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## CONTENTS

### EDITORIAL

- The end of NPS MedicineWise** 186  
D Rigby

### ARTICLES

- Administration of medicines to children: a practical guide** 188  
L Smith, C Leggett, C Borg

- Coronary artery disease in women** 193  
N Montarello, WP Chan

- Diuretics in the management of chronic heart failure: when and how** 200  
JS Magdy, J McVeigh, P Indraratna

- Blood pressure elevations in hospital** 205  
AA Mangoni, EA Jarmuzewska, GM Gabb, P Russell

### FEATURE

- Medicinal mishap** 208  
Osteonecrosis of the jaw and denosumab

- Latest news** 210  
*Wither Australian Prescriber?*

### NEW DRUGS 211

Asciminib for chronic myeloid leukaemia  
Decitabine/cedazuridine for chronic myelomonocytic leukaemia, myelodysplastic syndromes  
Elasomeran/imelasomeran for prevention of COVID-19  
Mecasermin for primary insulin-like growth factor-1 deficiency  
Pemigatinib for cholangiocarcinoma  
Selinexor for multiple myeloma

# The end of NPS MedicineWise

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## Keywords

drug policy, health professional education, quality use of medicines

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The National Prescribing Service was established in 1998, by the Department of Health and Family Services, to improve health outcomes by supporting the quality use of medicines (QUM).<sup>1</sup> The establishment of an independent, not-for-profit organisation working alongside government was considered progressive and insightful policy. Over the next 24 years the organisation, now known as NPS MedicineWise, built a trusted reputation for providing national leadership, education, behaviour change and resources to support QUM and medicines safety in Australia.

In March 2022, the Federal Government's budget included a redesign of the Quality Use of Diagnostics, Therapeutics and Pathology Program. Some functions of NPS MedicineWise would shift to the Australian Commission on Safety and Quality in Health Care, while others would be subject to new contestable funding arrangements.

These unexpected changes to the role and funding of NPS MedicineWise have led to a decision to end its operations in December 2022. It is therefore time to reflect on the impact of the organisation and its people, celebrate the achievements and look to the future of QUM and medicines safety in Australia.

The fundamental role of NPS MedicineWise is stewardship of the QUM objectives of the National Medicines Policy.<sup>2</sup> Early evidence-based strategies embraced the ethos of QUM with clinical audit and feedback, educational visiting and newsletters. Publications grew to include NPS News, RADAR, and, from 2002, *Australian Prescriber*, possibly the most widely read medical journal in Australia. As the impact, reach and credibility of NPS MedicineWise evolved, its range of initiatives grew.

A critical strength of NPS MedicineWise programs was behavioural intervention. When NPS MedicineWise was first established, some were suspicious that it was an arm of government set up to save money. However, over time, the organisation built trust, respect and credibility through well-designed interventions, with an evidence-based approach and being mindful of the complexity of prescribing and medication management.

One of the principles of QUM is partnership. NPS MedicineWise therefore worked collaboratively with member organisations, other associations and government to ensure its programs were grounded in issues important to consumers and other stakeholders.

An example of partnership is Choosing Wisely Australia, launched in 2015. This is a key social movement involving NPS MedicineWise working with health professional colleges, societies and associations to address low-value and unnecessary healthcare practices.

With a multidisciplinary view, the Prescribing Competencies Framework was developed. This describes prescribing expectations for all prescribers and also curriculum design for medical, pharmacy and allied health courses.<sup>3</sup>

NPS MedicineWise's MedicineInsight program provides important insight into real-world prescribing practices, supporting quality improvement in primary care and postmarket surveillance of medicines. Its reach at a local level also enables evaluation of the impact of NPS MedicineWise programs. NPS MedicineWise has delivered over \$1.1 billion in direct savings for the Pharmaceutical Benefits Scheme and Medicare Benefits Schedule, representing a twofold net return on investment for the government.<sup>4</sup>

Consumers are at the centre of every program and resource created by NPS MedicineWise. Their voice is present across every step of program needs assessment, design, delivery and evaluation. Innovative programs including Be MedicineWise Week, Good Medicine Better Health, Medicines Line and Adverse Medicine Events Line, mass audience campaigns such as Antibiotic Resistance Fighter, and the MedicineWise app have made a substantial contribution to the health literacy of consumers to enable Australians to make better decisions about their medicines and health.

A subsidiary, VentureWise, was established in 2015, to extend QUM activities, beyond those supported by government funding, to other areas of the health system. This was a strategic decision to raise revenue to build equity and financial stability for NPS MedicineWise.

In 2018, the Department of Health undertook a review to provide clarity and guidance on NPS MedicineWise governance, performance, transparency and accountability.<sup>5</sup> The review acknowledged the high quality and valued resources used in the delivery of the programs to support the Quality Use of Medicines and Diagnostics, but made recommendations for improvement. NPS MedicineWise accepted the recommendations in principle. It committed to

enhancements to deliver efficient, flexible and innovative QUM programs, while VentureWise was wound up in 2020.

The policy change announced in March 2022, to cease funding for NPS MedicineWise, was met with dismay and disappointment across the health sector. A change of government led to a rapid review to assess the appropriateness of the proposed redesign of the Quality Use of Diagnostics, Therapeutics and Pathology Program.<sup>6</sup> This desktop review occurred without much stakeholder consultation. When it reported in August 2022, the review identified several risks in the proposal. However, it supported moving QUM stewardship functions to a standards-based organisation,

accompanied by competitive tendering for program delivery and design.<sup>6</sup> As funding for NPS MedicineWise will therefore end on 31 December 2022, the board of directors had little choice but to close the organisation.<sup>7</sup>

The legacy of NPS MedicineWise must drive the future direction of QUM stewardship in Australia. NPS MedicineWise had a remarkable record of excellence, innovation and engagement, particularly with primary care and consumers. The imperative for an independent, evidence-based QUM voice in Australia remains more important than ever. ◀

*Conflicts of interest: Deborah Rigby was a Director of NPS MedicineWise from 2008 to 2020.*

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## ARTICLE

# Administration of medicines to children: a practical guide

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**Keywords**

drug formulation, oral administration, paediatrics, palatability, patient safety, taste

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**SUMMARY**

Getting children to take medicines can be difficult. There is no 'one-size-fits-all' approach.

When selecting medicines for children, it is important to consider the child's age, swallowing ability, ease of administration and accessibility of the product.

Ask the child, parent or caregiver about their preference for formulations and flavours.

There are different ways to alter the taste, aftertaste and mouth feel of medicines, which may help improve palatability.

Pharmacists or medicines information services can assist with advice on suitable formulations or methods of administration.

**Introduction**

Giving medicines to infants and children can be challenging. Children may refuse to take medicines for many reasons, such as fear, taste, embarrassment or inconvenience.

This problem is compounded by a lack of suitable formulations for paediatrics, restricting prescribing options and posing safety concerns. There is also limited information for parents and caregivers on how to give medicines to children, with most information coming from experience and anecdotal reports.

**Choosing the right formulation**

There is a well-recognised lack of suitable paediatric formulations available,<sup>1</sup> contributing to an increased risk of dosing errors and difficulties in administration. When selecting medicines for children, it is important to consider factors such as the child's age, swallowing ability, ease of administration and accessibility of suitable formulations of the product. Understanding the characteristics of each formulation can assist with choosing the most appropriate medicine for a child.

**Oral liquids**

Oral liquids are the preferred formulation for younger children as they are easier to swallow<sup>2</sup> and allow for flexible dosing based on the child's age and weight. Liquids may also be mixed with different flavours at the time of administration to help mask the taste and smell of a medicine.

However, liquid formulations are not without risk and can result in over- or underdosing, particularly in the following cases:

- Small volumes are required to be measured. Although smaller volumes may be preferable, the use of more concentrated liquids may create an additional risk, particularly with drop formulations that are marketed for adult use, but may sometimes be given to children (e.g. tramadol 100 mg/mL).<sup>3</sup> Their use can more easily result in 10-fold dosing errors, such as measuring 1 mL instead of 0.1 mL. This can be minimised by providing carers with an oral syringe marked with the correct dose and appropriate counselling.<sup>4</sup>
- Multiple formulations of the same active ingredient are available. For example, paracetamol oral liquids are available in concentrations of 24 mg/mL, 48 mg/mL, 50 mg/mL and 100 mg/mL. When discussing medicines for children, it is important for carers, clinicians and pharmacists to include instructions with the dose by weight (e.g. mg or micrograms) and dose by volume.

Oral liquids may contain excipients such as colourings, solvents and preservatives at concentrations that may not be suitable for children.<sup>5</sup> For example, furosemide (frusemide) oral solution contains 12.7% ethanol, which is typically considered insignificant in adults. However, it exceeds the maximum allowed ethanol content of 0.5% for children younger than six years of age, limiting the use of the proprietary furosemide (frusemide) product in this age group.<sup>6</sup>

Oral liquids often contain sugars to help improve palatability. It is important to consider the effects of sugar on teeth, particularly with chronic medicines. To minimise dental cavities, consider sugar-free formulations and encourage children to brush their teeth after taking a dose.<sup>7</sup>

### **Solid dosage forms**

If an oral liquid is not available, alternative oral formulations may be suitable. If a solid dosage form requires manipulation (chewing, crushing, dispersing, halving or breaking) to facilitate administration, particular drug properties should be considered:

- palatability
- physiochemical (e.g. acid labile or light sensitive)
- hazardous (e.g. irritant, cytotoxic)
- drug release kinetics (e.g. modified release, enteric coating).

### **Tablets**

Tablets are a suitable alternative to oral liquids, particularly when medicines are unpalatable.<sup>8</sup> However, a child's ability to swallow tablets must be considered. There is no established age at which children are able to swallow tablets, as it is a skill that must be learned.<sup>9</sup> Several resources are available for caregivers to assist with teaching children to swallow tablets or capsules (see Box). Some children may be able to swallow tablets from a young age, although most children are usually at least 8–10 years of age before they can routinely take tablets.<sup>10</sup> If prescribing or dispensing for a child, the child or carer should always be asked if they would prefer tablets or oral liquids.

Tablets are more accessible with easier storage and transport options than those for oral liquids. However, tablets have limited dose flexibility, decreasing the ability to prescribe weight-based doses.<sup>5</sup>

### **Box Useful resources**

Society of Hospital Pharmacists of Australia. Don't rush to crush. 4th ed. [Booklet].

NPS MedicineWise. How to give medicines to children.

Royal Children's Hospital, Melbourne. How to give medications to children. [Pamphlet].

Royal Children's Hospital, Melbourne. Teaching children how to swallow tablets and capsules.

Medicines for Children. Helping your child to swallow tablets.

Most tablets are intended to be swallowed whole, but some immediate-release preparations may be chewed, crushed, or halved or quartered using a tablet cutter.<sup>5</sup> Caution should be taken when manipulating tablets as this may result in a small portion of the dose being lost. This is particularly significant when giving medicines with a narrow therapeutic index. Additionally, most tablets are not formulated to be palatable, so crushing or dispersing them may impact a child's willingness to take the medicine.

### **Modified-release tablets**

Modified-release tablets should be swallowed whole, as chewing or crushing them may damage the modified-release formulation, causing toxicity by releasing the total amount of medicine at once.<sup>11</sup>

### **Capsules**

Some children may find capsules easier to swallow than tablets. However, capsules cannot be halved, which limits their dose flexibility.

