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INTRODUCTION


Drugs that affect the function of the heart and blood vessels are among the most widely used in medicine. Although these drugs may exert their primary effect either on the blood vessels or on the heart itself, the cardiovascular system functions as an integral unit. Thus, drugs that affect blood vessels are often useful in treating conditions in which the primary disorder lies in the heart.

This module covers foundation knowledge of common cardiac drugs and their pharmacological affects. The goal of this module is to review the pharmacological treatment used in management of Acute Coronary Syndromes.

Learning outcomes form this module are:

- Identify drug therapy for Acute Coronary Syndromes
- Indentify and demonstrate knowledge of using the NHF Angina Action Plan
- Identify and demonstrate knowledge:
  - Clopidogrel
  - Proton Pump Inhibitors
  - Statins
  - Hypertension
  - Dabigatran Etxilate
- Demonstrate knowledge of the use of antithrombotic medicines in general practice
- Identify current and future options for the management of heart failure
- Demonstrate understanding of the New Zealand Guideline for the Management of Chronic Heart Failure
HOW TO USE THE SELF-LEARNING PACKAGE

Follow these steps to complete the self-learning module:

1) Complete the pre reading at the start:
   a) Acute Coronary Syndromes – Pharmacological Treatment
   b) Drug Therapy for Acute Coronary Syndromes
   c) NHF Angina Action Plan
   d) Clopidogrel and Proton Pump Inhibitors
   e) An Update on Statins
   f) Hypertension – Pharmacological Management
   g) The Use of Antithrombotic Medicines in General Practice
   h) Dabigatran Etexilate
   i) Current and Future Options for the Management of Heart Failure
   j) New Zealand Guideline for the Management of Chronic Heart Failure

2) Complete the case study and the multi-choice question and evaluation, then return to the Cardiology CNE/CNS

Following the completion of this module you will receive 8 hours professional development time, which will be credited to your individual training database.
Acute coronary syndromes — pharmacological treatment

By Gary Fletcher, BSc, MRPharmS, and Andrew Worrall, MBChB, MRCP

The death rate from myocardial infarction has fallen since the 1960s, partly due to advances in drug therapy. This article describes the current drug treatment for acute coronary syndromes and highlights the role of the hospital pharmacist.

The term acute coronary syndrome (ACS) describes the spectrum of disease from acute myocardial infarction (MI) to unstable angina, as described in the first article of this feature (p285). The primary cause of these diseases is essentially the same — thrombosis of a coronary artery leading to ischemia and possibly infarction of the myocardium. The degree of ischemia or infarct size is related to the degree and location of the thrombosis.

Since the 1960s, when standard treatment was bed rest and defibrillation (when required), the death rate from acute MI has fallen. This steady decline in mortality has been due to a number of factors:

- Improved public information and education about the need to seek immediate medical attention when suspected cardiac chest pain is experienced.
- The introduction of new drug treatments (e.g., beta blockers in the late 1970s).
- The introduction of thrombolytic agents (in the 1980s).
- The development of coronary angioplasty and stenting (in the 1990s).

- The recognition of modifiable risk factors (e.g., hypertension, diabetes, smoking) and strategies for their management.

This article will review current drug treatments for ACS and the growing significance of primary percutaneous coronary intervention (PCI) as an alternative to thrombolysis in acute MI.

--- Initial Treatment

Successful treatment of ACS depends on the early recognition of symptoms and the prompt transfer of the patient to the accident and emergency department. The initial treatment of all ACS, given either by paramedic teams, or in A&E, is essentially the same.

The presentations of unstable angina and acute MI are often different. Generally, symptoms of acute MI are severe and sudden whereas non-ST elevation MI (NSTEMI, see p285) or unstable angina tends to develop over 24–72 hours or longer. In both cases the initial aim of treatment is to stabilize the condition and alleviate the patient’s pain and anxiety.

Stabilization is achieved by a combination of measures. Oxygen is given to maintain saturation levels and to improve oxygen delivery to the myocardium. Diamorphine, at an initial dose of 5mg (followed by a 2.5–5mg slow intravenous injection when required) is given for analgesia and to reduce the patient’s anxiety. This has the effect of reducing the adrenaline response, reducing heart rate and blood pressure, and thus reducing the oxygen demand of the myocardium. Morphine 10mg followed by further doses of 5–10mg by slow IV injection may be given as an alternative to diamorphine.

Metoclopramide 10mg IV injection is given for the control of nausea and sublingual glyceryl trinitrate is given to relieve or reduce chest pain.

In the coronary vessel, platelet aggregation and thrombus formation and extension is maintained by thromboxane A2 (TXA-2), which is produced by activated platelets, catalysed by the enzyme cyclo-oxygenase-1 (COX-1). Patients with suspected MI must be given aspirin (300mg) as soon as possible to limit further extension of the thrombus. Aspirin irreversibly inhibits COX-1 within platelets, inhibiting further production of TXA-2 and further platelet aggregation. Patients who are known to have an allergy to aspirin can be given clopidogrel 300mg.

On arrival at hospital, the patient will be connected to a 12-lead electrocardiogram recorder. A full blood count will be taken, as well as urea and electrolyte levels, liver function tests, a thyroid function test, lipid profile and glucose level. At this point, all patients with ST elevation or a new left bundle branch block (see p285) will be deemed to be presenting with acute MI. Immediate reperfusion with either thrombolysis or primary PCI is needed. All other patients presenting with suspected cardiac chest pain in the absence of...
definitive ST elevation will be investigated and risk stratified as having NSTEMI/ unstable angina, and troponin levels will be taken 12 hours after presumed onset of chest pain.

ST elevation MI

Reperfusion, by thrombolysis or primary PCI, is indicated for all patients presenting with chest pain consistent with an MI of less than 12 hours' duration from onset, who also have with any of the following:

- ST elevation >0.1mV in more than two contiguous ECG chest leads
- ST elevation >0.2mV in more than two contiguous limb leads
- New left bundle branch block

There are a number of advantages and disadvantages to each method of reperfusion. Primary PCI is the preferred option if the patient can be rapidly transferred to a centre providing high volume PCI procedures.

Thrombolysis

The benefit of early thrombolysis was clearly demonstrated in the GISSI-1 study. Thrombolysis is preferred in patients who present early (within the first three hours, or ideally within one hour). Thrombolysis within one hour of onset of symptoms results in a 50 per cent reduction in mortality compared with conservative treatment. A significant reduction in mortality has been shown when thrombolysis is administered within 12 hours, but the reduction is much lower than 50 per cent. After 12 hours there is no significant difference between thrombolysis and conservative treatment, although there is a trend towards reduced mortality. Late thrombolysis is therefore considered to be of minimal benefit compared with the risks. This emphasises the importance of prompt recognition of symptoms and appropriate administration of a thrombolytic agent. This is reflected in the National Service Framework for Coronary Heart Disease "call to needle" time of 60 minutes, meaning that all eligible patients should receive thrombolysis within one hour of initial contact with medical services.

Data from the sixth public report by the Myocardial Infarction National Audit Project show that in 2006/07 64 per cent of patients received thrombolysis within one hour of first calling for help, and 84 per cent of eligible patients received thrombolysis within the first 30 minutes of arrival at hospital.

Streptokinase, introduced in the 1980s, was the first treatment to restore flow in a thrombosed coronary artery. It is a protein derived from streptococci which converts plasminogen to plasmin. It is an antigenic protein, and is associated with a high incidence of hypotension and allergic reactions. Once administered, any subsequent administration may be rendered ineffective by neutralising antibodies.

Other thrombolytic drugs are tissue plasminogen activators (tPA) (eg alteplase) and newer tPAs (eg tenecteplase). Newer tPAs have a longer half-life and so can be more easily administered by bolus injection, rather than infusion as is necessary for streptokinase and alteplase. Exclusion criteria for thrombolysis include:

- Active bleeding (eg peptic ulceration, gastrointestinal bleed, osteoarthritic varices)
- High risk of bleeding (eg those over 75 years old)
- Coagulation disorder(s)
- Severe hypertension
- History of stroke/transient ischaemic attacks
- Surgery or trauma within the last three months
- Pregnancy
- Previous thrombolysis with streptokinase (in which case streptokinase is contraindicated)

Of all patients presenting with acute MI who are potentially eligible for thrombolysis, only 60 per cent will actually receive thrombolysis. Of the remaining 40 per cent, 15 per cent will have a contraindication, 15 per cent will present late, and 10 per cent will have a non-diagnostic ECG on admission. When given thrombolysis full reperfusion (demonstrated by resolution of ST elevation) is achieved in less than 60 per cent of cases. Complications include allergy to the thrombolytic agent, which can range from minor to major anaphylaxis. Anaphylaxis is rare, estimated to occur in about 0.1 per cent of patients undergoing thrombolysis. Haemorrhage requiring transfusion is rare, but bleeding at venepuncture sites is a common complication. There is also an increased risk of haemorrhagic stroke, particularly in older patients. Hypotension is a fairly common problem, especially during treatment with streptokinase.

Primary PCI

Primary PCI involves the passage of a catheter (mainly via the femoral artery) into the coronary arteries (see p249). This is viewed under X-ray by the injection of radio-opaque contrast medium via the catheter. Once the coronary vessels are visualised, a definitive identification of the thrombosed artery can be made and the artery can be opened by use of a balloon on the tip of the catheter thus achieving reperfusion of the infarcted myocardium. Stents are then inserted to maintain patency of the vessel.7 This technique allows targeted opening of the vessel, unlike systemic administration of thrombolytic agent.

It is imperative that patients have full platelet inhibition before primary PCI to reduce the risk of peri-procedural thrombosis due to further disruption of the plaque or in-stent thrombosis. This is achieved by the administration of clopidogrel (300–600mg) in conjunction with standard aspirin treatment. It should be administered as soon as possible, before the PCI. Additional peri-procedural platelet inhibition is achieved by administration of abciximab (a glycoprotein IIb/IIIa inhibitor) or bivalirudin (a direct thrombin inhibitor).

Primary PCI is the preferred option in patients presenting with acute MI where the procedure can be carried out within 90 minutes of first medical contact (ie a "door-to-balloon" time of less than 90 minutes). If a patient's "door to balloon" time exceeds 90 minutes, primary PCI would still be the preferred option if thrombolytic therapy was contraindicated or if the patient was at high risk of bleeding, in cardiogenic shock or presented with another high risk feature. Over 90 per cent of patients given a primary PCI have angiographic normal flow5 compared with the 50 per cent of patients given thrombolysis that achieve flow in the occluded artery.

Other advantages of primary PCI include:

- No risk of serious side effects (eg intracranial haemorrhage)
- Shorter inpatient stay
- Reduced risk of reinfection

Some patients have a known anaphylactic allergy to the radiographic contrast media used in angiography. Thrombolysis is the only treatment option for these patients.

Secondary STEMI treatment

Guidance from the National Institute for Health and Clinical Excellence (NICE) has been published recently regarding secondary treatment post-MI. It states that all patients who have had an acute MI should be offered a combination of aspirin, a beta blocker, a statin and an angiotensin-converting enzyme (ACE) inhibitor.4

Antiplatelet treatment

Antiplatelet treatment is essential in all patients with established cardiovascular disease in order to reduce the risk of coronary thrombosis. Aspirin should be continued for life at a dose of 75mg daily. Post-primary PCI, dual antiplatelet treatment with clopidogrel should be taken for a minimum of twelve months. Dual antiplatelet treatment is essential post-stenting due to the high incidence of in-stent thrombosis (approximately 20 per cent). Indeed, for patients considered to be at high risk, (eg young patients with previous ischaemic heart disease), where the culprit lesion is in a high risk vessel (eg left main stem
study including the Heart Protection Study, where improved outcome and reduction in death for all patients with established cardiovascular disease was shown in patients prescribed simvastatin 40mg daily. This mortality benefit was apparent irrespective of the initial cholesterol/ldl level.  

ACE inhibitors Up to 20 per cent of patients develop LVSD following acute MI. This group of patients has significantly increased mortality. The first study to show the benefit of ACE inhibition post-MI was the AIR study. It showed that treatment with ramipril in patients with clinical signs of heart failure produced a 27 per cent reduction in mortality at 15 months. This has been confirmed in several other studies including HOPE (ramipril) and more recently, EUROPA (perindopril). HOPE and EUROPA also suggest that all patients with coronary heart disease benefit from ACE inhibition irrespective of heart failure or hypertension.  

Following an infarction, the affected myocardium stretches and thins resulting in ventricular dilation. The remaining functioning myocardium undergoes hypertrophy to compensate for the resultant impairment of ventricular function. This cardiac remodelling is a powerful predictor of increased mortality. Angiotensin II can also act as a growth factor, promoting hypertrophy. Inhibition of angiotensin II can therefore inhibit this process. An ACE inhibitor (eg. ramipril) should be started 24-48 hours post-MI for patients whose condition has been stabilised, whether or not they have clinical symptoms of heart failure. ACE inhibitors reduce the afterload on the left ventricle due to inhibition of the renin-angiotensin system, reducing ventricular dilation. An ACE inhibitor should be initiated at a low dose and titrated up to the highest tolerated dose. Contraindications include hypotension, renal impairment, bilateral renal artery stenosis and allergy to ACE inhibitors. Serum electrolytes, renal function and blood pressure should be taken at baseline and after two weeks.

Aldosterone antagonists Current NICE guidance states that for patients with symptoms or signs of heart failure and LVSD an aldosterone antagonist licensed for post-MI treatment should be initiated within three to 14 days of the MI, preferably after ACE inhibitor therapy. The only drug currently licensed for this indication is spironolactone. This is in line with the results of the EPHESUS study, which found a 30-day risk reduction for all cause mortality of 43 per cent. After a maximum of 12 months’ treatment with eplerenone, patients with impaired LVSD can be treated with spironolactone in line with the NICE guideline on heart failure. Patients need to have their potassium levels and renal function monitored.

Dietary supplements Patients should be advised to increase their consumption of polyunsaturated fish oils and to eat a Mediterranean-style diet. NICE recommends that patients should eat at least 1g of omega-3 acid ethyl esters per week. This can come from either from two to four portions of oily fish or, for patients who are unable to maintain an adequate dietary intake, from 1g daily oral supplementation.

