Peripheral Artery Disease: Its Adverse Consequences With and Without CKD

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Rationale & Objectives: Chronic kidney disease (CKD) is a potent risk factor for macrovascular disease and death. Peripheral artery disease (PAD) is more common in patients with CKD and is associated with lower-limb complications and mortality. We sought to compare the prevalence of PAD in and outside the setting of kidney disease and examine how PAD affects the risk for adverse health outcomes, specifically lower-limb complications, cardiovascular events, and survival.

Study Design: Retrospective cohort study.

Setting & Participants: 453,573 adult residents of Manitoba with at least 1 serum creatinine measurement between 2007 and 2014.

Exposure: PAD defined by hospital discharge diagnosis codes and medical claims.

Outcomes: All-cause mortality, cardiovascular events, and lower-limb complications, including foot ulcers and nontraumatic amputations.

Analytical Approach: Survival analysis using Cox proportional hazards models.

Results: The prevalence of PAD in our study population was 4.5%, and patients with PAD were older, were more likely to be male, and had a higher burden of comorbid conditions, including diabetes and CKD. PAD was associated with higher risks for all-cause mortality, cardiovascular events, and lower-limb complications in patients with estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2, those with CKD GFR categories 3 to 5 (G3-G5), and those treated by dialysis (CKD G5D). Although HRs for PAD were lower in the CKD population, event rates were higher as compared with those with eGFR ≥ 60 mL/min/1.73 m^2. In particular, compared with patients with eGFR ≥ 60 mL/min/1.73 m^2 and without PAD, patients with CKD G5D had 10- and 12-fold higher risks for lower-limb complications, respectively (adjusted HRs of 10.36 [95% CI, 8.83-12.16] and 12.02 [95% CI, 9.58-15.08] for those without and with PAD, respectively), and an event rate of 75/1,000 patient-years.

Limitations: Potential undercounting of PAD and complications using administrative codes and the limited ability to examine quality-of-care indicators for PAD.

Conclusions: PAD is more common in patients with CKD G3-G5 and G5D compared with those with eGFR ≥ 60 mL/min/1.73 m^2 and frequently leads to lower-limb complications. Medical interventions and care pathways specifically designed to slow or prevent the development of lower-limb complications in this population are urgently needed.

Complete author and article information provided before references.

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Chronic kidney disease (CKD) is a major health problem with an increasing incidence and prevalence worldwide.[1] A large contributor to this increase has been the increasing incidence of diabetes, a leading cause of CKD. Both diabetes and CKD are potent independent risk factors for kidney failure, and the combination of diabetes and kidney failure requiring dialysis appears to be particularly adverse for patients, leading to an increased burden of both microvascular (retinopathy and neuropathy) and macrovascular (peripheral arterial disease [a pathologic systemic process of arteriolosclerosis and thrombosis leading to the narrowing and eventual occlusion of vessels in the extremities[2]], coronary artery disease, and cerebrovascular accidents) complications.[3-5]

In patients with CKD, peripheral artery disease (PAD) is common and is associated with substantial morbidity, mortality, and associated health care costs. According to the US National Health and Nutritional Examination Survey, 10.8% of individuals with diabetes and 18.2% of individuals with reduced estimated glomerular filtration rate (eGFR; <60 mL/min/1.73 m^2) have PAD, compared with only 3.6% of individuals without diabetes and 2.8% of those with eGFR at or above this threshold.[6]

The increased morbidity and costs associated with PAD are in large part linked to its association with foot complications. These complications include neuroischemic foot ulcers, gangrene, infections, and ultimately amputation.[7] Some of these complications are difficult to manage due to the synergistic effects of lack of protective sensation from neuropathy, reduced blood flow from the PAD, and the relative immune deficits from kidney failure. As a result, the recurrence rate of individuals with diabetic foot ulcers is high, at >50% within 3 years after initially healing.[7] One of the most serious complications of a foot ulcer is limb amputation, which results in major morbidity and disability for the patient and increased health care costs for the payer.[7,8]

Although the prevalence of PAD and lower-limb amputations in patients with kidney failure who are treated by dialysis has been studied,[9,10] little is known about the epidemiology of these diseases in CKD not requiring kidney replacement therapy (KRT). Information is also

lacking about how PAD itself or in association with kidney disease influences other adverse health outcomes, especially lower-limb complications. We sought to address these knowledge gaps and identify opportunities for improvement in CKD and PAD care by conducting a province-wide retrospective cohort study.

