UNSTABLE ANGINA
Supporting information

This guideline has been prepared with reference to the following:

NICE. Acute coronary syndromes. 2020. London. NICE

https://www.nice.org.uk/guidance/ng185

Jneid H, Anderson JL, Wright RS, 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. J Am Coll Cardiol 2012;60:645-81

http://www.sciencedirect.com/science/article/pii/S0735109712019596#

Immediate treatment

Oral aspirin improves the clinical outcome?
A collaborative overview and meta-analysis of 7 trials involving 4018 subjects demonstrated that anti-platelet therapy reduces the number of vascular deaths, strokes and MIs in patients with angina (NNT=31 for 1 to 3 years treatment) (ATC, 1994).
Aspirin reduces the risk of fatal or nonfatal MI by 71% in the acute phase, by 60% at 3 months, and by 52% at 2 years (Theroux, 1998), and its use is recommended in current guidelines from the European Society of Cardiology (Anon, 2007) and NICE (2010).

Anon. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The Task Force for the Diagnosis and Treatment of Non-ST-Segment
Elevation Acute Coronary Syndromes of the European Society of Cardiology. Europ Heart J 2007;28:1598–1660
http://eurheartj.oxfordjournals.org/content/28/13/1598

Anon. 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: Antiplatelet Trialists' Collaboration. BMJ 1994; 308: 81-106
http://www.bmj.com/content/308/6921/81.long

Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. Circulation 1998;97:1195-1206
http://circ.ahajournals.org/content/97/12/1195.long

Evidence Level: I

Buccal GTN improves the clinical outcome?
A placebo controlled RCT of 162 patients with unstable angina treated with GTN infusion demonstrated a reduction in episodes of angina (NNT=6) and s/l GTN usage (NNT=7) at 48 hrs. The effect on mortality is unclear (Karlberg, 1998). Patients with unstable angina who have buccal GTN have greater improvements in haemodynamic parameters than those on intra-venous isosorbide dinitrate (Lahiri, 1989). Buccal GTN patients experienced fewer side-effects over 24 hours than those given iv GTN. (NNT=3) (Dellborg, 1991).

Karlberg KE, Saldeen T, Wallin R, et al. Intravenous nitroglycerin reduces ischaemia in unstable angina pectoris: a double-blind placebo-controlled study. J Intern Med 1998; 243: 25-31
http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2796.1998.00253.x/full

Lahiri A, Bowles MJ, Brigden G, et al. Buccal nitroglycerin and intravenous isosorbide in unstable angina: double-blind study of acute administration. Am J Non-invasive Cardiol 1989; 3:281-9

Dellborg M, Gustafsson G, Swedberg K. Buccal versus intravenous nitroglycerin in unstable angina pectoris. Eur J Clin Pharmacol 1991; 41: 5-9

Evidence Level: II

Routine use of bisoprolol/diltiazem improves the clinical outcome?
A placebo controlled RCT demonstrated that oral metoprolol reduces the incidence of recurrent angina over 48 hours (NNT=9) (Anon, 1986). A second RCT (Gottlieb, 1986) found similar results over a 4-day period.
A systematic review (Held, 1989) has shown that verapamil and diltiazem reduce the incidence of reinfarction (NNT=68); the effect on mortality is unclear in the short term (Gobel, 1995; Yusuf, 1991), but a follow-up study has found low overall mortality 12 months after treatment (Gobel, 1998). One randomised comparative trial with 50 patients in each arm demonstrated that diltiazem is an effective alternative to beta-blockers (Theroux, 1985). Patients were followed-up for a mean of 5.1 months (range 1 to 15) and similar results were observed in both groups.