Unstable angina/NSTEMI

Although STEMI carries a higher risk of mortality in the short term, there is a higher mortality risk at six months with NSTEMI. Patients with high-risk features should be considered for emergency angiogram with a view to PCI. Intermediate and low risk patients should be considered for urgent angiogram (as an inpatient). Patients presenting with NSTEMI/unstable angina have broadly similar treatments to STEMI, apart from the fact that thrombolysis is not indicated. Unfractionated heparin or low molecular weight heparin in conjunction with antiplatelet treatment is used instead.

Antiplalet All patients with NSTEMI/unstable angina should be treated with aspirin 75mg daily and clopidogrel 75mg daily, with loading doses of 300mg given at presentation. The CURE trial demonstrated the benefit of adding clopidogrel to standard aspirin therapy, with a 20 per cent relative risk reduction of death, non-fatal MI and stroke, compared with aspirin and placebo, in patients with NSTEMI. Since there is little evidence of benefit beyond nine to 12 months of dual treatment, NICE recommends continuation of clopidogrel with aspirin for 12 months only (compared with four weeks post-MI or 12 months minimum post-primary PCI).

Glycoprotein IIb/IIIa receptor antagonists, such as tirofiban or eptifibatide are potent inhibitors of platelet aggregation. They inhibit the formation of fibrinogen cross-links between platelets. Although these drugs inhibit thrombus formation, trials suggest that glycoprotein IIb/IIIa inhibitors are only effective in high risk NSTEMI patients, or in patients suitable for PCI in whom the procedure is delayed, in conjunction with aspirin and heparin/LMWH.

Anticoagulation It has become commonplace to use low molecular weight heparin rather than unfractionated heparin in order to limit the extension of coronary thrombosis in NSTEMI/unstable angina. The ESSENCE trial demonstrated the superiority of enoxaparin at 1mg/kg twice daily over unfractionated heparin. Despite the greater cost of enoxaparin, it has greater
anti-factor Xa activity, does not require monitoring, and can be easily administered as a twice daily dose, making it the preferred choice. Enoxaparin should be continued until the patient has been free of angina for at least 24 hours. The recommended duration is two to eight days. For patients with impaired renal function (creatinine clearance <30 ml/min), enoxaparin dose should be given at 1mg/kg once daily.

Antianginal therapy. The use of beta blockers is well established in antianginal treatment and therapy should be initiated as early as possible, as for post-MI treatment, unless contraindicated. Although there is no clear evidence that treatment with other antagonists has any benefit in terms of mortality, the following drugs are often prescribed to relieve angina symptoms or for prophylaxis:

- **Isosorbide mononitrate** Isosorbide mononitrate is usually given as a once daily, modified release preparation, to avoid nitrate tolerance. It is given together with with glyceryl trinitrate spray when required.
- **Calcium channel blockers (eg. amlodipine, diltiazem)**. Diltiazem can be prescribed for patients who cannot tolerate beta blockers, due to its effects on cardiac electrical conduction, although this is not a licenced indication. Short acting agents (eg. nifedipine) should not be used because reflex tachycardia is a common initial side effect and can worsen angina symptoms.
- **Nicorandil**. Nicorandil can be added in combination with other antagonists.

With all antianginal medication, headache can be an initial problem, and may be severe. If this is a problem doses should be adjusted, maintaining adequate blood pressure.

Lipid lowering treatment. Patients should be started on a statin for the reasons given for post-MI patients.

ACE inhibitors. All patients with NSTEMI should be considered for treatment with an ACE inhibitor (eg. ramipril), unless contraindicated, in line with recommendations from the HOPE and EUROPA studies (see p208).

**Diabetes**

It has long been recognised that diabetes or impaired glucose tolerance is associated with poor prognosis post-MI. The first trial to demonstrate that tight diabetic control post-MI reduced long-term all-cause mortality was the DIGAMI study. This study showed that tight control of blood glucose levels (initially using a glucose-insulin infusion, followed by four times daily subcutaneous insulin injections) resulted in an absolute reduction in mortality of 11 per cent. The effect on increased survival post-MI seen at one year continued for at least a further 3.5 years, and was most apparent in patients who had not previously been treated with insulin and who were considered to be at low cardiovascular risk prior to MI.

A further study, the DIGAMI-2, demonstrated that there is no benefit in terms of MI survival of using subcutaneously injected insulin long term over standard oral antidiabetic medication and that tight glycaemic control is the key determinant of long term prognosis. Although the DIGAMI and DIGAMI-2 studies were limited to patients with acute MI, it is recognised that patients with NSTE MI also benefit from tight glycaemic control.

**Role of the pharmacist**

Ward-based pharmacists working in cardiology are in an ideal position to make an impact on patients’ drug therapy, both pre- and post-discharge.

Optimisation of drug treatment. As well as ensuring that the correct medicine is prescribed at the appropriate time, it is essential that consideration is given to the impact that combinations of drugs may have on blood pressure, heart rate, renal and liver function, haematology and electrolytes.

Patient education. Patient education is essential. It is common for patients who previously were not on any regular medication to leave hospital post-ACS on different drugs. This is often a cause of anxiety. A few minutes spent with the patient giving a simple explanation of the rationale for their medicines can often allay such anxieties and reduce the risk of non-compliance. It is also important that the patient understands potential side effects and their significance, for example, the importance of reporting any muscle pain while taking a statin.

Pharmacists as prescribers. With the establishment of pharmacist independent prescribing in the UK, the role of the specialist cardiac pharmacist could well extend into prescribing standard treatments post-ACS.

**References**

Drug Therapy for Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosing</th>
<th>Nursing Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>150-300mg orally, crushed or chewed, then 75-150mg daily</td>
<td>Contraindicated in active peptic ulcer disease, hepatic disease, bleeding disorders and aspirin allergy</td>
</tr>
<tr>
<td>Oxygen</td>
<td>2-4L by nasal prongs</td>
<td>Maintain oxygen saturation at 94-98%</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>1-2 sublingual sprays every 5 minutes (up to 3 times)</td>
<td>Assess for pain relief</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor blood pressure, cease medication if systolic blood pressure &lt;90-100mmHg</td>
</tr>
<tr>
<td>Morphine sulphate</td>
<td>2-3mg iv push, repeat every 5-15min until pain controlled</td>
<td>Indicated when pain not improved by glyceryl trinitrate</td>
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<tr>
<td></td>
<td></td>
<td>Assess for pain relief</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor blood pressure and respiratory status</td>
</tr>
<tr>
<td>β-blockers</td>
<td></td>
<td>Contraindicated in asthma, systolic blood pressure &lt;110mmHg, heart rate &lt;50bpm, 2nd or 3rd degree heart block and moderate to severe left ventricular impairment</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Administer oral dose within 24 hours of symptom onset and continue upon discharge</td>
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<tr>
<td>Atenolol</td>
<td></td>
<td></td>
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<tr>
<td>Carvedilol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td>Contraindicated in acute renal failure, hyperkalaemia, angioedema and pregnancy</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>Administer oral dose within 24 hours of symptom onset and continue upon discharge</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td></td>
<td>Assess for hypotension, decreased urine output, cough, hyperkalaemia and renal insufficiency</td>
</tr>
<tr>
<td>Enalapril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
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<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Administer oral dose in hospital with the aim of reducing LDL to &lt;1.6mmol/L</td>
<td>Simvastatin and pravastatin need to be given at bedtime. Atorvastatin and rosvastatin can be given at any time of the day</td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
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<tr>
<td>Rosuvastatin</td>
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<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Administer 300-600mg orally, then 75mg daily, continued on discharge</td>
<td>Contraindicated in active peptic ulcer disease, bleeding disorder, hepatic disease, or if coronary artery bypass graft surgery is planned within 5-7 days</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1mg/kg subcutaneously Q12H, continued for 48h, until pain resolves or until PCI</td>
<td>Monitor renal function, platelet count and bleeding time</td>
</tr>
</tbody>
</table>

Angina Action Plan
if you take GTN spray or tablets

Do you have your normal angina symptoms?

Yes
Stop what you are doing. Sit down and take 1 puff of your GTN spray or 1 GTN tablet, under your tongue

Wait 5 minutes

Do you still have angina?

Yes
Take 1 more puff of your GTN spray or 1 GTN tablet

Wait 5 minutes

No
If symptoms are more prolonged and severe and/or you feel faint, sweaty, sick or vomit – treat as a heart attack Call an ambulance Dial 111 immediately and use GTN as per Angina Action Plan

If you usually take GTN spray or tablets:
- Stop what you are doing. Sit down and take 1 puff of your GTN spray or 1 GTN tablet, under your tongue
- If your angina is relieved by rest or your GTN spray or tablet, you can resume your activities gently
- If your angina persists, you can take 1 more puff of your GTN spray or 1 GTN tablet after 5 minutes
- If your angina is not relieved after a further 5 minutes, treat as a heart attack – call an ambulance. Dial 111 immediately.

If your angina becomes more frequent, severe, lasts longer or happens when you are doing very little or resting, see your doctor in the next 24 hours.

This action plan is recommended by the Heart Foundation, however if you have received different advice, please discuss with your doctor or whoever prescribed you your medication.
Clopidogrel and proton-pump inhibitors

Clopidogrel is part of standard care for various cardiovascular atherothrombotic diseases. It is an inactive pro-drug that requires conversion to its active compound to have an antplatelet effect. Rarvet data suggest that pump inhibitors (PPIs) may inhibit this conversion and reduce the effectiveness of clopidogrel.

The aim of this bulletin is to provide an overview of the clopidogrel-PPI interaction and suggest management strategies when faced with co-prescription of these drugs.

Overview of clopidogrel-PPI interaction
The cytochrome P450 2C19 (CYP2C19) isoenzyme appears to be particularly important in the conversion of clopidogrel to the active metabolite. Patients with reduced function of CYP2C19 due to genetic polymorphisms (e.g. 15% of Caucasians) have significantly lower concentrations of the active metabolite of clopidogrel and higher rates of adverse cardiovascular outcomes compared to normal metabolisers. Drugs that are metabolised by CYP2C19 may competitively inhibit the conversion of clopidogrel to its active metabolite. There is a rapidly growing body of data that examines the possibility that PPIs interact with clopidogrel via this mechanism.

In vitro data
In vitro studies show that the different PPIs inhibit CYP2C19 to different extents. For example, lan索rew and omeprazole have been found to be significant inhibitors, whereas pantoprazole was shown to be a very weak inhibitor of CYP2C19.

Platelet aggregation data
Platelet aggregation studies are surrogate pharmacodynamic markers for the effectiveness of clopidogrel, with increased aggregation being predictive of poorer cardiovascular outcomes. An observational study of clopidogrel users showed that those on omeprazole had a ~25% increase in platelet aggregation compared to non-users (p=0.007). A subsequent randomised controlled trial of patients undergoing coronary artery stenting who were given aspirin and clopidogrel found a similar increase in platelet aggregation in those given omeprazole (20mg/day) compared with placebo (p=0.0001). Similar studies with pantoprazole have found conflicting results.

Clinical data
This is largely limited to observational studies, which have reported conflicting results regarding
- the presence of a clopidogrel-PPI interaction leading to increased adverse cardiovascular outcomes and
- the specificity of the interaction to PPIs that are potent CYP2C19 inhibitors.

There have been six observational studies published as original articles, including five retrospective cohort studies and one nested case-control study. Endpoints have included serious cardiovascular events such as myocardial infarction and stroke.

Two have concluded, with statistical significance, that combining PPIs with clopidogrel increases the risk of serious cardiovascular events by around 20%. Omeprazole was the predominant PPI in both of these studies. In one of these two studies, subgroup analysis found an absence of increased risk with pantoprazole. Three other studies did not show an association between PPI and cardiovascular events in the setting of clopidogrel use. In two of these, pantoprazole was the predominant PPI, whilst no breakdown of specific PPIs was provided in the third. It may therefore be argued that these five studies reflect the in vitro data, highlighting the difference between omeprazole and pantoprazole in terms of CYP2C19 inhibitory potency.

The results of a sixth study are at odds with the other five as pantoprazole was the main PPI and the study showed a statistically significant adverse cardiovascular interaction with clopidogrel.

Observational studies are inherently limited by the presence of residual confounding, which may have led to the findings in favour of an interaction being present. However, observational medication exposure typically causes a bias towards the null hypothesis as a result of non-adherence and over-the-counter medication use. Randomised controlled studies are therefore important in providing more definitive evidence. Of note, there has been one randomised controlled trial of a fixed-dose combination of omeprazole and clopidogrel compared with clopidogrel alone. The data from this study has provisionally reported as showing an absence of an adverse cardiovascular interaction between omeprazole and clopidogrel and a protective effect in terms of gastrointestinal bleeding. Formal publication of this study is awaited.

Conclusion and management strategies
The currently available data are strongly suggestive of a significant adverse interaction at the molecular level between clopidogrel and some PPIs (such as omeprazole), but is inconclusive at the clinical level. Until more definitive evidence is available, the possible risk posed by this interaction should be taken into account when contemplating co-prescription of clopidogrel with a PPI.

In this setting, the individual gastrointestinal benefit needs to be balanced against the cardiovascular risk. For example, a PPI may, overall, be beneficial where there is a low risk of cardiovascular disease but a high risk of haemorrhagic gastrointestinal events. When faced with co-prescription of clopidogrel and PPIs, an algorithm based on both PPI and non-PPI alternatives to those PPIs that are significant in vitro should be taken into account when contemplating co-prescription of clopidogrel with a PPI.

Module 5: Pharmacology: Treatment of Acute Coronary Syndrome, Hyperlipidaemia, Hypertension, heart Failure and Stroke Prevention. Prepared by: Jacqui Walker and Marie-Claire Pow, Christchurch Hospital

Pharmacy Department February 2012

The information contained within this bulletin is provided on the understanding that although it may be used to assist in your final clinical decision, the Clinical Pharmacology Department at Christchurch Hospital does not accept any responsibility for such decisions.
An update on STATINS

Key concepts

- The decision to initiate a statin should be based upon an individual’s risk of CVD, the likely benefit of treatment and potential adverse effects.
- Targets are generally not necessary in primary prevention, where any reduction in lipid levels results in a reduction in CVD risk.
- In secondary prevention, lipid levels should be viewed as a guide to management rather than targets to achieve.
- Simvastatin 20 - 40 mg is a reasonable starting dose for many people, although individual patient factors influence the choice of statin and intensity of treatment. People at highest CVD risk tend to benefit the most from higher doses or higher potency statins.
- After initiating statin treatment, creatine kinase should be checked when there are unexplained muscular symptoms, however no other monitoring is routinely required.
- Lipid-lowering agents other than statins may be considered for those who require additional lipid-lowering, when statins alone are not adequately controlling dyslipidaemia, or in cases of statin intolerance.
Current recommendations for statin use in New Zealand and international guidelines

New evidence is continually emerging on the use of statins, particularly in relation to their role in primary prevention of cardiovascular disease (CVD), specific dose regimens and treatment targets. This information, both in the lay press and medical literature, prompts reflection on current cardiovascular guidelines and consideration of whether there is anything new that represents a significant shift from current practice for primary care clinicians.

