Drugs Aging (2015) 32:391–400
DOI 10.1007/s40266-015-0261-1

ORIGINAL RESEARCH ARTICLE

Potentially Inappropriate Prescribing of Renally Cleared Drugs in Elderly Patients in Community and Aged Care Settings

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Published online: 30 April 2015

Abstract

Background Limited data are available on the prevalence of inappropriate prescribing of renally cleared drugs in elderly patients in Australia.

Objectives To quantify and compare the extent of inappropriate prescribing (defined as at least one drug prescribed in an excessive dose or when contraindicated with respect to renal function) of renally cleared drugs in elderly patients across the community and aged care settings, and to determine factors associated with patients being prescribed one or more potentially inappropriate renally cleared drugs.

Methods This retrospective study examined de-identified Home Medicines Review (HMR) and Residential Medication Management Review (RMMR) cases pertaining to 30,898 patients aged 65 years and over. Only 25 % ($n = 7625$) of these patients had documented information on their renal function. Among them, 4035 patients were prescribed at least one of the 31 renally cleared drugs examined in this study. For these patients, details including demographics, medications, medical conditions and pathology test results were extracted. Creatinine clearance was estimated using the Cockcroft–Gault formula, and the prevalence of inappropriate prescribing of the 31 drugs was examined on the basis of conformity with the recommendations in the *Australian Medicines Handbook*. Multivariate logistic regression was performed to determine the factors associated with patients being prescribed one or more potentially inappropriate renally cleared drugs.

Results The mean (±standard deviation) ages of the HMR patients ($n = 3315$; 59 % female) and RMMR patients ($n = 720$; 68 % female) were 78.3 ± 7.2 and 86 ± 7.3 years, respectively. Over one quarter of the patients ($n = 1135$ out of 4035; 28.1 %) prescribed the renally cleared drugs examined in this study had evidence of inappropriate prescribing of at least one of the drugs, with respect to their renal function. The drugs/drug classes most commonly prescribed inappropriately were perindopril, fenofibrate, glibenclamide, gliptins, metformin, olmesartan, bisphosphonates and strontium. The factors independently associated with patients being prescribed one or more potentially inappropriate renally cleared drugs were advancing age [odds ratio (OR) 1.06 per year increase, 95 % confidence interval (CI) 1.05–1.07; $P < 0.001$], the total number of renally cleared drugs prescribed (OR 1.44 per unit increase, 95 % CI 1.29–1.61; $P < 0.001$), presence of diabetes (OR 1.51, 95 % CI 1.30–1.76; $P < 0.001$), presence of heart failure (OR 1.38, 95 % CI 1.13–1.69; $P < 0.005$) and living in aged care facilities (OR 1.28, 95 % CI 1.06–1.5; $P < 0.05$).

Conclusion Inappropriate prescribing of renally cleared drugs is common in older Australians. Intervention studies to improve prescribing of renally cleared drugs in the elderly appear to be warranted.

Electronic supplementary material The online version of this article (doi:10.1007/s40266-015-0261-1) contains supplementary material, which is available to authorized users.

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Key Points

Aged care residents and community-dwelling older people are often prescribed renally cleared medicines that require dose adjustment with respect to renal function, outside the recommended guidelines. In this study, 25.9 % of Home Medicines Review patients and 37.9 % of Residential Medication Management Review patients were inappropriately prescribed at least one of the renally cleared drugs examined in the study.

The drugs/drug classes most commonly prescribed inappropriately were perindopril, fenofibrate, glibenclamide, gliptins, metformin, olmesartan, bisphosphonates and strontium.

The factors independently associated with patients being prescribed one or more potentially inappropriate renally cleared drugs were advancing age, the total number of renally cleared drugs prescribed, the presence of diabetes, the presence of heart failure and living in aged care facilities.

It is essential to consider renal function when prescribing renally cleared drugs for elderly patients. The need for dosage adjustment should be determined by measurement of renal function, and the optimal dose should be determined by consulting standard drug information sources.

It appears to be necessary to design an intervention programme targeted towards improving the prescribing of these medications.

