

ACUTE MYOCARDIAL INFARCTION 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>

Ibanez B, James S, Agewall S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-77

<https://academic.oup.com/eurheartj/article/39/2/119/4095042>

Investigations

What is the value of the High Sensitivity (HS) troponin assay in the diagnosis of acute MI?

A randomised controlled trial across ten secondary or tertiary care hospitals in Scotland evaluated the implementation of an hs-cTnI assay in consecutive patients who had been admitted to the hospitals' emergency departments with suspected acute coronary syndrome (Shah, 2018). Hospitals were randomly allocated to early (n=5 hospitals) or late (n=5 hospitals) implementation, in which the high-sensitivity assay and sex-specific 99th centile diagnostic threshold was introduced immediately after the 6-month validation phase or was deferred for a further 6 months. 48,282 consecutive patients were enrolled in total. The high-sensitivity assay reclassified 1771 (17%) of 10 360 patients with myocardial injury or infarction who were not identified by the contemporary assay. In those reclassified, subsequent myocardial infarction or cardiovascular death within 1 year occurred in 105 (15%) of 720 patients in the validation phase and 131 (12%) of 1051 patients in the implementation phase (adjusted odds ratio for implementation vs validation phase 1.10, 95% CI 0.75 to 1.61; p=0.620). The authors concluded that the use of a high-sensitivity assay was not associated with a lower subsequent incidence of myocardial infarction or cardiovascular death at 1 year. An observation study of 773 patients admitted for in-hospital care for chest pain suspicious of acute coronary syndrome found that high sensitive troponin was an effective diagnostic tool for identifying acute MI (Borna, 2014). Sensitivity and negative predictive value for acute MI alone were 80% and 93% on admission and 97% and 99% at 3-4 hours.

Borna C, Thelin J, Ohlin B et al. High-sensitivity troponin T as a diagnostic tool for acute coronary syndrome in the real world: an observational study. *Eur J Emerg Med*. 2014;21:181-8

Shah ASV, Anand A, Strachan FE et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet*. 2018;392:919-28

Evidence Level: II

Immediate treatment

A single 300 mg tablet of aspirin, chewed thoroughly and swallowed, improves the clinical outcome in patients with AMI?

A systematic review and sub group meta-analysis (9 trials, 20000 patients) of anti-platelet therapy after AMI demonstrated a reduction in the combined endpoint of re-infarction, stroke and vascular death at 30 days (NNT=26); the reduced risks of re-infarction (NNT=83) and stroke (NNT=50) have been demonstrated separately from the combined endpoint (ATC, 1994).

The ISIS-2 study, (Anon, 1988) showed that aspirin reduces 35 day vascular mortality compared with placebo. ISIS-2 also demonstrated that aspirin and streptokinase (7.8%, ARR 5% NNT=20) is more effective than either streptokinase (10.0%, ARR 2.8%, NNT=35) or aspirin alone (10.6%, ARR 2.2, NNT=45).

An observational study in 753 patients (Abdelnoor, 1999) showed that patients using aspirin at onset of symptoms of an acute myocardial infarction experienced less severe manifestations than those who did not.

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Abdelnoor M, Landmark K. Infarct size is reduced and the frequency of non-Q-wave myocardial infarction is increased in patients using aspirin at the onset of symptoms. *Cardiology* 1999;91:119-26

Anon. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;ii:349-60

Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged anti-platelet therapy in various categories of patients. *BMJ* 1994; 308: 81-106
<http://www.bmj.com/content/308/6921/81.long>

Evidence Level: I

The benefit of using IV diamorphine for pain relief outweighs any associated risks?

Benefits: In a double-blind, between-patient comparison of the effects of iv diamorphine 5 mg, methadone 10 mg, morphine 10mg and pentazocine 30 mg in 118 patients with suspected AMI (Scott, 1969), diamorphine achieved complete pain relief within 10 minutes in 47% of cases. This compared with 32% for methadone, 17% for morphine and 19% for pentazocine. Diamorphine is a potent opiate that in relieving pain reduces sympathetic drive thereby reducing cardiac work and myocardial oxygen demand. Opiates also reduce anxiety, again reducing cardiac work. Opiates such as morphine and diamorphine cause peripheral vasodilatation without decreasing LVEDP and this can be helpful if there is pulmonary oedema (Herlitz, 1989; Timmis, 1980).

Risks: A 244 patient cohort (Semenkovich, 1985) examined the deleterious effects of morphine, which is deacetylated in vivo and therefore probably mirrors the actions of diamorphine, in patients with suspected AMI. Adverse cardiovascular events were rare (2.2%) and limited to hypotension following the first dose. No conduction abnormalities were seen.

