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Cardiovascular disease

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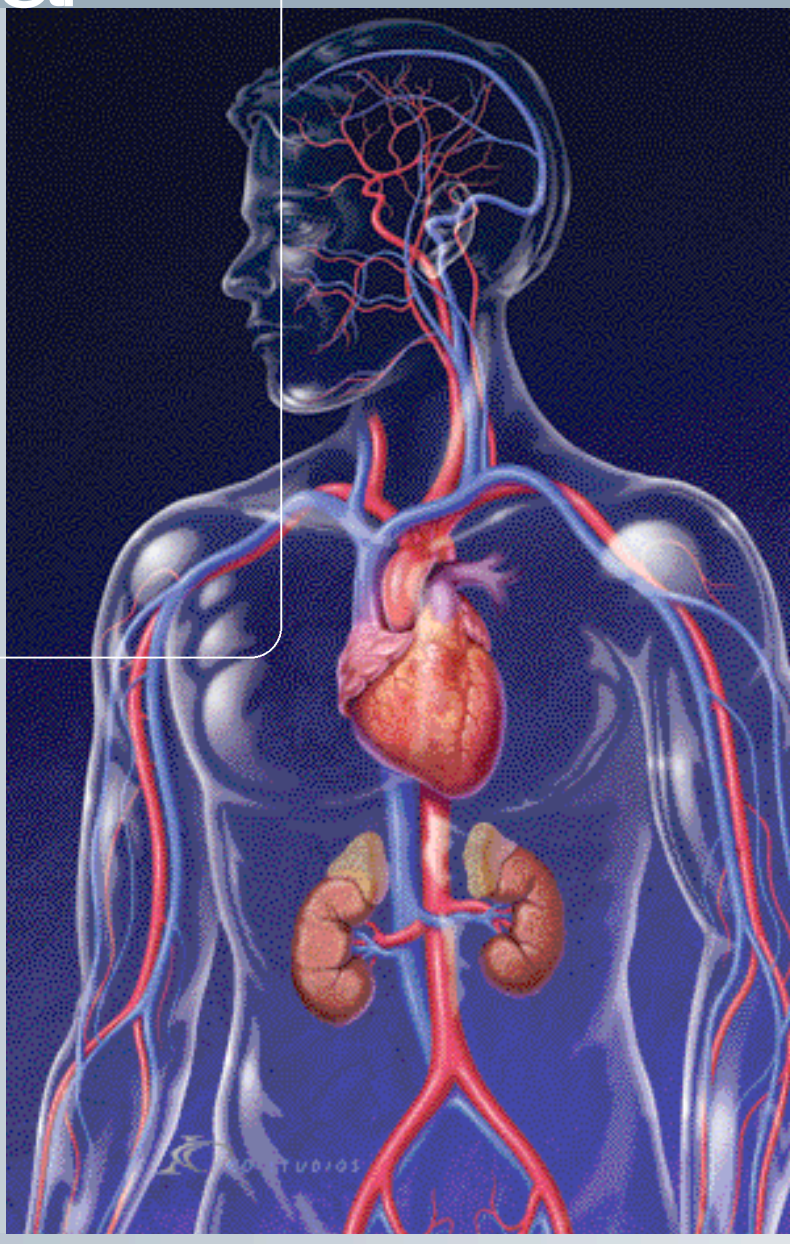

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Coronary heart disease

multiple risk factors and risk assessment

Identification and modification of known behavioural and environmental risk factors have the potential to reduce the large toll exacted by coronary heart disease.

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The burden of cardiovascular disease in Australia

Cardiovascular disease (CVD), which comprises heart attack, stroke and peripheral blood vessel disease, is the major cause of death and the leading cause of disability in Australia.[1] CVD is the cause of approximately 37% of all deaths, with one death occurring every 10 minutes. The direct costs of CVD constitute the largest economic health burden for Australia – an estimated $7.6 billion in 2004, which is 11% of all direct health spending.[2] Much of the burden associated with CVD relates to hospitalisation and residential care, particularly in the 12% of the population who are aged 65 years and over. Because of progressive ageing of the population and other factors, such as the increased use of pharmaceutical agents, the direct costs have been predicted to increase to approximately $11.5 billion by 2011.[2]

Coronary heart disease (CHD) is the most important single disease state in CVD. It is also an important paradigm for considering approaches to prevention and treatment of other chronic non-communicable diseases, such as diabetes and stroke.

Risk factors

The landmark INTERHEART study, a very large case–control study of myocardial infarction undertaken in 52 countries (including Australia), provides important information about risk factors and the potential for prevention of CHD.[3] This study showed that the population attributable risk (the percentage decrease in events if risk factors were at 'ideal' levels) for myocardial infarction was about 90% in both younger and older individuals. Findings did not differ between regions of the world or between men and women. Individual risk factors are discussed below in the context of the significant independent risk factors identified in the INTERHEART study.

IN SUMMARY

- **In the landmark INTERHEART study of myocardial infarction, the ApoB/ApoA1 ratio was the most powerful predictor of risk of myocardial infarction.**
- **In both men and women, potentially modifiable risk factors account for over 90% of the risk of an initial acute myocardial infarction.**
- **Stopping smoking by the age of 30 years eliminates the negative effect on an individual's life expectancy. Stopping at a later age is still beneficial.**
- **Smoking, elevated blood pressure and dyslipidaemia account for about 75% of the variations in risk for future CHD events in people without diabetes.**
- **Recent changes to PBS criteria for eligibility for subsidy of statins in people with diabetes acknowledge the high risk of CHD events in such patients.**
- **GPs have a key role in reinforcing education about the need for early presentation to hospital if patients with known CHD experience 10 to 15 minutes of chest pain that might herald the onset of myocardial infarction. Provision of an action plan can be of assistance.**
- **There is good evidence to support the use of aspirin (and clopidogrel in selected patients), statins, beta blockers and ACE inhibitors in patients with known CHD.**

Dyslipidaemia

The lipid measure used in the INTERHEART study was the apolipoprotein (Apo) ratio ApoB/ApoA1, which was the most powerful predictor of risk of myocardial infarction in the study. This is arguably a better measure of risk associated with dyslipidaemia than LDL cholesterol, HDL cholesterol, triglycerides, total cholesterol, and the total:HDL cholesterol ratio. This is because ApoB reflects the total atherogenic particle number, accounting for the increased atherogenicity of small dense LDL particles and risk associated with triglycerides. Both aspects are particularly important in the context of diabetes and the metabolic syndrome. ApoA1 reflects the antiatherogenic properties of HDL cholesterol. Importantly, the ApoB/ApoA1 ratio can be estimated from nonfasting blood samples.

