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Deprescribing Opportunities for Hospitalized Patients With End-Stage Kidney Disease on Hemodialysis: A Secondary Analysis of the MedSafer Cluster Randomized Controlled Trial

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Abstract

Background: End-stage kidney disease patients on dialysis have a substantial risk of polypharmacy due their propensity for comorbidity and contact with the health care system. MedSafer is an electronic decision support tool that integrates patient comorbidity and medication lists to generate personalized deprescribing reports focused on identifying potentially inappropriate medications (PIMs).

Objective: To conduct a secondary analysis of patients on regular hemodialysis included in the MedSafer randomized controlled trial to investigate the patterns of polypharmacy and evaluate the efficacy of the MedSafer deprescribing algorithms.

Design: Secondary analysis of a cluster randomized clinical trial.

Setting: Medical units in 11 acute care hospitals in Canada.

Patients: The MedSafer trial enrolled 5698 participants with an expected prognosis of >3 months, age 65 years and older, and on 5 or more daily home medications; 140 participants were receiving chronic hemodialysis.

Measurements: The primary outcome of the trial was 30-day adverse drug events (ADEs) post-hospital discharge, and a key secondary outcome was deprescribing.

Methods: Control patients received usual care (medication reconciliation), whereas clinicians caring for intervention patients received a MedSafer report that highlighted individualized opportunities for deprescribing.

Results: There were 70 patients in each of the control and intervention arms. The median number of home medications was 14 (compared with a median of 10 medications in the general trial population). The most frequent medications observed that were potentially inappropriate were proton pump inhibitors (potentially inappropriate in 55/76 users; 72.4%), diabetes medications in patients with a HBA1C <7.5% (36/65 users; 55.4%), docusate (27/27 users; 100%), gabapentinoids (27/36 users; 75%), and combination antiplatelet/anticoagulants (22/97 users; 22.7%). The proportion of PIMs deprescribed was higher during the intervention phase (28.8% vs 19.3%; absolute increase 9.4% [95% confidence interval 1.3%-17.6%]) compared with the control phase. There was no observed difference in ADEs at 30-day post-discharge between the control and the intervention groups. The most common ADE (n = 3) was gastrointestinal bleeding attributed to antiplatelet agents.

Limitations: This was a post hoc exploratory analysis, the original trial did not stratify by hemodialysis status, and the small sample size precludes drawing any definitive conclusions.

Conclusion: MedSafer facilitates deprescribing in hospitalized patients on hemodialysis. Larger-scale implementation of decision support software for deprescribing in dialysis and long-term follow-up are likely required to demonstrate an impact on ADEs.

Abrégé

Contexte: Le risque de polypharmacie est important chez les patients atteints d'insuffisance rénale terminale (IRT) sous dialyse en raison de leurs nombreuses comorbidités et de leurs contacts fréquents avec le système de santé. MedSafer est un outil électronique d'aide à la décision qui intègre les comorbidités et la liste de médicaments des patients pour générer des rapports de déprescription personnalisés, axés sur l'identification de médicaments potentiellement inappropriés (MPI).

Objectifs: Procéder à une analyse secondaire des patients sous hémodialyse inclus dans l'essai contrôlé randomisé MedSafer dans le but d'examiner les profils de polypharmacie et d'évaluer l'efficacité des algorithmes de déprescription de MedSafer.
Type d'étude: Analyse secondaire d'un essai clinique randomisé en grappes.
Cadre: Les unités médicales de onze hôpitaux de soins aigus au Canada.
Sujets: L'essai MedSafer a inclus 5698 patients de 65 ans et plus avec un pronostic attendu de plus de trois mois et prenant au moins cinq médicaments quotidiennement à domicile; 140 patients étaient traités par hémodialyse chronique.
Mesures: Le principal critère d'évaluation de l'essai était la survenue d'événements indésirables attribuables aux médicaments (ÉIM) dans les 30 jours suivant le congé de l'hôpital. Un des principaux critères d'évaluation secondaires était la déprescription.
Méthodologie: Les patients du groupe témoin recevaient les soins habituels (bilan comparatif des médicaments) alors qu'un rapport MedSafer soulignant les possibilités de déprescription individuelles était envoyé aux cliniciens qui prenaient en charge les patients du groupe d'intervention.
Résultats: Chaque bras de l'essai (témoin et intervention) comptait 70 sujets. Le nombre médian de médicaments pris à domicile était de 14 (comparativement à 10 dans la population générale de l'essai). Les médicaments les plus souvent cités comme potentiellement inappropriés étaient les inhibiteurs de la pompe à protons (55/76 patients; 72,4%), les médicaments contre le diabète chez les patients avec un taux d'HbA1c inférieur à 7,5% (36/65 patients; 55,4%), le docusate (27/27 patients; 100%), les gabapentinoïdes (27/36 patients; 75%) et les antiplaquettaires/anticoagulants combinés (22/97 patients; 22,7%). La proportion de MPI déprescrits était plus élevée dans la phase d'intervention que dans la phase témoin (28,8% c. 19,3%; augmentation absolue de 9,4% [IC 95%: 1,3 à 17,6%]). Aucune différence n'a été observée entre les deux groupes en ce qui concerne les ÉIM dans les 30 jours suivant le congé de l'hôpital. Une hémorragie gastro-intestinale attribuable aux agents antiplaquettaires était l'événement indésirable le plus fréquent (n = 3).
Limites: Il s'agit d'une analyse exploratoire a posteriori. L'essai initial n'a pas été stratifié selon le status en hémodialyse. La faible taille de l'échantillon ne permet pas de tirer des conclusions définitives.
Conclusion: MedSafer facilite la déprescription chez les patients hospitalisés qui reçoivent des traitements d'hémodialyse. Pour démontrer un éventuel impact sur les événements indésirables attribuables aux médicaments, il apparaît nécessaire de faire un suivi à plus long terme et à plus grande échelle du logiciel d'aide à la décision de déprescription en contexte de dialyse.