1 Introduction

Providing optimal care to the aging population has been, and is increasingly, an area of concern for health care professionals [1]. The process of selecting, prescribing and maintaining correct drug dosing is challenging in the elderly, partly because of the high prevalence of chronic disease states and the resultant multiple drug prescribing [2, 3]. Furthermore, age-related heterogeneity, coupled with an overall decline in bodily function, put these patients at high risk of toxicity [4, 5]. The glomerular filtration rate (GFR) decreases gradually at an average rate of 0.8 mL/min/1.73 m^2/year after the age of 40 years, and this decline accelerates after the age of about 65–70 years [6–8]. Therefore, optimal drug selection and dosing modification should be carried out in elderly patients in order to avoid the occurrence of adverse drug events (ADEs), particularly for renally cleared drugs [9, 10].

The need for drug dosage adjustment can be determined by measurement of the renal function of patients [11]. Previous overseas studies conducted in hospital settings and nursing homes have revealed that a high proportion of elderly patients are administered excessive doses of primarily renally cleared medicines [12–18]. Subsequently, the problem of dose inappropriateness has been addressed to some extent by general education and raising of awareness of medications requiring dosage adjustment and the need for routine assessment of renal function [15]. Approximately 20–50 % of elderly people in the Australian community setting are prescribed one or more potentially inappropriate medicines, with higher rates seen in residential aged care facilities [19–21]. Pharmacist-conducted medication reviews have been found to be effective in reducing the use of potentially inappropriate medicines in elderly people in the Australian community [22]. However, the prevalence of inappropriate prescribing in patients with renal impairment in community settings has received relatively little attention; particularly in Australia, there are limited data on the prevalence of inappropriate prescribing of renally cleared drugs in older community-based patients.

Given this background, we conducted this study to quantify and compare the extent of inappropriate use of renally cleared drugs in older patients across the community and in aged care settings, and to determine the factors associated with patients being prescribed one or more potentially inappropriate renally cleared drugs.

2 Methods

2.1 Ethics

Ethical approval for the study protocol was granted by the Tasmanian Health and Medical Human Research Ethics Committee (Hobart, TAS, Australia).

2.2 Data Source

This retrospective study examined a sample of de-identified Home Medicines Review (HMR) and Residential Medication Management Review (RMMR) cases pertaining to older Australians. HMR and RMMR are community-based collaborative services provided by general practitioners (GPs) and accredited pharmacists [23]. HMR services are provided to community-dwelling older individuals, whereas RMMR services are available to all permanent residents of Australian Government-funded aged care facilities. When requested by a GP, an accredited pharmacist conducts an HMR/RMMR. Information about the patient's medicines is collated, and a comprehensive

assessment is undertaken to identify, resolve and prevent medication-related problems. A report of this assessment is provided to the GP. On the basis of this report, the GP and the patient develop and implement a medication management plan.

2.3 Data Extraction

The RMMR and HMR services were conducted by accredited pharmacists in collaboration with GPs between January 2010 and June 2012. These de-identified cases were extracted from the database of Medscope, an information technology company providing decision support solutions for accredited pharmacists performing medication reviews. Approximately 12 % of Australian accredited pharmacists performing medication reviews utilize this system. This database includes information on each patient's medical conditions, medication and biochemical parameters. Demographic data (age, sex, weight), medical conditions, pathology test results and medications (including doses) were extracted into a database developed in Access 2010 software (Microsoft Corporation, Redmond, WA, USA).

2.4 Study Inclusion Criteria

All individuals aged 65 years and older who had serum creatinine levels reported and were prescribed one or more of the drugs under review were included in this study. We used a list of 31 renally cleared drugs that are prescribed commonly in the community setting and are recommended to be avoided or used with dose adjustment in older patients by the Department of Veterans' Affairs, Australia (see Table S1 in the Electronic Supplementary Material) [24].

