

Medical management after control of myocardial ischaemia

Key points

- A large evidence base and detailed guidelines are available to help guide management after an acute coronary syndrome (ACS) but tailoring this to individual patients can be challenging.
- Coronary revascularisation should be considered for all post-ACS patients with ongoing symptoms and critical coronary stenosis, left main disease or triple vessel coronary artery disease.
- All post-ACS patients should be given aspirin and statins. Use of a second antiplatelet medication, a β -blocker and an ACE inhibitor is determined by symptoms and the presence of left ventricular dysfunction.
- Prasugrel and ticagrelor are preferred over clopidogrel for use in dual antiplatelet therapy in most patients post ACS but have a higher bleeding risk.
- Use of an implantable cardioverter defibrillator is indicated in patients who had an MI more than 40 days previously and whose ejection fraction is persistently below 35%.

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After recovery from myocardial infarction, patients should receive aspirin and statin therapy and be evaluated regarding their need for coronary revascularisation, additional pharmacological treatment and possible device therapy.

The management of the patient who has experienced an acute coronary syndrome (ACS) requires a detailed assessment of their risk of future events, their risk of adverse events from medications and, particularly with the near universal use of antithrombotic therapy, their bleeding risk.

Fortunately, a large evidence base and detailed guidelines are available to help tailor post-coronary care management to the needs of the individual patient after an ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI).¹⁻⁶ Despite this, there are many challenges in matching the clinical trial evidence with the needs of the individual patient to provide effective secondary prevention.

EVALUATION OF THE PATIENT

The evaluation of the post-ACS patient needs to be carefully targeted to assess the following:

- the need for coronary revascularisation (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG])
- the ideal combination and duration of pharmacological management
- the possible role of device therapy (an implantable cardioverter defibrillator [ICD]).

In addition to assessing the patient's hospital course to judge the extent of myocardial damage and the extent of coronary disease, the tests discussed below help in this evaluation. The appropriate tests will differ between patients.

Coronary angiography

The extent and location of coronary artery disease (CAD) determines prognosis and the need for coronary revascularisation in the post-ACS patient, and this is best assessed with invasive coronary angiography. Angiography will often have been performed and the coronary anatomy

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established in the early stages of hospital treatment of patients with STEMI and those with NSTEMI who have been assessed as being at high risk of death or further coronary events. Its benefit in low- and intermediate-risk NSTEMI patients is limited.^{7,8} For post-ACS patients who have not had an in-hospital angiogram, early noninvasive testing or imaging can be used to decide on referral for angiography.

Computed tomography coronary angiography (CTCA) is being debated as a substitute for invasive coronary angiography. It has excellent diagnostic accuracy with a high negative predictive value (i.e. it can reliably rule out CAD), and it has a well-defined role in ruling out coronary disease in patients with chest pain assessed as being at low to intermediate risk of having significant CAD.⁹ However, when the patient is known to have had an ACS and may require intervention, invasive coronary angiography is preferable. Noninvasive fractional flow reserve derived from CTCA and stress myocardial CT perfusion are techniques currently in research and may define a more central role for CTCA in the future.^{10,11}

Echocardiography

Assessment of overall left ventricular (LV) function and regional wall motion in the post-coronary patient is best achieved with an echocardiogram. Serial echo assessment of LV function can assist not only in overall risk stratification but also in making decisions regarding implantation of a cardioverter defibrillator.¹²

Exercise electrocardiography

Despite the wide availability of more sophisticated tests, exercise stress electrocardiography remains a very useful tool for detecting residual myocardial ischaemia and is of particular value in regional centres where ready access to coronary angiography is not available. It is less accurate in assessing myocardial ischaemia in women than in men.¹³

Stress imaging studies

Noninvasive functional testing may be required to localise and assess the extent of myocardial ischaemia, and to determine the likely benefit from revascularisation. The choice between radionuclide myocardial perfusion imaging and



stress echocardiography depends on local access and expertise as they have similar overall diagnostic accuracy.^{14,15} Nuclear perfusion scanning has shown that patients with transient ischaemic dilatation on testing have poor prognosis and those with the greatest reduction in ischaemia following revascularisation are likely to benefit the most.¹⁶

Specialised investigations

The advanced cardiac imaging techniques of cardiac magnetic resonance imaging, dobutamine stress echocardiography and positron emission tomography can assess cardiac viability with a high specificity and sensitivity, and may be needed in specialised situations to establish whether an extensive area of ischaemic myocardium will benefit from revascularisation. These techniques are not performed routinely as identifying viable myocardium did not identify patients with better survival benefit from CABG in the Surgical Treatment for Ischemic Heart Failure (STICH) trial.¹⁷