Keywords
deprescribing, polypharmacy, chronic kidney disease, hemodialysis

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Introduction

The prevalence of end-stage kidney disease (ESKD) has increased globally, and more than 2 million people worldwide depend on renal replacement therapy.[1,2] Polypharmacy, often defined as the concurrent use of 5 or more medications, is also increasingly common in older, multimorbid populations.[3] Patients on maintenance dialysis are especially vulnerable to polypharmacy given their frequent comorbidities, including cardiovascular disease, hypertension, and diabetes.[4-7] Patients on dialysis also experience systemic complications of renal insufficiency, such as volume overload, electrolyte abnormalities, bone and mineral metabolism abnormalities, metabolic acidosis, anemia, and pain syndromes.[4,8] Consequently, a variety of clinicians may independently prescribe medications to treat associated comorbidities and manage secondary symptoms.

The proportion of patients with chronic kidney disease (CKD) and polypharmacy increases from 62% to 85% once they become dialysis dependent.[9] Patients with ESKD

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are prone to mega polypharmacy (prescription of 10 or more medications); in one study, the average number of distinct medications for patients receiving hemodialysis was 18.1 ± 5.9.[10] The actual pill burden is even higher than the number of medications prescribed; for example, in one dialysis cohort, while the average number of prescribed medications was 11 ± 4, patients were prescribed a median of 19 daily pills to consume.[11] Furthermore, threshold values for the estimated glomerular filtration rate (eGFR) as a means of defining CKD have been identified as a potential source for overdiagnosis and overtreatment, further increasing the likelihood of polypharmacy and prescription cascades.[12,13]

Polypharmacy can, in some circumstances, be indicated and beneficial; however, it also increases the risk of adverse drug events (ADEs), hospitalization, and death.[14,15] This may be due to "medication overload," distinct from polypharmacy, in that it arises from non-beneficial (or formerly beneficial) medications, collectively referred to as potentially inappropriate medications (PIMs).[16] Potentially inappropriate medications may carry risks that exceed their current/future benefits, are nonevidence based/non-beneficial, and add to pill burden. A study of patients with ESKD found that 75% of the cohort had potential drug-drug interactions, with approximately half of them classified as "serious" or "needing close monitoring"; they found a non-statistically significant association between the number of drug-drug interactions and the occurrence of ADEs.[17] Chronic PIMs are also associated with an increased length of hospital stay and a higher risk of death among patients with CKD of all stages.[18,19] As such, identifying and deprescribing PIMs are an important intervention to reduce pill burden, decrease individual and societal-level drug costs, improve quality of life, and decrease ADEs and premature or preventable death.[20,21] In addition, reducing the overall number of medications can ultimately improve adherence to more pertinent therapies.[22]

MedSafer is an electronic decision support tool that facilitates deprescribing by identifying and generating a prioritized list of PIMs for reassessment by clinicians. A recent randomized controlled trial using MedSafer in hospitalized patients demonstrated an increase in the amount of PIMs deprescribed compared with usual care alone, with a neutral impact on short-term ADEs in the 30-day post-hospital discharge.[23] Although polypharmacy and ADEs are well documented in patients on dialysis, few studies have reported on deprescribing interventions and follow-up outcomes for this population. Thus, the aims of this study were to (1) characterize the prescription patterns in a cohort of hospitalized patients with polypharmacy receiving maintenance intermittent dialysis, (2) identify PIMs that were flagged by MedSafer and subsequently deprescribed, and (3) describe the clinical outcomes following deprescribing in this subgroup of the largest inpatient deprescribing trial published to date.