A total of 30,898 elderly patients (aged 65 years or over) were identified in the database. Those who had their renal function reported ($n = 7625$) were selected for further analysis. Out of these, a total of 4035 patients who were taking at least one of the 31 renally cleared drugs in our list were included in the final sample. The creatinine clearance (CL_{CR}) was estimated using the Cockcroft–Gault equation [25]. For 1604 patients (1417 HMR, 187 RMMR) whose CL_{CR} could not be estimated, because of lack of weight data, the laboratory-estimated GFR (eGFR) provided in the database was used. For each drug, prescriptions were marked as 'appropriate dosage' when the prescribed dose was in conformity with the adjustment specified in the *Australian Medicines Handbook* (AMH) [26] with respect to the patient's renal function. Prescriptions were considered as 'inappropriate dosage' when the dose exceeded that recommended for the patient's renal function. Prescriptions were considered as 'contraindicated' if the AMH recommended avoiding their use in renal impairment on the basis of the patient's renal function. Both 'inappropriate dosage' and 'contraindicated' prescriptions were treated as inappropriate prescriptions.

Inappropriate prescribing is defined as a situation where the risk of adverse effects of a prescribed medication outweighs the desired clinical benefits of treating a particular condition [27]. It includes over-use of medications at a higher frequency or for longer durations than clinically indicated and use of multiple medicines that have recognized drug–drug interactions [28]. For our study purposes, we defined potentially inappropriate prescribing as use of a contraindicated medication or use of an inappropriately high dose with respect to the patient's renal function. For example, metformin prescribed at a dose of 2000 mg one daily to a patient with a calculated CL_{CR} greater than 60 mL/min would be considered appropriate, whereas the same prescription in an individual with a CL_{CR} of less than 60 mL/min would be inappropriate. Similar definitions for inappropriate prescribing in renal impairment have been reported in past studies [13, 14, 29].

2.5 Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) and Excel 2010 software (Microsoft Corporation). Descriptive statistics were presented as median, mean, standard deviation (SD) and range values, depending on normality. Univariate analysis (Mann–Whitney and chi-squared tests) followed by multivariate logistic regression were performed to determine the factors associated with patients being prescribed one or more potentially inappropriate renally cleared drugs.

The dependent variable was the presence or absence of inappropriate prescribing of at least one of the 31 drugs examined in the study, with respect to the patient's renal function. The independent variables included age, sex, setting (home or aged care facility), total number of drugs prescribed, total number of chronic medical conditions, and number of renally cleared drugs prescribed from our list. Also included were dichotomous variables (presence or absence) of heart failure, diabetes and hypertension, which have previously been recognized as major contributing factors for renal impairment [14, 30]. The independent variables with probability values (P values) of ≤ 0.1 in the univariate analysis were entered into the multivariate logistic regression analysis using the 'enter' method. All variables were assessed for multicollinearity prior to inclusion in the logistic regression model. The probability for stepwise entry was set at 0.01 and removal at 0.1 including a constant in the model. A P value of <0.05 was considered statistically significant.

3 Results

3.1 Patient Characteristics

The study sample included 4035 elderly patients who had their renal function reported and were prescribed at least one of the 31 renally cleared drugs under review. Approximately 18 % ($n = 720$) of these patients were residents of aged care facilities (i.e. RMMR cases), and 82 % ($n = 3315$) were from the community setting (i.e. HMR cases). The mean ± SD ages were 78.3 ± 7.2 years for the HMR patients and 86 ± 7.3 years for the RMMR patients. There was a female predominance in both the aged care setting (67.6 %) and the community setting (59.4 %). A high level of polypharmacy was identified in the study sample. The mean ± SD numbers of drugs prescribed per patient were 12.9 ± 4.6 and 13.5 ± 4.8 in the aged care and community settings, respectively (Table 1).

3.2 Prescribing Pattern for Renally Cleared Drugs

The majority of patients, 69.4 % ($n = 2801$ out of 4035), were prescribed only one renally cleared drug from our list; 24.4 % ($n = 986$ out of 4035) patients were prescribed two drugs from the list. Only 6.1 % ($n = 248$ out of 4035) patients were prescribed three or more renally cleared drugs from the list. Perindopril ($n = 762$) and metformin ($n = 762$) were the most commonly prescribed renally cleared drugs among patients who were on a single drug. Concomitant prescribing of perindopril with metformin ($n = 341$), perindopril with bisphosphonates ($n = 185$) and metformin with bisphosphonates ($n = 143$) were most common in patients who were prescribed two or more drugs.

