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# Immunisation and pregnancy – who, what, when and why?

#### **SUMMARY**

Only two vaccines are routinely recommended during pregnancy – influenza vaccine is recommended throughout, and pertussis vaccine is recommended at 28–32 weeks but can be given later.

Some other vaccines can be administered in special circumstances but are not routinely recommended.

All live attenuated vaccines are contraindicated in pregnancy, although there has been no evidence of adverse effects from inadvertent administration.

Recommending vaccination to pregnant women is important as evidence shows they are more likely to get vaccinated if their healthcare provider advises it.

It is important for healthcare providers to discuss the benefits and the safety of vaccination during pregnancy. In particular, pointing out the benefits for the baby is important in helping women decide.

#### Introduction

Immunisation is increasingly becoming a routine part of antenatal care, but there remains some confusion among healthcare providers and patients about what to do. Recommendation by the healthcare provider has been shown to be the most significant factor in a pregnant woman's decision to get vaccinated.<sup>1</sup> It is important to be aware of the current recommendations and how best to communicate them to pregnant women.

All pregnancy vaccination recommendations can be found in the Australian Immunisation Handbook, in particular section 3.3.2 – Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants. The Handbook is regularly updated and healthcare professionals are encouraged to check for these updates.<sup>2</sup>

## Recommendations for women planning pregnancy

The need for vaccination against hepatitis B, measles, mumps, rubella and varicella should be assessed as part of pre-conception care. When previous infection or vaccination history is uncertain, serology can be used to assess immunity to hepatitis B, measles, mumps and rubella. Serological testing for varicella is not reliable for assessing vaccine-induced immunity, although it can indicate previous natural infection.<sup>2</sup>

#### Recommendations for pregnant women

Current Australian guidelines recommend the seasonal influenza vaccine. When both tri- and quadrivalent vaccines are available, the quadrivalent vaccines (Fluarix Tetra or FluQuadri) are the preferred option, although the trivalent vaccines are all suitable if quadrivalent vaccines are not available (see section 4.7.4 of the Australian Immunisation Handbook).<sup>2</sup>

The other recommended vaccine for pregnant women is the adult pertussis dTpa vaccine (Adacel or Boostrix). The safety of influenza and pertussis vaccines is very good, and they can be administered at the same consultation.<sup>3</sup>

Close household contacts and carers such as siblings, partners and grandparents should also be up to date with all of their age-appropriate immunisations, such as rotavirus, varicella and MMR (measles-mumpsrubella) and particularly pertussis vaccine.

#### Influenza vaccination

The influenza vaccine should be administered with seasonal protection in mind so it protects pregnant women against strains circulating during the influenza season and protects babies likely to be born during that time. The vaccine is recommended during any trimester,<sup>4</sup> although the greatest risk of adverse outcomes from influenza for the pregnant woman is in

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#### Keywords

antenatal immunisation, influenza, pertussis, pregnancy, vaccines

#### Aust Prescr 2017;40:122-4

https://doi.org/10.18773/ austprescr.2017.046 the third trimester. There are excellent data showing that vaccination in pregnancy also protects the infant in the first few months of life.<sup>5,6</sup>

As there are challenges in obtaining seasonal influenza vaccine during the summer months, the emphasis should be on administration of the vaccine as early as possible after the seasonal vaccine formulation becomes available in the next year.

#### Pertussis vaccination

Pertussis infection is most severe in infants under the age of three months. Almost all deaths occur before six weeks of age which is the earliest the first vaccine dose can be given. High concentrations of maternal antibody, only achievable through vaccination during pregnancy and transmitted via the placenta to the baby, have been shown to give more than 90% protection against severe infection in the first three months of life.<sup>7,8</sup>

Although evidence on the optimal time for administration is rapidly evolving, current data support vaccination at 28–32 weeks gestation giving the highest infant antibody levels at birth (even in premature infants).<sup>9</sup> This conveniently corresponds to the usual time when glucose tolerance tests are conducted. However, the only efficacy data – from experience in England with an emergency vaccination in pregnancy program – showed that there was still significant protection with vaccination as late as 14 days before birth.<sup>7</sup> Based on recent advice from the Australian Technical Advisory Group on Immunisation,<sup>10</sup> if the pertussis vaccine is given earlier than 28 weeks but still during pregnancy, it need not be repeated.

# Which vaccines can be given in special circumstances?

While not routinely recommended, some vaccines can be administered to at-risk women, on a caseby-case basis. For example, vaccines that can be given to pregnant women at high risk of exposure include pneumococcal polysaccharide vaccine and hepatitis B (see Table 3.3.1 in the Australian Immunisation Handbook).<sup>2</sup>

#### Which vaccines are contraindicated?

Live attenuated viral and bacterial vaccines are contraindicated in pregnancy (see Box).<sup>2</sup> In most cases, the risk is hypothetical. For example, limited safety data available from inadvertent administration of rubella and varicella vaccines are reassuring.

# How many pregnant women get vaccinated?

Vaccine uptake has significantly improved in Australia over the past few years. In 2012, it was estimated that one in four pregnant women were immunised against influenza.<sup>11</sup> Uptake of influenza vaccine is thought to have more than doubled since then, with 60% of pregnant women immunised in 2015 (author's unpublished data).

Following the recommendation for antenatal pertussis vaccine in 2015, early estimates indicate approximately 70% of mothers received a pertussis vaccine in the third trimester of their pregnancy. Much of this success is owed to GPs, as more than two-thirds of antenatal vaccines are given in general practice.

Women who are recommended vaccines by a health provider are more than 10 times as likely to be immunised compared to those who are not.<sup>12,13</sup> Another important factor is easy access to vaccines – women are more willing to get vaccinated if it is available at the same time as an antenatal visit.<sup>11</sup>

#### Communicating vaccination to pregnant women

Pregnant women report being bombarded with advice about what they should and should not do. There is evidence that unless it is recommended by their healthcare provider, vaccination is not a priority.<sup>14</sup> Simply pointing out that it is recommended can often be enough for a pregnant woman to get vaccinated.

When recommending antenatal immunisation, it is important to remember that pregnant women trust their healthcare providers and are primarily interested in the health and well-being of their baby. More than 90% of pregnant women who are immunised report doing so to protect their baby,<sup>12</sup> therefore framing the benefits of vaccination to focus on the baby is important. Evidence from clinical trials shows maternal vaccination protects young infants from disease.<sup>5,7,15</sup> This knowledge is often the deciding factor for pregnant women to get vaccinated.

Unimmunised women often cite concerns about the safety of vaccination as a reason why they

#### Box Contraindicated vaccines in pregnancy

BCG (Bacillus Calmette-Guérin) against tuberculosis Oral typhoid Japanese encephalitis (Imojev) MMR (measles-mumps-rubella) MMRV (measles-mumps-rubella-varicella) Rotavirus Varicella against chickenpox Zoster against shingles

Source: Reference 2

#### Immunisation and pregnancy

refused it during pregnancy.<sup>12</sup> A number of studies have shown the safety of influenza and pertussis vaccines, and previous investigations in Australia have found that a similar proportion of pregnant women experience common adverse events as compared to non-pregnant women.<sup>16</sup> Providers should discuss common, expected reactions with their patients and reassure them about the safety of the vaccine for the baby. There is a large body of evidence supporting the safety of antenatal vaccination for the fetus. It shows no increase in the risk of preterm labour, low birthweight, congenital malformation or fetal death.<sup>3,17</sup> In fact, some studies have shown influenza vaccination during pregnancy is associated with a lower rate of stillbirth.<sup>18</sup>

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#### Conclusion

Vaccination during pregnancy is an effective strategy for protecting mothers during a time when they are often more vulnerable to infections such as influenza. Antenatal vaccination can also protect infants in the first few months of life, before they receive their first course of childhood vaccines. While antenatal vaccination is improving in Australia, more women and their infants could be offered protection against disease if every healthcare provider recommended vaccination to their pregnant patients. ◄

Conflict of interest: none declared

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## Letters to the Editor

#### **Disjointed medication management** systems in aged care

Aust Prescr 2017:40:125 https://doi.org/10.18773/austprescr.2017.048

In the February 2017 issue of Australian Prescriber, John Jackson and Elspeth Welsh discussed medication charts used in residential aged-care facilities. They highlighted the advantage of having prescribers, aged-care staff and pharmacists working from a single record of medication order information.<sup>1</sup> Their article focused primarily on problems with paper medication charts, and suggested that electronic charts may address the problems.

We wish to highlight issues with currently available electronic medication charts, also known as electronic medication administration records. Unfortunately, these are usually not integrated with GPs' clinical software. It is common practice for GPs to handwrite medication orders on paper charts which are copied and faxed or emailed to the residential aged-care facility's pharmacy. There the order is transcribed into an electronic system to populate the electronic medication administration record.<sup>2-4</sup> When a dose is altered or a drug is stopped the same process has to occur to update the electronic medication administration record. GPs usually also prepare separate Pharmaceutical Benefits Scheme (PBS) prescriptions via their clinical software or by hand.

These processes lead to the following:2-4

- multiple, sometimes conflicting, medication records
- delays in medication administration (or cessation) for unwell patients
- medication errors
- major inefficiencies for GPs, aged-care staff and pharmacists.

What is needed are fully integrated electronic medication management systems, in which GPs (and other prescribers) can initiate, modify and cease medications electronically, with the order automatically transmitted to the electronic medication administration record and the pharmacy, while also fulfilling PBS prescription requirements and linking with GPs' clinical records. This would be more efficient and have safety benefits.<sup>5,6</sup>

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#### John Jackson and Elspeth Welsh, the authors of the article, comment:



The letter highlights the risks associated with disjointed medication management systems whether they be hard copy, digital or hybrid systems. The official hard copy National Residential Medication Chart, developed to facilitate PBS prescribing and incorporating proven patient safety features, can only address some of the issues identified in the letter (e.g. multiple, sometimes conflicting, medication records). However, the current level of implementation has limited these benefits.

We agree that fully integrated electronic medication management systems are required in residential aged care. Some of the delays and inefficiencies will only be fully addressed by real-time, comprehensive electronic communication between aged-care staff, prescribers and pharmacists.

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

#### Acute pulmonary oedema

Aust Prescr 2017;40:126 https://doi.org/10.18773/austprescr.2017.051

After reading the article on managing acute pulmonary oedema,<sup>1</sup> I would like to point out the following. Pulmonary embolus causes pulmonary ischaemia not oedema. Nitrates do not cause coronary vasodilatation as they are already maximally dilated by way of autoregulation. Morphine causes coronary vasoconstriction in conscious dogs.<sup>2</sup>

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Megan Purvey and George Allen, the authors of the article, comment:

We have further reviewed the literature and agree that pulmonary embolus does cause regional ischaemia, but it is also listed as a precipitant of acute heart failure in the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.<sup>1</sup> Similarly, we were guided by the 2005 version of these guidelines which, when discussing nitrates, stated 'At low doses they only induce venodilation, but as the dose is gradually increased they cause the arteries, including the coronary arteries, to dilate'.<sup>2</sup>

We appreciate your clarification of morphineinduced coronary vasoconstriction<sup>3</sup> as a mechanism of why morphine may cause harm if used in acute pulmonary oedema.