Methods

Study Design

We performed an observational retrospective cohort study that analyzed patient-level data obtained by linking several administrative health service databases housed at the Manitoba Centre for Health Policy in Manitoba, Canada.[11] The study protocol was reviewed and approved by the University of Manitoba Health Research Ethics Board (ethics file number HS18574). Consent for this study was waived because line-level data analyzed were deidentified.

Data Sources

As with all Canadian provinces, Manitoba (population 1.3 million) has a government-administered, single-payer, universal insurance health care system. The Manitoba Centre for Health Policy has for the past 25 years housed and integrated the multiple administrative databases related to health and social services provided to Manitoba residents. The data sets used for the present study included The Manitoba Health Insurance Registry, Medical Services (physician claims), Discharge Abstract Database (hospital admissions), and Diagnostic Services of Manitoba (laboratory results). Individual patient-level data from these registries were linked using a scrambled deidentified version of the patients' Personal Health Identification Number, a unique 9-digit number assigned to each resident of Manitoba.

Study Population

Our patient population includes all Manitoba residents older than 18 years with at least 1 serum creatinine (Scr) measurement in the Diagnostic Services of Manitoba database between January 1, 2007, and October 31, 2014. Dialysis was ascertained by the presence of at least 2 claims for dialysis-related services in the medical services database within this same period.[12] Two or more claims were used to define this cohort because previous validated studies have found this to be the optimal case definition.[13] Claim codes can be found in Table S1. Patients who received a transplant or who had 2 additional dialysis claims before January 1, 2007 (prevalent dialysis patients) were excluded.

Exposure Variables of Interest

Baseline characteristics and comorbid conditions were ascertained from January 1, 2004, up until the individual's first Scr measurement and entry into the cohort (between January 1, 2017, and October 31, 2014). Primary exposure variables were PAD (present during the baseline period) and level of kidney function (categorized as eGFR $\geq$ 60 mL/min/1.73 m^2, non–KRT-requiring CKD GFR categories 3 to 5 [CKD G3-G5; eGFR $<$ 60 mL/min/1.73 m^2], and dialysis [CKD G5D]). eGFR was calculated using the Scr-based CKD-EPI equation.[14] PAD was defined using an *International Classification of Diseases* (*ICD*) code-based definition from Quan et al.[15] Additional sensitivity analyses were also performed using a more specific code-based definition for PAD, which is provided in Table S2. Baseline characteristics included demographic information (age and sex) and laboratory data (eGFR, urinary albumin-creatinine ratio, and glycated hemoglobin level). Comorbid conditions were based on the Charlson Comorbidity Index (excluding PAD), which included myocardial infarction, congestive heart failure, PAD, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, diabetes, paraplegia and hemiplegia, renal disease, cancer, moderate or severe liver disease, metastatic carcinoma, and HIV/AIDS.[16,17] The *ICD, Ninth* (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes used to define these conditions are presented in Table S3.

Outcomes

The main outcomes of interest included time to all-cause mortality, time to lower-limb complications (nontraumatic lower-limb amputations or foot ulcerations), and time to cardiovascular events (myocardial infarction, stroke, unstable angina, and congestive heart failure). Lower-limb amputations were described as any nontraumatic below-hip amputation. Repeat lower-limb complications and cardiovascular events were excluded. Outcomes were defined using *ICD-9* and *ICD-10-CA* codes from the Discharge Abstract Database and outlined in Tables S4 and S5.[15] End of follow-up for the study was December 31, 2014.

Statistical Analyses

Descriptive statistics were provided stratified by the presence of PAD at baseline and then further by CKD GFR category at baseline. Comparisons were performed using the appropriate statistical tests: analysis of variance or t test for normally distributed continuous variables, Kruskal-Wallis test or Wilcoxon rank sum test for non-normally distributed continuous variables, and χ^2 test for categorical variables. Event rates were calculated for the following outcomes: cardiovascular events (myocardial infarction, unstable angina, and stroke), all-cause mortality, and lower-limb complications (nontraumatic lower-limb amputations and foot ulcers) by taking the number of events and dividing by the total observed patient time and presented as rates per 1,000 patient-years. Cox proportional hazards models were applied to assess associations between the exposure variables of interest and time to all-cause mortality.

