

# Prescribing and deprescribing in chronic kidney disease



CPD 

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## Background

Chronic kidney disease (CKD) rarely occurs in isolation; multimorbidity is the norm. As a result, polypharmacy is common in people with CKD. Some medications are indicated to reduce the risk of cardiovascular disease and progression of CKD. In contrast, some medications may require dose reduction or cessation as a result of advancing stages of CKD.

## Objective

The aim of this article is to describe broad principles of managing the challenges and necessities of polypharmacy in patients with CKD.

## Discussion

Medications such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins and sodium-glucose co-transporter-2 inhibitors may reduce cardiovascular disease risk and/or reduce CKD progression, and their use should be balanced by likelihood of benefit. Medication cessation or dose reduction may be required to prevent medication accumulation, adverse medication events and kidney injury. Polypharmacy can be addressed with a collaborative Home Medicines Review and use of deprescribing tools, using a shared decision-making approach.

**CHRONIC KIDNEY DISEASE** (CKD) affects up to two million Australians, with 2500 commencing kidney replacement therapy each year and 14 diagnosed with kidney failure each day.<sup>1,2</sup> CKD is associated with increased cardiovascular disease (CVD) risk, and declining kidney function is associated with reduced health-related quality of life independent of other comorbidities.<sup>3,4</sup> However, CKD rarely occurs on its own. This means that multimorbidity and polypharmacy are the norm. While some medications are likely to optimise health outcomes, others may cause harm in isolation or in combination in people with CKD. In this article, the authors describe multimorbidity and polypharmacy in people with CKD, factors to consider when making prescribing decisions and tools to optimise prescribing. This discussion does not extend to people receiving renal replacement therapy.

## Multimorbidity in people with CKD

Multimorbidity is typically defined as the co-occurrence of two or more chronic conditions,<sup>5</sup> and is the norm in people with CKD. A study of 1741 people with CKD stage 3 attending English general practices found that only 4% had no comorbidities, with the most common comorbidities being hypertension, painful conditions, anaemia, ischaemic heart disease, diabetes and thyroid disorders.<sup>6</sup>

Multimorbidity in people with CKD is associated with higher rates of mortality, with risk increasing with the number of long-term conditions.<sup>7</sup> Multimorbidity is usually associated with polypharmacy.

## Polypharmacy and CKD

Polypharmacy, defined in the community setting as taking five or more medications regularly,<sup>8</sup> is very common among older Australians. People with CKD may also receive care from multiple healthcare professionals, further compounding the risk of polypharmacy. Polypharmacy can increase the risk of drug-drug interactions, high medication doses, complex medication regimens, medication costs, medication non-adherence and lower quality of life. In a recent 24-month prospective study in relatively healthy older adults, a greater cumulative medication exposure was associated with a decrease in estimated glomerular filtration rate (eGFR) at follow-up.<sup>9</sup> Polypharmacy may be appropriate for some older people with CKD, but is linked with an increased risk of adverse outcomes such as hospitalisation, reduced cognition, falls and mortality.<sup>10,11</sup> While associations with harm are well-documented, models of care and interventions to reduce polypharmacy have limited evidence on patient outcomes,<sup>12</sup> although adverse medication withdrawal events appear to be rare.<sup>10</sup>

The prevalence of polypharmacy increases with progression of CKD, ranging from 62% in people with stage 1 CKD to 86% in those with stage 3b CKD.<sup>13</sup> A German study of people with moderate CKD found that antihypertensives and lipid-lowering medications were the most frequently used medication classes, consistent with Australian guideline recommendations for this cohort,<sup>1</sup> followed by diuretics, platelet aggregation inhibitors and urate-lowering therapy. Eight in 10 people with CKD were taking five or more medications, with two in 10 individuals prescribed more than 10 medications per day.<sup>13</sup> Factors associated with higher odds of polypharmacy were older age, higher body mass index, higher CKD stage, CVD, diabetes, hypertension and dyslipidaemia. A study using electronic medical record data from 392 Australian general practices found that the mean number of medications prescribed to people with CKD was 8.2, with 35% of patients prescribed at least one potentially inappropriate medication.<sup>14</sup>

### Monitoring of CKD is important to guide prescribing decisions

Kidney Health Australia's *Chronic kidney disease (CKD) management in primary care* handbook provides recommendations for screening, monitoring and managing CKD on the basis of a 'traffic light' system that reflects the stage of CKD.<sup>1</sup>

CKD can lead to changes in medication pharmacokinetics by affecting absorption, distribution, metabolism and excretion as a result of reduced eGFR, proteinuria and subsequent hypoalbuminaemia, or fluid accumulation.<sup>15</sup> These factors should be considered when making prescribing and deprescribing decisions.

