


# Impact of cardiovascular events on mortality and progression of renal dysfunction in a Queensland CKD cohort

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## Abstract

**Aim:** Cardiovascular events (CVE) are common co-morbidities amongst patients with chronic kidney disease (CKD). The impact of CVE on the subsequent pattern and rate of deterioration of kidney function is not well described.

**Methods:** A retrospective cohort study of 1123 Royal Brisbane and Women's Hospital patients enrolled in the CKD.QLD registry from May 2011 to August 2017 was undertaken. Participants CVE data and renal function (eGFR CKD-EPI) were extracted from clinical records. Participants who ultimately started kidney replacement therapy (KRT) were imputed an eGFR of 8 mL/min/1.73 m<sup>2</sup> at the date of the first KRT treatment. Annualized percentage delta eGFR was used to explore the association between CVE and rate of renal deterioration. Mortality was ascertained through electronic health records.

**Results:** There were 235 CVE events amongst 222 participants over a period of 6 years. One hundred and forty-four participants experienced ischaemic heart disease (IHD), 51 participants had stroke, 40 participants had peripheral vascular disease (PVD) and 13 participants had more than one event. CVE were associated with significantly shorter time to death in participants who experienced one CVE compared with those without a CVE (1901.2 days vs 2259 days [ $P < .05$ ]). However, there was no significant change in the absolute mean delta eGFR between participants with CVE and without CVE after adjustment for age (3.8 mL/min/1.73 m<sup>2</sup> vs 3.8 mL/min/1.73 m<sup>2</sup> [ $P = .9$ ]). Furthermore, there was no significant difference in the progression to KRT in participants with CVE compared with participants without CVE (1315 days and 1052 days ( $P = .46$ )).

**Conclusion:** Cardiovascular events are associated with increased mortality in the CKD cohort. They were not associated with accelerated deterioration of kidney function.

## KEYWORDS

cardiovascular events, chronic kidney disease, delta eGFR, renal replacement therapy

Chronic kidney disease (CKD) is a risk factor for cardiovascular events (CVE). Furthermore, CVE may promote incident and progressive CKD leading to reciprocal disease promulgation. CVE are increased in non-dialysis CKD participants and are up to 10 times higher in participants on dialysis.<sup>1-10</sup> Chronic inflammation, oxidative stress related to reduction of nitric oxide production, and increased homocysteine exposure have all been postulated as factors that increase risk of CVE. Potential effector pathways include endothelial dysfunction, platelet accumulation and vascular injury.<sup>11,12</sup> Biological outcomes include higher mortality and progression of CKD.<sup>13-17</sup>

Although there have been many studies exploring the prevalence, risk factors and adverse outcomes of participants with CVE on a background of CKD, many are limited by small sample size<sup>18-20</sup> and insufficient adjustment for confounders.<sup>21,22</sup> Furthermore, there has been a deficit of studies exploring the association of CVE on rates of CKD progression. Therefore, we hypothesized that the occurrence of CVE in a CKD cohort increases mortality and progression of CKD. To evaluate this hypothesis, we explored the association between CVE such as coronary artery disease, stroke and peripheral vascular disease and mortality in participants with CKD. We also explored the impact of CVE on the progression of CKD via annualized rates of eGFR change.

## 1 | METHODS

### 1.1 | Source of data

CKD.QLD is a state-wide collaborative multidisciplinary research and practice program established in 2011.<sup>23</sup> It includes a CKD registry involving all participants who gave informed consent in the public health system in the state of Queensland, Australia. For this study the CKD registry of participants from the Kidney Health Service of the Royal Brisbane and Women's Hospital (Metro North Hospital and Health Service) was used. The database records date of birth, sex, medical background, co-morbidities, clinical pathology and primary diagnosis for renal disease. Further information such as CVE and hospitalizations, as required for this analysis, were obtained using integrated medical electronic records.

### 1.2 | Ethics

The study was approved by the following Human Research Ethics Committee; Royal Brisbane and Women's Hospital, Queensland Health (HREC/15/QRBW/294) and the Medical Research Ethics Committee, The University of Queensland (2011000029). The study has been prospectively approved with subsequent protocol amendments and extensions.

### 1.3 | Study Design

To investigate the association between CVE and CKD, we conducted a retrospective cohort study. We identified 1123 participants from

## SUMMARY AT A GLANCE

Retrospective analysis of 1123 CKD patients in this study demonstrated that cardiovascular events were associated with increased mortality in the CKD cohort, irrespective of the cause of CKD, suggesting the pathophysiology of cardiovascular and renal continuum.

the CKD.QLD registry from the Royal Brisbane and Women's Hospital. All participants were 18 years of age or older and were followed from May 2011 to death or a censor date of 31st August 2017. Participants were excluded if they were on kidney replacement therapy (KRT) (haemodialysis, peritoneal dialysis or had a kidney transplant) prior to the recruitment date. CVE consist of peripheral vascular disease, ischaemic heart disease (IHD) and stroke. The date of the CVE, number of hospitalizations and co-morbidities were obtained from electronic medical records (eMR). Renal function and other clinical pathology data were obtained from Pathology Queensland records (AUSLAB).