3.3 Extent of Inappropriate Prescribing Across the Aged Care and Community Settings

Over one quarter of the patients in the study sample ($n = 1135$ out of 4035; 28.1 %) had evidence of inappropriate prescribing of at least one of the renally cleared drugs. That included prescribing of an excessive dose (80.6 %; $n = 915$ out of 1135) or prescribing when contraindicated (19.4 %; 220 out of 1135). Overall, 71.8 % patients ($n = 2900$ out of 4035) in the study sample

Table 1 Characteristics of the study sample ($n = 4035$)

Characteristic	HMR patients		RMMR patients	
	Number (%)	Mean ± SD	Number (%)	Mean ± SD
Setting	3315 (82.2)		720 (17.8)	
Demographic characteristics				
Age (years)		78.3 ± 7.2		86.0 ± 7.3
Sex				
Male	1346 (40.6)		233 (32.4)	
Female	1969 (59.4)		487 (67.6)	
Health status				
Number of diagnoses per patient		10.03 ± 5.8		8.5 ± 3.7
Number of medications per patient		13.5 ± 4.8		12.9 ± 4.6
Number of renally cleared drugs from the drug list		1.4 ± 0.7		1.2 ± 0.5
Estimated creatinine clearance (mL/min)		62 ± 23		50 ± 24
Median (range)		60 (4–165)		46 (6–168)
Chronic kidney disease stage[a]				
Stage 1	422 (12.7)		56 (7.8)	
Stage 2	1279 (38.6)		131 (18.2)	
Stage 3	1422 (42.9)		396 (55)	
Stage 4	176 (5.3)		125 (17.3)	
Stage 5	16 (0.5)		12 (1.7)	
Medical conditions				
Hypertension	2691 (81.2)		431 (59.8)	
Diabetes	1677 (50.5)		307 (42.6)	
Heart failure	381 (11.4)		146 (20.2)	

HMR Home Medicines Review, *RMMR* Residential Medication Management Review, *SD* standard deviation

[a] See the CARI Guidelines [72]

received appropriate doses with respect to their renal function.

The incidence of inappropriate prescribing was higher in the RMMR patients; 25.9 % of the HMR patients and 37.9 % of the RMMR patients received inappropriate prescribing of at least one of the renally cleared drugs ($P < 0.001$). The drugs/drug classes most commonly prescribed inappropriately were perindopril, fenofibrate, glibenclamide, gliptins, metformin, olmesartan, bisphosphonates and strontium (Table 2). The extent of inappropriate prescribing of each drug, comparison between HMR and RMMR for inappropriate prescribing of individual drugs, and the most inappropriately drugs across HMR and RMMR are shown in Tables S2, S3 and S4, respectively, in the Electronic Supplementary Material.

Of the variables tested against inappropriate prescribing in the univariate analysis, age, living in the residential aged care setting, the number of renally cleared drugs prescribed, and the presence of hypertension, diabetes and heart failure were associated ($P \leq 0.1$), whereas the number of diagnoses, number of medications and sex were not. Table 3 presents the results of the multivariate logistic regression analysis. The factors independently associated with patients being prescribed one or more potentially inappropriate renally cleared drugs were advancing age [odds ratio (OR) 1.06 per year increase in age, 95 % confidence interval (CI) 1.05–1.07; $P < 0.001$], the total number of renally cleared drugs prescribed (OR 1.44 per unit increase, 95 % CI 1.29–1.61; $P < 0.001$), the presence of diabetes (OR 1.51, 95 % CI 1.30–1.76; $P < 0.001$), the presence of heart failure (OR 1.38, 95 % CI 1.13–1.69;