Most capsules are formulated to be swallowed whole. Some hard capsules (filled with powder or coated granules) may be opened and their contents mixed or sprinkled in food or drinks. Similarly, some soft capsules (filled with liquids or semisolids) may be chewed (e.g. colecalciferol).<sup>5</sup>

### **Oro-dispersible tablets**

Oro-dispersible dosage forms, including tablets, wafers and films, are formulated to disperse rapidly once placed on the tongue. Alternatively, they can be dispersed in a small volume of liquid before administration. These preparations may be useful in children, as they do not need to be swallowed whole or crushed.<sup>5</sup>

Oro-dispersible medicines are commonly formulated with additive flavours to help mask the taste. Due to their delicate composition, it may be difficult to half or quarter these dosage forms, limiting their dose flexibility.

### **'Making the medicine go down'**

There are some common 'Dos & Don'ts' for administering medicines to children, which depend on the type of formulation (Table 1). These suggestions are also outlined in a consumer-friendly leaflet (see Fig.).<sup>12</sup>

### **Taste**

Taste is a powerful deterrent for children and is thought to have evolved as a safeguard against ingesting toxic substances.<sup>13</sup> The unpleasant taste of a medicine can be improved by mixing it with various



ARTICLE

Administration of medicines to children: a practical guide

flavoured syrups or cordials (Table 2).<sup>6,7</sup> However, the child's taste preferences must be considered before mixing with flavours. Liquorice, peppermint and coconut flavours may taste reasonable to adults but may be disliked by children.<sup>14</sup>

Mixing medicines with a small amount of food or liquid is unlikely to cause drug-food interactions, even with medicines recommended to be given on an empty stomach (e.g. flucloxacillin). A small reduction in absorption of the medicine will pose less of a problem than that created by a child refusing to take the medicine at all.

Table 1 Common recommendations and precautions for administering medicines to children

Recommendations	Precautions
<b>Oral liquids, suspensions and elixirs</b>	
Use metric measures, such as a medicine syringe or cup	Do NOT use everyday utensils, such as teaspoons or tablespoons
Count oral drops on a spoon before administering	Do NOT administer drops directly from the bottle into the child's mouth
Mix oral liquids with a small amount of water or juice	Do NOT mix the medicine in large volumes
If the medicine is available in multiple flavours, ask the child for their preference	Do NOT mix the medicine with a child's essential foods (e.g. milk or formula), as the altered taste may cause future aversion to the essential foods
<b>Tablets, capsules and solid dosage formulations</b>	
Place the tablet in the middle of the tongue and follow with a large volume of liquid	Do NOT mix with honey in children younger than one year of age due to the potential risk of infant botulism
Try drinking a small amount of liquid from a bottle or using a straw	Do NOT give large volumes (i.e. aim for one mouthful)
Try halving or quartering tablets	Do NOT break modified-release, cytotoxic or hazardous medicines
Crush tablets between two spoons and mix with a small amount of soft food such as yoghurt, cold custard, fruit puree or jam	Do NOT crush modified-release, cytotoxic or hazardous medicines
Try dispersing the tablet in a small volume of liquid (water or juice)	
Check with a pharmacist if the tablets can be crushed or the capsules opened	
Encourage parents and caregivers to teach children how to swallow tablets. There are several resources to assist with teaching children to swallow solid dosage forms (see Box)	

## Aftertaste

The aftertaste of a medicine is a difficult issue to navigate, particularly if it prevents a child from accepting subsequent doses.<sup>13,14</sup> When administering a medicine, try and avoid the tongue, aiming oral liquids towards the back of the mouth against the cheek. Alternatively, consider swapping to a capsule or tablet formulation, which can be swallowed whole. Some children may find it more palatable to take a medicine via a straw or follow with a cold drink to lessen the aftertaste.

## Mouth feel

The mouth feel of a medicine may also be a deterrent for some children. To improve the feel of oral liquids, consider diluting in water or a flavoured drink to reduce their viscosity.<sup>13,14</sup> To combat the grittiness of crushed tablets or granules, try mixing with thick or gelatinous foods such as jelly, custard or spreads.

## Advice for prescribers

When prescribing medicines for children, some practical considerations include:

- minimising the dosing frequency where appropriate (e.g. prescribing cefalexin 12-hourly (twice a day) rather than six-hourly (four times a day))
- avoiding medicines that are known to be less palatable (e.g. flucloxacillin is known to be bitter, so using cefalexin as an alternative)
- using alternative routes of administration, especially for children who cannot tolerate oral fluids (e.g. using a rectal paracetamol formulation rather than an oral formulation).

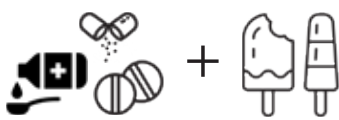
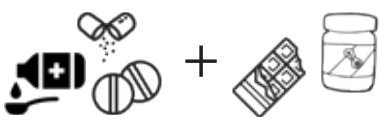
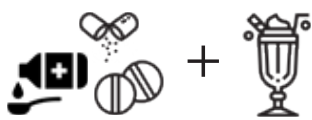
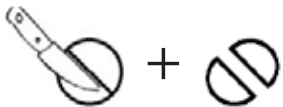
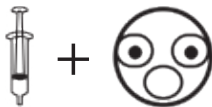

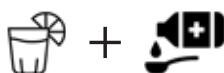

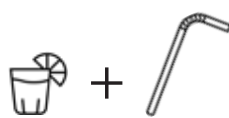
## Conclusion

There are several techniques and strategies that can be used to improve the palatability and acceptance of medicines by children. Often, there is no single solution, and instead, there are many strategies that may be implemented by the parent or caregiver. Further guidance may be obtained from the local pharmacist or medicines information service. ◀

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*Conflicts of interest:* none declared

Fig. Suggestions for administering medicines to children<sup>12</sup>

General		
 <p>Try cold treats like an ice cream or ice blocks to numb the tastebuds</p>	 <p>Try mixing with fatty foods like peanut butter or chocolate to coat the tastebuds</p>	 <p>Have the child's favourite drink ready to follow the medicine</p>
Tablets/capsules	Liquids	
 <p>Try cutting the tablet in halves before swallowing it*</p>	 <p>Try using an oral syringe, aiming towards the back of the mouth against the inner cheek Avoid the tongue</p>	
 <p>Try crushing the tablet or opening the capsule and sprinkling the contents on foods such as yoghurt or custard*</p>	 <p>Try mixing the medicine into a small amount of fruit juice before drinking†</p>	
 <p>Try crushing the tablet or opening the capsule and sprinkling the contents in a small amount of fruit juice*</p>	 <p>Try pouring the medicine in a small cup and drinking with a straw</p>	

\* Not all tablets and capsules can be altered. Confirm with your local pharmacist.

† The entire drink must be consumed to ensure the full dose has been taken.

Adapted from reference 12

Table 2 Tastes and masking flavours

Taste of the medicine	Examples*	Flavour to mask the taste of the medicine
Sour	Multivitamins (e.g. vitamin C)	Cherry, lemon, lime, mandarin, orange, strawberry, raspberry, pineapple
Bitter	Antibiotics Paracetamol Corticosteroids	Cherry, chocolate, liquorice, strawberry, peach, coffee, mint, lemon, lime, raspberry, tutti-frutti, orange, cinnamon
Sweet	Lactulose Sorbitol	Caramel, lemon, orange, vanilla, bubble-gum
Salty	Iron supplements Antihistamines Macrogol laxatives Oral rehydration solutions	Banana, caramel, cream, chocolate, grape, vanilla, raspberry, orange, cinnamon, nut, butter, butterscotch, maple
Any		Spreadable yeast extract, peanut butter, jam, honey, apple sauce, custard, ice cream

\* Common examples are based on patient reports, although any drug may be considered 'bad' tasting depending on subjective taste preferences.

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# Coronary artery disease in women

## SUMMARY

Cardiovascular disease is the leading global cause of death in women but remains underdiagnosed and undertreated.

Health professionals play an important role in improving the heart health of Australian women. Routine heart health checks should be offered to all women 45 years of age and older and to all Aboriginal and Torres Strait Islander women 30 years of age and older.

Cardiovascular risk assessment in women must include traditional and sex-specific risk factors, including their pregnancy history and early-onset menopause.

Women with pregnancy-related hypertensive and metabolic disorders have an increased long-term cardiovascular risk and require close monitoring.

Women with acute coronary syndrome may not experience classical chest pain. More often, they experience cardiovascular events in the absence of obstructive coronary disease and have poorer cardiovascular outcomes.

The recognition of sex-specific differences and more sex-specific trials are key to improving clinical outcomes.

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## Keywords

cardiovascular disease, cardiovascular risk, menopause, myocardial infarction with non-obstructed coronary arteries

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## Introduction

Cardiovascular disease, which encompasses heart disease, stroke and peripheral vascular disease, is the leading cause of illness and death in women worldwide. Biological and physical differences, such as a smaller body surface area, smaller coronary vessel size and sex hormone-mediated factors in women, are exacerbated by sociocultural factors and contribute to differences in the prevalence, presentation and natural history of cardiovascular disease between the sexes. Women with cardiovascular disease experience delays in diagnosis, are less likely to be treated in line with guidelines and standards, and have higher complication rates and worse outcomes than men. Women are significantly under-represented in clinical trials, and sex-specific diagnostic and management strategies are not included in current clinical guidelines.

## Epidemiology

Three out of every 10 female deaths in Australia are due to cardiovascular disease, including coronary artery disease.<sup>1</sup> It is estimated that between the ages of 45 and 64 years, one in nine women will develop some form of cardiovascular disease, which increases to one in three women after the age of 65 years.<sup>2–4</sup> Indigenous Australian women are particularly at risk, often at a younger age. In 2016, indigenous women aged 25 years and older experienced an acute coronary event in the form of myocardial infarction or unstable angina at a rate of 617 per 100,000 population. This

is 3.8 times more likely than in other Australian women.<sup>5</sup> Positively, the mortality rates of coronary artery disease have been declining in Australia in recent decades. From 2006 to 2016, the rate fell by 46% for women (from 78 to 44 per 100,000 population) and by 40% for men (from 135 to 84 per 100,000 population).<sup>5</sup> Further, between 2001 and 2016, the prevalence of acute coronary events (myocardial infarction and unstable angina) in Australian women fell by 57% (from 465 to 215 events per 100,000).<sup>5</sup> However, the rates of decline are lower in women under the age of 55 years, with a rise in strokes and myocardial infarcts.<sup>1</sup>

## Cardiovascular risk factors

Various traditional and sex-specific risk factors increase the risk of cardiovascular disease in women.

### Traditional risk factors

Traditional risk factors are more often under-recognised and undertreated in women than in men and affect the risk of cardiovascular disease differently between the sexes (Box 1).<sup>4,6–18</sup>

### Sex-specific risk factors

Several female-specific risk factors increase the risk of cardiovascular disease in women.

### Hormonal contraceptives

Combined hormonal contraceptives are associated with a 12-fold increase in the risk of acute myocardial infarction in women with hypertension<sup>19</sup> and should

**Box 1 Traditional cardiovascular risk factors in women****Hypertension**

The impact of hypertension on the risk of developing ischaemic heart disease seems consistent across the sexes.<sup>6</sup>

Although sex differences in the incidence of hypertension have not been found,<sup>6</sup> hypertension is undertreated in women,<sup>7</sup> leading to heart failure with preserved ejection fraction.<sup>8</sup>

**Dyslipidaemia**

The ratio of total cholesterol to high-density lipoprotein cholesterol is more powerfully associated with acute myocardial infarction in women than in men.<sup>4</sup>

**Diabetes**

Diagnosis occurs at a higher body mass index, older age and more advanced stage of disease progression in women than in men.