New Zealand Guidelines Group cardiovascular guidelines

The New Zealand guidelines for the use of lipid lowering agents as part of CVD risk management recommend the following:

- Treatment should be based on an individual’s five-year CVD risk
- Statin treatment should be initiated for people with known CVD or at high CVD risk
- Starting doses:
  - For people with a five-year CVD risk of 15 - 20%, simvastatin 20 mg (titrate if needed)
  - For people with known CVD or a CVD risk > 20%, simvastatin 40 mg
- Lowering of LDL-cholesterol is the primary indicator of optimum lipid management. Targets include total cholesterol < 4.0 mmol/L and LDL-cholesterol < 2.0 mmol/L.
- If LDL-cholesterol targets are not met, options include increasing simvastatin to 80 mg, substituting simvastatin for atorvastatin or combining simvastatin with niacin or ezetimibe.

United Kingdom NICE cardiovascular guidelines

The National Institute for Health and Clinical Excellence (NICE) guidance on lipid modification is presented in terms of primary and secondary prevention and recommendations are based on the ten-year risk of CVD. The following recommendations are given:

- Statin treatment for primary prevention is recommended when the CVD ten-year risk reaches 20%
- For both primary and secondary prevention the recommended initial dose for simvastatin is 40 mg

Comparison between Guidelines

A key difference between NZGG and NICE Guidelines is in the use of cholesterol targets. The NICE guidance recognises that more than half the patients will be unable to achieve traditional targets such as LDL-cholesterol < 2 mmol/L. Targets are now regarded as levels that can guide increases in dose or intensity of treatment in patients at greatest risk i.e. for secondary prevention. Measurement of lipid levels is considered unnecessary in lower risk patients i.e. for primary prevention.

It may appear that patients can be started on statin treatment at lower CVD risk in the United Kingdom. However recent risk/outcome data (which are still accumulating) indicate that CVD risk in New Zealand may be overestimated by up to 5%. This means that a patient calculated to have a 15% five-year CVD risk, is more likely to have a risk closer to 10%. If it is assumed that a 10% five-year CVD risk is equivalent to a 20% ten-year CVD risk, then it can be concluded that New Zealand recommendations are similar to United Kingdom recommendations.

For full details of the New Zealand Guidelines Group (NZGG) Cardiovascular Guideline, visit: www.nzgg.org.nz
When should statin treatment be initiated?

New Zealand guidelines recommend the use of a statin in the primary prevention of cardiovascular disease when the five-year CVD risk reaches 15–20%.¹

Increasingly people are being considered for statin treatment for primary prevention of CVD. The potential benefit of statins for primary prevention was highlighted by the landmark West of Scotland Coronary Prevention Study (WOSCOPS) which found a 31% reduction in coronary events with pravastatin compared with placebo.³ A recent meta-analysis of primary prevention trials concluded that statins improve survival and reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease.⁵

Included in this analysis was the JUPITER trial (see sidebar) which has caused much subsequent debate. This trial demonstrated that rosuvastatin reduced the rate of adverse cardiovascular events in people with increased CVD risk.⁶ However the patients included in the study had normal LDL-cholesterol levels to begin with and the CVD risk was defined by increased levels of high sensitivity CRP, a controversial surrogate marker of CVD risk.

Based on current evidence it may be appropriate to view lipid lowering treatment with statins as an intervention that can reduce relative cardiovascular risk (by approximately 20% to 30%) regardless of baseline LDL-cholesterol. The absolute benefit of treatment is proportional to the underlying absolute risk.⁷

Determining when the benefits of treatment outweigh its disadvantages (cost and adverse effects) requires estimation of the patient's underlying cardiovascular risk. Once a patient's cardiovascular risk is assessed, together with their doctor, they can decide whether a 20% to 30% relative risk reduction translates into an absolute risk reduction, large enough to be worth the cost and potential adverse effects of daily statin therapy.⁷

For example:
A 45-year-old non-smoking, non-diabetic, normotensive woman has a total cholesterol of 6.2 mmol/L and a HDL-cholesterol of 1.1 mmol/L. Her five-year risk of a cardiovascular event is assessed to be less than 2.5%. This could potentially be reduced by 0.5 to 0.75% if she were to be treated with a statin.

The GP and patient decide against the use of a statin as the absolute benefit of treatment is minimal (less than 1%) and does not warrant exposing the patient to the potential adverse effects of long-term statin therapy.

Acknowledging the limitations of CVD risk assessment

The calculation of CVD risk is limited by factors specific to individual patients. For example, using the charts in the New Zealand Cardiovascular Handbook may underestimate CVD risk for those who have:

- Total cholesterol ≥ 8 mmol/L
- Total cholesterol : HDL-cholesterol ratio ≥ 8
- Blood pressure consistently ≥ 170/100
- Diabetes with microalbuminuria for 10 years or with HbA₁c consistently ≥ 8%
- Family history of premature coronary heart disease or ischaemic stroke in a first-degree relative (father or brother < 55 years, mother or sister < 65 years)

And those who are:

- Māori, Pacific or from the Indian subcontinent
- Aged ≥ 75 years
- Aged < 35 years with known CVD risk factors
- Aged 20–34 years with diabetes
- Overweight
- High consumers of alcohol

For patients with these risk factors especially, lipid lowering drug treatment should be combined with advice on diet and lifestyle measures such as exercise, weight management, alcohol consumption and smoking cessation. Other risk factors should also be appropriately
addressed such as lowering raised blood pressure and managing diabetes.\textsuperscript{4,5}

For example, a 52-year-old man has an estimated five-year CVD risk of 10–15\% (calculated from the CVD risk tables). He reveals that he has a family history of premature coronary heart disease.

The GP decides that this patient should be moved up a risk category to >15\% on the basis of his family history and therefore a statin is indicated.

**How important are target lipid levels?**

New Zealand guidelines recommend the following optimal lipid levels (targets) for people with known cardiovascular disease, cardiovascular risk > 15\% or diabetes:\textsuperscript{1}

- Total cholesterol < 4.0 mmol/L
- LDL cholesterol < 2.0 mmol/L
- HDL cholesterol ≥ 1.0 mmol/L
- Triglycerides < 1.7 mmol/L

The traditional view on lipid levels is “the lower, the better”, which is technically correct from a disease-based point of view. However this view does not take into account how the treatment used to achieve this intervention will affect patient outcomes.\textsuperscript{8}

Although specific target levels are recommended in New Zealand Guidelines, it is now widely agreed that it is not necessary to treat to target lipid levels in primary prevention of CVD. Many patients are unable to achieve target lipid levels, potentially leading to lack of motivation and non-compliance with treatment.\textsuperscript{10}

**The JUPITER Study**

When results were first reported in 2008, the justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin (JUPITER) study was regarded by some as an important development in statin research. The results suggested that statins were beneficial in people with no history of CVD but assessed as being at increased CVD risk.\textsuperscript{6} However, since this time the JUPITER study has received much criticism.

One of the most controversial aspects of JUPITER was that trial participants had no known CVD and had cholesterol levels within normal ranges but were designated to be at increased CVD risk due to elevated high sensitivity C-reactive protein (hsCRP) levels. The use of hsCRP as a surrogate marker for CVD risk is debatable.

The absolute effect size of the study was relatively modest – for every 1000 patients who received rosuvastatin for one year, roughly six fewer primary-endpoint events (first major cardiovascular event including unstable angina, myocardial infarction, stroke and arterial revascularisation) and three fewer deaths occurred. Therefore a large number of people with low-CVD risk would have to be treated in order for any benefit to be derived.

The JUPITER study was terminated early, after only 1.9 years, instead of the planned four years, due to strong evidence of benefit in the treatment group. Early termination for benefit can provide an inflated estimate of benefit and underestimate harm.\textsuperscript{8} There was also no indication about the long-term safety of the very low LDL-levels which were achieved in the study.

The results of the JUPITER study were taken into account when the New Zealand Cardiovascular Guidelines Handbook was revised in 2009 by the New Zealand Guidelines Group. However the Group did not think it justified any change in practice.
Additional reasons for not using lipid level targets in primary prevention include:  

- Clinical trial evidence is based on using specific doses of specific medicines to treat people, rather than using medicines to achieve specific targets  
- The majority of studies that recruited selected populations did not find statin therapy reduced LDL-cholesterol below 2 mmol/L  
- Targets do not take into account the distribution of cholesterol levels in the population prior to commencement of treatment, nor differing responses or adherence to treatment  
- The adoption of targets may encourage indiscriminate use of either high-dose statins or combination lipid therapy

Target lipid levels are appropriate for guiding treatment in secondary prevention and for people with conditions that carry very high risk, such as those with familial hypercholesterolaemia.

Which statin and what dose should be prescribed?

The New Zealand guidelines recommend the following starting doses:

- For people with five-year CVD risk of 15–20% - simvastatin 20 mg (titrate if needed)  
- For people with known CVD or CVD risk >20% - simvastatin 40 mg

At comparable doses, statins are therapeutically equivalent in reducing LDL-cholesterol. The HDL-cholesterol elevating and triglyceride lowering effects are also similar among different statins at equivalent doses. While there are some pharmacokinetic differences between statins, choice can generally be guided by patient tolerability and cost. If high intensity statin treatment is indicated atorvastatin may be better tolerated than simvastatin.

Simvastatin

- Current guidelines, availability criteria and cost mean simvastatin is the most commonly prescribed statin in New Zealand

Atorvastatin

- Consider when more intensive statin therapy is required  
- Can be used in people with impaired renal function as no dose adjustment is required

Pravastatin

- Has the lowest potential for drug interactions as it is not extensively metabolised by cytochrome P450 isoenzymes

Initiating a statin

For primary prevention, the starting dose of a statin ranges from 20 – 40 mg. Table 1 outlines some specific scenarios in which a different dose or type of statin may be more appropriate.

Tolerance to dose and adverse effects

Moderate to high doses of statins are often used to ensure maximum LDL-cholesterol reductions. However, it is important to remember that most of the effect of a statin occurs at less than the maximum dose. For each doubling of the statin dose e.g. from 20 mg to 40 mg simvastatin, there is only a small, additional absolute reduction in cardiovascular events. In addition, higher doses are associated with greater adverse effects.
Table 1: Recommended statin doses

<table>
<thead>
<tr>
<th>Situation</th>
<th>Prescribing solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention of CVD (CVD risk ≥ 15%)</td>
<td>Simvastatin 20 – 40 mg</td>
</tr>
<tr>
<td>Patient with known CVD</td>
<td>Simvastatin 40 mg</td>
</tr>
<tr>
<td>Simvastatin not tolerated</td>
<td>Reduce dose if appropriate OR trial atorvastatin</td>
</tr>
<tr>
<td>Patient with severe renal insufficiency (creatinine clearance &lt; 30 mL/min)</td>
<td>Simvastatin 10 mg (use doses above 10 mg with caution) OR Consider changing to atorvastatin (no dose adjustment required in impaired renal function)</td>
</tr>
<tr>
<td>Risk of drug interactions e.g. amiodarone, verapamil, diltiazem, warfarin or combination with other lipid lowering agents</td>
<td>Consider switching to pravastatin (less potential for interactions, special authority criteria apply)</td>
</tr>
<tr>
<td>Intensive therapy required e.g. familial hypercholesterolemia, very high CVD risk</td>
<td>The maximum dose of simvastatin is 80 mg, with an increased risk of adverse effects and interactions at this level Consider switching to atorvastatin</td>
</tr>
</tbody>
</table>

For those patients who are unable to tolerate higher doses, or if there is the potential for drug interactions, lower doses may be safer and still provide worthwhile benefits.

If a patient experiences adverse effects with one particular statin, the dose can be lowered or the patient can be switched to another statin.22

Adverse effects of statin therapy are usually minor (Table 2). Asymptomatic elevation of transaminase levels can occur. However for some patients, adverse effects are more severe, sometimes leading to discontinuation of treatment.

Statin intolerance

Statin intolerance is defined as “the presence of clinically significant adverse effects that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised”.20

Table 2: Adverse effects related to statin use20

<table>
<thead>
<tr>
<th>Common</th>
<th>Gastrointestinal disturbance (abdominal pain, constipation, flatulence, acid reflux)</th>
<th>Headache</th>
<th>Myelgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less common</td>
<td>Sleep disturbances, including insomnia and nightmares</td>
<td>Memory loss</td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Rare</td>
<td>Serious muscular effects e.g. myopathy, rhabdomyolysis</td>
<td>Peripheral neuropathy</td>
<td>Interstitial lung disease</td>
</tr>
</tbody>
</table>
Statin intolerance is common and is thought to affect approximately 5 to 10% of people taking statins. A recent study found that a regimen of 2.5 mg simvastatin, taken every other day and titrated upward, was tolerated in more than 50% of previously statin intolerant patients, with satisfactory lipid lowering efficacy. Studies have also shown that low dose atorvastatin is tolerated and efficacious in people with previous statin intolerance.

What monitoring is required when prescribing a statin?

The New Zealand guidelines recommend that creatine kinase is checked in symptomatic patients taking statins. No other monitoring is routinely required.

Before initiating a statin:
- Measure baseline liver enzymes (ALT only required). The risk to the liver from statin treatment is negligible. Statins should not be withheld in patients with mildly raised baseline levels. However, do not initiate a statin if the ALT level is three or more times the upper limit of normal.
- A baseline creatine kinase level is not necessary. Awareness of risk and monitoring for symptoms is more important.

Monitoring during statin treatment:
- It is not necessary to routinely monitor liver function during treatment.
- Monitoring of creatine kinase is not required in people who are asymptomatic. If there is unexplained muscle pain, tenderness or weakness, statin treatment should be stopped and creatine kinase levels checked.

