Association of Potentially Inappropriate Medication Classes with Mortality Risk Among Older Adults Initiating Hemodialysis

Potentially Inappropriate Medications in Dialysis

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Abstract

Background

Older adults initiating dialysis have high risk of mortality and that risk may be related to potentially inappropriate medications (PIMs). Our objective was to identify and validate mortality risk associated with American Geriatrics Society Beers Criteria PIM classes and concomitant PIM use.

Methods

We used United States Renal Data System data to establish a cohort of adults aged ≥65 years initiating dialysis (2013-2014) and had no PIM prescriptions in the six months prior to dialysis initiation. In a development cohort (40% sample), adjusted Cox proportional hazards models were performed to determine which of 30 PIM classes were associated with mortality (or "high risk" PIMs). Adjusted Cox models were performed to assess association of number of "high risk" PIM fills/month with mortality. All models were repeated in the validation cohort (60% sample).

Results

In the development cohort (n=15,570), only 13 of 30 PIM classes were associated with higher mortality risk. Compared to those with no "high risk" PIM fills/month, patients having one "high risk" PIM fill/month had 1.29-fold (95% confidence interval [CI], 1.21-1.38) increased risk of death; those with two or more "high risk" PIM fills/month had 1.40-fold (95% CI:1.24-1.58) increased risk. These findings were similar in the validation cohort (n=23,569).

Conclusions

Only a minority of Beers Criteria PIM classes may be associated with mortality in the older dialysis population; however, mortality risk increases with concomitant use of "high risk" PIMs. Additional studies are needed to confirm these associations and their underlying mechanisms.

Keywords: inappropriate prescribing, renal failure, aged, medication management

Key Points

- Less than half of medication classes in the American Geriatrics Society Beers Criteria increase risk of death in older adults who are new to dialysis.
- For older adults who are new to dialysis, having more than one "high risk" medication classes may increase risk of experiencing death.

1. Introduction

With approximately 50% of older adults initiating dialysis experiencing death within a year, [1] there is a significant need to identify and mitigate risk factors. Polypharmacy is common among older adults receiving dialysis and is a risk factor for medication-related problems and related mortality.[2, 3] To support prescribing practices that minimize these complications, the American Geriatrics Society Beers Criteria is an important tool that provides a list of potentially inappropriate medications (PIMs) -- medications that carry greater risk of harm than benefit in older adults [4]. While the Beers Criteria includes guidance for medication use in older adults with reduced kidney function, it does not provide specific guidance for those receiving dialysis. Because PIMs are commonly prescribed to patients receiving dialysis,[5, 6] it is important to uncover evidence on mortality risk of PIMs in the older dialysis population. Such inquiry can inform both investigations of mechanisms underlying associations between PIMs and mortality and interventions targeting older adults receiving dialysis.

While several studies demonstrate prevalence and harm of PIMs in older adults with chronic kidney disease or no kidney disease at all [7-11], older adults receiving dialysis may have different levels of risk of harm from PIM use. First, risk associated with some PIMs may be altered in renal failure due to impaired renal clearance and/or lower cytochrome P450 metabolism of non-renally cleared medications [12]. Second, kidney disease often co-occurs with other conditions, such that an older adult receiving dialysis may have clinical indications for use of multiple PIMs (e.g., concomitant use of benzodiazepine and gabapentin) [13]. While multiple PIMs may confer greater risk of harm in other populations [14], it isn't clear if that would be the case among older dialysis patients

whose kidney failure alone, but also when combined with multimorbidity, and geriatric syndromes, limits their life expectancy [15].

Understanding the value of applying the AGS Beers Criteria to the older dialysis population can help dialysis clinicians prevent medication-related problems [16]. As an initial step, our objective was to identify mortality risk associated with having prescriptions for individual and multiple PIM classes. Because the prevalent dialysis population presents both survival bias and selection bias in relation to chronic PIM use, we selected a new PIM user design in a cohort of older adults new to dialysis to assess these associations.

