UNIVERSITY OF MANITOBA

Rady Faculty of Health Sciences
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Office of Graduate and Advanced Degree Education in Medicine

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Project Title: Epidemiology of Lower Limb Disease in Persons with Chronic Kidney Disease

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Summary (250 words max single spaced):

Background Diabetes and chronic kidney disease (CKD) are potent risk factors for kidney failure, vascular disease and death. The combination of diabetes and kidney failure requiring dialysis appears to lead to an increased burden in both microvascular and macrovascular complications. Of particular importance is peripheral vascular disease (PVD) and its association with mortality and lower limb complications.
Objective Determine the prevalence of PVD in patients with CKD and those on dialysis and to determine how PVD both individually and in association with reduced kidney function affects adverse health outcomes and survival.
Methods We performed a retrospective cohort study of over 450,000 adults that analyzed patient level data obtained by linking several provincial registries in Manitoba, Canada.
Results Patients with PVD and CKD stages 3-5 or on dialysis were found to have 2 times the risk of cardiovascular events compared to those with normal kidney function. The dialysis group had a nearly 10-fold increased risk of lower limb amputation [HR 9.3 (6.8-12.7)] and diabetic foot ulcers [HR 9.2 (6.6-12.6)]. PVD was also found to be an independent risk factor for all-cause mortality [HR 1.25 (1.22-1.28)] and lower limb disease [HR 3.92 (3.59-4.27)], adjusted for age, sex, CKD status and comorbid conditions.
Conclusion PVD is associated with increased all-cause mortality and lower limb complications. This effect is magnified in patients with CKD and especially those on dialysis. Programs providing upstream medical interventions to slow or prevent the development of lower limb complications in this population should be evaluated.

Acknowledgments (choose a or b):
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MD/PhD MD/MSc. BSc. (MED) MED II Research Program
Joe Doupe Annual Event Undergraduate Medical Student Research Symposium
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INTRODUCTION

Chronic kidney disease (CKD) is a major health problem with a rising incidence and prevalence worldwide.[1] A large contributor to this rise has been the rising incidence of diabetes, a leading cause of CKD. Both diabetes and CKD are potent, independent risk factors for kidney failure, vascular disease and death. 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, neuropathy and nephropathy) and macrovascular complications (peripheral vascular disease, coronary artery disease and cerebrovascular accidents).[2,3,4]

In patients with CKD and those on dialysis, peripheral vascular disease (PVD) is common and particularly important due the disproportionately high prevalence and substantial morbidity, mortality and healthcare costs associated with it. According to the US based National Health and Nutritional Examination Survey, 10.8% of individuals with diabetes and 18.2% of individuals with low kidney function (eGFR <60 ml/min per 1.73m^2) had peripheral arterial disease compared to only 3.6% of individuals without diabetes.[5]

The increased morbidity and costs associated with PVD are in large part linked to its association with foot complications. These complications include reduced sensation and proprioception, painful neuropathy, foot ulcers, infections, gangrene and amputations.[6] They are quite difficult to treat due to the combination of reduced blood flow from the PVD and other patient co-morbidities. As a result, it's been shown that within 3 years, the recurrence rate of foot ulcers is over 50%.[6] The most serious complication of a foot ulcer is amputation. Infected ulcers lead to gangrene and amputation, causing a significant amount of morbidity and considerable healthcare costs.[6,7]

While the prevalence of peripheral vascular disease and lower limb amputations in patients with kidney failure (on dialysis) has been studied, very little is known about the epidemiology of these diseases in non-dialysis CKD. Information is also lacking in regards to how PVD itself and in association with kidney disease affects other adverse health outcomes and survival. Through a province wide, retrospective cohort study we aimed to address these knowledge gaps and identify opportunities for improvement in CKD and PVD care.