For more information on monitoring, see “Liver Function Testing in primary care” (bpacnz, July 2007).

Statin induced myopathy

The risk of myopathy in people using statins is usually related to the dose they are taking, with higher risk associated with higher doses. Elderly people and people taking combination lipid-lowering treatments are also at greater risk.

Other risk factors for statin induced myopathy include:
- Underlying muscle disorders
- Past history of myopathy with any lipid-lowering drug
- Renal or liver impairment
- Multisystem diseases e.g. diabetes
- Untreated hypothyroidism
- Major surgery or trauma
- Co-prescription of drugs that inhibit cytochrome P450 (CYP3A4) e.g. fibrates, niacinamide, calcium channel blockers, ciclosporin, amiodarone, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin
- Vigorous exercise
- Alcohol misuse
- Excessive consumption of grapefruit juice

Management

For muscle pain without an elevated creatine kinase level, reduce the dose of the statin or trial a different statin. If symptoms do not resolve, discontinuation of the statin may be required.

If there are symptoms and the creatine kinase level is elevated between three to ten times normal, reduce the dose of the statin and monitor symptoms and creatine kinase level weekly. If symptoms do not resolve or creatinine kinase levels do not return to normal, discontinuation of the statin may be required.

If there are symptoms and the creatine kinase level is elevated greater than ten times normal, the statin should be discontinued immediately.
When should other lipid lowering agents be considered?

The New Zealand guidelines recommend that simvastatin is the first-line medicine of choice for lipid reduction.1

Evidence from clinical trials strongly supports the use of statins in preference to other lipid lowering agents. Statins reduce the risk of major coronary events, revascularisation rates and stroke, regardless of the initial lipid levels.6 In contrast to statins, the evidence of benefit to patient outcomes for other treatments is variable, ranging from reasonable evidence for niacin to no supportive evidence for ezetimibe (of long-term reduction in morbidity and mortality).9

Combination lipid-lowering treatment should generally be supervised by a specialist due to the increased risk of serious adverse effects such as rhabdomyolysis. Monitoring of liver function and creatine kinase should also be considered.10

For patients who require intensive lipid lowering treatment, combination treatment is considered to be no more effective than high-dose statin monotherapy, for improving clinical outcomes.14

Nicotinic acid

Niacin (also known as niacin or vitamin B3) has a long history of use for treating lipid disorders. It is particularly useful for increasing HDL-cholesterol levels. Niacin can be used alone or in combination with other lipid lowering medicines.

The addition of niacin to statin treatment significantly increases HDL-cholesterol and leads to additional LDL-cholesterol lowering along with lowering triglycerides and lipoprotein (a).17 Niacin increases HDL-cholesterol between 15% to 35%, compared to between 5% to 15% with statin treatment.17

There is some evidence that combination niacin acid and statin treatment has the potential to result in reductions in risk for adverse cardiovascular events. However, large-scale clinical outcome trials are needed to confirm this.17

There has been concern that niacin acid treatment may lead to worsening of glucose control in people with diabetes. Studies have shown that the use of niacin acid may increase fasting glucose levels, possibly requiring adjustment of the patient’s antihyperglycaemic regimen.17

The use of niacin acid is often limited by poor tolerability. At standard doses (1.5 to 4.5 g/day), flushing occurs in 80% of patients and pruritus, paresthesias and nausea each occur in about 20%.16 A combination product (Tredaptive) has now been developed, which combines extended release niacin acid (1000 mg) with a prostaglandin inhibitor laropiprant (20 mg). This combination has been shown to reduce flushing compared to placebo. Tredaptive is not funded and costs approximately $100 per month.

See, "Niacin acid/laropiprant (Tredaptive®) now available in New Zealand" (BPJ 24, Nov 2009).

Bottom line: Niacin acid could be considered in combination with a statin for those who require additional lipid-lowering, when statins alone are not adequately controlling dyslipidaemia. It may also be used as monotherapy for people who are intolerant of statins.

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor that reduces intestinal absorption of both dietary and biliary cholesterol.19 The precise role of ezetimibe relative to other lipid lowering drugs is unclear. A recent trial found that ezetimibe in combination with a statin is less effective than niacin acid combined with a statin.20 In addition the clinical benefits of ezetimibe, alone or in combination with a statin, on cardiovascular morbidity and mortality have not been established.24
Lifestyle interventions for lipid lowering

Lifestyle interventions, including dietary modification, exercise and weight management are an essential component for all people who require lipid lowering,\textsuperscript{22} and should accompany any pharmacological therapy.

<table>
<thead>
<tr>
<th>Dietary advice</th>
<th>Adopt a cardioprotective dietary pattern e.g.</th>
</tr>
</thead>
</table>
| “Small changes in eating habits can make a big difference” | \begin{itemize}  
  \item Consider adding plant sterol or stanol-fortified spreads  
  \item Eat oily fish regularly  
  \item Choose foods which are low in saturated fats and dietary cholesterol  
  \item Choose fruits and/or vegetables at every meal and for most snacks  
  \item Select whole grains, whole grain breads, or high fibre breakfast cereals in place of white bread and low fibre varieties  
\end{itemize}  |

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Complete a minimum of 30 minutes of moderate intensity physical activity e.g. brisk walking on most days of the week. This may be carried out all at once or accumulated in ten minute bouts during the day. People who are already doing this should increase the amount and intensity of their exercise if possible.</th>
</tr>
</thead>
</table>
| “Look for ways to build physical activity into your day” | Consider issuing a green prescription or referring to a local sports trust such as Push Play (http://pushplay.sparc.org.nz)

Lifestyle advice should promote “healthy heart” foods and an active lifestyle. In general the following lifestyle advice can be discussed.\textsuperscript{24}
The recommended dose of ezetimibe is 10 mg per day and there is no additional benefit in using higher doses.10

**Bottom line:** Ezetimibe may be considered in combination with a low dose statin in patients who are not able to tolerate high doses of statins. It may also be considered as an option for monotherapy for people who are intolerant to statins.

**Fibrates**

Fibrates are a class of medicines that are primarily used for the treatment of specific lipid abnormalities, such as hypertriglyceridaemia. Fibrates currently available in New Zealand are bezafibrate and gemfibrozil (not subsidised). Fenofibrate is often used in clinical trials but is currently not registered in New Zealand.

Fibrates are known to reduce coronary risk, especially in people with type 2 diabetes or with features such as high triglycerides, low HDL-cholesterol and excessive weight. This benefit may relate in part to the HDL-cholesterol raising effects of these medicines. However, while fibrates increase the level of HDL-cholesterol in most patients, they are much less effective than statins in lowering LDL-cholesterol and may need to be given in combination with a statin. This combination is effective but has been associated with an increased risk of myopathy.22

Combination treatment with a statin and a fibrate should usually be initiated under specialist advice.10

**Bottom line:** A fibrate e.g. bezafibrate, may be considered in combination with a statin in people with high triglyceride levels or low HDL-cholesterol levels, that have not responded to statin treatment alone, bearing in mind the increased risk of myopathy with combination treatment.

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**Caution over the use of red yeast rice supplements**

Red yeast rice, also known as chinese red rice, is a herbal medicine supplement which is promoted for use as a lipid-lowering agent. The active ingredients occur as a fermentation by-product of cooked rice on which red yeast has been grown. Supplements contain a naturally occurring form of the statin, lovastatin (mevinolin) along with several other mevinic acids and compounds such as sterols, isoflavones and monounsaturated fatty acids.23

The lovastatin compound, mevinolin, is likely to make the greatest contribution to the cholesterol lowering effect of this supplement, however the other ingredients may contribute to an additive effect on cholesterol lowering. Supplements may contain from 0 to 5 mg of “statin-like” substances in each capsule or tablet.23

Because red yeast rice supplements may contain significant amounts of statin-like substances, they can potentially cause the same adverse effects as statins e.g. myopathy and raised liver enzymes. Red yeast rice is also likely to be subject to the same interactions as statins e.g. grapefruit juice and prescription medicines such as amiodarone, verapamil, diltiazem and warfarin. Red yeast rice supplements may act additively with prescription statins and other lipid lowering medicines.23

In the USA, the Food and Drug Administration (FDA) considers red yeast rice supplements that contain statins to be unapproved drugs. The general consensus is that the use of red yeast rice supplements should be avoided.

Red yeast rice supplements do not presently appear to be commonly available in New Zealand, however the product is readily accessible via the internet.
ACKNOWLEDGMENT  Thank you to Professor Norman Sharpe, Medical Director, National Heart Foundation of New Zealand for expert guidance in developing this article.

References


18. Rosenson R. Lipid lowering with drugs other than statins and fibrates. UpToDate, 2010.


22. NHFA, CSANZ. National Heart foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ): Position statement on lipid management. Heart Lung Circ 2006;14:275-91.

Hypertension is a risk factor for many coronary events. However, blood pressure can usually be reduced with appropriate treatment, reducing the risk of stroke, coronary events, heart failure and renal failure.

Many different factors are involved in the pathogenesis of hypertension. These include increased cardiac output, increased peripheral resistance, vasoconstriction and reduced blood flow. The kidneys also play a role in the regulation of blood pressure by controlling sodium and water excretion, and the secretion of renin, which influences vascular tone and electrolyte imbalance. Neurological mechanisms such as the sympathetic nervous system and endocrine systems are also involved in blood pressure regulation. These systems are therefore targets for drug therapy to reduce blood pressure.

Target blood pressures: The optimal systolic blood pressure (SBP) is <140mmHg and the optimal diastolic blood pressure (DBP) is <85mmHg. A target SBP of 130mmHg and DBP of <80mmHg should be considered for patients with established atherosclerotic cardiovascular disease, diabetes or chronic renal failure. Guidance on initiating pharmacological treatment, as recommended by the British National Formulary, is summarised in Panel 1 (p.120).

Regardless of the severity of hypertension, all patients should be offered lifestyle advice to reduce their blood pressure. This includes advice on smoking cessation, weight reduction, exercise, alcohol intake and diet.

Drug classes: Commonly used classes of antihypertensive drugs are the thiazide diuretics (e.g., bendroflumethiazide), beta-blockers (e.g., propranolol, atenolol), angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril), angiotensin II antagonists (e.g., candesartan, losartan), calcium channel blockers (e.g., amlodipine, felodipine) and alpha-blockers (e.g., doxazosin).

Less commonly used drugs include vasodilator and centrally acting antihypertensives and, rarely, guanethidine, which is indicated for the treatment of hypertensive crisis.

Thiazide diuretics

Thiazide diuretics are moderately potent diuretics which lower blood pressure by inhibiting sodium reabsorption at the beginning of the distal convoluted tubule in the kidney, increasing sodium excretion and urine volume. Thiazides also have a direct vasodilatory effect on arterioles, sustaining the antihypertensive effect. They are well absorbed following oral administration, widely distributed and metabolised in the liver.

The diuretic effect of thiazides occurs within one to two hours of administration and continues for 12-24 hours, allowing once-daily administration.

The antihypertensive effect occurs at low thiazide doses and there is no additional benefit to blood pressure from increasing the dose, although additional diuresis can occur at higher doses.

The effects of thiazides on the renal tubule depend on the extent of their excretion, so thiazides may be less effective in patients with renal impairment.

Side effects: Increased urinary excretion with thiazide diuretics can lead to hypokalaemia, hyponatraemia and hypomagnesaemia. Hypercalcaemia can occur due to reduced excretion of calcium. Intolerance with the excretion of uric acid can cause hyperuricaemia, so thiazides should be used with caution in patients with gout. Thiazide diuretics can also cause hyperglycaemia due to impaired glucose tolerance (insulin resistance) leading to an increased risk of non-insulin dependent diabetes mellitus.

Other less common side effects include hyperlipidaemia, causing increases in low density lipoprotein and triglycerides and a reduction in high density lipoprotein (HDL). Up to 25 per cent of men treated...
Panel 1: Target blood pressures for pharmacological treatment

<table>
<thead>
<tr>
<th>Initial blood pressure</th>
<th>Complications*</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic ≥220mmHg or diastolic ≥160mmHg</td>
<td>No</td>
<td>Treat immediately</td>
</tr>
<tr>
<td>Systolic 180–219mmHg or diastolic 110–119mmHg</td>
<td>No</td>
<td>Confirm over one to two weeks and treat if these readings are sustained</td>
</tr>
<tr>
<td>Systolic 160–179mmHg or diastolic 100–109mmHg</td>
<td>Yes</td>
<td>Confirm over three to four weeks and treat if these readings are sustained</td>
</tr>
<tr>
<td>Systolic 160–179mmHg or diastolic 100–109mmHg</td>
<td>No</td>
<td>Advise lifestyle changes, initially reassess weekly and treat if these readings are sustained on repeat measurements over four to 12 weeks</td>
</tr>
<tr>
<td>Systolic 140–159mmHg or diastolic 90–99mmHg</td>
<td>Yes</td>
<td>Confirm within 12 weeks and treat if these readings are sustained</td>
</tr>
<tr>
<td>Systolic 140–159mmHg or diastolic 90–99mmHg</td>
<td>No</td>
<td>Advise lifestyle changes and reassess monthly. Treat persistent mild hypertension if the 10-year cardiovascular disease risk is 20 per cent</td>
</tr>
</tbody>
</table>

* Cardiovascular complications, target organ damage or diabetes

Side effects
- Blockade of beta-2 receptors in the bronchi can precipitate bronchospasm, even when cardioselective beta blockers are used. Other adverse effects of beta-blockers include bradycardia, impairment of myocardial contractility, and cold extremities caused by vasocstriction from blockade of beta-2 receptors in the smooth muscle of peripheral blood vessels.
- Awareness of hypoglycaemia in some patients with insulin-dependent diabetes mellitus can be reduced. This is because beta-blockers block sympathetic nervous system activity which is responsible for the warning signs of hypoglycaemia. Reduced sympathetic outflow may also account for the feelings of malaise experienced by some patients taking beta-blockers.
- Vivid dreams and nightmares can occasionally occur, especially with lipid soluble beta-blockers such as propranolol. Impotence can also occur. The non-selective beta-blockers can cause an increase in serum triglyceride levels and a decrease in HDL cholesterol.