For outcomes of time to lower-limb complications and cardiovascular events, cause-specific hazards models were used to assess associations between the exposure variables

of interest and outcome by treating the competing event of death before the outcome as censoring. Models were adjusted for the primary predictors of interest, PAD and kidney function, as well as age, sex, the weighted Charlson Comorbidity Index (excluding PAD), and the interaction between PAD and kidney function.[18] The proportional hazards assumption was evaluated by visual inspection of Schoenfeld residuals. Confidence intervals (CIs) were calculated for these adjusted hazard ratios (HRs) with alpha = 0.05. The 5-year cumulative incidence of lower-limb complications was compared in each kidney function group stratified by the presence of PAD at baseline using the cumulative incidence function method in the presence of competing events.

Results

Cohort Selection

During our study period from January 1, 2007, to October 31, 2014, the Diagnostic Services of Manitoba database had 3,962,421 Scr measurements in adults (aged > 18 years), of which eGFR could be calculated for 3,955,116 tests, with 460,451 unique individuals having at least 1 available eGFR. In addition, there were 1,407,632 medical services claims related to maintenance dialysis during the study period, resulting in 3,720 individuals with at least 2 claims. This led to a total population of 460,591, of whom 1,128 were excluded for being prevalent dialysis patients (with claims before January 1, 2007), 221 were excluded for receiving a kidney transplant, and 5,671 were excluded for invalid registration dates in the Manitoba Health Registry. The final cohort size totaled 453,573 individuals (Fig 1).

Population Characteristics

Of the 453,573 patients included our study, 20,600 (4.5%) had a diagnosis of PAD. The PAD group had a greater burden of kidney disease; in this group, 6,170 (30.0%) had CKD G3-G5 and 644 (3.1%) had CKD G5D. In the non-PAD group, the corresponding values were 43,395 (10.1%) and 1,926 (0.4%), respectively. Patients with PAD were older than those without (mean age of 69.0 ± 15.4 [standard deviation] vs 50.7 ± 19.7 [$P < 0.001$]). The burden of comorbid conditions, especially cardiovascular and cerebrovascular disease, was higher in those with PAD compared with those without. These findings are summarized in Table 1. Population characteristics stratified further by eGFR can be found in Table S6.

Outcomes in Patients With and Without PAD by Kidney Function

The impact of PAD and kidney function on the various adverse outcomes is summarized in Table 2 and Figure 2. In all analyses, patients without PAD and with eGFR ≥ 60 mL/min/1.73 m^2 were treated as the reference group.

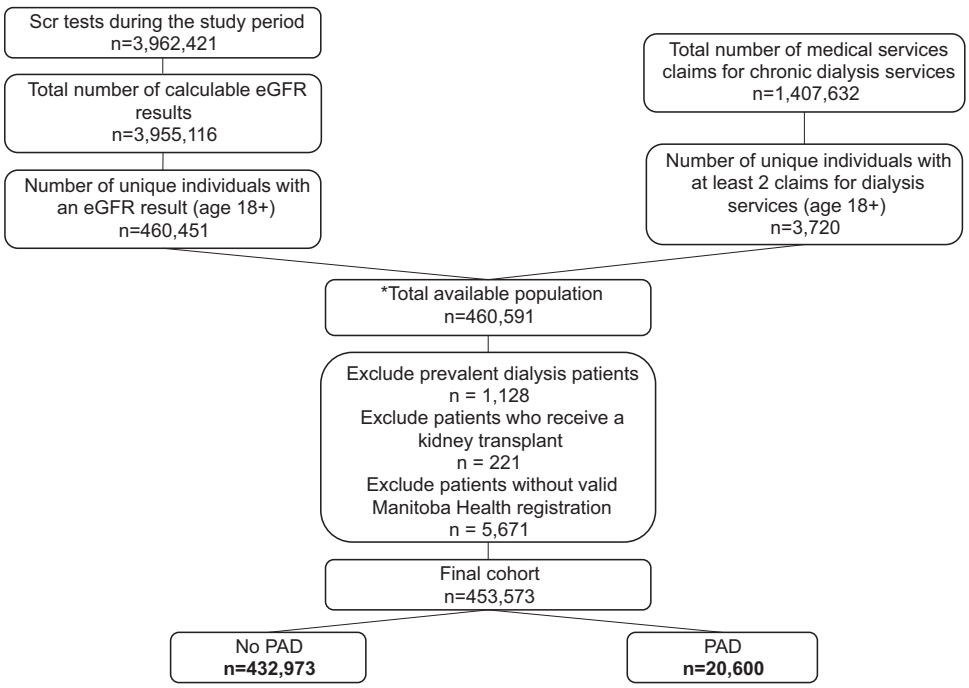

Figure 1. Flow diagram of cohort selection process. *Discrepancy between those with estimated glomerular filtration rate (eGFR) results and the total population is accounted for by individuals receiving dialysis without a serum creatinine measurement in our system (total = 140 patients). Abbreviation: PAD, peripheral artery disease.

