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Proton Pump Inhibitors Use in Kidney Transplant Recipients: A Population-Based Study

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Abstract

Background: Kidney transplant recipients are commonly prescribed proton-pump inhibitors (PPIs), but due to concern for polypharmacy, chronic use should be limited.

Objective: The objective was to describe PPI use in kidney transplant recipients beyond their first year of transplant to better inform and support deprescribing initiatives.

Design: We conducted a retrospective, population-based cohort study using linked health care databases.

Setting: This study was conducted in Alberta, Canada.

Patients: We included all prevalent adult, kidney-only transplant recipients between April 2008 and December 2017 who received their transplant between May 2002 and December 2017.

Measurements: The primary outcome was ongoing or new PPI use and patterns of use, including frequency and duration of therapy, and assessment of indication for PPI use.

Methods: We ascertained baseline characteristics, covariate information, and outcome data from the Alberta Kidney Disease Network (AKDN). We compared recipients with evidence of a PPI prescription in the 3 months prior to study entry to those with a histamine-2-receptor antagonist (H2Ra) fill and those with neither.

Results: We identified 1823 kidney transplant recipients, of whom 868 (48%) were on a PPI, 215 (12%) were on an H2Ra, and 740 (41%) were on neither at baseline. Over a median follow-up of 5.4 years (interquartile range [IQR] = 2.6-9.3), there were almost 45 000 unique PPI prescriptions dispensed, the majority (80%) of which were filled by initial PPI users. Recipients who were on a PPI at baseline would spend 91% (IQR = 70-98) of their graft survival time on a PPI in follow-up, and nephrologists were the main prescribers. We identified an indication for ongoing PPI use in 54% of recipients with the most common indication being concurrent antiplatelet use (26%).

Limitations: Our kidney transplant recipients have access to universal health care coverage which may limit generalizability. We identified common gastrointestinal indications for PPI use but did not include rare conditions due to concerns about the validity of diagnostic codes. In addition, symptoms suggestive of reflux may not be well coded as the focus of follow-up visits is more likely to focus on kidney transplant.

Conclusions: Many kidney transplant recipients are prescribed a PPI at, or beyond, the 1-year post-transplant date and are likely to stay on a PPI in follow-up. Almost half of the recipients in our study did not have an identifiable indication for ongoing PPI use. Nephrologists frequently prescribe PPIs to kidney transplant recipients and should be involved in deprescribing initiatives to reduce polypharmacy.

Abrégé

Contexte: On prescrit couramment des inhibiteurs de la pompe à protons (IPP) aux receveurs d'une greffe rénale; une pratique qui devrait cependant être limitée en raison de préoccupations liées à la polypharmacie.

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Objectif: Décrire l'utilisation des IPP chez les receveurs d'une greffe rénale au-delà de la première année post-greffe, afin de mieux informer et de soutenir les initiatives de déprescription.
Type d'étude: Étude de cohorte populationnelle rétrospective réalisée à partir des bases de données couplées du système de santé.
Cadre: Alberta, Canada.
Sujets: Nous avons recueilli les données d'avril 2008 à décembre 2017 de tous les adultes qui avaient reçu un rein seulement entre mai 2002 et décembre 2017.
Mesures: Le principal critère de jugement était la prise continue — ou une nouvelle ordonnance — d'IPP et les modalités d'utilisation, notamment la fréquence et la durée du traitement, ainsi que l'indication pour la prescription d'IPP.
Méthodologie: Nous avons vérifié les caractéristiques initiales, les informations covariées et les données sur les résultats colligées dans l'Alberta Kidney Disease Network (AKDN). Nous avons comparé des receveurs présentant des preuves d'une prescription d'IPP au cours des trois mois précédant l'entrée dans l'étude à des patients avec une ordonnance d'antagonistes des récepteurs de l'histamine-2 (aRH2), ainsi qu'à des patients n'ayant aucune de ces prescriptions.
Résultats: Nous avons identifié 1 823 receveurs d'une greffe rénale; 868 (48 %) recevaient un IPP, 215 (12 %) recevaient un aRH2 et 740 (41 %) ne recevaient aucun traitement à l'inclusion. Au cours d'un suivi médian de 5,4 ans (intervalle interquartile [IIQ]: 2,6-9,3), près de 45 000 ordonnances uniques d'IPP ont été délivrées, dont la majorité (80 %) avait été remplie par des utilisateurs initiaux d'IPP. Les receveurs qui prenaient des IPP à l'inclusion avaient passé 91 % (IIQ: 70-98) de leur temps de survie du greffon à prendre un IPP durant la période de suivi, et ces médicaments avaient été majoritairement prescrits par des néphrologues. Une indication justifiant l'utilisation continue d'un IPP était présente chez 54 % des receveurs; la plus courante étant l'utilisation concomitante d'un agent antiplaquettaire (26 %).
Limites: Les receveurs inclus dans notre étude ont accès à une couverture médicale universelle, ce qui peut limiter la généralisabilité des résultats. Nous avons repéré des indications gastro-intestinales courantes pour l'utilisation d'IPP, mais nous n'avons pas inclus les affections rares en raison de préoccupations concernant la validité des codes diagnostiques. Aussi, les symptômes évocateurs d'un reflux pourraient ne pas être bien codés, car les visites de suivi sont plus susceptibles de porter sur la transplantation rénale.
Conclusion: De nombreux receveurs d'une greffe rénale se voient encore prescrire un IPP dans l'année suivant la transplantation, ou au-delà, et sont susceptibles de continuer d'en prendre pendant le suivi. Près de la moitié des receveurs de notre étude n'avaient pas d'indication clairement identifiable de prendre un IPP en continu. Les néphrologues prescrivent fréquemment des IPP aux receveurs d'une greffe rénale et devraient être impliqués dans les initiatives de déprescription visant à réduire la polypharmacie.