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#### Ulipristal

Aust Prescr 2017;40:127 https://doi.org/10.18773/austprescr.2017.052

There are a few details concerning the new drug comment about ulipristal<sup>1</sup> that need to be clarified.

First, the copper intrauterine device is no longer the only option for emergency contraception after 72 hours as ulipristal is indicated for up to 120 hours after unprotected sex.

While the liver enzyme inducer interactions of ulipristal are mentioned, there is no mention that levonorgestrel emergency contraceptive pills have similar interactions.

There have been additional large postmarketing studies on pregnancy safety risks that are not

mentioned in the comment, but would be useful for healthcare professionals to know about.<sup>2</sup>

Finally, the statement 'it will be less effective if ovulation has already occurred' differs from the Australian product information. This states, 'if ovulation has already occurred, ulipristal is no longer effective'.

Philip Goldstone Medical Director Maries Stopes Australia Melbourne

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# Chronic heart failure

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#### Keywords

ACE inhibitors, aldosterone antagonists, angiotensin receptor antagonists, beta blockers, chronic heart failure, digoxin, neprilysin inhibitor, sartans

Aust Prescr 2017;40:128-36 https://doi.org/10.18773/ austprescr.2017.044



This article has a continuing professional development activity for pharmacists available at https://learn.nps.org.au

#### SUMMARY

The clinical diagnosis of heart failure should be confirmed by echocardiogram to determine the underlying mechanism and to measure the left ventricular ejection fraction. Heart failure with reduced ejection fraction and heart failure with preserved ejection fraction have different treatments but are often indistinguishable clinically.

Lifestyle modification and education on self-management are important strategies for all patients. Patients should monitor their symptoms and weight regularly.

Heart failure with reduced ejection fraction should be managed with ACE inhibitors, heart failure specific beta blockers, and aldosterone antagonists. These drugs all reduce mortality.

Angiotensin receptor antagonists should be used if the patient cannot tolerate ACE inhibitors. The combination of sacubitril and valsartan is indicated if patients remain symptomatic despite ACE inhibitors, beta blockers and aldosterone antagonists. Digoxin and diuretics may also have a role in treating persistent symptoms.

In heart failure with preserved ejection fraction no drug has been proven to reduce mortality. Patients should be treated cautiously with diuretics and have aggressive management of risk factors, particularly hypertension.

#### Introduction

Heart failure is present in 1–2% of the Australian population.<sup>1</sup> It is predominantly a disease of the elderly,<sup>2</sup> present in up to 10% of those aged over 80,<sup>3</sup> and this prevalence is rising.<sup>4</sup>

Heart failure is a syndrome in which the heart cannot provide adequate cardiac output to meet the metabolic requirements of the body and accommodate venous return. The diagnosis is mainly clinical, based on the presence of symptoms including dyspnoea, orthopnoea and fatigue, and signs such as pulmonary and peripheral oedema.

#### Pathophysiology

Heart failure is the end result of a number of different pathophysiological processes in which there is injury to the heart with loss or impairment of functioning myocardial cells.<sup>5</sup> Compensatory neurohormonal mechanisms are activated in order to maintain adequate cardiac function and tissue perfusion. Activation of the sympathetic nervous system increases heart rate and cardiac contractility, while activation of the renin–angiotensin– aldosterone system increases sodium reabsorption and water retention.

Although these responses are initially beneficial, prolonged overstimulation of the sympathetic nervous system and renin–angiotensin–aldosterone system results in maladaptive cardiovascular remodelling. The release of natriuretic peptides counteracts the vasoconstricting effects of the sympathetic nervous system and renin-angiotensin-aldosterone system.

#### **Ejection fraction**

Heart failure is often due to myocardial dysfunction and is broadly classified by left ventricular ejection fraction. When the left ventricular ejection fraction is less than 40% it is termed heart failure with reduced ejection fraction. If the ejection fraction is at least 50% the condition is called heart failure with preserved ejection fraction. This accounts for approximately half of all cases of heart failure.<sup>6</sup> Although the presentation is clinically indistinguishable from heart failure with reduced ejection fraction, the treatment is different.

Left ventricular ejection fraction in the range 40–49% has recently been termed 'mid-range' by the European Society of Cardiology.<sup>7</sup> However, given the variation in measuring left ventricular ejection fraction, this is a grey area which requires more research.

#### **Correcting the cause**

Underlying causes of heart failure need to be identified and managed. These include cardiovascular causes such as myocardial ischaemia or infarction, uncontrolled hypertension, valvular disease, atrial fibrillation and tachycardia, and pulmonary embolism. There are also systemic causes, such as infection, thyroid dysfunction, anaemia, poorly controlled diabetes, previous chemotherapy or radiotherapy and peripartum cardiomyopathy. Idiopathic or genetic causes include dilated cardiomyopathy, hypertrophic obstructive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Alcohol and substance abuse, for example amphetamines, can also cause heart failure. Acute triggers causing decompensation may include nonadherence to treatment, iatrogenic factors such as inappropriate drugs, and dietary indiscretions.

Comorbid disease may worsen heart failure or complicate its treatment. Over half of patients with heart failure reported five or more chronic conditions in a US community-based study.<sup>8</sup> While cardiac diseases including hypertension, hypercholesterolaemia, ischaemic heart disease and myocardial infarction are the more common comorbidities, chronic obstructive pulmonary disorder, diabetes, depression and renal failure are most strongly associated with adverse outcomes. Renal dysfunction with heart failure, termed cardiorenal syndrome, has a particularly poor prognosis.

#### **Non-drug interventions**

Ongoing education about self-management is key to caring for patients with heart failure.<sup>9</sup> Use of visual aids can support this education.<sup>10</sup>

A low-salt diet should be recommended, along with smoking cessation, minimal alcohol intake and regular exercise. A cardiac rehabilitation program<sup>11</sup> and a multidisciplinary heart failure team (doctors, nurses, pharmacists)<sup>12</sup> have been shown to be beneficial.

Early intervention by the GP to address signs and symptoms of heart failure identified by the patient can reduce hospitalisations for heart failure. An exacerbation of heart failure can be heralded by dyspnoea with usual daily activities, reduced exercise tolerance, abdominal bloating and poor appetite.

Patients should know the weight at which their condition was previously stable. They need to monitor their weight regularly so that they and their caregivers are alert to any weight gain which would suggest fluid retention. The patients need to know what to do when their weight rises above set limits, such as contacting their GP. A fluid restriction for volume overload may be required, with a flexible diuretic regimen if appropriate. Resources are available to help in preparing a heart failure action plan.<sup>10</sup>

# Drug therapy for heart failure with reduced ejection fraction

The goal of management of heart failure with reduced ejection fraction is to control symptoms, prevent progression of left ventricular dysfunction, decrease hospitalisation and improve survival. Drugs which block neurohormonal activation are the cornerstone of therapy. They include ACE inhibitors and beta blockers, as well as aldosterone antagonists (Table 1). A new combination of sacubitril and valsartan (a neprilysin inhibitor-angiotensin receptor antagonist) enhances neurohormonal modulation by increasing beneficial natriuretic peptides.

In order to obtain the maximal symptomatic and mortality benefits from these drugs, they should be up-titrated every 2–4 weeks providing that symptoms, heart rate, blood pressure, serum potassium and renal function remain within acceptable ranges (see Fig.).<sup>7</sup> Achievement of target doses can take weeks to months (Table 2). Drugs can be up-titrated together in the absence of symptomatic hypotension, however titrating more cautiously one at a time can distinguish which drug is causing an adverse effect. Adverse effects tend to improve over time. If a dose increase is not tolerated, the dose should be reduced and re-titrated once the patient is clinically stable. When significant adverse effects occur, switching to a different drug within the same class should be tried before permanently discontinuing therapy.

# ACE inhibitors and angiotensin receptor antagonists

ACE inhibitors are first-line therapy in heart failure with reduced ejection fraction and asymptomatic left-ventricular dysfunction. Their use results in a 3.8% absolute reduction (20% relative) in death, with reductions in myocardial infarction and hospitalisation for heart failure.<sup>13</sup> Beneficial effects occur early and continue long term, in all age groups. ACE inhibitors reduce the maladaptive effects of chronic renin– angiotensin–aldosterone system activation, including sodium and water retention, vasoconstriction, and cardiac hypertrophy and fibrosis. Studies of angiotensin receptor antagonists (sartans) have not shown a consistent reduction in mortality.<sup>14,15</sup> Sartans are therefore considered as a second choice, indicated only in patients intolerant of ACE inhibitors.

Treatment should begin soon after diagnosis, at the lowest dose. Up-titration is recommended if the blood pressure is 90 mmHg systolic or above, and is limited by symptoms rather than the measured blood pressure. If symptomatic hypotension occurs, other vasodilators should be reduced or stopped first and, provided the patient is not congested, diuretics should be reduced or ceased before reducing the ACE inhibitor dose.

A minor worsening of renal function (up to 30% reduction in estimated glomerular filtration rate (eGFR)) is generally acceptable. A small rise in potassium can be expected, but the ACE inhibitor dose should be halved if the potassium concentration exceeds 5.5 mmol/L. If an ACE inhibitor induces a chronic cough, a change to a sartan may be appropriate after other causes of cough have been excluded such as pulmonary oedema or underlying lung disease.