Table 2 Most inappropriately prescribed drugs in the study sample

Category	Drug	Patients [*n* (%)]			
		Total	Dose adjustment not required[a]	Inappropriately high dose	Contraindicated drug
Top 5 drugs prescribed inappropriately in high doses	Perindopril	1387	600 (43.2)	612 (44.1)	NA
	Fenofibrate	205	85 (41.4)	85 (41.5)	1 (0.4)
	Saxagliptin	15	11 (73.3)	4 (26.7)	NA
	Sitagliptin	183	127 (69.3)	41 (22.5)	NA
	Vildagliptin	51	36 (70.5)	11 (21.5)	NA
Top 5 drugs prescribed inappropriately when contraindicated	Glibenclamide	29	20 (68.9)	NA	9 (31.0)
	Alendronate	543	454 (83.6)	NA	89 (16.3)
	Strontium	160	139 (86.8)	NA	21 (13.2)
	Risedronate	457	412 (90.2)	NA	45 (9.8)
	Olmesartan	71	66 (92.9)	NA	5 (7.0)
Total inappropriate prescribing: high-dose + contraindicated drugs	Perindopril	1387	600 (43.2)	612 (44.1)	NA
	Fenofibrate	205	85 (41.4)	85 (41.5)	1 (0.4)
	Glibenclamide	29	20 (68.9)	NA	9 (31)
	Saxagliptin	15	11 (73.3)	4 (26.7)	NA
	Sitagliptin	183	127 (69.3)	41 (22.5)	NA
	Vildagliptin	51	36 (70.5)	11 (21.5)	NA
	Metformin	1514	203 (13.4)	272 (17.8)	54 (3.5)

NA not applicable

[a] Dose adjustment not required with respect to renal function

Table 3 Correlates of inappropriate prescribing in the multivariate logistic regression analysis

Variable	*P* value[a]	Exp(B)	95 % CI for Exp(B)
Age in years	<0.001	1.06	1.05–1.07
Number of renally cleared drugs	<0.001	1.44	1.29–1.61
Diabetes	<0.001	1.51	1.30–1.76
Heart failure	0.001	1.38	1.13–1.69
Living in the aged care setting	0.008	1.28	1.06–1.55

CI confidence interval, *Exp(B)* odds ratio

[a] All *P* values of <0.05 are statistically significant

$P < 0.005$) and living in aged care facilities (OR 1.28, 95 % CI 1.06–1.55; $P < 0.05$).

4 Discussion

The presence of renal impairment in older people is often under-recognized, leading to incorrect dosing [31]. Our findings suggest that both aged care residents and community-dwelling older people are often prescribed renally cleared medicines, outside the recommended guidelines. Overall, 28.1 % of the elderly patients ($n = 1135$ out of 4035) who were prescribed one of the drugs under review received at least one drug inappropriately with respect to their renal function.

Previous studies conducted outside Australia have reported rates of inappropriate dosing of renally cleared drugs in elderly patients ranging from 12 to 43 % in long-term care settings [13–15]. About 43 % of elderly patients received at least one of 20 renally cleared drugs inappropriately in a cohort of 456 patients in four long-term care facilities in Canada [13]. The drugs most frequently prescribed inappropriately were allopurinol, glyburide, ranitidine and metformin, and variables such as age, weight, the number of medications and the number of physicians prescribing in the facility were predictive of inappropriate prescribing with respect to CL_{CR} [13]. About 12 % of the patients had evidence of inappropriate prescribing of at least one of 21 renally cleared drugs in a longitudinal study of 3804 elderly patients in 133 nursing homes in the USA, and the factors associated with potentially inappropriate prescribing were age older than 85 years, obesity and multiple co-morbidities [14]. In a cross-sectional study by Rahimi et al. [15], 50 % of the patients were prescribed renally cleared drugs and 25 % of them had at least one medication dosed incorrectly with respect to their renal function. A recent study in aged care residents in Australia recognized metformin and perindopril as the most inappropriately prescribed renally cleared drugs in aged care settings [32].

The most inappropriately prescribed medications identified in our study were perindopril, fenofibrate, olmesartan, gliptins, metformin, bisphosphonates and strontium. Inappropriate prescribing of oral hypoglycaemics, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) and drugs for the treatment of bone diseases in elderly patients with renal impairment has been noted in various studies [12, 13, 33].