2. Methods

2.1 Study Design

We conducted an observational study to identify individual PIM classes associated with mortality in older dialysis patients. We used the United States Renal Data System (USRDS), including the Centers for Medicare & Medicaid Services (CMS) Medical Evidence form (CMS 2728) and Medicare claims (Parts A, B, and D), to establish the cohort and ascertain clinical characteristics, clinical events, and prescriptions. This study was reviewed by the Johns Hopkins School of Medicine Institutional Review Board and was determined to be exempt.

2.2 Study Population

From USRDS, we identified adults aged ≥65 years who were enrolled in Medicare Parts A, B, and D and initiated hemodialysis between 1/1/2013 and 12/31/2014. We selected these years to correspond with the 2013 introduction of Medicare Part D coverage for a specific PIM class, benzodiazepines [17]. We excluded patients who had prescription claims for PIMs (PIM ascertainment detailed below) in the six months prior to dialysis initiation, patients with missing race and body mass index (BMI) data, and those who became ineligible during the first 90 days after dialysis initiation. Reasons for this ineligibility included loss of Medicare coverage, change in dialysis modality, withdrawal from dialysis, kidney transplantation or mortality. With these criteria, we identified 39,319 patients who met eligibility (Figure 1). By randomization, 40% were assigned to a development cohort and 60% to a validation cohort.

2.3 Variables

We targeted 30 PIM classes listed in the 2019 American Geriatrics Society Beers Criteria (Supplemental Table 1). We compiled a comprehensive list of medications within each of the PIM classes in a systematic manner. First, informaticists used Micromedex, the control vocabularies of MEDLINE and Embase, and medication websites to generate a trade and generic medication name list. Second, this list was curated to allow medications with multiple mechanisms of action to be represented in more than one PIM class. We removed PIMs that with topical or ocular routes of administration. We imported the final list into Stata code to query Medicare Part D claims for PIMs.

We identified patients who were dispensed a prescription for a PIM based on the evidence for prescription claim. We defined PIM exposure in 30-day person-month windows to account for the highly variable intra-person PIM dispensing patterns observed. To account for as-needed use of several PIM classes, we allowed one 7-day grace period between the end of one prescription (date prescription filled + days' supply) and the fill date of the subsequent PIM prescription. There was no lag after the end of a prescription given the short-acting nature of PIMs. Similar to PIM exposure, we quantified PIM count for any given 30-day person-month.

Our primary outcome was all-cause mortality identified through USRDS Core Standard Analytic Files (Patients file) data, augmented through linkage with the Social Security Death Master File. We ascertained model covariates from the CMS 2728 form and diagnosis (International Classification of Diseases (ICD)-9) and procedural (healthcare common procedure coding system/current procedural terminology) codes in Medicare claims during the time between Medicare enrollment and 90 days after enrollment. These patient demographic and clinical characteristics included age, sex, race, ethnicity, BMI, diabetes, cardiovascular disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, history of cancer, drug dependence (i.e., dependence on illicit drugs), inability to ambulate, institutionalization, tobacco use, ESRD cause, and geographic region.

2.4 Statistical Analyses

With our development cohort, we estimated the risk of mortality associated with PIM dispensing for each of the 30 PIM classes using Cox proportional hazard models. Each model was censored for end of follow-up (9/1/2015), end of Medicare coverage, change in dialysis modality, withdrawal from dialysis, kidney transplantation or mortality. PIMs were treated as a time-varying exposure. For all analyses, we compared patients with a given PIM to those without that PIM to be consistent with previous research in patients undergoing dialysis.[18] This was appropriate because the indications for PIMs are broad and common in this population; furthermore, the indications are not

necessarily captured through claims. To minimize confounding, the models were adjusted for age, sex, race, ethnicity, diabetes, cardiovascular disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, history of cancer, drug dependence, inability to ambulate, institutionalization, tobacco use, ESRD cause, and geographic region. Of note, BMI had no association in univariate analyses so it was not included in final models.