NEED FOR CORONARY REVASCLARISATION

The increasingly wide use of early intervention in patients with STEMI or high-risk NSTEMI

INDICATIONS FOR CORONARY REVASCULARISATION IN PATIENTS POST ACS

Definite indications

- Ongoing symptoms with a critical coronary stenosis
 - PCI is the usual treatment
- Ongoing symptoms with left main or triple vessel coronary artery disease
 - CABG is the usual approach, but left main or multivessel PCI increasingly being used²⁰

Possible indications

- Triple vessel disease and left ventricular dysfunction
 - consider CABG surgery; extent of scarring versus viable myocardium not shown to affect outcome in recent STICH trial¹⁷
- Asymptomatic patient with tight residual stenosis
 - PCI only if stenosis is functionally significant
- Totally occluded infarct related artery
 - less enthusiasm for treating this indication since lack of support for the ‘open artery hypothesis’ demonstrated²¹

ABBREVIATIONS: ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; STICH trial = Surgical Treatment for Ischemic Heart Failure trial.

means that many patients with ACS have undergone coronary angiography and revascularisation in the early stages of their hospitalisation. For those who have not, the question of whether to refer for revascularisation is complex, with surprisingly little evidence to guide decision-making. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that revascularisation based solely on the coronary angiogram does not improve prognosis over optimal medical management, and there has been a reduction in the use of PCI since this trial.^{18,19} The definite and possible indications for revascularisation are summarised in the Box.

TABLE 1. DRUGS AND OTHER MANAGEMENT IN PATIENTS POST ACS

Patient category	Drug	Other management
Asymptomatic patient without LV dysfunction	<ul style="list-style-type: none"> • Aspirin 100 to 150 mg per day • Beta blockers (metoprolol 25 to 50 mg twice daily or atenolol 25 to 50 mg per day) • Statin (atorvastatin 80 mg per day or equivalent) • P2Y12 inhibitor antiplatelet agents (see Table 2) 	Consider referral for cardiac rehabilitation
Asymptomatic patient with LV dysfunction	<ul style="list-style-type: none"> • Aspirin, statin, P2Y12 inhibitor • Beta blockers (bisoprolol, carvedilol, nebivolol or extended release metoprolol) • ACE inhibitor or angiotensin receptor blocker • Aldosterone antagonist (spironolactone or eplerenone) 	If left ventricular dysfunction is persistent and severe (LVEF <35%), consider referral for implantation of ICD
Symptomatic patient	<ul style="list-style-type: none"> • As for asymptomatic patient without LV dysfunction • If angina: standard antianginal therapy • If dyspnoea: diuretics 	Refer for detailed evaluation including coronary angiography and consideration of PCI or CABG

ABBREVIATIONS: ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; LV = left ventricle; MI = myocardial infarction; PCI = percutaneous coronary intervention; STICH trial = Surgical Treatment for Ischemic Heart Failure trial.

Once it has been decided that a patient will benefit from revascularisation, the choice of PCI versus CABG is usually determined by the coronary anatomy, ideally after detailed discussion between the cardiac surgeon and the cardiologist. CABG is usually reserved for patients with extensive coronary disease; however, the role of multivessel or left main PCI in such patients is being evaluated.²⁰

In patients receiving PCI, it may be necessary to consider the duration of post-PCI dual antiplatelet therapy (DAPT). A shorter duration of DAPT may have to be considered in patients facing elective noncardiac surgery (for more detail, see the later section on P2Y12 inhibitors and DAPT).

Patients with a tight residual stenosis may present a therapeutic challenge. If the stenosed vessel cannot be shown on functional testing to be significant or if it supplies an akinetic scar, there is little

to be gained from PCI.

Enthusiasm for treating asymptomatic patients with a totally occluded vessel has been less since the ‘open artery’ hypothesis was tested in a randomised clinical trial and no benefit of late opening of the occluded artery was shown.²¹

IDEAL POST-ACS PHARMACOLOGICAL MANAGEMENT

The recommendations for pharmacological therapy after infarction have a large clinical trial evidence base, but matching this evidence to the needs of the individual patient can be challenging. The current recommendations for pharmacological and other management of post-MI patients are summarised in Table 1.