ACEIs and ARBs are recommended as first-line therapies in diabetic kidney disease and non-diabetic kidney disease with proteinuria [34]. In addition to lowering blood pressure, they have been found to reduce proteinuria and delay progression of chronic kidney disease (CKD) [35]. Benazepril therapy was associated with a reduction of 23 % in the rate of the decline in renal function and a 52 % reduction in the level of proteinuria [36]. A lower dose of these agents is sufficient to treat hypertension in moderate to severe chronic renal impairment [37, 38], but a dose increment or use of the maximum dose provides renoprotective benefits and slows CKD progression [39]. However, it is worth noting that an ACEI used for its renoprotective benefits may cause hyperkalaemia, hypotension and an acute decline in the GFR of up to 15 % from baseline [40, 41]. An acute decline in the GFR is not necessarily a reason to discontinue these drugs if the benefits outweigh the risk (particularly for patients with severe congestive cardiac failure) [42]. A recent observational study reported that discontinuing ACEIs and/or ARBs in patients with advanced CKD (stages 4 and 5) who are progressing to complete kidney failure/renal replacement therapy results in stabilization and improvement of kidney function and decreases or delays the need for dialysis [43]. A randomized, controlled trial called the STOP-ACEi trial, designed to confirm the association between stopping these drugs and stabilization of kidney function, is ongoing [44]. Until further safety data emerge, it is best to withhold its use in general practice in patients with severe renal impairment. If it is used, patients should be monitored with extreme caution, as there is no sufficient evidence of its safety. It is recommended that renal function and electrolyte levels be monitored while these drugs are prescribed in patients with CKD [34, 45]. Kidney Health Australia and the AMH recommend stopping use of ACEIs or ARBs if the decline in the GFR exceeds 25 % from the baseline value [26, 45].

Bisphosphonates (alendronate and risedronate) are recommended as first-line therapy for prevention of osteoporotic fractures and are widely used for treatment of osteoporosis in post-menopausal women [46]. The manufacturers suggest avoiding their use in severe renal impairment. However, patients who are at risk of fracture or who have osteoporosis are mainly elderly or post-menopausal women and may have an age-related decline in renal function or CKD. This creates a significant challenge for prescribers in managing osteoporosis in these high-risk patients. The prescribing restrictions of bisphosphonates in CKD have been based on the assumptions that chronic use of these drugs leads to a further decline in renal function and that retention of bisphosphonates in the skeleton increases, resulting in 'switching off' of bone turnover [47]. However, there are no robust data regarding alterations in pharmacokinetics and the impact on skeletal histology of bisphosphonate treatment in CKD patients [47]. Lack of strong scientific evidence and applicability of these recommendations in clinical settings have been recognized [48, 49]. On one hand, there are reports describing adverse renal events, such as acute tubular necrosis and tubulointerstitial damage pertaining to bisphosphonates, whereas

various studies have emphasized that bisphosphonates are safe even when there is a pronounced reduction in renal function [50–54]. The number of randomized, controlled trials conducted to guide renal dosing of bisphosphonates in CKD is limited. Furthermore, small sample sizes, short durations of treatment and the retrospective nature of these studies restrict the generalization of their findings [55]. Larger, longer-term, prospective studies on use of bisphosphonates in CKD patients are warranted to ascertain the risks and benefits associated with these drugs in renal impairment [55]. However, until the results of new studies confirm the safety of bisphosphonates in renal impairment and new guidelines for using bisphosphonates in elderly patients with renal impairment are put into routine clinical practice, the current prescribing information in the product information or the standard drug information sources should be followed. The current prescribing information suggests withholding bisphosphonates in patients with severe renal impairment and using reduced doses in those with mild to moderate renal impairment.

Another medication of particular interest was glibenclamide. It is well documented that there is a high risk of drug-induced hypoglycaemia associated with this drug if it is used in older people with renal impairment [56, 57]. The AMH recommends avoiding this drug in renal impairment and emphasizes using glipizide or glicazide [58]. In contrast, the manufacturer's product information recommends avoidance only in patients with severe renal impairment and suggests use with caution in those with moderate impairment [59].

Our logistic regression analysis identified older age, the presence of diabetes, heart failure, the number of renally cleared drugs (requiring dosage adjustment) prescribed, and living in the aged care setting as being associated with patients being prescribed one or more potentially inappropriate renally cleared drugs. Studies have shown that inappropriate prescribing of renally cleared drugs is more likely to occur in older people [13, 14]. There is an age-related decline in renal function in older patients, which warrants dose reduction or avoidance of renally cleared drugs. This natural decline in renal function markedly affects the clearance of drugs, even in the absence of CKD. Advanced age and the presence of renal impairment have been found to be the major pathophysiological factors not accounted for in drug dosing [60].