Alternatives: Other agents investigated include nalbuphine, buprenorphine, indoprofen, nicomorphine, pethidine and pentazocine (Lee, 1976). No evidence was identified suggesting that any other agent is better than morphine/diamorphine. Pentazocine appears to produce hazardous increases in preload and afterload thereby increasing myocardial oxygen demand. The advent of early thrombolysis has helped to reduce the severity and duration of MI pain (Kristensen, 1991).

Herlitz J. Analgesia in myocardial infarction. *Drugs* 1989; 37: 939-44

Lee G, DeMaria AN, Amsterdam EA, et al. Comparative effects of morphine, meperidine and pentazocine on cardiocirculatory dynamics in patients with acute myocardial infarction. *Am J Med* 1976; 60:949-55

Kristensen KS, Haarbo J, Munkvad S, et al. Early thrombolytic treatment reduces analgesic requirement in patients with myocardial infarction. *J Intern Med* 1991;229: 257-9

Scott ME, Orr R. Effects of diamorphine, methadone, morphine, and pentazocine in patients with suspected acute myocardial infarction. *Lancet* 1969;i:1065-7

Semenkovich CF, Jaffe AS. Adverse effects due to morphine sulphate: challenge to previous doctrine. *Am J Med* 1985; 79: 325-30

Timmis AD, Rothman MT, Henderson MA, et al. Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. *BMJ* 1980; 280: 980-2
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1601124/pdf/brmedi00014-0024.pdf>

Evidence Level: IV

In patients with AMI, who require IV diamorphine, the use of metoclopramide will reduce or prevent subsequent vomiting?

Single doses of diamorphine can cause nausea and vomiting and this side-effect is attenuated on repeat dosing. Diamorphine induced nausea and vomiting is mediated through the chemoreceptor trigger zone (CTZ). Metoclopramide is a dopamine antagonist that acts directly on the CTZ. It therefore follows that metoclopramide will reduce diamorphine induced emesis. No trials in myocardial infarction were identified.

Evidence Level: V

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In patients with AMI, thrombolytic therapy with streptokinase improves the clinical outcome in those who fulfil the indications for such treatment and who demonstrate none of the contraindications?

Benefits

The initial investigation of the role of streptokinase in MI was undertaken in 1958 (Fletcher, 1958). The first large RCT was the GISSI trial (Anon, 1986; Anon, 1987) comparing streptokinase with standard treatment. Aspirin was not given routinely and angiography, angioplasty and bypass surgery were rarely used. Streptokinase showed a reduction in in-hospital mortality in patients treated within 12 hours of the onset of MI (10.7% vs 13.0%, RRR 17.6%, NNT 43). This reduction in mortality was maintained at 1-2 years. Benefits were specifically seen in anterior infarction and in patients under 65 yrs (a non-statistically significant reduction in mortality was seen in older patients).

These findings were confirmed by the ISIS-2 trial (Anon, 1988). In this trial patients received placebo, aspirin, streptokinase or streptokinase plus aspirin. Streptokinase reduced mortality when compared with placebo and aspirin alone (ARR 2.8% vs placebo, 0.6% vs aspirin) but the greatest reduction in mortality was produced by streptokinase plus aspirin (ARR 5% vs placebo). Further analysis demonstrated sub-group benefit beyond that seen in GISSI including inferior infarction, age >60 yrs and patients presenting with bundle branch block.

Further trials with confirmatory evidence continue to be published (van Es, 2002; Hurlen, 2002). Systematic reviews and meta-analysis of thrombolytic therapy have been published and there is homogeneous recognition of the benefits of thrombolysis including streptokinase thrombolysis (Granger, 1992). Streptokinase is, furthermore, the most cost-effective thrombolytic drug (Boland, 2003).

Anon. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;ii:349-60

Boland A, Dundar Y, Bagust A, et al. Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation. *Health Technol Assess* 2003;7(15)

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0015078/>

Fletcher AP, Alkjaersig N, Smyrniotis, et al. The treatment of patients suffering from early myocardial infarction with massive and prolonged streptokinase therapy. *Trans Assoc Am Physicians* 1958;71: 287-96

Anon. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1986; i: 397-402

Anon. Long term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1987; II: 871-4

Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction: a review. *Drugs* 1992;44:293-325

Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin or both after myocardial infarction. *N Engl J Med* 2002;347:969-74

<http://www.nejm.org/doi/full/10.1056/NEJMoa020496#t=articleTop>

van Es RF, Jonker JJ, Verheugt FW, et al. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;360:109-13

Risks

Thrombolytic use is associated with an increase in bleeding risk. Bleeding is usually minor and at venepuncture sites. Life threatening haemorrhage does occur, including ventricular rupture and intracranial haemorrhage (ICH). It has been estimated that early complications including ICH and ventricular rupture cause 5 additional deaths per 1000 patients treated with SK. This is later compensated for by the net benefit of thrombolysis.

Non-cerebral bleeding: ISIS-3 (Anon 1992) reported the incidence of non-cerebral bleeding with streptokinase (SK) as 4.5% and with tPA as 5.4%. Transfusion for bleeding was required in 0.9% and 1%, respectively.