Table 1. Patient Characteristics at Baseline, Stratified by PAD Status

	No PAD	PAD	*P*
Population characteristics			
No. of patients	432,973 (95.5%)	20,600 (4.5%)	
Age, y	50.7 ± 19.7	69.0 ± 15.4	<0.001
Male sex	193,917 (44.8%)	10,785 (52.4%)	<0.001
Kidney function			
eGFR ≥ 60 mL/min/1.73 m^2	387,552 (89.5%)	13,786 (66.9%)	<0.001
CKD G3-G5	43,495 (10.1%)	6,170 (30.0%)	<0.001
CKD G5D	1,926 (0.4%)	644 (3.1%)	<0.001
Laboratory results			
eGFR, mL/min/1.73 m^2	93.5 ± 25.0	72.5 ± 25.2	<0.001
UACR, mg/mmol	1.1 [0.4-4.3]	2.4 [0.6-11.8]	<0.001
HbA_{1c}, %	6.7 ± 1.8	6.9 ± 1.7	<0.001
Comorbid conditions[a]			
Myocardial infarction	14,844 (3.4%)	2,895 (14.1%)	<0.001
Congestive heart failure	22,812 (5.3%)	4,372 (21.2%)	<0.001
Cerebrovascular disease	24,560 (5.7%)	4,676 (22.7%)	<0.001
Dementia	14,197 (3.3%)	1,769 (8.6%)	<0.001
Chronic pulmonary disease	122,362 (28.3%)	8,215 (40.0%)	<0.001
Connective tissue disease	15,563 (3.6%)	1,880 (9.1%)	<0.001
Peptic ulcer disease	13,657 (3.2%)	1,339 (6.5%)	<0.001
Mild liver disease	17,255 (4.0%)	834 (4.1%)	<0.001
Diabetes	69,032 (15.9%)	6,744 (32.7%)	<0.001
Paraplegia and hemiplegia	5,402 (1.3%)	691 (3.4%)	<0.001
Kidney disease	12,004 (2.8%)	2,505 (12.2%)	<0.001
Cancer	55,235 (12.8%)	4,512 (21.9%)	<0.001
Moderate or severe liver disease	2,918 (0.7%)	220 (1.0%)	<0.001
Metastatic carcinoma	6,993 (1.6%)	494 (2.4%)	<0.001
HIV/AIDS	697 (0.2%)	17 (0.1%)	<0.001

Note: Values for categorical variables given as count (percentage), for continuous variables, as mean ± standard deviation or median [interquartile range].
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HIV, human immunodeficiency virus; *ICD-9 (10), International Classification of Diseases, Ninth (Tenth) Revision*; PAD, peripheral artery disease; UACR, urinary albumin-creatinine ratio.
[a]Table S3 of the supplementary material provides the ICD-9 and -10 codes used to define the comorbid conditions.

Interaction Analyses

For all 3 adverse outcomes, we examined the interaction between PAD and level of kidney function (eGFR ≥ 60 mL/min/1.73 m^2, CKD G3-G5, and CKD G5D) in the proportional hazards models. There was an interaction between PAD and CKD G3-G5 or CKD G5D for lower-limb complications and cardiovascular events, and an interaction between PAD and CKD G3-G5 for all-cause death. In patients with CKD G3-G5 or CKD G5D, the HR in those with PAD differed less from the HR in those without PAD than was the case in patients with eGFR ≥ 60 mL/min/1.73 m^2, but absolute differences in event rates between those with PAD and those without were greater (Tables S7-S9).

Lower-Limb Complications

In patients with eGFR ≥ 60 mL/min/1.73 m^2, crude rates for lower-limb complications were 1.0 per 1,000 patient-years in those without PAD versus 9.8 for those with PAD. When adjusted for age, sex, and comorbid conditions, there was 6-fold increased risk in individuals with PAD compared with those without (HR, 6.06; 95% CI, 5.41-6.78).