**Obesity**

The Framingham Heart Study showed that the excess risk of cardiovascular disease from obesity was 64% in women versus 46% in men.<sup>9</sup>

**Smoking**

Tobacco use confers a 25% increase in the risk of developing coronary artery disease compared to that in men.<sup>10</sup>

**Systemic inflammation and auto-immune disorders**

These more commonly affect women and cause endothelial dysfunction and the acceleration of atherosclerosis, resulting in an increased risk of cardiovascular disease.<sup>11</sup>

**Sedentary lifestyle**

The increase in the risk of cardiovascular disease risk is greater in women (particularly older women) as they are more sedentary than men.<sup>12,13</sup>

**Psychosocial**

Physical and psychological abuse affects 15–71% of women and contributes to depression.<sup>14,15,16</sup>

Increased substance abuse including tobacco and alcohol in women who report partner violence independently contributes to an increased cardiovascular risk.<sup>17,18</sup>

be avoided in this subgroup. Progestogen-only contraceptives should be considered in women with an increased risk of acute myocardial infarction. Prior use of hormonal contraceptives does not increase the risk of subsequent cardiovascular disease.<sup>20</sup>

**Pregnancy-related disorders**

Hypertensive and metabolic disorders of pregnancy are also independently associated with an increased risk of maternal cardiovascular disease.<sup>21</sup> These include gestational hypertension, pre-eclampsia, eclampsia and placental abruption. Early onset (<34 weeks) and severe degrees of pre-eclampsia confer a particularly increased risk of maternal cardiovascular disease in later life,<sup>22</sup> potentially due to resultant endothelial dysfunction, which persists for many years after an affected pregnancy and is linked to atherosclerosis.<sup>23</sup> Women with gestational diabetes have an increased risk of subsequent cardiovascular disease, and more than 50% will go on to develop chronic type 2 diabetes mellitus.<sup>24</sup>

**Menopause**

Following menopause, the risk of cardiovascular disease rises substantially. This is possibly related to a sharp, sustained increase in low-density lipoprotein cholesterol around the time of the final menstrual period.<sup>25</sup> Lower concentrations of oestrogen and higher concentrations of androgen contribute to this increased risk.<sup>26</sup> Premature menopause increases the risk of cardiovascular disease before the age of 60 years.<sup>27</sup>

**Menopausal hormone therapy**

Randomised controlled trials have not shown any benefit in primary or secondary prevention with the use of hormone replacement therapy. Oestrogen use results in a small but significantly increased risk of cardiovascular events, particularly in women starting therapy 20 or more years after menopause or at least from 70 years of age.<sup>28</sup> In women with acute myocardial infarction, menopausal hormone therapy should be discontinued.<sup>29</sup>

**Other hormonal factors**

Early menarche (<12 years of age), young age at first birth, a history of miscarriage, stillbirth, preterm birth, low-birthweight babies and hysterectomy are independently associated with an increased risk of cardiovascular disease in later life.<sup>30</sup> This is possibly mediated by increased systemic inflammation<sup>30</sup> and endothelial dysfunction, which accelerate atherosclerosis.<sup>31</sup> Polycystic ovarian syndrome is associated with a heightened risk of cardiovascular disease, specifically coronary artery disease.<sup>32</sup> The clustering of insulin resistance, obesity and metabolic syndrome, which leads to type 2 diabetes, dyslipidaemia and hypertension, may be causal.<sup>33</sup>

**Cancer radiotherapy and chemotherapy**

Radiation can cause coronary endothelial injury leading to a pro-inflammatory state, the rupture of vessel walls, platelet aggregation, thrombosis and the replacement of damaged intima by myofibroblasts, resulting in vessel stenosis and atherosclerosis.<sup>34</sup> Women with a history of breast cancer receiving radiotherapy show a relative 7.4% increase in the risk of cardiovascular events with each gray of radiation exposure.<sup>35</sup> Furthermore, for reasons that are unclear, women treated with mantle or mediastinal radiation for Hodgkin lymphoma have a significantly higher cardiovascular event rate and mortality compared to those in men, highlighting the need for increased surveillance.<sup>36</sup> Reduced cardiovascular-specific survival has also been reported in women treated with radiation for cervical and uterine cancers.<sup>37</sup>

## Cardiovascular risk assessment

Cardiovascular risk should be assessed differently in men and women (Box 2). The Framingham Risk Score underestimates the risk of cardiovascular disease in women.<sup>38</sup> The Reynolds Risk Score<sup>39</sup> is best suited for women.<sup>40</sup> This 10-year cardiovascular risk prediction algorithm for women older than 45 years of age includes two additional risk variables. These are the high-sensitivity C-reactive protein concentration and a parental history of premature coronary artery disease before 60 years of age (Table).

No sex-specific risk factors are included in any available primary prevention risk assessments. Further research that promotes the incorporation of female-specific risk factors in this algorithm would improve the accuracy of cardiovascular risk assessment in women.

## Types of coronary artery disease

There are differences between men and women across different types of coronary artery disease.

### Coronary artery disease

Obstructive coronary artery disease generally manifests similarly in women and men, with the most common symptom being central chest pain. In women, there is a greater likelihood of chest pain onset at rest, during sleep or when under mental stress. Women also more frequently present atypically with pain in the upper back, arms, neck and jaw, as well as presenting with dyspnoea, diaphoresis, indigestion, nausea, palpitations, dizziness and weakness.<sup>41</sup> Furthermore, the proportion of women aged 55 years and younger presenting with acute coronary syndrome without chest pain is significantly greater than the proportion of men (19% vs 13.7%).<sup>42</sup> As a result, they are at a greater risk of being discharged home with evidence of acute coronary syndrome compared to men.<sup>43</sup>

Women with coronary artery disease also more frequently develop symptomatic heart failure than men. This may be due to the impact of co-existent hypertension, an important risk factor for coronary artery disease, which leads to a greater incidence of left ventricular hypertrophy that is less responsive to antihypertensive therapy in women, resulting in diastolic dysfunction and heart failure with preserved ejection fraction.<sup>44</sup>

### Ischaemia with non-obstructive coronary artery disease

Ischaemia with non-obstructive coronary disease is a condition due to coronary microvascular dysfunction or epicardial vascular spasm. It is more common in women, especially at 45–65 years of age.<sup>45</sup> If this

## Box 2 Coronary artery disease in women compared to men

### Presentation

Similar to men, where most experience central chest pain, but onset is more often at rest

Atypical symptoms more frequent, including pain in the upper back, arms and jaw, and diaphoresis, dyspnoea, indigestion, nausea, dizziness, fatigue and palpitations

Absence of chest pain more often in acute coronary syndrome

Ischaemia and myocardial infarction more often in the setting of non-obstructive coronary artery disease

Takotsubo syndrome a common cause of myocardial infarction

### Diagnosis

Reynolds Risk Score more accurate than the Framingham Risk Score

Better prognostic information from CT coronary angiography than from functional testing

Coronary angiography used less often after positive exercise stress test results

### Treatment

Statins used less in angina and after myocardial infarction

Similar coronary stent use

Less frequent coronary artery bypass grafting

Table Reynolds Risk Score for cardiovascular risk in women<sup>39</sup>

Risk factor	Measure
Age	years
Systolic blood pressure	mmHg
Diabetes mellitus	<input type="checkbox"/> Yes <input type="checkbox"/> No
Current smoker	<input type="checkbox"/> Yes <input type="checkbox"/> No
High-density lipoprotein cholesterol	mmol/L
Total cholesterol	mmol/L
High-sensitivity C-reactive protein	mg/L
Parental history of premature coronary artery disease aged <60 years	<input type="checkbox"/> Yes <input type="checkbox"/> No

The Reynolds Risk Score is an online calculator that uses a risk prediction algorithm to predict the 10-year cardiovascular event risk, for myocardial infarction, ischaemic stroke, coronary revascularisation and cardiovascular mortality (<5% = low risk, 5–9% = moderate risk, 10–19% = moderate-to-high risk, ≥20% = high risk).<sup>40</sup>

condition or coronary stenosis is not diagnosed, many women are mistakenly presumed to not have heart disease and are not treated, which increases their risk of adverse cardiac events. A comprehensive meta-analysis has revealed an overall estimated incidence of all-cause mortality or myocardial infarction of 0.98 per 100 person-years in patients with non-obstructive coronary disease compared with 0.2 per 100 person-years in a similarly matched general population. In addition, 50% of patients with non-obstructive coronary disease will experience

repeated episodes of ischaemic chest pain, similar to those with obstructive coronary artery disease, further underscoring the importance of the condition. Functional coronary angiography is needed to evaluate macroscopic resistance, coronary flow reserve and microvascular resistance to confirm the diagnosis that is otherwise missed on routine non-invasive testing.<sup>46</sup>

### ***Myocardial infarction with non-obstructive coronary artery disease***

Myocardial infarction with non-obstructive coronary artery disease (MINOCA) is roughly three times more common in women than in men.<sup>47</sup> This is based on a pooled analysis of 10 studies that recruited both patients with MINOCA and myocardial infarction with obstructive coronary artery disease (MI-CAD).<sup>48</sup> Furthermore, approximately 25% of patients with MINOCA have ongoing angina, equivalent to the prevalence in patients with MI-CAD.<sup>47</sup> The pathophysiology is unknown in approximately a quarter of MINOCA cases. Processes involving the epicardial vessels and coronary microvascular disease, which prevent an increase in myocardial blood flow in response to an increased oxygen demand, may be responsible. There may also be an overlap with mild forms of Takotsubo syndrome.<sup>49</sup>

### ***Takotsubo syndrome***

Takotsubo syndrome accounts for 7.5% of cases of acute myocardial infarction in women, with 90% of cases occurring in postmenopausal women aged 50–75 years.<sup>50–52</sup> It is triggered by emotional or physical stress, which is associated with enhanced sympathetic activity. Patients present with chest pain and ECG changes characteristic of acute coronary syndrome but without angiographically obstructive coronary artery disease. These patients have reversible left ventricular ballooning. Cardiac arrest occurs in 5.9% of patients.<sup>53</sup>

### ***Spontaneous coronary artery dissection***

In at least 25% of women aged 60 years or younger, spontaneous coronary artery dissection causes acute myocardial infarction, with conventional risk factors often being absent. It is the most common cause of myocardial infarction associated with pregnancy, primarily occurring in the third trimester or postpartum.<sup>54</sup> The risk of recurrence is substantial with a pathological process independent of atherosclerotic disease. While strategies to prevent spontaneous coronary artery dissection include avoiding hormonal therapy and future pregnancies, there is currently a lack of evidence that allows for treatment guidelines to be established.