Methods

Study Design and Population

This study was a secondary analysis of the MedSafer cluster randomized controlled trial which has been previously published.[23] In brief, patients were enrolled to the study from 11 Canadian acute care hospitals in Montreal, Toronto, Ottawa, Kingston, Edmonton, Calgary, and Vancouver between August 2017 and January 2020. Study units were medical clinical teaching units (staffed by internal medicine or subspecialists of internal medicine) or general medical units (staffed by family medicine practitioners). The original MedSafer trial and data collection methods were approved by each site's respective research ethics approval boards. No novel data were collected for the purpose of this secondary analysis.

The eligibility for enrolment into the primary trial included (1) 65 years of age or older, (2) on 5 or more daily medications prior to admission, (3) admitted to an inpatient medical unit, (4) covered by provincial health insurance, (5) with an expected prognosis of >3 months. Admission notes were reviewed by a trained research assistant, and prehospital medications were evaluated by the pharmacy team conducting a best possible medication history (BPMH). The BPMH was input into MedSafer at enrollment and modified at discharge to account for differences in the exit prescriptions. Patients with repeated admissions were only eligible for enrollment once, during their first admission.

There were 2 study phases in the trial: (1) a control period, where patients received usual care (medication reconciliation) and any deprescribing was based on the clinical teams' usual practice, and (2) the intervention period, where the team was given a report generated by MedSafer with a list of individualized deprescribing opportunities. Reports were generated based on evidence-based guidelines for safer prescribing in older adults, which were cross-referenced with medical conditions, laboratory values, and home medication lists. Potentially inappropriate medications were defined according to criteria from the American Geriatrics Society, the STOPP criteria (Screening Tool of Older Persons' Prescriptions), and Choosing Wisely.[24-26] MedSafer contains specific recommendations for patients with an eGFR <30 or a known history of CKD.

Potentially inappropriate medications were categorized by expert consensus as: (1) high-risk PIMs (harms outweigh benefits for most; eg, combination blood thinners), (2) intermediate-risk PIMs (harms may approximate benefits, clinical judgment required; eg, proton pump inhibitors [PPIs] in the absence of an evidence-based indication), and (3) low-risk PIMs (little or no added value, shown to be ineffective, adding to pull burden; eg, docusate). Deprescribing reports were provided to the treating team (including the unit pharmacist) within 3 days of admission and at discharge were faxed to the patient's self-identified usual treating physician(s) and

community pharmacy. Deprescribing was performed by the treating team.

In the MedSafer software, PIMs generally generate unique rules; however, rarely the same drug might trigger more than one alert (eg, opioids are highlighted in chronic non-cancer pain and further emphasized in patients with concurrent cirrhosis, due to the added risk of hepatic encephalopathy). In most cases where 2 alerts are found, the software prioritizes the higher risk category to the clinician to avoid alert fatigue.

Each of the 3 study clusters entered the intervention phase at different, randomly determined times; this design was chosen for all sites to benefit from the potential success of the intervention. Able and consenting patients were followed up with a 30-day post-discharge interview using a variation of the Australian adverse reaction and drug event report[27] to review medication changes, any changes in symptoms, and planned and unplanned visits to medical professionals to evaluate if an adverse event (eg, fall, ER visit, hospitalization, or an unplanned visit to a medical professional) or an ADE (defined as a 5 or 6 on the 6-point Leap and Bates scale) took place following discharge. Complete details of the post-discharge interview have been previously described.[28]

The original MedSafer trial population was used to select the subgroup of patients undergoing maintenance hemodialysis prior to admission. Patients on short-term hemodialysis for reversible causes were not included. Patients were excluded if they died during the index admission or if they were transferred to another center to receive ongoing care (ie, the post-discharge medications and vital status were unknown). The main outcomes of this secondary analysis were to describe the type and frequency of PIMs in this population and to evaluate differences in deprescribing at discharge.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences software (IBM Corp., Armonk, NY, USA). Descriptive analyses were used to present various parameters with continuous variables expressed as a mean ± standard deviation. Means or medians were compared using independent sample *t* tests and Mann-Whitney *U* tests, where appropriate. Categorical variables were reported as medians with interquartile ranges (IQRs), and chi-square tests were performed to investigate differences between the intervention and control group. All hypothesis testing was conducted using 2-sided probability values with $P = .05$ as a threshold for significance.

Results

A total of 140 patients on dialysis were included in this study, with 70 in the intervention arm and 70 in the control arm (Table 1). Patients in each group were similar in terms of age (median 73 [IQR 68.7-84.9] and 76 [IQR 68.7-82] years old) and sex (32.9% and 35.7% females). The control group had more prior hospital admissions in the last year compared with the intervention group (median of 1 [IQR 0-2] in control versus 0 [IQR 0-1] in intervention). Both groups were similar with respect to most comorbidities which included: hypertension, diabetes mellitus, ischemic heart disease, dyslipidemia, and/or anemia. The proportion of peripheral vascular disease was higher in the intervention than in the control group (34.3% vs 17.1%; $P < .05$).

