Although substantial advances have been achieved in the acute management of MI and improved early survival, there remains a risk of approximately one in five for death or further MI within five years of hospital discharge. Most deaths in the first five years are after hospital discharge – 68 per cent for ST segment elevation MI (STEMI), 86 per cent for non-ST segment elevation MI (non-STEMI) – and hence secondary prevention is of critical importance.

This review outlines the scope of pharmacological management in secondary prevention of MI and highlights the key large-scale trials that have formed the evidence base for national and international guidelines.

The role of cardiac rehabilitation and lifestyle measures is of critical importance but is beyond the scope of this review.

**Antiplatelets**

**Aspirin**

Aspirin acts primarily by cyclo-oxygenase inhibition (see Figure 1) and has been tested extensively in both primary and secondary prevention trials. A systematic review of 135,000 patients compared antiplatelet therapy versus control in secondary prevention, and aspirin reduced the risk of vascular events (nonfatal MI, nonfatal stroke and vascular death) in patients with previous MI (NNT=28 for two years) and acute MI (NNT=27 for one month). In a further systematic review of six randomised trials in 6500 patients with a history of MI or cerebrovascular event, there was an 18 per cent (relative risk – RR 0.82, 95% CI 0.70–0.99) reduction in all-cause mortality (NNT=67) and a 30 per cent (RR 0.70, 95% CI 0.60–0.80) reduction in vascular events (NNT=19) with an increased risk of bleeding (NNH=100).
The dosage of aspirin in secondary prevention is debated. The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events – Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial failed to show improved clinical efficacy with high- (300–325 mg per day) compared to low-dose (75–100 mg) aspirin. There were fewer G I bleeds in patients on low-dose aspirin and current ESC guidelines recommend low-dose aspirin for long-term secondary prevention.4

Further data from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, investigating patients with STEMI treated with percutaneous coronary intervention (PCI), showed that high-dose aspirin was associated with major bleeding with no beneficial effect on ischaemic events.5

Clopidogrel

Clopidogrel reduces platelet activity by adenosine diphosphate receptor blockade (see Figure 1) and has been tested in both non-STEMI and STEMI patients. Comparing dual therapy to aspirin alone, a systematic review involving three trial groups – Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) and Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)6 – showed a 1.2 per cent absolute reduction in the composite end-point for death, stroke or MI from 10.4 to 9.2 per cent (NNT=86).7

The CURE study compared clopidogrel plus aspirin versus placebo plus aspirin in patients with non-STEMI.8 The COMMIT study compared clopidogrel versus placebo in addition to aspirin in patients primarily presenting with STEMI.9 There was a significant 1 per cent increase in the risk of major bleeding (NNH=100) in the CURE cohort but no difference in fatal bleeding in COMMIT.

Newer antiplatelet agents

Two new platelet receptor antagonists, prasugrel (Efient) and ticagrelor (Brilique), have been tested and approved as both showed improved outcomes compared with clopidogrel in the context of acute coronary syndromes (ACS). Clopidogrel and prasugrel are prodrugs of active metabolites and bind irreversibly to P2Y₁₂ platelet receptors in contrast to ticagrelor, which acts directly (see Figure 1).

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) trial randomised patients with ACS undergoing PCI to prasugrel (60mg followed by 10mg once daily) or clopidogrel (300mg followed by 75mg once daily). The study showed a 1 per cent (1.4 vs 2.4 per cent) reduction in cardiovascular mortality (NNT=100) and a 2 per cent (4.9 vs 7 per cent) reduction in recurrent MI (NNT=48) at 30 days in the prasugrel group but with an increased in risk of both life-threatening and fatal bleeding.10 The TRITON-TIMI 38 study, however, only included patients scheduled for PCI and the randomised intervention was applied only after coronary anatomy had been defined (predominantly in the catheterisation laboratory).

A more recent study – Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) – randomised patients after ACS to clopidogrel or prasugrel, on top of aspirin 75mg, in patients with non-STEMI not suitable for PCI or bypass surgery. There was no overall benefit with prasugrel over clopidogrel (cardiovascular mortality, recurrent MI or stroke) and similar rates of bleeding.11

The Study of Platelet Inhibition and Patient Outcomes (PLATO) randomised patients with ACS to ticagrelor (180mg loading followed by 90mg twice daily) or clopidogrel (300–600mg loading dose...
followed by 75mg daily). The randomised treatment was applied at presentation. At 12 months there was a significant reduction in cardiovascular death (3.4 vs 4.3 per cent, NNT=111) and MI (5.3 vs 6.6 per cent, NNT=77) with no significant differences in rates of major bleeding (although increased non-CABG bleeding).12

Heart rate-limiting agents

Beta-blockers

Substantial evidence supports the use of beta-blockade in patients with STEMI, but the evidence largely pre-dates current reperfusion therapies and pharmacotherapy. The beneficial effects seen in ACS patients are likely to be driven by several mechanisms including reduced sympathetic drive and risk of malignant arrhythmias, improved rate control and diastolic coronary perfusion and reduced blood pressure and cardiac afterload.