In patients with CKD G3-G5, crude rates were 3.9 and 18.9 per 1,000 patient-years in those without PAD and with PAD, respectively. The corresponding adjusted HRs were 2.12 (95% CI, 1.89-2.38) and 6.61 (95% CI, 5.74-7.61), respectively.

Patients with CKD G5D had the highest crude rates for lower-limb complications, at 40.5 versus 74.9 per 1,000 patient-years in those without and with PAD, respectively. This corresponded to HRs of 10.36 (95% CI, 8.83-12.16) and 12.02 (95% CI, 9.58-15.08), respectively.

At each level of kidney function, the cumulative incidence of lower-limb complications at 5 years was higher in those with PAD compared with those without. The highest absolute risk was seen in patients with CKD G5D with PAD, with a cumulative incidence of 26% (compared to 17% in their counterparts without PAD).

Cardiovascular Events

In patients with eGFR ≥ 60 mL/min/1.73 m^2, the presence of PAD resulted in nearly a 4-fold increase in crude rates of cardiovascular events (13.3 in those without PAD vs 51.3 in those with). In these patients, this corresponded

Table 2. Event Rates for the Outcomes of Interest and a Multivariate Cox Proportional Hazards Model by Presence and Severity of CKD

Outcome	eGFR ≥ 60 mL/min/1.73 m²		CKD G3-G5		CKD G5D		F/U Time, y
	Event Rate[a]	Hazard Ratio	Event Rate[a]	Hazard Ratio	Event Rate[a]	Hazard Ratio	
Lower-limb complications[b]							3.62 (1.39-5.96)
No PAD	1.0	1.00 (reference)	3.9	2.12 (1.89-2.38)	40.5	10.36 (8.83-12.16)	
PAD	9.8	6.06 (5.41-6.78)	18.9	6.61 (5.74-7.61)	74.9	12.02 (9.58-15.08)	
CV events[b]							3.40 (1.20-5.79)
No PAD	13.3	1.00 (reference)	75.1	1.47 (1.43-1.51)	114.9	2.63 (2.39-2.89)	
PAD	51.3	1.56 (1.49-1.63)	141.0	1.91 (1.82-2.01)	206.1	2.79 (2.42-3.22)	
Death[c]							3.65 (1.41-5.97)
No PAD	21.4	1.00 (reference)	115.4	1.29 (1.26-1.31)	141.3	1.70 (1.58-1.82)	
PAD	70.7	1.24 (1.20-1.28)	179.3	1.41 (1.36-1.47)	250.3	1.91 (1.72-2.12)	

Note: Models were adjusted for PAD, kidney function (eGFR ≥ 60 mL/min/1.73 m², CKD G3-G5, or dialysis), age, sex, weighted Charlson Comorbidity Index (excluding PAD), and the interaction between kidney function and PAD. Confidence intervals presented with alpha = 0.05. *ICD-9* and *ICD-10* code definitions for lower-limb complications and CV events can be found in Supplementary Tables S4 and S5. An interaction between PAD and CKD is noted for all outcomes except for death and dialysis. Detailed results are presented in Supplementary Tables S7 to S9, and additional sensitivity analyses are presented in Supplementary Tables S10 to S11. Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; D, dialysis; eGFR, glomerular filtration rate; F/U, follow-up; G, glomerular filtration rate category; *ICD-9 (10)*, *International Classification of Diseases, Ninth (Tenth) Revision*; PAD, peripheral artery disease.
[a]Per 1,000 patient-years.
[b]Cause-specific models incorporating the competing risk for death.
[c]Cox proportional hazards model.

to a 56% increased risk for cardiovascular events with versus without PAD (HR, 1.56; 95% CI, 1.49-1.63).

In patients with CKD G3-G5, there was almost a 2-fold increase in crude rates comparing those without and with PAD (75.1 and 141.0 per 1,000 patient-years in those without vs with PAD). A similar trend was seen with the corresponding HRs (1.47 [95% CI, 1.43-1.51] and 1.91 [95% CI, 1.82-2.01], respectively).