Patients on hemodialysis were prescribed a median of 14 (IQR 10-17) daily home medications (compared with a median of 10 medications in the general MedSafer trial population). A total of 93.6% patients had at least one PIM identified (Table 2). The total number of PIMs identified by MedSafer was similar in both groups (a median of 2.5 [IQR 1.7-4] and 2.5 [IQR 1-4] PIMs per patient in the intervention and control groups, respectively). The proportion of PIMs deprescribed was significantly higher in the intervention than in the control arm (28.8% vs 19.3%, absolute increase of 9.4%; 95% confidence interval 1.3-17.6%).

The most common prescribed drugs in this cohort and the frequency of common PIMs are shown in Figure 1. The 5 most common medication classes prescribed to the total cohort (n = 140) were any antiplatelet or anticoagulant (combined 97/140 users, 69%), statins (88/140, 63%), PPIs (76/140, 54.3%), diabetes medications (65/140, 46.4%), and renin angiotensin aldosterone inhibitors (40/140, 28.6%). The most common PIMs identified among study participants were PPIs (55/76 users; 72.4%), diabetes medications in the context of tight glycemic control (HBA1C <7.5%; 36/65 users; 55.4%), docusate (27/27 users; 100%), gabapentinoids (27/36 users; 75%), and combinations of antiplatelets and/or anticoagulants (22/97 users; 22.7%).

The most common PIMs deprescribed in the control and intervention groups are shown in Figure 2. In particular, the intervention resulted in higher proportions of deprescribing (1) docusate (50% vs 35.3%), (2) diabetes medications (42.3% vs 39.1%), and (3) PPIs (17.2% vs 11.5%) compared with the control arm. Gabapentinoids were deprescribed more frequently in the control group than in the intervention group (42.9% vs 15.4%).

Figure 3 outlines PIMs stratified by risk category, both overall in the subset that was deprescribed. In the control arm, 47% (39/83) of high-risk, 42.3% (33/78) of intermediate-risk, and 40.8% (20/49) of low-risk PIMs were stopped. Of the PIMs identified in the intervention, 59.8% (52/87) of high-risk, 54.8% (34/62) of intermediate-risk, and 62.5% (35/56) of low-risk PIMs were deprescribed.

The outcomes of deprescription are summarized in Table 3. The intervention and control groups did not differ in terms of readmissions or number of adverse events, including ADEs. There were 3 ADEs in the control period, which consisted of 2 gastrointestinal (GI) bleeds and 1 musculoskeletal-related injury. The intervention phase had 2 ADEs: 1 GI

Table 1. Patient Background Characteristics and Most Common Comorbidities.

	Intervention (n = 70)	Control (n = 70)
Age at admission (median, IQR)	73 (68.7-84.9)	76 (68.7-82)
Females	23 (32.9%)	25 (35.7%)
Admitted from long-term care	2 (2.9%)	6 (8.6%)
Previous admissions in the last year (median, IQR)	0 (0-1)*	1 (0-2)*
History of ≥20 pack-years	17 (24.3%)	19 (27.1%)
Hypertension	59 (84.3%)	58 (82.9%)
Diabetes mellitus	48 (68.6%)	46 (65.7%)
Ischemic heart disease	40 (57.1%)	31 (44.3%)
Dyslipidemia	31 (44.3%)	33 (47.1%)
Anemia	33 (47.1%)	30 (42.9%)
Congestive heart failure	33 (47.1%)	22 (31.4%)
Valvulopathy	27 (38.6%)	21 (43.8%)
Atrial fibrillation	24 (34.3%)	20 (28.6%)
Diabetic nephropathy	25 (35.7%)	15 (21.4%)
Hypothyroidism	21 (30.0%)	17 (24.3%)
Peripheral vascular disease	24 (34.3%)**	12 (17.1%)**
Gout	19 (27.1%)	14 (20.0%)
Gastrointestinal hemorrhage	18 (25.7%)	15 (21.4%)
Ischemic stroke	15 (21.4%)	14 (20.0%)
Chronic obstructive pulmonary disease	17 (24.3%)	11 (15.7%)

Note. IQR = interquartile range.
*$P < .05$ Mann-Whitney *U* test. **$P < .05$ chi-square test.

Table 2. Overview of PIMs.

	Intervention (n = 70)	Control (n = 70)	*P* value
Number of home medications per patient (median, IQR)	13 (10-16)	14 (10-18)	.178
Patients with ≥10 medications	54 (77.1%)	57 (81.4%)	.532
Patients with ≥1 PIM identified	66 (94.3%)	65 (92.9%)	.730
Number of PIMs identified per patient (median, IQR)	2.5 (1.7-4)	2.5 (1-4)	.946
Patients with ≥1 PIM stopped	32 (48.5%)	25 (38.5%)	.247
Number of PIMs deprescribed per patient (median, IQR)	0 (0-1.2)	0 (0-1)	.123
Total PIMs identified	205	212	.584
Number of PIMs stopped	59 (28.8%)	41 (19.3%)	<.02

Note. PIMs = potentially inappropriate medications; IQR = interquartile range.

bleed and 1 patient with weakness and confusion. Both GI bleeds in the control arm were attributed to a single prescribed antiplatelet agent, and the GI bleed in the intervention arm was attributed to a combination of 2 prescribed antiplatelets agents.