While manufacturers' dosing recommendations for medications are often based on Cockcroft-Gault estimates, eGFR based on the Chronic Kidney Disease Epidemiology Collaboration equation is also a valid estimate and can be used to inform dosage decisions or whether medications are contraindicated.<sup>16</sup> For adults at each end of the spectrum in terms of size and height, it may be appropriate to use an uncorrected eGFR that is not normalised to a body surface area of 1.73 m<sup>2</sup>.<sup>17</sup> Table 1 lists commonly prescribed medications that may require dose reduction or cessation. Additional information is available in resources such as the *Australian Medicines Handbook*, Therapeutic Guidelines and the approved product information.

Medications that may be of benefit in reducing progression of CKD or development of associated cardiovascular complications include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), statins and sodium-glucose co-transporter-2 (SGLT2) inhibitors in people with CKD both with and without diabetes.<sup>1,18</sup> Commonly prescribed medications that can

adversely affect kidney function include nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, lithium, gentamicin, proton pump inhibitors, and the combination of an ACE inhibitor/ARB, diuretic and NSAID/COX-2 inhibitor.<sup>1,19</sup> Appropriately identifying and recording a diagnosis of CKD in the medical record can facilitate detection of potentially inappropriate prescribing by clinical decision support tools. Some electronic medical record systems will provide medication alerts when a medication that may be contraindicated or require dose adjustment is prescribed for a person with a coded diagnosis of CKD. It should be noted that these warnings often reflect the product information and may not reflect current guideline recommendations. For example, some electronic medical record alerts state that metformin is contraindicated in renal impairment, while resources such as the *Australian Medicines Handbook* advise this medication can be used with appropriate dose reduction in patients with creatinine clearance >15 mL/min.<sup>20</sup> Third-party tools that integrate with the electronic medical record to optimise safe prescribing are being developed.

### Determining which medications are likely to be of benefit

Medication count (polypharmacy), and screening tools such as the American Geriatrics Society 2019 Updated Beers

**Table 1. Commonly prescribed medications that may require dose reduction or cessation in people with chronic kidney disease\***

Diabetes medications	Antimicrobial medications	Cardiovascular medications	Pain medications	Other
<ul style="list-style-type: none"> <li>• Acarbose</li> <li>• Exenatide</li> <li>• Glibenclamide</li> <li>• Gliclazide</li> <li>• Glimepiride</li> <li>• Glipizide</li> <li>• Insulin</li> <li>• Metformin</li> <li>• Saxagliptin</li> <li>• Sitagliptin</li> <li>• Vildagliptin</li> </ul>	<ul style="list-style-type: none"> <li>• Famciclovir</li> <li>• Trimethoprim</li> <li>• Valaciclovir</li> </ul>	<ul style="list-style-type: none"> <li>• Apixaban</li> <li>• Dabigatran</li> <li>• Digoxin</li> <li>• Fenofibrate</li> <li>• Rivaroxaban</li> <li>• Sotalol</li> <li>• Spironolactone</li> </ul>	<ul style="list-style-type: none"> <li>• Gabapentin</li> <li>• Opioid analgesics</li> <li>• Nonsteroidal anti-inflammatory drugs</li> <li>• Pregabalin</li> </ul>	<ul style="list-style-type: none"> <li>• Allopurinol</li> <li>• Benzodiazepines</li> <li>• Colchicine</li> <li>• Denosumab</li> <li>• Lithium</li> </ul>

\* Note that this is not an exhaustive list.

Criteria and the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert doctors to the Right Treatment (START) can be used as a starting point to identify people with CKD who may benefit from a medication review (Table 2).<sup>21,22</sup>

Deprescribing involves 'discontinuing drugs that are either potentially harmful or no longer required'.<sup>23</sup> Prescribing and deprescribing decision making is not black and white and requires individual patient assessment, including consideration of

multimorbidity, likely risks and benefits, and patient preferences. Medication review is ideally carried out by a general practitioner (GP) given their generalist expertise and role as coordinator of care, in collaboration with a pharmacist, and can be incorporated in annual health checks or as part of a GP Management Plan or Health Assessment. Medicare Benefits Schedule (MBS) items are available for Home Medicines Review (Item 900) and Residential Medication Management Reviews (Item 903) and recent program

changes in April 2020 allow for up to two additional pharmacist follow-up services where clinically appropriate.

