

Quality Use Of Medicines In Patients With Chronic Kidney Disease

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Abstract

Objective: To determine the extent of potentially inappropriate prescribing (PIP; defined as the use of a contraindicated medication or inappropriately high dose according to the kidney function) of renally-cleared medications commonly prescribed in Australian primary care, based on two measures of kidney function. A secondary aim was to assess agreement between the two measures.

Design: Retrospective analysis of routinely collected de-identified Australian general practice patient data (NPS MedicineWise MedicinesInsight from January 1, 2013, to June 1, 2016; collected from 329 general practices). **Setting & Participants:** All adults (aged ≥ 18 years) with chronic kidney disease (CKD) presenting to general practices across Australia.

Results: A total of 48,731 patients met the Kidney Health Australia (KHA) definition for CKD and had prescriptions recorded within 90 days of measuring serum creatinine (SCr)/estimated glomerular filtration rate (eGFR). Overall, 28,729 patients were prescribed one or more of the 49 medications of interest. Approximately 35% (n=9,926) of these patients had at least one PIP based on either the Cockcroft-Gault (CG) equation or eGFR (CKD-EPI; CKD-Epidemiology Collaboration Equation). There was good agreement between CG and eGFR while determining the appropriateness of medications, with approximately 97% of the medications classified as appropriate by eGFR also being considered appropriate by the CG equation.

Conclusion: This study highlights that PIP commonly occurs in primary care patients with CKD and the need for further research to understand why and how this can be minimised. The findings also show that the eGFR provides clinicians a potential alternative to the CG formula when estimating kidney function to guide drug appropriateness and dosing.

Background

The prevalence of chronic kidney disease (CKD) is rapidly increasing worldwide, alongside its complications.[1–3] Most people with CKD are prescribed a multitude of drugs to treat the underlying cause of kidney disease, or its numerous complications and comorbidities.[2, 3] The reduction in kidney function requires adaptation of treatment regimens as the pharmacokinetics and pharmacodynamics of many drugs are altered. Dosing errors are common in CKD and can cause adverse effects and poor outcomes.[2]

Previous studies have reported potentially inappropriate prescribing (PIP) of medications in CKD (defined as the use of a contraindicated medication or inappropriately high dose according to the kidney function) ranging from 13% to 80%, with most of the medications being initiated in the community setting.[2, 4] In Australia, the prevalence of PIP in patients with renal impairment in primary care has received less attention. One study reported that 32% of patients with CKD were receiving PIP at the time of admission to hospital.[2]

The automated reporting of estimated glomerular filtration rate (eGFR) calculated from the modification of diet in renal disease (MDRD) or CKD epidemiology collaboration equation (CKD-EPI) is now routinely provided by laboratories whenever a serum creatinine (SCr) value is measured, as a tool to enhance the identification and classification of CKD.[5] Most of the drug dosing studies to date, however, have used the Cockcroft-Gault (CG) equation to estimate kidney function as creatinine clearance (CrCl), which includes a weight component.[6] While the CG equation is still the preferred equation for drug dosage adjustment by most drug information sources, it is cumbersome to calculate in the busy context of a general practice consultation.

Given this background, the main objective of this study was to determine the extent of PIP of renally-cleared medications commonly prescribed in Australian primary care, based on two separate estimates of kidney function (CG and CKD-EPI).

Methods

This retrospective study included data collected by MedicineInsight, developed and managed by NPS MedicineWise. MedicineInsight is a large-scale national data program in Australia to extract and collate longitudinal, whole-of-practice data from the clinical information systems of consenting general practices. De-identified patient data collected include demographics, encounters (not including progress notes), diagnoses, prescriptions and pathology tests. As of July 2017, MedicineInsight had recruited 650 general practices with data pertaining to 3.6 million patients.[3, 7, 8] The Institutional Human Research Ethics Committee approved the study (H0015651).

