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ORIGINAL RESEARCH ARTICLE

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

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Abstract

Background and Objective Older adults initiating dialysis have a 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 US Renal Data System data to establish a cohort of adults aged ≥ 65 years initiating dialysis (2013–2014) and had no PIM prescriptions in the 6 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 the association of the 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 a higher mortality risk. Compared with those with no "high-risk" PIM fills/month, patients having one "high-risk" PIM fill/month had a 1.29-fold (95% confidence interval 1.21–1.38) increased risk of death; those with two or more "high-risk" PIM fills/month had a 1.40-fold (95% confidence interval 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.

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 (AGS) Beers Criteria is an important tool that provides a list of potentially inappropriate medications (PIMs)—medications that carry a 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

Key Points

Less than half of medication classes in the American Geriatrics Society Beers Criteria increase the 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 the risk of experiencing death.

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commonly prescribed to patients receiving dialysis [5, 6], it is important to uncover the evidence on the 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.

The prevalence of PIMs in older adults with advanced chronic kidney disease ranges from 24 to 66% [7–10], and the risk of harm includes adverse drug events and, in some instances, hospitalizations and death [8, 11, 12]. However, 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 because of impaired renal clearance and/or lower cytochrome P450 metabolism of non-renally cleared medications [13]. Hemodialysis may provide clearance of some PIMs; however, the extent of PIM clearance depends on the medication's properties (i.e., water solubility, protein bound, molecular weight, volume of distribution) and is highly variable [14]. Second, kidney disease often co-occurs with other conditions, such that an older adult receiving dialysis may have clinical indications for the use of multiple PIMs (e.g., concomitant use of benzodiazepine and gabapentin) [15]. While multiple PIMs may confer a greater risk of harm in other populations [16], it is not clear if that would be the case among older patients receiving dialysis whose kidney failure alone, but also when combined with multimorbidity, and geriatric syndromes, limits their life expectancy [17].

Understanding the value of applying the AGS Beers Criteria to the older dialysis population can help dialysis clinicians prevent medication-related problems [18]. As an initial step, our objective was to identify the 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 long-term 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

This is an observational study to identify individual PIM classes associated with mortality in older dialysis patients. The US Renal Data System, including the Centers for Medicare and Medicaid Services Medical Evidence form (2728) and Medicare claims (Parts A, B, and D), was used 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 the US Renal Data System, the study population included 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. These years corresponded with the 2013 introduction of Medicare Part D coverage for a specific PIM class, benzodiazepines [12]. The exclusion criteria included patients who had prescription claims for PIMs (PIM ascertainment detailed below) in the 6 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, 39,319 patients met eligibility (Fig. 1). By randomization, 40% were assigned to a development cohort and 60% to a validation cohort. Table 1 of the Electronic Supplementary Material (ESM) provides a comparison of patient characteristics among those who met eligibility and those who did not.

2.3 Variables

The exposure variables were the 30 PIM classes listed in the 2019 AGS Beers Criteria that are "considered potentially inappropriate in most older adults" (Table 2 of the ESM) [4]. A comprehensive list of medications within each of the PIM classes was compiled 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 with topical or ocular routes of administration. The final list was imported into Stata code to query Medicare Part D claims for PIMs.

Evidence for a prescription claim was used to identify patients who were dispensed a prescription for a PIM. Potentially inappropriate medication exposure was defined 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, one 7-day grace period was allowed 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, the PIM count was quantified for any given 30-day person-month.

The primary outcome was all-cause mortality identified through USRDS Core Standard Analytic Files (patient file) data, augmented through linkage with the Social Security