Intracranial haemorrhage: The incidence of ICH is reported to be 0.4% with SK and 0.7% with tPA. A database of patients, from 7 published trials, who suffered ICH after thrombolysis was used to identify risk factors. Multivariate analysis indicated that age >65 yrs (OR 2.2, 95% CI 1.4-3.5), weight <70kg

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(OR 2.1, 95% CI 1.3-3.2), hypertension on admission (OR 2.0, 95% CI 1.2-3.2) or tPA use (OR 1.6 CI 1.0-2.5) place the patient at risk. Overall the incidence of ICH after SK is 0.26% with none of the above risk factors, 0.96% with 1, 1.32% with 2 or 2.17% with 3.

Stroke: Streptokinase is associated with an excess of 4 strokes per 1000 patients treated. This translates to 2 additional deaths per 1000 patients treated.

Hypotension: See below.

Other: SK causes fever in between 5 and 30% of cases; this is thought to be a delayed hypersensitivity reaction and responds to paracetamol. SK is antigenic; allergy-type reactions were reported in 3.6% (0.3% requiring treatment) of SK patients enrolled in ISIS-3 compared with 0.8% (0.1% requiring treatment) receiving tPA. Rare complications reported with SK include splenic rupture, aortic dissection and cholesterol embolisation, although a causative association is not proven.

Anon. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41299 cases of suspected acute myocardial infarction. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. Lancet 1992;339:753-70

Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results of all randomised trials of more than 1000 patients. Lancet 1994; 343:311-22

Simoons ML, Maggioni AP, Knatterud G, et al Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. Lancet 1993; 342: 1523-8

Evidence Level I/II

Is thrombolytic therapy of benefit in the over-75 age group?

Unpublished data from the Fibrinolytic Therapy Trialists' Collaborative Group (White, 2000) shows that in patients over 75 presenting with ST-segment or bundle branch block within 12 hours of symptom onset, thrombolytic therapy reduces the mortality rate by 15% (from 29.4% with control treatment to 26.0%; P = 0.03). This represents 34 lives saved per 1000 patients treated, which is twice the benefit seen in patients <55 years (16 lives saved per 1000 treated).

White HD. Debate: Should the elderly receive thrombolytic therapy, or primary angioplasty? Curr Control Trials Cardiovasc Med 2000;1:150-4

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC59621/>

Evidence Level: III (Unpublished data)

In patients with AMI, the routine use of oxygen improves the clinical outcome?

An updated Cochrane review of 4 trials in a total of 430 patients (Cabello, 2016) found "no evidence from randomised controlled trials to support the routine use of inhaled oxygen in people with AMI, and we cannot rule out a harmful effect.

Cabello JB, Burls A, Emparanza JI et al. Oxygen therapy for acute myocardial infarction. Cochrane Database of Systematic Reviews 2016

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007160.pub4/full>

Evidence Level: I

In patients with AMI, the routine use of a beta-blocker such as atenolol given IV or by mouth improves the clinical outcome?

Beta-blockers reduce myocardial oxygen demand by lowering heart rate and blood pressure. They should also decrease wall stress limit infarct size, reduce cardiac rupture, improve ventricular function and decrease mortality. They may also reduce the incidence of early arrhythmia (Yusuf, 1983).

A 2019 systematic review of 63 RCTs (including a total of 85,550 participants) found that at 'less than three months follow-up', beta-blockers versus placebo or no intervention probably reduced the risk of a reinfarction during follow-up (risk ratio (RR) 0.82, 98% confidence interval (CI) 0.73 to 0.91) with an absolute risk reduction of 0.5% and a number needed to treat for an additional beneficial outcome (NNTB) of 196 participants (Safi, 2019). However, the authors found little or no effect of beta-blockers when assessing all-cause mortality (RR 0.94, 97.5% CI 0.90 to 1.00) with an absolute risk reduction of 0.4% and cardiovascular mortality (RR 0.99, 95% CI 0.91 to 1.08) with an absolute risk reduction of

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0.4%. Regarding angina, it is uncertain whether beta-blockers have a beneficial or harmful effect (RR 0.70, 98% CI 0.25 to 1.84) with an absolute risk reduction of 7.1%. None of the trials specifically assessed nor reported serious adverse events according to International Conference on Harmonization - Good Clinical Practice.

Safi S, Sethi NJ, Nielsen EE et al. Beta-blockers for suspected or diagnosed acute myocardial infarction. *Cochrane Database Syst Rev* 2019;17;12:CD012484
<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012484.pub2/full>

Yusuf S, Sleight P, Rossi P, et al. Reduction in infarct size, arrhythmias and chest pain by early intravenous beta-blockade in suspected myocardial infarction. *Circulation* 1983;67: 132-41

Evidence Level: I

Atorvastatin 80mg is indicated for all patients with an estimated glomerular filtration rate (eGFR) > 30?