METHODS

We performed an observational, retrospective cohort study that analyzed patient level data obtained by linking several provincial registries from Manitoba, Canada housed at the Manitoba Centre for Health Policy (MCHP). These databases included: The Manitoba Health Insurance Registry, Medical Services (physician claims), Canadian Institute for Health Information (CIHI), Discharge Abstract Database (DAD) (hospital admissions), Diagnostic Services of Manitoba (DSM) (laboratory results), the Drug Program Information Network (DPIN) database (drug prescriptions), and Manitoba Renal Program (MRP) database (dialysis). We determined all primary and secondary diagnoses using International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) for hospital admissions and used codes from the 9th revision (ICD-9-CM) for both hospital admissions and medical services. Individual patient-level data from these registries were linked using the patients Personal Health Identification Number (PHIN), a unique 9-digit number for each resident of Manitoba. The study protocol was reviewed and approved by the University of Manitoba Health Research Ethics Board (ethics file number HS18574). Linkage of data was approved and performed by the Manitoba Center for Health Policy (MCHP).

Study Population

Our patient population includes all adult Manitoba residents with at least one serum creatinine measurement obtained between January 1st 2007 and November 30th 2015. The study population was then stratified by estimated glomerular filtration rate (eGFR) into three groups: dialysis, eGFR < 60ml/min/1.73m^2 and eGFR > 60ml/min/1.73m^2 using the CKD-EPI study equation. Dialysis was ascertained by appearance in the MRP dialysis database, or the presence of at least two claims for dialysis-related services in the medical services database.

Baseline characteristics and comorbidities were ascertained between January 1st 2004 up until the individual's first serum creatinine measurement and entry into the cohort. Baseline characteristics included: demographic information (age and sex), laboratory data (eGFR, urine albumin-to-creatinine ratio (ACR), HbA1C), comorbidities [PVD, acute myocardial infarction (MI), atrial fibrillation, congestive heart failure (CHF), diabetes, diabetic foot ulcer, ischemic heart disease, malignancy, stroke and transient ischemic attack (TIA)], baseline procedures (lower limb amputation, catheterization, coronary arterial bypass graph and percutaneous transluminal coronary angioplasty) as well as statin prescriptions. The same stratification and analysis listed above was performed on all those with PVD diagnosed in the baseline period as a subset analysis.

Outcomes

Primary outcomes included all-cause mortality, peripheral vascular disease, lower limb complications (amputations and diabetic foot ulcers) and cardiovascular events (MI, CHF, stroke and unstable angina). These were defined using ICD-9 and ICD-10 codes from databases housed at the Manitoba Centre for Health Policy (MCHP) repository including outpatient physician claims from the Manitoba Health Services Commission (MHSC) and hospital discharge databases (CIHI-DAD).

Statistical Methods

Descriptive statistics were provided for the entire population, stratified by CKD status, and stratified by presence of PVD at baseline. Rates were calculated for cardiovascular events (MI, CHF, unstable angina and stroke), all-cause mortality, and lower limb complications (lower limb amputations and diabetic foot ulcers). To account for differences in population demographics, we also calculated age and sex adjusted hazard ratios of these adverse events.

Our primary longitudinal analysis included: (1) Univariate cox proportional hazards model associating our primary outcome PVD with all-cause mortality and a composite of lower limb complications (amputation and diabetic foot ulcer). (2) Multivariate cox proportional hazards model associating our primary outcome PVD with all-cause mortality and the composite of lower limb complications, adjusting for demographic information (age and sex), CKD status and comorbidities (atrial fibrillation, CHF, ischemic heart disease, malignancy, stroke, TIA) in both, with the addition of diabetes in the analysis of all-cause mortality.

The 5-year cumulative incidence of death was compared in each CKD disease group (dialysis, stages 3-5, and normal eGFR) stratified by the presence of PVD at baseline using the Kaplan-Meier method. The cumulative incidence of lower limb complications (diabetic foot ulcers and amputations) was assessed in the entire population stratified by the presence of PVD at baseline.

RESULTS

Population Characteristics

Between January 2007 and November 2015, 458,426 patients had at least one measurement of serum creatinine. Of these, 51,705 had an eGFR < 60/ml/min/1.73m^2, and 1,366 were receiving dialysis at baseline. Patients with stages 3-5 CKD were found to be older than those receiving dialysis (74.4 vs. 56.4 years), and older than those with normal eGFR (74.4 vs. 48.5 years). The burden of comorbidity was higher among those receiving dialysis and with reduced kidney function, with over an 11-fold prevalence of CHF among those on dialysis, and over 8-fold prevalence of CHF among those with stages 3-5 CKD in comparison to those with normal eGFR. There was nearly a 4-fold prevalence of diabetes among those receiving dialysis in comparison to those with normal eGFR. Peripheral vascular disease was also highest among those receiving dialysis (15.6%), and similarly elevated among those with stages 3-5 CKD (10.9%) in comparison to those with normal eGFR (3.4%). Lower limb complications increased substantially with declining kidney function, with a nearly 10-fold increase in stages 3-5 CKD and substantially greater still in the dialysis population. Statin use was low across all groups, the highest being 40% in the CKD population. These findings are summarized in Table 1.