Beta blockers

Guidelines recommend long-term treatment with β-blockers for all patients who have had a STEMI. This recommendation

TABLE 2. P2Y12 INHIBITOR ANTIPLATELET DRUGS

Drug	Loading dose	Maintenance dose	Prodrug requiring conversion	Cost
Clopidogrel	300 or 600 mg*	75 mg once daily	Yes	Low
Prasugrel	60 mg	10 mg once daily	Yes	Mod
Ticagrelor	180 mg	90 mg twice daily	No	High

* Although the clopidogrel loading dose of 300 mg is recommended, a dose of 600 mg is widely used because of faster onset of action.

is based on evidence obtained from clinical trials conducted in the 1980s, well before the current era of early intervention, near universal use of statin therapy and widespread use of DAPT.²² The role of β -blockers in the post-STEMI patient who has had a successful coronary reperfusion with restoration of LV function to normal and no evidence of residual myocardial ischaemia remains doubtful.²³ The recommendations for the patient who has had a small NSTEMI that was treated with PCI are based on even less strong evidence because these patients have not been included in any clinical trials.

It would be acceptable practice to consider cessation of β -blockers several months after hospital discharge in a post-MI patient who has minimal residual coronary stenosis, no evidence of residual myocardial ischaemia and no LV dysfunction, particularly if the β -blockers are associated with side effects.

Aspirin

Aspirin at a dose of 75 to 325 mg a day indefinitely is recommended for patients after infarction in all guidelines for the management of STEMI and NSTEMI. It is a low-cost and effective treatment, associated with a significant 25% reduction in major vascular events, or an absolute risk reduction of 35 vascular events per 1000 patients treated over two years.²⁴ Observational studies suggest that bleeding complications are fewer with the lower dose but randomised allocation to low dose (100 mg or less) versus standard dose (101 to 325 mg) showed no differences in bleeding.²⁵ Enteric

coated formulations may be associated with fewer adverse gastric effects than buffered aspirin, but the data remain unclear.²⁶

P2Y12 inhibitors and DAPT

The use of two antiplatelet agents together – aspirin and a P2Y12 inhibitor – is an evolving area. Most of the clinical experience with DAPT has been with clopidogrel but there are now newer agents available in this class, namely ticagrelor and prasugrel. The characteristics of these drugs are summarised in Table 2. They are usually used with aspirin (DAPT) but may occasionally be considered without if there is a contraindication to aspirin; however, their efficacy as monotherapy has not been established.

Ticagrelor and prasugrel are more effective than clopidogrel but carry a higher bleeding risk. They are, however, preferred for most patients after STEMI or NSTEMI unless the patient's bleeding risk is excessive.²⁷ Prasugrel and clopidogrel are prodrugs that require conversion to their active form; ticagrelor is administered in its active form. Up to 30% of patients are nonresponders or poor responders to clopidogrel, placing them potentially at higher risk of stent thrombosis.²⁸ However, recent studies have shown that dosing based on platelet responsiveness to clopidogrel is unhelpful.^{29,30}

Prasugrel is more effective than clopidogrel in reducing coronary events but has not had widespread uptake. This is because the definitive trial was conducted only in patients who had undergone coronary angiography (and therefore the efficacy of

early use in the emergency department has not been shown), and there was an increase in bleeding in the early phase of treatment.³¹ Prasugrel is ineffective in patients managed conservatively (i.e. not revascularised).³² Care is required in patients who are aged 80 years and older, who weigh 60 kg or less or who have renal impairment. It has not been established how long treatment with prasugrel should be continued after an MI or PCI.

Ticagrelor is also more effective than clopidogrel at preventing stroke, MI or death, as demonstrated in the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial.³³ It is also associated with an increase in non-CABG bleeding risk but as the trial evidence supporting its use did not require prior coronary angiography, it is becoming the preferred agent for initial treatment.³⁴ If patients require urgent coronary artery bypass surgery, CABG-associated bleeding risk is potentially decreased with ticagrelor because of its shorter half-life. However, the shorter half-life may be a disadvantage in patients with poor compliance/adherence as ticagrelor requires twice daily dosing and missed doses may increase the risk of MI, stent thrombosis and death.

The current recommendations for duration of DAPT are summarised in Table 3. These recommendations reflect consensus advice and, despite their wide acceptance, are not well based in evidence.