A post hoc analysis of the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) Study investigated the effect of focused atorvastatin 80mg therapy versus usual care on cardiovascular outcomes in 2,442 patients with coronary heart disease with and without chronic kidney disease (Koren, 2009). Compared with usual care, atorvastatin therapy reduced the relative risk of a primary outcome by 28% in patients with CKD (HR, 0.72; 95% CI, 0.54 to 0.97; P = 0.02) and 11% in patients without CKD (HR, 0.89; 95% CI, 0.74 to 1.07; P = 0.3) (P for treatment by CKD interaction = 0.2). There was no decrease in eGFR in atorvastatin-treated patients during the course of the study.

A subanalysis of 10,001 patients from the TNT (Treating to New Targets) study (Shepherd, 2008) found that, compared with atorvastatin 10 mg, atorvastatin 80 mg reduced the relative risk of major cardiovascular events by 32% in patients with CKD (HR = 0.68; 95% CI 0.55 to 0.84; p = 0.0003) and 15% in patients with normal eGFR (HR = 0.85; 95% CI 0.72 to 1.00; p = 0.049). The authors concluded that "Aggressive lipid lowering with atorvastatin 80 mg was both safe and effective in reducing the excess of cardiovascular events in a high-risk population with CKD and CHD."

Koren MJ, Davidson MH, Wilson DJ, et al. Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. *Am J Kidney Dis* 2009;53:41-50

Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol* 2008;51:1448-54

Evidence Level: II

In patients with AMI, those admitted to a coronary care unit are more likely to survive?

There is some historical evidence that patients treated on CCU have lower mortality rates; however, this does not reflect the interventions now undertaken as part of routine care such as thrombolysis, aspirin and beta-blockade. One cohort study (Karlson, 1992) demonstrates lower 1 year mortality in CCU treated patients (26% c.f. 41%). However, patients treated outside the CCU had a different risk factor pattern including higher age and a higher prevalence of previous cardiovascular disease. A 2016 review found that "few studies have rigorously assessed clinical outcomes in CCU compared with non-ICU settings. Such studies are all observational in nature and the majority are limited by small sample sizes and a high risk of intangible confounding" (Silverman, 2016).

Karlson BW, Herlitz J, Wiklund O, et al. Characteristics and prognosis of patients with acute myocardial infarction in relation to whether they were treated in the coronary care unit or in another ward. *Cardiology* 1992;81:134-44

Silverman MG & Morrow DA. Hospital triage of acute myocardial infarction: Is admission to the coronary care unit still necessary? *Am Heart J*. 2016;175:172-4

Evidence Level: IV

Administration of thrombolytic therapy within 20 minutes of the patient's arrival improves clinical outcome when compared to thrombolytic therapy given after this time?

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The timing of thrombolytic use in relation to the onset of symptoms is important. Animal studies have demonstrated that an occlusion persisting for 15-30 minutes does not generally result in significant myocardial damage (Boersma, 1996). Data from the GISSI trial (Anon, 1986) shows that benefit, in terms of reduced mortality, is time dependent. Patients who received streptokinase within 1 hour of the onset of symptoms had 47% reduction in mortality. These survival advantages persist for at least 10 years (Baigent, 1998).

Anon. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet 1986; i: 397-402

Baigent C, Collins R, Appleby P, et al. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. BMJ 1998;316:1337-43
<http://www.bmj.com/content/316/7141/1337.long>

Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-5

Evidence Level: I

In patients who have received streptokinase more than 3 days previously, the repeated use of streptokinase is likely to be ineffective due to the presence of streptokinase antibodies?

Streptokinase and anistreplase are antigenic and their administration often leads to antibody formation (Jennings, 1996). In a study that included 36 patients whose titres were measured for at least 5 days after thrombolysis (Lee, 1993), antibody was present in 19.4% by day 4. One patient could have neutralised 1.97 million units of streptokinase by day 4. Another study (Gorog, 1999) compared thrombolytic therapy in 28 patients who had previously received streptokinase for myocardial infarction with 15 controls. Spontaneous thrombolysis was poor in the previously-treated group, with 17 of the 28 failing to respond at all. In contrast, thrombolysis was achieved in all but one of the control group. Confusion remains over the time period over which antibody level returns to normal, which could be from 24 to 54 months (McGrath, 1995; Buchalter, 1993). One randomised, double-blind multicentre patency comparison study involving 333 patients (Fears, 1992) showed no difference between thrombolytic effect and pre-treatment antibody levels. These levels were, however, relatively low as none of the study population had previously received streptokinase.