Smoking

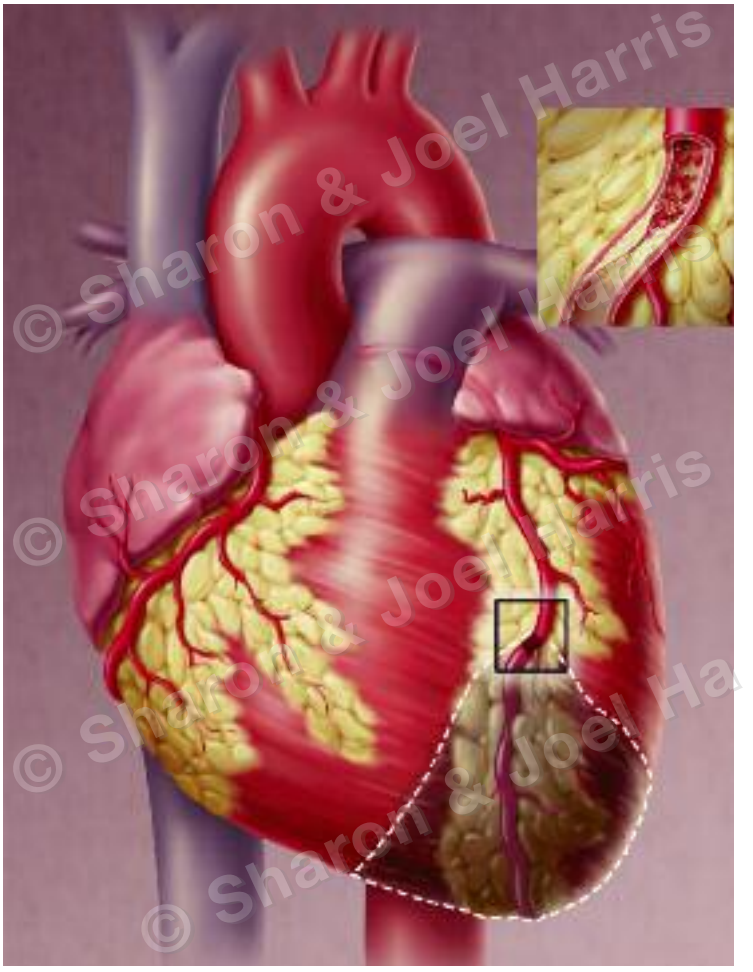
A subsequent analysis of the INTERHEART study has provided more detailed information relating to the risk of myocardial infarction associated with smoking.[4] The increase in risk was significant when as few as two to four cigarettes were smoked daily and increased in a linear manner as the number of cigarettes increased. The analysis also showed the risk to be very similar for different methods of tobacco use.

Important results were also obtained from a recent study of the long term risk associated with smoking and the effect of stopping at different ages.[5] Over a follow up period of 50 years, British doctors who smoked had a decrease in average life expectancy of about 10 years if they did not stop. However, this shortening in life expectancy was eliminated when smoking was stopped by the age of 30 years. The associated 'reward' decreased with increasing age for stopping smoking, but benefits accrued even for stopping up to the age of at least 60 years.

Hypertension

The risk associated with blood pressure above the ideal level (systolic blood pressure of 115 mmHg) is greater for stroke than for CHD,[6] but it is still important for the latter and other cardiac manifestations (e.g. heart failure). The risk relationships are continuous, and use of the terms 'hypertension' and 'normotension' is arbitrary and therefore somewhat misleading. The concept of a continuous risk relationship is also applicable to other risk factors (e.g. dyslipidaemia).

Coronary heart disease



CHD is the principal health problem for Western countries such as Australia. Population-wide measures and aggressive treatment of high risk individuals are complementary approaches to prevention and management.

Diabetes

The AusDiab survey has shown that about 7.4% of the Australian population have diabetes and another 16.4% have impaired glucose tolerance and/or impaired fasting glucose.[7] Again, the risk associated with abnormal glucose state represents a continuous relationship.[8]

continued

The increased risk of CHD associated with diabetes is higher for women than for men.[9] This relates partly to greater abnormalities in women in other risk factors such as blood pressure associated with diabetes. Higher risk with diabetes could also reflect less aggressive approaches to treatment being used in women.

Abdominal adiposity

The INTERHEART study showed that the risk of myocardial infarction is associated particularly with the measure of waist circumference, rather than with body mass index (BMI), a finding that has emerged in a number of other studies. It is therefore recommended that abdominal circumference be measured as well as, or in preference to, BMI.[10] Abdominal adipose tissue is associated particularly with inflammatory cytokine release and abnormalities in hormonal levels that predispose to atherosclerosis.

Psychosocial factors

In the INTERHEART study, the risk of myocardial infarction associated with depression and other psychosocial factors such as social isolation was of the same order of magnitude as that associated with more conventional risk factors, such as dyslipidaemia, elevated blood pressure and smoking. This association was independent of other risk factors. An Australian systematic review came to a similar conclusion.[11]

Fruit and vegetable intake

Although the INTERHEART study found higher intake of fruit and vegetables to be protective against myocardial infarction, trials of such intervention are difficult to fund and to perform. However, the association with other risk factors, such as blood pressure, is well established.

Exercise

Physical activity is protective against CHD and results in decreased blood pressure, a more favourable lipid profile and less overweight. The current recommended level is at least 30 minutes of moderate activity, such as brisk walking, on most days.

Alcohol consumption

Results from the INTERHEART study showed alcohol consumption to be protective against myocardial infarction in older individuals. However, recent studies have been less conclusive than older epidemiological reports in establishing the level of this protection. This may relate to more effective control for confounding factors and higher overall quality of more recent studies. It is not recommended that individuals drink alcohol only to gain any protective effect against CHD. High alcohol consumption is also associated with elevated blood pressure.

At risk populations

Social, ethnic, cultural and geographic factors contribute to CHD risk. Aboriginal and Torres Strait Island peoples, for example, are at much higher risk than the general Australian population.[12]

CHD prevention

An approach to risk assessment

The absolute risk of future CHD and CVD events in the general population and subgroups is depicted in Figure 1. The concepts of absolute risk and relative risk are described in the box on page 5.

Estimation of absolute risk in order to distinguish high risk individuals in the general population is based on application of multivariate risk equations that weight for the importance of independent risk factors. Such equations are derived from longitudinal follow up of cohorts; those in current use in Australia are based on observations from the Framingham Heart Study, which was initiated in Massachusetts, USA, in 1948. The New Zealand cardiovascular risk calculator (www.nzgg.org.nz) and other online tools (e.g. www.absoluterisk.com) are also based on Framingham data.

There is a need to develop contemporary local risk equations that have been validated in different Australian subpopulations.[12] There is also a need to refine risk assessment by possible inclusion of additional important variables, such as psychosocial and socioeconomic factors, and to establish how best to deal with advancing age, which is the single most important driver of absolute risk. Present risk equations favour increased treatment of elderly patients (typically, after subclinical atherosclerosis has developed) and ignore the great number of quality life years that remain for younger individuals. This is particularly relevant as about one-third of

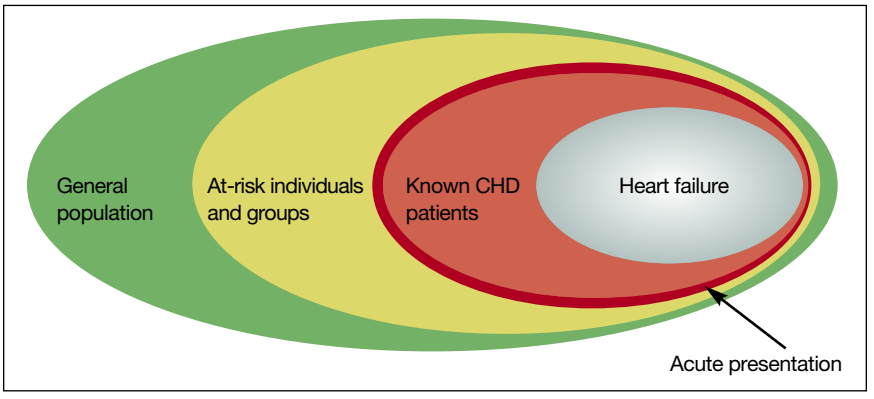


Figure 1. Absolute risk of future CHD or CVD events in the general population and subgroups. At-risk individuals are those with other diseases (e.g. diabetes, chronic kidney disease), extreme levels of risk factors, and Aboriginal and Torres Strait Islander peoples.