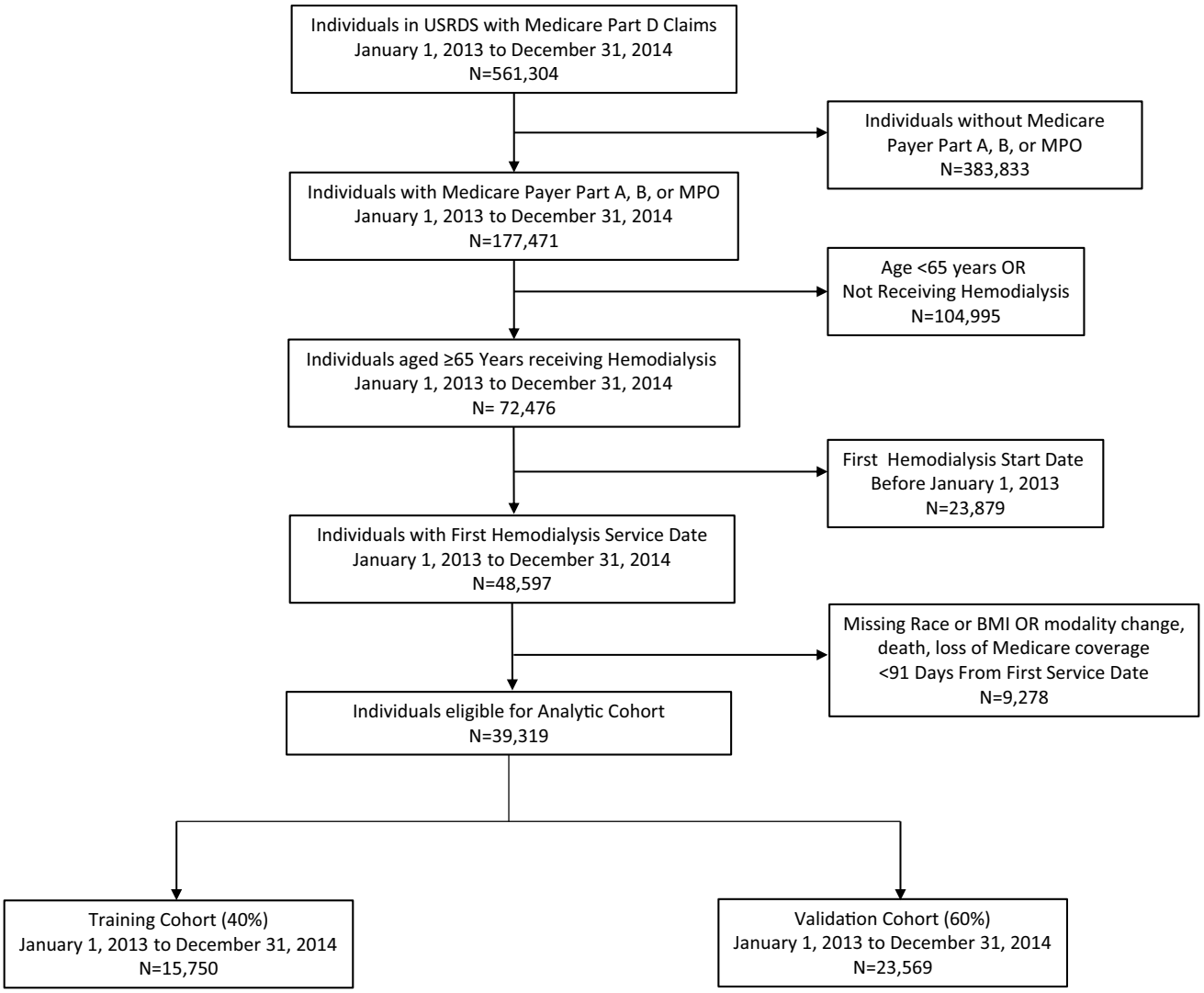

Fig. 1 Cohort selection flow. *BMI* body mass index, *MPO* Medicare Primary, Other, *USRDS* US Renal Data System

Death Master File. This outcome was ascertained for each individual so there were no patients lost to follow-up. Model covariates were ascertained from the Centers for Medicare and Medicaid Services 2728 form and diagnosis (International Classification of Diseases, Ninth Revision) 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 mellitus, 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, end-stage renal disease (ESRD) cause, and geographic region.

2.4 Statistical Analyses

The development cohort was used to estimate 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 the end of the follow-up (9/1/2015), end of Medicare coverage, change in dialysis modality, withdrawal from dialysis, kidney transplantation, or mortality. Potentially inappropriate medications were treated as a time-varying exposure. For all analyses, patients with a given PIM were compared to those without that PIM to be consistent with previous research in patients undergoing dialysis [19]. 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 the final models.

Potentially inappropriate medications were grouped as "high risk" or "low risk" based on the trend of the hazard ratio (HR): if the HR was > 1, irrespective of its confidence interval including 1 or not, the PIM was assigned as "high risk". Potentially inappropriate medications with an HR < 1 were all assigned as "low risk". After identifying "high-risk" PIMs, those with an HR > 1 for mortality, descriptive statistics of cohort characteristics were performed, stratified by the number of "high-risk" PIM fills within any given month (none, one, and two or more). Further, the risk of mortality associated with a "high-risk" PIM fill count in any given month (none, one, and two or more) was estimated using the Cox proportional hazards model (adjusting for same covariates described above). The validation cohort was used to repeat these models. In a combined cohort, interaction terms were added to the model to test for the interaction between PIM count and age (65–70 years and > 70 years) and sex. A two-sided α of 0.05 was used to indicate a statistically significant difference. Only complete cases were included in the 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, TX, USA).