Patients with PVD

A subset of the population, all those with documented PVD at baseline, were also analyzed. The total population consisted of 19,518 patients, 5,655 of which had CKD and 213 on dialysis. Again, the CKD group was substantially older than the dialysis population (77.8 vs 61.7) and the normal eGFR population (77.8 vs 64.1). The dialysis cohort had a substantially greater burden of diabetic foot ulcers and lower limb amputations at baseline with approximately 40% suffering from lower limb amputation and 26% with diabetic foot ulcers, in comparison to 2.7% of the CKD population and 1% of those with normal eGFR for both. Statin use was again greatest in the CKD cohort with 58.5% of the cohort having a baseline prescription, followed by 42.9% of the normal eGFR cohort and only 27.7% of the dialysis cohort (Table 2). Overall, comparing the PVD population to the entire study population (Table 1 vs Table 2), the PVD patients in general had a much greater comorbidity burden, especially in terms of lower limb complications.

Outcome Events

Outcome rate calculations for those with PVD stratified by CKD status took into account 78,560 patient years of follow up with a mean follow up across all groups of 4.2 years. The crude rates for lower limb complications were approximately 5 per 1000 patient years in patients with normal eGFR and 12 and 38 for CKD and dialysis respectively. Once age and sex adjusted, the incident risk increased 2 fold in the CKD population and over 9 fold in those with dialysis.

Crude rates for CV events in the normal eGFR group range from 20 (unstable angina) to 42.8 (CHF) per 1000 patient years. On average these rates doubled to tripled in the CKD cohort but dropped slightly from the CKD to those on dialysis. However, once age and sex adjusted, hazard ratios were similar between the CKD and dialysis cohorts, approximately 2 fold greater than the normal eGFR group.

Crude rates for mortality in the normal eGFR group was 54.1 per 1000 patient years, doubling in the dialysis group and tripling in the CKD cohort (109.5 and 150.3 respectively). However, when age and sex adjusted, the incident risk in death was greatest in the dialysis population [HR 2.7 (2.3-3.3)], double that of the CKD cohort [HR 1.5 (1.5-1.6)].

Mortality

As might be expected, PVD amongst all cohort groups was associated with a substantial decrease in 5-year survival as shown by the Kaplan Meier curves generated (Figures 1-3). The normal eGFR cohort showed the largest relative risk associated with PVD and survival. Despite this, the CKD and dialysis cohort with PVD showed a substantially larger absolute risk of death in those with PVD compared to the normal eGFR cohort.

Table 3 shows the results of the univariate and multivariate cox proportional hazards model analysis looking at death as the primary outcome. Univariate analysis shows baseline PVD is associated with a 3 fold increased incident risk of all-cause mortality. When adjusted for both age, sex and CKD status, as well as age, sex, CKD status and comorbidities, the association of PVD and mortality remained significant [HR 1.31 (1.28-1.35) and 1.25 (1.22-1.25) respectively].

Lower Limb Complications

Univariate analysis shows baseline PVD is associated with a 9-fold increased incident risk of lower limb complications. Multivariate models show when adjusted for age, sex and CKD status (Model 1) and the additional comorbidities (Model 2), the association remains strongly positive with hazard ratios of 4.69 (4.30-5.11) and 3.92 (3.59-4.27) respectively.

Figure 4 shows a Kaplan Meier curve for those with and without PVD with the endpoint as the composite of lower limb complications. This further illustrates the association between PVD and lower limb complications as there is an over 6-fold relative risk for those with PVD over those without.