We grouped PIMs as "high risk" or "low risk" based on trend of hazard ratio (HR): if HR >1, irrespective of its confidence interval including 1 or not, the PIM was assigned as "high risk". PIMs with HR<1 were all assigned as "low risk". After identifying "high risk" PIMs, those with HR>1 for mortality, we performed descriptive statistics of cohort characteristics stratified by number of "high risk" PIM fills within any given month (none, one, and two or more). Further, we estimated the risk of mortality associated with "high risk" PIM fill count in any given month (none, one, and two or more) using Cox proportional hazards model (adjusting for same covariates described above). Using our validation cohort, we repeated these models. In the combined cohort, we added interaction terms to the model to test for interaction between PIM count and age (ages 65 to 70 and >70) and gender. We used a two-sided α of 0.05 to indicate a statistically significant difference. Only complete cases were included in regression models. The only variables with missing data were race (<1%) and (BMI) (<1%). Proportional hazards models were confirmed visually by graphing the log-log plot of survival and statistically using Schoenfeld residuals. All analyses were performed using Stata 14.2/MP for Linux (College Station, Texas).

3. Results

3.1 Mortality risk of PIM classes

Among patients in the development cohort (n=15,750), the median (IQR) time to death was 0.64 (0.33, 1.07) years. Among the 30 PIM classes, mortality risk was higher among patients with any exposure (compared to those without) to 13 PIM classes (Table 1; Figure 2). Among these 13 "high risk" PIM classes, the most prevalent in descending order were opioids [HR 1.27 (1.2, 1.34)] (54.6%), corticosteroids [HR 1.12 (1.01, 1.24)] (20.7%) and benzodiazepines [HR 1.18 (1.08, 1.29)] (18.6%). Table 2 shows the remaining 17 "low risk" PIM classes in which the risk of mortality was not higher among those with PIM exposure. Among those PIMs includes proton pump inhibitors, antihypertensives, and insulin.

3.2 Cohort characteristics

During the observation period, only 31% (n=4,909) In the development cohort had no exposure to any of the "high risk" PIMs, while 51% (n=8,048) and 18% (n=2,793) had one and two or more fills in any given month, respectively. Compared to those with none or only one fill for a "high risk" PIM, those with two or more fills for a "high risk" PIM within any given month had a greater proportion of men, comorbid conditions like chronic obstructive pulmonary disease, peripheral vascular disease, and cancer, as well as functional limitations, including inability to ambulate, institutionalization, and disabled employment status (Table 3).

3.3 PIM count and Mortality Risk

Compared to those with no "high risk" PIM fills/month, patients having one "high risk" PIM fill/month were 1.29-fold (95% confidence interval [CI], 1.21-1.38) more likely to die; those with two or more "high risk" PIM fills/month were at a 1.40-fold (95% CI:1.24-1.58) increased risk. There were no differences in the association of PIM count by age (p=0.54) or gender (p=0.69).

3.4 Validation

The validation cohort (n=23,569) had similar demographic and clinical characteristics to the development cohort (Supplemental Table 2), as well as, median (IQR) time to death [0.64 (0.33-1.06) years]. Using the validation cohort, we found hazard ratios for mortality to be similar to the development cohort (Figure 2; Supplemental Tables 3). Compared to those with no "high risk" PIM fills/month, patients having one "high risk" PIM fill/month were 1.27-fold (95% confidence interval [CI], 1.21-1.34) more likely to die; those with two or more "high risk" PIM fills/month were at a 1.30-fold (95% CI:1.17-1.45) increased risk.

4. Discussion

We examined mortality risk associated with 30 unique AGS Beers Criteria PIM classes in a nationally representative cohort of incident older hemodialysis patients. While most (n=17) PIM classes had no association with increased mortality, we found 13 of these PIM classes carried a risk of mortality (indicated by HR >1), primarily those representing psychoactive medications (e.g., opioids, corticosteroids, and benzodiazepines). Compared with those without any "high risk" PIMs, those with 2 or more "high risk" PIMs or one "high risk" PIM had 40% and 29% greater hazard of mortality, respectively. These findings show that most PIMs included in the

Beers criteria may not increase mortality risk and suggests additional studies may be warranted to create criteria tailored for the older dialysis population.