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ACE inhibitors

Angiotensin-converting enzyme (ACE) inhibitors competitively inhibit the formation of angiotensin II from its inactive precursor angiotensin I, which is found in the blood, blood vessels, kidney, heart, adrenal gland and brain. Angiotensin II is a potent vasoconstrictor which also promotes aldosterone release and central and peripheral sympathetic activity. Inhibiting its formation therefore reduces blood pressure. If the renin-angiotensin-aldosterone system is already activated (eg, due to sodium depletion, or diuretic therapy), the antihypertensive effect of ACE inhibitors will be greater.

ACE is also responsible for the breakdown of kinins, including bradykinin, which have a vasodilatory effect. Inhibition of this breakdown effect results in a more pronounced antihypertensive effect.

There are significant pharmacokinetic differences between the ACE inhibitors. Captopril is rapidly absorbed but has a short duration of action, so is useful for initial assessment of how a patient will respond to ACE inhibition. The first dose of an ACE inhibitor should be administered at night because a profound drop in blood pressure may occur; this effect is enhanced in patients with low sodium levels.

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Angiotensin II antagonists

Angiotensin II receptors are found in blood vessels and other targets. They are subclassified into AT1 and AT2 receptors. The AT1 receptor mediates the pharmacological responses of angiotensin II, such as vasoconstriction and aldosterone release, and is therefore the target for drug treatment. The role of the AT2 receptor is less well understood.
Panel 2: New NICE guidelines

The most recent guidance from the National Institute for Health and Clinical Excellence on the treatment of hypertension is as follows:

Step 1: In hypertensive patients aged 55 years or older or in black patients of any age, first choice therapy should be a calcium channel blocker or thiazide-type diuretic. In patients under 55 years, the first choice for initial therapy should be an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin II receptor antagonist if ACE inhibitors are not tolerated).

Step 2: If an additional drug is required, adding an ACE inhibitor to a calcium channel blocker or a diuretic (or vice versa) is recommended.

Step 3: If treatment with these drugs is required then the combination of an ACE inhibitor (or angiotensin II receptor antagonist), calcium channel blocker and thiazide-type diuretic should be used.

Step 4: If a fourth drug is required then a higher dose of thiazide diuretic should be considered, or an alternative diuretic, beta-blocker or alpha blocker.
All drug doses should be uptitrated as per the British National Formulary.

Many tissues contain enzyme pathways which are capable of converting angiotensin I into angiotensin II without using ACE. Therefore there may be advantages in blocking the renin-angiotensin system via the AT₁ receptor antagonist pathway with an angiotensin II receptor antagonist. Angiotensin II receptor antagonists have many properties similar to those of ACE inhibitors, although they do not inhibit the breakdown of kinins. Because of the renal effects, ACE inhibitors and angiotensin II receptor antagonists are contraindicated in bilateral renal artery stenosis and in severe stenosis of the artery supplying a single functioning kidney.

Side effects of ACE inhibitors and angiotensin-II receptor antagonists
Before starting treatment with an ACE inhibitor or angiotensin II receptor antagonist a patient’s renal function and electrolyte levels should be checked. This monitoring should continue during treatment because both classes of drug can occasionally impair renal function.

Both ACE inhibitors and angiotensin II receptor antagonists cause hyperkalaemia due to reduced aldosterone production, so potassium supplements and potassium sparing diuretics should be avoided in these patients.

The difference between the two classes is that a dry cough is a common side effect of ACE inhibitors, exhibited in up to 15 per cent of patients. Angiotensin II receptor antagonists are not associated with the cough because they do not interfere with the inhibition of bradykinin breakdown.

Calcium channel blockers
Calcium channel blockers (less correctly called calcium channel antagonists) reduce calcium ion influx into myocardial cells, the cells within the specialised conducting
system of the heart, and the cells of vascular smooth muscle. The effect of this is to reduce myocardial contractility, depress the formation and propagation of electrical impulses within the heart and promote vasodilator activity, interfering with the constriction of vascular smooth muscle. All of these are calcium ion-dependent processes.

There are three classes of calcium channel blockers: the dihydropyridines (e.g., nifedipine and amloidipine), the phenylalkalamines (verapamil) and the benzothiazepines (diltiazem). The dihydropyridines have distinct peripheral vasodilator properties so are effective antihypertensives while verapamil and diltiazem have cardiac effects and are used to reduce heart rate and prevent angina. All calcium channel blockers are metabolised by the liver.

**Side effects** Facial flushing, headache and swelling of the ankles are often seen, due to the vasodilatory effect of the dihydropyridine calcium channel blockers. Abdominal pain and nausea may also occur.

The gastrointestinal tract is also affected by the influx of calcium ions so calcium channel blockers often cause gastrointestinal disturbances, which may include constipation.

--- **Alpha-blockers**

Alpha-blockers (alpha-1 adrenergic blocking agents) block peripheral alpha-1 adrenoceptors, causing vasodilatory effects due to relaxation of vascular smooth muscle. They are indicated for resistant hypertension.

**Side effects** Alpha-blockers can cause postural hypotension, which is commonly seen after administration of the first dose. Alpha-blockers may be beneficial in older men because they may improve symptoms of prostate enlargement.

--- **Other groups**

Vasodilator antihypertensive drugs (e.g., hydralazine, minoxidil) lower blood pressure by relaxation of vascular smooth muscle. Centrally acting antihypertensives (e.g., clonidine, methyldopa, moxonidine) act on alpha-2 adrenoceptors or related receptors in the brainstem, reducing sympathetic outflow to the heart, blood vessels and kidneys, leading to a reduction in blood pressure.

**Side effects** Vasodilator antihypertensives can cause fluid retention. Liver function tests should be monitored during treatment with hydralazine because it is heptically cleared. Hydralazine has also been associated with systemic lupus erythematosus. Minoxidil has been associated with hypertrichosis (hirsutism) and so may be unsuitable for use in women. Centrally acting agents are not specific or selective enough to avoid central nervous system side effects such as sedation, dry mouth and drowsiness, which commonly occur. Methyldopa has a similar mechanism of action to clonidine but can cause immunological side effects, including pyrexia, hepatitis and haemolytic anaemia.

--- **Choice of therapy**

An update of the National Institute for Health and Clinical Excellence guideline on hypertension was published last year (see Panel 2, p121), together with the British Hypertension Society, as recently published clinical trials provided further evidence for the treatment of hypertension. The main changes to the NICE guideline are that beta-blockers are no longer the recommended first line treatment for any patient group. Beta-blockers were found to be less effective at reducing major cardiovascular events, especially stroke, than other types of antihypertensives. Atenolol was the beta-blocker used in most of the studies. When the trials which used atenolol were excluded from the

--- **Figure 1: Diagrammatic representation of the National Institute for Health and Clinical Excellence guidelines for the treatment of hypertension (adapted from reference 2).**
review, the evidence base for the use of beta-blockers in the treatment of hypertension was much weaker than for the other drug classes. It was concluded that, in the absence of other compelling indications for a beta-blocker (e.g., angina), they should not be recommended as an initial treatment for hypertension.

Beta-blockers were also found to be less effective than ACE inhibitors or dihydropyridine calcium channel blockers in reducing the risk of diabetes, especially in patients already taking a thiazide diuretic. If a patient taking beta-blockers requires a second drug, an ACE inhibitor or calcium channel blocker should be added, rather than a thiazide.

### Special considerations

**Pregnancy**
Centrally acting agents have a poor CNS profile. However, methyldopa is used in pregnancy, due to its long-term safety data and beta-blockers are used in the third trimester. Intravenous labetolol is reserved for use in pregnancy in a hypertensive crisis. A controlled release formulation of nifedipine has also been used in pregnancy but is unlicensed.

**Ethnic group**
Thiazide diuretics and the dihydropyridine calcium channel blockers are more effective than beta-blockers in Afro-Caribbean patients. ACE inhibitors and angiotensin II antagonists have been shown to increase the risk of stroke in this group of patients and are therefore not recommended as first line therapy.

**Elderly**
The new NICE guidance states that thiazide diuretics or dihydropyridine calcium channel blockers should be the first line therapy in elderly people. However, attention should be paid to renal function during treatment with a thiazide because the elderly are more at risk of renal impairment. Patients over 80 years old should be offered the same treatment as patients aged over 55 years.

**Diabetes**
Patients with diabetes may require a combination of antihypertensive drugs to achieve their optimal target blood pressure. ACE inhibitors are the initial treatment of choice because they can delay the progression of microalbuminuria to nephropathy. Patients with diabetic nephropathy should be treated with an ACE inhibitor or an angiotensin II receptor antagonist to minimise the risk of further renal deterioration, even if their blood pressure is normal.

**Renal disease**
ACE inhibitors can reduce or abolish glomerular filtration and can cause severe and progressive renal failure. They are therefore contraindicated in patients with bilateral renal artery stenosis. However, ACE inhibitors are unlikely to have an adverse effect on overall renal function in patients with unilateral renal artery stenosis. A dihydropyridine calcium channel blocker can be added if further blood pressure lowering is required, but thiazide diuretics may be ineffective.

**Systolic hypertension**
Isolated systolic hypertension (ISH) is defined as an SBP of greater than 160 mmHg with a DBP less than 90 mmHg. Patients with ISH should be offered the same treatment as patients with raised SBP and raised DBP because ISH carries the same risk of complications.

The dihydropyridine calcium channel blockers have been used in the treatment of isolated systolic hypertension in the elderly, especially where a thiazide diuretic is contraindicated.

**Accelerated hypertension**
Accelerated or very severe hypertension, defined as a DBP of greater than 140 mmHg, requires urgent medical attention. Beta-blockers such as atenolol or labetolol or the dihydropyridine calcium channel blockers are indicated for this condition. DBP should be reduced to 100-110 mmHg during the first 24 hours. Blood pressure should be reduced further over the next two to three days using a combination of diuretics, vasodilators and ACE inhibitors, if required.

If intravenous treatment is required then sodium nitroprusside or glyceryl trinitrate is recommended.

### The cardiologist

As a member of the multidisciplinary team, the pharmacist has an important role to play in the treatment of hypertension.

To aid concordance or ensure compliance with a medication regimen the pharmacist can give information about the benefits and side effects of drugs so that patients can make an informed decision about their treatment. This information should include why the medicine is needed and the risks of not taking it. Practical points, such as ensuring that the medicine is prescribed once daily if possible, may also improve adherence.

Other medicines that a patient is taking should also be reviewed. Concurrent non-steroidal anti-inflammatory drugs, the oral contraceptives pill, gliclazide, and sympathomimetics can all increase blood pressure. These medicines some of which can be bought over the counter, should be avoided in patients with high blood pressure.

It is important to remember that a patient may have additional co-morbidities. The pharmacist can advise and review coexisting disease states to ensure the most appropriate therapy choice is made.

To help reduce costs, pharmacists can also ensure that non-proprietary drugs are prescribed when appropriate.

### References


### Further reading


The use of ANTITHROMBOTIC MEDICINES in general practice

A CONSENSUS STATEMENT
In July 2011, a consensus forum was held in Wellington to discuss the use of antithrombotic medicines in general practice. This was attended by representatives from primary care, secondary care, bpaoc, PHARMAC and the New Zealand Guidelines Group.

The conditions discussed were:

- Primary and secondary prevention of cardiovascular disease (including ischaemic stroke)
- Treatment after haemorrhagic stroke
- Prevention from thromboembolic events in patients with prosthetic heart valves or with haemodynamically significant valvular disease
- Venous thromboembolism (VTE) prophylaxis (post-surgery and for long haul travel) and treatment

The antithrombotic medicines associated with these conditions are: aspirin, clopidogrel, warfarin, dipyridamole and dabigatran (all fully funded with no restrictions on prescribing), enoxaparin and rivaroxaban (funded under Special Authority restriction).

This consensus statement represents the opinions of the experts involved, and although based on trial evidence, also reflects clinical practice. The advice given may therefore differ from some current guidelines.

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**Forum Participants:**

- Professor Carl Burgess – Wellington School of Medicine, University of Otago, Chair Pharmacology and Therapeutics Advisory Committee, PHARMAC
- Steve Caldwell – Chief Executive, New Zealand Guidelines Group
- Associate Professor John Carter – Haematologist, Capital & Coast DHB
- Dr John Fink – Medical Director of Stroke Foundation, Neurologist Canterbury DHB
- Rebecca Harris – Editor, Best Practice Journal, bpaoc
- Dr Sisira Jayathilassa – General Physician and Geriatrician, Hutt Valley DHB, Pharmacology and Therapeutics Advisory Committee, PHARMAC
- Dr Nigel Lever – Cardiologist, Auckland DHB
- Associate Professor Stewart Mann – Head of Department, Wellington School of Medicine, University of Otago, Cardiologist, Capital & Coast DHB
- Dr Peter Moodie – General Practitioner, Medical Director PHARMAC
- Mr Allan Panting – Orthopaedic Surgeon, Nelson Marlborough DHB
- Dr Ralph Stewart – Cardiologist, Auckland DHB
- Professor Murray Tilleyard – Chief Executive, bpaoc, Professor of General Practice, Dunedin School of Medicine, University of Otago
- Dr Jim Vause – General Practitioner, Chair New Zealand Guidelines Group Board
- Dr Sharyn Willis – General Practitioner, Clinical Programme Developer, bpaoc
- Dr Howard Wilson – General Practitioner, Deputy Chair Pharmacology and Therapeutics Advisory Committee, PHARMAC
- Stephen Woodruffe – Therapeutic Group Manager, PHARMAC
- Dave Woods – Pharmacist, Clinical Programme Developer, bpaoc
- Dr Sue Anne Yee - Therapeutic Group Manager, PHARMAC
Primary prevention of cardiovascular disease including stroke—people without atrial fibrillation

Consensus

The role of aspirin for primary prevention of cardiovascular disease (CVD), including stroke, is controversial. Current evidence does not justify the routine use of low-dose aspirin, for the primary prevention of CVD in apparently healthy individuals, because of the potential risk of serious bleeds and the lack of beneficial effect on mortality. However, patients at high CVD risk (defined in the New Zealand Cardiovascular Guidelines as a cardiovascular risk of more than 15%) may benefit from aspirin.6

Primary prevention of cardiovascular disease including stroke—people without atrial fibrillation:

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>100 mg daily</td>
<td>Lifelong</td>
<td>Cardiovascular risk &gt; 15% only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Individual assessment required</td>
</tr>
</tbody>
</table>

Evidence

Current evidence does not recommend the routine use of aspirin for the primary prevention of cardiovascular disease. Most guidelines continue to recommend aspirin for primary prevention in patients who are at increased CVD risk (e.g. >15%), however, individual assessment is required as recent evidence does not support routine use of aspirin in patients with risk factors such as diabetes and hypertension.