## **Diagnosis of cardiovascular disease**

Women are not referred as often as men for appropriate diagnostic and therapeutic procedures for cardiovascular disease.<sup>55</sup> A biased view that coronary artery disease preferentially affects men may lead to underestimation of its severity in women, resulting in lower rates of invasive testing and intervention.<sup>56,57</sup> Such biases may be more extreme in younger patients due to a lower incidence of coronary artery disease in younger women.<sup>58</sup> Clinicians may also be concerned about the safety of invasive procedures in women.<sup>59</sup> Women have higher risks of bleeding and vascular complications following percutaneous coronary intervention and surgery, which may lead to a greater reluctance to intervene.<sup>60,61</sup>

### ***Risk assessment***

The presence of diabetes, smoking habits and a family history of premature coronary artery disease are risk factors of cardiovascular disease.<sup>62</sup> In the presence of these factors, the risk is greater in women than in men.<sup>56,63,64</sup>

### ***Non-invasive testing***

Stress tests, involving either exercise or drugs to mimic the effects of exercise, are used primarily for the diagnosis and risk stratification of obstructive coronary artery disease. Exercise testing is associated with a higher false-positive rate of diagnosis in women than in men due to a lower pre-test probability of the disease.<sup>65</sup> Exercise echocardiography is often preferred to stress nuclear imaging or CT coronary angiography in women because of concerns about radiation exposure, particularly to the breasts. However, CT coronary angiography may provide greater prognostic information than that provided by functional stress testing in women. Men appear to derive similar prognostic value from both types of tests.<sup>66</sup>

### ***Invasive testing***

Some studies have shown sex-based differences in the use of coronary angiography, which may reflect physicians' failure to refer women with positive exercise stress test results,<sup>67</sup> leading to poorer patient outcomes. In one study, women with a positive exercise stress test result were more likely than men to have no further cardiac evaluation (62% vs 38%). At three years, this difference was associated with a higher incidence of acute myocardial infarction or death in non-revascularised women (14.3% vs 6% per year in men).<sup>68</sup> Other studies, however, have shown similar rates of coronary angiography following acute myocardial infarction.<sup>69</sup>



## Cardiovascular disease treatment

The management of cardiovascular disease in women must take into account sex-specific factors including the size of coronary vessels, bleeding risk and hormonal status, as well as potential pharmacokinetic and pharmacodynamic differences.

### Revascularisation

Compared to men, women are nearly as likely to undergo percutaneous coronary angioplasty but less likely to undergo coronary artery bypass grafting.<sup>70</sup> It is unclear whether this represents bias or appropriate treatment given the higher mortality in women following coronary artery bypass grafting linked to increased comorbidities including smaller coronary vessels.

### Cardiovascular pharmacotherapy

In younger women, dual antiplatelet therapy results in an increased risk of heavy menstrual bleeding and anaemia and needs close monitoring. Discussions about contraception use are important, as statins and ACE inhibitors are contraindicated in pregnancy. Prescribing may differ in women based on their reproductive age, other hormonal treatments and use of contraceptives.

Women with cardiovascular disease are more likely to receive nitrates, calcium channel blockers and sedatives and less likely to receive aspirin and statins than men,<sup>71</sup> likely reflecting the higher prevalence of non-atherosclerotic cardiovascular disease. Statin use after acute myocardial infarction is also significantly lower in women than in men. This is partly physician driven and may be appropriate when myocardial infarction is due to MINOCA, which is more commonly encountered in women. However, low statin use in women with MI-CAD may be related to a reduced awareness among physicians of the risks of recurrent heart disease in women and a reduced likelihood to

consider heart disease as the main threat to women's health. Even women themselves often view cancer as a greater health threat. This may explain why women less often fill scripts for statins after myocardial infarction compared to men.<sup>72</sup> To date, there is no evidence to support that statins are safer in men than in women. A large meta-analysis suggested that statin use to prevent major cardiovascular events has similar effectiveness in women and men,<sup>73</sup> and thus a poorer outcome in women is likely due to current practice.

## Conclusion

Current guidelines for the diagnosis, investigation and treatment of cardiovascular disease do not discriminate between the sexes and are derived from male-dominant studies. Women remain more likely to experience delays in diagnosis and are less likely to receive guideline-directed care.

Attention to the differing contributions of traditional risk factors such as the presence of diabetes, physicians' compliance with established guidelines for the management of hyperlipidaemia, and a focus on lifestyle factors are fundamental to reducing the risk of cardiovascular disease in women. In addition, recognising the importance of sex-specific risk factors, such as hypertensive and metabolic disorders of pregnancy, are vital to improving outcomes.

While sex-specific cardiovascular research has increased significantly in recent years, this has not translated into changes in guideline-recommended care, nor has it improved clinical outcomes for women. Fundamentally, cardiovascular disease in women remains understudied, underdiagnosed and undertreated. Until this is addressed, women will continue to experience disproportionately high cardiovascular morbidity and mortality. ◀

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## ARTICLE

# Diuretics in the management of chronic heart failure: when and how

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congestive heart failure, mineralocorticoid receptor antagonists, thiazides

*Aust Prescr* 2022;45:200–4<https://doi.org/10.18773/austprescr.2022.069>**SUMMARY**

Heart failure is an increasingly prevalent condition resulting in recurrent hospitalisations and significant mortality and morbidity.

The management of heart failure has evolved, and multiple drugs have an established mortality benefit in heart failure with reduced ejection fraction.

Although the focus should be on ensuring that patients are treated with the maximum tolerated doses of these guideline-directed therapies, diuretics continue to play a key role in the management of clinical congestion in all forms of heart failure.

Clinicians play a key role in heart failure management. Familiarity with the role of diuretics and their dosing and monitoring is critical.

**Introduction**

Heart failure affects approximately 2% of the adult Australian population, and the prevalence is increasing.<sup>1</sup> The natural history of the condition is characterised by episodes of acute decompensation, with significant associated mortality.<sup>2</sup> Heart failure can be classified as heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). HFrEF is characterised by impaired contractility of the left ventricular myocardium with a left ventricular ejection fraction (LVEF) below 50%. HFpEF is characterised by diastolic dysfunction that limits the filling of the left ventricle, although the LVEF remains greater than 50%.

The management of HFrEF has evolved over the last two decades and multiple drug classes have an established mortality benefit, including angiotensin receptor–neprilysin inhibitors, ACE inhibitors, beta blockers, mineralocorticoid receptor antagonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors. The primary aim is to establish patients on the maximum tolerated doses of these guideline-directed medical therapies, all of which reduce heart failure-related mortality. However, patients with hypervolaemia should also be treated with diuretics for symptom relief. When euvolaemia is achieved, diuretic therapy should be reduced or stopped where possible to prioritise these mortality-reducing drugs.

**Principles of diuretic therapy**

In heart failure, the abnormal cardiac filling and resultant high venous pressures can lead to the typical symptoms and signs of 'clinical congestion', including dyspnoea (particularly orthopnoea and paroxysmal

nocturnal dyspnoea), an elevated jugular venous pressure, hepatic enlargement and tenderness, peripheral oedema, pulmonary oedema and the formation of ascites. In patients with heart failure and clinical congestion, diuretics are first-line therapy to improve symptoms. While they may not have an established mortality benefit, diuretics were used as background therapy in most patients in the pivotal trials that showed the survival benefit of the aforementioned heart failure therapies.<sup>1</sup> The aim of using diuretics is to achieve euvolaemia. Once this is achieved, the diuretic dose should be reduced to the lowest effective dose or potentially discontinued.

Loop diuretics are the most frequently used diuretics due to their rapid onset and efficacy.<sup>3</sup> Acting on the sodium–potassium–chloride symporter of the ascending limb of the loop of Henle, loop diuretics promote the excretion of sodium and chloride, as well as potassium.<sup>2</sup> Furosemide (frusemide) is the most commonly used first-line therapy, which is typically started at a dose of 20–40 mg once daily in the outpatient setting. Patients who are furosemide (frusemide)-naïve typically have greater diuresis when the drug is started. If there is no response, the dose should be increased to reach the required threshold of diuresis.<sup>4</sup> The typical total daily dose for maintenance ranges between 40 mg and 240 mg. In the setting of advanced renal failure, daily doses up to 500 mg may be needed, and liaison with the treating nephrologist is recommended. To optimise the effect, it is recommended to divide the daily dose into morning and midday doses if more than 80 mg is required in a day.

Although furosemide (frusemide) is the only loop diuretic on the Pharmaceutical Benefits Scheme (PBS), there are other drugs in the class with differing pharmacological properties, including bumetanide. The oral bioavailability of bumetanide is high (approximately 80–90%), while that of furosemide (frusemide) varies. As such, a direct conversion is not consistently reliable, although in general, oral furosemide (frusemide) 40 mg is considered to be equivalent to oral bumetanide 0.5–1 mg.<sup>2</sup> Some clinicians favour the use of bumetanide for its higher oral bioavailability over furosemide (frusemide) in the setting of significant peripheral oedema, as bowel wall oedema may limit absorption.<sup>5</sup> A recent systematic review, however, did not show a significant benefit over furosemide (frusemide).<sup>6</sup> Given that furosemide (frusemide) contains a sulfonamide moiety, it carries a potential risk of cross-reactivity in the setting of sulfonamide allergies.<sup>7</sup> Etacrynic acid (which does not contain the sulfonamide moiety) is an alternative loop diuretic for patients with sulfonamide allergies.

### Refractory congestion and sequential nephron blockade

If congestion persists despite adequate dosing of loop diuretics, clinicians should consider 'sequential nephron blockade', the addition of diuretics that exert their effects at successive components of the nephron. However, it should be noted that sequential nephron blockade is a potent combination. While the combination can be more effective, it carries an increased risk of renal dysfunction and electrolyte imbalance and so should be used cautiously, particularly in elderly patients. This approach includes the concurrent use of thiazide diuretics and mineralocorticoid receptor antagonists. Thiazides act more distally in the nephron, by blocking the sodium–chloride co-transporter in the distal convoluted tubule.<sup>2</sup> Thiazide-like diuretics, which lack the benzothiadine backbone in their molecular structure, also act on the same transporter but have a longer elimination half-life.<sup>8</sup> The addition of thiazides may help overcome diuretic resistance, which can arise from prolonged use of a loop diuretic and the resultant nephron remodelling and increased sodium reabsorption.<sup>9</sup>

A readily available thiazide is hydrochlorothiazide, which can be started at 12.5–25 mg per day, and increased up to a total of 50 mg per day. Several thiazide-like diuretics can also be used, including indapamide, metolazone and chlortalidone, without strong evidence for the superiority of one drug.<sup>4</sup>

Some clinicians favour the potent diuretic metolazone in the setting of refractory congestion, although it is a highly specialised drug with restrictions on

prescribing and is generally dispensed from hospitals. While it may be dosed daily in the acute setting, in the non-acute environment, doses of metolazone can be reduced to 2.5–5 mg once weekly.

### Monitoring and adverse effects of diuretics

Given the potential for renal dysfunction and electrolyte imbalance (particularly hypokalaemia and hyponatraemia, the latter especially with thiazide diuretics), regular monitoring is required. Monitoring of electrolytes (particularly sodium and potassium), urea and creatinine should be performed 1–2 weeks after starting or adjusting diuretic doses, and eventually every six months in the long term.<sup>1</sup>

Abnormal potassium concentrations are associated with increased mortality in heart failure.<sup>1,3</sup> Diuretics, as well as the other heart failure therapies, can change potassium concentrations. Dietary measures are helpful in addressing both low and high potassium concentrations and should be used. Increasing the dose of mineralocorticoid receptor antagonists can also be used to mitigate the hypokalaemia induced by diuretics, if not already at the maximum tolerated dose. Occasionally, potassium supplementation may be required with close monitoring.