Our findings are consistent with prior studies. Studies that have explored individual PIM classes have identified that opioids and short acting benzodiazepines when codispensed with opioids are associated with mortality in patients receiving dialysis [18]. Additionally, studies that include all PIMs as a single exposure variable, have demonstrated that mortality risk is increased when any PIM is present in separate cohorts of nursing home residents and community-dwelling older adults [19-21]. We build on this existing literature by examining the mortality risk of PIMs of individual PIM classes among older adults receiving dialysis and identifying that risk is only apparent with a subset of Beers Criteria PIMs.

This study's findings provide hints to understand why some PIMs were associated with mortality in older adults receiving dialysis. Compared to patients without "high risk" PIM prescriptions, patients with "high risk" PIMs had higher comorbidity burden and a larger proportion had difficulty with ambulation (a marker for disability), which may suggest presence of frailty, a known risk factor for mortality. Because prior studies demonstrate a plausible link between PIMs and frailty [22, 23], this study implies that those with "high risk" PIMs also have other characteristics that predispose them to earlier mortality.

Compared to the PIM classes that had lower hazards for mortality, those PIM classes with increased hazards for mortality ("high risk" PIMs) were predominantly psychoactive medications, opioids and benzodiazepines, as shown in prior studies [17, 18]. In contrast, PIMs with lower risk of mortality are prescribed for common comorbidities, such as HTN, DM, heart disease, neuropathic pain, and depression. Some of these "low risk" PIM classes, while not associated with mortality, may be associated with geriatric conditions which can yield serious adverse outcomes, such as falls or confusion [10, 11, 24]. Older adults receiving dialysis consider medication management, including prevention of medication-related problems, as an unmet need.[25] Therefore, additional studies are needed to explore risk of all PIM classes in the dialysis population on geriatric conditions and confirm the designation of "high" and "low" risk. For now, clinicians prescribing "high risk" PIMs for older adults receiving dialysis should consider shared decision-making discussions on deprescribing and/or switching to safer alternatives or non-pharmacological therapies [16, 26].

Our study highlights that the presence of multiple "high risk" PIMs is associated with increased mortality. This is likely due to codispensed short-acting benzodiazepine and opioid prescriptions [17]. This combination along with opioids and gabapentin or multiple meds with anticholinergic effects, can increase risk of sedation and related complications include overdose and subsequent death [4, 27]. Additional studies are needed to uncover all combinations of PIMs that are prevalent and contribute to harm in the older dialysis population. For now, clinicians should recognize the heightened mortality risk when multiple "high risk" PIMs are prescribed and reconsider initiation of additional "high risk" PIMs in patients who are already prescribed one.

Our studied leveraged the robust prescription claims and nationally representative sample of new users of PIMs initiating dialysis and explored risk for individual PIM classes. However, this study has limitations. As with all claims-based pharmacoepidemiologic studies, possession of PIM is not equivalent with actual use. The limited accuracy of this exposure variable may explain some of the effect estimates that are towards the null. Not only that, actual exposure may be more than accounted for which would strengthen the effect estimates towards mortality risk. Because we explored all PIM classes, our study design did not allow us to optimally minimize confounding by indication for individual PIM classes. This approach was selected because the evidence for specific indications in claims for all PIM classes can be insufficient. Still, this study provides foundational evidence to support additional studies that would explore individual PIM classes with an active comparator using propensity score methods for more definitive evidence on risk of harm. Similarly, we acknowledge that use of mortality as our outcome does not allow for evaluation of the causal pathway of how PIMs contribute to risk of harm. Additional work is needed to explore more specific medication-related harm for geriatric conditions. Last, this study included only incident patients with Medicare coverage prior to dialysis initiation so the results may have limited generalizability to prevalent patients, those with alternative insurance coverage, or those who have history of PIM use. Still, this approach minimized bias related to survival and prior PIM exposure.

5. Conclusion

This study identified a subset of AGS Beers Criteria PIMs that are associated with mortality in older adults who are new to dialysis and new PIM users, and demonstrate higher risk when multiple PIMs are present. While additional studies are warranted to confirm this risk for individual medication classes, this evidence provides caution

for initiation of "high risk" PIMs and supports additional research to develop a tailored PIMs list for the older dialysis population.