The Antithrombotic Trialists' (ATT) Collaboration was a key meta-analysis of primary prevention studies and showed a 0.06% reduction only in absolute risk with the use of aspirin. There was no significant difference in cardiovascular mortality rate and the authors concluded that the benefit of using aspirin for primary prevention in low risk populations was very small. This and other similar evidence changed the way clinicians viewed the use of aspirin for primary prevention.5,9

This view has been reinforced in recent publications. Calculations from the ATT data have shown that the number needed to be treated (NNT) with aspirin for one year to prevent one cardiovascular event was 1666.8 Updated meta-analyses have now included a total of nine primary prevention trials. Similar conclusions have been reached in these studies:

- Although aspirin reduced the risk of total cardiovascular events and non-fatal myocardial infarction, there was no significant reduction in the incidence of stroke, total coronary heart disease, cardiovascular mortality and all cause mortality.8
- If 1,000 people were treated with aspirin for five years, 2.9 major cardiovascular events would be prevented but aspirin would cause 2.8 major bleeds.7

The evidence of benefit of aspirin for primary prevention of stroke in people who have diabetes is also inconclusive, with several trials showing no benefit from the use of aspirin in these people.6,9,10

There is evidence that statins should be used as first-line treatment for primary prevention in people who have moderate to high CVD risk.11 The addition of aspirin for these people appears to give no further benefit because the increased risk of bleeding offsets any improvement in cardiac morbidity.5
Consensus

Anticoagulation is recommended for the primary prevention of stroke in people with non-valvular atrial fibrillation (AF) who are at moderate or high risk of stroke. Both stroke and bleeding risk should be considered when making the decision to anticoagulate, using assessment tools such as CHADS₂ and HAS-BLED (see “Stroke risk assessment tools” over page). Co-morbidities, monitoring requirements and patient preference should also be considered when determining whether anticoagulation is suitable for a patient.

Once the decision to anticoagulate has been made, the next decision is which oral anticoagulant to use, i.e. warfarin or dabigatran.

Treatment of other modifiable risk factors such as hypertension, dyslipidaemia and smoking should also be initiated for all patients with AF.

For further information on choosing between dabigatran and warfarin, see “The use of dabigatran in general practice”, BJP 38 (Sep, 2011).

Assessment of stroke risk and management using CHADS₂ and CHA₂DS₂-VASc

<table>
<thead>
<tr>
<th>CHADS₂ score ≥2</th>
<th>Medicine</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anticoagulant - warfarin or dabigatran</td>
<td>Warfarin: dose to attain INR 2–3</td>
<td>Lifelong</td>
<td>Creatinine clearance must be calculated if dabigatran considered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dabigatran: Aged under 80 years – 150 mg, twice daily, if creatinine clearance &gt;30 mL/min</td>
<td></td>
<td>Use dabigatran with caution if &lt;60kg or creatinine clearance 30-50 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aged over 80 years* – 110 mg, twice daily, if creatinine clearance &gt;30 mL/min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| CHADS₂ score <2 | Calculate CHA₂DS₂-VASc score |

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc score ≥ 2</th>
<th>Anticoagulant - warfarin or dabigatran</th>
<th>As above</th>
<th>Lifelong</th>
<th>Creatinine clearance must be calculated if dabigatran considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA₂DS₂-VASc score 1</td>
<td>Anticoagulant or aspirin (with preference for anticoagulation)</td>
<td></td>
<td></td>
<td>Use dabigatran with caution if &lt;60kg or creatinine clearance 30-50 mL/min</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score 0</td>
<td>No treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* There is some suggestion that a lower dose of dabigatran is appropriate for patients aged > 75 years, but at this stage no changes have been made to dosing recommendations in the medicine datasheet.
**Stroke risk assessment tools**

The risk of stroke in people with AF can be evaluated using a risk stratification tool such as CHADS\textsubscript{2} or the updated version, CHA\textsubscript{2}DS\textsubscript{2}-VASc, preferred by many clinicians. The updated tool puts greater emphasis on increasing age (≥ 75 years) and also incorporates additional risk factors for stroke - female gender, age group 65 – 75 years and a history of vascular disease, e.g. myocardial infarction, peripheral arterial disease.\textsuperscript{11} Scores for each tool are calculated as follows:

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2}</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age 75 years or older</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Previous Stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, peripheral vascular disease)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–75 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female gender)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

N.B. Maximum score is 9 as age is either allocated one or two points

If the CHADS\textsubscript{2} score is ≥ 2, the patient should be anticoagulated. If a patient has a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of less than 2, CHA\textsubscript{2}DS\textsubscript{2}-VASc can be used to further evaluate risk and to guide treatment choice.

A patient with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 0 is truly low risk and does not need anticoagulation and may not even need aspirin. Anticoagulation is recommended for people with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score ≥ 1.

Aspirin may be considered as an option for patients with AF who are unsuitable for anticoagulation, e.g. patients with severe liver disease, recent history of gastrointestinal bleeding.

**HAS-BLED**

This tool can be used to calculate the risk of bleeding when considering anticoagulant use. A score of ≥ 3 indicates a patient who may be at high risk of bleeding complications.\textsuperscript{12}

<table>
<thead>
<tr>
<th>HAS-BLED Bleeding Risk Score\textsuperscript{13}</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (systolic blood pressure &gt; 160 mm Hg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal and liver function</td>
<td>1 point each</td>
</tr>
<tr>
<td>Stroke (past history)</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding (previous history of bleeding or predisposition to bleeding)</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs (unstable, high or insufficient time within therapeutic range)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (&gt; 65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (including concomitant use of aspirin, other antiplatelet agents and NSAIDs)</td>
<td>1 point each</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

\textsuperscript{12} For further information about HAS-BLED, see “The warfarin dilemma”, BPJ 31 (Oct, 2010).
Secondary prevention of stroke* – people without atrial fibrillation

*For people where the initial event was non-haemorrhagic

**Consensus**

In a patient with a history of transient ischaemic attack (TIA) or stroke who does not have AF, antiplatelet treatment for secondary prevention should be initiated (provided there are no contraindications). Although aspirin has been shown to be effective in the secondary prevention of non-embolic stroke, there is evidence that treatment with clopidogrel is slightly more effective than aspirin. The combination of aspirin and modified release dipyridamole is slightly more effective than aspirin alone and provides similar benefits to treatment with clopidogrel. However, clopidogrel monotherapy is simpler and usually better tolerated by patients.

Treatment of other modifiable risk factors such as hypertension, dyslipidaemia and smoking cessation should also be initiated for all patients.

The management of TIA and a minor stroke are largely the same and both should be regarded as a medical emergency. The highest risk of a stroke is within the first week (particularly in the first 48 hours) after a TIA. If a patient presents with signs and symptoms of a stroke which are still present after one hour, then this event should be regarded as a stroke as the majority of “true” TIA’s resolve within one hour. The main difference in management is that all patients with stroke should be referred immediately to hospital for investigation prior to commencing antithrombotic treatment due to the possibility of intracerebral haemorrhage (ICH). Antiplatelet treatment should be initiated immediately after resolution of symptoms for patients with TIA to avoid delay prior to assessment as the risk of ICH is extremely low.

For further information see “Transient ischaemic attack” (Page 30)

### Secondary prevention of stroke – people without atrial fibrillation

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Loading dose of 300 mg followed by 75 mg daily</td>
<td>Lifelong</td>
<td>Although evidence and consensus opinion favours clopidogrel monotherapy first line, combination treatment with aspirin and dipyridamole or aspirin monotherapy remain alternative first-line choices</td>
</tr>
<tr>
<td>Second-line:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin + dipyridamole</td>
<td>Aspirin 100 mg and dipyridamole 150 mg* twice daily</td>
<td>Lifelong</td>
<td>Consider for patients who cannot tolerate clopidogrel</td>
</tr>
<tr>
<td>Third-line:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>Aspirin 100 mg</td>
<td>Lifelong</td>
<td>Consider for patients who cannot tolerate clopidogrel or dipyridamole</td>
</tr>
</tbody>
</table>

*The funded strength of dipyridamole in New Zealand is the 150 mg long-acting tablet, however, in the majority of clinical trials the dose used was 200 mg extended release capsules, twice daily.
Evidence

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial found that clopidogrel significantly reduced the risk of the combined outcomes of ischaemic stroke, myocardial infarction or death in people with atherosclerotic cardiovascular disease. There was an approximately 9% reduction in relative risk of these events (N.B. figures for absolute risk were not reported). However, among the subgroup of people who had previous stroke, there was no significant difference in outcomes between aspirin or clopidogrel monotherapy (p value 0.26). The combination of aspirin and clopidogrel has not been shown to provide any greater benefit in preventing stroke and dual antplatelet treatment significantly increases the risk of bleeding. This combination is, however, effective in acute coronary syndromes.

The Prevention Regimen for Effectively Avoiding Second Strokes (PROGRESS) trial looked at the combination of modified-release dipyridamole with aspirin compared to clopidogrel. The results showed similar risks and benefits with each antplatelet regimen.

Evidence from the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) found treatment with aspirin and dipyridamole, compared with aspirin monotherapy, resulted in a reduction in absolute risk of 1.0% per year.

Secondary prevention of stroke* – people with atrial fibrillation

*For people where the initial event was non-haemorrhagic

Consensus

Oral anticoagulants have been shown in a number of randomised controlled trials to be effective in reducing stroke in people with AF. Individualised bleeding risk should be considered prior to anticoagulation.

In addition to oral anticoagulation treatment, a patient with a TIA or stroke, who has AF, should also be started on a statin and an antihypertensive (usually an ACE inhibitor) unless there are contraindications. Aspirin should only be used in the immediate post-stroke period before the establishment of effective anticoagulation or in patients who are unable to tolerate ongoing oral anticoagulation.

Secondary prevention of stroke – people with atrial fibrillation

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant – warfarin or dabigatran</td>
<td>Warfarin: dose to attain INR 2–3</td>
<td>Lifelong</td>
<td>Stop aspirin and clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Dabigatran:</td>
<td></td>
<td>Creatinine clearance must be calculated if dabigatran considered</td>
</tr>
<tr>
<td></td>
<td>Aged under 80 years – 150 mg, twice daily, if creatinine clearance &gt; 30 mL/min</td>
<td></td>
<td>Use dabigatran with caution if weight &lt; 60kg or creatinine clearance 30–50 mL/min</td>
</tr>
</tbody>
</table>
Evidence
There is evidence that oral anticoagulation with warfarin reduces stroke risk more effectively than aspirin in people with AF.\textsuperscript{22} If oral anticoagulation is contraindicated, not indicated or is declined by the patient, aspirin should be prescribed, as it reduces the risk of stroke compared to placebo.


In the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), which included people with AF aged over 75 years, the risk of a primary endpoint (stroke, intracranial haemorrhage or arterial embolism) was significantly lower with warfarin (1.8%) compared with aspirin (3.8%), and there was no evidence that warfarin caused more bleeding complications than aspirin.\textsuperscript{24}

Secondary prevention after haemorrhagic stroke

Consensus
Patients with a suspected haemorrhagic stroke should be referred immediately to hospital (do not give aspirin) and decisions on treatment will be made in hospital after appropriate imaging has been completed.

In a general practice setting, decisions on treatment for patients who have a history of intracranial haemorrhage (ICH) may be difficult. Treatment choices are not straightforward, e.g., in a patient who has a history of ICH, who subsequently develops AF. The decision regarding medicines in these patients will depend on the individual patient circumstances, the site of the ICH, the underlying pathology, and co-morbidities. The care of these patients requires discussion with, and usually referral to, secondary care. Accurate documentation of the history of ICH must be available to guide treatment decisions.

Patients who do not have a documented history of ICH, but who may recall a problem or have information in their patient notes that may raise suspicion of a past ICH need to have this history clarified – this role will generally fall to the primary care team.

Secondary prevention of acute coronary syndrome*\textsuperscript{18}

Consensus
Early combination treatment with dual antiplatelet medicines is highly effective in patients with acute coronary syndromes. Treatment choice depends on the type and outcome of the event, the time since it occurred and the stability of the patient.

Evidence
In patients with acute coronary syndrome without ST-segment elevation, combined treatment with clopidogrel and aspirin gave a 20% reduction in relative risk of MI, stroke and cardiovascular death.\textsuperscript{25}

Clopidogrel and aspirin should be used in combination for patients who have had angioplasty, insertion of a bare metal or a drug-eluting stent. The duration of treatment is usually 12 months except if a bare metal stent is used, where treatment is required for a minimum of six months, as outlined in the table over the page.