Medication review includes considering whether a medication is potentially inappropriate (or no longer required) or if it is a consequence of a prescribing cascade (ie prescribed to address adverse effects associated with another medication), and assessing its short and potential long-term impacts on health outcomes. Consideration of possible withdrawal effects or recurrence of the underlying

**Table 2. Resources to facilitate deprescribing and communication with patients**

Tool	URL	Organisation	Description
<i>Chronic kidney disease (CKD) management in primary care</i>	<a href="https://kidney.org.au/health-professionals/ckd-management-handbook">https://kidney.org.au/health-professionals/ckd-management-handbook</a>	Kidney Health Australia	A list of medications that may need to be reduced in dose or ceased in people with CKD, as well as commonly prescribed medications that can adversely affect kidney function
Medications and kidney disease	<a href="https://kidney.org.au/your-kidneys/treatment/medications-kidney-disease">https://kidney.org.au/your-kidneys/treatment/medications-kidney-disease</a>	Kidney Health Australia	Consumer resources for medication management and sick-day management for people with CKD
The kidney failure risk equation	<a href="https://kidneyfailurerisk.com">https://kidneyfailurerisk.com</a>	Seven Oaks Chronic Disease Innovation Centre	Includes four- and eight-factor risk equations for progression to kidney failure and shared decision-making resources
<i>RACGP aged care clinical guide (Silver Book): Polypharmacy</i>	<a href="http://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/silver-book/part-a/polypharmacy">www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/silver-book/part-a/polypharmacy</a>	The Royal Australian College of General Practitioners	A summary of polypharmacy, medications to use with caution in older people and links to tools including: <ul style="list-style-type: none"> <li>• Beers Criteria</li> <li>• McLeod Criteria</li> <li>• START, STOPP</li> <li>• Medication Appropriateness Tool</li> </ul>
Deprescribing resources	<a href="http://www.primaryhealthtas.com.au/resources/deprescribing-resources">www.primaryhealthtas.com.au/resources/deprescribing-resources</a>	Primary Health Network Tasmania	Consumer resources, deprescribing videos and deprescribing guides for medications including opioids, nonsteroidal anti-inflammatory drugs, antihypertensives and antihyperglycaemics, including a summary of factors favouring continuation and deprescribing
Deprescribing resources	<a href="https://deprescribing.org/resources">https://deprescribing.org/resources</a>	Bruyère Research Institute	Deprescribing guidelines, infographics and videos to inform deprescribing of proton pump inhibitors, antihyperglycaemics, antipsychotics, benzodiazepines and cholinesterase inhibitors
Resources for safer medication use	<a href="http://www.pimsplus.org">www.pimsplus.org</a>	<ul style="list-style-type: none"> <li>• Department of Family Medicine at McMaster University</li> <li>• American Society of Consultant Pharmacists</li> <li>• TaperMD</li> </ul>	Consumer information, product information, notes about risk and tapering guides
Patient decision aids	<a href="https://decisionaid.ohri.ca/AZlist.html">https://decisionaid.ohri.ca/AZlist.html</a>	Ottawa Hospital Research Institute	A list of decision aids for medication and other management decisions
Shared decision making	<a href="http://www.safetyandquality.gov.au/our-work/partnering-consumers/shared-decision-making">www.safetyandquality.gov.au/our-work/partnering-consumers/shared-decision-making</a>	Australian Commission on Safety and Quality in Health Care	Resources and training on shared decision making

health condition is also important when deciding whether to cease or taper the dose of the medication.<sup>24</sup> The Tangri risk equation can be used to calculate a two-year and five-year risk of progression to kidney failure. Shared decision-making resources that demonstrate the potential impact of blood pressure lowering, ACE inhibitor and SGLT2 inhibitor use may assist in guiding decision making.<sup>25,26</sup>

This may also be used to guide decision making where the risks may outweigh the long-term benefits of some medications. Shared decision making also plays a part in deprescribing, with most older adults and caregivers of older adults willing to have a medication deprescribed if recommended by their doctor, with qualitative work finding that a patient's regular GP was a strong influence in decisions to either continue or cease a medication.<sup>27</sup> Ongoing monitoring for possible withdrawal symptoms and re-emergence of symptoms of the original health condition are also suggested.

### Tools that can aid deprescribing and optimising patient choice

Reducing exposure to potentially inappropriate polypharmacy has been identified as a national priority.<sup>28</sup> A number of tools can be used to guide deprescribing assessment and support shared decision making (Table 1). Most tools have been developed for use in older adults, although have broader application.