3 Results

3.1 Mortality Risk of PIM Classes

Among patients in the development cohort ($n = 15{,}750$), the median (interquartile range) time to death was 0.64 (0.33–1.07) years and the mortality rate was 6.4 (6.2–6.6) deaths per 10,000 person-years. Among the 30 PIM classes, mortality risk was higher among patients with any exposure (compared with those without) to 13 PIM classes (Table 1; Fig. 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. Proton pump inhibitors, antihypertensives, and insulin are among those PIMs.

3.2 Cohort Characteristics

During the observation period, only 31% ($n = 4909$) in the development cohort had no exposure to any of the "high-risk" PIMs, while 51% ($n = 8048$) and 18% ($n = 2793$) had one and two or more fills in any given month, respectively. Compared with 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 such as 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 with 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 sex ($p = 0.69$).

Table 1 "High-risk" 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

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, end-stage renal disease cause, and geographic region

CI confidence interval, *HR* hazard ratio, *PIM* potentially inappropriate medication

[a]PIM classes associated with mortality (based on an HR > 1)

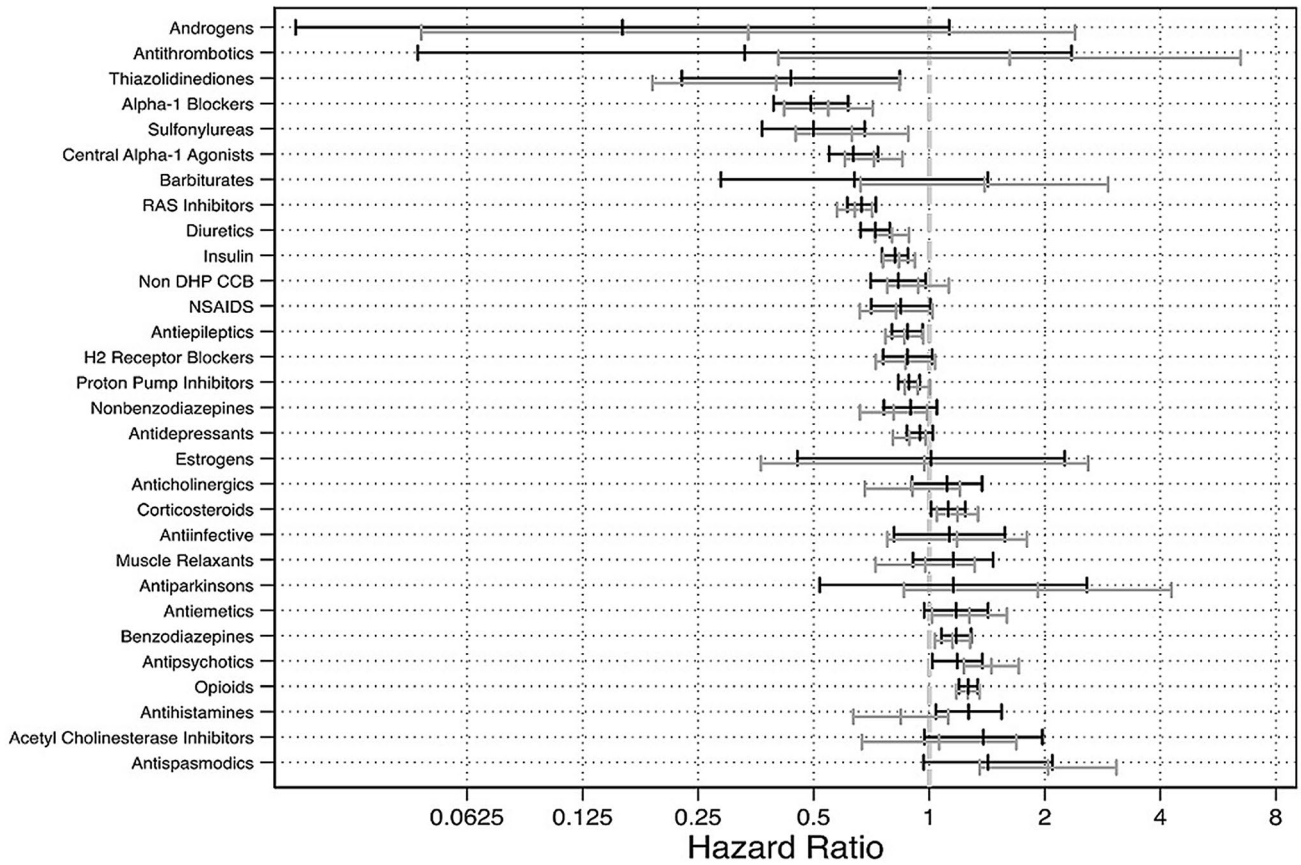

Fig. 2 Forest plot of potentially inappropriate medication (PIM) classes and mortality risk in development and validation cohorts**.** Plot shows the development cohort in *black* ($N = 15{,}750$) and the validation cohort in gray ($N = 23{,}569$). Adjusted hazard ratios (and 95% confidence intervals) shown, adjusting for age, sex, race, ethnicity, diabetes mellitus, cardiovascular disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, history of cancer, drug dependence, tobacco use, inability to ambulate, institutionalization, end-stage renal disease (ESRD) cause, and geographic region. *Non DHP CCB* non-dihydropyridine calcium channel blockers, *NSAIDS* non-steroidal anti-inflammatory drugs, *RAS* renin-angiotensin-system, *USRDS* US Renal Data System