Anon. Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both: report of The Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group. Br Heart J 1986; 56: 400-13 http://heart.bmj.com/content/56/5/400.long

Gobel EJ, Hautvast RW, van Gilst WH, et al. Randomised, double-blind trial of intravenous diltiazem versus glyceryl trinitrate for unstable angina pectoris. Lancet 1995; 346:1653-7

Gobel EJ, Van Gilst WH, De Kam PJ, et al. Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris. Eur Heart J 1998;19:1208-13 http://eurheartj.oxfordjournals.org/content/19/8/1208.full-text.pdf

Gottlieb SO, Weisfeldt ML, Ouyang P, et al. Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. Circulation 1986;73:331-7 http://circ.ahajournals.org/content/73/2/331.long

Theroux P, Taeymans Y, Morissette D, et al. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. J Am Coll Cardiol 1985; 5:717-22

Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. Am J Cardiol 1991; 67: 1295-7

Evidence Level: II

Dalteparin by subcutaneous injection until 24 hours after the pain has been relieved improves the clinical outcome?
A Cochrane review of 8 studies in 3118 patients (Andrade-Castellanos, 2014) found no evidence for difference in overall mortality between groups treated with heparin and placebo (RR = 0.84; 95% CI 0.36 – 1.98).
A meta-analysis of randomised trials comparing LMWH with unfractionated heparin in a total of 13320 patients (Le Nguyen, 2001) found similar risk ratios for death (RR 0.98; 95% CI 0.73-1.31), death/MI (RR 0.86; 95% CI 0.74-1.01), death/MI/recurrent angina/revascularisation (RR 0.89; 95% CI 0.74-1.07) and major haemorrhage (RR 1.01; 95% CI 0.81-1.25).
Of the different LMWHs available, only enoxaparin has been shown to reduce the risk of coronary events in patients with non-ST segment elevation acute coronary ischemia (Turpie, 2001; Goodman, 2000).
Findings from the FRISC II trial indicate that treatment with dalteparin extended to 3 months results in a significant reduction in the combined incidence of death, MI, or revascularisation (RR reduction 13%; p=0.031) (Husted, 2002; Kontny, 2001).

Goodman SG, Cohen M, Bigonzi F, et al. Randomized trial of low molecular weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease: one-year results of the ESSENCE Study. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events. J Am Coll Cardiol 2000;36:693-8 http://www.sciencedirect.com/science/article/pii/S0735109700008081

Husted SE, Wallentin L, Lagerqvist B, et al. Benefits of extended treatment with dalteparin in patients with unstable coronary artery disease eligible for revascularization. Eur Heart J 2002;23:1213-8

Kontny F. Improving outcomes in acute coronary syndromes: the FRISC II trial. Clin Cardiol 2001;24(3 Suppl):I3-7

Le Nguyen MT, Spencer FA. Low molecular weight heparin and unfractionated heparin in the early pharmacologic management of acute coronary syndromes: a meta-analysis of randomized controlled trials. J Thromb Thrombolysis 2001;12:289-95 http://content.onlinejacc.org/article.aspx?articleid=1126499

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Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N. Heparin versus placebo for acute coronary syndromes. Cochrane Database of Systematic Reviews 2014. Art. No.: CD003462
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003462.pub3/full

Turpie AG, Antman EM. Low-molecular-weight heparins in the treatment of acute coronary syndromes. Arch Intern Med 2001;161:1484-90
http://archinte.jamanetwork.com/article.aspx?articleid=648496

Evidence Level: I

Referral to cardiology

Clopidogrel (300mg followed by 75mg daily) is indicated if troponin T is raised >0.05 ng/mL?
A randomised trial (the "CURE" trial) in 12,562 patients with unstable angina or NSTEMI (Yusuf, 2001) found that the absolute risk reduction for the composite end point of cardiovascular death, non-fatal myocardial infarction, and stroke for those who took both aspirin and clopidogrel (in the dose stated above) was 2.1% (P<0.001; RR 0.8, 95% CI 0.72 - 0.9).
A Cochrane systematic review (Squizzato, 2011) found that: "No new studies were identified from the updated searches. A total of two RCTs were found: the CHARISMA and the CURE study. The CURE study enrolled only patients with a recent non-ST segment elevation acute coronary syndrome. The use of clopidogrel plus aspirin, compared with placebo plus aspirin, was associated with a lower risk of cardiovascular events (OR: 0.87, 95% CI 0.81 to 0.94; P<0.01) and a higher risk of major bleeding (OR 1.34, 95% CI 1.14 to 1.57; P<0.01). Overall, we would expect 13 cardiovascular events to be prevented for every 1000 patients treated with the combination, but 6 major bleeds would be caused. In the CURE trial, for every 1000 people treated, 23 events would be avoided and 10 major bleeds would be caused. In the CHARISMA trial, for every 1000 people treated, 5 cardiovascular events would be avoided and 3 major bleeds would be caused."