Keywords
Alberta, Choosing Wisely, epidemiology, kidney transplantation, population-based research

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Introduction

Proton-pump inhibitors (PPIs) are frequently prescribed medications in the ambulatory care setting (8%-10% of all prescriptions).[1,2] The Canadian Association of Gastroenterology recommends that chronic PPI use (defined as >8 weeks) be limited to patients with specific indications including prior gastrointestinal bleed (GIB) or concurrent non–steroidal anti-inflammatory drug (NSAID) use.[3] Choosing Wisely Canada suggests discontinuation of PPI should be trialed at least once per year due to concerns of adverse events.[3-5] As with the general population, long-term PPI use in kidney transplant recipients has been linked to complications, such as hip fractures, kidney dysfunction, and mortality.[5]

In the kidney transplant recipient population, PPIs are often prescribed immediately post-transplant for prophylaxis against peptic ulcer disease caused by high-dose prednisone or dyspepsia due to mycophenolate acid. In addition to potential complications of chronic PPI use, increased pill burden in this population is associated with non-adherence and poor quality of life.[6,7] Therefore, reassessment of PPI use beyond the first year of transplant, when immunosuppression dosage is typically at its lowest, may be considered to minimize complications and reduce pill burden. To better inform and support deprescribing initiatives, we performed a retrospective population–based study to quantify and characterize ongoing PPI use in kidney transplant recipients beyond their first year of transplant.

Methods

Design and Setting

We conducted a retrospective population–based cohort study using linked health care databases within the Alberta Kidney

Disease Network (AKDN), which incorporates data from Alberta Health, the provincial health ministry.[8] Over 99% of Alberta residents are registered with Alberta Health and have universal access to hospital care and physician services. We followed guidelines for the reporting of observational studies (Supplemental Table S1) and a protocol approved by the research ethics boards at the University of Alberta and the University of Calgary, with a waiver of patient consent.

Data Sources

We ascertained baseline characteristics, covariate information, and outcome data from the AKDN records (Supplemental Table S2). The Alberta Health database contains information on demographic data, vital statistics, and diagnostic and procedural information for inpatient and outpatient physician services. We identified kidney transplant recipients from the Alberta Kidney Care (AKC) North and South databases, which provide care to all patients in the province treated with kidney replacement therapy, including dialysis and kidney transplantation. The Pharmaceutical Information Network (PIN) captures prescription drug information on all medications dispensed in Alberta since January 1, 2008, and includes information on drug dosage, day supply, and prescribing physician specialty. The PIN database was used to identify prescription fills for PPIs and histamine-2-receptor antagonists (H2Ras) as well as other relevant medications including immunosuppression, antiplatelets, anticoagulants, and NSAIDs (Supplemental Table S3). These databases have been previously used for research on health services and health outcomes in the kidney transplant recipient population.[9-13]

Population

We included all prevalent adult, kidney-only transplant recipients between April 1, 2008 and December 31, 2017 who received their transplant between May 1, 2002 and December 31, 2017 in Alberta, Canada (accrual period). We excluded pediatric recipients (<18 years old) and recipients of a previous non-kidney organ transplant or a simultaneous multi-organ transplant, including kidney-pancreas. Recipients were excluded if they died, emigrated from the province, or experienced graft failure (defined as return to maintenance dialysis) within the first year of their transplant or prior to April 1, 2008. Thus, to be included in the study, recipients must have survived to April 1, 2008 or the 1-year post-transplant date with a functioning graft, whichever came later (designated the index date). Recipients were followed from the index date until the first of death, graft failure (defined as return to maintenance dialysis or re-transplantation), emigration, or end of study period (March 31, 2019). The last eligible transplant date for cohort entry was December 31, 2017 for a last designated index date of December 31, 2018. In Alberta, the rate of emigration is <1%.[14,15] The cohort creation is shown in Supplemental Figure S1, and a schematic of the study design is presented in Supplemental Figure S2.