DISCUSSION

In our province wide population study of more than 450,000 adults, we found that PVD was common and associated with multiple serious adverse outcomes including lower limb complications, cardiovascular events and death. This impact of PVD is further magnified by the presence of co-existing CKD, and patients with both diseases have markedly high rates of adverse events. In particular, PVD is associated with a nearly two-fold increase in the risk of major cardiovascular events in patients with CKD, and a nearly 10-fold higher risk of lower limb events in patients on dialysis. Together, these findings highlight the disease burden of PVD and CKD in combination, and suggest that urgent interventions to reduce the risk of CV and lower limb complications in these population are needed.

The effects of PVD on dialysis has been well studied over the past decade. One of the most notable studies was the DOPPS study, a nation-wide prospective observational study with a total hemodialysis population of 29,873, 7,411 of which were diagnosed with PVD. This study, like ours, found an independent association between PVD with mortality.[8] However, what this study lacked was the association between end stage CKD and PVD which our study highlights.

Previous studies in single centers have examined the epidemiology of PVD.[4,9,10] One specific study out of Cleveland examined 6 year mortality within a CKD and PVD cohort (n=210) and found a mortality of 45%, less than what we found in our 5 year mortality follow up (52%) with similar numbers for their PVD only group (26%).[11] Differing PVD definitions, as they used an ABI of <0.9 compared to our study which used diagnosis codes from providers as well as regional and demographic differences can explain this variability, but both found a significant increase in mortality. Another smaller study out of France (n=1,010) also found a significant

increase in unadjusted, 1-year mortality [HR 3.44 (2.25-5.27)] and amputation [HR 2.37 (1.62-3.48)] in CKD stage 5 vs non CKD with PVD.[12] However, due to limited power, they could not find a significant association with amputation after fully adjusting for covariates.

Our study clearly shows in patients with PVD, dialysis is an independent risk factor for lower limb complications and is consistent with other studies on the topic. In a cohort of 326 patients with CKD and diabetes from the United Kingdom, those on dialysis (n = 139) had significantly higher amounts of prevalent foot ulcers [OR 5.1 (2.3-11)] and prior amputations [OR 2.6 (1.2-5.6)] in comparison to those with CKD only. A recent Australian study of 218 dialysis patients, mirror these results as well. They found even higher rates of amputation and diabetic foot ulcers in their baseline period than ours, 13.3% and 24.8% respectively.[13] Our study however is by far the largest to look at this relationship and the increased power allowed us to be the first to look at this relationship in patients with both PVD and dialysis. In addition, a retrospective case series out of the UK found cumulative incidence of foot ulcerations and amputation increased before the initiation of dialysis, correlating this to complications of end stage renal disease and not dialysis itself. Our study shows there does exist a relationship between lower limb complications and reduced kidney function (CKD stage 3-5). However, because the effect in those currently on dialysis is greatly magnified, it is very likely that some aspect of dialysis itself has a substantial effect on the development of these complications.[14]

To determine whether those with PVD were being optimally managed, we looked at baseline statin use in all our cohorts. Statin use has also been highly studied over the past decade due to its positive effects and relatively low adverse outcomes. Several studies have found protective effects in terms of major amputations, CV events and mortality in PVD patient.[15–17] As a result, statins are listed in all of the major guidelines as first line treatment for risk prevention in patients with PVD (Class 1) with a high level of evidence to support its use (level B evidence).[18–20] However, even despite the evidence to support its use, we found that only 58.5% of the CKD population and 27.7% of the dialysis population with PVD were prescribed a statin at any time during the baseline period. We do understand that there is some justification for the low prescribing in dialysis patients due to conflicting evidence on their effectiveness in this population.[21] However, there is a large body of evidence supporting the benefit of statins in terms of mortality and cardiovascular events in CKD alone, let alone the extra indication for CKD patients with comorbid PVD.[22] Some have argued that poor statin prescribing along with other risk factor reducing medications due to a lack of PVD specific symptomatology resulting in low PVD recognition in the primary care setting.[23,24] However, in our study, because we used PVD diagnosis codes and did not screen for an ABI target, these individuals had documented PVD, acknowledged by a medical provider, but still not prescribed a statin.