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first CHD presentations result in sudden death or fatal myocardial infarction.

Extreme levels of risk factors and age

Multivariate risk equations relate particularly to individuals who do not have extreme abnormalities of individual risk factors. In general, the Framingham equations should not be applied to people:

- under 20 or over 79 years of age
- with total cholesterol levels above 8 mmol/L, or
- who have blood pressure above 180/105 mmHg.

Diabetes

Risk of CHD events varies among people with diabetes. However, it has been established that important determinants of risk include:[14]

- length of time since diabetes was diagnosed
- dyslipidaemia (in particular)
- blood pressure
- adequacy of glycaemic control, as measured by HbA_{1c} level.

Recent changes to PBS criteria for eligibility for subsidy of statins in people with diabetes acknowledge the high risk in such patients. Furthermore, evidence supports the setting of aggressive targets for blood pressure[15] and LDL cholesterol and adequate glycaemic control[16] in such patients.

Chronic kidney disease

Patients with chronic kidney disease have a much higher risk of death due to CHD and associated conditions.[17] Potential novel risk factors for CHD in patients with chronic kidney diseases include homocysteine, markers of inflammation and oxidative stress, advanced glycation end-products and arterial stiffness and calcification. However, conventional risk factors are still important and guidelines recommend aggressive control of blood pressure, in particular. The value of statin therapy has been demonstrated for lesser degrees of renal impairment, but trials are ongoing to examine the place of these agents in chronic kidney disease. Future research must concentrate on the role of markers of kidney disease, such as microalbuminuria, in CVD risk assessment.

Aboriginal and Torres Strait Islander peoples

An alarming increase in age-specific mortality rates is occurring among Aboriginal and Torres Strait Islander peoples compared with the general population. CHD is the major reason for the difference in life expectancy, which is, on average, 15 to 20 years shorter for indigenous Australians. Care systems must address inequalities in access to, and delivery of, appropriate care and preventive measures to indigenous people.

Preventing CHD events: using absolute risk and relative risk

Absolute risk describes the actual risk of events occurring during a defined period of time in the future. It is usually expressed as a percent likelihood in the next five or 10 years. The concept of absolute risk is applied particularly to the assessment of risk in individuals who have not previously experienced clinical events, but it extends to all subgroups. The risk of future CHD events is highest in people who have already been hospitalised with diagnosed CVD.

Relative risk is an expression of risk relative to others of the same age and gender. For estimating CHD risk, relative risk is inferior to absolute risk because it excludes the two most important drivers of risk – age and gender. Therefore, absolute risk remains the method of choice for identifying patients who need aggressive treatment.

Clinical discord may occur between absolute and relative risk. Individuals with a high relative risk and moderate or low absolute risk are primarily protected by their relative youth, and they will eventually develop a high absolute risk if appropriate behavioural intervention such as the Smoking, Nutrition, Alcohol and Physical activity (SNAP) program is not commenced.[13] An approach to dealing with discord between relative risk and absolute risk is shown in Figure 2 below.

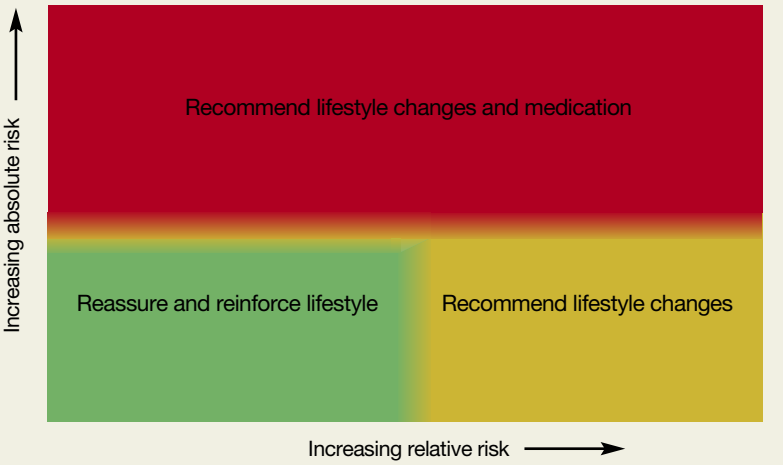

Figure 2. Discord between relative risk and absolute risk in an individual can occur. For example, a young woman with moderately elevated total cholesterol may be at low absolute risk but high relative risk of CHD (orange box). She is very unlikely to benefit from a statin or other drug and just as likely to have an adverse effect from medication; she should therefore simply receive behaviour modification advice.

Acute coronary syndromes

Unfortunately, surveys by the National Heart Foundation of Australia over the last 10 years have not shown any decrease in the median time to hospital presentation for people with possible myocardial infarction.[18] It is also disappointing that the delay in presentation is no different for those with a previous diagnosis of CHD compared with the general population. For patients with known CHD, GPs have a key role in assisting and reinforcing education about the need for early hospital presentation if they experience 10 to 15 minutes of chest pain that might herald the onset of myocardial infarction. Provision of an action plan for chest pain or discomfort, including advice about use of antianginal medication and emergency action, can assist such patients.

Patients with known CHD

An important analysis based on data linkage in Western Australia has shown that over a three-year period about half of all CHD deaths and nonfatal myocardial infarctions occurred in individuals who had been hospitalised during the previous 15 years with a diagnosis of CHD and remained alive (Michael Hobbs, personal communication). This observation mandates the need for systems such as CHD patient registries that might enable automatic recall and prescription of proven therapies to patients with CHD. Patient concordance remains a major challenge.

The evidence base supporting the use of aspirin (and clopidogrel ([Iscover, Plavix] in selected patients), statins (irrespective of cholesterol levels), beta blockers (particularly in patients with previous large myocardial infarction or associated heart failure) and ACE inhibitors in this context is one of the most robust in medicine.

Concluding comments

CHD is the principal health problem for Western countries such as Australia and is rapidly becoming so for other world regions. Genes may have a modulating role, but nearly all of the individual variations in risk for myocardial infarction relate to behavioural and environmental factors. Population-wide measures and aggressive treatment of high risk individuals are complementary approaches to tackling the very large toll exacted by CHD.[19] MT

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TIA and stroke

a management guide for GPs

The incidence of stroke in Australia is about 46,000 per year. It is the third most common cause of death in this country (about 15,000 per year) and a major cause of disability. All GPs need to be aware of rapid changes occurring in management.