Proton-Pump Inhibitor/Histamine-2-Receptor Antagonist Prescriptions

We identified transplant recipients who had evidence of a PPI or H2Ra prescription in the 3 months prior to and including their index date. For most recipients, immunosuppression around the first year of transplant, including prednisone, should be at the lowest dose and so PPI and H2Ra use may no longer be indicated. If a patient had been prescribed a PPI prior to this, but was not on a PPI at their index date, they were not considered to be on a PPI.[16] Proton-pump inhibitors of interest included those commonly prescribed in Canada: pantoprazole, omeprazole, lansoprazole, rabeprazole, esomeprazole, and dexlansoprazole. Chronic PPI use was defined as a prescription fill of greater than 8 weeks in duration.[3] Histamine-2-receptor antagonists prescribed in Canada included ranitidine, cimetidine, famotidine, and nizatidine. We excluded recipients who had evidence of both PPI and H2Ra prescription fills in the 3 months before their index date to compare mutually exclusive groups (n = 17).

Baseline Characteristics

Baseline characteristics were obtained at the index date. Demographic data such as age and sex were determined from the Alberta Health administrative database. While specific race/ethnic groups cannot be identified in this database, more than 75% of the Alberta population is white.[17] Postal codes were linked to the Canadian Census using the Postal Code Conversion file to determine median neighborhood household income quintile (level 5 being the highest) as well as rural vs urban location of residence. Baseline characteristics were complete except for income and residence location (<1% of recipients). Those with missing data for income were re-categorized into the middle (third) quintile and those with missing data for location of residence were re-categorized as urban.

We used the AKC North and South program databases for transplant-related data such as pre-transplant dialysis modality, dialysis duration, and time since transplant. Graft function at the index date was determined by calculating the estimated glomerular filtration rate (eGFR, based on the 2009 Chronic Kidney Disease Epidemiology Collaboration equation) using the mean of all outpatient serum creatinine measurements in the 3 months prior to and including the index date.[18] Albuminuria was defined by all outpatient random spot urine measurements in the 3 months prior to and including the index date (albumin-creatinine ratio [ACR], protein-creatinine ratio [PCR], or urine dipstick). If multiple albuminuria measurements were available, the median value

was calculated. Albuminuria was categorized based on the KDIGO (Kidney Disease: Improving Global Outcomes) Chronic Kidney Disease (CKD) definition as normal/mild (A1: ACR <3 mg/mmol, PCR <150 mg/g, or dipstick negative or trace), moderate (A2: ACR 3-30 mg/mmol, PCR 150-500 mg/g, or dipstick 1+), or heavy (A3: ACR >30 mg/mmol, PCR >500 mg/g, dipstick ≥2+), as previously described.[9]

Comorbidities were identified by the presence of one or more diagnostic codes from April 1994 up to and including the index date, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Statistical Classification of Diseases, Tenth Revision (ICD-10) coding algorithms for physician claims and hospitalization data.[19-21] Comorbidities were defined using validated algorithms, whenever possible (Supplemental Table S2). We identified comorbidities for which PPI use may be indicated including gastroesophageal reflux disease (GERD), peptic ulcer disease, *Helicobacter pylori* infection, prior upper GIB, and concurrent NSAID, antiplatelet, or anticoagulant use.[22-24]

For the index prescription fill, we reported the type of PPI or H2Ra used, the daily dose prescribed, and the prescribing physician specialties. Proton-pump inhibitor dose was categorized as low, standard, or high dose (Supplemental Table S4).[25] High-dose PPI use is often indicated in the setting of recent upper GIB and *H pylori* infection.[25] Finally, the PIN database was used to identify relevant baseline medication use, including immunosuppressive agents, antiplatelet, anticoagulant, NSAIDs, and cardiac medications (Supplemental Table S3).

Outcomes

The primary outcome was evidence of a PPI prescription fill in follow-up. At the prescription level, we described patterns of PPI use including the total number of PPI prescriptions in follow-up, type of PPI prescribed, the daily dose prescribed, the median duration of each prescription, the number of chronic PPI prescriptions, and the specialty of the physician prescriber. At the recipient level, we assessed the median number of PPI prescriptions per recipient and how many recipients were using PPI chronically. To assess overall exposure duration, we determined the percentage of graft survival time in follow-up that the recipient was on a PPI defined as: ([total days supplied of PPI]/[total days of graft survival in follow-up]) × 100%. Based on the last prescription fill in follow-up, we also determined the proportion of recipients who had an identifiable gastrointestinal indication for ongoing PPI use. We assessed for the concurrent use of medications in the 3 months prior to the last prescription in follow-up, the presence of GERD, peptic ulcer disease, and/or *H pylori* infection in the 3 years prior, and any history of upper GIB since 1994.

Statistical Analysis

Descriptive variables were expressed as counts with percentages and medians with interquartile ranges (IQRs), where appropriate. We compared baseline characteristics of recipients with an index prescription for a PPI to those with an H2Ra and neither using χ^2 and Kruskal-Wallis test, where appropriate. Statistical analyses were performed using R version 4.1.2 (R-project.org). A P-value of <.05 was used to define statistical significance.