In conservatively managed ACS (i.e. patients who have not undergone PCI or CABG), it is recommended that DAPT be continued for 12 months, although the major benefits in the definitive trial (using clopidogrel) were in the first six weeks.³⁵ The ideal duration of DAPT remains unclear and is currently the subject of two major trials. The Dual Antiplatelet Therapy (DAPT) study is evaluating whether treatment should be continued for greater than 12 months and the Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study whether the duration

of treatment can be shortened to six rather than 12 months.^{36,37} The risk of stent thrombosis may depend on the type of stent used, with at least one trial showing that six months of DAPT may be adequate for some of the newer drug-eluting stents.³⁸ DAPT may be continued longer for those patients at high risk of a thrombotic event or with heavy thrombus burden at coronary angiography. Drug-eluting balloons (DEB) and bioresorbable scaffolds are not often used in patients who have had an ACS and the optimal duration of DAPT with these newer treatments is unknown.

Patients with stents need to be aware that premature disruption of DAPT carries a particularly high risk of stent thrombosis and, if necessary, be encouraged to remind their surgeon of this risk if undergoing a procedure.³⁹

Statins

Statin therapy is an essential part of the post-ACS regimen, with an average reduction in post-coronary events of 25 to 30% and an absolute reduction for each 1.0 mmol/L reduction in LDL cholesterol of 48 major vascular events per 1000 patients treated.^{40,41} Commencing the statin in hospital will enhance adherence over subsequent months.⁴²

The statin with the strongest evidence in the post-coronary patient, based on the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) study, is 80 mg of atorvastatin.⁴³ The safety of high dose atorvastatin (80 mg) has been confirmed.⁴⁴

The target LDL cholesterol level for patients after a coronary event is below 2.0 mmol/L.⁴⁵ It remains unclear whether a patient who achieves a reduction of LDL cholesterol to target levels with 80 mg of atorvastatin should be changed to a lower dose of statin, but it may be reasonable to do this to limit side effects. A trial of high dose (80 mg) of simvastatin was associated with a higher than acceptable incidence of myopathy.⁴⁶ Although rosuvastatin has been shown to be effective in high-risk cohorts,

TABLE 3. DURATION OF DAPT POST ACS

Intervention	DAPT duration
Balloon angioplasty*	1 to 3 months
Bare metal stents	3 to 4 months
Drug eluting stents	12 months†
Complex stenting or high risk complex coronary anatomy	Indefinite
Patients who have not had PCI	3 to 12 months (longer for those at high risk of thrombosis)

ABBREVIATIONS: ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention.

* Patients with planned surgery may have balloon angioplasty or bare metal stent placement to limit the duration of DAPT and allow early surgery.

† Shorter duration DAPT may be adequate for patients who have newer drug eluting stents, but this remains unclear.

there is no specific trial to support its use in patients post infarction. Ezetimibe, either alone or in conjunction with statins, has the potential to lower LDL cholesterol levels but to date there are no data to demonstrate any clinical benefit.⁴⁷

Other lipid modulations

Lowering triglycerides

There is no clear-cut benefit for lowering triglyceride levels in patients who have had an MI. Trials of gemfibrozil and bezafibrate have not been sufficiently persuasive to establish fibrate therapy in patients who have had a coronary event, and a large trial with fenofibrate did not achieve its primary end point of preventing coronary events in patients with type 2 diabetes, who are at relatively high risk of such events.⁴⁸⁻⁵⁰

Raising HDL cholesterol

To date there is no drug available that effectively raises HDL cholesterol levels. Although cholesteryl ester transfer protein (CETP) inhibitors can increase levels of HDL cholesterol, they have not been shown to improve outcomes. A large trial of torcetrapib in patients with stable coronary heart disease demonstrated an increased mortality with use of this CETP inhibitor.⁵¹ A large study of dalcetrapib in patients with ACS showed an effective raising of HDL cholesterol but no effect on

outcomes.⁵² A preliminary study of anacetrapib showed it could lower LDL cholesterol levels as well as raise HDL cholesterol levels, but a large outcomes study with anacetrapib has not been reported.⁵³

Omega-3 fatty acids

Fish oil-derived omega-3 fatty acids have been shown to moderately reduce total and sudden post-coronary deaths but it is not clear if this is by a triglyceride-lowering effect or other mechanisms.⁵⁴

ACE inhibitors and angiotensin receptor blockers

ACE inhibitors have a clear-cut role in patients with cardiac failure and significant LV dysfunction but their use in the absence of post-coronary LV dysfunction confers only modest benefits.^{55,56} Angiotensin receptor blockers as alternative therapy to ACE inhibitors have been trialed in post-coronary patients but the evidence base is not as extensive as it is for the use of ACE inhibitors post infarction.⁵⁷