We used MedicineInsight data from January 1, 2013 to June 1, 2016, collected from 329 general practices distributed across Australia. Patients were initially included if at the time of data extract they were aged at least 18 years, met the Royal Australian College of General Practice (RACGP) definition of an “active” patient (attended at least three times at the same general practice within a two-year period), and could be diagnosed with CKD based on their laboratory pathology results (having two or more eGFR values less than 60 mL/min/1.73m², and/or two urinary albumin/creatinine ratios (ACR) \geq 3.5 mg/mmol in females or \geq 2.5 mg/mmol in males, at least 90 days apart).[1]

A total of 60,433 patients out of 1.48 million (approximately 4%) in the dataset met the Kidney Health Australia (KHA) guidelines for the diagnosis of CKD.[1] For assessing the quality use of medicines (QUM) in kidney disease we included a total of 49 medications, which were part of a national campaign to improve prescribing in the elderly in 2012.[9] The list was adapted to include some medications that were commonly associated with PIP in other research.[2] Patients’ medications were included if they were prescribed within 90 days following the pathology test. PIP was defined as prescribing of a medication that is contraindicated or at an inappropriately high dose according to the patient’s kidney function. Appropriateness was assessed using the Australian Medicines Handbook (AMH).[10] Only medications that had clear recommendations were included in the analysis. Medications with ambiguous dosage

adjustment recommendations were excluded from the analysis e.g. *Ramipril- "In patients with renal impairment, elderly or taking a diuretic, initially 2.5mg once daily".*[10]

Statistical Analysis

Descriptive statistics were used to describe the data, with mean \pm standard deviation (SD) and percentages/proportions. PIP of medications, i.e. both potentially contraindicated and inappropriately dosed medications, were compared for appropriateness between the CKD-EPI and CG equations (patients with weight and height documented). The level of agreement in evaluating appropriateness between the equations was calculated by Cohen's kappa and Gwet first-order agreement coefficient (AC1).[11] For Cohen's Kappa, a value of <0.6 was defined as poor agreement, $0.6-0.8$ as moderate agreement, 0.8 to <0.9 as good agreement and ≥ 0.9 as excellent agreement. Gwet AC1 provides an alternative in circumstances where Kappa is low despite a high level of agreement and has been shown to provide a more stable inter-rater reliability coefficient than Cohen's kappa.[11] All data cleaning and manipulation, and statistical analyses were completed using the statistical and graphical computing language of R.[12] A p value of <0.05 was considered statistically significant.

Results

A total of 48,731 patients met the KHA definition for CKD and had prescriptions recorded within 90 days of measuring kidney function. Overall, 28,729 patients were prescribed one or more of the 49 medications of interest (*Table 1*).. Over 90% of these patients ($n = 25,975$) were ≥ 65 years of age and 55.7% ($n = 15,993$) were female. The mean (SD) number of medications and medical conditions were 8.4 (3.8) and 2.2 (1.0), respectively. Over 80% ($n = 23,998$) of the patients had hypertension, while over 40% had diabetes and/cardiovascular disease ($n = 13,292$ and $13,611$, respectively). Among the 28,729 patients, almost all 98.5% ($n = 28,315$) were in Stage 3, 4 and 5 CKD. The most common drug class prescribed across the study sample were agents pertaining to the renin-angiotensin system (RAS).

Potentially inappropriate prescribing

A breakdown of PIP across the different stages of CKD is provided in *Figure 1*. Overall, 35% ($n = 9,926$) patients had at least one PIP based on either CG CrCl or eGFR. Approximately 6.5% ($n = 1,866$) and 1.8% ($n = 505$) were prescribed 2 and 3 or more potentially inappropriate medications (PIMs), respectively (*Table 2*).. A total of 1,171 patients (4.1%) were prescribed both a contraindicated medication and a medication at an inappropriate dose as per their kidney function.

Analgesics, prescribed across 7.2% patients ($n = 2,082$), were the most frequent inappropriate class of medication [$n = 1,536$ (73.8% of patients prescribed the drugs)] followed by medications for diabetes [prescribed $n = 8,730$ (30.4%); PIP $n = 3384$ (44.1%)] and beta-blockers [prescribed $n = 4,832$ (16.8%); PIP $n = 1,849$ (38.2%)]. Vildagliptin [prescribed $n = 355$ (1.2%); PIP $n = 274$ (77.2%)] followed by fenofibrate

[prescribed n = 1,939 (6.7%); PIP n = 1,346 (69.4%)] were the most commonly prescribed medications at an inappropriate dose, whilst dapagliflozin [prescribed n = 296 (1%); PIP n = 245 (82.8%)] followed by alendronate [prescribed n = 791(2.8%); PIP n = 251 (31.7%)] had the highest rates of use when contraindicated either by CG CrCl or eGFR (*Table 3*). Codeine, glibenclamide and gliclazide were associated were PIP in all patients prescribed these drugs, as the AMH recommends their avoidance in renal impairment, and these were excluded from the final analysis.