Results

Baseline Characteristics

There were 1823 prevalent adult kidney transplant recipients included in the study. Of these, 868 (48%) were on a PPI, 215 (12%) were on an H2Ra, and 740 (41%) were on neither therapy at their index date. The patient characteristics are shown in Table 1. The median age was 53 years (IQR = 41-63) and 36% were female. Median baseline eGFR was 59 mL/min/1.73 m^2 (IQR = 46-72), and this was not significantly different between the 3 groups. At baseline, there was an indication for PPI use in 55% of the PPI group ($P < .001$). The recipients on a PPI were older, had more comorbidities, and more likely to have an indication for PPI use compared with the recipients on neither drug at the index date ($P < .001$). An identifiable indication did not differ between the PPI and H2Ra groups ($P = .6$). Most initial PPI prescriptions were for pantoprazole (65%), were standard dose (68%), and prescribed by nephrologists (64%) (Supplemental Table S5). All recipients in the H2Ra group were prescribed ranitidine (100%). The PPI group was more likely to have a higher median number of prescriptions compared with the H2Ra and neither groups (18 vs 14 vs 7, respectively, $P \leq .001$).

PPI Use in Follow-up: Prescription-Level Analysis

The median follow-up time was 5.4 years (IQR = 2.6-9.3). Overall, there were 44 917 unique PPI prescriptions in follow-up with 35 730 (80%) being prescribed to the recipients on a PPI at baseline (Table 2). Pantoprazole was the most prescribed PPI, and nephrologists were the main prescribers of PPIs in all 3 groups.

PPI Use in Follow-up: Recipient-Level Analysis

Kidney transplant recipients who were on a PPI at baseline were more likely to be prescribed a PPI in follow-up compared with those who were on an H2Ra or neither (96% vs 27% vs 46%, respectively) (Table 3 and Figure 1). These recipients also had a higher median number of PPI prescriptions (26 vs 7 vs 10, respectively, $P < .001$). The PPI group spent a significantly higher percentage of their graft survival time in follow-up on a PPI compared to the H2Ra and neither

Table 1. Baseline Characteristics of Kidney Transplant Recipients With a Prescription for a PPI, H2Ra, or Neither at the Index Date.

Characteristic	Total cohort (N = 1823)	PPI user (n = 868)	H2Ra user (n = 215)	Neither (n = 740)	*P*
Demographics					
Age, *y*	53.3 [41.0-62.5]	55.8 [44.3-63.9]	53.0 [39.9-61.4]	50.2 [37.8-60.7]	<.001
≥65	343 (19)	198 (23)	41 (19)	104 (14)	<.001
Female	660 (36)	306 (35)	76 (35)	278 (38)	.6
Socio-economic status					
Lowest quintile	440 (24)	227 (26)	41 (19)	172 (23)	.03
Second quintile	376 (21)	170 (20)	45 (21)	161 (22)	
Middle quintile	368 (20)	188 (22)	49 (23)	131 (18)	
Fourth quintile	322 (18)	131 (15)	48 (22)	143 (19)	
Highest quintile	317 (17)	152 (18)	32 (15)	133 (18)	
Urban residence	1647 (90)	778 (90)	199 (93)	670 (91)	.4
Distance to transplant center, *km*	22.5 [13.1-109.0]	22.5 [13.5-133.1]	24.0 [13.4-60.2]	22.4 [12.5-97.8]	.3
≤50	1230 (67)	570 (66)	150 (70)	510 (69)	.3
50.1-150	182 (10)	90 (10)	22 (10)	70 (9)	
150.1-300	180 (10)	93 (11)	25 (12)	62 (8)	
>300	231 (13)	115 (13)	18 (8)	98 (13)	
Transplant-related characteristics					
Pre-transplant modality					
Hemodialysis	1058 (58)	552 (64)	119 (55)	387 (52)	<.001
Peritoneal dialysis	459 (25)	206 (24)	62 (29)	191 (26)	
Pre-emptive	186 (10)	75 (9)	29 (13)	82 (11)	
Missing	120 (7)	35 (4)	5 (2)	80 (11)	
Dialysis duration, *y*	2.4 [1.3-3.9]	2.7 [1.6-4.0]	2.5 [1.2-4.6]	2.0 [1.1-3.3]	<.001
Previous kidney transplant	104 (6)	56 (6)	7 (3)	41 (6)	.2
Transplant era					
2002-2006	491 (27)	158 (18)	43 (20)	290 (39)	<.001
2007-2011	532 (29)	286 (33)	60 (28)	186 (25)	
2012-2017	800 (44)	424 (49)	112 (52)	264 (36)	
Transplant to index date, *y*	1.0 [1.0-1.5]	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.0 [1.0-2.8]	<.001
Index date					
2008-2010	807 (44)	322 (37)	77 (36)	408 (55)	<.001
2011-2013	329 (18)	186 (21)	34 (16)	109 (15)	
2014-2018	687 (38)	360 (41)	104 (48)	223 (30)	
Index eGFR,[a] mL/min/1.73 m^2	58.9 [46.1-72.0]	58.1 [44.3-72.5]	58.3 [48.6-72.6]	59.8 [47.3-71.2]	.3
>90	121 (7)	65 (7)	14 (7)	42 (6)	.2
60-89	717 (39)	333 (38)	83 (39)	301 (41)	
30-59	804 (44)	398 (46)	103 (48)	303 (41)	
15-29	104 (6)	58 (7)	6 (3)	40 (5)	
<15	14 (1)	6 (1)	0	8 (1)	
Missing	63 (3)	8 (1)	9 (4)	46 (6)	
Albuminuria[a]					
Normal/mild	1473 (81)	733 (84)	171 (80)	569 (77)	<.001
Moderate	167 (9)	76 (9)	25 (12)	66 (9)	
Severe	90 (5)	40 (5)	8 (4)	42 (6)	
Missing	93 (5)	19 (2)	11 (5)	63 (9)	
Comorbidities[b]					
Hypertension	1741 (96)	843 (97)	208 (97)	690 (93)	<.001
Diabetes mellitus	676 (37)	375 (43)	75 (35)	226 (31)	<.001
Myocardial infarction	80 (4)	52 (6)	4 (2)	24 (3)	.004
PCI or CABG	144 (8)	100 (12)	9 (4)	35 (5)	<.001
Heart failure	356 (20)	200 (23)	38 (18)	118 (16)	.001
Atrial fibrillation	131 (7)	80 (9)	10 (5)	41 (6)	.005

