The Effect of Hospitalization on Potentially Inappropriate Medication Use in Older Adults with Chronic Kidney Disease

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Abstract

Objectives: Potentially inappropriate medications (PIMs) use is associated with increased morbidity and mortality in chronic kidney disease (CKD). However, there is paucity of data on how hospitalization affects PIMs use in older adults with CKD. Therefore, we aimed to measure the impact of hospitalization on PIMs use in older CKD patients, and identify factors predicting PIMs use.

Methods: A retrospective cohort study was conducted in older adults (≥ 65 years) with CKD admitted to an Australian tertiary care hospital over a 6-month period. PIMs use was measured, upon admission and at discharge, using the Medication Appropriateness Index (MAI) and Beers criteria (2015 version) for medications recommended to be avoided in older adults and under certain conditions.

Results: The median age of the 204 patients was 83 years (interquartile range (IQR): 76-87 years) and most were men (61%). Overall, the level of PIMs use (MAI) decreased from admission to discharge [median (IQR): 6 (3-12) to 5 (2-9); $p < 0.01$]. More than half of the participants (55%) had at least one PIM per Beers criteria on admission, which reduced by discharge (48%; $p < 0.01$). People admitted with a higher number of medications (β 0.72, 95% CI 0.56 to 0.88) and lower eGFR values (β -0.11, 95% CI -0.18 to -0.04) had higher MAI scores after adjusting for age, sex and Charlson's comorbidity index (CCI).

Conclusions: PIMs were commonly used in older CKD patients. Hospitalization was associated with a reduction in PIMs use, but there was considerable scope for improvement in these susceptible individuals.

Keywords: Beers criteria, chronic kidney disease, Medication Appropriateness Index, elderly, potentially inappropriate medications

1 Introduction

2 People with chronic kidney disease (CKD) often have multiple morbidities and, consequently,
3 are prescribed multiple medications¹. Common comorbidities in CKD patients, such as
4 diabetes and hypertension, can also pose a risk of progression to end-stage kidney disease. To
5 delay disease progression and to manage coexisting conditions, CKD patients typically have
6 to take multiple medications, including treatments for hypertension, anemia, mineral and
7 bone disorders, and albuminuria². As such, the number of medications prescribed to these
8 patients is one of the highest among chronic diseases³. Pharmacotherapy in older CKD
9 patients is further complicated by age-related physiological changes that can affect the
10 pharmacokinetics and pharmacodynamics of many medications⁴. Therefore, older adults with
11 CKD are both more prone to receiving potentially inappropriate medications (PIMs) and at
12 high risk of adverse outcomes from medications⁵.

13 Most studies on CKD have defined PIMs based on the lack of dosage adjustment of renally
14 cleared medications or the use of medications contraindicated according to renal function⁶.
15 However, older CKD patients have complex medication regimens that necessitate a more
16 comprehensive evaluation of medication appropriateness. Various explicit and implicit
17 criteria are available to measure PIMs use in older people. While the former are criterion-
18 based, the latter rely on clinical judgment. Explicit measures are designed for universal use in
19 all patients, whereas implicit measures tend to be patient-specific, and thus require access to
20 detailed clinical data⁷. Beers criteria⁸ is one of the most widely used explicit measures, while
21 the Medication Appropriateness Index (MAI)⁹ is a frequently used implicit measure. The
22 latter, although time-consuming and mostly reserved for research purposes, is reliable in
23 evaluating changes in the quality of prescribing over time¹⁰.

The use of PIMs in older people is not only common but also led to detrimental clinical outcomes¹¹. Hospital admissions provide health professionals an opportunity to re-evaluate patients' medication regimens and address identified problems. Although hospitalization is generally associated with substantial changes in medication regimens¹², there are conflicting reports on its effect on PIMs use in older population¹³⁻¹⁵. Moreover, there is a scarcity of data on how hospitalization and the clinical care involved affects PIMs use in older adults with CKD. Therefore, the aims of our study were: i) to evaluate the effect of hospitalization on PIMs use in older patients with CKD, using both the MAI and Beers criteria, ii) to identify factors predicting the use of PIMs at hospital admission, and iii) to evaluate the association between Beers criteria and the MAI in measuring PIMs use in older adults with CKD.'