3.4 Validation

The validation cohort ($n = 23{,}569$) had similar demographic and clinical characteristics to the development cohort (Table 3 of the ESM), similar median (interquartile range) time to death [0.64 (0.33–1.06) years] and mortality rate [6.4 (6.2–6.6) deaths per 10,000 person-years]. Using the validation cohort, we found HRs for mortality to be similar to the development cohort (Fig. 2; Table 4 of the ESM). Compared with those with no "high-risk" PIM fills/month, patients having one "high-risk" PIM fill/month were 1.27-fold (95% 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 the mortality risk associated with 30 unique AGS Beers Criteria PIM classes in a nationally representative cohort of incident older patients receiving hemodialysis. 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 an HR > 1), primarily those representing psychoactive medications (e.g., opioids, corticosteroids, and benzodiazepines). Compared with those without any "high-risk" PIMs, those with two or more "high-risk" PIMs or one "high-risk" PIM had a 40% and 29% greater hazard of mortality, respectively. These findings

Table 2 "Low-risk" 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

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

CI confidence interval, *HR* hazard ratio, *NSAIDs* non-steroidal anti-inflammatory drugs, *PIM* potentially inappropriate medication, *RAS* renin-angiotensin-system

[a]PIM classes not associated with mortality (based on an HR < 1)

show that most PIMs included in the Beers Criteria may not increase the 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 co-dispensed with opioids are associated with mortality in patients receiving dialysis [19]. 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 [20–22]. 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 with patients without "high-risk" PIM prescriptions, patients with "high-risk" PIMs had a higher comorbidity burden and a larger proportion had difficulty with ambulation (a marker for disability), which may suggest the presence of frailty, a known risk factor for mortality. Because prior studies demonstrate a plausible link between PIMs and frailty [23, 24], this study implies that those with "high-risk" PIMs also have other characteristics that predispose them to earlier mortality.

Compared with 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 [12, 19]. In contrast, PIMs with a lower risk of mortality are prescribed for common comorbidities, such as hypertension, diabetes, heart disease, neuropathic pain, and depression. Some of these "low-risk" PIM classes, while not associated with mortality, may be associated with geriatric conditions that can yield serious adverse outcomes, such as falls or confusion [25–27]. Older adults receiving dialysis consider medication management, including prevention of medication-related problems, as an unmet need [28]. Therefore, additional studies are needed to explore the 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 [18, 29].

Our study highlights that the presence of multiple "high-risk" PIMs is associated with increased mortality. This is likely because of co-dispensed short-acting benzodiazepine and opioid prescriptions [12]. This combination, along with opioids and gabapentin or multiple medications with anticholinergic effects, can increase the risk of sedation and related complications including overdose and subsequent death [4, 30]. 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 the 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

Table 3 Characteristics of the development cohort stratified by a "high-risk" PIM count[a]

Patient characteristics	0 PIMs ($N=4909$)	1 PIM ($N=8048$)	≥2 PIMs ($N=2793$)
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 mellitus	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

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

[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 the Centers for Medicare & Medicaid Services 2728 form

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 the risk of harm. Similarly, we acknowledge that the use of mortality as our outcome does not allow for evaluation of the causal pathway of how PIMs contribute to the risk of harm. Additional work is needed to explore more specific medication-related harm for geriatric conditions. We did not adjust for polypharmacy in our models; however, polypharmacy is present in over 70% of the dialysis population so accounting for polypharmacy may not considerably change our findings [2, 31, 32]. 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 a history of PIM use. Still, this approach minimized bias related to survival and prior PIM exposure.

5 Conclusions

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

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-023-01039-z.

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Declarations

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Conflict of Interest Rasheeda K. Hall, Abimereki D. Muzaale, Sunjae Bae, Stella M. Steal, Lori M. Rosman, Dorry L. Segev, and Mara McAdams-DeMarco have no conflicts of interest that are directly relevant to the content of this article.

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 Participate Not applicable.

Consent for Publication Not applicable.

Data Availability The datasets generated and analyzed during the current study have been supplied by the USRDS but restrictions apply to the availability of these data, which were used under a data use agreement, and thus are not publicly available.

Code Availability The datasets generated and analyzed during the current study have been supplied by the USRDS but restrictions apply to the availability of these data, which were used under a data use agreement for the current study, and thus 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.

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