If aspirin is not tolerated, clopidogrel can be used as monotherapy.\textsuperscript{26} Allergy or intolerance to both aspirin and clopidogrel is rarely seen, however, aspirin desensitisation therapy is available in some clinics around the country.
## Secondary prevention of acute coronary syndrome

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Medicine</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>After acute event: no stent</td>
<td>Aspirin and clopidogrel</td>
<td>Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily</td>
<td>12 months</td>
<td>After 12 months stop clopidogrel</td>
</tr>
<tr>
<td>After acute event: bare metal stent</td>
<td>Aspirin and clopidogrel</td>
<td>Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily</td>
<td>12 months (do not stop treatment in first 6 months)</td>
<td>After 12 months stop clopidogrel</td>
</tr>
<tr>
<td>After acute event: drug eluting stent</td>
<td>Aspirin and clopidogrel</td>
<td>Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily</td>
<td>12 months (do not stop treatment in this period)</td>
<td>After 12 months stop clopidogrel</td>
</tr>
<tr>
<td>After acute cardiac event patients with indications for anticoagulation, e.g. AF</td>
<td>Aspirin and warfarin</td>
<td>Aspirin 100 mg daily and warfarin – dose to attain INR 2-3</td>
<td>Lifelong anticoagulation</td>
<td>Warfarin is the preferred anticoagulant for these patients *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin for 6-12 months or lifelong if high CVD risk and lower bleeding risk</td>
<td></td>
<td>Clopidogrel may also be given for 6-12 weeks although there is an increased risk of bleeding</td>
</tr>
<tr>
<td>After acute cardiac event patients with a mechanical heart valve</td>
<td>Warfarin and aspirin</td>
<td>Warfarin – dose to attain INR 2.5-3.0 for aortic valve prosthesis, 3.0-3.5 for mitral valve prosthesis</td>
<td>Lifelong anticoagulation</td>
<td>Warfarin is the preferred anticoagulant for these patients †</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin 100 mg daily and in selected patients, clopidogrel 300 mg loading dose followed by 75 mg daily</td>
<td></td>
<td>The risk of bleeding is substantially increased in patients taking warfarin, aspirin and clopidogrel and this combination should be used in consultation with a cardiologist</td>
</tr>
<tr>
<td>High risk patients: multiple events in more than one vascular territory, e.g. MI and stroke</td>
<td>Aspirin and clopidogrel</td>
<td>Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily</td>
<td>Lifelong</td>
<td>Treatment for these high risk patients often requires secondary care input</td>
</tr>
<tr>
<td>Stable patients: no acute cardiac event in past 12 months †</td>
<td>Aspirin</td>
<td>If the event was cardiac: aspirin 100 mg daily</td>
<td>Lifelong</td>
<td></td>
</tr>
</tbody>
</table>

N.B. Table excludes the immediate use of 300 mg aspirin used in the acute treatment of ACS

* Warfarin is preferred to dabigatran in these patients because:
  - There is a possible increase in the risk of MI with dabigatran use
  - Dabigatran is not currently indicated for use in patients with prosthetic valves or haemodynamically significant valvular disease

† In all stable patients >12 months post ACS, the combination of aspirin and anticoagulation is not usually required, but may be appropriate in selected high risk patients. Consultation with a cardiologist is recommended.
Prevention of thromboembolic events: post elective surgery

Consensus
Prophylaxis for the prevention of thromboembolic events post elective surgery is the responsibility of the surgeon, however, General Practitioners should be aware of the requirements and of the length of the post-operative course so that medicines are not continued (or discontinued) in error.

Prevention of thromboembolic events: post elective surgery

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran*</td>
<td>220 mg (as 2 x 110 mg), once daily, if creatinine clearance &gt; 50 mL/min 150 mg (as 2 x 75 mg), once daily, if creatinine clearance between 30-50 mL/min</td>
<td>Hip replacement: up to 35 days post-op Knee replacement: 10 days post-op</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg sub cut, once daily</td>
<td>7-10 days</td>
<td>Dose reduced to 20 mg once daily in severe renal impairment (Creatinine clearance &lt;30 mL/min)</td>
</tr>
<tr>
<td>Rivaroxaban*</td>
<td>10 mg tablet, once daily</td>
<td>Hip replacement: up to 5 weeks post-op Knee replacement: up to 2 weeks post-op</td>
<td>Special authority criteria apply Contraindicated in hepatic disease</td>
</tr>
</tbody>
</table>

*indicated for use after elective orthopaedic surgery

Prevention of thromboembolic events: prosthetic valves or haemodynamically significant valvular disease

Consensus
Warfarin is currently the only anticoagulant recommended for people with prosthetic heart valves or haemodynamically significant valvular disease (usually mitral valve stenosis). Dabigatran is currently not recommended for this indication. Anticoagulation treatment for these people will usually be initiated in secondary care. Aspirin is generally not effective for the prevention of thromboembolic events in these people although the risk of events is higher with no treatment.

Some patients may require combination treatment with warfarin and aspirin but guidelines differ in their recommendations regarding this.

Evidence
Patients with haemodynamically significant valvular heart disease or prosthetic valves were excluded from the RE-LY trial. Some patients with these conditions who are currently on warfarin must not be switched to dabigatran.
N.B. Patients who have valvular disease (excluding patients with severe mitral stenosis or prosthetic valves) but are in sinus rhythm do not usually require anticoagulation.

Prevention of thromboembolic events: prosthetic valves or haemodynamically significant valvular disease

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Warfarin – to attain INR of 2.5-3.5*</td>
<td>Lifelong</td>
<td>Dabigatran not indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If high risk, aspirin may also be added</td>
</tr>
</tbody>
</table>

*The recommended INR range may vary depending on the type and location of the prosthetic valve

Prevention of thromboembolic events from long haul travel

Consensus

There is a risk of venous thromboembolism (VTE) during travel, particularly with longer flights (> four hours).

People at high risk of VTE include those with pro-thrombotic states (e.g. deficiencies of antithrombin III, protein C, protein S), a history of previous VTE, recent surgery or a significant medical illness. In these people consideration should be given to the use of:

- Correctly fitted compression stockings which reduce the incidence of VTE by approximately 18 times in high risk people
- Prophylactic low molecular weight heparin (one injection on the day of travel). There is evidence to support the use of enoxaparin, although this medicine is not funded for this indication.

There is currently no evidence to support the use of dabigatran or rivaroxaban for VTE prophylaxis during travel. Aspirin is not adequate for prophylaxis and the risks of adverse effects (e.g. bleeding) outweigh the benefits of treatment. Routine use of prophylactic medicines for long haul travel is not necessary for people with no risk factors for VTE.

The following advice should be given to all people who are travelling long distances:

- Sitting in an aisle seat provides more opportunity for movement. Also consider exercising leg muscles while seated and walking whenever possible.
- Ensure adequate hydration and avoid alcohol, particularly if combined with sedative medicines.

Treatment of VTE

Treatment for VTE is increasingly initiated in the community with the availability of low molecular weight heparin (LMWH). LMWH is used until an INR level of 2–3 is attained for two consecutive days. Warfarin is used simultaneously, with the duration of treatment varying with individual circumstances.

Dabigatran is not currently indicated for use in the treatment of VTE.
Dabigatran etexilate

Dabigatran etexilate, a novel oral anticoagulant, has recently been licensed in NZ. It is a prodrug, which is metabolised to the active agent dabigatran. This bulletin focuses on its pharmacokinetics, interactions, dosing, and compares it with warfarin.

Indications

Dabigatran etexilate is currently licensed and fully funded in NZ for thrombophrophylaxis in non-valvular atrial fibrillation (AF) and post-major orthopaedic surgery. Multi-centre randomised controlled studies (RCT) support these indications. For example, the RE-LY trial (N=18000) compared dabigatran etexilate 150 mg twice daily with warfarin for AF. Similar embolic rates were seen with both drugs (1.11 vs. 1.69%/yr, respectively, P = 0.34). The INR in the warfarin group was therapeutic for approximately 64% of the study period. Dabigatran etexilate is not yet licensed for treatment of venous thromboembolism in NZ, although a RCT (RE-COVER-I, 2005) reported that it is comparable to warfarin for this indication at 6 months of treatment and follow-up.

Mechanism of action

Dabigatran is a reversible direct thrombin inhibitor. Thrombin (factor IIa) is a plasma enzyme that catalyses the conversion of fibrinogen to fibrin, which is central to coagulation.

Pharmacokinetics

Dabigatran is a highly polar compound and is thus not absorbed via the gastrointestinal tract. The prodrug, dabigatran etexilate, was developed to overcome this issue. However, dabigatran etexilate still only has an oral availability of 7%. This is because the prodrug is a substrate of P-glycoprotein (P-gp), an efflux transporter localised on the luminal membrane of intestinal epithelial cells. Following absorption, the prodrug is rapidly converted to dabigatran by esterases, with peak dabigatran concentrations within 2 hours after oral administration in healthy subjects. Dabigatran is then extensively reabsorbed with an average of 80% of a dose excreted unchanged in urine (fu) of 0.8. With normal renal function, dabigatran has a half-life of 12 hours. Of note, dabigatran itself is not considered a P-gp substrate.

Interactions

Pharmacokinetic: As dabigatran etexilate is a P-gp substrate, it is vulnerable to the effects of drugs that are inhibitors (e.g. amiodarone, carvedilol, verapamil) or inducers (e.g. rifampicin) of this transporter (see the Pink Book for lists of P-gp-related drugs). As P-gp is involved in the removal of dabigatran etexilate from the intestinal epithelial cells, the oral availability of dabigatran etexilate increases with a P-gp inhibitor and decreases with a P-gp inducer. For example, peak dabigatran concentrations increased by 60% with chronic verapamil use. Pharmacodynamic: Co-administration of dabigatran etexilate with other antithrombotic agents increases the risk of bleeding.

Dosing

in patients with normal renal function (i.e. 'standard dosing'):

- Non-valvular AF: 150 mg twice daily.
- Post-major orthopaedic surgery: 110 mg within hours post-surgery, followed by 220 mg daily from the next day onwards. In patients with impaired renal function, the first dose is the same as that for 'standard dosing', but subsequent doses should be adjusted for renal impairment:

1. Estimate the glomerular filtration rate (GFR, mL/min) using either the Cockcroft & Gault formula, or the MDRD value supplied by the lab (accuracy is improved by correcting for the patient’s body surface area).
2. Incorporate the GFR and fu of 0.8 into the 'fu formula' (found in Prescribing in Renal Impairment, Pink Book) to calculate the maintenance dose-rate:

\[
\text{Dose-rate}_{\text{patient}} = \left(1 - fu\right) \times \left(\frac{\text{GFR}}{100}\right) \times \text{Dose-rate}_{\text{standard}}
\]

These guidelines are in contradistinction to the drug company’s advice, which downplays the influence of GFR on dosing. In patients with GFR < 30 mL/min (excluded from the RCTs), use of dabigatran etexilate is not recommended. Dosing should also take into account relevant drug interactions e.g. in the presence of P-gp inhibitors, dose-rate reduction should be considered. More specific advice may be sought from the CDHB Drug Information Service (extension 69000).

Switching to and from dabigatran etexilate

Parenteral anticoagulation to dabigatran etexilate: The first dose is given within 2 hours before the next dose of the parenteral anticoagulant would have been due (had it not been ceased). Warfarin to dabigatran etexilate: Start dabigatran etexilate when INR < 2.0 following warfarin cessation. Dabigatran etexilate to warfarin: If GFR > 50 mL/min, start warfarin 3 days before ceasing dabigatran etexilate; if 31-50 mL/min, start 2 days before; if 15-30 mL/min, start 1 day before.

Adverse effects

When used for AF (150 mg twice daily), the major bleeding event rate with dabigatran etexilate was found to be similar to warfarin (3.1 vs. 3.4%/yr, P = 0.31). Dyspnea is more common with dabigatran etexilate than warfarin (11.3% vs. 5.8%, P < 0.001). This is likely to be due to its tartaric acid content that provides an acidic microenvironment to enhance dissolution and absorption.

Dabigatran etexilate versus warfarin

Warfarin has occupied a unique position in therapeutics as the preeminent oral anticoagulant for decades. It is contrasted with dabigatran etexilate in the table below. The main purported advantage of dabigatran etexilate is the apparent reduced need for lab coagulation monitoring. There may be situations where this monitoring is desirable, although there is a lack of evidence with this. The high fu of dabigatran means that renal function should be monitored, especially in those at high risk of, or already with, significant renal impairment. Further, its poor oral availability makes it vulnerable to potentially large increments in drug exposure e.g. with P-gp inhibitors. Finally, the uncertainty and paucity of data regarding strategies to reverse its anticoagulation is also a major concern.

Advantages and disadvantages of dabigatran etexilate versus warfarin

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Lab coagulation monitoring not routine</td>
<td>- Minimal experience with lab coagulation monitoring</td>
</tr>
<tr>
<td>- No CYP enzyme interactions</td>
<td>- P-gp interactions</td>
</tr>
<tr>
<td>- Rapid onset</td>
<td>- ? safer with hepatic impairment</td>
</tr>
<tr>
<td>- Less mature safety database</td>
<td>- Efficacy of reversal strategies unclear</td>
</tr>
</tbody>
</table>

The information contained within this bulletin is provided on the understanding that although it may be used to assist in your final clinical decision, the Clinical Pharmacology Department at Christchurch Hospital does not accept any responsibility for such decisions.
Current and future options for the management of heart failure

In this science article, John Sherwood, Mark Ashton, Claire Newton and Sumita Biles examine the pathophysiology of heart failure, current treatments available, and research and development into new treatments.

Chronic heart failure is an increasing problem worldwide. There are around 900,000 people with heart failure in the UK, and almost as many with damaged hearts but without any symptoms of heart failure. Heart failure is a complex syndrome of symptoms and signs. If left untreated, it has a poor prognosis, but mortality and morbidity can be greatly improved by early, targeted treatment.

The most common causes of chronic heart failure in the UK are coronary heart disease and hypertension, with many patients having had an myocardial infarction in the past. Associated risk factors, such as aging population, increases in the rates of diabetes mellitus and hyperlipidaemia, and smoking, have also contributed to the increasing prevalence of heart failure in the UK.

Pathophysiology

The heart acts as a pump to support physiological circulation. Any disruption to the normal functioning of the heart can lead to heart failure and decreased cardiac output. This, in turn, decreases the perfusion of metabolising tissues and reduces the function of many organ systems. The most common symptoms of heart failure are breathlessness, fatigue at rest or on minimal exertion and fluid retention (eg, ankle swelling). Diagnosis of heart failure is based on history, examination and investigations, such as echocardiography.

Patients with heart failure are almost equally divided into those with left ventricular systolic dysfunction (LVSD) and those with heart failure but with preserved ejection fraction. LVSD is the fraction of blood ejected by the left ventricle during the contraction phase of the cardiac cycle (systole). Although the general approach to care is the same whether systolic function is reduced or not, most of the current evidence on drug treatment is for heart failure due to LVSD. The heart works on two main compensatory mechanisms to maintain adequate tissue perfusion. These are the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAS). Activation of the SNS causes vasoconstriction. LVSD increases blood pressure, heart rate and cardiac afterload. The SNS also causes an increase in renal vascular resistance thereby reducing renal perfusion and increasing renin secretion.

Renin is an enzyme that stimulates the production of angiotensin I and, in turn, angiotensin II. Angiotensin II can also stimulate the adrenal cortex to produce aldosterone. Activation of the RAS can increase sodium and water retention in the body, causing oedema and a rise in blood pressure.