Agreement between eGFR (CKD-EPI) and CrCl (CG equation)

Overall, there was good agreement between CG CrCl and eGFR (CKD-EPI) when determining the appropriateness of medications. Approximately 97% of medications that were classified as appropriate by eGFR were considered to be appropriate by the CG equation, while 88.1% and 61.1% of the medications considered to be contraindicated and inappropriately dosed by eGFR, were considered to be contraindicated and inappropriately dosed by the CG equation, respectively (*Figure 2*). The top 3 medications in disagreement between the two equations are presented in *Table 4*. A total of 40 medications from the 49 of interest, that had been rated PIP at least once, were tested for inter-rater agreement. Twenty-seven medications scored a Cohen's kappa value <0.6 whereas Gwet's AC1 scores were between 0.75–1.0.

Discussion

The results demonstrate that Australian general practice patients with CKD are frequently prescribed PIP. Approximately 35% of the patients were prescribed at least one PIP. The findings have corroborated the high rate of potentially contraindicated medications and inappropriate dosing found in international studies, including a systematic review that reported rates of PIP between 13% to 80%.[2, 4] These results highlight the need for further research to determine the reasons, leading to interventions to optimise prescribing in patients with CKD in general practice.

The extent of PIP in our study and the previous literature highlights the complexity of prescribing in CKD and could be due to the contribution of several factors. Firstly, in Australia there is a lack of up-to-date accessible guidelines on drug dose adjustments in patients with impaired kidney function. Another important aspect to consider is the inconsistencies with dosage adjustment recommendations between different drug information sources, as well as the product information of different brands of the same drug.[13, 14] It is important to note that most drug information sources provide dosage adjustment based on the CG equation rather than eGFR formulae (MDRD/CKD-EPI), whilst eGFR (especially CKD-EPI) based formulae have been found to be the most accurate indicator of kidney function.[15] Secondly, many of the recommendations based on the CG equation are questionable due to the variability in creatinine assays at the time and were prior to SCr being isotope dilution mass spectrometry (IDMS) standardised. CG-estimated GFR results are 5–10% higher using the standardised SCr measurements compared to the non-standardised SCr and relying on the CG equation could lead to unintended consequences, including

insufficient dose adjustments for kidney function.[16, 17] However, the clinical significance of this theoretical issue is unknown and needs to be evaluated further. Hence, current recommendations include using either CG equation due to considerable experience with the formula even if it is based on creatinine assays not in use. It is also appropriate to use eGFR formula (CKD-EPI) for most drugs without body surface area (BSA) adjustment.[1, 15]

The nature of the electronic health record (eHR) may also be a potential factor for PIP. The current eHR may not alert prescribers to appropriately adjust dosages of medications cleared by the kidney unless the patient has CKD recorded as a diagnosis. Only 20% of the patients included had a formal diagnosis of CKD documented whilst all patients had laboratory evidence of CKD and this lack of coding of CKD as a condition may have had a role in the PIP findings.[7, 8] Furthermore, in many older people with stable eGFR values from 45–59 mL/min/1.73 m² debate on the definition and staging of CKD exists as to whether CKD may be over diagnosed. However, these values are a sign of impaired kidney function that could affect the clearance of drugs. Hence, it is essential to consider renal function when prescribing renally-cleared medications as the PIP may lead to adverse outcomes.