Patients with CKD G5D again had the highest crude incident rates, at 114.9 and 206.1 per 1,000 patient-years in those without and with PAD, respectively. However, the presence of PAD had a smaller relative effect (the corresponding HRs were 2.63 [95% CI, 2.39-2.89] and 2.79 [95% CI, 2.42-3.22], respectively).

At each level of kidney function, the cumulative incidence of lower-limb complications at 5 years was again higher in those with PAD compared with those without. The absolute rates increased substantially with worsening kidney function; there was a cumulative incidence at 5 years of 28% in those with CKD G3-G5 without PAD, 46% in those with CKD G3-G5 and PAD, 41% in those with CKD G5D without PAD, and 55% in those with CKD G5D with PAD.

Mortality

In patients with eGFR ≥ 60 mL/min/1.73 m², we found a 3-fold increase in crude event rates comparing those without versus with PAD (21.4 vs 70.7 per 1,000 patient-years, respectively). This corresponded to a modestly greater risk in those with versus without PAD in our adjusted model (HR, 1.24; 95% CI, 1.20-1.28).

In patients with CKD G3-G5, crude rates were 115.4 and 179.3 per 1,000 patient-years in those without and with PAD, respectively. The corresponding adjusted HRs were 1.29 (95% CI, 1.26-1.31) and 1.41 (95% CI, 1.36-1.47), respectively.

Crude rates were highest in the CKD G5D population, with almost a 2-fold difference between those without versus with PAD (141.3 vs 250.3 per 1,000 patient-years). However, PAD again had a smaller relative effect when adjusted for covariates (HRs of 1.70 [95% CI, 1.58-1.82] and 1.91 [95% CI, 1.72-2.12], respectively).

At each level of kidney function, the cumulative incidence of lower-limb complications at 5 years was again higher in those with PAD compared with those without. The absolute rates increased substantially with worsening kidney function, with a cumulative incidence at 5 years of 41% in those with CKD G3-G5 without PAD, 56% in those with CKD G3-G5 and PAD, 51% in those with CKD G5D without PAD, and 73% in those with CKD G5D with PAD.

Discussion

In this large population-based study, we found that PAD was common in those with reduced kidney function and associated with multiple serious adverse outcomes. Although the relative impact of PAD was lower in the presence of coexisting CKD G3-G5 or CKD G5D, both groups of patients had markedly high crude rates of all adverse events. In particular, the risk for lower-limb complications was extremely high in those with PAD and CKD G5D, with a cumulative incidence > 25%. Together, these findings highlight the disease burden of PAD and CKD in combination and suggest that urgent interventions to reduce the risk for mortality and lower-limb complications in this population are needed.