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Table 1 Drugs used	in heart failure with reduced left	ventricular ejection fraction		
Drug	Indications	Mechanism	Adverse effects	Precautions
ACE inhibitors	First-line therapy when LVEF <40%	Reduces vasoconstriction Reduces sodium reabsorption Reduces aldosterone	Hypotension Worsening renal function Hyperkalaemia Chronic cough Angioedema	Previous angioedema Other drugs that increase potassium
Angiotensin receptor antagonists (sartans)	If intolerant of ACE inhibitors	Reduces vasoconstriction Reduces sodium reabsorption Reduces aldosterone	Hypotension Worsening renal function Hyperkalaemia	Other drugs that increase potassium
Beta blockers	First-line therapy when LVEF <40%	Reduces sympathetic activity Has antiarrhythmic effects Reverses remodelling	Hypotension Bradycardia Fatigue Bronchospasm Impotence Worsening heart failure Masking hypoglycaemia	2nd and 3rd degree heart block Asthma Chronic obstructive pulmonary disease – exclude significant reversibility
Aldosterone antagonists	If symptomatic despite ACE inhibitor and beta blocker and LVEF <40%	Is a weak diuretic Reduces effects of aldosterone	Hyperkalaemia Worsening renal function Hypotension Gynaecomastia (spironolactone)	Other drugs that increase potassium
Sacubitril with valsartan	Heart failure LVEF <35% In place of ACE inhibitor or angiotensin receptor antagonist	Causes vasodilation Reduces sympathetic activity Enhances diuresis	Angioedema Hypotension	Previous angioedema A 36-hour ACE inhibitor washout is an absolute requirement before starting
Diuretics	Relief of congestive symptoms	Reduces retention of sodium and water	Renal dysfunction Hypokalaemia Worsened gout	Other drugs that lower potassium
Ivabradine	Heart rate 77 beats/min or higher despite beta blocker, or intolerant to beta blocker Sinus rhythm	Reduces heart rate in sinus rhythm	Visual disturbances (phosphenes) Headache Bradycardia Atrial fibrillation	3rd degree atrioventricular block Sinoatrial block Stop if atrial fibrillation develops Prolonged QT syndrome
Digoxin	Heart failure in sinus rhythm with symptoms despite ACE inhibitor, beta blocker, aldosterone antagonist, diuretic. Atrial fibrillation	Is a weak positive inotrope Reduces heart rate Increases vagal tone	Bradycardia Digoxin toxicity	Narrow therapeutic range requires monitoring Interacting drugs Impaired renal function
LVEF left ventricular e	jection fraction			



Class I recommendation

Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective

Class II recommendation

Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure

a New York Heart Association Class II-IV

- b If ACE inhibitor not tolerated or contraindicated, use angiotensin receptor antagonist
- c If aldosterone antagonist not tolerated or contraindicated, use angiotensin receptor antagonist
- d With hospital admission for heart failure in the last six months or with elevated natriuretic peptides
- e With elevated natriuretic peptides
- f In dose equivalent to enalapril 10 mg twice daily
- g With a hospital admission for heart failure in the previous year as per Pharmaceutical Benefits Scheme criteria
- h Cardiac resynchronisation therapy is
  - recommended if QRS ≥130 msec and left bundle branch block in sinus rhythm
  - considered if QRS ≥130 msec without left bundle branch block in sinus rhythm, or for atrial fibrillation provided a strategy to ensure biventricular capture in place

Source: Adapted from Figure 7.1 of reference 7, with permission

ARTICLE

#### Table 2 Recommended target doses

	Daily starting dose	Daily target maintenance dose
ACE inhibitors		
Captopril	6.25 mg x3	25-75 mg x2
Enalapril	2.5 mg	10-20 mg x2
Fosinopril	5–10 mg	20-40 mg
Lisinopril	2.5 mg	20-40 mg
Perindopril arginine	2.5 mg	5–10 mg
Perindopril erbumine	2 mg	4-8 mg
Quinapril	5 mg	20-40 mg
Ramipril	2.5 mg	5–10 mg
Angiotensin receptor inhibitors	5	
Candesartan	4-8 mg	32 mg
Valsartan	40 mg x2	160 mg x2
Losartan	50 mg	150 mg
Beta blockers		
Bisoprolol	1.25 mg	10 mg
Carvedilol	3.125 mg	25 mg x2
Metoprolol extended release	23.75 mg	190 mg
Nebivolol	1.25 mg	10 mg
Aldosterone antagonists		
Eplerenone	25 mg	50 mg
Spironolactone	25 mg	50 mg
Neprilysin inhibitor/angiotensi	n receptor antagonist	
Sacubitril with valsartan	49/51 mg	97/103 mg

#### Beta blockers

Beta blockers are another important first-line therapy for heart failure with reduced ejection fraction. Given with ACE inhibitors, they are associated with a 4.3% absolute reduction (24% relative reduction) in all-cause mortality and comparable reductions in hospital admissions for patients in sinus rhythm.<sup>16</sup> Beta blockers reduce myocardial oxygen demand, protect from ischaemia, have antiarrhythmic effects and reduce sudden cardiac death. Only beta blockers that have been shown to be effective in heart failure should be used. These are bisoprolol,<sup>17</sup> carvedilol,<sup>18,19</sup> extended-release metoprolol succinate,<sup>20</sup> and nebivolol if the patient is over 70 years old (as this drug has only been evaluated in the elderly).<sup>21</sup> All patients with heart failure with reduced ejection fraction should be given beta blockers. Start soon after an ACE inhibitor, once the patient is clinically stable and euvolaemic. At first the symptoms of heart failure may worsen so the smallest dose should be used. Aim to titrate up to the target dose or as high as tolerated. Heart rate, blood pressure and symptoms of congestion should be reviewed after each up-titration.

Absolute contraindications to beta blockers include second or third degree atrioventricular block. If these occur, a pacemaker or cardiac resynchronisation therapy should be considered to enable continuation of therapy. Asthma is only a relative contraindication. Chronic obstructive pulmonary disease should be assessed with lung function tests before deciding not to give beta blockers. If there is no significant airway reversibility, the patient should be able to tolerate beta blockers. Usually the impact of beta blocker therapy on lung function tests is minimal and without clinical relevance.<sup>22</sup>

The dose should be reassessed if clinical deterioration occurs or the heart rate is under 50 beats per minute. As with ACE inhibitors, asymptomatic hypotension does not require a change of therapy. If symptomatic, consider reducing other vasodilators first, or the dose of any diuretic if there is no congestion, before deciding to reduce the dose of beta blocker. Bisoprolol and metoprolol have a less vasodilating effect and may be better tolerated if the blood pressure is borderline, however the additional vasodilating effects of carvedilol may offset the early worsening of heart failure.

#### Aldosterone antagonists

Aldosterone antagonists improve survival across the full spectrum of heart failure with reduced ejection fraction. There is an 11% absolute reduction (30% relative) in mortality in severe heart failure,<sup>23</sup> a 7.6% absolute reduction (37% relative) in mortality and cardiovascular hospitalisation in mild heart failure,<sup>24</sup> and a 2.3% absolute reduction (15% relative) in death in patients with heart failure after myocardial infarction.<sup>25</sup> Aldosterone antagonists block the adverse effects of aldosterone activation, which includes sodium and water reabsorption, and cardiovascular fibrosis. These drugs are markedly underused and should be added to ACE inhibitors and beta blockers in all patients who remain symptomatic.

Serious hyperkalaemia can occur, especially with underlying renal impairment. Serum potassium should be closely monitored, at one week and one, two and three months after starting or increasing the dose, then every three months to 12 months, and then four-monthly thereafter. The starting dose can be halved if diabetes or renal impairment is present (Table 2). The dose should be halved if potassium exceeds 5.5 mmol/L, and ceased if it is more than 6.0 mmol/L. Gynaecomastia can occur in men, but is less common with eplerenone than with spironolactone.

#### Sacubitril with valsartan

Sacubitril with valsartan is a new combination which was shown to be superior to enalapril in a large head-to-head trial, with an absolute reduction of cardiovascular death and heart failure hospitalisation of 4.7% (20% relative reduction).<sup>26</sup> Sacubitril is a neprilysin inhibitor. It inhibits the degradation of vasoactive peptides including natriuretic peptides, thereby enhancing their beneficial effects such as vasodilation and diuresis. The combination reduces sympathetic tone, aldosterone and myocardial fibrosis and hypertrophy.

Sacubitril with valsartan can replace an ACE inhibitor or sartan if symptoms persist despite optimal medical therapy.<sup>7,27</sup> This combination may become first-choice therapy in the future, given its efficacy. However, currently it should be used when a patient has been stabilised on an ACE inhibitor, beta blocker and aldosterone antagonist.

Previous angioedema (due to any cause) is a contraindication. A 36-hour ACE inhibitor washout period is an absolute requirement to reduce the risk of angioedema. The combination lowers the blood pressure more potently and therefore can cause hypotension. This improves over time, but can be addressed by reducing the dose of other vasodilators or halving the starting dose of sacubitril with valsartan.

#### Other drugs

Other therapies can be added to the essential drugs for heart failure (beta blockers, ACE inhibitors and aldosterone antagonists). They can also be considered secondary choices if the first-line drugs are not tolerated.

#### Diuretics

Loop diuretics are used by most patients at some stage for symptomatic control of heart failure. They should be used in addition to ACE inhibitors and beta blockers in patients with heart failure with reduced ejection fraction if there is associated symptomatic congestion. Diuretics can often be reduced as doses of neurohormonal blockers are increased.

A small dose of a thiazide or a potassium-sparing diuretic can be added to furosemide (frusemide) or bumetanide for a short period. This has a synergistic diuretic effect for patients with peripheral oedema resistant to treatment with a loop diuretic. Renal function and potassium need to be closely monitored.

#### Ivabradine

A raised resting heart rate is a marker of cardiovascular risk.<sup>28</sup> Ivabradine reduces heart rate by inhibiting the sinus node, and results in a 5% absolute reduction (18% relative) in the risk of either cardiovascular mortality or heart failure hospitalisations.<sup>29</sup> It is used in heart failure with sinus rhythm when the left ventricular ejection fraction is less than 35% as an add-on to an ACE inhibitor, aldosterone antagonist and maximally tolerated beta blocker if the heart rate is at least 77 beats per minute.<sup>29</sup> It can be used if the patient cannot tolerate a beta blocker.

Ivabradine can only be used in sinus rhythm. It does not affect blood pressure, intracardiac conduction or myocardial contractility. It may cause visual symptoms, including flashing lights, which are not associated with retinal damage, and which usually resolve spontaneously. Stop ivabradine if atrial fibrillation develops.

#### Digoxin

Digoxin is useful for symptomatic control of heart failure in sinus rhythm, but only after therapy with an ACE inhibitor, beta blocker, aldosterone antagonist and diuretic has been optimised. It is a weak positive inotrope and increases vagal tone. In atrial fibrillation digoxin slows the heart rate by reducing atrioventricular nodal conduction.<sup>30</sup> Digoxin does not improve survival, but can reduce hospitalisations associated with heart failure and improves symptoms.<sup>31</sup> It should be used at a low dose in sinus rhythm, aiming for a serum digoxin of 0.5-0.9 nanogram/mL measured at least six hours after oral dosing.<sup>32</sup> Digoxin toxicity may result from deteriorating renal function or dehydration, with symptoms most commonly including nausea, vomiting and drowsiness.<sup>33</sup> Digoxin may also be useful for rate control in the treatment of atrial fibrillation in heart failure.

#### Hydralazine plus isosorbide dinitrate

High-dose hydralazine is an arterial vasodilator. Isosorbide dinitrate is predominantly a venodilator. The combination can be used with a beta blocker if the patient is intolerant of ACE inhibitors and sartans. Specialist advice should be sought.

#### Devices

An implantable cardioverter defibrillator should be considered for primary or secondary prevention of ventricular arrhythmias if left ventricular ejection fraction is 35% or less to reduce the risk of sudden death and all-cause mortality.<sup>34</sup> This may be implanted alone, or may be combined with cardiac resynchronisation therapy (or biventricular pacing) if the QRS duration on the ECG is prolonged at

#### Chronic heart failure

130 milliseconds or above with left bundle branch block morphology. This reduces mortality and heart failure hospitalisations and improves symptoms.

# Heart failure with preserved ejection fraction

Compared to those with a reduced ejection fraction, patients with heart failure with preserved ejection fraction are older, more likely to be female and to have hypertension, atrial fibrillation, diabetes or obesity. The mechanism probably relates to a combination of pathophysiological processes including increased myocardial stiffness, abnormal myocardial relaxation and increased arterial stiffness.