Hyponatraemia is frequent, occurring in up to 20% of patients hospitalised with heart failure, and is also associated with higher mortality in heart failure.<sup>1,3</sup> The presence of hyponatraemia should prompt an assessment of fluid status. Hyponatraemia is usually dilutional in the setting of hypervolaemia, which may respond to fluid restriction. Occasionally it is due to diuretics, particularly thiazides and thiazide-like diuretics, and if the patient is not hypervolaemic, the clinician should reconsider the need for diuretics.<sup>1</sup>

Hyperuricaemia is common among patients with heart failure. Prescribers should be aware of the risk of gout exacerbations associated with diuretics, particularly thiazides.<sup>1</sup>

Clinicians must also be aware of the rare complication of ototoxicity with loop diuretics, typically with high-dose intravenous therapy or in the setting of impaired renal function. Concurrent use of other potentially ototoxic drugs, such as aminoglycosides, also increases the risk.<sup>10</sup>

Prescribers should also be mindful of the potential for interactions with other heart failure therapy. Diuretic doses may need to be reduced to mitigate the risk of adverse effects of hypotension and hypovolaemia when starting beta blockers, renin–angiotensin system blockade or SGLT2 inhibitors.<sup>11</sup>

Primary care physicians play a key role in titrating diuretics, particularly following hospitalisation, when

## ARTICLE

## Diuretics in the management of chronic heart failure: when and how

early outpatient follow-up has been shown to reduce readmissions.<sup>12</sup> The doses of diuretics are often increased during admissions for exacerbations of heart failure, and patients are instructed to follow up with their GPs in the week following discharge for further titration. On follow-up, assessments of body weight, fluid status, renal function and electrolytes should be performed to ensure that a patient is euvolaemic. Once euvolaemia is established, the goal is to ensure a patient's body weight remains stable at their dry weight, by ensuring compliance with fluid restrictions and gentle adjustments in the dose of diuretics. Should a patient become hypovolaemic, then clinicians should reduce the dose of diuretics until the body weight returns to baseline. While exact dose alterations must be individualised, furosemide (frusemide) doses are often reduced by 40 mg (although the adjustments are greater in the setting of high-dose diuretics). Follow-up at 1–2 weeks following a dose adjustment is crucial.

Clinicians can trial stopping diuretics in patients with heart failure who are stable on optimal therapy, have not been recently hospitalised due to heart failure, and are receiving a dose of up to 80 mg furosemide (frusemide). The dose can gradually be reduced, and patients should be closely monitored for rebound hypervolaemia.<sup>13</sup>

### Diuretics in renal dysfunction

Renal impairment often coexists with heart failure and is an independent predictor of mortality.<sup>3</sup> However, acute increases in creatinine during diuretic treatment are common and do not necessitate a reduction in the dose, particularly if congestion is present.<sup>4</sup> Data suggest that these increases in creatinine in response to diuresis are usually transient and do not worsen outcomes. Moreover, in patients with pre-existing renal impairment, a higher dose of diuretics is required to exert the same effect. Diuretics form part of the treatment of cardiorenal syndromes by improving ventricular filling and reducing renal venous pressures, thereby enhancing renal perfusion.<sup>14</sup>

### Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists are one of the proven pillars of therapy for HFrEF. Despite being classed as potassium-sparing diuretics, their benefit occurs through neurohormonal modulation and effects on ventricular remodelling rather than diuresis itself.<sup>15</sup> In the kidneys, aldosterone antagonists modulate the expression and activity of sodium and potassium channels in the distal nephron.<sup>2</sup> Spironolactone and eplerenone doses are identical.

They should be started at low doses (e.g. 12.5 mg daily), particularly in the setting of diabetes or renal impairment. International guidelines recommend up-titration over 1–2 months to 25–50 mg daily,<sup>3</sup> although the risk of hyperkalaemia is higher when the dose of spironolactone or eplerenone is 50 mg and above.

Mineralocorticoid receptor antagonists should be avoided or used cautiously in patients with stage IV–V chronic kidney disease or a potassium concentration above 5 mmol/L. With each dose adjustment, electrolytes and renal function should be checked at 1–2 weeks and then monthly for three months, before eventually stretching out to every six months. If the estimated glomerular filtration rate (eGFR) reduces by more than 30% or potassium concentration rises above 5.5 mmol/L, the mineralocorticoid receptor antagonist should be reduced and may need to be stopped altogether if the potassium concentration rises above 6 mmol/L. Spironolactone can also cause gynaecomastia and, if this occurs, it may be substituted with eplerenone.<sup>1</sup> However, eplerenone is only listed on the PBS for HFrEF, specifically after acute myocardial infarction.

### Sodium-glucose co-transporter 2 inhibitors

SGLT2 inhibitors have shown benefits for both HFrEF and HFpEF. Dapagliflozin or empagliflozin are recommended in all patients with HFrEF already receiving optimal treatment with an ACE or angiotensin receptor–neprilysin inhibitor, a beta blocker and a mineralocorticoid receptor antagonist, irrespective of the presence of diabetes.<sup>3</sup> Dapagliflozin has recently been included on the PBS for the treatment of HFrEF, improving patient access to the drug.

Although it is not thought to be the primary mechanism responsible for their benefits in terms of cardiovascular death and heart failure-related hospitalisation, SGLT2 inhibitors have diuretic and natriuretic properties, giving them an added benefit of reducing congestion.<sup>3</sup> If a patient is euvolaemic on starting SGLT2 inhibitors, the prescriber can consider reducing the dose of diuretics. A reversible reduction in the eGFR by up to 30% often occurs after starting SGLT2 inhibitors and should not lead to premature discontinuation.<sup>3</sup> The evidence in favour of SGLT2 inhibitors in HFpEF is also evolving, and they are currently recommended in HFpEF guidelines.<sup>16</sup>

Clinicians should be mindful of the adverse effects of SGLT2 inhibitors. While there are conflicting data about a possible increased urinary tract infection risk, the risk of fungal genital infection is increased



3–5-fold.<sup>17</sup> SGLT2 inhibitors can also result in hypovolaemia and euglycaemic ketoacidosis.<sup>17</sup> Due to their mild diuretic effect, reducing or stopping loop or thiazide diuretics should be considered if a patient is euvoalaemic. Patients should also be instructed to withhold their SGLT2 inhibitors perioperatively and during ‘sick days’.<sup>17</sup>

### Carbonic anhydrase inhibitors

There is renewed interest in the use of acetazolamide for acute decompensated heart failure. Acetazolamide is a carbonic anhydrase inhibitor, which inhibits the reabsorption of sodium and bicarbonate in the proximal tubule. The randomised, placebo-controlled Acetazolamide in Acute Decompensated Heart Failure with Volume Overload trial included hospitalised patients with acute decompensated heart failure who were also receiving intravenous loop diuretics. In this trial, the addition of intravenous acetazolamide resulted in a greater incidence of successful early decongestion, without increasing the rate of adverse events.<sup>18</sup> This promising finding offers another potential drug to assist in the challenge of achieving decongestion in decompensated heart failure, although it should be noted that the use of SGLT2 inhibitors was a contraindication and that the drug was administered intravenously in this trial. Further evidence is required to determine whether there is a role for oral acetazolamide in the primary care setting.

### Non-pharmacological fluid management

In patients with congestive heart failure, a 1.5 L fluid restriction can be considered on the basis of biological plausibility, although the supporting evidence is lacking.<sup>1</sup> In patients without clinical congestion, fluid restriction is not recommended.

Self-management is a key component of the management of heart failure, and heart failure action plans should be instituted where possible. Numerous practical clinical resources are available for patients, including the NPS MedicineWise program on heart failure, which was developed in collaboration with the Heart Foundation and provides a succinct outline of the goals in heart failure and how to achieve them. The program also offers a practical guide to assist GPs in the up-titration of heart failure medicines. The Heart Foundation’s ‘Heart Failure Resources for Patients’ also offers a range of practical resources for patients to assist with self-management.

A self-care written strategy encourages weight monitoring, adherence to drugs, fluid management and physical activity, and alerts patients to the early signs and symptoms of congestion. Rapid weight gain (e.g. 2 kg over two days) is likely to be related to hypervolaemia and should prompt patients to consult with their GP or other supervising healthcare professional. In motivated and competent patients, a flexible diuretic plan can enable patients to safely titrate diuretic doses in response to hypervolaemia. For example, a patient is recommended to take 40 mg furosemide (frusemide) if their body weight increases by more than 2 kg over two days.

Exercise programs should be considered for patients with heart failure. There is good-quality evidence supporting the role of exercise in improving physical fitness, quality of life and hospital admissions in the heart failure population.<sup>1</sup> Regular, moderate-intensity exercise has well-demonstrated safety and efficacy and is recommended for all patients with heart failure.

Nurse-led clinics have been shown to improve survival, reduce hospitalisations and reduce the time required to achieve optimal doses of therapy.<sup>1</sup> If oral diuretics are insufficient, intravenous administration may be suitable and can be provided in the outpatient setting, either by the local heart failure service or the treating GP (particularly in the rural setting), thereby avoiding hospital admissions.

### Conclusion

While the aim of heart failure management should be the initiation and up-titration of guideline-directed medical therapies with a proven mortality benefit, diuretics still play an important role in the management of symptomatic congestion in all forms of heart failure. When euvoalaemia is achieved, diuretics may be stopped or flexibly used in conjunction with a heart failure action plan in selected patients, allowing for further up-titration of the proven guideline-directed therapies. Furosemide (frusemide) is typically the first-line diuretic. Combinations of diuretics can result in significant clinical improvement, although prescribers should be cognisant of possible additive adverse events such as electrolyte abnormalities, renal impairment and hypovolaemia. An understanding of dosing, monitoring and adverse events is critical for GPs managing heart failure. ◀

*Conflicts of interest: none declared*

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# Blood pressure elevations in hospital

## SUMMARY

Long-term hypertension control in the community significantly reduces cardiovascular risk. However, the benefit of controlling acute elevations of blood pressure in hospitalised patients is unclear.

In-hospital elevations of blood pressure are relatively common and might not reflect poorly controlled blood pressure before admission. The measurement of blood pressure in hospital patients significantly differs from the best practice recommended for primary care and outpatients.

Recent observational studies suggest that the pharmacological treatment of acute, asymptomatic, in-hospital elevations of blood pressure may have no benefit. However, it may increase the risk of in-hospital and post-discharge complications.

Pending the development of robust inpatient measurement protocols, acute blood pressure elevations in hospitalised patients should not routinely require antihypertensive treatment in the absence of symptoms or acute end-organ damage. Rather, such elevations should facilitate follow-up of blood pressure and other cardiovascular risk factors after discharge.

## Introduction

Long-term control of hypertension in patients living in the community effectively reduces cardiovascular morbidity and mortality. There is a substantial evidence base informing national and international hypertension management guidelines.<sup>1-3</sup> However, the evidence is less clear for a benefit from rapid control of acute, asymptomatic, uncomplicated elevations of blood pressure. In the hospital setting, elevation of blood pressure may trigger calls for urgent assessments by medical emergency teams.<sup>4,5</sup> Current hypertension guidelines do not address asymptomatic in-hospital blood pressure elevations or recommendations regarding their diagnosis, management and follow-up.<sup>1-3</sup>

## Epidemiology and causes of in-hospital hypertension

Acute elevations of blood pressure during an admission to hospital are common. However, there are currently no published data on the epidemiology of asymptomatic blood pressure elevations in Australian hospitals.


One international review reported a prevalence of in-hospital hypertension of 24–87%, however it included studies published between 1982 and 2009 which might not reflect current inpatient populations. Furthermore, the definition of in-hospital hypertension varied across the studies, including a history of hypertension on admission and various thresholds for systolic and diastolic blood pressure according to clinic or ambulatory blood pressure monitoring criteria.<sup>6</sup>

A more recent study captured information regarding pre-admission and in-hospital blood pressure control in a cohort of 14,915 older adults admitted for non-cardiac reasons within the US Veterans Administration Health System. Nearly half of the patients with uncontrolled blood pressure during admission had well-controlled blood pressure before admission.<sup>7</sup> It is currently unknown whether these observations can be extrapolated to Australia.