Secondary prevention with beta-blockers remains controversial. Based on a systematic review of 82 randomised clinical trials in over 50 000 patients with acute or prior MI, beta-blockers reduced risk of death by 23 per cent (NNT=42 for two years) in 31 of the trials with extended follow-up. There was, however, no mortality benefit in the remaining 51 short-term trials.13

Current ESC guidelines advocate beta-blockade in all STEMI patients without contraindications and in patients with non-STEMI and evidence of depressed left ventricular function.14,15

Calcium-channel blockers

Current guidelines do not advocate prophylactic use of calcium-channel blockers in the acute phase of MI and there is a trend towards harm.14,15 In the chronic phase verapamil may be helpful to prevent reinfarction and death. Rate-limiting calcium-channel blockers are a reasonable (but less evidence-based) option in

Table 1. Treatment recommendations from ESC guidelines

- dual antiplatelet therapy with P2Y12 inhibitor (ticagrelor or prasugrel) added to aspirin is recommended for 12 months
- clopidogrel is recommended for patients unable to receive ticagrelor or prasugrel
- in patients with a previous MI (>12 months) aspirin is recommended for secondary prevention, indefinitely

Beta-blockers, ACE inhibitors and lipid-lowering therapy

- oral treatment with beta-blockers is recommended in patients with heart failure or depressed left ventricular function
- ACE inhibitors should be considered in all patients especially in co-existing heart failure, left ventricular systolic function, STEMI or diabetes
- statin therapy with a target LDL concentration of <1.8mmol per litre initiated early after admission

Figure 2. Mechanism of action of ACE inhibitors and ARBs on the renin-angiotensin-aldosterone system
Renin-angiotensin-aldosterone axis (RAAS)

The primary aim of RAAS modulators is to inhibit angiotensin-II, facilitating reduction of both afterload and preload and hence reducing myocardial strain (see Figure 2). In addition angiotensin-II inhibition exerts positive effects on post-infarct remodelling and these agents are specifically beneficial in patients with depressed left ventricular function, hypertension, diabetes or chronic kidney disease. Patients intolerant of ACE inhibitors should be switched to angiotensin-II receptor blockers (ARBs). 16

ACE inhibitors reduce death, recurrent MI and heart failure admissions in patients with coronary artery disease with and without depressed left ventricular function, although efficacy varies across trials. The Heart Outcomes Prevention Evaluation (HOPE) trial randomised over 9000 patients with vascular disease (identified as coronary artery disease, stroke or peripheral vascular disease) to ramipril 10mg vs placebo and showed a 3.6 per cent (14.1 vs 17.7 per cent) reduction in a composite end-point of cardiovascular death, MI or stroke (NNT=28). 17

One placebo-controlled systematic review combining three studies with over 5000 postinfarction patients with depressed left ventricular function showed a reduction in mortality (23.4 vs 29.1 per cent, NNT=18) and reinfarction (10.8 vs 13.2 per cent, NNT=42). 18

The evidence for the use of ACE inhibitors or ARBs in patients with preserved left ventricular function is less robust for reduction in all-cause mortality (NNT=66–209) or reinfarction (NNT=62–278). 19

An ARB should be used if ACE inhibitors are not tolerated (primarily due to side-effects such as cough or angioedema).

Lipid-lowering therapy

Statins

Statins inhibit HMG-CoA reductase preventing the hepatocytic conversion of acetyl-CoA into cholesterol (see Figure 3). The benefits of statin therapy in secondary prevention are unequivocal. A meta-analysis of 19 placebo-controlled trials in patients with coronary artery disease showed a 25 per cent reduction in coronary death or nonfatal MI. 20

The Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study randomised over 20 000 patients, the majority of them with underlying coronary disease or previous MI, to placebo or simvastatin 40mg. The study showed a 12 and 17 per cent reduction in all-cause mortality (NNT=57) and cardiovascular mortality (NNT=85) respectively. There was a 26 per cent reduction in any major coronary event (NNT=33). 21

A systematic review of 8000 ACS patients with two-year follow-up evidence suggests that intensive is more efficacious that moderate lipid-lowering statin therapy (all-cause mortality 3.5 vs 8.9 per cent respectively, NNT=19), 22 mostly evident for atorvastatin 23–25 with some evidence for high-dose simvastatin. 26

Statins are usually well tolerated but myalgia is frequently reported (although in clinical trials statins have not been shown to significantly increase risk of myalgia compared to placebo). 27 Rarely statins can induce rhabdomyolysis. Occasionally they also cause liver dysfunction and should be used cautiously in patients with chronic liver disease and those with alcohol dependence. Liver function should be monitored prior to commencement of statins and three months after initiation. Following this, liver function should be checked biannually.

