 2010;56(4):642–50.
5. •• Jaffe AS, Apple FS. High-sensitivity cardiac troponin: hype, help, and reality. *Clin Chem*. 2010;56(3):342–4. *This paper brings perspective to the issue of the high-sensitive cardiac troponin.*
6. • Weber M, Bazzino O, Estrada JJJ, Miguel R, Salzberg S, Fuselli JJ, Liebetrau C, Woelken M, Moellmann H, Nef H, Hamm C. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. *Am Heart J*. 2011;162(1):81–8. *This is an analysis of data from two ACS registries and useful especially when high-sensitivity assays are done in TnT negative patients.*
7. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med*. 2009;361(9):858–67.
8. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304(22):2503–12.
9. • Thygesen K, Mair J, Katus H, Plebani M, Venge P, Collinson P, Lindahl B, Giannitsis E, Hasin Y, Galvani M, Tubaro M, Alpert JS, Biasucci LM, Koenig W, Mueller C, Huber K, Hamm C, Jaffe

- AS. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J*. 2010;31(18):2197–204. *This expert consensus statement from the European Society of Cardiology outlines the principles for the application of various biomarkers in acute cardiac care.*
10. •• Nagesh CM, Roy A. Role of biomarkers in risk stratification of acute coronary syndrome. *Indian J Med Res*. 2010;132(5):627–33. *This is a good review of cardiac biomarkers, especially of their relevance and use in management of NSTEMI.*
 11. Keller T, Tzikas S, Zeller T, Czyz E, Lillpopf L, Ojeda FM, Roth A, Bickel C, Baldus S, Sinning CR, Wild PS, Lubos E, Peetz D, Kunde J, Hartmann O, Bergmann A, Post F, Lackner KJ, Genth-Zotz S, Nicaud V, Tiret L, Münzel TF, Blankenberg S. Copeptin improves early diagnosis of acute myocardial infarction. *JACC*. 2010;55(19):2096–106.
 12. Narayan H, Dhillon OS, Quinn PA, Struck J, Squire IB, Davies JE, Ng LL. C-terminal proavopressin (copeptin) as prognostic marker after acute non ST elevation myocardial infarction—leicester acute myocardial infarction peptide II (LAMP II) study. *Clin Sci*. 2011;121(2): 79–89.
 13. Reichlin T, Hochholzer W, Stelzig C, Laule K, Freidank H, Morgenthaler NG, Bergmann A, Potocki M, Noveanu M, Breidhardt T, Christ A, Boldanova T, Merki R, Schaub N, Bingisser R, Christ M, Mueller C. Incremental value of copeptin for rapid rule out of acute myocardial infarction. *J Am Coll Cardiol*. 2009;54(1):60–8.
 14. •• Charpentier S, Maupas-Schwalm F, Courmot M, Elbaz M, Botella JM, Lauque D. Combination of copeptin and troponin assays to rapidly rule out non-ST elevation MI in the emergency department. *Acad Emerg Med*. 2012;19(5):517–24. *This study concludes that the combined assay improves early diagnostic accuracy of NSTEMI though insufficient to safely rule out the diagnosis at time of presentation.*
 15. Giannitsis E, Kehayova T, Vafaie M, Katus HA. Combined testing of high-sensitivity troponin T and copeptin on presentation at prespecified cutoffs improves rapid rule-out of non-ST-segment elevation myocardial infarction. *Clin Chem*. 2011;57(10):1452–5.
 16. • Ambrosio G, Del Pinto M, Tritto I, Agnelli G, Bentivoglio M, Zuchi C, Anderson FA, Gore JM, Lopez-Sendon J, Wyman A, Kennelly BM, Fox KA. Chronic nitrate therapy is associated with different presentation and evolution of acute coronary syndromes: insights from 52,693 patients in the Global Registry of Acute Coronary Events. *Eur Heart J*. 2010;31(4):430–8. *This very large multinational registry study strongly suggests that use of nitrates is associated with less severe acute coronary event.*
 17. Miller CD, Roe MT, Mulgund J, Hoekstra JW, Santos R, Pollack CV Jr, Ohman EM, Gibler WB, Peterson ED. Impact of acute beta-blocker therapy for patients with non-ST-segment elevation myocardial infarction. *Am J Med*. 2007;120(8):685–92.