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For stroke, perhaps above all other medical conditions, there is a need for a seamless continuum of care from the acute presentation, through management in hospital or other healthcare facility, to integration back into the community. With the availability of level I evidence to show that the burden of stroke may be reduced by specific strategies for the acute phase as well as effective forms of secondary prevention, management is changing rapidly. This article discusses current approaches to management, and highlights the specific roles that GPs play – these are summarised in the box on page 9. The evidence underlying changes in management approaches is also explained (see the box on page 10).[1-10]

There are now three specific strategies in acute stroke management that have been proven to improve outcomes (that is, are supported by level I evidence). Specifically:

- administration of intravenous tissue plasminogen activator (tPA; alteplase [Actilyse]) within three hours of stroke onset may increase the number of patients improving to virtually no clinical deficit by about 30%[1,2]
- administration of aspirin within 48 hours of ischaemic stroke onset may reduce death and nonfatal stroke in about nine patients per 1000 treated[3,4]
- management in a stroke care unit may reduce mortality and the need for institutionalised care by about 20%.[5,11]

Pre-hospital management

For the stroke patient, time is brain. The GP's initial tasks are to recognise the symptoms and signs of an acute transient ischaemic attack (TIA) or stroke (Table 1), and to facilitate rapid transfer to a healthcare facility where the strategies listed above can be put into place with minimal delay. If there is any doubt about the diagnosis, the patient should be transferred to hospital for further investigation. Differential diagnoses are listed in Table 2.

A number of factors have been identified that may prolong hospital arrival times. These include lack of recognition of cause of symptoms, non-ambulance transport, GP contact, less severe

IN SUMMARY

- **Stroke is one of the major causes of death and disability in Australia.**
- **All patients with acute stroke should be referred directly to a hospital with imaging facilities (CT and/or MRI), and preferably a stroke unit that provides thrombolytic therapy.**
- **Management in a stroke unit can reduce long term outcomes of death and dependency.**
- **Risk factor identification and management are important.**
- **Early rehabilitation of patients in a multidisciplinary team environment is ideal.**
- **Rural GPs are in a unique position to take on multiple roles in stroke management (physician, service co-ordinator, staff and family educator, and support service).**

Table 1. Symptoms and signs of TIA and stroke

- Motor symptoms: weakness or clumsiness (unilateral or bilateral)
- Sensory symptoms: altered feeling on one side of the body
- Difficulty swallowing
- Speech or language disturbance: slurred speech, difficulty with reading or understanding
- Vestibular dysfunction
- Unsteady gait/cerebellar features
- Visual symptoms: loss of vision in one eye, loss of visual field, diplopia
- Nonfocal symptoms: generalised weakness, incontinence, imbalance, altered state of consciousness, dizziness

Table 2. Differential diagnoses

- Migraine
- Syncope
- Epilepsy (Todd's palsy)
- Intracranial structural lesions
- Encephalopathy
- Encephalitis
- Multiple sclerosis
- Transient global amnesia
- Peripheral neuropathy or myopathy
- Metabolic derangement – e.g. hypoglycaemia
- Peripheral causes of vertigo, such as benign postural vertigo

stroke, ischaemic stroke, living alone and being asleep at stroke onset.

The fact that 'GP contact' delays transfer to hospital may seem paradoxical, but it is understandable given that GPs cannot always immediately attend the home to establish the diagnosis.[12] Hence, it is crucial that they, having being contacted by a patient or carer by telephone, act to facilitate rapid ambulance (ideally) or other mode of transport to hospital if there is reasonable suspicion that stroke has occurred.

Hospital care

After transfer to hospital has been effected, time is still the most important factor. The GP has an important role in a number of the steps involved.

Clinical confirmation of diagnosis

Rapid triage by a nurse trained to recognise the symptoms and signs of stroke is helpful, and expeditious clinical evaluation should establish the diagnosis more clearly. The presentation of the stroke syndromes can often be divided according to the vascular territories using, for example, the Oxford classification of cerebral infarction, which may assist in management. It is also important to identify risk factors such as hypertension, atrial fibrillation, diabetes, cigarette smoking, hyperlipidaemia, a past history of stroke and previous ischaemic heart disease.

Brain imaging

Computed tomography (CT) remains the workhorse of acute stroke management, and has the important advantage over magnetic resonance imaging (MRI) of immediately distinguishing between haemorrhage (increased signal) and infarction (usually little change within the first few hours). Examples are shown in Figures 1a and b.

MRI is becoming more readily available – diffusion-weighted MRI (DWI) has the great advantage of detecting acute ischaemia almost immediately after stroke onset when a CT scan would still be negative. In fact, about one-third of clinically proven TIAs have MRI ischaemic changes, particularly in DWI, that correspond with the clinical presentation. This subset of patients may have a different clinical course compared with patients with TIAs but without MRI (DWI) changes.[13,14]

MRI also provides better resolution than CT for imaging the posterior fossa and brainstem.

Acute management with tPA and/or aspirin

Therapy with intravenous tPA may be considered if:

- the length of time from symptom onset is less than three hours
- CT scans are essentially normal
- blood pressure is less than 185/110 mmHg
- the coagulation profile is normal, and
- there are no other contraindications to thrombolysis.

For every 100 patients treated within three hours, 12 patients will have little or no residual clinical deficit (i.e. the number needed to treat to benefit one individual is about eight).[1] tPA was licensed for use in managing stroke in appropriate centres in August 2003.

Oral aspirin (150 to 300 mg) should be administered as early as possible, preferably within 48 hours of stroke onset. Note, however, that tPA and aspirin are never given before brain imaging.

Ultrasound of carotid or vertebrobasilar arteries

Carotid and transcranial Doppler ultrasound may show focal narrowing in the internal carotid artery and the posterior circulation, respectively. Each patient's suitability for surgical intervention (carotid endarterectomy) should be considered before he or she is subjected to the test. Significant symptomatic stenosis in the internal carotid artery is defined as 70% or more.

Management in a stroke care unit

Level I evidence is now available to show that managing acute stroke patients in a stroke care unit reduces the risk of death and dependency at one year by about 20% compared with management in a general ward,[5] and, therefore, the former approach should now be mandatory. There has been a general recommendation that stroke

care units be established Australia-wide,[15] and the initiative is being taken up by a number of States and Territories. At present, however, only 23% of Australians have access to stroke care unit facilities.

Minimum investigation set

To define the type of stroke and associated comorbidities, a minimum set of investigations is recommended. This comprises brain CT, chest x-ray, full blood examination, erythrocyte sedimentation rate, random blood sugar, urea, creatinine and electrolytes, and ECG.

Transoesophageal echocardiography is an additional investigation that may be used to detect aortic arch atheroma as an embolic source if no obvious cardiac or large artery sources have been identified. In patients with atrial fibrillation or recent acute myocardial infarction, this investigation is not usually indicated unless more information about cardiac function is required.

Management of medical complications

Each complication should be managed on its merits. These include:

- infections (e.g. pneumonia, urinary tract infections)
- deep venous thrombosis (DVT) or pulmonary embolism
- cardiac failure, fluid imbalance
- hypertension
- hyperglycaemia
- cardiac arrhythmias/cardiac infarction
- pressure sores
- urinary and bowel problems
- seizures
- falls.