Discussion

Our study highlights the prevalence of polypharmacy in patients on dialysis and the role that deprescribing decision support can serve to help alleviate the medication burden for these patients. Deprescribing is often a time-consuming and challenging process, particularly in patients with multiple comorbidities, such as ESKD. MedSafer highlights opportunities for deprescribing to clinicians.

The potential utility of an electronic deprescribing tool such as MedSafer for patients on dialysis is considerable, given 4 out of every 5 patients in this cohort were taking more than 10 medications and 93.6% of individuals had at least one PIM identified. The median number of PIMs per patient in the entire study population was 2.5 (IQR 1-4), which provides sufficient opportunity for deprescribing.

The effect size of the intervention was higher in the entire MedSafer population than in the hemodialysis subgroup. There are a few hypotheses to explain this: first, this could be a matter of power. The dialysis group is much smaller than the overall trial population. Second, we highlighted PIMs, and clinicians may have independently judged that these medications were in fact more appropriate in the dialysis population than in the general MedSafer population. Or

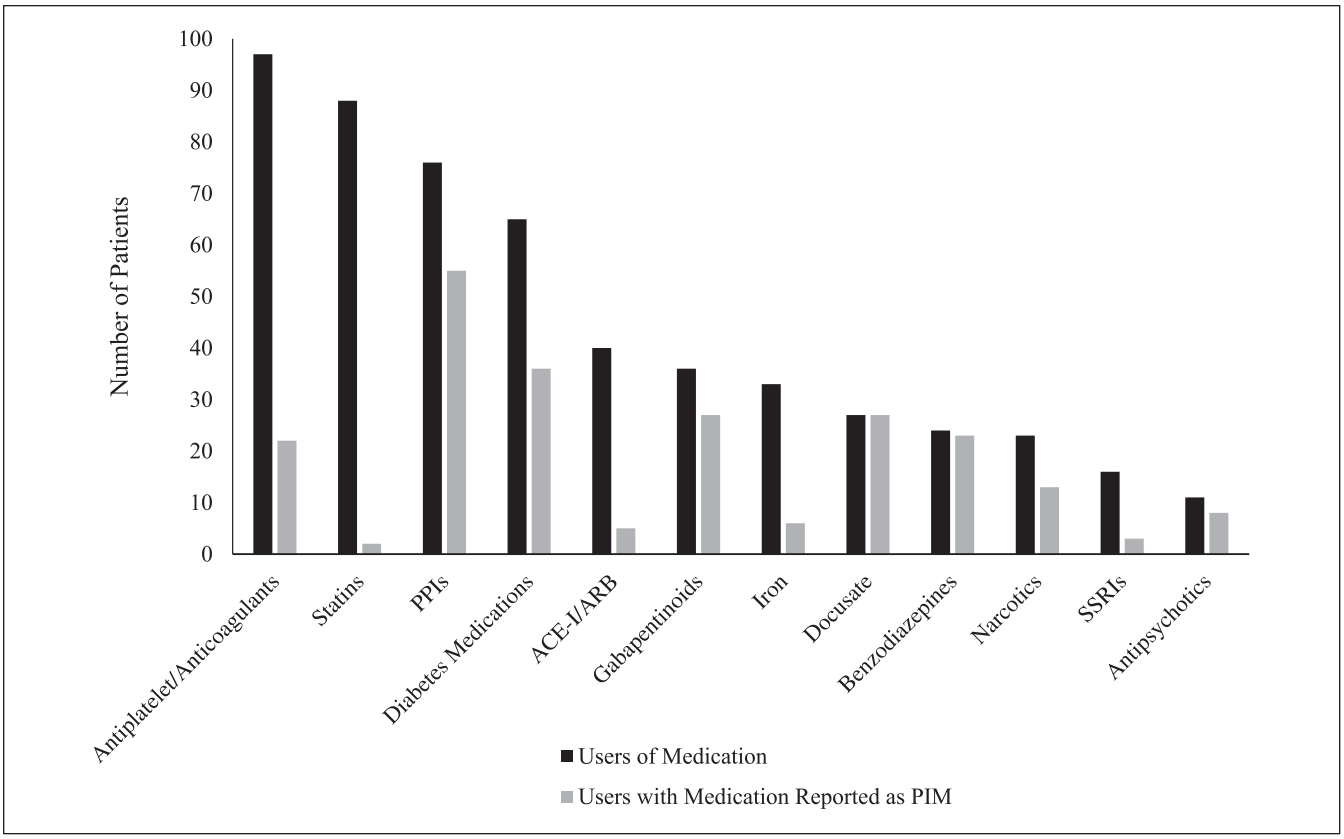

Figure 1. Frequency of drugs consumed in cohort (n = 140) and the proportion of flagged PIMs.
Note. PIM = potentially inappropriate medication; PPIs = proton pump inhibitors; ACE-I/ARB = angiotensin converting enzyme inhibitors/angiotensin receptor blockers; SSRIs = selective serotonin reuptake inhibitors.