The agreement between the two equations (CG and CKD-EPI) was excellent, with 97% of the medications rated as appropriate by eGFR being also rated as appropriate by the CG equation. Previous studies comparing drug doses derived from eGFR equations and CG have commonly reported discordance rates between 10% and 40%.[18, 19] These results highlight that for most patients with renal impairment the same recommendation between eGFR or CG estimate can be used, with any difference in the kidney function estimate unlikely to lead to an overdose [20] However, it is important for some drugs, and the potential clinical significance of disagreement between eGFR and CG-based dosing regimens should be minimised by using sound clinical judgment.[21] For example, our study showed that rivaroxaban was one of the medications associated with disagreement between the equations. A recent study by Szummer et al comparing eGFR (CKD-EPI, MDRD) and the CG equation suggested that when prescribing one of the novel oral anticoagulants, the CG equation should be considered, as it provides a more conservative approach for avoiding drug exposure and reducing the risk of bleeding.[22] A similar approach is recommended by the National Kidney Disease Education Program (NKDEP) in the USA and by KHA, where eGFR can be used for dosage adjustment for most drugs (without BSA adjustment) except for drugs with a narrow therapeutic index (e.g. anticoagulants), where conservative kidney function estimates and corresponding doses are recommended, particularly if therapeutic drug monitoring is not readily available.[15]

Most of the medications with PIP were consistent with previous studies.[2] Antidiabetic agents and cardiovascular drugs were commonly associated with PIP, which is not surprising given that both diabetes and CVD often co-exist with CKD. Almost half of our patients were being treated for diabetes and CVD. A large proportion of oral antidiabetic agents are excreted by the kidney.[10] It is likely that concomitant chronic diseases complicate and confound the treatment of each other. These medications are adjusted frequently in response to cardiac, renal or electrolyte disturbances, and are at a higher risk of being potentially inappropriate.

It is important to note that for some medications commonly prescribed in the study (for example, atenolol) clinical markers, such as heart rate and blood pressure, are often more important than kidney function in guiding dosage adjustment. Additionally, some medications do not have adequate published data in patients with renal impairment and may have been conservatively recommended as to be avoided rather than having an increased potential for toxic effects.[10]

Our study also showed that PIP was common across all stages of CKD. Although stages 1, 2 and 3a CKD seldom impact on the prescribing of renally cleared medications, several common medications such as metformin, gliptins and SGLT2 inhibitors do have specific recommendations in patients with early stages of CKD. Previous studies in patients with advanced CKD have shown contrasting results. Some studies have reported that in patients with advanced CKD the likelihood of PIP is less due to more vigilant monitoring and nephrology consultations, while other studies have shown an increased number of problems.[23–25] Further research to understand the phenomenon of PIP in general practice is needed, possibly leading to the design of interventions to optimise medication prescribing in patients with CKD. Optimal use of current eHR systems to flag renally-impaired patients so that PIP is identified is likely to be part of an intervention.

The major strength of the current study is that it assessed prescriptions in primary care in a large cohort of patients. Previous Australian studies of inappropriate drug prescriptions in CKD have focussed on older people in the community and aged care settings, or when patients were admitted to the hospital.[4] However, the study does have some limitations. Prescribers may not always have had pathology results available at the time of prescribing. However, we evaluated the extent of PIP for medications prescribed within 90 days of the availability of a kidney function assessment. We did not examine any adverse clinical outcomes associated with PIP.

Conclusion

Our study highlights that PIP is common in Australian general practice, underlining the complexity of prescribing for patients with CKD. Understanding situations where prescribing is truly inappropriate would assist in the design of interventions to improve safe medication prescribing in patients with CKD. Our study also shows that although CrCl using the CG formula has been the most common method of estimating kidney function for drug dosing purposes for over 40 years, the widespread availability and extensive clinical use of eGFR now provides clinicians with a potential alternative. However, careful consideration of the risk-benefit ratio of individual drugs and doses within each patient is warranted.

Abbreviations

AC1: agreement coefficient

ACR: albumin/creatinine ratio

AMH: Australian Medicines Handbook

BSA:body surface area

CVD:Cardiovascular disease

CKD: chronic kidney disease

CKD-EPI: CKD-Epidemiology Collaboration Equation

CG:Cockcroft-Gault

CrClcreatinine clearance

eHR:electronic health record

eGFR:estimated glomerular filtration rate

IDMS:isotope dilution mass spectrometry

KHA:Kidney Health Australia

MDRD: modification of diet in renal disease

NKDEP:National Kidney Disease Education Program

PIP: potentially inappropriate prescribing

QUM: quality use of medicines

RACGP: Royal Australian College of General Practice

SCr:serum creatinine

SGLT2:sodium glucose cotransport inhibitors

Declarations

Ethics approval and consent to participate (provide full name of ethics committee).