Significant hypertension is not an uncommon finding in the acute stroke setting, and generally there is no need for intervention in ischaemic stroke unless the systolic pressure is above 220 mmHg or the diastolic pressure is above 120 mmHg. Fortunately, elevated blood pressure at admission usually settles within hours, or within a few days at most.

Pressure stockings are essential for preventing DVT; subcutaneous heparin is often used in patients who cannot be mobilised or with a history of DVT or pulmonary embolus.[16]

Speech assessment is important for patients with speech impairment, and appropriate dietary advice is essential for those with swallowing difficulties.

Early rehabilitation

Although there is rapidly accumulating evidence that rehabilitation improves clinical outcomes, it is uncertain how early this should occur. Nevertheless, it is generally considered that rehabilitation should usually be commenced as soon as practicable, and this is the practice in most stroke care units.

The GP's role in managing patients with stroke

Pre-hospital management

- Recognising the symptoms and signs of acute transient ischaemic attack (TIA) or stroke
- Facilitating rapid transfer to a healthcare facility where acute stroke management strategies can be put into place with minimal delay

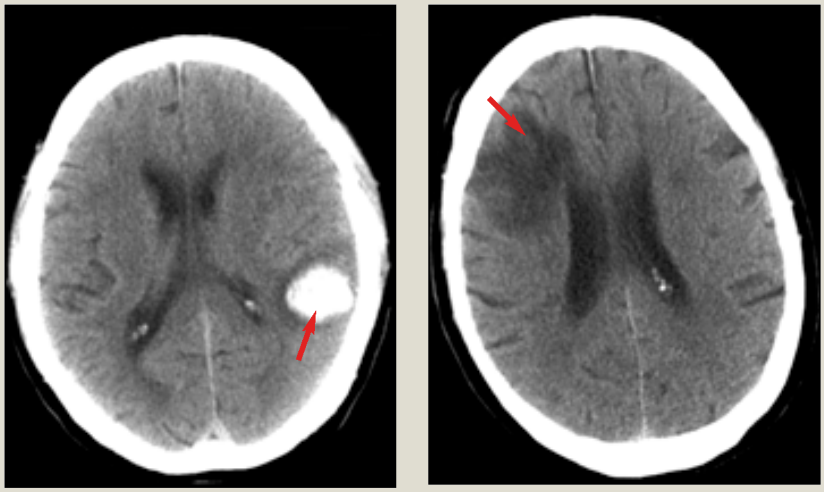
Hospital care

- Assisting with medical management (in some hospitals)
- Providing additional medical and historical information about patients to hospital doctors
- Preparing family and carers for the patient's discharge
- Liaising with 'hospital in the home' or 'rehabilitation in the home' programs
- Care-planning with hospital team for discharge

Community care

- Implementing secondary prevention strategies
- Re-integrating stroke patients into the community

CT imaging in acute stroke management



Figures 1a and b. CT scans are mandatory for all stroke patients and crucial in making decisions about therapy. a (left). An area of haemorrhage appears white (arrow). b (right). Cerebral infarcts (arrow) appear darker than normal brain.

continued

Early secondary prevention

Based on their risk factor profile, people who have experienced a TIA may have a risk of stroke of up to 31% within the next seven days.[17] Conversely, in patients who have experienced an ischaemic stroke preceded by a TIA, 43% of these TIAs will have taken place within seven days before the ischaemic stroke.[18] Thus it is crucial to instigate appropriate investigations and secondary prevention as early as possible.

There is now level I evidence that at least four early strategies for secondary prevention may improve long term outcomes after TIA or stroke. Some of these may be initiated in hospital, but most often they are commenced by the GP when the patient has returned to the community. These strategies are discussed in the section 'Secondary prevention' below.

Discharge planning

Of the patients with stroke who enter

Newer strategies for reducing the burden of stroke: a look at the evidence

Acute management

There is now level I evidence for three acute management strategies in reducing the burden of stroke: tissue plasminogen activator (tPA), aspirin and care in a stroke care unit. This is summarised in Table A.

Table A. Benefits (avoidance of death or disability) of acute interventions

Strategy	Absolute risk reduction	Number needed to treat*	Potential benefit per 1000 cases of stroke in Australia†
Tissue plasminogen activator (tPA) 0-3 hours[1,2]	11.0	9	11†
Aspirin[3,4]	1.2	83	6†
Stroke care unit[5,6]	5.6	18	46†

* The number of patients needed to be treated in one year to avoid one death or disability per year.

† Case reduction of death and dependency from an estimated number of stroke cases in Australia in 1998 sourced from several Australian studies.[6]

The evidence relies on a number of pivotal trials and meta-analyses that have been conducted over the last 10 years. Of these strategies, the number of patients needed to treat to obtain benefit for one individual is most favourable for tPA. It should be noted that although tPA does increase the risk of symptomatic intracranial haemorrhage (about 7% of patients), it does not appear to increase mortality.[1,2] tPA is now licensed in Australia for management of stroke in appropriate centres.

Aspirin is less effective than tPA, but it is cheaper and safer. There is no evidence that intravenous or subcutaneous heparin is of benefit.[3]

Management of patients in a stroke care unit is effective and safe, and should not be particularly expensive. Even in smaller hospitals, a stroke care unit can be established and operated by reorganising existing resources.

Secondary prevention

Level I evidence now exists for at least four early strategies for secondary prevention in improving long term outcomes after TIA or stroke, including use of antiplatelet agents, blood pressure lowering, warfarin and carotid endarterectomy. This is summarised in Table B.

Table B. Benefits of secondary prevention strategies

Strategy	Relative risk reduction	Absolute risk reduction	Number needed to treat*
Antiplatelet agent[4]	23	1.0	100
Blood pressure lowering[7]	28	2.2	45
Warfarin[8]	67	8.0	12
Carotid endarterectomy[7,9,10]	44	3.8	26

* The number of patients needed to be treated in one year to avoid one recurrent stroke per year.

hospital, about 20% will die during their stay and the remainder will be discharged:

- directly home (33%)
- to rehabilitation centres (33%)
- to nursing homes (only about 10%).

For the two-thirds who go either home or to rehabilitation, early planning is essential. Increasingly, patients are being discharged early with the support of 'hospital in the home' programs, in which ongoing medical management of stroke comorbidities is undertaken. The use of 'rehabilitation in the home' programs is an increasingly common trend.

Community care

The GP, who may have been involved during the early phases of stroke onset and hospital care, assumes an even more important role in caring for a patient after discharge from hospital. The main management issues for GPs include use of secondary prevention strategies, and it is helpful to have a checklist to ensure that all appropriate steps are taken. GPs are also involved in reintegrating the patient into the community.