Methods

Study design and population

This was a retrospective study conducted at a 500-bed tertiary care hospital in Tasmania, Australia. People aged ≥ 65 years with a documented diagnosis of CKD and/or estimated glomerular filtration rate (eGFR) value of <60 mL/min/1.73m² for at least three months, who were prescribed at least one medication and were admitted for longer than 24 hours between January 2015 and June 2015, were included in the study. Exclusions were individuals (i) receiving any form of renal replacement therapy (dialysis or transplant), (ii) who were critically ill with a stay in the intensive care unit, (iii) with acute kidney injury, based on documentation in medical records or a marked increase in serum creatinine, (iv) who died during admission or (v) with incomplete documentation of information. This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee, University of Tasmania, Australia (H0016044).

Data collection

Patient demographic, laboratory, comorbidity and medication information were extracted from the Digital Medical Record (DMR). The medical progress notes and discharge summaries were reviewed to record admission and discharge medications. Important laboratory markers, such as serum creatinine and eGFR values, estimated via the CKD epidemiology collaboration (CKD-EPI) equation¹⁶, at points closest to admission and discharge, were recorded. The eGFR reported by the laboratory was used to identify and classify patients into different stages of CKD (see Table 1). For patients with recorded weight, creatinine clearance (CLcr) was calculated via the Cockcroft-Gault equation¹⁷ using creatinine measurements at points closest to admission and discharge. While actual body weight was used in estimating CLcr for people with normal body weight, adjusted body weight was applied to obese individuals (body mass index >30 kg/m²)¹⁸.

For this study, admission medications were drugs listed on the patient record on the first day of hospitalization before any changes were made by clinicians (reflecting drugs that were being taken prior to hospitalization), whereas discharge medications were those prescribed for continuation after the last day of hospitalization. The total number of medications included all medicines, including vitamins and minerals, taken regularly or ‘as needed’ by patients. The active ingredients of combination medications were counted separately¹⁹. Short-term medications, such as antibiotics and analgesics, were excluded from the evaluation of PIMs. The presence of co-existing diseases was quantified using Charlson’s comorbidity index (CCI)²⁰.

The Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization was employed to record and classify medications²¹. The reason for admission and comorbidities were coded using the International Classification of Diseases (ICD-10)²².

Evaluation of PIMs

PIMs use was evaluated using the MAI⁹ and the updated Beers criteria⁸. The MAI measures the level of PIMs using detailed clinical and laboratory data. This tool, as an implicit tool, can better identify PIMs use than explicit criteria, with ability to predict adverse drug events²³. Studies have also indicated that the MAI has an acceptable inter- and intra-rater reliability²³.

The MAI consists of ten pharmacotherapeutic components including indication, effectiveness, dosage, directions for use and practicality of the directions, drug-drug and drug-disease interactions, the relative expense of medications, duplication of therapy and duration of treatment. Each criterion has rating instructions to assess appropriateness. For items rated as inappropriate, different weighted scores ranging between 1 and 3 (e.g. 3 for “indication”, 2 for “drug interactions” and 1 for “therapeutic duplication”). The MAI scores per patient were then derived by summing the MAI scores of each medication for the patient. The total MAI scores range between 0 and 18, with higher MAI scores reflecting a higher level of medication inappropriateness.