Statements and Declarations

Funding: This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant R01DK120518 (award to Dr. McAdams DeMarco). Research reported in this publication was also supported by the National Institute on Aging under Award Numbers K76AG059930 (awarded to Dr. Hall) and K08AG065520-01 (awarded to Dr Muzaale) of the National Institutes of Health. D.L.S. was supported by grant K24AI144954 from the National Institute of Allergy and Infectious Diseases (NIAID). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This research is also supported by the American Society of Nephrology Foundation for Kidney Research. The findings and interpretation do not necessarily represent the official views of this foundation.

These sponsors did not have a deciding role in the study design, analysis, interpretation of the data, writing of the report, or the decision to submit the report for publication.

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

Conflicts of Interest: The authors declare that they have no competing interests.

Availability of Data and Materials: The datasets generated and analyzed during the current study have been supplied by the United States Renal Data System (USRDS) but restrictions apply to the availability of these data, which were used under data use agreement, and so are not publicly available.

Ethics approval: This study was approved by the Johns Hopkins School of Medicine Institutional Review Board. All methods were performed in accordance with relevant regulations and guidelines.

Consent to participant: Not applicable.

Consent for publication: Not applicable.

Code availability: The datasets generated and analyzed during the current study have been supplied by the United States Renal Data System (USRDS) but restrictions apply to the availability of these data, which were used under data use agreement for the current study, and so are not publicly available.

Author contributions: research idea and study design: AM, RH, MMD; data acquisition: DS; data management: LR, SS, AM, RH; data analysis/interpretation: AM, SB, RH, MMD; statistical analysis: AM, SB; manuscript draft and revision: all authors; supervision or mentorship: MMD.

Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Acknowledgements: The authors thank Donna Crabtree for assistance in formatting the supplemental material.

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335 **Table 1.** "High-risk" potentially inappropriate medication (PIM) classes.[a]

PIM Class	HR (95% CI)	Proportion (%) in Cohort
Antispasmodics	1.42 (0.97 - 2.09)	1.0
Acetylcholinesterase Inhibitors	1.38 (0.97 - 1.97)	0.7
Opioids	1.27 (1.20 - 1.34)	54.6
Benzodiazepines	1.18 (1.08 - 1.29)	18.6
Antipsychotics	1.18 (1.02 - 1.37)	6.0
Antiemetics	1.18 (0.97 - 1.42)	6.3
Antiparkinsons	1.16 (0.52 - 2.58)	0.3
Antiinfective	1.13 (0.81 - 1.57)	2.3
Corticosteroids	1.12 (1.01 - 1.24)	20.7
Anticholinergics	1.11 (0.90 - 1.37)	4.1
Estrogens	1.01 (0.45 - 2.25)	0.3

336 [a]PIM Classes associated with Mortality (based on HR >1)

337 The mortality risk was obtained from a Cox proportional regression model adjusting for

338 age, sex, race, ethnicity, diabetes, cardiovascular disease, peripheral vascular disease, hypertension, chronic

339 obstructive pulmonary disease, history of cancer, drug dependence, tobacco use, inability to ambulate,

340 institutionalization, ESRD cause, and geographic region. HR – heart rate; PIM - potentially inappropriate medication

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Table 2. "Low-risk" potentially inappropriate medication (PIM) classes.[a]

PIM Class	HR (95% CI)	Proportion (%) in Cohort
Antidepressants	0.95 (0.87 - 1.02)	25.1
Proton Pump Inhibitors	0.89 (0.83 - 0.94)	40.6
Antiepileptics	0.88 (0.80 - 0.96)	20.7
H2 Receptor Blockers	0.88 (0.76 - 1.02)	8.5
NSAIDS	0.84 (0.71 - 1.01)	9.3
Non-dihydropyridine Calcium Channel Blockers	0.83 (0.70 - 0.98)	6.8
Insulin	0.81 (0.75 - 0.88)	31.5
Barbiturates	0.64 (0.29 - 1.42)	0.3
Central Alpha-1 Agonists	0.64 (0.55 - 0.74)	13.4
RAS Inhibitors	0.61 (0.61 - 0.73)	32.1
Sulfonylureas	0.50 (0.37 - 0.68)	3.7
Alpha-1 Blockers	0.49 (0.39 - 0.61)	6.8
Thiazolidinediones	0.44 (0.23 - 0.84)	1.0
Antithrombotics	0.33 (0.05 - 2.35)	0.1
Androgens	0.16 (0.02 - 1.13)	0.3