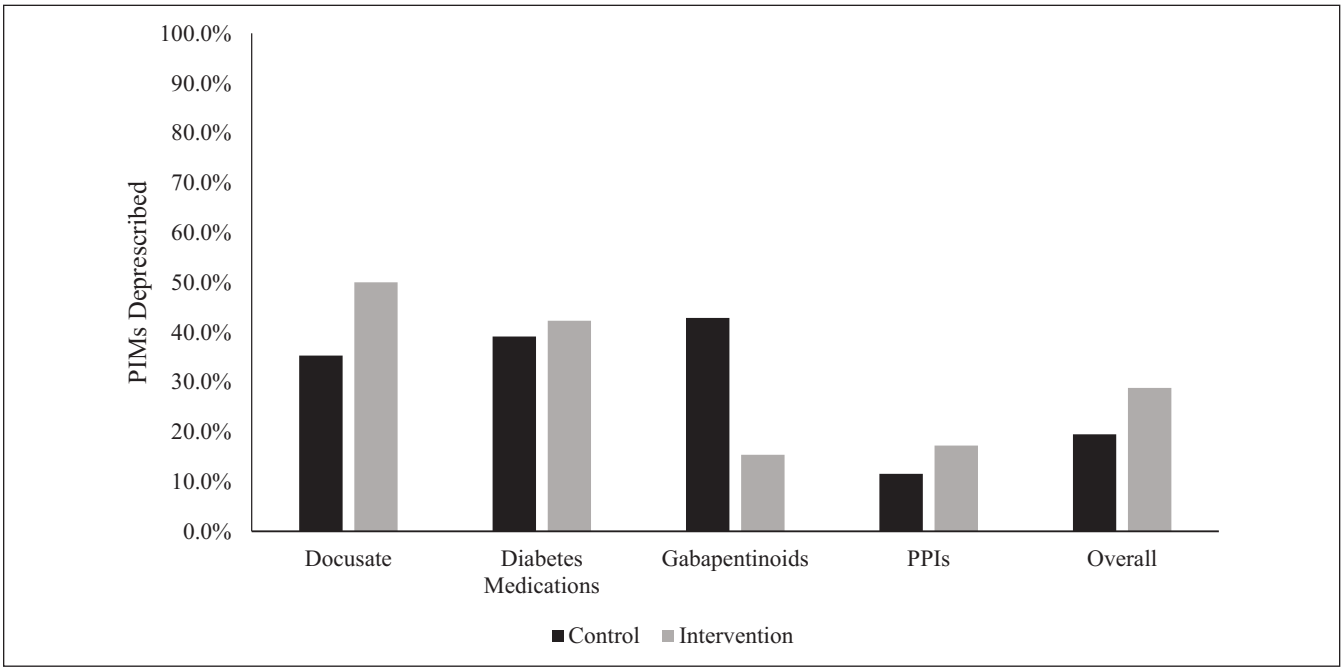

Figure 2. Most common PIMs/PIM classes and the deprescription proportions in the control versus intervention groups.
Note. PIMs = potentially inappropriate medications; PPIs = proton pump inhibitors.