The University of Tasmania Human Research Ethics Committee approved the study (H0015651). As this was a retrospective study no consent was required from the participants.

Consent to publish

All authors listed have consented to the publication

Availability of data and materials

Yes, if required after appropriate grant of permission from MedicineInsight

Competing interests:

Jan Radford serves on the data governance board of NPS MedicineWise. None of the other authors have any competing interest

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Authors' Contributions

Conception and study design: R. L.C; data acquisition: R. L. C., JR, GP; data analysis R. L. C., TS, AK, JS; Data critique and interpretation: All authors; manuscript preparation: RLC; Manuscript critique: All authors. All authors have read and approved the final version of the manuscript.

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Tables

Table 1: Characteristics of the study sample (n=28,729)

<u>Demographics</u>	<u>Number (%)</u>
Age (years)	
· 20-29	6 (0.02)
· 30-39	61 (0.21)
· 40-49	257 (0.89)
· 50-59	1,039 (3.62)
· 60-69	4,234 (14.74)
· 70-79	10,219 (35.57)
· 80-89	10,434 (36.32)
· 90+	2,479 (8.63)
Male Gender	12,736 (44.3)
CKD Risk Factors	
· Hypertension	23,998 (83.2)
· CVD	13,611 (47.4)
· Diabetes	13,292 (46.3)
Number of medications [Mean (SD)]	8.42 (3.75)
Top 5 medications categorised according to the ATC groups	
· Agents acting on the renin-angiotensin system	20,391 (71.0)
· Analgesics	16,084 (56.0)
· Drugs for acid-related disorders	15,861 (55.2)
· Antithrombotic drugs	11,691 (40.7)
· Diuretics	10,965 (38.2)
Stages of CKD	
· Stage 1 $\geq 90\text{mL}/\text{min}/1.73\text{m}^2$	27(0.1)
· Stage 2 60-89 mL/min/1.73m ²	387 (6.8)
· Stage 3a 45-59 mL/min/1.73m ²	18,553 (64.6)
· Stage 3b 30-44 mL/min/1.73m ²	7539 (26.2)
· Stage 4 15-29 mL/min/1.73m ²	1955 (6.8)
· Stage 5 <15 mL/min/1.73m ²	268 (0.9)

CVD- Cardiovascular disease; ATC-Anatomical Therapeutic Chemical classification system

Table 2: Potentially inappropriate medications (PIMs) in the study sample

Characteristic	Number (%)
PIMs	
0	18,803
1	(65.4)
2	7,555 (26.3)
≥3	1,866 (6.5)
	505 (1.8)
Patients with potentially inappropriate dose	7,312 (25.5)
0	21,417
1	(74.5)
2	5,983 (20.8)
≥3	1,143 (4.0)
	186 (0.6)
Patients with potentially contraindicated medication	3,786 (13.2)
0	24,943
1	(86.8)
2	3,494 (12.2)
≥3	265 (0.9)
	27 (0.1)
Patients with both potentially inappropriate dose and contraindicated medication	1,171 (4.1)