Buchalter MB, Suntharalingam G, Jennings I, et al. Streptokinase resistance: when might streptokinase administration be ineffective? Br Heart J 199;68:97-8
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1025185/pdf/brheartj00035-0009.pdf>

Fears R, Hearn J, Standing R, et al. Lack of influence of pretreatment antistreptokinase antibody on efficacy in a multicenter patency comparison of intravenous streptokinase and anistreplase in acute myocardial infarction. Am Heart J 1992;124:305-14

Gorog DA, Ahmed N, Davies GJ. Platelet reactivity and streptokinase resistance following antecedent streptokinase therapy for myocardial infarction. Cardiology 1999;91:56-9

Jennings K. Antibodies to streptokinase: once is enough. BMJ 1996;312:393-4
<http://www.bmj.com/content/312/7028/393.long>

Lee HS, Cross S, Davidson R, et al. Raised levels of antistreptokinase antibody and neutralization titres from 4 days to 54 months after administration of streptokinase or anistreplase. Eur Heart J 1993;14:84-9

McGrath K, Hogan C, Hunt D, et al. Neutralising antibodies after streptokinase treatment for myocardial infarction: a persisting puzzle. Br Heart J 1995;74:122-3
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC483985/pdf/brheartj00165-0026.pdf>

Evidence Level: IV

In patients with AMI in whom streptokinase is likely to be ineffective, recombinant tissue plasminogen activator (rPA or rt-PA) will be effective as a thrombolytic?

The GUSTO trial data (Anon, 1993), which involved 41021 patients, showed a 14% reduction (95% CI, 5.9%-21.3%) in mortality for accelerated t-PA compared to streptokinase. Streptokinase is still the

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treatment of choice where possible as it is cheaper and does not carry the increased risk of stroke that has been found in some other studies (Smith, 1999; Gurwitz, 1998).

Anon. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction: the GUSTO investigators. *N Engl J Med* 1993;329:673-82
<http://www.nejm.org/doi/full/10.1056/NEJM199309023291001>

Gurwitz JH, Gore JM, Goldberg RJ, et al. Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. *Ann Intern Med* 1998;129:597-604

Smith BJ. Thrombolysis in acute myocardial infarction: analysis of studies comparing accelerated t-PA and streptokinase. *J Accid Emerg Med* 1999;16:407-11
<http://emj.bmj.com/content/16/6/407.long>

Evidence Level: II

In patients treated with rPA, the concurrent use of heparin improves the outcome?

The GUSTO trial (Anon, 1993) involving 41,021 patients found the lowest mortality of the four treatment groups (6.3%) in those given intravenous heparin in addition to tPA.

Anon. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction: the GUSTO investigators. *N Engl J Med* 1993;329:673-82

Evidence Level: II

Patients with NSTEMI should be given clopidogrel in a loading dose of 300 mg (600 mg in those who are unstable and likely to require catheter lab management within 24 hr)?

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial (Yusuf, 2001) randomised 12562 patients with unstable angina/NSTEMI to placebo or clopidogrel (loading dose of 300 mg followed by 75 mg daily for 3 to 12 months. All patients also received aspirin (75-325 mg daily). The composite end point of cardiovascular death, MI or stroke occurred in 11.5% of the placebo group vs 9.3% of the clopidogrel group (RR 0.80; P<.001). A reduction in recurrent ischaemia was noted within the first few hours following randomisation, but neither short nor long term mortality was improved.

A comparative study in two series of 20 patients each, one group that had been treated with clopidogrel and the other treated with a daily 75 mg dose for >= 1 month (Kastrati, 2004), found that platelet inhibition was enhanced in both groups (from 90 +/- 9% to 51 +/- 19% and from 52 +/- 14% to 33 +/- 12% respectively).

A high loading dose of 600 mg clopidogrel was associated with a 35% reduction of the risk for early adverse events (OR 0.65; 95% CI 0.43-0.98) in a study of 864 consecutive patients about to undergo coronary artery stenting (Pache, 2002).

A double-blind, randomised trial in 60 patients (von Beckerath, 2005) has established that doses of > 600 mg do not provide additional benefit, although results of a later trial in 103 patients (Montalescot, 2006) suggest that a 900 mg loading dose may induce a greater antiplatelet effect than 600 mg. This remains to be confirmed by further studies.

Kastrati A, von Beckerath N, Joost A, et al. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. *Circulation* 2004;110:1916-9
<http://circ.ahajournals.org/content/110/14/1916.long>

Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol* 2006;48:931-8

Pache J, Kastrati A, Mehilli J, et al. Clopidogrel therapy in patients undergoing coronary stenting: value of a high-loading-dose regimen. *Catheter Cardiovasc Interv* 2002;55:436-41

von Beckerath N, Taubert D, Pogatsa MG, et al. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. *Circulation* 2005;112:2946-50
<http://circ.ahajournals.org/content/112/19/2946.long>

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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

Evidence Level: II

Subsequent management

Routine prescription of low dose aspirin to be continued indefinitely improves the clinical outcome?