No drug has been shown to improve survival,<sup>35</sup> however recent data suggest that in a subset of patients with heart failure and preserved ejection fraction, aldosterone antagonists may improve clinical outcomes.<sup>36</sup> Sacubitril with valsartan was found to be beneficial in a phase II study.<sup>37</sup> The combination is therefore currently under evaluation for heart failure with preserved ejection fraction.

Diuretics should be used judiciously and over-diuresis avoided. Treatment should focus on aggressive control of concurrent conditions particularly hypertension. Atrial fibrillation should be managed according to guidelines, using a rate control strategy and anticoagulation initially, with a trial of rhythm control for persistent symptoms. Myocardial ischaemia, obesity and anaemia should be addressed. Exercise training can improve guality of life.

#### Withdrawal of treatment

Substantial improvements in symptoms are seen after starting drug therapy and often patients will feel back to normal. Left ventricular ejection fraction can sometimes return to normal or close to the normal range. Drugs that confer a survival benefit, in particular ACE inhibitors and beta blockers, should not be stopped, as this may lead to a recurrence of heart failure.<sup>38</sup> Diuretics and digoxin (in sinus rhythm) may be reduced and stopped if the patient remains stable.

When the goals of treatment move to palliation and symptom control, ACE inhibitors, beta blockers and aldosterone antagonists should be continued if possible, as they improve symptoms. Down-titration of doses may be needed if hypotension or issues with renal function and electrolytes occur. Statins and digoxin if not being used for atrial fibrillation can be withdrawn. Deactivation of an implantable cardioverter defibrillator should be considered in a patient entering the palliative phase of their illness, or in a patient making an informed end-of-life decision.<sup>39</sup> This decision should be undertaken by the patient, their family, GP and specialist.

#### Drugs to avoid

Many drugs have been shown to exacerbate heart failure.<sup>40</sup> Non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors should be avoided as they cause salt and water retention and impair renal function. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) should be strictly avoided in heart failure with reduced ejection fraction due to their negative inotropic effect. Antiarrhythmic drugs (except beta blockers and amiodarone) and tricyclic antidepressants have pro-arrhythmic potential. Corticosteroids result in salt and water retention. Pioglitazone and some dipeptidyl peptidase 4 (DPP-4) inhibitors may increase the risk of heart failure. Non-potassium sparing diuretics can contribute to digoxin toxicity by causing hypokalaemia, and digoxin concentrations can be increased by amiodarone and spironolactone.

Potential drug-drug interactions occur with various complementary therapies, including St John's wort, black cohosh and grapefruit juice. These should be avoided.

#### Conclusion

The type of heart failure determines its treatment. Echocardiography should be used to confirm the underlying aetiology. Patient education is key to successful management.

ACE inhibitors and beta blockers are the cornerstone of therapy for heart failure with reduced ejection fraction. Aldosterone antagonists are added if the patient is still symptomatic. These three drugs reduce mortality and morbidity. Digoxin and diuretics may also be useful if symptoms persist. The combination of valsartan with sacubitril is an evolving alternative to ACE inhibitors in heart failure with reduced ejection fraction. Drug doses need to be titrated to maximally tolerated doses to obtain the most benefit on symptoms and survival.

No drugs have been shown to improve survival in patients who have heart failure with preserved ejection fraction. Treatment should focus on related problems such as hypertension.

Conflict of interest: none declared

# Q:

#### SELF-TEST QUESTIONS

*True or false?* 1. Digoxin improves survival in patients with heart failure

2. Angiotensin receptor antagonists improve survival in patients who have heart failure with a preserved left ventricular ejection fraction

Answers on page 159

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#### SUMMARY

Naloxone is a competitive antagonist at opioid receptors. It can be administered to reverse the effects of an opioid overdose.

In the face of increasing overdose deaths, from both prescription opioids and heroin, a wide range of people may benefit from increased access to naloxone. It has now been made available on the Pharmaceutical Benefits Scheme and over-the-counter from pharmacies.

After brief training, numerous evaluation studies have confirmed naloxone can be safely administered by laypeople, and is effective in reversing opioid overdose with no abuse potential.

Health professionals are uniquely placed to identify those at risk of opioid toxicity and provide them with a life-saving drug. Training can also be offered to the family and friends of the person at risk of overdose.

#### Introduction

Accidental opioid overdose continues to increase in Australia, now contributing to an average of 1.5 deaths daily.<sup>1</sup> While heroin (diacetylmorphine) may receive more media attention, prescription opioids are now responsible for more overdose deaths. There is therefore a broad and growing population affected by, and at risk of, opioid overdose. Importantly, opioid overdose deaths are preventable.

In the USA, an opioid overdose epidemic has seen a trebling in opioid-related mortality in recent years. In response, expanding the distribution of the opioid antagonist naloxone has been widely recommended.<sup>2-4</sup> Naloxone reverses potentially fatal respiratory depression. Over 18 years, up until 2014, there were approximately 152 000 naloxone kits distributed or prescribed, and over 26 000 successful reversals of overdose were reported.<sup>5</sup>

In Australia the first community distribution program began in the Australian Capital Territory in 2011.<sup>6</sup> There are now small naloxone programs in many areas. Most were established through peer and consumer organisations or drug and alcohol services, but naloxone has not been widely available. On 1 February 2016 naloxone became available as a Schedule 3 medicine. This means it is now available as an over-the-counter drug without prescription, as well as on prescription and subsidised through the Pharmaceutical Benefits Scheme (PBS).

#### Pharmacology

Naloxone is a competitive antagonist at opioid receptors. It has a fast onset of action and short half-life. When administered in the presence of an opioid, naloxone displaces the opioid at the receptor and thus reverses its effects – most importantly it reverses the respiratory depression which causes death. This works for all opioid drugs, such as heroin, oxycodone and morphine. When given intramuscularly naloxone takes a few minutes to start working and its effects last for about an hour. It is approved in Australia for intramuscular, intravenous and subcutaneous use and has been successfully used by ambulance and paramedical staff for the treatment of opioid overdose for over 40 years.

The concept behind broader availability of naloxone, or 'take-home naloxone,' is that this drug has very few adverse effects, has no abuse potential, and is very effective at reversing the effects of opioids.<sup>7</sup> When given to healthy volunteers with no recent opioid exposure, it has no clinical effect.<sup>8</sup> If naloxone is given to someone who is unresponsive for a reason other than opioid toxicity, naloxone is extremely unlikely to cause harm. The greatest risk is transient opioid withdrawal symptoms in someone who is opioid dependent. However, these are uncommon when starting doses of 400–800 micrograms are used.

#### **Community supply**

Most deaths from overdose occur in the presence of another person. In relation to overdoses involving illicit drugs, there may be a reticence to call an ambulance because of fear of police involvement. Broader availability of naloxone among those using and injecting illicit drugs and their friends and family can be life-saving.

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#### Keywords

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This article has a continuing professional development activity for pharmacists available at https://learn.nps.org.au

#### ARTICLE

#### Community use of naloxone for opioid overdose

Around half of the overdoses of prescription opioids involve patients with chronic pain. These patients often have little understanding of the risks of overdose, especially the risks associated with the concomitant use of central nervous system depressants, such as alcohol and benzodiazepines. They and their friends and families need training and it is essential for GPs and pharmacists to facilitate this. Training must include highlighting the risks of overdose and how best to intervene. For this group of patients access to naloxone presents a very good opportunity for early, pre-hospital intervention. Preliminary research in Australia indicates that most chronic pain patients prescribed opioids would either expect to be offered naloxone or would appreciate it.<sup>9</sup> There is therefore a role and an opportunity to consider naloxone supply in a range of populations at risk of opioid overdose.10

The feasibility of a take-home naloxone supply has been demonstrated in Sydney with 30 successful overdose reversals reported in a trial of 83 participants.<sup>11</sup> This is in addition to numerous international studies that have shown that supplying naloxone for layperson administration is safe, feasible and cost-effective.<sup>12-16</sup> The World Health Organization now recommends naloxone as a strategy to reduce overdose deaths.<sup>17</sup>

Among GPs and pharmacists, experience with naloxone may be limited, but there is strong support from pharmacists for overdose prevention and naloxone supply.<sup>18</sup> GPs and pharmacists are uniquely placed to engage with high-risk individuals and their friends and families. It is essential that health professionals are supported to better identify which patients need naloxone, and to train these patients appropriately.

The wider provision of take-home naloxone with overdose training means that a life-saving drug may be immediately available in the place an overdose occurs. Anyone may purchase naloxone over-thecounter, regardless of their own personal risk of overdose. Naloxone may also be prescribed to anyone at risk of overdose, and provided at reduced cost through the PBS.

#### Training

Research shows that laypeople can be trained in 5-10 minutes to appropriately identify an overdose, and intervene. This includes the administration of naloxone.<sup>19</sup> While longer and more detailed training should be available when requested, and could include CPR, evidence shows that brief intervention is effective<sup>19</sup> and may facilitate uptake, whereas longer training may prove a disincentive. Key steps involve positioning the patient to enable breathing, rescue breaths if willing and able, and naloxone injection into the thigh or deltoid (see Box). The training should emphasise the importance of calling an ambulance because sometimes the duration of action of the opioid will exceed that of naloxone. Subsequent doses of naloxone or ongoing medical supervision may be required.

A simple one-page document highlighting important points and summarising the training should be provided. Training resources as well as further background information are available at http://creidu.edu.au/naloxone and www.copeaustralia.com.au/resources.

#### Who should have naloxone?

Any person at risk of an opioid overdose, or those likely to be present at an opioid overdose, should be considered for training. This includes patients on prescribed opioids, particularly those with risk factors for opioid toxicity. It includes anyone using illicit opioid drugs, especially those attending detoxification and rehabilitation services, but also patients taking opioid substitution therapy like methadone and buprenorphine. Regardless of whether opioid use is licit or illicit, anyone at risk of opioid overdose should be considered for naloxone.

The greatest risk of overdose death is when there is a reduced or absent tolerance to opioids. This is often seen after a period of reduced use such as following detoxification or prison. The risk is also high when opioids are taken with other central nervous system depressants, notably alcohol and benzodiazepines. These key risk factors are important to include in any brief training.

### Box Key training information for the use of naloxone

#### Signs of overdose include:

- reduced respiratory rate and depth (that is, not breathing or snoring deeply and turning blue)
- reduced responsiveness, unconsciousness (that is, you cannot wake them up)
- small or pinpoint pupils.

When opioid overdose is suspected:

- position the person to open their airway
- give a few quick mouth-to-mouth breaths if willing and able
- call an ambulance and immediately give an intramuscular dose of naloxone 400 micrograms (in thigh or deltoid)
- continue rescue breathing, and repeat naloxone 400 micrograms every 2–3 minutes until the person begins to wake up.