Table 3: Medications with potentially inappropriate prescribing

Medications with potentially inappropriate dose	Patients prescribed N (%)	Patients with inappropriately high dose drug N (%)	Medications potentially contraindicated	Patients prescribed N (%)	Patients with potentially contraindicated medication N (%)
Antidiabetic Medications			Antidiabetic Medications		
ildagliptin	355 (1.2)	274 (77.2)	Dapagliflozin	296 (1.0)	245 (82.8)
saxagliptin	205 (0.7)	117 (57.1)	Acarbose	81 (0.3)	12 (14.8)
sitagliptin	1,534 (5.3)	742 (48.4)	Exenatide	313 (1.1)	18 (5.8)
metformin	8,046 (28.0)	2,885 (35.9)	Metformin	8,046 (28.0)	37 (0.5)
logliptin	17 (0.1)	5 (29.4)	Anticoagulant Medications		
Lipid Lowering Medications			Rivaroxaban	1,230 (4.3)	99 (8.0)
rosuvastatin	1,939 (6.7)	1,346 (69.4)	Dabigatran	492 (1.7)	34 (6.9)
atorvastatin	8,529 (29.7)	525 (6.2)	Apixaban	938 (3.3)	40 (4.3)
Antihypertensive Medications			Cardiovascular Medications		
atenolol	4,832 (16.8)	1,849 (38.3)	Moxonidine	1,675 (5.8)	447 (26.7)
lisinopril	1,675 (5.8)	43 (2.6)	Spironolactone	3,050 (10.6)	665 (21.8)
Antiarrhythmics			Bisphosphonates		
amiodarone	2,567 (8.9)	24 (0.9)	Alendronate	791 (2.8)	251 (31.7)
Anticoagulant Medications			Risedronate	619 (2.2)	118 (19.1)
rivaroxaban	1,230 (4.3)	237 (19.3)	Others		
dabigatran	492 (1.7)	39 (7.9)	Teriparatide	7 (0.0)	2 (28.6)
Bisphosphonates			Strontium	205 (0.7)	43 (21.0)
ibandronate	10 (0.03)	5 (50)	Dextropropoxyphene	105 (0.4)	33 (31.4)
zoledronate	24 (0.1)	1 (4.2)	Pramipexole	523 (1.8)	100 (19.1)
Antihistamines			Probenecid	115 (0.4)	1 (0.9)
levocetirizine	283 (1.0)	170 (60.1)			
loratadine	15 (0.1)	3 (20.0)			
cetirizine	261 (0.9)	50 (19.2)			
Psychotropic Medications					
amisulpride	6 (0.02)	4 (66.7)			
escitalopram	572 (2.0)	70 (12.2)			
venlafaxine	846 (2.9)	87 (10.3)			
desvenlafaxine	1050 (3.7)	47 (4.5)			
trazodone	150 (0.5)	6 (4.0)			
Neurological Medications					
gabapentin	571 (2)	67 (11.7)			
gabapentin	341 (1.2)	30 (8.8)			
levetiracetam	179 (0.6)	9 (5)			
pregabalin	4,642 (16.2)	190 (4.1)			

ramipexole	523 (1.8)	3 (0.6)			
<i>Others</i>					
olterodine	20 (0.1)	2 (10.0)			
olifenacin	458 (1.6)	21 (4.6)			

Table 4: Top 3 medications considered in disagreement between CG CrCl and eGFR (CKD-EPI)

CKD-EPI eGFR	CG Equation	Medication	N (%)
Appropriate	Contraindicated	Spironolactone	229 (27.8)
		Alendronate	186 (22.5)
		Risedronate	105 (12.7)
	Inappropriate dose	Atenolol	501 (32.3)
		Metformin	272 (17.5)
		Sitagliptin	169 (10.9)
Contraindicated	Appropriate	Moxonidine	270 (30.5)
		Spironolactone	241 (27.3)
		Dapagliflozin	177 (20)
	Inappropriate dose	Moxonidine	7 (46.7)
		Metformin	4 (26.7)
		Rivaroxaban	4 (26.7)
Inappropriate dose	Appropriate	Metformin	1,812 (35.5)
		Fenofibrate	915 (17.9)
		Atenolol	675 (13.2)
	Contraindicated	Rivaroxaban	13 (52.0)
		Metformin	12 (48.0)