The primary investigator (WT) piloted the MAI on ten patients prior to formal assessment and discussed the ratings with three other investigators (STZ, BW & RC). After discussion, it was deemed essential to take out two elements of the criteria, ‘practicality of directions’ and ‘expense’, for reliability and objectivity reasons. Therefore, because of these modifications, the MAI score of a patient in our study could range between 0 and 15. Moreover, when assessing the ‘direction for use’, we slightly modified the recommended approach. For instance, while the administration of oral antidiabetics, oral corticosteroids and phosphate binders with food was deemed mandatory to mention, we did not rate a medication inappropriate based on the absence of recommendations like ‘avoid the use of grapefruit juice’.

To determine the appropriateness of doses of renally-cleared medications, the CLcr cut-off values in the MAI were used, along with the Australian Medicines Handbook (AMH)²⁴. Of note, the latest MAI tool has updated recommendations for some renally-cleared medications. When inconsistencies arose between MAI and AMH on the CLcr cut-off values, the latter was used.

Statistical analyses

Data were checked for normality of distribution via Shapiro-Wilk's p -value of > 0.05 and visual inspection of histograms and Q-Q plots. Normally distributed continuous variables were reported as mean $\pm$ SD, and as median (interquartile range [IQR]) when non-normally distributed. Frequency (percentage) was used to report proportions and categorical variables.

The primary outcome variable was the use of PIMs pre- and post-hospitalization. The nonparametric Wilcoxon signed rank test was used for comparison of the MAI scores on admission and discharge. The McNemar test was applied for comparison of the proportion of patients receiving PIMs according to MAI and Beers criteria on admission and discharge. Spearman's correlation was used to determine the relationship between Beers and MAI and adjusted median scores of MAI were reported for people taking different number of medications from Beers criteria, using the Predxcat command of STATA (version 15 (StataCorp LLC, TX USA)).

For the multivariate analyses, potential confounders including age, sex, CCI and eGFR, were selected *a priori* based on a p -value of <0.25 in univariate analyses. To determine factors associated with patients' MAI scores, a linear regression model was applied, with coefficients (β) and 95% confidence intervals (CIs) used to report associations. On the other hand, factors associated with the use of Beers criteria medication(s) were identified using the Poisson regression model. In this case, PIMs use was recorded as a count outcome and associations

were reported using incidence rate ratios (IRR) with 95% CIs. Associations were deemed significant at the level of $p < 0.05$ and analyses were conducted using STATA.

Results

Patient characteristics

Overall, 1897 patients with eGFR values of $<60\text{mL}/\text{min}/1.73\text{m}^2$ were admitted at least once during the specified study period. Of these, 204 older adults fulfilled the inclusion criteria and were screened for medication and laboratory information (Figure 1). A diagnosis of CKD was formally documented in 59% of these patients. The median (IQR) age of the patients was 83 (76-87) years and they were predominantly men (61%). The median eGFR value was $38\text{ mL}/\text{min}/1.73\text{m}^2$ at both admission and discharge. CLcr was estimated for 55 (27%) patients with a documented weight in the DMR. Heart failure was the most common primary diagnosis upon hospitalization (13.7%), with hypertension and diabetes mellitus (type 2) being the most common comorbidities, identified in 71% and 36% of patients, respectively (Table 1). Sixteen percent of admissions were due to a range of infectious conditions.

The use of PIMs

On admission, based on the MAI, 89.2% of patients were receiving medications rated as inappropriate on at least one criterion; this significantly decreased to 83.3% on discharge (Table 2). The median MAI (95% CI) score also declined from 6 (3-12) on admission to 5 (2-9) on discharge ($p < 0.01$). Drug-drug interactions (27.6%) and incorrect dosing (20.8%) were commonly identified problems at admission, whereas drug-drug interactions (28.5%) and ineffective medications (19.1%) were common at discharge.

Similarly, 55.4% of patients had at least one PIM from the Beers criteria at admission and this decreased to 48% at discharge ($p < 0.01$). Nearly 15% of patients had multiple

medications from Beers criteria. Furthermore, the inappropriate use of renally-cleared and/or nephrotoxic medications was identified in 21.1% of patients at admission and 15.7% at discharge.