#### Naloxone supply

Naloxone is available in Australia in prefilled syringes or ampoules. The current prefilled syringe product is known as Prenoxad and contains 2 mg (five 400 microgram doses in a single-use syringe). Importantly this product already contains a needle tip for administration. Ampoules each contain 400 micrograms, and a 3 mL syringe and a 23 g needle are needed to allow administration. Needles can be purchased or may be available through programs that supply clean injecting equipment. Additional materials may be considered, such as skin wipes, gloves and a face mask for rescue breathing.

There is no limit to the quantity of naloxone that may be provided. A supply of multiple doses is recommended as a single dose may not be sufficient to reverse an overdose. Ideally a minimum of two 400 microgram doses should be provided to allow for repeat dosing, or the possibility of a broken ampoule. A PBS prescription enables the supply of five 400 microgram ampoules, or one prefilled and singleuse syringe with five 400 microgram doses.

#### **Common myths and misconceptions**

Reviews have found that expanding the provision of naloxone is not associated with greater risk-taking by patients or any increase in drug use. Another review of two studies that specifically examined opioid use among those who trained with naloxone found a reduction in drug use.<sup>20</sup>

Naloxone will work even with more potent opioids, such as fentanyl. While higher doses of naloxone may be required, a fentanyl overdose can be reversed with naloxone. Buprenorphine has a particularly high affinity at the opioid receptor site so may also require higher doses of naloxone to reverse its effects.<sup>21,22</sup>

Another source of concern is that the recipient will awaken with acute withdrawal and display aggression. Australian experience suggests this problem is uncommon, especially when starting with doses of 400–800 micrograms.<sup>6,11</sup>

#### Conclusion

Deaths from accidental opioid overdose can be prevented by naloxone. Australian healthcare providers need to identify patients at risk of opioid overdose and be actively involved in the provision of brief training and facilitation of naloxone supply. This should involve greater over-the-counter availability as well as increasing prescriptions. A minimum of two 400 microgram naloxone doses along with needles and 3 mL syringes (for ampoules) should be provided, in addition to training. Evidence suggests this can safely and effectively reduce overdose deaths. ◄

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# Lipid lowering in renal disease

#### SUMMARY

Statins reduce the risk of cardiovascular disease in patients with chronic kidney disease who do not require dialysis. However, this benefit diminishes with progression of kidney disease and in transplant recipients.

Current evidence suggests that statins may not reduce cardiovascular risk in patients with advanced chronic kidney disease requiring dialysis.

Evidence for fibrates is more limited but they appear to reduce lipids and cardiovascular events in patients with mild to moderate chronic kidney disease.

There is little evidence for the benefit of starting statins in patients on haemodialysis.

#### Introduction

Chronic kidney disease is characterised by either reduced glomerular filtration rate (GFR) or significant proteinuria. This is associated with increased cardiovascular mortality, which becomes more than 10-fold greater in those on dialysis compared with the general population.<sup>1-3</sup> Renal transplantation lowers this risk, but cardiovascular disease remains the leading cause of death for transplant patients.<sup>4-6</sup>

A characteristic pattern of lipid abnormalities affects those with chronic kidney disease<sup>7,8</sup> and is implicated in the high rates of cardiovascular morbidity and mortality in this population.<sup>9,10</sup> Traditional cardiovascular risk factors such as diabetes and hypertension also contribute. These are prevalent in the chronic kidney disease population along with the proposed cardiovascular risk associated with oxidative stress, inflammation, insulin resistance, anaemia and disturbances of mineral metabolism.

Although statins reduce cardiovascular disease in those at increased risk,<sup>11,12</sup> their effect is less clear in people with chronic kidney disease as most lipidlowering trials exclude these patients or focus on those receiving haemodialysis.

#### Dyslipidaemia

Dyslipidaemia contributes to atherosclerosis and is a modifiable risk factor for cardiovascular disease in the general population. Decreasing low-density lipoprotein (LDL) cholesterol by 1 mmol/L reduces major coronary events by approximately 23% in people with intact renal function.<sup>11-19</sup> This is not found in chronic kidney disease. These patients have a different lipid profile – triglycerides are increased, and LDL may also be lower and decreases even further with dialysis.<sup>7</sup> High-density lipoprotein (HDL) may also be lower<sup>5,7,20,21</sup> and is often defective in the removal of cholesterol from macrophages<sup>22</sup> and in nitric oxide production.<sup>23</sup> These changes are likely to exacerbate uraemic endothelial dysfunction.

In patients on haemodialysis, there is a U-shaped relationship between serum cholesterol and mortality with very low and very high concentrations being risk factors for mortality.<sup>24,25</sup> This is related to the effects of survival bias, malnutrition and inflammation.<sup>26</sup> Some studies report higher mortality in dialysis patients with lower serum cholesterols compared to dialysis patients with normal or high serum cholesterol,<sup>27,28</sup> and others show similar results to what is seen in the general population.<sup>29</sup>

In non-dialysis chronic kidney disease there is an unclear relationship between cholesterol and mortality.

Patients with nephrotic-range proteinuria and hypoalbuminaemia have elevated total serum cholesterol,<sup>7</sup> which according to rat models relates to an upregulation of HMG-CoA reductase.<sup>30</sup> Non-diabetic, non-nephrotic patients with chronic kidney disease also show accelerated atherosclerosis, but in the absence of hypercholesterolaemia.<sup>10</sup>

#### Lipid-lowering treatment in chronic kidney disease

Few studies have looked specifically at lipid-lowering therapy in patients with chronic kidney disease. Most evidence is derived from subgroup or post hoc analyses.

#### Patients not on dialysis

A meta-analysis of statin efficacy in non-dialysis chronic kidney disease stages 1–5 reported an overall decreased risk for cardiovascular mortality and nonlethal cardiovascular events.<sup>31</sup> Statins resulted in a

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#### ARTICLE

#### Lipid lowering in renal disease

RR\* of 0.72 (95% Cl<sup>+</sup> 0.66–0.79) for major cardiovascular events, 0.55 (95% Cl 0.42–0.72) for myocardial infarction, 0.79 (95% Cl 0.69–0.91) for allcause mortality and an uncertain effect on stroke (RR 0.62, 95% Cl 0.35–1.12). Adverse events with statins included elevated creatinine kinase and liver function abnormalities. There was no evidence of an effect on renal function.<sup>31</sup>

The benefit of statins appears to diminish with progression of chronic kidney disease. This probably contributes to the inconsistent relationship in studies between cholesterol-lowering therapy and cardiovascular outcome in chronic kidney disease.<sup>32-40</sup> In a more recent meta-analysis, statin therapy reduced the risk of first major vascular event by 21% (RR 0.79, 95% CI 0.77–0.81) per mmol/L reduction in LDL cholesterol. Smaller relative effects on major vascular events, major coronary events and vascular mortality were observed as GFR declined.<sup>41</sup>

The SHARP trial,<sup>32</sup> which enrolled patients with predialysis chronic kidney disease and those on dialysis, evaluated daily simyastatin 20 mg plus ezetimibe 10 mg or placebo. In the pre-dialysis cohort of 6247 patients (mean GFR of 26.6 mL/min/1.73 m<sup>2</sup>), LDL cholesterol fell by 0.85 mmol/L over five years. These patients had a 17% RR reduction in major atherosclerotic events (RR 0.83, 95% CI 0.74-0.94) compared with placebo and the number needed to treat was 48. This compares favourably with numbers needed to treat in primary prevention studies of statins in the general population.<sup>42,43</sup> There was a significant reduction in non-haemorrhagic stroke (RR 0.75, 95% CI 0.60-0.94) and in arterial revascularisation procedures (RR 0.79, 95% CI 0.68–0.93), but no effect on progression of chronic kidney disease.44

The rate of adverse events in the SHARP trial was low – myopathy was reported in 0.02% of patients and there was no evidence of increased hepatitis, gallstones, pancreatitis or malignancy in the lipid-lowering group. While this is the largest trial of lipid-lowering drugs in patients with chronic kidney disease to date, it failed to evaluate the role of a statin or ezetimibe alone. Other trials of lipid-lowering therapy in non-dialysis chronic kidney disease show considerable heterogeneity both in study design and impact on cardiovascular end points. For trial details see the Table.<sup>32-39</sup>

Evidence for fibrates in chronic kidney disease is limited. However, a meta-analysis evaluating the evidence for cardiovascular benefit with use of benzafibrate (2 studies), gemfibrozil (2 studies) and fenofibrate (4 studies) reported that fibrates reduced serum lipids, albuminuria and major cardiovascular events (RR 0.70, 95% CI 0.54–0.89) in a subgroup of patients with a GFR 30–59.9 mL/min/1.73 m<sup>2</sup> but had no effect on all-cause mortality.<sup>45</sup> Fibrates were associated with serum creatinine elevations (33 micromol/L, p<0.001) but not an increase in risk of progression to end-stage kidney disease, although the confidence intervals for this outcome were very wide (RR 0.85, 95% CI 0.49–1.49). There was no clear effect of fibrates in patients on dialysis with respect to cardiovascular outcomes or mortality.

#### Guidelines

Overall evidence suggests that statin therapy in nondialysis chronic kidney disease reduces the risk of major cardiovascular events similar to the reduction seen in the general population. The greatest benefit for statins and fibrates in chronic kidney disease appears to be in patients with mild to moderate renal impairment (GFR 30–60 mL/min).<sup>31,40,45</sup> However, the Pharmaceutical Benefits Scheme (PBS) does not subsidise statin therapy for chronic kidney disease in the absence of other indications.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines<sup>46</sup> recommend statin therapy for all chronic kidney disease patients aged 50 years or older and for younger patients who have additional risk factors for coronary heart disease.

While there is no evidence of more adverse events with higher doses of statins compared to the general population, the KDIGO guidelines recommend reducing the dose in individuals with a GFR of less than 60 mL/min/1.73 m<sup>2</sup>. This is based on reduced renal excretion, increased polypharmacy and comorbidity as well as the doses of statin used in chronic kidney disease trials.<sup>46</sup> The guidelines advise against a statin/fibrate combination in patients with chronic kidney disease.