The results from this study have very clear and relevant implications both clinically and in terms of further research. Clinically, the increased prevalence of PVD in CKD and dialysis, and the poor outcomes associated with it, indicates a population with substantial morbidity, mortality and healthcare costs. Because of this, there is a need for close monitoring of complications and initiation of risk reduction and disease modifying therapy in this population. Our secondary analysis on baseline statin use also shows that currently they are being underserviced by the healthcare system. As a result, policies should be put in place that focus on proper complication screening methods and risk reduction therapy in patients with documented PVD. Very important, would be increased funding for foot care (exams, podiatry services and aggressive management) for patients with PVD on dialysis due to their extremely high rates of lower limb complications. Implementations of care protocols such as this have been shown to improve clinical outcomes and reduce hospitalizations.[25] In terms of research, we have clearly shown a strong association between dialysis and lower limb complications. Many hypotheses

exist as to why this is, such as atherosclerotic changes or arterial stiffening. However, studies focusing on the biology of this association need to be performed so that policies can better focus on the primary mechanism of disease, increasing their efficacy.

Limitations

The limitations of the study include inaccuracies in administrative codes imputed by physicians which we used for many of our outcome and baseline disease definitions. Studies have shown the specificity for this data to be overall quite high, however the sensitivity varies based on the outcome and can lead to discrepancies.[26] As well, because we can only identify medications that were prescribed by a physician using DPIN and have no information for their indication, quality indicators for PVD such as acetylsalicylic acid and smoking cessation could not be determined Finally, because this was an epidemiology study, we were unable look into the biology behind the associations found in our study.

CONCLUSIONS

PVD is common in patients with renal impairment and even more so in those on dialysis. PVD alone is a potent risk factor for CV events, lower limb complications and death. This effect is magnified in patients with PVD and decreased kidney function or on dialysis. Most remarkable of all, is the association between dialysis and lower limb complications. This significant burden of disease associated with high morbidity and mortality has clear implications on both the patient's quality of life and costs on the healthcare system. However, many patients who could benefit from risk reduction therapies such as statins, do not appear to be receiving them, showing potential gaps in optimal care. It is imperative that policies be put in place to offer optimal risk reduction therapy and close monitoring for downstream events for both PVD patients with renal impairment and those on dialysis.

TABLES AND FIGURES

Table 1: Patient characteristics at baseline, stratified by CKD stage.

	Normal eGFR	CKD Stage 3-5	Dialysis	Total Population
Population Characteristics				
Total n	405,355	51,705	1,366	458,426
Age	48.5 (18.6)	74.4 (13.8)	56.4 (16.2)	51.5 (19.9)
Sex (% Female)				
Labs				
eGFR	98 (84-113)	46 (36-54)	7 (5-15)	95 (77-111)
Urine ACR	0.8 (0.3-2.9) n=67031	3.3 (0.7-18.6) n=14084	13.9 (1.1-60.9) n=248	1.0 (0.3-4.1) n=81363
HbgA1C	6.7 (1.8) n=78378	7.0 (1.7) n=14808	6.7 (1.6) n=1025	6.7(1.8) n=94211
Comorbidities				
Acute MI	4393 (1.1%)	1189 (2.3%)	61 (4.5%)	5643 (1.2%)
Atrial Fibrillation	13962 (3.4%)	7525 (14.6%)	143 (10.5%)	21630 (4.7%)
Congestive Heart Failure	6743 (1.7%)	7490 (14.5%)	266(19.5%)	14499 (3.2%)
Diabetes	51466 (12.7%)	14972 (29.0%)	673 (49.3%)	67111 (14.6%)
Diabetic Foot Ulcer	386 (0.1%)	317 (0.6%)	86 (6.3%)	789 (0.2%)
Ischemic Heart Disease	133396 (32.9%)	40958 (79.2%)	1206 (88.3%)	175560 (38.3%)
Hypertension	153476 (37.9%)	43524 (84.2%)	1216 (89.0%)	198216 (43.2%)
Malignancy	109792(27.1%)	20019 (38.7%)	356 (26.1%)	130167 (28.4%)
Peripheral Vascular Disease	13650 (3.4%)	5655 (10.9%)	213 (15.6)	19518 (4.3%)
Stroke	65 (0.02%)	49 (0.1%)	7 (0.5%)	121 (0.03%)
Transient Ischemic Attack	7409 (1.8%)	3083 (6.0%)	80 (5.9%)	10572 (2.3%)
Baseline Procedures				
Lower Limb Amputation	158 (0.04%)	150 (0.3%)	86 (6.3%)	393 (0.1%)
Catheterization	9053 (2.2%)	2841 (5.5%)	177 (13.0%)	12071 (2.6%)
Coronary artery bypass graph	1178 (0.3%)	537 (1.0%)	55 (4.0%)	1770 (0.4%)
Percutaneous transluminal coronary angioplasty	140 (0.03%)	38 (0.1%)	0 (0.0%)	178 (0.04%)
Statin use	67233 (16.6%)	20687 (40.0%)	300 (22.0%)	88220 (19.2%)

Table 2: Patient with PVD at baseline, stratified by CKD stage.