Cholesteryl ester transfer protein inhibitors

More recently cholesteryl ester transfer protein (CETP) inhibitors (not currently available in the UK)
have been tested but with mixed results. They inhibit plasma CETP, which exchanges triglycerides from plasma VLDL and LDL for cholesterol esters from HDL, resulting in raised HDL concentrations and lower LDL concentrations (see Figure 3).

The Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial randomised over 1500 patients with coronary heart disease and taking a statin to either anacetrapib or placebo. Anacetrapib reduced LDL by a further 40 per cent and nearly tripled HDL levels. There was, however, no difference in the composite cardiovascular end-point, although the study was not adequately powered for death or MI.28 Similar results were noted for dalcetrapib, in the dal-OUMES trial, which was terminated early, with a significant increase in HDL cholesterol but no reduction in risk of cardiovascular events in patients following incident ACS.29

Conclusion
The keystones of secondary prevention after MI are pharmacological therapy, cardiac rehabilitation and lifestyle measures, especially smoking cessation. Development of new and more potent pharmacological agents has the potential to further improve morbidity and mortality after ACS but most gains, on a population basis, would be achieved with improved adherence to secondary prevention guidelines.

The recent development of higher-sensitivity biomarkers has improved our diagnostic accuracy for defining ACS, making secondary prevention even more important.30,31

Declaration of interests
None to declare.

Figure 4. Summary of pharmacological and nonpharmacological management in the secondary prevention in MI

References
For each section, one of the statements is false – which is it?

1a. After MI, the risk of death or further MI within five years of hospital discharge is approximately 1 in 10
1b. 68 per cent of deaths after STEMI occur within five years of hospital discharge
1c. 86 per cent of deaths after non-STEMI occur within five years of hospital discharge
1d. The keystones of secondary prevention after MI are pharmacological therapy, cardiac rehabilitation and lifestyle measures, especially smoking cessation

2a. Aspirin acts primarily by cyclo-oxygenase inhibition
2b. The CURRENT-OASIS 7 showed no improvement in clinical efficacy but more gastrointestinal bleeding events with high-compared to low-dose aspirin
2c. A systematic review of secondary prevention trials showed that aspirin reduced the risk of vascular events in patients with previous MI and acute MI
2d. A systematic review of six randomised trials in 6300 patients with a history of MI or cerebrovascular events showed that the NNH for increased risk of bleeding was 19

3a. The active metabolites of clopidogrel and prasugrel bind irreversibly to P2Y12 platelet receptors
3b. The TRILOGY ACS trial showed no difference between clopidogrel and prasugrel, both in combination with aspirin, in cardiovascular mortality, recurrent MI or stroke in patients with non-STEMI not suitable for PCI or bypass surgery
3c. The TRITON-TIMI 38 trial showed that clopidogrel is associated with a higher risk of fatal and life-threatening bleeding than prasugrel in patients with ACS undergoing PCI
3d. In the PLATO trial, ticagrelor reduced the incidence of cardiovascular death and MI compared with clopidogrel at 12 months

4a. Evidence supporting the use of beta-blockade in patients with STEMI largely predates current reperfusion therapies and pharmacotherapy
4b. The beneficial effects of beta-blockade in ACS patients are driven partly by reduced sympathetic drive and improved diastolic coronary perfusion
4c. In a systematic review of randomised trials in patients with acute or prior MI, 31 trials with extended follow-up showed that beta-blockers reduce the risk of death by 23 per cent
4d. Current guidelines recommend prophylaxis with a calcium-channel blocker in the acute phase of MI

5a. ACE inhibitors and ARBs are specifically beneficial in patients with depressed left ventricular function
5b. ACE inhibitors should not be used in post-STEMI patients with diabetes or chronic kidney disease
5c. The HOPE trial showed that ramipril reduced the incidence of the composite end-point of cardiovascular death, MI or stroke by 3.6 per cent compared with placebo in patients with vascular disease
5d. An ARB should be used if ACE inhibitors are not tolerated due to cough or angioedema

6a. Statins reduce coronary death or nonfatal MI by 25 per cent in patients with coronary artery disease
6b. Although myalgia is frequently reported with statins, clinical trials have not shown a significantly increased risk compared with placebo
6c. Over two years, intensive statin therapy does not reduce mortality by more than moderate statin therapy in patients with ACS
6d. After the first three months, liver function should be checked biannually during treatment with a statin

Resources

Guidelines


CPD: Secondary prevention of MI

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