Secondary prevention

The evidence-based secondary stroke prevention strategies that need to be implemented where appropriate are as follows:

- antiplatelet agents
  - aspirin[4]
  - clopidogrel (Iscover, Plavix)[19]
  - aspirin with dipyridamole (Asasantin SR)[20,21]
- blood pressure lowering agents
  - using perindopril (Coversyl) alone or with indapamide[22] (a combined preparation [Coversyl Plus] is available)
  - for patients with a previous history of stroke there is some evidence that ramipril (Ramace, Tritace) may be effective[23]
- warfarin (Coumadin, Marevan), in patients in atrial fibrillation[8,24]
- carotid endarterectomy, in symptomatic patients with carotid stenosis of 70% or more[9,10]
- lipid lowering agent (atorvastatin [Lipitor]) in ischaemic stroke.[25]

The box on page 10 summarises the benefits of the first four of these secondary prevention strategies.

Compared with the use of aspirin alone, clopidogrel has been shown to further reduce the relative risk of vascular events, including ischaemic stroke, by about 8.7% (CAPRIE).[19] The major use of clopidogrel is in the setting of further cerebrovascular events despite the use of aspirin or in the patient who cannot tolerate aspirin due to its side effects.

Compared with the use of aspirin alone, the combination of aspirin and dipyridamole also shows a relative reduction of risk of stroke or death by a further 13% (ESPS-2).[20] This has recently been confirmed by another trial (ESPRIT),[21] and makes this combination a suitable alternative to aspirin as first line antiplatelet therapy in secondary prevention of ischaemic stroke. This trial, which compared aspirin with combination therapy of aspirin plus dipyridamole in patients with TIA or minor ischaemic stroke, showed a relative risk reduction of 20% in reaching the primary end point (composite of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction or major bleeding complication) in the combination group compared with the aspirin only group.[21] The other major use of the combination of aspirin and dipyridamole is in the setting of further cerebrovascular events despite the use of aspirin.

For patients with nonvalvular atrial fibrillation one should aim for an INR of 2.5 (range, 2.0 to 3.0).[24] Heparin is still occasionally used as a prelude to warfarin, but evidence for this is lacking.[3]

A recent prospective randomised controlled study has shown that in patients with recent ischaemic stroke or TIA and serum LDL cholesterol levels between 2.6 and 4.9 mmol/L, atorvastatin 80 mg/day reduced the five-year absolute risk of fatal or nonfatal stroke by 2.2% compared with placebo (SPARCL).[25] The five-year risk of major cardiovascular events was also reduced by 3.5%. This means that 46 patients will need to be treated over a period of about five years to prevent one stroke. However, there was a slight increase in the incidence of haemorrhagic stroke (adjusted hazard ratio 1.66) in the treatment group. Hence atorvastatin should be used only in patients with ischaemic stroke.

Risk factor modification measures are also important. These include cessation of cigarette smoking and avoidance of heavy alcohol consumption. In addition, blood glucose in patients with diabetes should be strictly controlled (although

Special issues for rural GPs

- Access to CT and duplex ultrasound. Can this be arranged urgently? If not, the patient should be transferred.
- More complete medical management. In many instances the GP may be the sole medical manager, hence a knowledge of level I evidence for acute care (tPA, aspirin, stroke unit management) as well as secondary prevention strategies (antiplatelet agents, warfarin, blood pressure lowering, referral for carotid endarterectomy or lipid lowering) is essential. If not, the patient should be referred or transferred.
- Facilitating the continuum of care from acute presentation through to rehabilitation and community adjustment. Rural GPs are probably even more involved in this than urban GPs.
- Family and emotional support, which are crucial in the recovery process. Depression is not uncommon among stroke patients.

there is no level I evidence to support this recommendation).

Re-integration

Adjustments to the patient's environment may be required because he or she may need to be re-introduced to work or home activities gradually. Increased stress on carers is likely, sometimes with attendant illnesses. In some instances, respite care may need to be arranged.

Role of the rural GP

Rural GPs are faced with additional challenges for managing patients with stroke or TIA – these are described in the box on page 11. Therefore, awareness of the evidence base for management strategies is most important – particularly if they undertake more complete medical management. Since access to specialist services is more limited in rural areas, GPs usually assume greater responsibility, thus making it even more important that they are aware of the need to refer to rural based specialists when appropriate (for example, for carotid endarterectomy).

Resources

The National Stroke Foundation (NSF) produced a set of clinical guidelines for acute stroke management in 2003.

Final comments

The management of stroke is changing quite rapidly with the introduction of the evidence based strategies discussed in this article. The role of the GP remains central. MT

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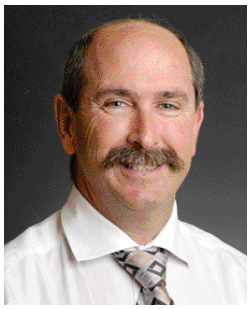
The kidney
victim or villain in heart failure?

Deteriorating renal function is often a complication of heart failure, and kidney disease itself can lead to cardiomyopathy. The combination of renal failure and heart failure is referred to as the cardiorenal syndrome; management of this syndrome requires the careful adjustment of medications.



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Heart failure is a common cause of hospital admissions in the over 65-year-old population. During admission, patients with heart failure may develop renal failure due to attempts to treat fluid overload. In addition, many patients with heart failure who are hospitalised have renal insufficiency. Unfortunately, the prognosis of these patients is grim. The combination of both kidney and heart failure is now referred to as the cardiorenal syndrome, a situation that poses difficult management decisions for clinicians. It can be tricky to differentiate clinically which organ is the 'victim' and which is the 'villain'. Also, medications targeting renal impairment may interfere independently with cardiac function and vice versa.

How does heart failure impact on renal function?

Simplistically, heart failure is a result of diastolic or systolic dysfunction. Diastolic heart failure is characterised by the inability of the myocardium to relax adequately during diastole and results in symptoms of pulmonary congestion. Systolic heart failure reflects reduced cardiac output.

The left ventricular ejection fraction (LVEF), measured by echocardiography or nuclear testing, is often used to investigate heart failure. A reduction in LVEF, whether diastolic or systolic in origin, may cause renal hypoperfusion (a result of hypovolaemia, neurohormonal-stimulated vasoconstriction or low cardiac output syndrome). Renal hypoperfusion eventually leads to sodium and water retention.

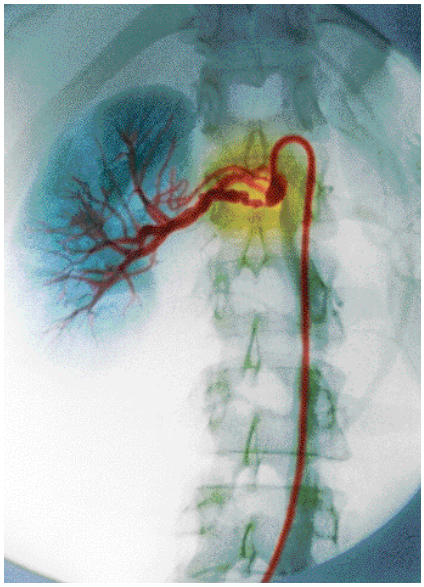
Diastolic dysfunction is found in a substantial proportion of patients with the cardiorenal syndrome. Up to half of all patients with the cardiorenal syndrome have a LVEF of greater than 40%, and many patients have associated hypertension, diabetes or impaired baseline renal function.