It is well known that polypharmacy is one of the contributing factors for potentially inappropriate prescribing in patients over 65 years of age [61]. In our analysis, we looked only at the occurrence of inappropriate prescribing (use of excessive doses or prescribing despite contraindications with respect to CL_{CR}) of drugs that are known to be problematic in older patients with declining renal function. We found that the more drugs (requiring dose adjustment) that were prescribed, the higher the likelihood of inappropriate dosing with respect to the patient's renal function.

Diabetes is one of the most common diseases in elderly patients that contributes to the development of CKD [62, 63]. It has been recognized that co-morbidities such as diabetes increase the likelihood of potentially inappropriate prescribing in older people [3]. Patients with diabetes are at increased risk of receiving inappropriate dosing with respect to their renal function. Because several drugs requiring dose adjustment are often prescribed in diabetes, and the disease itself is associated with renal impairment, patients with diabetes are at higher risk of inappropriate dosing with respect to their renal function. CKD is associated with an increased prevalence of heart failure, and heart failure itself is a major contributor to CKD [64]. Thus, many medications require dose modification in patients with heart failure because of the associated decline in renal function. Therefore, it would be best to monitor renal function while prescribing newer drugs, nephrotoxic drugs or renally cleared drugs in patients with diabetes or heart failure.

A recent retrospective study in Australia examining RMMR reports from 911 aged care residents found that 48 % of the residents had CKD and 16 % of them received inappropriate prescriptions of renally cleared medications [32]. Similarly, we also observed that inappropriate prescribing of renally cleared medications was common among residents of aged care facilities, and our analysis demonstrated that aged care residents were more likely to receive inappropriate prescribing with respect to their renal function. This could be attributable to the fact that there was a higher prevalence of CKD in aged care patients, as documented by their lower mean CL_{CR} values.

It appears to be necessary to design an intervention programme targeted towards improving the prescribing of these medications. Computerized alerts at the time of electronic prescribing have been proven to be effective in improving dosing of primarily renally cleared medications [65]. Other possible approaches would be conducting education/training programmes for GPs and pharmacists, geared towards recognizing drugs that require caution when used in renal impairment and patients at risk.

A limitation of this study was that we could not determine clinical outcomes, such as ADEs, associated with inappropriate prescribing. Furthermore, the prescribers might have used a different information source other than the AMH for renal drug dosing. The conflicting recommendations for dosing of renally cleared drugs among the commonly used drug information sources have been recognized [58, 59]. Also, CL_{CR} could not be calculated for all patients, because of lack of weight data; thus, the laboratory-based Modification of Diet in Renal Disease (MDRD) eGFR was used to identify inappropriate prescribing.

Traditionally, the CL_{CR} estimated from the Cockcroft–Gault equation has been used for dosing purposes. However, the recent recommendations from Kidney Health Australia, the National Kidney Disease Education Program (NKDEP), the US Food and Drug Administration (FDA) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) suggest that the MDRD-based eGFR can be used for dosing of non-critical drugs in primary settings [66–72]. The eGFR reported in our study database were based on the MDRD formula. The medication review cases were collected prior to adoption of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for reporting the eGFR in Australian laboratories [73]. However, some of the ranges for renal function were quite narrow, and this, together with use of the eGFR as a substitute for CL_{CR} in some patients, may have led to significant confounding in this study.

Our study was limited to drugs in the Department of Veterans' Affairs list, generally for chronic medical conditions, so we excluded some other renally important drugs, such as antibiotics. This might have led to an underestimation of the extent of the prevalence of inappropriate prescribing.

5 Conclusion

Potentially inappropriate prescribing of renally cleared drugs is common in older Australians in community and aged care settings. Intervention studies to improve prescribing of renally cleared drugs in the elderly appear to be warranted.

Acknowledgments The four authors listed undertook all work related to this study; there were no other contributors. No sources of funding were used in the preparation of this article. The authors have no potential conflicts of interest that are directly relevant to the content of this article.

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