Figures

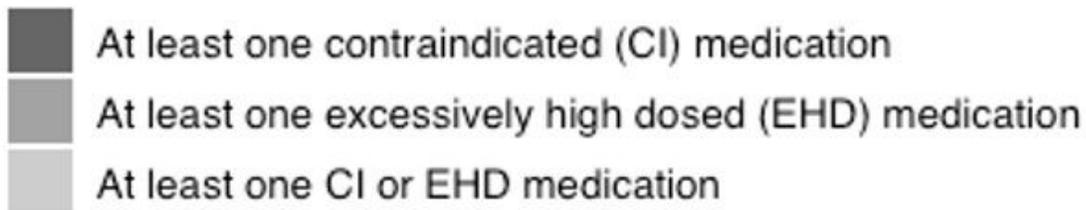
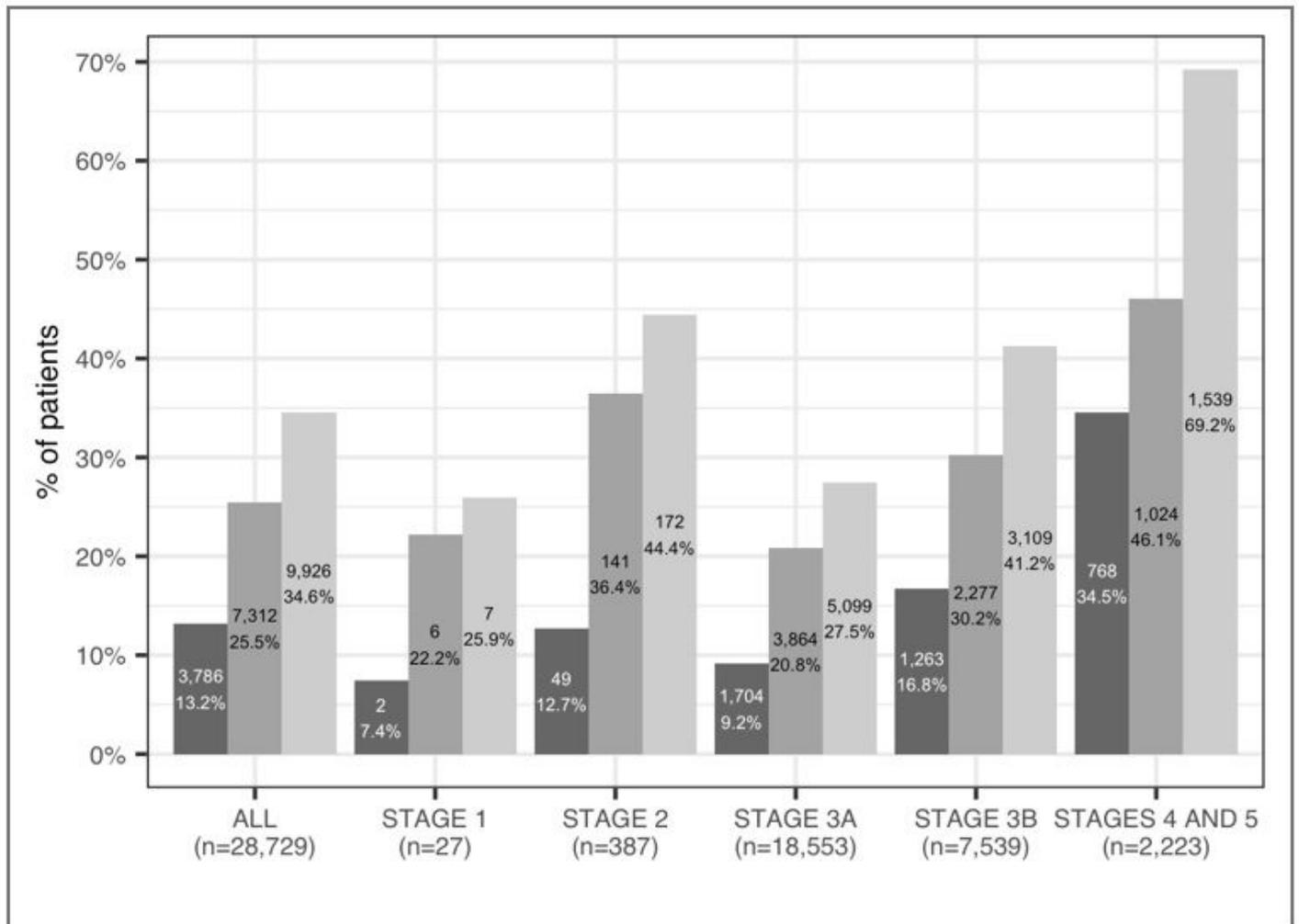
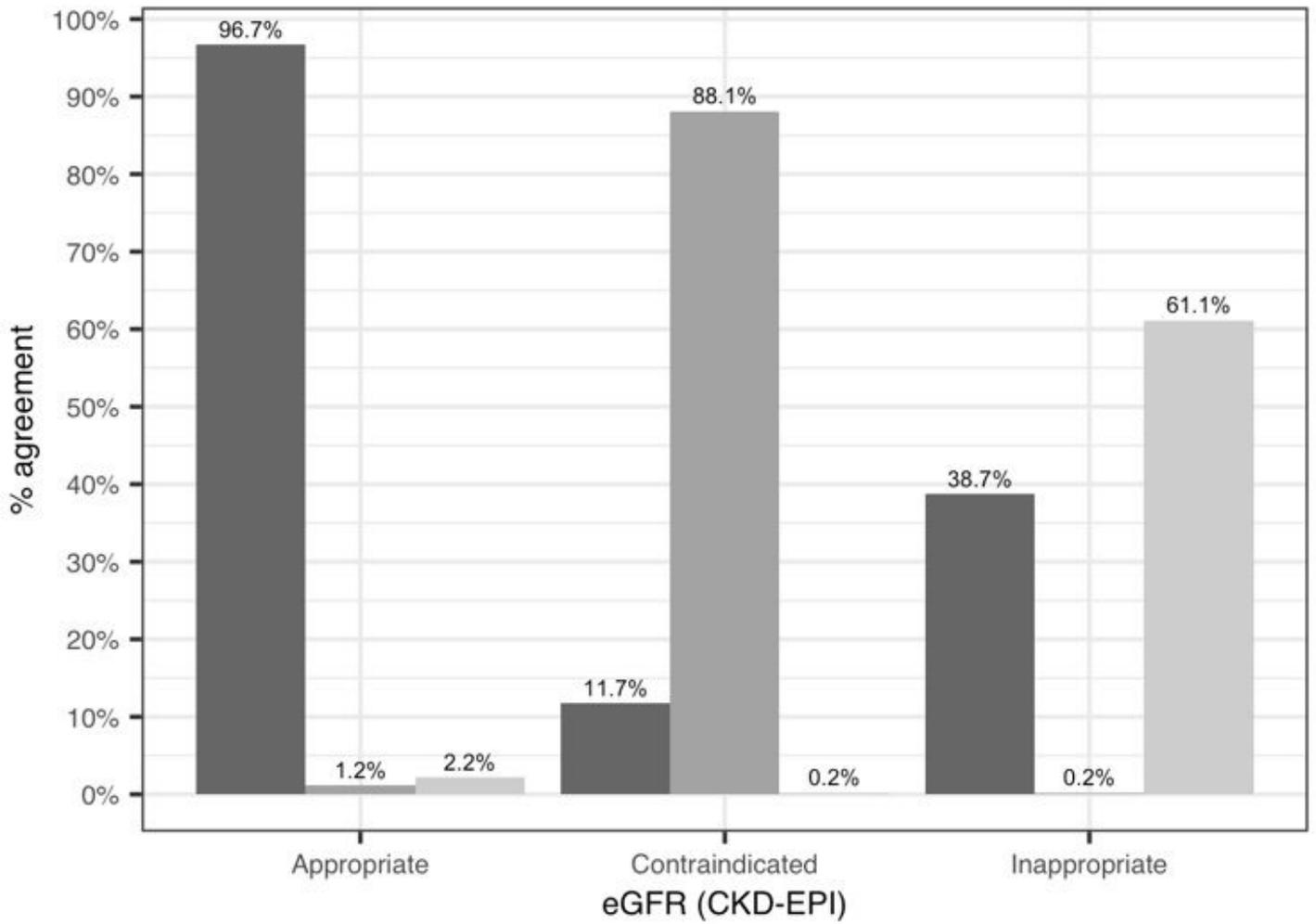


Figure 1

Potential inappropriate prescribing as per CKD stage



Cockcroft-Gault

- Appropriate
- Contraindicated
- Inappropriate

Figure 2

Agreement of equations in determining PIP