Kidney Health Australia's Caring for Australasians with Renal Impairment (CARI) guidelines are more expansive in their recommendations. They advocate treating all patients with mild-moderate chronic kidney disease with a statin or statin/ezetimibe combination regardless of cardiovascular risk.<sup>47</sup> There are no recommended targets for LDL cholesterol and lipid concentrations based on a diagnosis of chronic kidney disease.<sup>46,47</sup>

#### Patients on dialysis

In addition to the SHARP trial,<sup>32</sup> there have been two major placebo-controlled randomised trials of statin therapy in haemodialysis patients –  $4D^{39,48}$  and AURORA.<sup>38</sup> The 4D study evaluated the effect of 20 mg atorvastatin on cardiovascular disease and death. It included only patients with diabetes and a high cardiovascular disease burden. Despite a profound

<sup>\*</sup> relative risk

<sup>&</sup>lt;sup>+</sup> confidence interval

Table Majo	r lipid-lowe	ring trials in c	hronic kidney d	lisease and dialysis	populations			
Trial	Number of patients	Population	Duration	Statin dose (fixed vs titrated)	Treatment- naïve* or treatment- experienced	Relative hazards for cardiovascular events	Absolute risk reduction in cardiovascular events	Changes in LDL
PREVEND IT 2004 <sup>33</sup>	864	CKD (stage 1)	Mean 4 years	Pravastatin 40 mg	Naïve	HR 0.87 (95% Cl 0.49–1.57), p=0.647	0.8%	LDL reduction 1.0 mmol/L at 4 years
AFCAPS/ TexCAPS <sup>34</sup>	304	CKD (stages 3 and 4)	Mean 5.3 years	Lovastatin 20 mg dose titrated as per LDL levels at 3 months	Naïve	Adjusted HR 0.31 (95% CI 0.13-0.72), p≤0.01 Unadjusted HR 0.41 (95% CI 0.18- 0.91)	7.7%	LDL reduction 1.1 mmol/L at study end
JUPITER 2010 <sup>35</sup>	3267	CKD (stages 3 and 4)	Median 1.9 years	Rosuvastatin 20 mg	Naïve	HR 0.55 (95% Cl 0.38-0.82), p=0.002	1.9%	LDL reduction 1.4 mmol/L at 4 years
ALLIANCE 2009 <sup>36</sup>	579	CKD (stage 3)	Median 4.5 years	Atorvastatin 10 mg titrated to LDL every 4 weeks vs 'usual care', continuation of existing lipid-lowering drugs	Continuation without washout or run-in	HR 0.72 (95% CI 0.54-0.97), p=0.02	8.6%	LDL reduction 1.3 mmol/L at study end
LIPS substudy 2004 <sup>37</sup>	310	СКD	Mean 3.8 years	Fluvastatin 40 mg twice a day	Naïve	HR 0.52 (Cl not specified), p=0.004	14%	LDL reduction 0.8 mmol/L at 6 weeks
AURORA 2009 <sup>38</sup>	2776	Dialysis	Median 3.8 years Mean 3.2 years	Rosuvastatin 10 mg	Naïve	HR 0.96 (95% CI 0.84-1.11), p=0.59	0.3%	LDL reduction 1.1 mmol/L at 3 months
4D 2005 <sup>39</sup>	1255	Dialysis	Mean and median of 4 years	Atorvastatin 20 mg	Discontinued <sup>+</sup> with 4-week run-in	HR 0.92 (95% Cl 0.77-1.10), p=0.37	1.4%	LDL reduction 1.3 mmol/L at 4 weeks‡
SHARP 2011 <sup>32</sup>	9270	Mixed	Median 4.9 years	Simvastatin 20 mg plus ezetimibe 10 mg	Discontinued <sup>+</sup> with 6-week run-in	HR 0.83 (95% CI 0.74-0.94), p=0.0021	2.1%	LDL reduction 0.85 mmol/L at study end
Cl confiden CKD chronic k	ce interval idney disease							

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Any patient previously taking a statin at randomisation had their statin discontinued over a run-in period.

Note that LDL levels also fell in the placebo group but more slowly.

The statin is newly introduced to a patient who has never previously taken a statin.

HR hazard ratio LDL low-density lipoprotein

\* + ++

ARTICLE

#### Lipid lowering in renal disease

reduction of LDL cholesterol early in the trial, there was no significant impact on major cardiovascular events or all-cause mortality. A higher rate of haemorrhagic stroke was observed in the atorvastatin group. Post hoc analysis revealed that atorvastatin was beneficial with respect to cardiac events and all-cause mortality in patients with a high baseline LDL.<sup>48</sup>

AURORA investigated the effect of rosuvastatin in haemodialysis patients and likewise found no significant impact on major cardiovascular events.<sup>38</sup> The study also reported an increased incidence of fatal haemorrhagic stroke with rosuvastatin in patients with diabetes, reinforcing the adverse outcomes noted in the 4D study. While the SHARP trial reported a reduction in major atherosclerotic events in the study population overall, a subgroup analysis of those on dialysis revealed no benefit (RR 0.9, 95% CI 0.75–1.08).<sup>32</sup>

A recent meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration indicated there was no benefit in terms of major vascular events, major coronary events or vascular mortality to support statin use in dialysis patients.<sup>41</sup>

#### Guidelines

Taken together, the available evidence for statin therapy in patients on dialysis suggests minimal to no benefit and possible risk of harm. The KDIGO guidelines conclude that statins cannot be recommended for prevention of cardiovascular events in these patients. They advise against commencing statins with the caveat that patients with recent coronary events and young patients awaiting renal transplantation may derive benefit despite a lack of current data to support this claim.<sup>46</sup> There is no conclusive evidence to guide care for patients already on a statin or statin/ezetimibe who commence dialysis.<sup>5</sup>

#### After renal transplantation

Recipients of renal transplants suffer the burden of chronic kidney disease due to the legacy effect of chronic uraemia before transplantation, as well as the risk associated with graft dysfunction in the posttransplantation period. Immunosuppression increases their susceptibility to infection and chronic inflammation, and promotes dyslipidaemia, hypertension, obesity

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and hyperglycaemia. All of these changes are likely to increase their cardiovascular risk.<sup>49-51</sup>

The ALERT<sup>52</sup> study is the largest randomised placebo-controlled trial of statins in a renal transplant population. After 5.1 years of follow-up, the trial failed to show an overall decrease in major cardiovascular events with fluvastatin despite significant reductions in cholesterol. Fewer cardiac deaths and non-fatal myocardial infarctions were seen in the treatment group (RR 0.65, 95% CI 0.48–0.88) compared to placebo but the frequency of coronary revascularisation procedures was not significantly different. A two-year open-label extension of ALERT indicated a significant difference in time to major cardiovascular event (RR 0.79, 95% CI 0.63–0.99) and a 29% reduction in cardiac death or non-fatal myocardial infarction (hazard ratio 0.71, 95% CI 0.55–0.93).<sup>53</sup>

A recent systematic review included several smaller trials of statins after kidney transplantation. It reported no significant cardiovascular or mortality benefits but suggested that statin therapy may increase risk of stroke.<sup>54</sup>

#### Guidelines

The KDIGO and CARI guidelines recommend statins in kidney transplant recipients but, given the potential for drug interactions, suggest low doses and cautious up-titration particularly when co-administering with ciclosporin.<sup>46,47</sup> When switching from tacrolimus to ciclosporin, statin doses should be reduced.<sup>46</sup>

#### Conclusion

Statin therapy appears to offer some benefit in patients with renal disease who are not on dialysis and to a more limited extent after transplant. There is no evidence to support commencing statins in those receiving dialysis. Evidence supports the safety of statins in chronic kidney disease but caution is advised with high doses and when there is a potential for drug-drug interactions.

Conflict of interest: none declared

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# Encouraging adherence to long-term medication

#### SUMMARY

Non-adherence to medicines is common in patients with chronic disease and in those prescribed preventive medication. It can be intentional, unintentional, or both.

Non-adherence reduces the effectiveness of prescribed medicines and may lead the prescriber to escalate treatment unnecessarily and potentially dangerously.

Patient education, shared decision making, pharmacist support and motivational interviewing reduce intentional non-adherence.

Interventions to reduce unintentional non-adherence address patient factors including misunderstanding, confusion or forgetfulness, and factors beyond the patient's control such as cost.

Patients should be asked about adherence at every consultation. A collaborative communication style is effective, using the patient's own expressions and responding to their cues. Normalising non-adherence, and starting with open questions then following up with more specific probes, can also help.

Electronic reminders, such as text messaging, have been shown to increase medication adherence.

#### Introduction

In developed countries approximately 50% of patients living with chronic disease do not adhere to treatment recommendations.<sup>1</sup> A similar proportion do not take preventive medicines as prescribed.<sup>2</sup> Some patients do not start their prescribed drugs. Of those who do, many subsequently discontinue. Nonadherence is a major reason why treatments shown to be efficacious in trials are often less effective in clinical practice.

Non-adherence can be classified as intentional or unintentional.<sup>3</sup> Both reasons may contribute to non-adherence in an individual.

#### Intentional non-adherence

Intentional non-adherence is when a patient actively decides not to take a drug or follow treatment recommendations. It is likely to reflect the patient's attitudes to medicines in general, and their specific beliefs and concerns about the treatment recommended and the disease being treated.<sup>4</sup> A study of 99 adults and young people living with asthma identified several themes that predicted adherence to preventer medication. These included the perceived necessity of treatment, safety concerns, acceptance of disease chronicity, beliefs about treatment effectiveness, ease of use and satisfaction with asthma management.<sup>5</sup> The opinions of friends and family, concerns about adverse effects, and

experience of adverse effects were particularly salient. Studies of intentional non-adherence to other types of medication for a wide range of diseases have shown similar results.<sup>6</sup> These findings illustrate the importance of patients' own experiences and the views of significant others in informing the decision to take medicines.

#### **Unintentional non-adherence**

Unintentional non-adherence is unplanned by the patient. Causes include misunderstanding or forgetfulness, and factors beyond the patient's control such as an inability to access prescribed treatment. Multiple studies have shown that treatment complexity, cognitive impairment, cost and other practical difficulties (e.g. opening medicine bottles or difficulty swallowing pills) may reduce adherence.<sup>1</sup>

#### **Detecting non-adherence**

Non-adherence reduces the patient's potential to benefit from treatment. It may also lead to unnecessary and potentially dangerous escalation of medicines.

Clinicians are poor at detecting non-adherence. In a study of 1169 patients being treated for hypertension, their doctors recognised non-adherence in fewer than half of those whose pharmacy records indicated significant gaps in dispensing. Prescribers often

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intensified treatment even when they suspected significant non-adherence.<sup>7</sup> Patients should be asked about adherence at every consultation, and a poor response to treatment should always prompt detailed enquiry. A number of standardised questionnaires have been developed to measure adherence but they are not readily incorporated into routine clinical use and their psychometric properties are limited in that setting.<sup>8</sup>

Patients should be asked about adherence at every consultation A small number of studies have examined different styles of questioning by prescribers for detecting non-adherence.<sup>9-11</sup> Effective strategies include a collaborative style, using the patient's own expressions in responding to their utterances and cues, normalising non-adherence, and starting with open questions then following up with more specific probes (see Box).

In one study, questions that asked directly about missed doses were almost four times more likely to elicit disclosure of non-adherence than other question types.<sup>11</sup> Disclosure can be followed up with a more detailed enquiry and discussion of ways to promote adherence and overcome barriers.

# Addressing intentional non-adherence

A systematic review explored patient-centred interventions to improve adherence, including patient education, shared decision making and pharmacist support.<sup>12</sup> Many educational interventions resulted in better adherence and greater patient knowledge. However, their impact on adherence typically decreased over time. Shared decision making (including the use of decision aids) increased patient

# Box Asking about adherence to medicines during a consultation

Doctor:	How are you going with taking your pills?
	[Open question using the patient's usual name for their tablets]
Patient:	Yes, good
Doctor:	Remembering to take them regularly?
	[Gentle probe question]
Patient:	Yes, usually
Doctor:	Many people forget to take their pills occasionally
	[Normalising statement responding to patient's answer to the probe question]
Patient:	Hmm
Doctor:	Just thinking about the last couple of weeks – have you missed taking your pills any occasion?
	[Specific probe asking directly about missed doses]

knowledge, but adherence improved in only two out of four studies.<sup>12</sup> Adherence also improved with interventions by pharmacy staff, when they were tailored to patient needs, often involving both face-toface and telephone encounters.