As illustrated in Figure 2, we evaluated the association between MAI and the use of medications from Beers criteria. The median MAI scores consistently increased with the number of PIMs from Beers criteria at admission (Spearman's coefficient=0.68) and discharge (Spearman's coefficient=0.65).

Medications involved in PIMs

Based on MAI, cardiovascular agents were identified as PIMs in more than half (55%) of admitted patients, which decreased after hospitalization (47%) (Figure 3). Similarly, benzodiazepines, proton pump inhibitors (PPIs) and antiarrhythmic medications were among common PIMs identified using Beers criteria (Table 4).

Factors associated with the use of PIMs

On multivariate analyses, a higher number of medications was associated with higher MAI scores at hospital admission (β 0.72, 95% CI 0.56 to 0.88), whereas eGFR was inversely associated with MAI (β -0.11, 95% CI -0.18 to -0.04) (Table 3a). Similarly, based on Beers criteria, the number of medications was independently associated with the use of PIMs at hospital admission, after adjusting for age, sex, comorbidity and eGFR (IRR 1.10 95% CI 1.06-1.14) (Table 3b).

Discussion

To our knowledge, this is the first study to evaluate the impact of hospitalization on medication appropriateness in older adults with CKD. The findings revealed a high level of PIMs use in this patient group, which decreased with hospitalization. The reported MAI scores are like other hospital studies targeting a general older population^{10, 25}. The proportion of patients prescribed PIMs from Beers criteria declined significantly from admission to discharge (55% vs 48%). This prevalence is higher than that reported in studies from Europe^{26, 27} and comparable to an Australian finding²⁸. In contrast, our prevalence is lower than a recent study from the United States, that reported an increased prevalence following hospitalization of elderly patients – 62.3% at hospital admission and 66.6% at discharge¹⁵.

Our study indicates that hospitalization was associated with a reduction in PIMs use. This is consistent with prior Australian studies that showed a similar trend after hospitalization^{29, 30}, whereas studies from Europe and the United States have reported an increase in PIMs after hospitalization^{15, 31}. These discrepancies could be attributed to differences in study setting and the healthcare system, the population group targeted, and the tools applied in measuring medication appropriateness.

The findings of this study highlight that older adults with CKD have additional risks of PIMs identified using criteria such as MAI and Beers. In addition to the inappropriate prescribing of renally-cleared medications identified using the AMH, additional PIMs were captured using these criteria. This corresponds with a previous study from France that suggested the use of Beers criteria with renal dosage adjustment guidelines could identify added risks in older people with CKD.³² Further, another study also demonstrated that the use of the British National Formulary with Beers criteria resulted in a higher prevalence of PIMs.⁵ This

1 highlights the importance of using such criteria for targeting patients prone to PIMs and
2 consequently at risk of adverse drug events.

3 The use of MAI resulted in the identification of more PIMs than using Beers criteria. This is
4 because the MAI, as an implicit measure, addresses broad aspects of pharmacotherapy. For
5 example, dosage appropriateness is one element of MAI that explicit measures do not address.
6 Drug-drug interactions was another important prescribing quality indicator assessed using the
7 MAI. Major drug interactions were identified in 20% and 18% of patients at admission and
8 discharge, respectively. An example was the concomitant use of amiodarone and warfarin, an
9 interaction that increases the risk of bleeding³³. Other clinically relevant interactions from
10 this study included the use of angiotensin-converting enzyme inhibitors with potassium-
11 sparing diuretics and the use of multiple central nervous system-acting medications. Although
12 the MAI identified more PIMs than Beers criteria, the time it takes for evaluation makes it
13 less feasible for actual clinical use. Nevertheless, our study demonstrated a strong association
14 between Beers criteria and MAI. Therefore, in clinical practice, the former can serve as a
15 surrogate measure for evaluation of PIMs use in these patients¹⁰. Of note, the updated Beers
16 criteria have dosage recommendations for some renally-cleared medications and major drug
17 interactions, which boosts its potential as a standalone PIMs measure in older CKD patients.