## Measurement

A critical issue in relation to in-hospital blood pressure elevations is how blood pressure is measured in hospital. The methods used are likely to differ from current recommendations designed for primary care and outpatient settings. For example, the methods for clinic blood pressure measurement emphasise the importance of repeated readings (typically three) taken in a standardised fashion in a quiet environment.<sup>1-3</sup> Out-of-office measurements (24-hour ambulatory blood pressure monitoring, or home blood pressure monitoring) are also important in the accurate diagnosis of hypertension.<sup>1-3,8</sup>

A study in a UK hospital highlighted why inpatient blood pressure measurement may be unreliable. Blood pressure was measured once only (96% of measurements), an incorrect cuff size was used (36%), and staff and patients were conversing during the measurement (41%).<sup>9</sup> This study casts doubt on the use of these measurements as a justification for starting or increasing antihypertensive treatment for inpatients who are asymptomatic.

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## Keywords

blood pressure, cardiovascular risk, hypertension, in-hospital blood pressure elevations

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## ARTICLE

## Blood pressure elevations in hospital

In addition to the method of measurement, factors contributing to the high prevalence of in-hospital blood pressure elevations include uncontrolled pain, noise, anxiety and disrupted sleep patterns. There may also be an interruption to the regular doses taken by patients already on antihypertensive drugs.<sup>10</sup>

### Physicians' attitudes towards in-hospital hypertension

A few studies have examined the attitude of doctors towards treatment. In a survey of 181 US hospital residents, most (79%) regarded controlling blood pressure in hospital as important or very important, and decisions regarding blood pressure lowering should be based on current national guidelines (66%). Many residents (44%) considered drugs should be started or adjusted if the systolic blood pressure was mildly high (140–159 mmHg) and that patients with in-hospital blood pressure elevations should be discharged on the antihypertensive regimen prescribed in hospital (91%).<sup>11</sup>

In another survey, about a third of hospital doctors would transfer an asymptomatic patient to an intensive care unit because of high blood pressure even in the absence of target organ damage. The average blood pressure that would prompt the transfer was 210/117 mmHg for house officers and 193/110 mmHg for other hospital doctors.<sup>10</sup>

In Australia, the wide adoption of set criteria for calling rapid medical emergency teams to respond to specific alterations of vital parameters<sup>4,5</sup> might lead hospital doctors to treat acute elevations of blood pressure even in absence of symptoms or acute end-organ damage. However, as previously discussed, there is no available information regarding the incidence and the treatment of acute, asymptomatic blood pressure elevations by Australian hospital medical emergency teams.

### Management

Studies of in-hospital blood pressure elevations have primarily reported the acute effects of treatment on the blood pressure rather than clinical outcomes. For example, in a study of medical inpatients with asymptomatic hypertension, hydralazine or labetalol given orally or intravenously acutely reduced blood pressure in 85% of patients. In 22% the systolic blood pressure was reduced by at least 25% within six hours.<sup>12</sup> Such an acute and excessive reduction in blood pressure could decrease cerebral and myocardial perfusion. This approach should be avoided except in particular circumstances such as hypertensive emergencies with end-organ damage (e.g. aortic dissection or acute renal failure).<sup>13,14</sup> Clinical features of hypertensive emergencies may include

chest pain, severe headache, confusion, blurred vision, nausea and vomiting, severe anxiety, dyspnoea, seizures and reduced consciousness. Papilloedema is a hallmark of malignant hypertension and can be seen on examination of the optic fundi.

### Outcomes

Observational studies published since 2018 have reported the effect on clinical end points of starting or increasing antihypertensive treatment in hospital. One study reported that 14% of older patients admitted for non-cardiac reasons were discharged with new or intensified antihypertensive treatment. Among those who started treatment, 29% received renin-angiotensin system inhibitors, 42% beta blockers, 27% calcium-channel blockers, 11% thiazide diuretics and 12% other antihypertensives. More than half (52%) of the patients whose treatment was intensified had well-controlled blood pressure before admission. The probability of antihypertensive intensification was 25% for patients with moderately elevated blood pressure and 42% for those with severe elevations.<sup>7</sup>

In another study, patients discharged with a new or intensified antihypertensive regimen were more likely to be readmitted (hazard ratio (HR) 1.23, 95% confidence interval (CI) 1.07–1.42, number needed to harm (NNH) 27, 95% CI 16–76) or experience serious adverse events within 30 days (HR 1.41, 95% CI 1.06–1.88, NNH 63, 95% CI 34–370). In secondary analyses, new or intensified inpatient treatment was associated with an increased risk of cardiovascular events within 30 days of discharge (HR 1.65, 95% CI 1.13–2.40).<sup>15</sup>

The association between inpatient treatment initiation or intensification and specific end points was studied in 22,834 adults admitted with non-cardiac diagnoses at 10 hospitals in the USA. At least one hypertensive reading was recorded in 78% of patients. Of these, 33% were treated mainly with oral antihypertensives. After controlling for patient and blood pressure characteristics, treatment was associated with an increased risk of in-hospital acute kidney injury (odds ratio (OR) 1.36, 95% CI 1.21–1.52) and myocardial injury (OR 2.23, 95% CI 1.56–3.20). By contrast, there were no significant differences in the risk of in-hospital stroke, length of stay, myocardial infarction within 30 days and blood pressure control one year after discharge.<sup>16</sup>

A cohort study matched 4219 patients admitted without a primary cardiovascular diagnosis who received antihypertensive drugs on an as-needed basis, in addition to scheduled antihypertensives, with 4219 patients who only received scheduled antihypertensives. The former group had an increased risk of an abrupt lowering of systolic blood pressure by more than 25% within one hour of administration

(OR 2.05, 95% CI 1.56–2.71), acute kidney injury (OR 1.24, 95% CI 1.09–1.42), ischaemic stroke (OR 8.5, 95% CI 1.96–36.79), death (OR 2.36, CI 1.26–4.41), and prolonged hospitalisation (4.7 vs 2.9 days). Ischaemic events were more frequent with abrupt blood pressure reductions and more doses of as-needed drugs. Notably, 93% of the as-needed drugs were given intravenously, with hydralazine (53%) and labetalol (43%) being the most common drugs.<sup>17</sup>

The results of these observational studies, primarily conducted in the USA, suggest that proactively managing asymptomatic in-hospital blood pressure elevations does not confer clear benefits. Treatment may be associated with significant adverse outcomes, at least in the short term.

## Conclusion

There is overwhelming evidence of the benefit of identifying and treating hypertension in the community. However, little is known about the clinical significance of common, asymptomatic and short-term blood pressure elevations in hospitalised patients. This is compounded by the variability of how blood pressure is measured in hospital, the lack of consideration for an individual patient's overall cardiovascular risk and the absence of evidence about drug treatment and follow-up strategies.

Recent studies, albeit with the limitations of observational data, suggest that the as-needed use, initiation, or intensification of antihypertensive drugs

in asymptomatic patients admitted for non-cardiac reasons provides no clinical benefit. It is, however, associated with an increased risk of in-hospital and post-discharge complications.

A significant problem in investigating in-hospital blood pressure elevations and their management is the lack of robust protocols for inpatient blood pressure measurement. A more robust assessment would facilitate diagnosis and risk stratification, as well as the planning of appropriately designed intervention studies assessing the efficacy and safety of specific drugs and post-discharge follow-up strategies. Only then can the clinical significance of asymptomatic in-hospital blood pressure elevations be appropriately determined in Australia and worldwide.

At present, it appears that acute blood pressure elevations in asymptomatic hospitalised patients do not routinely require drug treatment. The criteria used by hospital medical emergency teams require review and revision, in relation to blood pressure elevations without alterations in other vital parameters, to prevent unnecessary and potentially dangerous antihypertensive treatment.

Blood pressure elevations in hospital should prompt consideration of post-discharge assessments to check the blood pressure and the need for starting long-term treatment. In this context, a clear communication with GPs is essential to appropriately plan investigations and management. ◀

*Conflicts of interest: none declared*

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# Osteonecrosis of the jaw and denosumab

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**Keywords**

bisphosphonates, denosumab, medication-related osteonecrosis of the jaw, osteoporosis

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**Case**

The patient was an 87-year-old female with hypothyroidism, cardiovascular disease and gastro-oesophageal reflux disease. Her regular treatments were thyroxine, apixaban and esomeprazole. She had also been diagnosed as having osteoporosis and had received one injection of denosumab.

The left mandibular premolars were decayed so the patient was referred to an oral and maxillofacial surgeon for extraction of teeth 34 and 35. This extraction was performed seven months after her denosumab injection. Bone turnover measured by serum C-terminal telopeptide was 176 pg/mL, which is within the range for postmenopausal women. Initial healing had occurred when the patient was reviewed one week after surgery.

The woman presented again 11 weeks after the extractions with pain, swelling and exposed bone. She had been given another injection of denosumab 10 days after the extraction.

Medication-related osteonecrosis of the jaw was diagnosed. This was treated conservatively with chlorhexidine mouth rinses, analgesics and a short course of cephalosporin for the soft tissue infection. The C-terminal telopeptide was low at 116 pg/mL.

Symptoms persisted for six months after the last denosumab injection. X-rays showed a sequestrum (Fig.). As the C-terminal telopeptide was by then returning to normal (230 pg/mL), the sequestrum was removed under local anaesthesia and the wound primarily closed. One month later, when the area was healed, the denosumab was recommenced.

**Comment**

Despite having no clear guidelines to favour denosumab, it has substantially replaced the oral bisphosphonates as the first-line treatment for osteoporosis in Australia.<sup>1</sup> Denosumab is effective when given as a six-monthly 60 mg subcutaneous injection and has few adverse reactions. The main concern medically is that, if denosumab is discontinued or the injection is substantially delayed, there is a risk of vertebral fracture. This means effectively that, once started, the patient must remain on denosumab or another antiresorptive drug for the rest of their life.

Medication-related osteonecrosis of the jaw is a well-documented severe complication of dental extractions in patients on the oral bisphosphonates. It has been assumed that the risk with denosumab is similar to that with bisphosphonates.<sup>2</sup> This is incorrect. In the 2022 update of its position paper, the American Association of Oral and Maxillofacial Surgeons has stated that the risk is a magnitude higher for denosumab than the oral bisphosphonates.<sup>3</sup> The risk is 0.3%.

Minimising the risks of these two serious complications requires opposing actions. To avoid vertebral fractures denosumab should not be delayed, whereas to avoid medication-related osteonecrosis of the jaw, time is needed for a return to the normal bone turnover to allow wound healing.

**Fig. Stage 2 medication-related osteonecrosis of the jaw**



Note sequestrum



## Conclusion and recommendations

Medication-related osteonecrosis of the jaw can occur following oral surgery if denosumab is recommenced before bony healing of the socket. If there is uncertainty about bone turnover, it should be measured at the time of the extraction.<sup>3</sup>

The Box shows evidence-based recommendations drawn from a prospective trial of 546 patients taking denosumab for osteoporosis, who had 1082 dental extractions, and another study of 13 patients who developed osteonecrosis.<sup>4,5</sup> Besides dental extractions, another risk group is patients with dental implants that sometimes lose integration during antiresorptive treatment. ◀

*Conflicts of interest: none declared*

## Box Recommendations for dental care in patients treated with denosumab<sup>4,5</sup>

### Risk factors

Factors include being female, aged over 70 years, having comorbidities, and taking antiresorptive drugs for over four years.

### Communication

Prescribers, dentists and patients should communicate with each other.

### Determination

Determine dental health, the need for extractions, and presence of implants. Dentist to consider alternative treatment.

### Timing

Wait until six months after last injection for extractions.

Measure fasted C-terminal telopeptide if not sure of bone turnover.

Delay next dose of denosumab for one month after extraction until bone healing has occurred.

Avoid excessive delay or discontinuation of denosumab.

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## Wither *Australian Prescriber*?