(Continued)

Table 1. (Continued)

Characteristic	Total cohort (N = 1823)	PPI user (n = 868)	H2Ra user (n = 215)	Neither (n = 740)	*P*
Stroke or TIA	230 (13)	135 (16)	19 (9)	76 (10)	.001
PVD	269 (15)	165 (19)	34 (16)	70 (9)	<.001
GERD	331 (18)	214 (25)	23 (11)	94 (13)	<.001
Peptic ulcer disease	160 (9)	115 (13)	8 (4)	37 (5)	<.001
Helicobacter pylori	186 (10)	105 (12)	19 (9)	62 (8)	.04
Liver disease	119 (7)	61 (7)	11 (5)	47 (6)	.6
Chronic pulmonary disease	420 (23)	246 (28)	43 (20)	131 (18)	<.001
Dementia	18 (1)	11 (1)	2 (1)	5 (1)	.5
Cancer	285 (16)	151 (17)	35 (16)	99 (13)	.08
Indication for PPI prescription at baseline[c]					
GERD	151 (8)	106 (12)	7 (3)	38 (5)	<.001
Peptic ulcer disease	46 (3)	34 (4)	2 (1)	10 (1)	.001
Helicobacter pylori	111 (6)	61 (7)	12 (6)	38 (5)	.3
Prior upper GIB	211 (12)	138 (16)	20 (9)	53 (7)	<.001
Single/dual antiplatelet	369 (20)	215 (25)	78 (36)	76 (10)	<.001
Anticoagulant	93 (5)	60 (7)	6 (3)	27 (4)	.003
NSAIDs	25 (1)	16 (2)	2 (1)	7 (1)	.3
High-dose prednisone (>10 mg daily)	110 (6)	54 (6)	19 (9)	37 (5)	.1
Any of the above	807 (44)	474 (55)	113 (53)	220 (30)	<.001
Medications[d]					
Median number of prescriptions	12 [7-22]	18 [11-29]	14 [10-24]	7 [3-12]	<.001
Immunosuppression use					
Prednisone	1218 (67)	696 (80)	164 (76)	358 (48)	<.001
Cyclosporine	68 (4)	42 (5)	2 (1)	24 (3)	.02
Tacrolimus	1247 (68)	617 (71)	159 (74)	471 (64)	.001
MMF	545 (30)	281 (32)	26 (12)	238 (32)	<.001
MPA	648 (36)	330 (38)	122 (57)	196 (26)	<.001
Azathioprine	110 (6)	70 (8)	9 (4)	31 (4)	.002
Sirolimus	119 (7)	46 (5)	25 (12)	48 (6)	.003
Other medications					
Single antiplatelet	357 (20)	208 (24)	76 (35)	73 (10)	<.001
Dual antiplatelet[e]	12 (1)	7 (1)	2 (1)	3 (0.4)	.5
Combination therapy	16 (1)	9 (1)	1 (0.5)	6 (1)	.7
ACEi/ARB	640 (35)	345 (40)	85 (40)	210 (28)	<.001
Beta-blocker	590 (32)	355 (41)	84 (39)	151 (20)	<.001
Calcium channel blocker	680 (37)	377 (43)	92 (43)	211 (29)	<.001
Diuretic	300 (16)	186 (21)	28 (13)	86 (12)	<.001
Statin	710 (39)	398 (46)	110 (51)	202 (27)	<.001
Fibrate	23 (1)	15 (2)	3 (1)	5 (1)	.2
Ezetimibe	43 (2)	23 (3)	8 (4)	12 (2)	.1

Note. Data are presented as number (%) or median [interquartile range]. The index date is the later of either April 1, 2008 or the 1-year post-transplant date. PPI = prescribed proton-pump inhibitor; H2Ra = histamine-2-receptor antagonist; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; TIA = transient ischemic attack; PVD = peripheral vascular disease; GERD = gastroesophageal reflux disease; GIB = gastrointestinal bleed; NSAID = non–steroidal anti-inflammatory drug; MMF = mycophenolate mofetil; MPA = mycophenolic acid; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ACR = albumin-creatinine ratio.