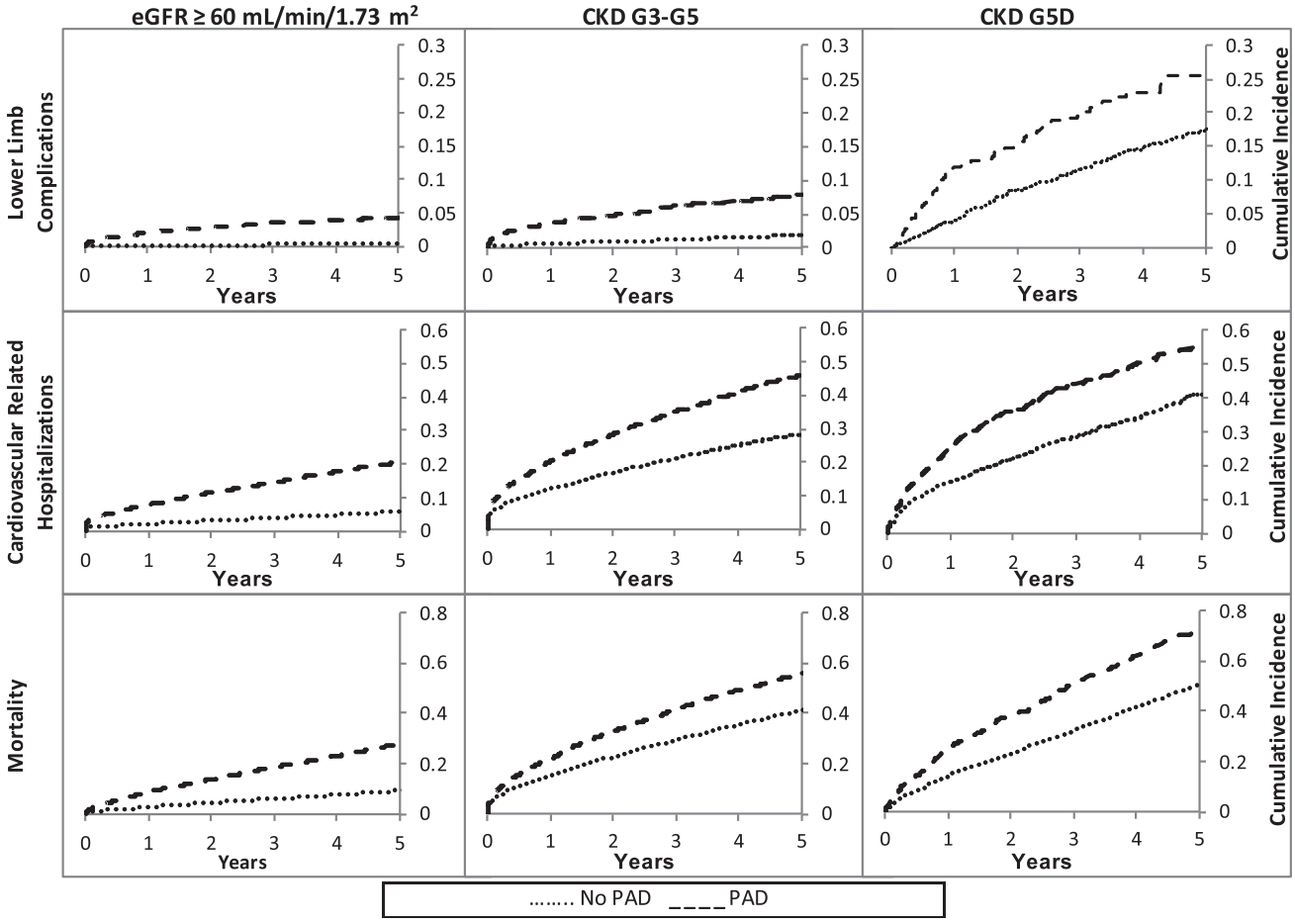

Figure 2. Cumulative incidence of lower-limb complications, cardiovascular-related hospitalizations, and mortality by kidney function with and without peripheral artery disease (PAD). Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

The effects of PAD on survival in patients receiving dialysis has been well studied during the past decade.[9,10] The DOPPS investigators examined the association of PAD with mortality in 29,873 patients receiving hemodialysis, of whom 7,411 had PAD, and found PAD to have a strong independent association with mortality and cardiovascular events.[10] However, this study did not report on lower-limb complications or amputations, both of which are exceedingly common in patients receiving dialysis and associated with substantial morbidity. Similarly, other investigators used data from the USRDS Dialysis Morbidity and Mortality Study and found that PAD was common in the dialysis population and associated with several traditional and nontraditional risk factors.[19] Since that time, several other studies have examined the relationship between PAD and adverse outcomes, but most have been limited by small sample size, single-center representation, and a lack of patients with earlier stages of CKD.[5,20,21]

The epidemiology of PAD in those with non–KRT-requiring CKD was clearly defined in a recent multicenter meta-analysis of 817,084 individuals from Matsushita et al.[22] In this study, both eGFR and albuminuria were independently associated with PAD incidence. In comparison to those with eGFR of 95 mL/min/1.73 m^2, the incidence of PAD was 1.2- to 2-fold higher in those with CKD G3-G5. This is congruent with our results, which found that 30% of our PAD group had CKD G3-G5 compared with only 10% in our non-PAD group. Matsushita et al[22] also reported a steady increase in incident amputations as eGFR decreases, with the highest risk group (patients with eGFR < 30 mL/min/1.73 m^2) having a 2.6-fold increased risk (HR, 2.59; 95% CI, 1.97-3.40) compared with the reference group (eGFR ≥ 90 mL/min/1.73 m^2). Although still significantly elevated, this is lower than our calculated risk of 6.61 (95% CI, 5.74-7.61) comparing those with CKD G3-G5 with those with eGFR ≥ 60 mL/min/1.73 m^2. This difference likely reflects differences between the studies in outcome definition (we included lower-limb ulceration, which is markedly more common than amputation and represents a meaningful intermediate clinical end point on the pathway to an

amputation) and reference group definition (our comparator group had eGFR ≥ 60, not 90, mL/min/1.73 m^2).