**John Dowden**

Editor in Chief,  
*Australian Prescriber*

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*Australian Prescriber* was first published by the Department of Health in 1975.<sup>1</sup> In 2002, the Department of Health outsourced the publication to the National Prescribing Service,<sup>2</sup> now known as NPS MedicineWise. Following recent changes to its funding, NPS MedicineWise will cease all operations by 31 December 2022. This creates some uncertainty about the future of *Australian Prescriber*.

The need for an independent journal of therapeutics was reaffirmed in the first Policy on the Quality Use of Medicines in 1992.<sup>3</sup> In turn, that policy became part of the National Medicines Policy.<sup>4</sup> It is therefore important to sustain the publication of independent information about medicines.

*Australian Prescriber* has fared well in the reviews of NPS MedicineWise.<sup>5,6</sup> The recent rapid review of the budget decision affecting NPS MedicineWise reported a need ‘...to allocate outstanding NPS MedicineWise functions, most notably ongoing preparation and publication of *Australian Prescriber*’.<sup>6</sup> Around the time of this review, over 30 specialist colleges and societies

expressed support for *Australian Prescriber* and more than 8000 health professionals signed an open letter to the Minister of Health and Aged Care in favour of the journal.

There is clearly much goodwill for *Australian Prescriber* to continue but, at the time of writing, the outlook is unclear. At present, the plan is for the Department of Health and Aged Care to find a new publisher for *Australian Prescriber* through a competitive tendering process.

Currently, it is unknown who the new publisher will be and when it will take over. Sadly, it is known that the entire editorial team will be made redundant, along with all the other employees of NPS MedicineWise, before Christmas. However, the team and the independent Editorial Executive Committee have already prepared articles for publication in 2023. It is therefore hoped that any interruption to the publication of *Australian Prescriber* will be brief.

To be continued... ◀

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# New drugs

## Asciminib

**Approved indication: chronic myeloid leukaemia**

**Scemblix (Novartis)**

**20 mg and 40 mg film-coated tablets**

Tyrosine kinase inhibitors are the mainstay of treatment for chronic myeloid leukaemia.<sup>1</sup> However, patients may develop resistance to treatment and some patients do not respond to tyrosine kinase inhibitors because they have a genetic mutation (T315I). As resistance may be related to the binding site on the tyrosine kinase molecule, there has been a search for drugs that use an alternative binding site.

Asciminib is a tyrosine kinase inhibitor with a different binding site. It has also been called a STAMP inhibitor (as it specifically targets the ABL myristoyl pocket).

Depending on the dose, asciminib tablets are taken once or twice daily without food, as food reduces absorption. While most of the dose will be excreted unchanged in the faeces, asciminib is also metabolised by cytochrome P450 (CYP) 3A4. Its concentrations will therefore be increased by inhibitors of CYP3A4, such as clarithromycin and azole antifungal drugs, and decreased by inducers, such as rifampicin.

Asciminib itself is an enzyme inhibitor, so it will raise concentrations of substrates of CYP3A4, such as midazolam and fentanyl, and substrates of CYP2C9, such as warfarin. Although concentrations of asciminib will be increased, no dose adjustments are recommended for patients with liver or kidney disease.

An early indication of the efficacy of asciminib came from a dose-escalation study. This involved 150 patients who had been unable to tolerate tyrosine kinase inhibitors or who had been previously treated with at least two different tyrosine kinase inhibitors. All the patients had the Philadelphia chromosome and 22% had the T315I mutation. Molecular responses were used to assess efficacy. In the patients without the T315I mutation who could be evaluated, 37% (37/99) had a major molecular response within six months. A major molecular response was achieved by 24% (4/17) of the patients with the mutation by 12 months.<sup>2</sup>

An open-label phase III trial studied previously treated patients with chronic myeloid leukaemia who were Philadelphia chromosome positive, but did not have a T315I mutation. One group of 157 patients was randomised to receive asciminib 40 mg twice daily

while 76 took bosutinib, another tyrosine kinase inhibitor, 500 mg once daily. The median follow-up was 14.9 months with the molecular response being assessed at 24 weeks. There was a major molecular response in 25% of the patients taking asciminib and 13.2% of the bosutinib group.<sup>3</sup> This advantage for asciminib was still present when the patients were reviewed at 96 weeks.

A higher dose of asciminib has been tried in patients with the T315I mutation. In this open-label trial, 52 previously treated patients with chronic myeloid leukaemia were given asciminib 200 mg twice daily. Among the evaluable patients, 40.8% (20/49) had a major molecular response by 24 weeks. At 96 weeks there was a response in 46.9% (23/49).<sup>4</sup>

In the phase III trial, 5.8% of the patients stopped asciminib because of adverse effects compared with 21.1% of the bosutinib group.<sup>3</sup> A common adverse effect is myelosuppression, particularly thrombocytopenia, and this may require treatment to be withheld or stopped. Full blood counts are required every two weeks for the first three months of treatment. Serum lipase and amylase should also be monitored as some patients will develop pancreatitis. Blood pressure should be checked as hypertension is a common adverse effect. As a few patients will develop prolongation of the QT interval, the ECG should be monitored. In the trial using asciminib 200 mg twice daily there were hypersensitivity reactions in 26.9% of the patients.<sup>4</sup> As asciminib is likely to be harmful to the fetus, it should not be used in pregnancy.

The evidence for the safety and efficacy of asciminib is currently limited. For example, the Australian product information states that the safety profile is based on a total of 356 patients. As a molecular response is a surrogate outcome, it is too early to know if asciminib improves survival. It would also be useful to know how asciminib compares to ponatinib which is also approved for previously treated patients and those with the T315I mutation.

**T** manufacturer provided the product information

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The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

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The Transparency Score is explained in *New drugs: transparency*, Vol 37 No 1, *Aust Prescr* 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

## Decitabine/cedazuridine

**Approved indication: chronic myelomonocytic leukaemia, myelodysplastic syndromes**

**Inqovi (Otsuka)**

**35 mg/100 mg tablets**

Chronic myelomonocytic leukaemia and the myelodysplastic syndromes are disorders of stem cells. As many patients are not eligible for a stem cell transplant, they are treated with cytotoxic drugs such as azacitidine. Another option, not previously marketed in Australia, is decitabine. This inhibits DNA methyltransferase. As abnormal DNA methylation may be involved in myeloid malignancies, decitabine may improve the differentiation of cells and lead to apoptosis of abnormal cells.

Treatment with azacitidine or decitabine can require intravenous infusions for several consecutive days every month. By combining decitabine with cedazuridine, oral therapy is now possible.

The oral bioavailability of decitabine is low because the molecule undergoes first-pass metabolism by the enzyme cytidine deaminase found in the liver and gut. Cedazuridine inhibits this enzyme and therefore increases the bioavailability of oral decitabine. As the absorption of decitabine is reduced by food, the tablet should be taken on an empty stomach. The bioavailability of cedazuridine may be affected by gastric pH so drugs that increase pH should not be taken within four hours. Decitabine is mainly metabolised while the absorbed portion of the cedazuridine dose undergoes renal elimination. No dose modification is recommended for patients with mild hepatic impairment or mild to moderate renal impairment. The effects of more severe impairment are unknown.

A phase II trial compared patients' exposures to decitabine when it was given as 20 mg/m<sup>2</sup> intravenously and as 35 mg orally in combination with 100 mg cedazuridine. Eighty patients with chronic myelomonocytic leukaemia or myelodysplastic syndromes received one formulation for one cycle of treatment then switched to the other formulation for the second cycle. The oral formulation was used in subsequent cycles. For the fixed-dose combination, the exposure (area under the time-concentration curve) was 97.6% of that of the intravenous dose.<sup>1</sup>

The 80 patients in the phase II trial received treatment in cycles of five days every 28 days for a median of seven cycles. Based on blood counts and bone

marrow examination, 60% of the patients responded to treatment with 21% having a complete response. The median duration of the complete responses was 13.3 months. For all patients, the median overall survival was 18.3 months.<sup>1</sup>

A phase III trial also used a crossover design between oral and intravenous therapy for the first two cycles followed by the fixed-dose combination. This also found that each formulation resulted in a similar exposure to decitabine. At the time of writing, the full results of the trial are yet to be published. Information on 133 patients treated for a median of 8.2 months shows a complete response in 21%. Some patients ceased to be dependent on transfusions.

Most patients will have serious adverse effects from decitabine/cedazuridine. These include neutropenia, anaemia, and thrombocytopenia which can lead to haemorrhage. Blood counts must be checked regularly as abnormalities will require treatment to be delayed or reduced. Dose adjustment may also be needed for non-haematological toxicity such as elevated creatinine or liver enzymes. Less serious, but frequent, adverse effects include fatigue, nausea, dizziness, diarrhoea and constipation. Five of the 80 patients in the phase II trial stopped treatment because of adverse effects.<sup>1</sup>

While decitabine/cedazuridine is easier to administer than azacitidine, it is uncertain how the outcomes of treatment compare. Evaluating the combination will be easier when the results of the phase III trial become available.

**T** manufacturer provided the AusPAR and the product information

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## Elasomeran/imelasomeran

### **Approved indication: prevention of COVID-19 Spikevax bivalent original/Omicron (Moderna) multi-dose vials containing 0.1 mg/mL**

Vaccines against SARS-CoV-2 became available during 2021. However, in November 2021 the Omicron variant of the virus emerged and became the dominant strain. Several sub-lineages of the Omicron variant subsequently appeared. The vaccines developed earlier in the pandemic were less effective against Omicron. Vaccine manufacturers have therefore needed to develop new products to improve protection. Clinical trials are ongoing, but data have been provided to regulatory agencies to enable emergency or provisional use of the new products. The provisional approval of elasomeran/imelasomeran in Australia is for use as a booster dose in adults.

Elasomeran was the main component of a messenger RNA (mRNA) vaccine approved in 2021. Imelasomeran is also a mRNA vaccine, but is based on the spike protein of Omicron lineages. The two vaccines are enclosed in lipid nanoparticles to enable them to enter cells after intramuscular injection. Each 0.5 mL dose contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran. After entry into cells the vaccines' mRNA stimulates the production of spike proteins. This generates an immune response which may prevent subsequent infection with SARS-CoV-2.

At present, the evidence for this bivalent vaccine is based on its immunogenicity in adults. One trial is studying people who have previously received two doses and a booster of elasomeran. A group of 437 adults was given the bivalent vaccine and 377 were given another dose of elasomeran as their second booster. By 29 days after these boosters, antibody titres against SARS-CoV-2 had increased in both groups. There was no difference between the bivalent vaccine and elasomeran alone in stimulating antibodies against an ancestral variant of the virus. When considering the Omicron variant, the response was greater in the group given the bivalent vaccines (geometric mean ratio 1.7).

Most people will have adverse effects to a booster of elasomeran or the bivalent vaccine. These are usually mild or moderate and resolve in a few days. Approximately 80% will have pain at the injection site. There may also be swelling at the injection site and axilla. Erythema was more frequent with the bivalent vaccine (6.9% vs 3.7%). Very common systemic effects include headache, fatigue, myalgia and arthralgia.

While the combination of elasomeran and imelasomeran produces neutralising antibodies, the effectiveness of this bivalent booster is yet to be confirmed. The ongoing study was not designed to evaluate effectiveness, but it found that after a median follow-up of 43 days, 3.2% of those given the bivalent vaccine were infected by SARS-CoV-2 compared with 1.9% of the elasomeran group after a median of 57 days. No participants needed hospital admission. While the adverse effects will probably resemble those of elasomeran, the safety data are limited in size and duration. Reporting adverse events, following a bivalent booster dose, to the Therapeutic Goods Administration is therefore particularly important.