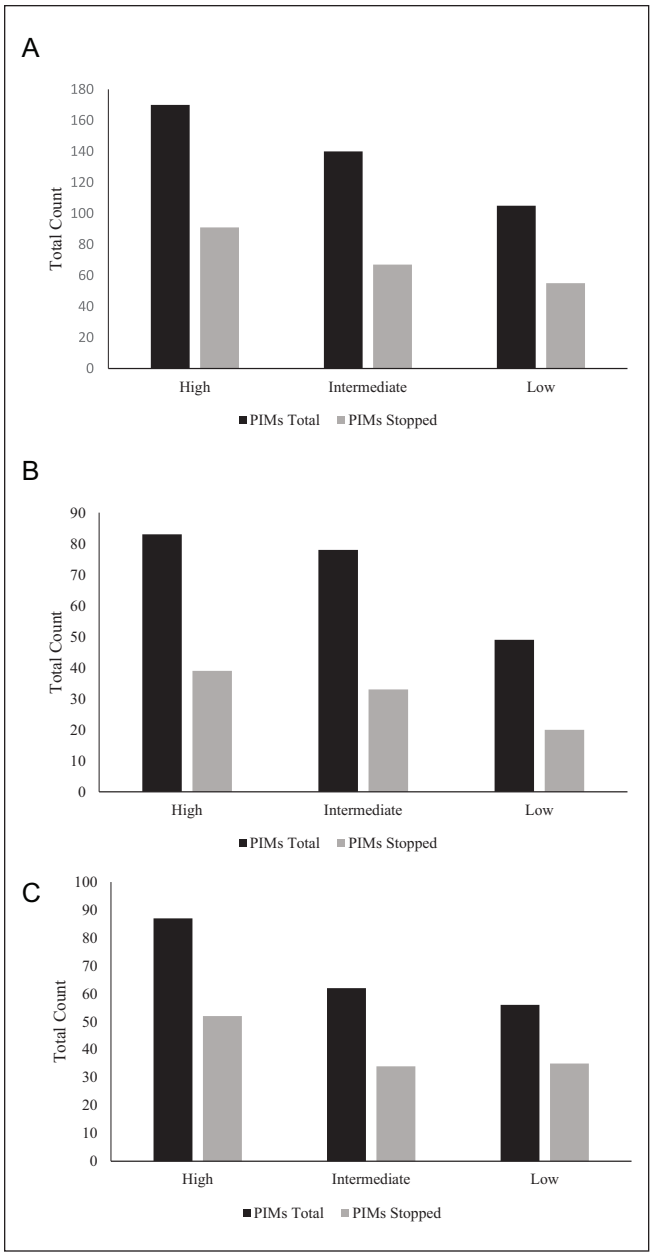

Figure 3. Total count of high-, intermediate-, and low-risk PIMs identified and deprescribed in the (A) whole cohort, (B) control, and (C) intervention group.
Note. PIMs = potentially inappropriate medications.

third, current guidelines for deprescribing need to be adapted for the dialysis population to make the recommendations more specific for this population. We believe this third point is highly relevant and has added recently published dialysis-specific deprescribing algorithms to MedSafer. Future interventional studies are planned to examine whether the addition of these specific rules leads to higher rates of deprescribing.

During the intervention phase, the proportion of PIMs deprescribed increased by about 10%, meaning that for every 10 PIMs that were reported, an additional PIM was deprescribed compared with usual care. Although there were more PIMs deprescribed in the intervention group, the number of active PIMs at discharge per patient was similar. This is likely due to the small sample size analyzed in the study.

Encouragingly, the effect of the intervention lasted following discharge; in the main MedSafer study, the vast majority (92.8%) of deprescribed medications remained stopped at 30 days.[23] Importantly, the intervention was not associated with higher rates of hospital readmissions, adverse events, or ADEs in the first month following discharge, which should serve to reassure clinicians that deprescribing during an acute care hospitalization could be for patients on hemodialysis.

The intervention was also effective across all risk categories of PIMs. While high-risk PIMs are clearly important to stop as they may increase the risk of ADEs,[29] stopping intermediate-risk and low-risk PIMs is also critical to reduce pill burden, increase quality of life, and decrease costs for patients and society.[11,30]

Studies analyzing deprescription for patients on dialysis are scarce despite having one of the highest pill burdens of all patient demographics.[11] Patients on dialysis are also more vulnerable to adverse events secondary to polypharmacy due to reduced drug metabolism.[31] A small quality improvement study was developed and validated their own deprescription tool for patients on a hemodialysis ward. Only 5 target medication classes were identified (quinines, diuretics, alpha-1 blockers, PPIs, and statins). After the tool was applied, 31 of 40 target medications were deprescribed and only 5 of 31 medications were re-prescribed at 6-month follow-up.[32] The high rates of deprescription in this quality improvement intervention are encouraging and may reflect a concerted effort for a small number of drug classes, as well as the development of a tool that was specific to hemodialysis patients.

Recently, the first set of deprescribing algorithms for patients on hemodialysis was developed to reduce polypharmacy. A total of 9 medication-specific algorithms were created for alpha-1 blockers, benzodiazepines, gabapentinoids, loop diuretics, PPIs, prokinetic agents, quinines, statins, and urate-lowering agents (ULAs).[33]

The general rules contained in MedSafer included several of the aforementioned drug classes. However, these new guidelines had some additional rules (related to statins, ULAs, loop diuretics, and alpha-1 blockers) that could increase the number of PIMs identified by MedSafer in patients receiving dialysis. We have since updated MedSafer to incorporate these additional rules and are conducting a prospective interventional deprescribing study in outpatient dialysis units in Montreal, Canada.

The addition of CKD-specific rules that address the marginal benefits of both acetylsalicylic acid in primary prevention and long-term dual antiplatelet therapy in secondary prevention of thrombotic events in patients on dialysis could

Table 3. Patient Outcomes of Deprescription.