18 Overall, medications acting on cardiovascular and nervous systems were the most common
19 classes of medications identified as PIMs according to MAI. In contrast, benzodiazepines,
20 anticholinergics, opioids, and PPIs were common medication classes identified using Beers
21 criteria. Furthermore, the use of benzodiazepines, opioids, and anticholinergics was identified
22 in patients with dementia, delirium, and history of falls. Prior studies have also identified the
23 inappropriate use of benzodiazepines, anticholinergics and antihypertensive medications in
24 older adults^{5, 27}. Despite the improvement in medication appropriateness after hospitalization,
25 many PIMs remained unchanged. The use of PPIs without clear indications, or for treating

gastro-esophageal reflux disease for longer than eight weeks, frequently persisted after hospitalization. This finding adds to the PPI over/inappropriate prescribing reported elsewhere³⁴. Medication review, educating health professionals, and the use of decision support systems were among strategies suggested to control the use of PPIs³⁴.

Our results also showed that the use of PIMs identified solely based on eGFR did not decrease significantly with hospitalization, although there was a trend in that direction. This results perhaps reflects the observation that the most common PIMs in this category at discharge were metformin and spironolactone. Although metformin has been frequently identified as an inappropriate medication in CKD^{6, 30}, the incidence of lactic acidosis associated with its use has been found to be negligible and guidelines relating its use are generally becoming more relaxed, especially in the mild to moderate stages of CKD³⁵.

Having many medications and lower eGFR were associated with a higher level of PIMs, as measured by MAI. Similarly, the number of medications also predicted the use of PIMs from Beers criteria. These findings are consistent with previous studies that identified the number of medications and renal function as predictors of PIMs use in CKD patients⁶.

This study has some strengths and limitations. This is the first study to measure the appropriateness of medications using both implicit and explicit measures in hospitalized people with CKD. However, the exclusion of patients because of incomplete records is one of the limitations of the study and may have influenced the outcomes reported. Another limitation was the lack of weight documentation for most patients (recorded in 27% of patients), making it impossible to estimate CLcr. Nevertheless, it has been suggested that the use of eGFR in place of CLcr is acceptable for non-critical medications³⁶. Finally, we have measured the extent of unnecessary medications or medications not recommended for use in older individuals, but not the level of underuse of recommended medications. Finally,

Conclusions and future directions

Older adults with CKD are prone to high levels of medication inappropriateness. Hospitalization resulted in a reduction in the use of PIMs, although a considerable proportion of patients still had some form of medication inappropriateness at discharge. Having many medications remained a strong predictor of the use of PIMs, as measured using the MAI and Beers criteria. While it is important to investigate the association between PIMs use, especially higher MAI scores, and patient outcomes in older CKD patients, healthcare professionals should be aware of the potential risks associated with having multiple medications. These risks, along with potential benefits, should be assessed in each individual patient.

Transparency

Disclosure of funding

The authors declare no conflict of interest.

Authors Contributions: WT, STZ, RC, BW have contributed to the conception, design, analyses and manuscript preparation. GP, MJ, and CM have contributed in the analyses, reviewing intellectual content and manuscript preparation.

Declaration of financial/other relationships

WHT, STZ, RC, BW, GP and CM have no relevant financial interests or other relationships to declare.

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3 **Figure captions**

4 **Figure 1** Flow diagram of study participants including reasons for exclusion

5 **Figure 2** People with higher number of inappropriate medications from Beers criteria scored
6 higher on medication appropriateness index (MAI), both at admission and discharge, after
7 adjusting for age, sex, eGFR and Charlson's comorbidity index

8 **Figure 3** Percentage of patients with at least one potentially inappropriate medications (PIMs)
9 from different classes of medications at admission and discharge.

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