	Normal eGFR	CKD Stage 3-5	Dialysis	Total Population
Population Characteristics				
Total n	13650	5655	213	19,518
Age	64.1 (15.8)	77.8 (10.1)	61.7 (12.0)	68.1 (15.6)
Sex (% Female)	46.1	46.3	46.0	46.2
Labs				
eGFR	85.9 (74.4-96.7)	44.8 (33.7-52.8)	8.2 (5.7-14.3)	76 (55-91)
Urine ACR	1.2 (0.4-4.5) n=3119	4.9 (1.1-23.0) n=1561	6.4 (0.4-100.5) n=34	1.8 (0.5-9.0) n=4714
HbgA1C	6.8 (1.6) n=3323	7.1 (1.7) n=1636	7.3 (1.9) n=171	6.9 (1.7) n=5130
Comorbidities				
Acute MI	358 (2.6%)	216 (3.8%)	19 (8.9%)	593 (3.0%)
Atrial Fibrillation	1433 (10.5%)	1198 (21.2%)	35 (16.4%)	2666 (13.7%)
Congestive Heart Failure	834 (6.1%)	1251 (22.1%)	66 (31.0%)	2151 (11.0%)
Diabetes	3208 (23.5%)	1994 (35.3%)	166 (77.9%)	5368 (27.5%)
Diabetic Foot Ulcer	161 (1.2%)	150 (2.7%)	55 (25.8%)	366 (1.9%)
Ischemic Heart Disease	9495 (69.6%)	5242 (92.7%)	205 (96.2%)	14942 (76.6%)
Hypertension	9773 (71.6%)	5341 (94.5%)	207 (97.2%)	15321 (78.5%)
Malignancy	5570 (40.8%)	2433 (43.0%)	55 (25.8%)	8058 (41.3%)
Stroke	19 (0.1%)	17 (0.3%)	6 (2.8%)	42 (0.22%)
Transient Ischemic Attack	864 (6.3%)	598 (10.6%)	26 (12.2%)	1488 (7.6%)
Baseline Procedures				
Lower Limb Amputation	158 (1.2%)	150 (2.7%)	85 (39.9%)	393 (2.0%)
Catheterization	1037 (7.6%)	562 (9.9%)	49 (23.0%)	1648 (8.4%)
Coronary artery bypass graph	242 (1.8%)	145 (2.6%)	19 (8.9%)	406 (2.1%)
Percutaneous transluminal coronary angioplasty	13 (0.1%)	9 (0.2%)	0 (0.0%)	22 (0.1%)
Statin use	5851 (42.9%)	3308 (58.5%)	59 (27.7%)	9218 (47.2%)

Table 3: Event rates for the outcomes of interest and a multivariate cox proportional hazards model stratified by CKD stage.