A randomised, double-blind, placebo-controlled trial in 796 patients (Wallentin, 1991) found that those given aspirin 75 mg/day had reduced risk of myocardial infarction or death (RR 0.52, CI 0.37-0.72) after 12 months.

A meta-analysis of 287 RCTs in a total of 212000 patients (ATC, 2002) found that the risk of “any serious vascular event” was reduced by around 25% in those taking low dose aspirin (75-150 mg/d).

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

Wallentin LC. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization: Research Group on Instability in Coronary Artery Disease in Southeast Sweden. *J Am Coll Cardiol* 1991;18:1587-93

Evidence Level: I

Routine prescription of clopidogrel 75mg orally daily for one year improves the clinical outcome?

A prospective analysis of data from 5886 patients enrolled in the Acute Coronary Syndromes registry (including 3795 who did, and 2091 who did not receive clopidogrel as well as aspirin at discharge) showed a significant reduction in 1-year mortality for the patients in the clopidogrel group (OR 0.48, 95% CI 0.48 – 0.61) (Zeymer, 2006).

A randomised trial in 45,852 patients (Chen, 2005) found that adding clopidogrel 75mg daily to aspirin 162mg daily resulted in a 9% (95% CI 3-14) proportional reduction in death, reinfarction or stroke.

Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-21

Zeymer U, Gitt AK, Junger C, et al. Effect of clopidogrel on 1-year mortality in hospital survivors of acute ST-segment elevation myocardial infarction in clinical practice. *Eur Heart J* 2006;27:2661-6

Evidence Level: II

Routine prescription of a beta-blocker to be continued indefinitely (if tolerated) improves the clinical outcome?

The lifelong use of beta-blockers after a myocardial infarction (MI) has been the standard of care based on trials performed before the era of revascularization, when heart failure was common. Large randomized trials in the mid-1980s demonstrated that beta-blockers played a major role in improving the in-hospital and long-term survival of patients admitted for MI (Beta-Blocker Heart Attack Trial Research Group 1982, Hjalmarson 1981).

However, the implementation of rapid myocardial reperfusion led to a substantial survival benefit and a reduction of heart failure because of reduced infarct size. Modern large longitudinal registries did not provide sufficient evidence to support long-term beta-blocker therapy in patients with uncomplicated acute MI. In 2012, investigators of the REACH (Reduction of Atherothrombosis for Continued Health) registry matched 6758 patients with a propensity score to evaluate the effects of long-term β -blocker prescription on a composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke. After a median follow-up of 42 months, the investigators concluded that long-term prescription of β -blockers was not associated with a reduction of major cardiovascular events in patients with prior MI (16.9 vs. 18.6%, respectively; hazard ratio [HR] 0.90; 95% CI 0.79–1.03) (Bangalore, 2012).

A 2019 systematic review of RCTs concluded that beta-blockers probably reduce the short-term risk of a reinfarction and the long-term risk of all-cause mortality and cardiovascular mortality (Safi, 2019).

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Meta-analyses showed that beta-blockers versus placebo or no intervention probably reduce the risk of all-cause mortality (RR 0.93, 97.5% CI 0.86 to 0.99) with an absolute risk reduction of 1.1%, and cardiovascular mortality (RR 0.90, 98% CI 0.83 to 0.98) with an absolute risk reduction of 1.2%. However, it is uncertain whether beta-blockers have a beneficial or harmful effect when assessing major adverse cardiovascular events (RR 0.81, 97.5% CI 0.40 to 1.66) with an absolute risk reduction of 1.7%; reinfarction (RR 0.89, 98% CI 0.75 to 1.08) with an absolute risk reduction of 0.9%; and angina (RR 0.64, 98% CI 0.18 to 2.0).

A 2024 French RCT investigated the appropriate duration of treatment with beta-blocker drugs after a myocardial infarction (Silvain, 2024). A randomized, noninferiority trial conducted at 49 sites, randomly assigned patients with a history of myocardial infarction to interruption or continuation of beta-blocker treatment. A total of 3698 patients underwent randomization. The median time between the last myocardial infarction and randomization was 2.9 years, and the median follow-up was 3.0 years. A primary-outcome event (a composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons) occurred in 432 of 1812 patients (23.8%) in the interruption group and in 384 of 1821 patients (21.1%) in the continuation group (risk difference, 2.8%; 95% CI] <0.1 to 5.5). Hence the authors concluded that interruption of long-term beta-blocker treatment was not found to be noninferior to a strategy of beta-blocker continuation.

Bangalore S, Steg G, Deedwania P et al. β -Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012;308:1340–9

Béta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA*. 1982;247:1707–14

Hjalmarson A, Elmfeldt D, Herlitz J et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet*. 1981;2:823–7

Safi S, Sethi NJ, Nielsen EE et al. Beta-blockers for suspected or diagnosed acute myocardial infarction. *Cochrane Database Syst Rev*. 2019;12:CD012484
<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012484.pub2/full>

Silvain J, Cayla G, Ferrari E et al. Beta-Blocker Interruption or Continuation after Myocardial Infarction. *N Engl J Med*. 2024;391:1277-86

Evidence Level: I

Monitoring treatment

An ACE inhibitor should be given to patients with cardiac failure who have no major contraindications to their use?