Motivational interviewing is a patient-centred counselling technique that aims to encourage behaviour change by reinforcing positive intentions and challenging negative ideas. It has been shown to improve adherence in a variety of settings.<sup>13,14</sup> However, not all studies show benefit and the time pressures of routine clinical practice can limit applicability.<sup>15</sup>

# Reducing unintentional non-adherence

Interventions that address unintentional nonadherence seek to reduce barriers and improve the patient's ability to take medicines as prescribed. A wide range of strategies has been studied.

#### Cost

Out-of-pocket cost is a well-recognised barrier to accessing medicines.<sup>16</sup> In a recent survey, the Australian Bureau of Statistics reported that 7.6% of patients who had received a prescription delayed getting the medicine, or did not get it at all, due to cost. The proportion was even higher in areas of disadvantage.<sup>17</sup> Prescribers may be able to reduce the impact of cost by, for example, prescribing generic or lower cost medicines when appropriate. Pharmacists may also assist patients by recommending lower cost brands.

#### Drug regimen

on

Patients can be confused by the number and variety of medicines they need to take. Adherence has long been known to be inversely associated with the complexity of the regimen.<sup>18</sup> Prescribers should aim to simplify this as much as possible. Discussion with a pharmacist may assist, particularly with tailoring appropriate preparations, formulations and packaging for the individual (e.g. people with an inability to swallow).<sup>19</sup> These consultations may be rebatable in Australia using the Medicare medication management review items. It may be possible to reduce the frequency of administration, introduce combination medicines, or even deprescribe in some instances.<sup>20</sup>

It is good practice to provide patients with a printed list of their medicines and the times of day when they should be administered. Alternatively, the patient may be encouraged to use a smartphone app such as the NPS MedicineWise MedicineList+. The patient's understanding of their regimen should be checked. For patients with cognitive impairment, the support of a carer to encourage or assist with administration is essential. Brand swapping when medicines are dispensed may cause confusion and impair adherence. Pharmacists have a responsibility to educate patients if they swap brands, and prescribers should explain to patients and carers when they may be offered a choice.

Fixed-dose combinations can be helpful for patients on multiple medicines, and have been shown to improve adherence in some circumstances.<sup>21</sup> Starting treatment with combination medicines has a strong evidence base in the management of HIV and other infections. For conditions such as hypertension, the evidence for starting with more than one medicine is mixed, but the strategy should be considered.<sup>22</sup>

#### Patient reminders

Reminder packaging, which incorporates a date or time for a medicine to be taken, is an effective way of promoting adherence and has been shown to improve biological outcomes in type 2 diabetes and hypertension.<sup>23</sup> Drug administration aids are a form of reminder packaging and may be particularly helpful for patients prescribed multiple medicines. However, they are not suitable in all circumstances.<sup>24</sup> The stability of some drugs may be compromised by repackaging.<sup>25</sup> Patients with impaired cognition, eyesight or dexterity often have difficulty using them. Repackaging by the pharmacist may increase the cost to the patient and filling a compartmentalised box at home can lead to errors. Also, such boxes are rarely childproof.<sup>26</sup>

There is strong evidence that regular reminders are an effective strategy for increasing adherence.<sup>27</sup> Electronic devices can assist with this. In a randomised controlled trial, 143 adults with asthma used combination fluticasone propionate/salmeterol inhalers with attached electronic monitoring devices. The device recorded inhaler activation and provided twice-daily reminders for missed doses to those in the intervention group. Over six months, adherence was over 50% higher in the intervention group than in the control group.<sup>28</sup>

A meta-analysis evaluating the use of text messaging in adults with chronic disease found it doubled the odds of adherence across 16 randomised controlled trials. The effect was not dependent on message characteristics such as personalisation, two-way communication or daily frequency.<sup>29</sup>

As new information and communication technologies develop, new strategies for promoting and monitoring adherence are emerging. An example is 'smart pills' which send a signal to an external monitor when a tablet has been ingested. The signal can be linked to automated adherence reminders and to a medication reconciliation system.<sup>30</sup>

#### Conclusion

Medicines do not work if they are not administered. Non-adherence, whether by intent or due to cost, complexity, or forgetfulness, is a major cause of reduced effectiveness and hence of preventable morbidity and mortality. Evidence-based strategies are available to address both intentional and unintentional non-adherence.

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# The role of cardiac imaging in clinical practice

#### SUMMARY

The selection of cardiac imaging modality depends on the indication, individual patient characteristics and local accessibility.

In many cases echocardiography, including stress echocardiography, can provide the required clinical information and avoids radiation exposure.

CT coronary angiography is increasingly used to detect coronary artery disease in patients with an intermediate risk and in those with equivocal stress test results.

Cardiac MRI studies are ordered by a patient's cardiologist as an adjunct to other imaging modalities when further clarification is warranted.

#### Introduction

A variety of clinical presentations including dyspnoea, chest pain, syncope and palpitations may arouse suspicion of cardiovascular disease. Following a clinical history and examination, imaging of the heart may be required. Cardiac imaging is also used to monitor patients with known pathology in many cardiovascular diseases such as interval monitoring of aortic stenosis.

The choice of cardiac imaging modality depends on the disease being investigated, individual patient characteristics and the accessibility of tests. Assessment of dyspnoea and investigation for coronary artery disease are two of the most common clinical scenarios that may require cardiac imaging. Imaging is also indicated in the diagnosis of cardiomyopathy, and structural or congenital heart disease.

#### Dyspnoea

If a cardiac aetiology is suspected, a targeted investigative approach with clinical follow-up is prudent to ensure correct diagnosis and appropriate specialist referrals.

#### Chest X-ray

Chest X-ray has a role in the preliminary assessment of cardiovascular disease. An increase in heart size and the presence of increased pulmonary vascular markings or pleural effusions may indicate pulmonary congestion secondary to cardiac failure. A chest X-ray may also help exclude pulmonary pathology such as infection, malignancy or fibrosis. Importantly, a normal chest X-ray cannot reliably exclude cardiac aetiology in a patient presenting with dyspnoea. It may not show significant pathologies including valvular heart disease and pulmonary arterial hypertension.

#### Echocardiography

Transthoracic echocardiography has many uses (see Box) and is relatively accessible. It can be extremely useful for evaluating dyspnoea. In many cases it provides structural and functional information that indicates a particular diagnosis (see Fig.).

Echocardiography can provide diagnostic information in suspected cases of cardiac failure and in the diagnosis of valvular heart disease when a patient is found to have a murmur that warrants investigation. Congenital heart disease such as septal defects can be identified on echocardiography. Echocardiography can also provide a non-invasive estimation of pulmonary arterial systolic pressure and identify other features consistent with the presence of pulmonary arterial hypertension.

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#### Keywords

cardiac MRI, computed tomography coronary angiography, echocardiography, nuclear cardiology, X-ray

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#### Box Uses of transthoracic echocardiography

Quantification of ventricular and atrial size Measurement of left and right ventricular ejection fraction Detection of left ventricular hypertrophy Detection of features of diastolic dysfunction Estimation of left atrial pressure Estimation of pulmonary artery systolic pressure (see Fig. 1d) Detection of regional wall motion abnormalities (which may indicate underlying ischaemic heart disease) Assessment of valvular lesions (including their mechanism and severity) Detection and quantification of intra-cardiac shunts





- a Left ventricle chamber measurement in the parasternal long-axis view
- b Colour doppler demonstrating central aortic regurgitation
- c Tricuspid regurgitant jet evident on colour doppler imaging
- d Peak velocity of the tricuspid regurgitant jet (used to estimate pulmonary artery systolic pressure) this is unable to be adequately detected in approximately 30% of patients undergoing echocardiography
- e Video demonstrating a dilated left ventricle with severe left ventricular dysfunction [see online version]
- f Video demonstrating a case of hypertrophic cardiomyopathy with markedly increased myocardial wall thickness, systolic anterior motion of the mitral valve and dynamic left ventricular outflow tract obstruction [see online version]

A limitation of echocardiography is the difficulty in obtaining interpretable ultrasound images in some patients. For example, in those with obesity or lung disease (like emphysema) the ability of echocardiographic images to be transmitted across airspace is compromised due to increased lung volumes.

#### When imaging for dyspnoea is inconclusive

When initial cardiac imaging is non-diagnostic or inconclusive and respiratory conditions have been excluded, coronary artery disease should be considered.

#### **Coronary artery disease**

The accurate diagnosis of coronary artery disease, either non-obstructive or obstructive, is crucial in guiding management for patients presenting with chest pain (Table).<sup>1</sup>

#### Stress ECG

Stress ECG is a cheap, safe and accessible test but it has low sensitivity and specificity for coronary artery disease, and therefore has a limited role in evaluating patients with chest pain. It can be used for assessing low-risk patients who present to an emergency department with chest pain when acute coronary syndrome has been excluded. It also has a limited role in patients with known coronary artery disease to assess symptom control with medical therapy and can help to identify those who may benefit from augmented anti-anginal therapy or coronary revascularisation.<sup>2,3</sup>

#### Stress echocardiography

Stress echocardiography provides an effective, noninvasive assessment of patients with chest pain. The added structural and functional information gained from this test can often be very useful. It is generally accessible and diagnostically reliable. Compared with nuclear stress perfusion studies, it avoids radiation exposure, has greater specificity and is substantially less costly to the public health system. It can be performed using a bicycle or treadmill, or with pharmacological stress (e.g. with dobutamine) in those unable to exercise.

#### CT coronary angiography

CT coronary angiography directly visualises the coronary arteries for both non-obstructive and obstructive coronary artery disease. Thus, it is considered a highly effective first-line investigation in patients with a low-intermediate predicted risk of coronary artery disease.<sup>2</sup> However, it does not tell the physician whether a coronary stenosis is haemodynamically significant, which requires a functional study such as stress echocardiography or nuclear stress perfusion. Detection of coronary plaque via CT coronary angiography may help to determine whether medical therapy such as long-term statins are indicated.

CT coronary angiography is also very useful for patients with an equivocal result from a stress test. Radiation exposure is lower than with invasive coronary angiography and nuclear stress perfusion testing. CT is also significantly less expensive and avoids the small associated risks of invasive coronary angiography. A heart rate of 60 beats per minute or less is required to optimise image quality for adequate interpretation. Temporary oral and intravenous beta blockers in combination with ivabradine are used to achieve this.