	eGFR>60ml/min per 1.73m^2				CKD Stages 3-5				Dialysis			
Outcome	**Events (%)**	**PY**	**Event Rate**	**Hazard Ratio***	**Events (%)**	**PY**	**Event Rate**	**Hazard Ratio***	**Events (%)**	**PY**	**Event Rate**	**Hazard Ratio***
Amputation	291 (2.1)	56,632	5.1	Ref	204 (3.6)	19,158	10.5	2.0 (1.6-2.4)	49 (23.0)	1,233	39.7	9.3 (6.8-12.7)
Diabetic Foot Ulcer	280 (2.1)	56,711	4.9	Ref	246 (4.4)	19,029	12.9	2.8 (2.3-3.4)	46 (21.6)	1,238	37.2	9.2 (6.6-12.6)
MI	1113 (8.2)	53,901	20.6	Ref	769 (13.6)	17,702	43.4	1.6 (1.4-1.7)	39 (18.3)	1,267	30.8	1.9 (1.4-2.7)
Stroke	1313 (9.6)	53,754	24.4	Ref	812 (14.4)	17,716	45.8	1.1 (1.0-1.2)	31 (14.6)	1,300	23.8	1.27 (0.9-1.8)
CHF	2,252 (16.3)	52,572	42.8	Ref	2,274 (38.9)	15,146	150.1	2.0 (1.9-2.1)	92 (40.4)	1,245	73.9	2.3 (1.8-2.8)
Unstable angina	1059 (7.8)	53,246	19.9	Ref	576 (10.2)	17,687	32.6	1.2 (1.1-1.4)	21 (9.9)	1,302	16.1	1.1 (0.7-1.7)
Death	3,117(22.8)	57,575	54.1	Ref	2,949 (52.1)	19,624	150.3	1.5 (1.5-1.6)	149 (70.0)	1,361	109.5	2.7 (2.3-3.3)

***Cox proportional hazards model is adjusted for age and sex**

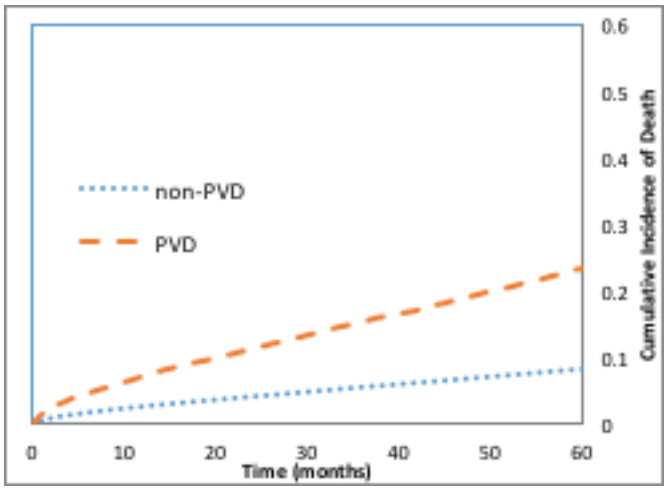

Figure 1: Kaplan Meier curve comparing the 5-year survival of patients with and without PVD at baseline within the normal eGFR cohort (eGFR >60ml/min/1.73m^2)

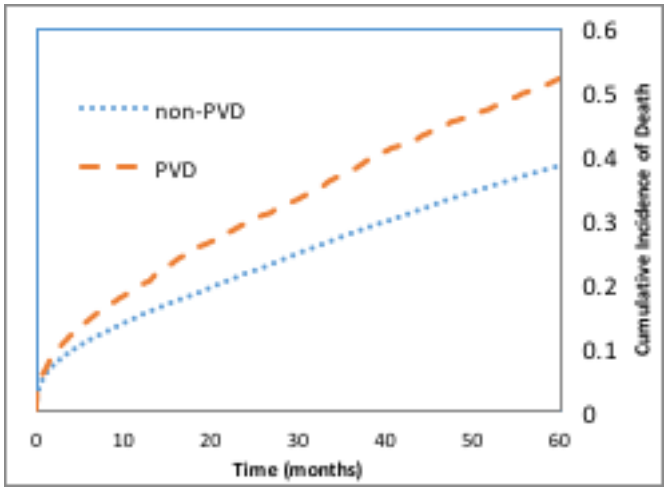

Figure 2: Kaplan Meier curve comparing the 5-year survival of patients with and without PVD at baseline within the CKD cohort (eGFR 0-60ml/min/1.73m^2)

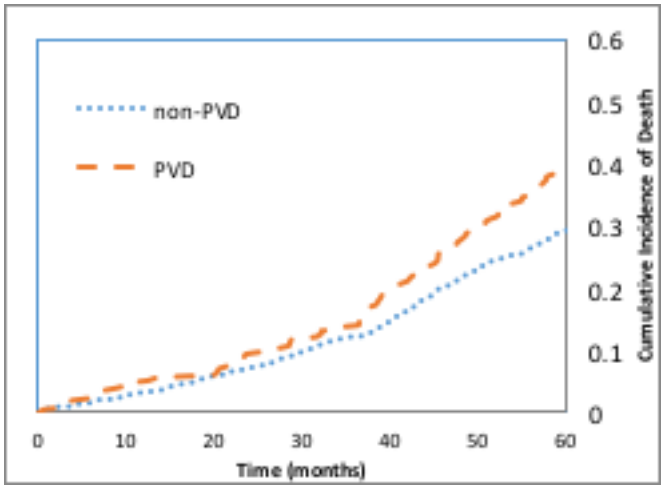

Figure 3: Kaplan Meier curve comparing the 5-year survival of patients with and without PVD at baseline within the dialysis cohort