A systematic overview of 5 long-term RCTs in a total of 12763 patients (Flather, 2000) found that (in the 3 trials in post-infarction patients: n=5966) mortality was lower with ACE inhibitors than with placebo (702/2995 [23.4%] vs 866/2971 [29.1%]). Benefits were observed early after the start of therapy and persisted long term.

Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;355:1575-81

Evidence Level: I

Patients in whom pain persists should be given IV beta-blockers?

The use of IV beta-blockers can reduce pain in MI but opiates are more effective (Everts, 1999; Herlitz, 1986; Waagstein, 1984).

Everts B, Karlson B, Abdon NJ, Herlitz, Hedner T. A comparison of metoprolol and morphine in the treatment of chest pain in patients with suspected acute myocardial infarction: the MEMO study. *J Intern Med* 1999; 245: 133-41

Herlitz J, Hjalmarson A, Waagstein F. Beta blockade and chest pain in acute myocardial infarction. *Am Heart J* 1986;112:1120-6

Waagstein F, Hjalmarson A. Double blind study of the effect of cardioselective beta-blockade on chest pain in acute myocardial infarction. *Acta Med Scand* 1984;215: 349-54

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Evidence Level: II

Early mobilisation improves outcome?

A randomised, multi-centre trial in 742 patients with uncomplicated myocardial infarction (West, 1979) compared early (5 days after) to late (10 days after) mobilisation. No difference was found in either morbidity or mortality during the first year, but increased mortality during the second and third years was noted in the early mobilisation group. These findings led to some disquiet about early mobilisation (Evans, 1983).

A 10-year follow-up by the same team (West, 1985) however, found that this difference was not statistically significant and therefore not a contraindication to early mobilisation.

A prospective study in 163 patients (Lindvall, 1979) showed that it was possible to identify a low-risk group that was suitable for early mobilisation. No patients in the rapidly-mobilised group (n=42) died in hospital and only one during 6-month follow-up. This compared to 17 and 28 respectively in the conventionally-mobilised group (n=121). These findings were confirmed in later, randomised studies (Rowe, 1989; Topol, 1988; Ahlmark, 1979).

A systematic review and meta-analysis of 15 trials involving 2658 patients (Herkner, 2003) found that the 1332 patients assigned to a short period of bed rest (2-12 days) fared no worse (in terms of death, reinfarction, post-infarction angina or thromboembolic events) than those assigned to prolonged bed rest (5-28 days). An updated version of this study, reaching the same conclusions, has been published as a Cochrane systematic review (Herkner, 2007).

Ahlmark G, Ahlberg G, Saetre H, et al. A controlled study of early discharge after uncomplicated myocardial infarction. *Acta Med Scand* 1979;206:87-91

Evans DW. Early ambulation after myocardial infarction. *J R Coll Physicians Lond* 1983;17:217-19

Herkner H, Thoennissen J, Nikfardjam M, et al. Short versus prolonged bed rest after uncomplicated acute myocardial infarction: a systematic review and meta-analysis. *J Clin Epidemiol* 2003;56:775-81

Herkner H, Arrich J, Havel C, et al. Bed rest for acute uncomplicated myocardial infarction. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD003836
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003836.pub2/full>

Lindvall K, Erhardt LR, Lundman T, et al. Early mobilization and discharge of patients with acute myocardial infarction: a prospective study using risk indicators and early exercise tests. *Acta Med Scand* 1979;206:169-75

Rowe MH, Jelinek MV, Liddell N, et al. Effect of rapid mobilization on ejection fractions and ventricular volumes after acute myocardial infarction. *Am J Cardiol* 1989;63:1037-41

Topol EJ, Burek K, O'Neill WW, et al. A randomized controlled trial of hospital discharge three days after myocardial infarction in the era of reperfusion. *N Engl J Med* 1988;318:1083-8

West RR, Henderson AH. Randomised multicentre trial of early mobilisation after uncomplicated myocardial infarction. *Br Heart J* 1979;42:381-5
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC482171/pdf/brheartj00212-0009.pdf>

West RR, Henderson AH. Long term survival of patients mobilised early after acute myocardial infarction. *Br Heart J* 1985;53:243-7
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC481750/pdf/brheartj00111-0007.pdf>

Evidence Level: I

Revascularisation improves outcome in patients with AMI and ischaemic changes during exercise testing?