	Intervention (n = 70)	Control (n = 70)	*P* value
Readmissions	12 (17.1%)	15 (21.4%)	.520
Active PIMs at discharge (median, IQR)	2 (2-4)	3 (2-4)	.367
Adverse event post-discharge	22 (31.4%)	23 (32.9%)	.856
Days to adverse event post-discharge (median, IQR)	10 (6.7-23.2)	9 (4-14)	.295
Patients with an ADE	3 (4.3%)	2 (2.9%)	.649
GI bleed ADE attributed to antiplatelet(s)	2 (66.7%)	1 (50%)	.559

Note. PIMs = potentially inappropriate medications; ADE = adverse drug event; IQR = interquartile range; GI = gastrointestinal.

be very beneficial. Antithrombotics were the most prescribed medication class in this study with 69.3% of the cohort taking at least one antithrombotic; nearly a quarter of all users had at least one of these identified as a PIM. Crafting-designated deprescribing guidance for antithrombotics in dialysis will be important as the most common ADE post-discharge was GI hemorrhage requiring hospitalization, attributed to one or more antiplatelet agents. Furthermore, other studies have found that warfarin, for example, is associated with similar harms and benefits given an overall higher risk of bleeding in patients on dialysis.[34,35]

Gabapentinoids are a frequently prescribed medication in dialysis despite being associated with significantly higher risks for developing altered mental status, falls, and fractures in this population.[36] There are several alternative pharmacologic and non-pharmacologic approaches to gabapentinoids for managing neuropathic pain, pruritis, and restless leg syndrome. Three quarters of gabapentinoid users were flagged as potentially inappropriate; unexpectedly, this medication class was deprescribed more frequently in the control arm. This finding could be due to random differences in the initial indication of the gabapentinoid prescription and the ease of finding a suitable alternative, or the consequence of a statistical outlier as several different medications were considered in this study. We have now updated MedSafer to include a more targeted message (in addition to the existing generic message) that clearly explains why this medication class is associated with harmful side effects in dialyzed patients.

There are limitations to our study. First, this was a post hoc exploratory analysis of endpoints not previously specified in the original trial, and as such there is always a chance of finding chance associations. However, the primary trial also demonstrated significant results using MedSafer as a deprescribing intervention for a general population of patients with polypharmacy.[23] Of note, the primary trial did not stratify by hemodialysis status; while the prevalence of most underlying comorbidities was statistically similar between groups (Table 1), it is important to interpret results with this in mind. Second, only 140 individuals were included in this study, which may affect the scalability and generalizability of our results; however, this sample was derived from a large group of approximately 5700 hospitalized patients across several institutions and provinces which were randomized to control or intervention group. Despite the current study's small sample size, to our knowledge, this is the largest randomized controlled deprescription intervention in a population of patients undergoing maintenance hemodialysis. Finally, as discussed, future versions of the software would benefit from integrating validated tools for shared decision-making for many of the medications that lack evidence on the harms and benefits in dialysis populations, particularly antithrombotics.

Conclusion

It is important to periodically evaluate and reweigh the risks and benefits of medications for all patient populations over time, with the development of new comorbidities, after experiencing functional decline, or when goals of care are adjusted. Based on this secondary analysis of our large clinical trial, electronic decision support can facilitate deprescribing in patients receiving dialysis. Reducing medication overload in the dialysis population could help improve quality of life, in addition to minimizing iatrogenic morbidity and mortality. Larger scale studies with long-term follow-up are needed to further establish the safety of deprescribing in this population and to demonstrate reductions in ADEs. Future studies that our group is planning will implement dialysis-specific rules to explore whether these will increase the effectiveness of MedSafer for electronically guided deprescribing.

Ethics Approval

Patients consented to have their data used for research on polypharmacy in the initial consent form that was provided for the primary MedSafer study. The data were collected and anonymized in compliance with the Research Ethic Boards of each of the 11 institutions. This secondary analysis did not require any novel data collection. Participants also consented to use of administrative data for up to 12 months, though this was not used for the present analysis.

Author Contributions

Conceptualization—J.M., E.B.C., T.P., N.T., E.G.M.; methodology—J.M., T.C.L., E.G.M.; validation—J.M., T.C.L.; formal analysis—J.M.; investigation—all authors; resources—E.G.M.; data

curation—J.M., T.C.L., E.G.M.; writing—original draft—J.M., E.G.M.; writing—review and editing—all authors; visualization—J.M., E.G.M.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Drs McDonald and Lee are the cocreators of MedSafer and own MedSafer CORP. The intellectual property is shared with McGill University. MedSafer was funded by grants from the Canadian Institutes for Health Research, the Canadian Frailty Network, and the Centre for Ageing and Brain Health Innovation. Drs McDonald and Lee receive salary support for research from the Fond de recherche santé Québec. The other authors have no disclosures to declare.

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