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](#) in the USA, the [European Medicines Agency](#) and the [Therapeutic Goods Administration](#).

## Mecasermin

### Approved indication: primary insulin-like growth factor-1 deficiency

#### Increlex (Ipsen)

#### vials containing 10 mg/mL solution

Some children fail to grow as expected because of an insensitivity to growth hormone. One cause is a deficiency of insulin-like growth factor-1 (IGF-1), as in Laron syndrome. In affected children, there is an abnormality in the growth hormone receptor. As a result, growth hormone fails to stimulate the synthesis of IGF-1 in the liver. This leads to slow growth and very short stature. In untreated patients the final height can be 4–10 standard deviations below the mean.

Genetic engineering has enabled the production of mecasermin, a recombinant human IGF-1. It has been available overseas for more than 10 years. Mecasermin is given twice daily by subcutaneous injection. It should be given shortly before or after a meal to reduce the risk of hypoglycaemia. The half-life of mecasermin is about six hours. It is metabolised in the liver and kidneys, but there is no information about how impairment of these organs might affect the drug's pharmacokinetics. Doses are based on body weight and adjusted according to adverse reactions and growth. Treatment continues until epiphyseal fusion.

Primary IGF-1 deficiency is a very rare condition. Clinical trials have therefore been small and mostly open label.

One open-label trial of mecasermin has followed 76 children with severe IGF-1 deficiency for up to 12 years. In the first year of treatment, growth increased from a baseline of 2.8 cm/year to 8 cm/year. The higher the dose, the faster the growth. Growth velocities remained above baseline for up to eight years of follow-up.<sup>1</sup> There were 21 children, treated for an average of 10 years, who reached an adult or near-adult height. They were an average of 13.4 cm taller than they would have been without treatment.<sup>2</sup>

Some of the adverse effects of an insulin-like growth factor are related to its mechanism of action. For example, some children will have seizures related to hypoglycaemia.<sup>1</sup> Blood glucose monitoring is recommended when the dose is changed and when a child is unwell or has reduced oral intake.

Giving a growth factor can cause hypertrophy of some tissues. The growth of lymphoid tissue in the tonsils and adenoids<sup>1</sup> can lead to chronic middle ear effusions, snoring and sleep apnoea. IGF-1 may have a role in cancer so children treated with mecasermin could have an increased risk of benign and malignant neoplasia.

Headache is a common adverse effect, but can be a symptom of intracranial hypertension. Fundoscopy is recommended particularly if there are other symptoms such as vomiting or altered vision.

An echocardiogram is recommended before treatment. Valve incompetence and cardiomegaly are uncommon adverse effects.

A European database of children being treated with IGF-1 therapy contained a safety population of 188 patients. The most frequent serious adverse events recorded in the database were hypoglycaemia, adenotonsillar hypertrophy and injection-site reactions.<sup>3</sup>

The approval of mecasermin in Australia is restricted to children who have the most severe manifestations of primary IGF-1 deficiency. Other causes of the deficiency must be excluded before beginning treatment. Mecasermin is not intended for secondary forms of IGF-1 deficiency such as hypopituitarism, malnutrition or chronic steroid therapy.

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At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](https://www.fda.gov/) in the USA, the [European Medicines Agency](https://www.ema.europa.eu/) and the [Therapeutic Goods Administration](https://www.tga.gov.au/).

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## NEW DRUGS

*Aust Prescr* 2022;45:216  
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## Pemigatinib

### Approved indication: cholangiocarcinoma

#### Pemazyre (Specialised Therapeutics)

#### 4.5 mg, 9 mg and 13.5 mg tablets

Cancers of the bile duct (cholangiocarcinoma) are relatively rare. Surgery may not be possible and relapse rates are high. Even with combination chemotherapy, the prognosis is poor. In patients with metastatic disease, survival may be less than 12 months.

Genetic research has found that some patients have alterations in the genes for fibroblast growth factor receptors (FGFR). These receptors may induce the proliferation of cancer cells. As the receptors contain tyrosine kinases, a kinase inhibitor could have beneficial effects.

Pemigatinib is an inhibitor of FGFR1, 2 and 3.

A dose of 13.5 mg is taken once daily for 14 days followed by a seven-day break. Food has little effect on absorption. Most of the dose is metabolised by cytochrome P450 (CYP) 3A4 and excreted in the faeces. Dose reductions are recommended for patients with severe liver or kidney disease. Reductions are also required if inhibitors of CYP3A4, such as itraconazole, cannot be avoided. Inducers of CYP3A4, such as phenytoin, should be avoided and St John's wort is contraindicated. Proton pump inhibitors should also be avoided as they reduce pemigatinib concentrations in some patients. As pemigatinib is an inhibitor of P-glycoprotein, doses should be separated by at least six hours from drugs such as digoxin.

A phase II open-label trial studied pemigatinib in 146 previously treated patients with locally advanced or metastatic cholangiocarcinoma. Most (107) of the patients had alterations of FGFR2. After a median follow-up of 17.8 months, 35.5% of this group had a response to treatment. The median duration of the response was 7.5 months with a median progression-free survival of 6.9 months. At the time the trial was published, median overall survival was 21.1 months.<sup>1</sup>

Inhibition of FGFR increases serum phosphate concentrations. In the phase II trial 60% of the patients developed hyperphosphataemia.<sup>1</sup> This in turn can cause precipitation of calcium crystals and

possibly hypocalcaemia, seizures and arrhythmias. Patients may require a low-phosphate diet and phosphate-lowering therapy, but these might need to be discontinued during treatment breaks to avoid hypophosphataemia.

Other very common adverse events during the phase II trial included alopecia, dysgeusia, stomatitis, nausea and diarrhoea.<sup>1</sup> Dry eyes are common and, less frequently, retinal detachment can occur. Regular eye examinations are required. Overall, 9% of the patients stopped treatment because of adverse events, while many others required dose interruptions or reductions.

In animal studies, pemigatinib was toxic to the fetus. Pregnancy should be avoided and male patients should not father a child while taking pemigatinib.

Any benefit of pemigatinib appears to be limited to patients with abnormalities of FGFR2. Although only 2.8% (3/107) of these patients had a complete response, the overall response rate may be better than the response to second-line chemotherapy.<sup>1</sup> Another trial is investigating how pemigatinib would compare to chemotherapy as a first-line treatment for unresectable or metastatic cholangiocarcinoma. At present, pemigatinib is only provisionally approved for previously treated patients with abnormalities of FGFR2. Whether its benefit is sustained, or is reduced by the development of resistance to treatment, requires further study.

**T** manufacturer provided relevant information

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The Transparency Score is explained in *New drugs: transparency*, Vol 37 No 1, *Aust Prescr* 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.



## Selinexor

### Approved indication: multiple myeloma

#### Xpovio (Antengene)

#### 20 mg film-coated tablets

Exportin-1 is an essential nuclear exporter of many tumour suppressor proteins, growth regulator proteins and several classes of messenger RNAs, including those of oncogenic proteins. It is overexpressed in several cancers including multiple myeloma.

Selinexor is a selective inhibitor of exportin-1. This inhibition leads to marked accumulation of the tumour suppressor proteins and growth regulator proteins in the nucleus and reduced expression of several oncoproteins, resulting in cell cycle arrest and apoptosis of cancer cells.

Selinexor is indicated in combination with bortezomib and dexamethasone as a treatment for multiple myeloma in patients who have received at least one therapy previously. The drug is also indicated with dexamethasone as a treatment for relapsed or refractory multiple myeloma in patients who have received at least three therapies previously and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory medicinal product and an anti-CD38 monoclonal antibody.

Selinexor should be swallowed whole with water, with or without food, and should not be crushed, chewed, broken or divided. For multiple myeloma, the dose is based on a 35-day cycle and is given with bortezomib and dexamethasone. For relapsed or refractory multiple myeloma, selinexor is given with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity.

Selinexor is a substrate of cytochrome P450 (CYP) 3A4, and so its exposure might be reduced with the concomitant use of strong CYP3A4 inducers, such as rifampicin, St John's wort and phenytoin. The drug's mean half-life after an 80 mg dose is 6–8 hours. The dose does not need to be adjusted in patients with renal impairment or mild to moderate hepatic impairment.

Selinexor with dexamethasone was studied in the single-arm, open-label phase II STORM trial, which included 122 patients with triple-class refractory multiple myeloma. They had previously been treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids and an alkylating drug and had disease that was refractory to at least one proteasome inhibitor, one immunomodulatory drug and daratumumab. When assessed by the reduction in myeloma protein concentration, a partial response or better

was observed in 26% of the patients. The median progression-free survival was 3.7 months.<sup>1</sup>

Selinexor in combination with bortezomib and dexamethasone was studied in the open-label, active-controlled, phase III BOSTON trial. This randomised 402 patients with multiple myeloma who had previously been treated with one to three lines of therapy, including proteasome inhibitors. In this trial, the median progression-free survival was 13.9 months in the 195 patients who received the triplet combination, compared with 9.5 months in the 207 patients who received bortezomib and dexamethasone only. The objective response rate was also significantly higher in the patients who received the triplet combination (76.4% vs 62.3%).<sup>2</sup>

In the STORM trial, the most common grade 3–4 adverse events were thrombocytopenia (59%, which then resulted in grade 3 or higher bleeding events in six patients), anaemia (44%), hyponatraemia (22%) and neutropenia (21%). Treatment-emergent adverse events led to discontinuation in 18% of the patients and two deaths.<sup>1</sup> In the BOSTON trial, the most frequent grade 3–4 adverse events in the patients who received the triplet combination were thrombocytopenia (39% vs 17% without selinexor), fatigue (13% vs 1%), anaemia (16% vs 10%) and pneumonia (11% vs 11%). Grade 2 or higher peripheral neuropathy was less frequent with the triplet combination (21% vs 34% without selinexor). Treatment-emergent adverse events led to discontinuation in 21% of the patients and four deaths with the triplet combination compared with 16% of patients and one death without selinexor.<sup>2</sup>

Thrombocytopenia, neutropenia, neurological toxicities, hyponatraemia and infections are all potential adverse reactions to selinexor that can be life-threatening. The drug can also lead to severe gastrointestinal toxicities, fatigue, weight loss, anorexia, dizziness, tumour lysis syndrome and new onset or exacerbation of cataracts. Patients are advised to avoid driving or operating machines if they experience dizziness or a confusional state. Most patients will require dose reductions to manage adverse events. Detailed dosage modification guidelines to manage adverse haematologic and nonhaematologic reactions are provided in the Australian product information for selinexor.

Based on animal studies, selinexor might impair fertility. Patients are advised to use effective contraceptive options during and for one week after stopping treatment. The drug has not been studied in children or pregnant women. The drug has similar efficacy in patients older than 75 years of age, but they have a higher incidence of adverse effects.

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NEW DRUGS

A once-weekly regimen of selinexor with dexamethasone alone or with dexamethasone and bortezomib is an effective treatment option for patients with multiple myeloma. It has modest efficacy in patients with triple-class refractory disease. However, patients and clinicians must be mindful of the many potential adverse reactions, which should be managed appropriately.

**T** **T** manufacturer provided additional useful information

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## Correction

### Bariatric surgery and medicines [Correction]

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The article on bariatric surgery and medicines (*Aust Prescr* 2022;45:162-6) has been corrected.

[View corrected article.](#)

In the Figure showing four common procedures in bariatric surgery, the third image from the left depicting one anastomosis gastric bypass was incorrect. The Figure has now been replaced using the correct image for this procedure.

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