Several small cross-sectional studies have suggested an association between dialysis status and risk for lower-limb complications. In a United Kingdom–based cohort of 326 patients with CKD and diabetes, those receiving dialysis (n = 139) had a significantly higher prevalence of foot ulcers (odds ratio [OR], 5.1; 95% CI, 2.3-11) and prior amputations (OR, 2.6; 95% CI, 1.2-5.6) in comparison to those with non–KRT-requiring CKD.[4] An Australian study of 218 dialysis patients also reported a high prevalence of amputation (13.3%) and diabetic foot ulcers (24.8%).[9] Our finding that dialysis is an independent risk factor for lower-limb complications in patients with PAD provides robust and rigorous validation of this association in a much larger population-based cohort and provides greater certainty in the estimates of risk. The exponential increase in risk for lower-limb complications in patients receiving dialysis, along with the significant morbidity and mortality associated with amputations, identifies a high-risk population that may benefit from intervention.

The results from our study have clinical, policy, and research implications. The increased prevalence of PAD in CKD G3-G5 and CKD G5D is relevant to clinicians, who should consider screening for occult PAD through regular ankle-brachial index testing and treating risk factors for lower-limb complications aggressively in patients with CKD G3-G5 or CKD G5D. Because the cost-utility of screening and case management pathways is largely based on absolute risk, our study strongly supports piloting these types of interventions and testing their efficacy and generalizability in the dialysis population, for which the absolute risk is extreme. Increased provision of foot care (examinations, foot care services, and aggressive management of complications) in patients with diabetes and those receiving dialysis has been shown to improve clinical outcomes and reduce hospitalizations.[23,24] Therefore, such interventions should be considered in those with PAD receiving dialysis as a policy-level intervention by health care payers. Our observation of an accelerated evolution of PAD in patients receiving dialysis is also congruent with observations of accelerated vascular disease in this population. The biology of vascular disease in non–KRT-requiring CKD and dialysis is not attributable entirely to atherosclerosis and may be substantially different than in patients with normal kidney function.[25] Studies examining the underlying mechanisms of PAD are needed to help identify novel targets for intervention.

Our study has several strengths, including a rigorous retrospective cohort design, large sample size, and use of large well-validated administrative data sets representing a population-based cohort of patients.

Our study also has limitations; specifically, the use of administrative codes for measurement of outcomes yields good specificity but modest sensitivity.[26] Our prevalence and incidence rates may thus represent an underestimate of the true rate. Misclassification of outcome may also occur due to imperfect specificity; however, it is unlikely that misclassification differed systematically between the groups and thus should not bias estimates of relative risk. We also had limited ability to examine quality-of-care indicators for PAD, such as screening for PAD, acetylsalicylic acid use, and smoking cessation. Finally, the CKD-EPI equation is inaccurate in individuals with lower muscle mass and amputations, leading to a falsely elevated eGFR. However, muscle mass information was not available in our database.

In conclusion, PAD is common in patients with CKD G3-G5 or CKD G5D and is a potent risk factor for cardiovascular events, lower-limb complications, and death. Patients with PAD receiving dialysis should be considered at extreme risk for lower-limb amputation or ulceration, and trials of screening and treatment strategies for these downstream complications should be prioritized in this population.

Supplementary Material

Supplementary File (PDF)

Table S1: Manitoba Health tariff codes used to define dialysis and kidney transplantation.

Table S2: Parameter estimates for the models with more specific *ICD* code-based definition for PAD.

Table S3: *ICD-9* and *ICD-10* codes used to define PAD and co-morbid conditions used in the weighted Charlson co-morbidity index.

Table S4: *ICD-9* and *ICD-10* codes used to define cardiovascular events.

Table S5: *ICD-9* and *ICD-10* codes used to define lower-limb complications and foot ulcers.

Table S6: Patient characteristics at baseline, stratified by the presence of PAD, eGFR, and dialysis status.

Table S7: Parameter estimates for the models predicting death.

Table S8: Parameter estimates for the models predicting lower-limb complications in the presence of the competing risk of death.

Table S9: Parameter estimates for the models predicting cardiovascular events in the presence of the competing risk of death.

Table S10: Parameter estimates for the models with eGFR as a continuous variable.

Table S11: Sensitivity analysis on the outcome of death including PAD, MI, and CBVD.

Article Information

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