Current treatments

Treatment of heart failure is based on targeting both the SNS and the RAS. The National Institute for Health and Clinical Excellence (NICE) has recently produced updated guidelines on the treatment of heart failure.1 Especially, for those with preserved ejection fraction, it is imperative to control co-morbidities such as hypertension, ischaemic heart disease and diabetes and to provide lifestyle advice (eg, smoking cessation).

A loop diuretic should be used as needed for symptom control of congestion and fluid retention. For those with LVSD, there is a stepwise approach to treatment depending on response and function. First-line pharmacological treatments include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for those who cannot tolerate an ACE inhibitor. These both work to inhibit the RAS. It is known that angiotensin II is an important factor in cardiac remodeling and left ventricular dysfunction.2 In addition, a beta-blocker licensed for the treatment of heart failure is also recommended. These drugs work by suppressing the SNS and RAS to provide cardio-protection.

If a patient remains symptomatic following treatment with both an ACE inhibitor and a beta-blocker, an aldosterone antagonist should be introduced. Aldosterone has an important role in the pathophysiology of heart failure. It causes sodium retention and potassium loss, and may contribute to sympathetic activation, parasympathetic inhibition, endothelial dysfunction and vascular fibrosis. These effects have provided the incentive to

About the authors

John Sherwood, MPharm, is senior lecturer in pharmacy practice, Mark Ashton is senior lecturer in medicinal chemistry and Claire Newton is a final-year undergraduate pharmacy student, all at the School of Pharmacy, University of Sunderland. Sumita Biles is a GP at Monteviot Medical Centre, Newcastle (email john.sherwood@sunderland.ac.uk).
investigate the potential benefit of drugs that lower plasma aldosterone levels or antagonise its effects. ACE inhibitors and ARBs cause a decrease in plasma aldosterone concentration, but this is only temporary. As treatment continues, the level of aldosterone returns to normal and, in some patients, may exceed the normal level. This phenomenon, known as aldosterone escape to ACE inhibitors, may offset some of the cardioprotective effects seen with ACE inhibitors or ARBs.4

Until recently, spironolactone was the only aldosterone antagonist licensed for heart failure. Spironolactone also blocks androgen receptors and is an agonist at progesterone receptors. This can lead to gynaecomastia, impotence and decreased libido. It can also cause hyperkalaemia, which is a particular risk if it is combined with ACE inhibitors. Spironolactone significantly reduces rates of mortality, decreases hospital admissions and improves symptoms in patients with heart failure who are already receiving standard heart failure therapy.5

Eplerenone is a derivative of moexipril, an aldosterone antagonist similar to spironolactone. The moexipril molecule was modified with the aim of reducing the likelihood of the unwanted effects characteristic of spironolactone. Eplerenone is 100 times more specific for the aldosterone receptor than spironolactone. It is also much less potent at blocking androgen receptors than spironolactone and has no activity at progesterone receptors.5 However, like spironolactone, it can cause hyperkalaemia. It is licensed for use in addition to standard therapy with angiotensin-converting enzyme (ACE) inhibitors and a beta-blocker in patients with left ventricular systolic dysfunction (LVEF < 40%) and symptomatic heart failure.6

However, no recent study found that adding an aldosterone antagonist to standard therapy for patients with mild heart failure did reduce death from cardiovascular causes and hospital admissions. Whether spironolactone would produce the same results at a much lower acquisition cost is unknown.6

Current area of research

Natriuretic peptides

An important component of cardiac remodeling is provided by the natriuretic peptides (NPs) atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). The levels of ANP and BNP are elevated in both long-standing heart failure and hypertension. The level of BNP is often measured to confirm a diagnosis of heart failure and it is known that eplerenone reduces the level of BNP in plasma. ANP is produced and released by cardiomyocytes, while BNP is produced and released by both cardiomyocytes and cells of the central nervous system.6

BNP is a vasodilatory peptide produced in vascular endothelium cells. Both ANP and BNP exhibit a range of actions. The main effects include natriuresis, arterial vasodilation, the inhibition of sympathetic nervous function, inhibition of endotoxin, inhibition of vasopressin and adrenocorticotrophic hormone. All three peptides exert their respective effects by binding to G protein-coupled membrane receptors — natriuretic peptide receptors (NPRs).6

NPR-A binds ANP and BNP, NPR-B binds CNP and NPR-C binds all natriuretic peptides.6

Due to the important role of NPs in cardiovascular homeostasis, there has been a lot of interest in using them to treat heart failure and a recombinant human BNP called tiosildilide is approved for the short-term treatment of congestive heart failure in the US. Originally licensed in 2001, a number of studies suggested that tiosildilide was limited to a higher incidence of death than conventional treatments for heart failure and, as a result, tiosildilide was discontinued and a large phase III trial is under way to try to clarify the situation.

A new synthetic NP therapy is under development by Nature Therapeutics Inc. CD-NP is a combination of two fragments of NPs and is currently undergoing phase II trial. The peptide is composed from dendrimeric NP (originally isolated from the venom of the green mamba snake, but also present in humans) and CNP. CD-NP binds to all NPRs and has a number of favourable characteristics, including antifibrotic effects, renal-enhancing properties (produced by the BNP component), and relaxation of veins.6

Cinacalcet

Nitric oxide (NO) is produced in endothelial cells in response to a number of factors, including the shear stress caused by blood flow and a range of endogenous molecules, such as vasopressin, bradykinin, thrombin, catecholamines, oxytocin, endothelin-1 and histamine. Each of the endogenous molecules activates a specific receptor that is coupled to a G-protein, which, in turn, activates endothelial NO synthase, which produces NO. The NO generated causes the inhibition of a number of processes, including the production of endothelin-1, the expression of adhesion molecules and the contraction of vascular smooth muscle. The effects of NO are mediated through its activation of the cytosolic enzyme soluble guanylate cyclase (sGC). The activation of sGC by NO causes the conversion of guanosine 3′,5′-monophosphate (cGMP). cGMP is an important signalling molecule involved in the regulation of a number of cellular processes, which, ultimately, lead to vasodilation. Due to the central role played by sGC, a number of companies are pursuing development programmes in this area. Bayer has a candidate in phase III trial called cidaclopid (BAY 58-2667), which is a potent activator of sGC. A particularly attractive feature of cidaclopid is its duration of action, which is longer than comparable medicines based on NO.6

Conclusion

Heart failure represents a significant financial challenge for the NHS. With an ageing population and the fact that the disease tends to be more closely associated with those over 65 years of age, the situation is not going to improve any time soon. It is for this reason that there is urgent need for research into new treatments for heart failure.

References


NEW ZEALAND GUIDELINE FOR THE MANAGEMENT OF CHRONIC HEART FAILURE

Non-Pharmacological Management
- General counselling (compliance, prognosis)
- Record weight daily (for diuretic titration)
- Avoid smoking
- Regular exercise
- Low-salt diet
- Limited alcohol

Treatment Algorithm

Clinical Heart Failure
Left ventricular systolic dysfunction

Fluid Overload?

Yes

No

Diuretic
ACE inhibitor

ACE inhibitor

Diuretics
- Titrate according to symptoms and dry weight
- Mild CHF - thiazide alone may suffice (eg bendrofluazide 2.5-5mg daily)
- Moderate-severe CHF - loop diuretic (eg initially frusemide 40mg daily)
- Monitor K+ / creatinine weekly during titration, then 3 monthly
- K+ supplementation usually not required with concomitant ACE inhibitor
- Serious hyperkalaemia can arise with combination of high-dose K+ - sparring diuretic and ACE inhibitors (see also spironolactone)
- In cases of resistant oedema, double the daily dose of diuretic, rather than give the same dose twice daily

ACE inhibitors
- Start at a low dose (eg captopril 6.25mg tds, enalapril 2.5mg daily)
- Titrate to target dose over 2-3 weeks (eg captopril 25-50mg tds, cilazapril 5mg daily, enalapril 10mg bid, quinapril 10-20mg bid)
- Risk of first-dose hypotension if SBP <90mmHg, or over-duress
- Consider lower dosages if elderly or renal impairment
- Monitor K+ / creatinine / BP weekly while titrating
- Contraindications: K+ >5.5mmol/L, creatinine >0.25mmol/L, symptomatic hypotension or SBP <80mmHg, angioedema

Spironolactone
- Consider for patients with New York Heart Association class III/IV (moderate-severe) CHF symptoms
- Recommended dose = 25mg daily
- Hyperkalaemia/renal failure may arise if higher doses are used with ACE inhibitor
- Contraindications: K+ >5.5mmol/L, creatinine >0.25mmol/L
- Monitor K+ / creatinine 2-4 days after starting
- 10% of males may suffer breast pain or gynaecomastia

DIGOXIN
- Consider for patients in AF or in sinus rhythm if CHF is severe and not controlled with ACE inhibitor and diuretic
- If normal renal function - start with 0.25mg daily and check levels in 1 week
- If elderly or renal impairment - start at 0.125 or 0.0625mg daily, check levels in 2-3 weeks
- Toxicity: confusion, anorexia, nausea, visual disturbance, arrhythmias
- Drugs which increase levels: antibiotics, amiodarone, digltazene, verapamil, quinidine

Beta-blockers
- Consider for patients with chronic stable CHF and:
  - mild-moderate symptoms
  - minimal signs of congestion
  - stable for one month on adequate doses of ACE inhibitors and diuretics
- Contraindications: asthma, 2nd/3rd degree heart block, symptomatic hypotension, SBP <80mmHg, HR <50bmp
- Initiation and titration may require referral (see NHF CHF Doctors Guide)
Multiple Choice Questions

1. Which of the following drugs can cause peripheral oedema?
   a. Furosemide
   b. Metoprolol
   c. Amlodipine
   d. Bendrofluazide
   e. 

2. Which antihypertensive would you recommend first-line for a 60 year-old man with no other co-morbidities?
   a. Losartan
   b. Quinapril
   c. Atenolol
   d. Bendrofluazide

3. Which of the following drugs should be withheld or used with caution in a patient with acute renal impairment? (There may be more than one correct answer)
   a. Aspirin
   b. Atorvastatin
   c. Candesartan
   d. Clopidogrel
   e. Dabigatran
   f. Digoxin
   g. Diltiazem
   h. Enalapril
   i. Furosemide
   j. Metoprolol
   k. Spironolactone
   l. Warfarin

4. How early should enoxaparin be withheld before a patient undergoes an angiogram?
   a. 24 hours
   b. 12 hours
   c. 2 hours
   d. Does not need to be withheld
5. Which of the following statements is true?
   a. Clopidogrel may decrease the efficacy of omeprazole
   b. Pantoprazole may increase the efficacy of clopidogrel
   c. Lansoprazole may increase the side effects of clopidogrel
   d. Omeprazole may decrease the efficacy of clopidogrel

6. A patient is changing from enoxaparin 100mg Q12H to dabigatran 150mg BD. The last dose of enoxaparin was given at 0900h. When should the first dose of dabigatran be given?
   a. 1200h on the same day
   b. 1700h on the same day
   c. 2100h on the same day
   d. 0800h on the following day

7. Which of the following drugs should be withheld or used with caution in a patient with bradycardia? (There may be more than one correct answer)
   a. Aspirin
   b. Candesartan
   c. Clopidogrel
   d. Dabigatran
   e. Digoxin
   f. Diltiazem
   g. Enalapril
   h. Furosemide
   i. Metoprolol
   j. Spironolactone
   k. Warfarin

8. Which of the following is a common side effect related to statin use?
   a. Memory loss
   b. Sexual dysfunction
   c. Gastrointestinal disturbance
   d. Rhabdomyolysis
Case Study

Mr P is a 48 year-old man who is admitted with sudden onset, crushing, central chest pain. It is not pleuritic or associated with shortness of breath.

On examination Mr P appears unwell, grey and slightly diaphoretic. Temperature = 36˚C, Heart rate = 60bpm and regular, Heart sounds dual, Blood pressure is 112/66, Respiratory rate = 18/min.

Mr P is given glyceryl trinitrate spray sublingually, morphine 5mg IV, oxygen and an aspirin 300mg tablet to chew.

Q1: What monitoring is required when giving someone glyceryl trinitrate spray for the first time?

Q2: Why is aspirin given immediately?

Q3: Why is Mr P told to chew the aspirin tablet instead of swallowing it whole?
Q4: What would you do if Mr P told you he was allergic to aspirin?

Q5: How does morphine work to relieve chest pain?

Electrocardiogram (ECG) shows sinus rhythm and ST elevation in V1-V4. Chest x-ray shows clear lung fields and a narrow mediastinum. Computer tomography of the aorta (CTA) excludes an aortic dissection. An echocardiogram demonstrates severe left ventricular (LV) impairment, with a left ventricular ejection fraction (LVEF) of 20-30% and apical and apicoseptal akinesis. Troponin I = 0.06.

Diagnosis = Acute anterior ST-elevating myocardial infarction (STEMI) with early cardiogenic shock.

Mr P is transferred urgently to the cardiac catheterisation lab where he undergoes primary percutaneous intervention (PCI) to his left anterior descending coronary artery (LAD) with a drug-eluting stent (DES).

Mr P is given clopidogrel po 300mg stat prior to transfer to the cardiac catheterisation lab, followed by clopidogrel 75mg once a day for six months and aspirin 100mg once a day.

Q6: Why is Mr P given clopidogrel?
Q7: Give an example of one side effect Mr P could experience while he is taking clopidogrel and how it could be managed.

Q8: How long should Mr P take aspirin for?

On day 2 Mr P is started on metoprolol CR 47.5mg po daily and atorvastatin 80mg po daily

Q9: Why is Mr P given metoprolol and atorvastatin?
Q10: List four contraindications to the use of beta-blockers. What would you do if Mr P had one of these conditions?

On day 3 Mr P’s blood pressure is 106/56 and heart rate is 54 bpm. He has a cardiac echocardiogram that shows his LVEF is still only 30%. Mr P’s metoprolol is changed to carvedilol 6.25mg po BD, and he is started on cilazapril 2.5mg po daily.

Q11: What monitoring is recommended when starting someone on an ACE inhibitor?

Two hours after his first dose of cilazapril, Mr P complains of feeling lightheaded. His blood pressure is now 85/50.

Q12: What would you do?
Mr P is given a glyceryl trinitrate spray to take home with him to use if he experiences chest pain in the future.

Q13: What directions would you give him regarding (a) when to use the spray, (b) how to use the spray and (c) when to call an ambulance?
Note: ____________________________________________________________

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