Inappropriate activation of the renin–angiotensin system invariably occurs in heart failure, and excessive activation of this system has been implicated in the progression of chronic kidney disease. In addition, patients may have concurrent

IN SUMMARY

- **Increasingly, patients are being diagnosed with both heart and renal failure – the cardiorenal syndrome.**
- **Careful adjustment of cardiovascular medications allows treatment of heart failure without compromising kidney function.**
- **When managing patients with heart failure, be alert for signs of fluid retention and changes in blood pressure and always consider underlying renal disease.**
- **Important laboratory values to determine in patients with heart and renal failure include concentrations of electrolytes, estimated glomerular filtration rate and haemoglobin level.**

continued



PHOTOLIBRARY

Figure 1. Renal artery stenosis (coloured x-ray). The presence of widespread vascular disease in a patient should increase a clinician's suspicion for significant renal artery stenosis.

intrinsic renal disease secondary to long-standing hypertension, diabetes or atherosclerosis. Usually, more than one causal factor is present. Hence there are a number of pathophysiological changes that, in combination, act synergistically to aggravate both kidney and cardiac failure.

How does renal failure impact on cardiac function?

Cardiovascular disease (CVD) is a major problem in patients with chronic renal failure: almost half of the deaths in patients with end-stage kidney disease are due to cardiac causes. Even a slight decrease in kidney function correlates with a substantial increase in CVD risk and higher mortality, independent of other known risk factors.

Kidney failure can result in left ventricular (LV) dilatation due to volume overload or LV hypertrophy due to high blood pressure. It is rare to find one of these disorders of LV function in isolation. Renal failure is invariably associated with the presence of hypertension. This may be associated with either high or low renin concentrations. In addition, renal failure may lead to salt and water retention.

Anaemia is a common finding complicating both renal and cardiac dysfunction and is discussed later.

There have been several trials exploring the impact of renal dysfunction in patients with heart failure. In fact, kidney failure, as gauged by the estimated glomerular filtration rate (eGFR), is the single most powerful predictor of mortality, exceeding cardiac functional status and LVEF.

What is the impact of drugs used to treat heart or renal failure?

A significant number of cardiovascular drugs are prescribed by both cardiologists and nephrologists as they have beneficial effects on both the kidney and the heart. For example, ACE inhibitors have both antihypertensive and renoprotective effects. However, other drug classes may be beneficial to one organ but not the other. For example, diuretics prescribed for congestive heart failure are associated with renal hypoperfusion.

Diuretics

Often patients with heart failure are discharged from hospital on a combination of frusemide, either spironolactone (Aldactone, Spiractin) or eplerenone (Inspra), and possibly a low dose thiazide diuretic. This combination attempts to reduce intravascular volume and the symptoms of congestion or fluid overload. Although frusemide may reduce congestive symptoms, only spironolactone and eplerenone have been shown to produce a mortality benefit in heart failure.

It is important to advise patients taking diuretics that they must restrict their total fluid intake to less than 1500 mL/day.

ACE inhibitors and angiotensin II receptor blockers

ACE inhibitors are widely prescribed for hypertension and heart failure and as renoprotective drugs in kidney disease. They act on the kidney by reducing glomerular pressure, which may result in a decrease in eGFR. Generally, most nephrologists would tolerate up to a 20 to 25% increase in creatinine level in patients who have started ACE inhibitor (or angiotensin II receptor blocker [ARB]) therapy before investigating for renovascular disease. ACE inhibitors and ARBs can cause a precipitous rise in creatinine in patients with bilateral renal artery stenosis. Stimulation of angiotensin II in patients with renal artery stenosis causes severe glomerular efferent artery constriction in the kidney. Reducing angiotensin II concentrations with either ACE inhibitors or ARBs lowers intraglomerular pressure, causing a dramatic fall in GFR and a resultant rise in serum creatinine concentration. The association between carotid, coronary, peripheral and renal atherosclerotic vascular diseases is high, and the presence of widespread vascular disease should increase a clinician's suspicion for significant renal artery stenosis (Figure 1).

Patients with heart failure often have low blood pressure, and this can limit the dose of ACE inhibitor or ARB that may be prescribed. Reducing the diuretic dose for a short period may allow either the initiation of a low dose ACE inhibitor or an escalation of the current dose. Patients with heart failure who cannot tolerate ACE inhibitors or ARBs because of severe hypotension, significant worsening of renal function or hyperkalaemia have a very high mortality (approximately 50% at six months).

ARBs are a relatively recent addition to the cardiovascular armamentarium. The Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality-Added (CHARM-Added) trial showed that candesartan (Atacand) reduced death and hospitalisations when added to ACE inhibitor therapy in patients with chronic heart failure. In addition, the Japanese Combination Treatment of Angiotensin-II Receptor

Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial demonstrated a reduction in proteinuria and slower decline in renal function with the combination of losartan (Cozaar) and trandolapril (Gopten, Odrik) than with either medication alone. The Irbesartan in Diabetic Nephropathy Trial (IDNT) and the Irbesartan in Patients with Type II Diabetes Microalbuminuria Study (IRMA-II) confirmed a benefit of irbesartan (Avapro, Karvea) in diabetic nephropathy, both in microalbuminuric and overtly proteinuric patients. In IDNT, irbesartan produced better renal protection than the calcium channel blocker amlodipine (Norvasc) in patients with hypertensive type 1 diabetes, reducing the chance of diabetic nephropathy developing into renal failure. In IRMA-II, higher doses of irbesartan reduced the progression of renal insufficiency. Hence, ARBs may be advantageous for certain patient groups – for example, heart failure patients with diabetes and microalbuminuria.

Increasingly, the combination of an ACE inhibitor and ARB is being prescribed to patients with multiple conditions. However, in those with hypertension, this combination may not be as potent as combining either medication individually with a low dose thiazide diuretic.

Beta blockers

Beta blockers are widely prescribed to patients with heart failure. As well as treating heart failure, they may lower blood pressure but have no other specific renoprotective effects. Although the elimination routes of various beta blockers may differ, dose adjustments for patients with renal impairment are not necessary in practice. Pulse rate and blood pressure are the major dose limiting factors of beta blocker treatment.

Statins

Although not prescribed to treat heart failure, statins are often used in patients with ischaemic cardiomyopathy to slow progressive coronary atherosclerosis. Some observational studies suggest that statins may slow the progression of chronic kidney disease, and randomised placebo controlled trials are currently being undertaken to explore this hypothesis.

Oral hypoglycaemics

Oral hypoglycaemics are not used to treat heart or renal failure *per se*, but they are often coprescribed in patients with these conditions because of the high incidence of diabetes. The dosage of metformin must be lowered as a patient's renal function deteriorates, and extra caution is needed in those with concurrent heart failure because of the risk of developing lactic acidosis. No clear guidelines exist for reducing the metformin dose as renal function declines. One suggested approach is to reduce the dose when the eGFR is below 60 mL/min but to cease treatment before the eGFR reaches 30 mL/min.

Thiazolidinediones (pioglitazone [Actos], rosiglitazone [Avandia]) may cause fluid retention. They should not be used in patients with severe heart failure and they should be prescribed with extreme caution to those with moderate heart failure. Patients taking thiazolidinediones should be advised to be vigilant for signs of fluid retention.