 18. • Brandler E, Paladino L, Sinert R. Does the early administration of beta-blockers improve the in-hospital mortality rate of patients admitted with acute coronary syndrome? *Acad Emerg Med*. 2010;17(1):1–10. *This systematic review of literature over a 44 year period failed to demonstrate a convincing in-hospital mortality benefit with use of β -blockers early in the course of acute or suspected MI.*
 19. • Jois P. NSTEMI and STEMI: therapeutic updates 2011. *Emerg Med Rep*. 2011;32(1):1–7. *This review neatly summarises the evidence for the current recommendations on use of β -blockers in NSTEMI.*
 20. Hansen JF. Treatment with verapamil after an acute myocardial infarction. Review of the Danish studies on verapamil in myocardial infarction (DAVIT I and II). *Drugs*. 1991;42(Suppl 2):43–53.
 21. Teo K, Yusuf S, Sleight P, et al. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the ongoing telmisartan alone and in combination with ramipril global endpoint trial/telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease (ONTARGET/TRANSCEND) trials. *Am Heart J*. 2004;148(1):52–61.
 22. Meine TJ, Roe MT, Chen AY, et al. Association of IV morphine use and outcomes in acute coronary syndromes: results from the CRUSADE quality improvement initiative. *Am Heart J*. 2005;149(6):1043–9.
 23. •• 2012 Writing Committee Members, Jneid H, Anderson JL, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2012;126(7):875–910. *This is the latest guidelines by ACCF/AHA on the management of patients with UA/NSTEMI.*
 24. Khalil R, Han L, Jing C, Quan H. The use of risk scores for stratification of non-ST elevation acute coronary syndrome patients. *Exp Clin Cardiol*. 2009;14(2):e25–30.
 25. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7): 835–42.
 26. Lakhani MS, Qadir F, Hanif B, et al. Correlation of thrombolysis in myocardial infarction (TIMI) risk score with extent of coronary artery disease in patients with acute coronary syndrome. *J Pak Med Assoc*. 2010;60(3):197–200.
 27. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. *Arch Intern Med*. 2003;163(19):2345–53.
 28. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation*. 2000;101(22):2557–67.
 29. Brilakis ES, Wright RS, Kopecky SL, et al. Association of the PURSUIT risk score with predischARGE ejection fraction, angiographic severity of coronary artery disease, and mortality in a nonselected, community-based population with non-ST-elevation acute myocardial infarction. *Am Heart J*. 2003;146(5):811–8.
 30. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J*. 2008;16(6): 191–6.
 31. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby KL, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV Jr, Peterson ED, Alexander KP. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) bleeding score. *Circulation*. 2009;119(14):1873–82.
 32. Stone W, White HD, Ohman EM, Bertrand ME, Lincoff AM, McLaurin BT, et al. Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial Investigators. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Lancet*. 2007;369(9565):907–19.
 33. •• National Institute for Health and Clinical Excellence. Unstable Angina and NSTEMI. NICE Clinical Guidelines 94. 2010. <http://www.nice.org.uk/nicemedia/live/12949/47921/47921.pdf>. Accessed 15 Oct 2012. *These 2010 NICE guidelines summarize the principal recommendations for NSTEMI care in an extremely organized manner.*

34. Antiplatelet Trialists' Collaboration Collaborative overview of randomised trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81–106.
35. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849–60.
36. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfapyrazone, or both in unstable angina: results of a Canadian multicenter trial. *N Engl J Med*. 1985;313(22):1369–75.
37. Cohen M, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users: primary end points analysis from the ATACS trial: antithrombotic Therapy in Acute Coronary Syndromes Research Group. *Circulation*. 1994;89(1):81–8.
38. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1983;309(7):396–403.
39. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336(14):973–9.
40. The RISC Group risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet*. 1990;336(8719):827–30.
41. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med*. 1988;319(17):1105–11.
42. Serebruany VL, Malinin AI, Eisert RM, et al. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. *Am J Hematol*. 2004;75(1):40–7.
43. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360(4):354–62.
44. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360(4):363–75.
45. Collet J, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, Payot L, Brugier D, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009;373(9660):309–17.
46. FDA drug safety communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. Food and Drug Administration (FDA), 25 March 2010. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm204253.htm>. Accessed 12 Aug 2012.
47. U.S. Food and Drug Administration. Drugs. Public Health Advisory: Updated Safety Information about a drug interaction between clopidogrel bisulfate (marketed as Plavix) and omeprazole (marketed as Prilosec and Prilosec OTC). Food and Drug Administration (FDA), November 17, 2009.
48. Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet*. 2010;376(9748):1233–43.
49. • Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363(10):930–42. *This very large prospective study demonstrated no significant difference between a 7-day, double-dose and standard dose clopidogrel or between higher-dose or lower-dose aspirin for primary outcome of cardiovascular death, myocardial infarction and stroke, Double-dose clopidogrel was associated with a significant reduction in stent thrombosis.*
50. Purkayastha S, Athanasiou T, Malinovsky V, et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. *Heart*. 2006;92(4):531–2.
51. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann F-J, Michelson AD, Angiolillo DJ, Hod H, Montalescot G, Miller DL, Jakubowski JA, Cairns R, Murphy SA, McCabe CH, Antman EM, Braunwald E. PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the prasugrel in comparison to clopidogrel for inhibition of platelet activation and aggregation thrombolysis in myocardial infarction 44 trial. *Circulation*. 2007;116(25):2923–32.
52. Small DS, Farid NA, Payne CD, Weerakkody GJ, Li YG, Brandt JT, Salazar DE, Winters KJ. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *J Clin Pharmacol*. 2008;48(4):475–84.
53. Wiviott S, Braunwald E, McCabe C, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy S, Riesmeyer J, Weerakkody G, Gibson C, Antman E. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001–15.
54. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–57.
55. Storey RF, Bliden K, Patil SB, Karunakaran A, Ecob R, Butler K, Teng R, Wei C, Tantry US, Gurbel P. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol*. 2010;56(3):185–93.
56. • Cannon C, Harrington R, James S, Ardissino D, Becker R, Emanuelsson H, Husted S, Katus H, Keltai M, Khurmi N, Kontny F, Lewis B, Steg P, Storey R, Wojdyla D, Wallentin L, the PLATELET Inhibition and Patient Outcomes (PLATO) Investigators. Ticagrelor compared with clopidogrel in acute coronary syndromes patients with a planned invasive strategy (PLATO): a randomized double-blind study. *Lancet*. 2010;375(9711):283–93. *This very large randomized, prospective study clearly demonstrated that use of ticagrelor in patients with acute coronary syndromes resulted in lesser incidence of cardiovascular death, myocardial infarction or stroke, than with clopidogrel, though the rates of major bleeding were the same in both group.*
57. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, Horrow J, Husted S, James SK, Mahaffey KW, Nicolau JC, Scirica BM, Storey RF, Vintila M, Ycas J, Wallentin L. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery results from the PLATO (platelet inhibition and patient outcomes) trial. *J Am Coll Cardiol*. 2011;57(6):672–84.
58. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J*. 2006;27(9):1038–47.
59. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol*. 2007;50(19):1844–51.

60. •• Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlat C, Pomar JL, Reifart N, Ribichini FL, Schaliq MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2010;31(20):2501–55. *This authoritative review of the evidence for myocardial revascularization provided by the ESC and EACTS is the basis for their revascularization guideline.*
61. Giugliano RP, White JA, Bode C, Armstrong PW, Montalescot G, Lewis BS, van't Hof A, Berdan LG, Lee KL, Strony JT, Hildemann S, Veltri E, Van de Werf F, Braunwald E, Harrington RA, Califf RM, Newby LK, the EARLY ACS Investigators. Early versus delayed, provisional eptifibatid in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2176–90.
62. Kastrati A, Mehilli J, Neumann F-J, Dotzer F, ten Berg J, Bollwein H, Graf I, Ibrahim M, Pache J, Seyfarth M, Schuhlen H, Dirschinger J, Berger PB, Schomig A, for the Intracoronary Stenting, Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 Trial I. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA*. 2006;295(13):1531–8.
63. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Moliterno DJ, Heeschen C, Hamm CW, Robbins MA, Kleiman NS, Theroux P, White HD, Topol EJ. Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes. Gradient of benefit related to the revascularisation strategy. *Eur Heart J*. 2002;23(18):1441–8.
64. Stone GW, Bertrand ME, Moses JW, Ohman EM, Lincoff AM, Ware JH, Pocock SJ, McLaurin BT, Cox DA, Jafar MZ, Chandna H, Hartmann F, Leisch F, Strasser RH, Desaga M, Stuckey TD, Zelman RB, Lieber IH, Cohen DJ, Mehran R, White HD. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUTY timing trial. *JAMA*. 2007;297(6):591–602.
65. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet*. 2000;355(9219):1936–42.
66. Harrington RA, Becker RC, Cannon CP, Gutterman D, Lincoff AM, Popma JJ, Steg G, Guyatt GH, Goodman SG. Antithrombotic therapy for non-ST-segment elevation acute coronary syndromes: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):670S–707S.