In a meta-analysis of randomised trials comparing primary percutaneous transluminal coronary angioplasty (PTCA) to thrombolysis (Weaver, 1997), the 30-day mortality rate was found to be lower among patients in the PTCA group (4.4% vs 6.5%). The combined end points of mortality/nonfatal reinfarction at 30 days were also lower in the PTCA group (7.2% vs 11.9%).

A retrospective review of 1,073 Mayo Clinic patients (Velianou, 2000) showed that the 30-day mortality rate for AMI decreased from 10.1% to 5.2% between 1991-1997. The 1-year mortality rate also decreased (from 13.4% to 10.4%) during the same period. This was directly related to improvements in the techniques used for PTCA and its accompanying pharmacotherapy.

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Velianou JL, Wilson SH, Reeder GS, et al. Decreasing mortality with primary percutaneous coronary intervention in patients with acute myocardial infarction: the Mayo Clinic experience from 1991 through 1997. *Mayo Clin Proc* 2000;75:994-1001

Weaver WD, Simes J, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA* 1997;278:2093-8

Evidence Level: I

Discharge and follow-up

Mortality is doubled in smokers and 3.5 times greater if total cholesterol exceeds 6.5 mmol/L?

Data from the Multiple Risk Factor Intervention Trial (MRFIT) involving 316099 men showed that crude death rates for those with a total serum cholesterol of more than or equal to 6.3 mmol/l were 30.7 compared with 7.4 for those less than 4.7 mmol/l (Neaton, 1992). Crude death rates for those smoking up to 25 cigarettes a day were 22.7 compared with 12.1 for non-smokers.

A meta-analysis of 12 cohort studies (Wilson, 2000) on smoking cessation after MI found relative risk reductions across studies of 15% - 61%. The number needed to stop smoking to save 1 life was calculated as 13.

A retrospective cohort study of 2619 MI patients (Rea, 2002) found a relative risk of 1.51 (95% CI 1.10-2.07) of recurrent coronary events in those who remained active smokers following discharge.

An apparent paradox indicating lower short-term mortality of smokers following MI (smoker's paradox) is probably due to their lower average age on presentation (Andrikopoulos, 2001) and to higher case-mortality before reaching hospital (Sonke, 1997).

Andrikopoulos GK, Richter DJ, Dilaveris PE, et al. In-hospital mortality of habitual cigarette smokers after acute myocardial infarction: the "smoker's paradox" in a countrywide study. *Eur Heart J* 2001;22:776-84

Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men. *Arch Intern Med* 1992;152:56-64

Rea TD, Heckbert SR, Kaplan RC, et al. Smoking status and risk for recurrent coronary events after myocardial infarction. *Ann Intern Med* 2002;137:494-500

Sonke GS, Stewart AW, Beaglehole R, et al. Comparison of case fatality in smokers and non-smokers after acute cardiac event. *BMJ* 1997;315:992-3
<http://www.bmj.com/content/315/7114/992>

Wilson K, Gibson N, Willan A, et al. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Arch Intern Med* 2000;160:939-44

Evidence Level: III

In patients with a total cholesterol >5mmol/l, lipid lowering therapy (statin if LDL-C>3.2mmol/l and fibrate if triglyceride>4.5mmol/l) reduces the risk of subsequent MI?

A large, placebo-controlled, double-blind randomised trial in 9014 patients (Anon, 1998) found that the group given a statin had reduced mortality (6.4% vs 8.3%) over a 6 year follow-up period. The study population had a broad range of initial cholesterol levels (4.0 - 7.0 mmol/l) and ages (31-75).

A much smaller trial (Arntz, 2000) found similar benefits in a group of patients given pravastatin on average 6 days following MI. After 2 years, 16 of 70 patients in this group had suffered a further event, compared to 29 of 56 patients in the control group.

Two meta-analyses of cholesterol-lowering therapy (Gould, 1995; Holme, 1995) have indicated that fibrates, which increase HDL and reduce triglycerides, also increase the risk of non-CHD mortality and total mortality. Latest generation fibrates like bezafibrate do not, however, appear to have these adverse effects (Ericsson, 1998; Ericsson, 1997).

Anon. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57

Arntz HR, Agrawal R, Wunderlich W, et al. Beneficial effects of pravastatin (+/- colestyramine/niacin) initiated immediately after a coronary event (The Randomized Lipid-Coronary Artery Disease [L-CAD] Study). *Am J Cardiol* 2000;86:1293-8

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Ericsson CG. Results of the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) and an update on trials now in progress. Eur Heart J 1998;19(Suppl H):H37-41

Ericsson CG, Nilsson J, Grip L, et al. Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (the Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT]). Am J Cardiol 1997;80:1125-9

Gould AL, Rossouw JE, Santanello NC, et al. Cholesterol reduction yields clinical benefit: a new look at old data. Circulation 1995;91:2274-82
<http://circ.ahajournals.org/content/91/8/2274.long>

Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. Am J Cardiol 1995;76:10C-17C

Evidence Level: I/II

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