#### CT coronary calcium scoring

Detection and quantification of coronary artery calcification using multidetector computer tomography has emerged as a technique that may predict the risk of future cardiovascular events in individuals at intermediate risk of coronary artery disease. The degree of calcification can be quantified (via a score) and the patient's burden can be graded into age-specific quartiles. Multiple, large observational studies have shown that those with significantly elevated scores are at greater risk of myocardial infarction. The absence of calcification is also highly predictive of the absence of significant coronary stenosis and confers a favourable cardiac prognosis.<sup>4</sup> Calcification scores have no role in the evaluation of patients presenting with chest pain. Its use is reserved for assessing the risk of future cardiac events and to

#### Table Cardiac imaging for detection of coronary artery disease

	Cost* (MBS)	Sensitivity (%)	Specificity (%)	Radiation	Comments
Exercise stress ECG	\$152.15	68	70-77	-	Limited role. Primarily in the evaluation of low-risk chest pain
Exercise/dobutamine <sup>†</sup> stress echocardiography	\$261.65	80-85	84-86	-	Generally accessible and provides additional structural and functional information
CT coronary angiogram	\$700.00	85-99	64-90	2-5 mSv	Evaluation of chest pain in patients with intermediate risk and in those with equivocal stress test
Nuclear stress perfusion	\$565.30- \$834.90	85-90	70-75	9–11 mSv	Role in patients with stress echocardiography that cannot be interpreted (poor ultrasound images, previous myocardial infarction, bundle branch block)

MBS Medicare Benefits Schedule

\* as of December 2016

<sup>†</sup> dobutamine can be used in those with limited mobility Source: Reference 1

#### DIAGNOSTIC TESTS

#### Cardiac imaging in clinical practice

guide clinicians about whether primary prevention of ischaemic heart disease with statin therapy is appropriate. This is reserved for patients with an intermediate risk determined using a risk calculator such as the Framingham Risk Score.<sup>4</sup> Despite data from numerous observational studies, improvement in cardiovascular outcomes in those who take primary prevention therapy in the context of an elevated calcification score remains contentious.<sup>4</sup>

#### Nuclear stress perfusion

Nuclear stress perfusion has a role in the evaluation of chest pain in specific clinical settings such as patients with bundle branch blocks, poor echocardiographic images and in those with previous myocardial infarction or previous coronary artery bypass surgery. Local availability of other tests may also necessitate its use.

Similar to stress echocardiography, nuclear stress perfusion can be performed with exercise or drugs. The indications for a nuclear stress perfusion study are similar to stress echocardiography. However, because of its higher cost, radiation exposure and lower specificity, nuclear stress perfusion is reserved for when stress echocardiography cannot be interpreted or is unavailable.

# Cardiomyopathy, structural heart disease and congenital heart disease

Transoesophageal echocardiography and cardiac MRI have a role in a number of clinical scenarios and are useful adjuncts when there is not enough other diagnostic information.

#### Transoesophageal echocardiography

Transoesophageal echocardiography is generally performed with both local (oral lidocaine (lignocaine) topical spray) and intravenous anaesthesia.

It is useful for:

- diagnosis of infective endocarditis
- clarifying the mechanism and severity of valvular heart disease (such as mitral regurgitation)
- assessment of cardiac shunts (such as atrial septal defects)
- assessment of left atrial appendage performed before cardioversion to exclude thrombus
- identification of a cardiac source of embolism or a predisposing congenital heart lesion in patients diagnosed with a cryptogenic stroke
- providing additional diagnostic information to transthoracic echocardiography in assessment of prosthetic heart valves in cases of suspected prosthetic valve dysfunction or prosthetic valve endocarditis.

When assessing congenital heart disease, transoesophageal echocardiography can overcome many of the limitations of transthoracic echocardiography in delineation and visualisation of cardiac chambers, intra-cardiac shunts and in the monitoring of patients with previous surgery. Examples of its use in congenital heart disease include identifying and quantifying atrial septal defects and anomalous pulmonary venous drainage, and detecting the complications of previous corrective surgery for congenital heart disease.

#### Cardiac MRI

Cardiac MRI is very specialised and access is limited. In Australia, cardiologists request cardiac MRI when additive information to other testing is required. The only current indications with a Medicare rebate are the assessment of a cardiac mass, congenital heart disease and in bicuspid aortic valve disease.<sup>5</sup> It is useful in bicuspid aortic valve disease for detecting and monitoring associated aortopathy, detecting the presence of aortic coarctation and in quantifying the severity of aortic regurgitation by measuring regurgitant volumes.

Cardiac MRI avoids the repeated radiation exposure of CT in those requiring interval studies. However, it has a number of important contraindications and completion of an MRI safety questionnaire is required before undertaking a study. Contraindications include patients with metallic implants (such as aneurysm clips and neurostimulators) and those with an implanted cardiac pacemaker or defibrillator. However, a growing number of cardiac devices are now considered to be compatible with MRI (termed MRI-conditional).<sup>6</sup>

Cardiac MRI may be useful in the following cardiomyopathies:

- hypertrophic cardiomyopathy
- arrhythmogenic right ventricular cardiomyopathy (due to its superior ability in comparison to transthoracic echocardiography for visualising the right ventricle)
- infiltrative cardiomyopathies (such as sarcoidosis or amyloidosis).

Cardiac MRI is the imaging modality of choice to diagnose myocarditis by detecting myocardial inflammation and myocardial oedema using a number of specific MRI sequences.<sup>7</sup>

#### Conclusion

Thorough clinical assessment before requesting cardiac imaging is crucial in formulating a differential diagnosis so that the appropriate test is requested and the imaging study can be targeted effectively.

Cardiac imaging is an integral aspect in the diagnosis and monitoring of cardiovascular

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disease. CT coronary angiography and cardiac MRI are both relatively recent in their clinical use compared to echocardiography and nuclear cardiac studies, but both provide extremely valuable and additive information to other modalities when used appropriately.

Conflict of interest: none declared

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# Complications with oxycodone and naloxone

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#### Case 1

A 43-year-old woman with metastatic breast cancer was admitted with constipation. She had liver metastases, ascites and impaired synthetic function (Child-Pugh B),<sup>1</sup> but aspartate aminotransferase and alanine aminotransferase were within normal limits. Her analgesia was changed from sustained-release morphine to a combination product of prolongedrelease oxycodone with naloxone. Within two hours of the first dose she developed severe pain. This was uncontrolled by morphine and ketamine infusion.

The pain persisted for 12 hours after receiving the prolonged-release oxycodone with naloxone. The patient was recommenced on her previous morphine regimen and achieved ongoing stable pain control.

#### Case 2

A 50-year-old man with metastatic prostate cancer had increasing pain despite increasing doses of prolonged-release oxycodone with naloxone (up to 40/20 mg twice daily) plus controlledrelease oxycodone (10 mg twice daily). The man reported no effect from using immediate-release oxycodone for breakthrough pain. He had liver metastases but aspartate aminotransferase and alanine aminotransferase were within normal limits (Child-Pugh A).

The prolonged-release oxycodone with naloxone was ceased and controlled-release oxycodone 20 mg twice daily was commenced (a significantly lower opioid dose). Within two days, the patient's pain and functional status greatly improved enabling his cancer therapy to be resumed.

#### Case 3

A 51-year-old man with a sacral chondrosarcoma and poorly controlled pain became narcotised (lifethreatening overdose) when prolonged-release oxycodone with naloxone was ceased while on a stable dose of methadone. Once the methadone was cleared over the next few days his analgesia was significantly improved on a comparatively lower dose morphine infusion (without the multiple adjuvant analgesics previously required). He had no liver metastases, normal aspartate aminotransferase and alanine aminotransferase (Child-Pugh A) with fatty liver on ultrasound.

#### Comment

The combination of prolonged-release oxycodone with naloxone is marketed to reduce pain and opioidinduced constipation. Naloxone aims to counteract the effect of oxycodone on the gut over 12 hours as it antagonises opioid receptors in the gastrointestinal tract. As naloxone then undergoes extensive first-pass metabolism in the liver, insignificant amounts enter the systemic circulation. In healthy people its bioavailability is less than 3%. The combination is contraindicated in moderate-severe liver dysfunction (Child-Pugh B–C).

We have observed prescription of higher than recommended doses and the commencement or continuation of prolonged-release oxycodone with naloxone despite deteriorating liver function. This needs to be avoided. If a patient with liver impairment is changed from oxycodone with naloxone to a single opioid formulation, start with a lower equivalent dose of the new opioid (i.e. 50% of the approximate equianalgesic dose) and monitor the patient carefully for adverse effects or toxicity.<sup>2</sup>

In cases 1 and 2 liver metastases appeared to be associated with a systemic effect of naloxone, despite normal or only mildly abnormal liver function. In case 3, the patient became narcotised due to the methadone effect after the opioid antagonist effect of naloxone had worn off. The patient's naloxone concentrations may have been higher than expected due to fatty liver disease, or through an interaction with methadone which has been shown to reduce the metabolism of naloxone.<sup>3</sup>

These and other published cases<sup>4-6</sup> suggest reduced first-pass metabolism results in increased concentrations of naloxone reaching the systemic circulation and antagonising the effect of opioids. This causes reduced analgesia and elevates the risk of opioid overdose when changing between opioids. The explanation could be a reduced liver capacity to metabolise naloxone.

#### Recommendations

We suggest:

- not using prolonged-release oxycodone with naloxone if there is any degree of liver dysfunction as there is a risk of poor analgesia or withdrawal
- avoiding prolonged-release oxycodone with naloxone in combination with other long-acting opioids, especially methadone

 further research to understand how to safely cease or rotate the prolonged-release oxycodone with naloxone when prescribed alone or with other opioids to reduce the risk of opioid toxicity.

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### Paediatric Injectable Guidelines. 5th ed.

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Aust Prescr 2017;40:158 https://doi.org/10.18773/ austprescr.2017.049

#### Lilley L, Legge D.

Parkville, Vic.: The Royal Children's Hospital Melbourne; 2016.

#### 90 pages

#### Also available online at www.rch.org.au/pig

The latest edition of this book contains 287 up-todate drug monographs. They provide advice on preparation and administration of injectable medications. The information is specific to the paediatric setting with details such as powder

The Rayal Diddewys Hospital

Paediatric Injectable Guidelines 5th edition

volume to calculate part vial doses, maximum concentrations to reduce fluid volume, and line access considerations. Precautions around administration are also given without distracting the user with unnecessary detail.

Some monographs, however, lack specialised detail that is occasionally required in the

paediatric setting. For example, dilution advice for subcutaneous injection of small doses of enoxaparin is not included but hopefully will be considered for future editions.

The Parenteral Nutrition and Fat Emulsion compatibility information is an extremely valuable section of the book. It provides advice on intravenous drugs which can and cannot be run concurrently via Y-site. Users should, however, interpret the information with caution to ensure their patient's parenteral formulation is comparable to The Royal Children's Hospital Melbourne preparations.

With safety features such as tall-man lettering, easy-to-read formatting and concisely written information, it is an essential resource to have in a busy environment. The book is physically robust. It is resilient to water and does not glare under bright lighting. These guidelines provide reliable, comprehensive and specific information for practitioners working in paediatric settings.



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