Squizzato A, Keller T, Romualdi E, et al. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD005158
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005158.pub3/full

Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502
http://www.nejm.org/doi/full/10.1056/NEJMoa010746#t=articleTop

Evidence Level: I

Subsequent management

Continued use of low dose aspirin affects the clinical outcome?
In the RISC study (796 patients) and Yusuf meta-analysis (2500 patients), patients with unstable coronary artery disease who took aspirin indefinitely were less likely to die or have a MI in the next 3 months (NNT = 10) (RISC, 1990; Yusuf, 1988). In the ATC systematic review that included 70000 patients, continued benefit for at least 3 years was recorded (Anon, 1994).
In a later meta-analysis from the ATC (Anon, 2002), doses between 75-325 mg/day were all found to have a positive effect on recurrence and mortality rates. No additional benefits occurred with doses higher than 150 mg/day.

Anon. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients: Antithrombotic Trialists′ Collaboration. BMJ 2002;324:71–86
http://www.bmj.com/content/324/7329/71

Anon. Collaborative overview of randomised trials of antiplatelet therapy I: Prevention of death, MI and stroke by prolonged antiplatelet therapy in various categories of patients: Antiplatelet Trialists' Collaboration. BM J 1994; 308: 81-106
http://www.bmj.com/content/308/6921/81

Anon. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease: the RISC group. Lancet 1990; 336: 827-30

Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. JAMA 1988; 260:2259-63

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Evidence Level: I

Isosorbide mononitrate improves the clinical outcome in patients who are responding to immediate treatment?
Isosorbide dinitrate has haemodynamic properties similar to GTN but a longer duration of action. Experimental studies (Willis, 1976) show that haemodynamic effect is maintained for 3 to 4 hrs after sublingual or oral dosing compared to 15 to 30 min after GTN.
Isosorbide mononitrate, in contrast to the dinitrate, has nearly 100% bioavailability following oral administration and is thus preferred for its rapid action (Thadani, 1988; Anon, 1984).

Anon. Is isosorbide mononitrate better than the dinitrate? Drug Ther Bull 1984;22(2):7-8

Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. Clin Pharmacokinet 1988;15:32-43

Willis WH, Russell RO, Mantle JA, et al. Hemodynamic effects of isosorbide dinitrate vs nitroglycerin in patients with unstable angina. Chest 1976; 69;15-22
http://journal.publications.chestnet.org/data/Journals/CHEST/20975/15.pdf

Evidence Level: IV

GTN infusion improves the clinical outcome in patients who are not responding to buccal GTN, atenolol/diltiazem and heparin?
A randomised, double-blind, placebo-controlled study of GTN infusion in 162 patients (Karlberg, 1998) found that fewer patients in the treatment group had more than 2 new attacks of chest pain lasting <20 min or 1 new attack >20 min, despite sublingual GTN (13 vs 25, P<0.03).
A prospective case series of 16 patients unresponsive to buccal GTN (Nashed, 1994) found that all 16 responded quickly to IV boluses, with no adverse effects.
No trial evidence shows long-term benefits from the administration of nitrates, however (Newby, 2001).

Karlberg KE, Saldeen T, Wallin R, et al. Intravenous nitroglycerin reduces ischaemia in unstable angina pectoris: a double-blind placebo-controlled study. J Intern Med 1998;243:25-31
http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2796.1998.00253.x/full

Nashed AH, Allegra JR, Larsen S, et al. Bolus i.v. nitroglycerin treatment of ischemic chest pain in the ED. Am J Emerg Med 1994;12:288-91

Newby DE, Fox KA. Unstable angina: the first 48 hours and later in-hospital management. Br Med Bull 2001;59:69-87
http://bmb.oxfordjournals.org/content/59/1/69.long