Calcium channel blockers

Although not specifically used to treat heart or kidney failure, calcium channel blockers are often coprescribed to manage

Table. Management strategies when pathology results are outside the normal range

Hyponatraemia
Advise patients to reduce their fluid intake
Consider reducing doses of medications that may affect serum sodium levels
Omit thiazide diuretic

Hypokalaemia
Advise patients to increase their intake of foods that are high in potassium
Advise patients to increase their intake of, or prescribe, potassium supplements

Hyperkalaemia
Advise patients to stop taking potassium supplements
Advise patients to reduce their intake of foods that are high in potassium
Advise patients to avoid salt substitutes that are potassium chloride, and the fibre supplement, Metamucil, which has a high potassium content
Ask patients about their use of COX-2 inhibitors and other NSAIDs

Elevated creatinine
Review diuretic dose
Review ACE inhibitor and angiotensin II receptor blocker dose, but aim to continue treatment with these medications if possible
Consider other causes (obstructive, renovascular or nephritis)

Hyperuricaemia
Reduce uric acid levels with allopurinol only if patients develop clinical gout

Anaemia
Exclude haematinic deficiency by measuring ferritin/transferrin saturation, vitamin B_{12} levels, folic acid levels

Foods that have a high sodium content

- Baking powder and soda
- Bread
- Breakfast cereals
- Condensed milk
- Crackers and other savoury biscuits
- Luncheon meats
- Margarine and butter
- Meat and fish pastes
- Mineral waters (some types)
- Monosodium glutamate
- Olives
- Processed meats such as sausages, bacon and ham
- Processed and natural cheeses
- Salad dressings
- Salted nuts, popcorn, potato chips, pretzels
- Silverbeet and spinach
- Sauces: sweet and sour, soy, Worcestershire and BBQ sauces
- Takeaway packaged food
- Tinned vegetables and juices
- Vegemite and Marmite

Foods that have a high potassium content

- Avocados
- Apricots
- Baked beans
- Bananas
- Cauliflower
- Cereals
- Chocolate
- Dried fruits
- Juices: grapefruit, orange and tomato
- Kiwi fruit
- Nuts
- Potatoes
- Tomatoes
- Turnips
- Yoghurt
- Salt substitutes (often potassium chloride)

hypertension. Verapamil (Anpec, Cordilox, Isoptin, Veracaps) should not be used with a beta blocker as heart block may result. This may also occur to a lesser extent with coprescription of diltiazem and a beta blocker, although bradycardia is not infrequent. If possible advise patients to take their own pulse for a few weeks after commencing that combination or after dosage adjustment. The dihydropyridine class of drugs (amlodipine [Norvasc], felodipine [Felodur, Plendil], nifedipine and to a lesser extent lercanidipine [Zanidip]) often cause ankle swelling, especially at maximum dosages. This may be confused with fluid retention from worsening heart or renal failure.

How do you interpret pathology results?

Patients with heart and kidney disease require frequent blood tests to monitor their cardiovascular and renal function. The table summarises the management of patients whose pathology results fall outside the normal range and the box on page 17 provides some tips for rural GPs.

Electrolytes

Electrolyte disturbance is common in patients with heart and/or kidney failure and depends on the drug combinations and doses chosen to treat patients. Sodium concentrations may fall below 130 mmol/L and potassium concentrations may rise or fall. For example, increasing the diuretic dose or adding another diuretic can result in the sodium concentration falling within a week. Electrolytes should be rechecked two weeks after hospital discharge in heart failure patients with renal impairment as the impact of dose changes made in hospital may not be seen for several weeks. Dietary management of sodium and potassium intake may be required. The boxes on this page list foods that have high sodium or potassium content.

Renal function

The typical pathology report may show that a patient's urea concentration has increased out of proportion to the creatinine concentration – for example, urea 32 mmol/L, creatinine 175 µmol/L. This reflects renal hypoperfusion. Often higher concentrations of urea and creatinine have to be tolerated to keep the patient euvolaemic, as opposed to having fluid overload and congestive symptoms. Trying to optimise fluid status and achieve the lowest urea and creatinine concentrations possible can be a difficult balance to achieve. There is no specific cut-off when the urea is considered to be too high; urea itself is not a toxin, but rather a marker of other ureamic toxins.

Uric acid

Uric acid is an excellent marker of the degree of intravascular depletion. Cardiac patients with renal impairment who are taking high dose diuretics may have uric acid levels as high as 0.7 to 0.8 mmol/L. Uric acid has not been confirmed as a risk factor for progressive renal failure, although this is currently being explored. At present, hyperuricaemia is treated only if patients develop clinical gout.

An acute attack of gout can be treated with colchicine (Colgout, Lengout), or with prednisone (Predsone, Panafcort, Sone) or prednisolone (Predsolone, Panafcortelone, Solone) in divided doses (10 mg in the morning and 5 mg at night). Once the acute attack has subsided, allopurinol

is used to reduce uric acid levels.

The chronic use of COX-2 inhibitors and other NSAIDs for gout is contraindicated in patients with renal impairment. Also, the propensity of these drugs to cause salt and water retention in patients may precipitate or worsen heart failure.

Anaemia

Anaemia is common in patients with heart failure, and early observational studies have demonstrated progressive anaemia as heart failure worsens. Anaemia is also often recognised in patients with chronic kidney disease, in whom relative erythropoietin deficiency is a common causal mechanism. ACE inhibitors and ARBs lower endogenous erythropoietin production.

Patients with heart failure must be screened for iron deficiency. Ferritin is the best marker of iron stores but can be falsely elevated in patients with acute inflammation. Serum iron is not a useful marker.

Warfarin (Coumadin, Marevan) and the platelet inhibitors, aspirin and clopidogrel (Iscover, Plavix), which are often prescribed in combination, increase the risk of gut blood loss.

Small interventional studies with epoetin (Eprex, NeoRecorman), a recombinant human erythropoietin, have shown an improvement in heart failure symptoms and reduced hospitalisation rates; however, larger placebo controlled trials with darbepoetin (Aranesp) are awaited to confirm this. Current government reimbursement for epoetin is limited to patients who have haemoglobin concentrations less than 100 g/L.

Assessing cardiovascular and renal function: tips for rural GPs

- Frequent blood tests are needed to manage patients with heart and kidney disease.
- Check electrolytes, urea, creatinine and haemoglobin levels one to two weeks after the dosages of diuretic, ACE inhibitors or angiotensin-II receptor blockers have been altered.
- Contact a kidney specialist or cardiologist if a patient's potassium concentration is >6.0mmol/L, urea >20 mmol/L or creatinine >200 µmol/L.
- Keep lists available of foods that have a high sodium and high potassium content to give to patients who need to avoid these electrolytes.

Conclusion

As clinicians become better at managing heart and renal failure, increased patient survival will lead to more cardiomyopathy and nephropathy complications. Patients with heart failure and deteriorating renal function need careful adjustment of their medications, often with input from both a cardiologist and a kidney specialist. MT

DECLARATION OF INTEREST: Dr Roger has acted as an adviser to Amgen and F. Hoffmann-La Roche.