[a]PIM Classes not associated with Mortality (based on HR <1)

The mortality risk was obtained from a Cox proportional regression model adjusting for age, sex, race, ethnicity, diabetes, cardiovascular disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, history of cancer, drug dependence, tobacco use, inability to ambulate, institutionalization, ESRD cause, and geographic region. HR – heart rate; NSAIDS – non-steroidal anti-inflammatory drugs; PIM - potentially inappropriate medication; RAS – renin-angiotensin-system

Table 3. Characteristics of development cohort stratified by "high-risk" potentially inappropriate medication (PIM) count.[a]

	0 PIMs (N=4,909)	1 PIM (N=8,048)	≥2 PIMs (N=2,793)
Age, median years [IQR]	74.3 [69.4-80.1]	74.3 [69.4-80.1]	73.7 [68.9-79.7]
Female, %			
Race, %			
White	72.4	73.3	79.1
Black	21.5	21.8	18.2
Other[b]	6.1	5.0	2.8
Hispanic Ethnicity, %	12.4	11.4	9.8
Comorbid Conditions[c], %			
Diabetes	57.8	58.9	57.0
Cardiovascular Disease	59.3	60.4	61.8
Peripheral Vascular Disease	11.8	13.5	14.1
Hypertension	89.4	88.8	87.8
COPD	10.4	13.1	17.4
History of Cancer	8.8	9.5	11.3
Drug Dependence	0.6	1.0	1.4
Tobacco Use	2.9	3.9	4.8
Inability to Ambulate	18.2	18.6	23.5
Institutionalized	12.3	11.3	17.1
ESRD Cause, %			
Diabetes	46.5	46.3	43.6
Hypertension	37.2	35.6	34.3
Glomerulonephritis	4.2	4.8	5.4
Other	12.2	13.3	16.8
Geographic Region, %			
New England	3.7	3.4	3.9
Mideast	22.3	18.2	15.1
Great Lakes	18.3	17.3	18.6
Plains	4.9	6.1	6.1
Southeast	23.4	28.6	30.3
Southwest	10.4	11.1	9.8
Rocky Mountain	1.5	1.4	2.0
Farwest	15.6	14.1	14.2

[a]Number of "High Risk" PIMs in any given month.

[b]Other includes Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other or Multiracial, and Unknown

[c]Refers to comorbidities, substance use and functional status reported on CMS 2728 form.

COPD - chronic obstructive pulmonary disease; ESRD – end stage renal disease; IQR – interquartile range; PIM - potentially inappropriate medication

Figure Legends

Figure 1. Cohort selection flow.

Figure 1 Legend: BMI, body mass index; MPO: Medicare Primary, Other; USRDS – United States Renal Data System

Figure 2. Forest plot of PIM classes and mortality risk in development and validation cohorts. PIM - potentially inappropriate medication

Figure 2 Legend: Plot shows in black (development cohort, N=15,750) gray and (validation cohort, N=23,569). Adjusted hazard ratios (and 95% confidence intervals) shown, adjusting for age, sex, race, ethnicity, diabetes, cardiovascular disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, history of cancer, drug dependence, tobacco use, inability to ambulate, institutionalization, ESRD cause, and geographic region. ESRD – end stage renal disease; Non DHP CCB – non-dihydropyridine calcium channel blockers; NSAIDS – non-steroidal anti-inflammatory drugs; USRDS – United States Renal Data System

Supplemental Material

Table 1. List of medications included within each PIM class.

Table 2. Baseline characteristics of the validation cohort.

Table 3. Hazards of mortality for each PIM class in the validation cohort.