Aldosterone blockade

Spironolactone and eplerenone have clear-cut benefits in patients with cardiac failure and LV function.⁵⁸ Meticulous monitoring of potassium levels is required, particularly in patients taking concomitant ACE inhibitors.⁵⁹

Calcium channel blockers

The calcium channel blockers have not been shown to have a clear-cut benefit on prognosis and are not recommended for routine use in patients after infarction. Verapamil and diltiazem are contraindicated in post-MI patients who have LV dysfunction.^{60,61} Amlodipine use has been shown to be safe in the presence of LV dysfunction.⁶²

Antiarrhythmic drugs

Antiarrhythmic drugs have not been shown to improve prognosis for post-MI patients, and their use in this setting is not recommended.⁶³

Nitrate therapy

Nitrates are indicated for patients with symptomatic angina but do not have a role in the management of angina-free post-MI patients.⁶⁴

Diuretics

Diuretics are useful for the symptomatic relief of cardiac failure but have not been convincingly shown to improve prognosis.⁶⁵ It is important to review the need for ongoing diuretic therapy at the time of hospital discharge of patients who have had an MI to avoid problems with hypovolaemia and electrolyte disturbances.

Digoxin

Digoxin does not have any clear-cut role in patients after infarction except in those who require it in addition or as an alternative to β -blockers for rate control of atrial fibrillation (AF).⁶⁶

Coumarins and new oral anticoagulants

The coumarin anticoagulant warfarin, a vitamin K antagonist, does not have a clear-cut role in preventing recurrence of a coronary event in post-MI patients. However, patients who have had a large infarction may benefit from a period of warfarin anticoagulation to prevent stroke, and there is an obvious role for warfarin anticoagulation if an intracardiac thrombus is shown on echocardiography.^{67,68}

Three new oral anticoagulants are now available for the prevention of stroke and systemic embolism in patients with non-valvular AF: apixaban, dabigatran and rivaroxaban. Dabigatran is a direct thrombin inhibitor, and apixaban and rivaroxaban are factor Xa inhibitors. To date, apixaban and rivaroxaban have been tested in the post-coronary patient, and neither has been shown to have a role in this setting. Rivaroxaban was shown to reduce recurrences but at an increased risk of bleeding.⁶⁹ Apixaban did not reduce recurrent ischaemic events and caused increased bleeding.⁷⁰

The management of patients with recent ACS and AF presents particular challenges. Recent data from a small randomised study of subjects requiring anticoagulation and PCI (the What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting [WOEST] trial), demonstrated that double therapy (clopidogrel and warfarin) was associated with significantly less bleeding than triple therapy (aspirin, clopidogrel and warfarin) without any increased risk of thrombotic events.⁷¹ Another study provides some evidence that patients with AF undergoing PCI may be more effectively managed with warfarin and clopidogrel than with triple therapy.⁷²

However, to date there are no data to guide the use of the new oral anticoagulants with the newer P2Y₁₂ inhibitors (prasugrel and ticagrelor), which are becoming standards of care.

DEVICE THERAPY

The early implantation of an ICD in patients who have had an MI has not been shown to deliver any additional benefit.⁷³ However, patients who had an MI more than 40 days previously and whose LV ejection fraction (LVEF) is persistently below 35% should have an ICD implanted, particularly if they have other risk factors such as New York Heart Association functional class greater than II, age over 70 years, mild renal dysfunction, QRS duration more than 0.12 s and AF.⁷⁴ Recent evidence indicates that reassessment of LVEF after MI is being

performed less frequently than desirable and many patients suitable for ICD implantation are being overlooked.⁷⁵

Patients who have had ventricular fibrillation during the early hours of their MI do not need an ICD.

CONCLUSION

Contemporary management of the patient who has had an ACS and does not have ongoing myocardial ischaemia should be tailored to the patient's clinical characteristics and local access to coronary angiography or noninvasive imaging modalities. Aggressive medical management has proven benefit for secondary prevention and adherence to evidence-based guidelines should be the aim for every patient.

Coronary revascularisation is indicated for patients with persisting symptoms and high-risk, extensive ischaemia. Implantable defibrillators should be considered in those who have persisting severe LV dysfunction (ejection fraction less than 35%). **MT**

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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