[a]Median values calculated using mean eGFR and median albuminuria (ACR, PCR, or urine dipstick) for each recipient, using all outpatient measurements in the 3-month look-back window prior to and including the index date.

[b]Assessed by the presence of diagnostic or procedural codes, based on validated algorithms, where applicable, from April 1994 up to and including the index date (Supplemental Table S2).

[c]Assessed on the index date with a look-back window of 3 years for GERD, peptic ulcer disease, and *Helicobacter pylori*, since 1994 for any history of upper GIB, and 3 months for concurrent medication use.

[d]Medications were identified as any prescription filled during the 3-month look-back window prior to and including the index date.

[e]Dual antiplatelet use was defined as evidence of either a combination pill with 2 antiplatelet formulations (eg, ASA-dipyridamole tablet) or prescriptions for 2 different antiplatelets in the 3-month look-back window prior to and including the index date. Combination therapy was defined as evidence of a prescription fill for ≥1 antiplatelet and ≥1 anticoagulant in the 3-month look-back window prior to and including the index date.

Table 2. PPI Prescriptions in Follow-Up in Kidney Transplant Recipients on a PPI, H2Ra, or Neither at Baseline.

Prescription-level analysis	PPI user (n = 35730)	H2Ra user (n = 1208)	Neither (n = 7979)
Type of PPI			
Pantoprazole	22208 (62)	819 (68)	4090 (51)
Omeprazole	9997 (28)	242 (20)	2822 (35)
Lansoprazole	2239 (6)	104 (9)	413 (5)
Rabeprazole	761 (2)	38 (3)	264 (3)
Esomeprazole	467 (1)	5 (0.4)	377 (5)
Dexlansoprazole	58 (0.2)	0	13 (0.2)
Dose category[a]			
Low dose	134 (0.4)	3 (0.2)	64 (1)
Standard dose	24733 (69)	730 (60)	5075 (64)
High dose	10863 (30)	475 (39)	2840 (36)
Duration			
Median days supplied	28 [14-30]	28 [14-30]	30 [14-90]
Chronic prescriptions[b]	8251 (23)	212 (18)	2969 (37)
Prescriber			
General practice	5477 (15)	413 (34)	1284 (16)
Nephrologist	23795 (67)	542 (45)	4938 (62)
Gastroenterologist	96 (0.3)	5 (0.4)	259 (3)
Surgery[c]	760 (2)	32 (3)	230 (3)
Other	678 (2)	64 (5)	145 (2)
Missing	4924 (14)	152 (13)	1123 (14)

Note. Data are presented as N (%) or median [interquartile range]. Exposure category determined by either PPI, H2Ra, or Neither prescribed in the 3-month look-back window prior to and including the index date. PPI = proton-pump inhibitor; H2Ra = histamine-2-receptor antagonist.
[a]Defined by the National Institute for Health Care and Excellence guidelines (Supplemental Table S4).
[b]Defined as prescriptions with a duration ≥8 weeks.
[c]Includes general surgery, vascular surgery, and urology.

Table 3. Recipient-Level Analysis of PPI Use in Follow-Up in Kidney Transplant Recipients on a PPI, H2Ra, or Neither at Baseline.

Recipient-level analysis	PPI user (N = 829) (96%)	H2Ra user (N = 58) (27%)	Neither (N = 341) (46%)	*P*
Median number of PPI prescriptions per recipient	26 [11-51]	7 [3-21]	10 [3-29]	<.001
≥3 PPI prescriptions	779 (94)	44 (76)	257 (75)	<.001
Chronic prescriptions[a]	580 (70)	33 (57)	246 (72)	.06
Percent time in follow-up on PPI[b]	91 [70-98]	22 [7-43]	38 [8-74]	<.001
Indication for PPI prescription in follow-up[c]				
GERD	70 (8)	6 (10)	32 (9)	.8
Peptic ulcer disease	17 (2)	1 (2)	6 (2)	.9
Helicobacter pylori	48 (6)	5 (9)	13 (4)	.2
Prior upper GIB	153 (18)	8 (14)	49 (14)	.2
Antiplatelet	214 (26)	18 (31)	80 (23)	.4
Anticoagulant	105 (13)	5 (9)	33 (10)	.3
NSAID	22 (3)	0	14 (4)	.2
High-dose prednisone (>10 mg daily)	28 (3)	5 (9)	29 (9)	<.001
Any of the above	447 (54)	38 (66)	184 (54)	.2

Note. Data are presented as N (%) or median [interquartile range]. Exposure category determined by either PPI, H2Ra, or neither prescribed in the 3-month look-back window prior to and including the index date. All patients included in this table were patients who had at least 1 PPI prescription in follow-up. PPI = proton-pump inhibitor; H2Ra = histamine-2-receptor antagonist; GERD =gastroesophageal reflux disease; GIB = gastrointestinal bleed; NSAID = non–steroidal anti-inflammatory drug.
[a]Defined as prescriptions with a duration ≥8 weeks.
[b]Percentage of graft survival time that the recipient was on a PPI (defined as: total days supplied of PPI/total days of graft survival × 100%) from index date until end of follow-up.
[c]We assessed for the concurrent use of medications in the 3 months prior to the last prescription in follow-up, the presence of GERD, peptic ulcer disease, concurrent medication use and/or *Helicobacter pylori* infection in the 3 years prior, and any history of upper GIB since 1994.