67. Murphy S, Gibson C, Morrow D, Van de Werf F, Menown I, Goodman S, Mahaffey K, Cohen M, McCabe C, Antman EM, Braunwald E. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. *Eur Heart J*. 2007;28(17):2077–86.
68. Blazing MA, de Lemos JA, White HD, Fox KA, Verheugt FW, Ardissino D, DiBattiste PM, Palmisano J, Bilheimer DW, Snapinn SM, Ramsey KE, Gardner LH, Hasselblad V, Pfeffer MA, Lewis EF, Braunwald E, Califf RM. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA*. 2004;292(1):55–64.
69. Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest*. 1990;86(2):385–91.
70. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM, ACUTY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355(21):2203–16.
71. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J*. 2001;142(6):952–9.
72. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289(7):853–63.
73. Stone G, Ware J, Bertrand M, Lincoff A, Moses J, Ohman E, White H, Feit F, Colombo A, McLaurin B, Cox D, Manoukian S, Fahy M, Clayton T, Mehran R, Pocock S, for the ACUTY Investigators. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUTY trial. *JAMA*. 2007;298(21):2497–506.
74. Sabatine MS, Antman EM, Widimsky P, Ebrahim IO, Kiss RG, Saaiman A, Polasek R, Contant CF, McCabe CH, Braunwald E. Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial. *Lancet*. 2009;374(9692):787–95.
75. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354(14):1464–76.
76. Mehta SR, Steg PG, Granger CB, Bassand JP, Faxon DP, Weitz JI, Afzal R, Rush B, Peters RJ, Natarajan MK, Velianou JL, Goodhart DM, Labinaz M, Tanguay JF, Fox KA, Yusuf S. Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra study in percutaneous coronary intervention: a randomized evaluation (ASPIRE) pilot trial. *Circulation*. 2005;111(11):1390–7.
77. • Anderson JA, Hirsh J, Yusuf S, Johnston M, Afzal R, Mehta SR, Fox KA, Budaj A, Eikelboom JW. Comparison of the anticoagulant intensities of fondaparinux and enoxaparin in the organization to assess strategies in acute ischemic syndromes (OASIS)-5 trial. *J Thromb Haemost*. 2010;8(2):243–9. *This study suggested that a lower intensity of anticoagulation (such as with fondaparinux) than used in the past may be sufficient to prevent recurrent ischaemic events and death in patients with ACS concurrently on aspirin and clopidogrel.*
78. Mehta SR, Cannon CP, Fox KA, Wallentin L, Boden WE, Spacek R, Widimsky P, McCullough PA, Hunt D, Braunwald E, Yusuf S. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA*. 2005;293(23):2908–17.
79. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol*. 2006;48(7):1319–25.
80. Yan AT, Yan RT, Tan M, Eagle KA, Granger CB, Dabbous OH, Fitchett D, Grima E, Langer A, Goodman SG. In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. *Am J Cardiol*. 2005;96(7):913–6.
81. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA,

- Murphy SA, Spacek R, Swahn E, Wallentin L, Windhausen F, Sabatine MS. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. 2008;300(1):71–80.
82. • Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, Lagerqvist B, Wallentin L. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol*. 2010;55(22):2435–45. *This meta-analysis of patient data from randomized trials with 5-year outcomes (FRISC-II, ICTUS and RITA-3) showed that a routine invasive strategy reduced long-term rates of cardiovascular death or MI, especially in high-risk patients.*
83. •• Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D. ESC Guidelines for the Management of Acute Coronary Syndromes in Patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2011;32(23):2999–3054. *This is an exceptionally well organized presentation of the recommendations for management of NSTEMI in Europe.*
84. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2165–75.
85. • Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, Stuckey T, Tcheng JE, Mehran R, Lansky AJ, Grines CL, Stone GW. Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol*. 2010;55(14):1416–24. *This large-scale study of patients presenting with NSTEMI clearly demonstrated that delays to PCI exceeding 24 hours for NSTEMI patients was associated with higher adverse events and suggests that urgent angiography and triage to revascularization remains a priority for such patients.*
86. Nyman I, Wallentin L, Areskog M, Areskog NH, Swahn E. Risk stratification by early exercise testing after an episode of unstable coronary artery disease. The RISC Study Group. *Int J Cardiol*. 1993;39(2):131–42.
87. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. *J Am Coll Cardiol*. 2002;40(2):251–6.