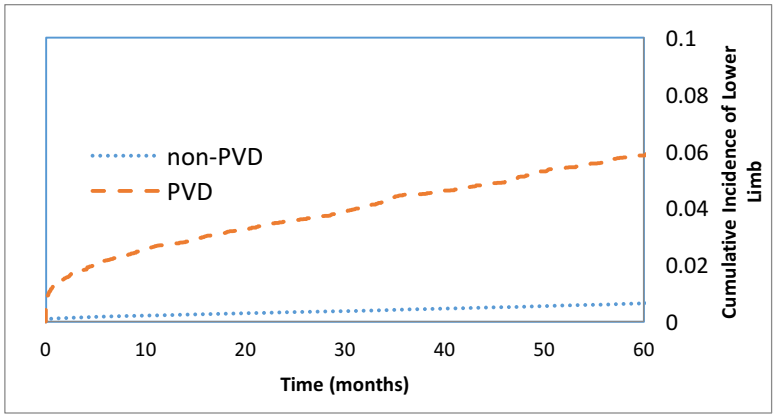

Figure 4: Kaplan Meier curve comparing the 5-year cumulative incidence of lower limb complications in patients with and without PVD at baseline.

Table 4: Univariate and Multivariable cox proportional hazards models with the primary outcome of all-cause mortality.

		Models	
Variable	**Unadjusted**	**1**	**2**
Peripheral Vascular Disease	3.07 (2.99 – 3.15)	1.31 (1.28 – 1.35)	1.25 (1.22-1.28)
Age		1.07 (1.07 – 1.07)	1.07 (1.07-1.07)
Sex (Male vs. Female)		1.39 (1.36 – 1.41)	1.34 (1.32-1.37)
eGFR >60 vs eGFR > 60 ml/min/1.73m^2		1.51 (1.48-1.54)	1.42 (1.40-1.45)
Dialysis vs. eGFR > 60 ml/min/1.73m^2		3.47 (3.23-3.74)	2.92 (2.71-3.15)
Diabetes			1.29 (1.27-1.32)
Atrial fibrillation			1.13 (1.11-1.16)
Congestive heart failure			1.86 (1.81-1.91)
Ischemic heart disease			0.87 (0.85-0.88)
Malignancy			1.24 (1.22-1.26)
Stroke			1.32 (1.03-1.69)
Transient ischemic attack			1.08 (1.04-1.11)
Akaike Information Criterion (AIC)	1453209	1365687	1361881

Table 5: Univariate and Multivariable cox proportional hazards models with the primary outcome of composite of lower limb outcomes.

		Models	
Variable	**Unadjusted**	**1**	**2**
Peripheral Vascular Disease	9.02 (8.32-9.79)	4.69 (4.30-5.11)	3.92 (3.59-4.27)
Age		1.02 (1.01-1.02)	1.00 (1.00-1.00)
Sex (Male vs. Female)		1.98 (1.84-2.13)	1.86 (1.73-2.01)
eGFR >60 vs eGFR > 60 ml/min/1.73m^2		3.52 (3.22-3.85)	2.73 (2.50-2.98)
Dialysis vs. eGFR > 60 ml/min/1.73m^2		18.97 (16.32-22.04)	8.90 (7.62-10.40)
Atrial fibrillation			0.87 (0.77-0.98)
Congestive heart failure			2.53 (2.29-2.81)
Ischemic heart disease			5.46 (4.86-6.14)
Malignancy			0.53 (0.48-0.57)
Stroke			2.29 (1.32-3.96)
Transient ischemic attack			0.83 (0.69-0.98)
Akaike Information Criterion (AIC)	73766	71304	69778

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