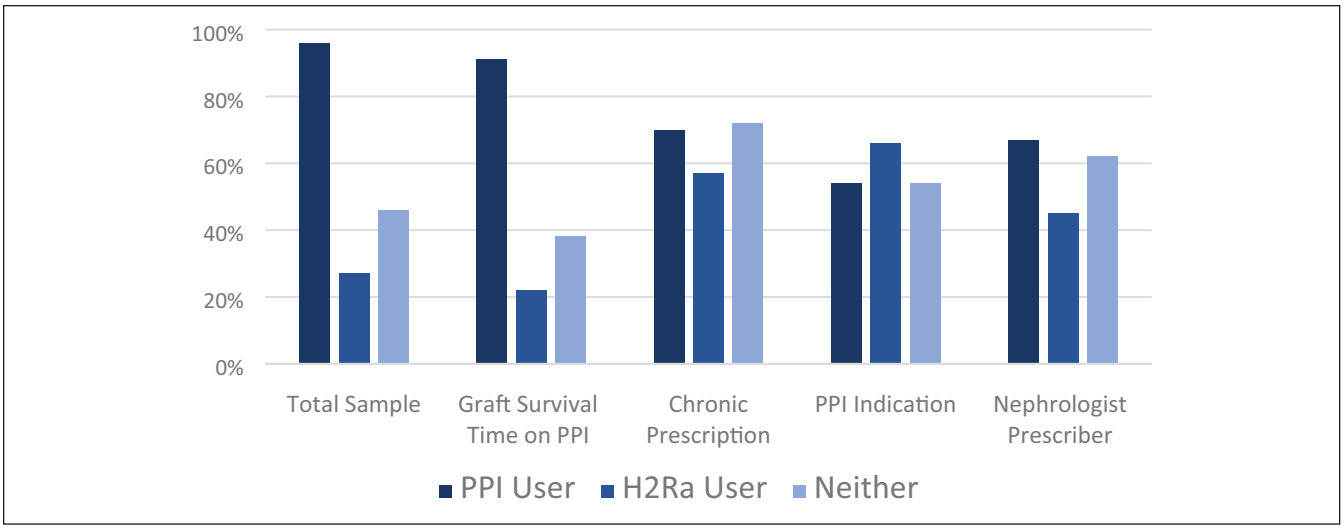

Figure 1. PPI use in kidney transplant recipients by exposure group at the index date.
Note. The first columns represent the proportion of recipients from the main cohort who were prescribed a PPI in follow-up. The subsequent columns consider only those recipients who had at least 1 PPI prescription in follow-up. Proton-pump inhibitor indication was assessed at last PPI prescription filled in follow-up with a look-back window of 3 years for GERD, peptic ulcer disease, *Helicobacter pylori*, since 1994 for any history of GIB, and 3 months for concurrent medication use including antiplatelet, anticoagulant, high-dose prednisone >10 mg daily, and/or NSAIDs. Proportion of nephrologist prescribers is based on total prescription-level data. PPI = proton-pump inhibitor; H2Ra = histamine-2-receptor antagonist; GERD = gastroesophageal reflux disease; GIB = gastrointestinal bleed; NSAID = non–steroidal anti-inflammatory drug.

groups (91% vs 22% vs 38%, respectively, $P < .001$). We identified an indication for ongoing PPI use in 54% of recipients with the most common indication being concurrent antiplatelet use (26%). In follow-up, 341 (46%) recipients in the neither group were prescribed a PPI with an identifiable indication being present in 54% of recipients.

Discussion

In our cohort of 1823 kidney transplant recipients, almost half were prescribed a PPI at baseline and most of these recipients continued their PPI. Proton-pump inhibitor users spent 91% of their graft survival time in follow-up on a PPI over a median of 5 years. Despite this, an indication for prescription was only identified in about half of recipients. We found that nephrologists were the main prescribers of PPIs.

In our cohort, 48% of kidney transplant recipients were prescribed a PPI at baseline which is similar to other studies (45%-54%).[26,27] This likely reflects the degree of comorbidity in transplant recipients as only 8%-10% of the general population are prescribed PPIs.[1] The recipients in the PPI group were more likely to have cardiac and vascular comorbidities compared with the recipients in the H2Ra and neither groups. This may explain why the most common indication was concurrent antiplatelet prescription. Kidney transplant recipients are also at higher risk of GIB. Previously, Sood et al[28] reported that the 3-year cumulative incidence rate of upper GIB for kidney transplant recipients was 1.6% compared with 0.2% in the general population in Ontario, Canada. Thus, it is not surprising that many kidney transplant recipients are prescribed PPIs given their cardiovascular comorbidities and risk of GIB.