Evidence Level: II

Urgent coronary arteriography (with a view to revascularisation) should be considered in patients who fail to settle, whose GTN infusion cannot be withdrawn, or those with ST segment depression?
Earlier comparative trials of early versus late coronary angioplasty did not show any statistical benefit from a conservative approach (Antoniucci, 1996; Steg, 1997). Neither was any conclusive benefit in mortality from early invasive treatment demonstrated (Natarajan, 2001), although shorter hospital stay, lower drug use, and fewer readmissions were recorded (Steg, 1997).
Later studies have, however, shown clear clinical benefits associated with an early invasive approach.
A randomised multicentre trial in 1,810 patients (Fox, 2002) found that, at 4 months, 86 (9.6%) of 895 patients in the intervention group had died or had an MI or refractory angina, compared with 133 (14.5%) of 915 patients in the conservative group (RR 0.66; 95% CI 0.51-0.85; P=0.001).
A randomised controlled trial in 2,220 patients (Cannon, 2001) used a primary end point which was a composite of death, nonfatal MI, and readmission for acute coronary syndrome at 6 months. Results were 15.9% for invasive vs 19.4% for conservative management (OR 0.78; 95% CI 0.62-0.97; P=0.025).
In a prospective randomised multicentre study in 2,457 patients (Anon, 1999), using a composite endpoint of death or MI, results were 9.4% for invasive vs 12.1% for conservative treatment (RR 0.78; 95% CI 0.62-0.98).
A meta-analysis of data from 7 trials involving 9212 patients (Mehta, 2005) showed that the early invasive strategy was superior to the selectively invasive one in reducing myocardial infarction, severe

angina, and rehospitalisation during long-term follow-up (mean, 17 months). It was, however, associated with a 60% increase in in-hospital mortality and a 36% increase in the rate of death or myocardial infarction among patients who were troponin-positive.
Another meta-analysis using the same data (Choudhry, 2005) came to a similar conclusion.
A trial of early vs selective invasive therapy in 1200 high-risk (troponin-positive) patients (de Winter, 2005) failed to show superiority for the early invasive strategy, as mortality at one year was identical in both groups at 2.5%.
A Cochrane systematic review of 5 studies in 7818 patients (Hoenig, 2010) found that mortality showed a trend to hazard with an invasive strategy (RR 1.59, 95% CI 0.96 to 2.64). The invasive strategy did not reduce death on longer-term follow up. Myocardial infarction rates assessed at 6 to 12 months (5 trials) and 3 to 5 years (3 trials) were significantly decreased by an invasive strategy (RR 0.73, 95% CI 0.62 to 0.86; and RR 0.78, 95% CI 0.67 to 0.92 respectively). The incidence of early (< 4 month) and intermediate (6 to 12 month) refractory angina were both significantly decreased by an invasive strategy (RR 0.47, 95% CI 0.32 to 0.68; and RR 0.67, 95% CI 0.55 to 0.83 respectively), as were early and intermediate rehospitalization rates (RR 0.60, 95% CI 0.41to 0.88; and RR 0.67, 95% CI 0.61 to 0.74 respectively). The invasive strategy was associated with a two-fold increase in the RR of peri-procedural myocardial infarction (as variably defined) and a 1.7-fold increase in the RR of (minor) bleeding with no hazard of stroke.

Anon. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Lancet 1999;354:708-15

Antoniucci D, Santoro GM, Bolognese L, et al. Early coronary angioplasty as compared with delayed coronary angioplasty in patients with high-risk unstable angina pectoris. Coron Artery Dis 1996; 7: 75-80

Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-87
http://www.nejm.org/doi/full/10.1056/NEJM200106213442501#t=articleTop

Choudhry NK, Singh JM, Barolet A, et al. How should patients with unstable angina and non-ST-segment elevation myocardial infarction be managed? A meta-analysis of randomized trials. Am J Med 2005;118:465-74

de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005;353:1095-104
http://www.nejm.org/doi/full/10.1056/NEJMoa044259#t=articleTop

Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 2002;360:743-51

Hoenig MR, Aroney CN, Scott I. Early invasive versus conservative strategies for unstable angina & non-ST-elevation myocardial infarction in the stent era. Cochrane Database of Systematic Reviews 2010.: CD004815
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004815.pub3/full

Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomised trials. JAMA 2005;293:2908-17
http://jama.jamanetwork.com/article.aspx?articleid=201087

Natarajan M. Unstable angina. Clin Evid 2001;6:189-200

Steg PG, Himbert D, Seknadji P. Revascularization of patients with unstable coronary artery disease: the case for early intervention. Am J Cardiol 1997; 80:45E-50E

Evidence Level: I

Atorvastatin 80 mg orally daily is indicated if eGFR >/= 30 mL/min?
A pooled analysis of data from 8.658 participants in the A to Z and PROVE-IT-TIMI 22 trials (Murphy, 2007) showed that, by 8 months, achieved low-density lipoprotein levels were lower in the group with intensive (80 mg daily) statin therapy (median 64 mg/dl, interquartile range 51 to 81) than in the group with moderate (40 mg daily) statin therapy (median 87 mg/dl, interquartile range 71 to 107) (p <0.001). All-cause mortality was significantly reduced in the group with intensive statin therapy compared with the group with moderate statin therapy (3.6% vs 4.9%, hazard ratio 0.77, 95% CI 0.63 to 0.95, p = 0.015), without significant interaction by trial (interaction p = 0.63). The reduction in all-cause mortality with intensive statin therapy was consistent across key subgroups. On the basis of

these findings, 1 death was prevented for every 95 patients treated with high-dose statin therapy for 2 years.
A Cochrane systematic review (Adams, 2015) investigated atorvastatin on LDL-cholesterol over the dose range of 10 to 80 mg/d and found that over this range, blood LDL-cholesterol is decreased by 37.1% to 51.7%. It was also found that that atorvastatin decreases blood total cholesterol and LDL-cholesterol in a linear dose-related manner over this dose range.

Murphy SA, Cannon CP, Wiviott SD, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). Am J Cardiol 2007;100:1047-51

Adams SP, Tsang M, Wright JM. Lipid-lowering efficacy of atorvastatin. Cochrane Database of Systematic Reviews 2015: CD008226
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008226.pub3/full

Evidence Level: I

Discharge and follow-up

Exercise ECG is a reliable predictor of the need for coronary revascularisation in patients with no clinical signs suggestive of aortic stenosis or hypertrophic cardiomyopathy?
The exercise ECG has been shown to be a helpful risk stratification procedure (Lindhal, 1997; Nyman, 1993). The presence of ST depression on the resting ECG does not impair detection of ischaemia by the exercise ECG, but may produce a higher false-positive rate (Kalaria, 1998). The presence of ischaemia, whether symptomatic or not, should be an indication for revascularisation (Nyman, 1992). It has been suggested (Newby, 2001) that exercise ECG may be falsely reassuring since unstable angina may be precipitated by thrombus formation on a small, non-stenotic plaque.

Kalaria VG, Dwyer EM. Ability of the exercise electrocardiogram test to detect ischemia in stable coronary artery disease patients with ST-segment depression on the resting electrocardiogram. Am Heart J 1998;135:901-6

Lindahl B, Andren B, Ohlsson J, et al. Risk stratification in unstable coronary artery disease: additive value of troponin T determinations and pre-discharge exercise tests: FRISK Study Group. Eur Heart J 1997; 18:762-70
http://eurheartj.oxfordjournals.org/content/ehj/18/5/762.full.pdf

Newby DE, Fox KA. Unstable angina: the first 48 hours and later in-hospital management. Br Med Bull 2001;59:69-87
http://bmb.oxfordjournals.org/content/59/1/69.long

Nyman I, Wallentin L, Areskog M, et al. Risk stratification by early exercise testing after an episode of unstable coronary artery disease: the RISC Study Group. Int J Cardiol 1993; 39:131-42

Nyman I, Larsson H, Areskog M, et al. The predictive value of silent ischemia at an exercise test before discharge after an episode of unstable coronary artery disease. Am Heart J 1992;123:324-31

Evidence Level: II

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