### A word of caution

The International Group for Reducing Inappropriate Medication Use & Polypharmacy has published recommendations at both the individual patient and policy level to optimise prescribing decisions.<sup>29</sup> They caution about the use of guidelines and tools to inform decision making. These include:

- Older people are underrepresented in clinical trials. Older adults and those with later stages of CKD (eGFR <30 mL/min/1.73 m<sup>2</sup>) are often excluded from trials.
- Single-disease models and incentivisation can result in potentially inappropriate treatment.

A single-disease approach will result in polypharmacy; combinations of medications may negate the benefits of individual medication. Pay for performance for individual conditions and rigid guideline compliance may drive potentially inappropriate prescribing and polypharmacy.

- Decisions in older patients with complex health needs should routinely consider expected survival and quality of life, giving the highest priority to patient/family preferences. GPs, working in collaboration with pharmacists, are ideally placed to provide a holistic review of medications tailored to the individual, the likelihood of benefit from medication and patient preferences (Box 1).
- Employ mixed implicit and explicit approaches to identify potentially inappropriate polypharmacy. Tools can help to identify patients with CKD who could benefit from a closer examination of medication appropriateness and safety through a comprehensive medication review, but should not be used in isolation.<sup>30</sup>

### Medication management strategies that accompany prescribing and deprescribing

The starting point for deprescribing involves ensuring an accurate and complete medication list is available, including non-prescription medicines.<sup>28</sup> Resources on medication reconciliation and taking a best possible medication history are available from the NPS MedicineWise website.

After medication reconciliation and deprescribing, people with CKD may benefit from medication simplification strategies to reduce the complexity of the medication regimen.<sup>21</sup> The Medication Regimen Simplification Guide for Residential Aged Care (MRS GRACE) tool has been applied in community and residential aged care settings to reduce tablet burden and number of medication dosing times.<sup>31</sup> For individuals who receive medications administered from a dose administration aid, communication with the community pharmacy and carers involved in medication administration may be required.

Follow-up education and provision of an updated medication list that describes the indication and anticipated duration of use or next review date for each medication can assist people who self-manage medications. Pharmacists can assist with providing these activities during a Home Medicines Review.

### Conclusion

Multimorbidity and polypharmacy are the norm for people with CKD. Incorporation of regular, proactive medication review

### Box 1. Case study

Max, aged 62 years, was recalled to his general practice for a review of his CKD, which is related to type 2 diabetes. Max's most recent eGFR was 44 mL/min/1.73 m<sup>2</sup> and his albumin:creatinine ratio was 4.2 mg/mmol, consistent with stage 3b CKD. His general practitioner is managing his CKD consistent with Kidney Health Australia's orange clinical action plan.<sup>1</sup> Max's blood pressure is 142/92 mmHg (consistently elevated) and HbA1c is 7.4%. On review of his medication list, Max reports regular use of ibuprofen for pain related to knee osteoarthritis. He purchases ibuprofen over the counter and rarely takes his blood pressure tablets because he does not remember to use them. He is not keen on taking medication.

Max's risk of progression to kidney failure in the next five years is low using the kidney failure risk equation (1.56%); however, his cardiovascular disease risk score is high using the cardiovascular disease risk calculator (>15% over five years). Max is motivated to reduce his cardiovascular disease risk, and decides to commence an ACE inhibitor and a statin. Using motivational interviewing, Max identifies that he can add an alarm to his smartphone to remind him to take his medication, and that he will participate in a group physiotherapy session to try to improve the pain and function in his knee. He agrees to cease ibuprofen because it can adversely affect his kidney function and trial paracetamol for pain relief. He is referred to the Kidney Health Australia and National Heart Foundation of Australia websites to learn more about CKD and cardiovascular disease risk. A review appointment is planned to discuss how Max is tolerating his medication, if his strategies to take them regularly is effective, and to review his diabetes management.

*ACE, angiotensin converting enzyme; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin*

for people with CKD into general practice workflow can ensure that patients are prescribed medications that are likely to result in positive health outcomes while minimising adverse events.

## Key points

- A focus on prescribing guided by disease-specific guidelines is likely to result in polypharmacy for people with CKD and multimorbidity.
- GPs, working in collaboration with pharmacists, are best placed to undertake a holistic review of medication use.
- Beers Criteria, START and STOPP are examples of tools that can assist medication reviews.
- Home Medicines Reviews (MBS Item 900) may be beneficial for people with CKD and polypharmacy.
- Identification and appropriate recording of CKD in electronic medical records can facilitate clinical decision support to optimise prescribing.

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