Kidney transplant recipients are vulnerable to polypharmacy given their underlying multi-morbidity.[27] In our cohort, the median number of prescriptions at baseline was 12 (IQR = 7-22), which was similar to other studies.[27] In 1 paper, kidney transplant patients who had ≥10 medications self-reported lower scores of physical functioning, social function, energy/fatigue, and higher pain using the Kidney Disease Quality of Life-Short Form questionnaire.[6] Lower self-reported quality of life has been independently associated with increased mortality in stable kidney transplant recipients.[29] In addition, other adverse outcomes have been associated with long-term PPI use in recipients including hip fractures and mortality.[5] Conflicting evidence for the association with PPI use and acute rejection and/or worsening graft function exist, and studies with longer follow-up are needed.[5,30] Regardless, it is reasonable to reduce polypharmacy in this high-risk population with reassessment of ongoing PPI use as recommended by national campaigns, such as Choosing Wisely Canada.[3]

In the dialysis population, which has a similarly high prevalence of PPI use, deprescribing initiatives have been shown to be effective.[27,31,32] In a Canadian study by McIntyre et al,[32] 67% of patients without an identifiable indication for PPI were able to discontinue therapy with 75% staying off PPI after 6 months. However, deprescribing PPIs can be challenging as it may lead to rebound gastric hypersecretion resulting in recurrent symptoms and/or bleeding ulcers in select patients.[33] Another Canadian study

found that only 30% of patients with kidney failure who were prescribed a PPI had an approved indication.[34] Unfortunately, almost half of the group who had their PPI discontinued were restarted within 8 weeks due to symptoms and/or GIB.[34] In addition, there is limited evidence that deprescribing initiatives actually lead to improved clinical outcomes. Systematic reviews in the elderly general population have suggested that deprescribing initiatives reduce all-cause mortality, but these were based on studies with low-to-moderate quality of evidence.[35,36] The potential benefits of deprescribing unnecessary medications include reduced pill burden, improved quality of life, lower risk of drug interactions, and limited cost to the patient and health care system. In our study, nephrologists were the main prescribers of PPIs and may benefit from validated deprescribing tools to reduce PPI use in kidney transplant recipients.

Our study has several strengths including the use of linked health care databases to study PPI prescriptions in almost 2000 kidney transplant recipients over a follow-up of 5 years. Whereas prior studies have presumed indefinite use and relied on patient self-report or 1-time prescription fill,[15,37] we captured all prescriptions dispensed provincially. We were able to calculate the graft survival time in follow-up spent on a PPI and attempted to identify indications for chronic PPI use to inform potential deprescribing initiatives. However, there are limitations worth noting. Our recipients have access to universal health care coverage which may limit the generalizability of our results in regions with different health care delivery and practices. We captured provincial prescription fills but did not have data on the indication for new or ongoing use. In addition to this, we were not able to account for over-the-counter medication use, such as for H2Ra or NSAID, which may have led to misclassification of the exposure groups and an underestimation of the indication for PPI use. While we attempted to identify common gastrointestinal indications for PPI use, we did not include rare conditions and Barrett's esophagitis due to concerns about the validity of the diagnostic codes.[38] Given the retrospective design, there may have been confounding variables that we were not able to account for. In addition, symptoms suggestive of reflux may not be well coded as the focus of follow-up visits is more likely to focus on kidney transplant. A prospective study would have provided more granularity for PPI indication but would have been time-consuming and costly to conduct.

Conclusions

In conclusion, 48% of kidney transplant recipients are prescribed a PPI at or beyond the 1-year post-transplant date and those who are taking a PPI are likely to spend most of their follow-up and graft survival time on a PPI. Only half of PPI prescriptions in all groups were associated with an identifiable gastroenterological indication. Targeted approaches to reduce pill burden and unnecessary PPI prescriptions may improve quality of life and reduce medication non-adherence in this high-risk population. Future research is needed to determine whether deprescribing initiatives lead to improved outcomes in kidney transplant recipients.

List of Abbreviations

ACR, albumin-to-creatinine ratio; AKDN, Alberta Kidney Disease Network; AKC, Alberta Kidney Care; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; GIB, gastrointestinal bleed; H2Ra, histamine-2-receptor antagonist; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Statistical Classification of Diseases, Tenth Revision; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; NSAID, non–steroidal anti-inflammatory drug; PCR, protein-creatinine ratio; PIN, Pharmaceutical Information Network; PPI, proton-pump inhibitor.

Ethics Approval and Consent to Participate

This study was approved by the research ethics boards at the University of Alberta and the University of Calgary with waiver of patient consent.

Consent for Publication

The authors have consented to publication of this manuscript.

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Author Contributions

J.K. and N.N.L. participated in research design. A.C. participated in data analysis. J.K. drafted and revised the manuscript. All authors were involved in data interpretation and final approval of the manuscript.

Declaration of Conflicting Interests

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Data Availability

The authors are not able to make their data set available to other researchers due to our contractual arrangements with the provincial health ministry (Alberta Health), who is the data custodian. Researchers may make requests to obtain a similar data set at https://albertainnovates.ca/our-health-innovation-focus/the-alberta-spor-support-unit/.

Supplemental Material

Supplemental material for this article is available online.

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