### 1.4 | Statistical analysis

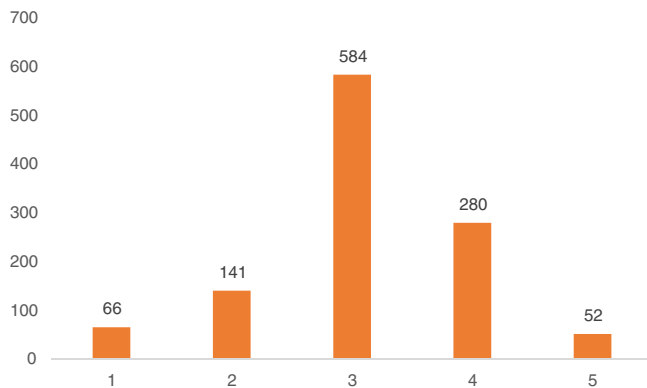
SPSS was used for data analysis. To aid in the analysis, the concept of annualized percentage delta eGFR was used. The annualized percentage delta eGFR was calculated by calculating the percentage change in eGFR in comparison to initial eGFR (results close to the year 2011) (CKD-EPI) and then the result divided by the time in years. (annualized percentage delta eGFR =  $[100 \times (\text{end eGFR} - \text{start eGFR}) / \text{start eGFR}] \times (365 / \Delta \text{days})$ ). Participants on KRT or participants who died with renal failure as a cause were imputed an eGFR of 8 mL/min/1.73 m<sup>2</sup> at the date of the first treatment or at the time of death from renal failure. *T* test and chi-square test were used in order to determine the association between CVE, hospitalizations and progression of kidney disease. Kaplan Meier analysis was used to determine the association between CVE and mortality in participants with CKD. A *P* value <.05 was regarded as statistically significant.

## 2 | RESULTS

### 2.1 | Baseline characteristics of CVE and non-CVE groups

A total of 1123 participants were included from the RBWH CKD.QLD registry. Participants had a median follow-up of 1870 days. The range of follow-up was a minimum of 151 days and a maximum of 2479 days with a range of 2328 days. The baseline was the participant's entry to the database in year 2011.

There was a total of 126 incident participants who started KRT during follow-up. Of these, 105 participants went onto dialysis and



**FIGURE 1** Distribution of participants according to the CKD stages

**TABLE 1** Characteristics of CKD.QLD (RBWH) participants with and without cardiovascular events

	Patients with incident CVE (n, percent %)	Patients without incident CVE, (n, percent %)	P
<i>Baseline features</i>			
Age	71.4 (12.4)	65.6 (16.8)	<.05
Baseline eGFR	36.4 (16.5)	43.4 (21.6)	<.05
Baseline urate	0.46 (0.13)	0.42 (0.11)	<.05
BMI	30.9 (7.7)	30.8 (8)	.8
Diabetes	144, 65%	383, 43%	<.05
Hypertension	182, 82%	651, 72%	<.05
Dyslipidaemia	118, 53%	368, 41%	<.05
<i>Co-morbidities and outcome</i>			
IHD	126, 57%	205, 23%	<.05
Stroke	46, 21%	73, 8%	<.05
PVD	69, 31%	88, 10%	<.05
Heart failure	24, 11%	62, 7%	.7
Gout	49, 22%	161, 18%	.2
Progression to KRT	23, 10%	47, 5%	.4

Abbreviations: BMI, body mass index; CVE, cardiovascular events; IHD, ischaemic heart disease; KRT, kidney replacement therapy; PVD, peripheral vascular disease.

21 participants had a kidney transplant. Upon entry to the database, there were 66 participants in CKD stage 1, 141 participants in CKD stage 2, 584 participants in CKD stage 3, 280 participants in CKD stage 4 and 52 participants in CKD stage 5 (Figure 1). A total of 222 participants developed a CVE over the observation period while 901 participants did not (Table 1). Compared with those without a CVE, those with CVE experienced greater frequency of diabetes (65% vs 43%,  $P < .05$ ), hypertension (82% vs 72%,  $P < .05$ ), dyslipidaemia (53 vs 41%,  $P < .05$ ), previous history of strokes (21% vs 8%,  $P < .05$ ), previous history of IHD (57% vs 23%,  $P < .05$ ) and history of peripheral vascular disease (31% vs 10%,  $P < .05$ ).

The mean age of participants at consent date were significantly older in the CVE group (71.4 years) compared with non-CVE group

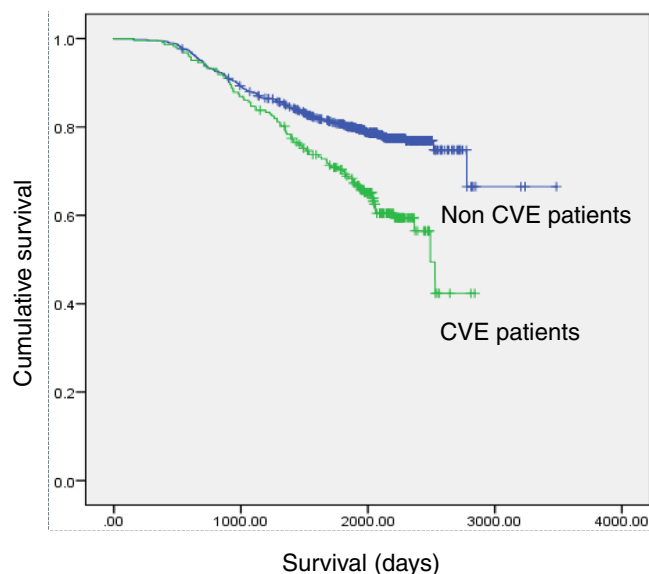
(65.6 years,  $P < .05$ ) Furthermore, urate levels on entry to the registry was significantly higher with CVE (0.46 mmol/L vs 0.42 mmol/L,  $P < .05$ ). The initial mean eGFR on entry to the database was also significantly lower in the CVE group (36.4 mL/min/1.73 m<sup>2</sup> vs 43.4 mL/min/1.73 m<sup>2</sup>,  $P < .05$ ). However, there was no significant difference in body mass index (BMI) (30.9 vs 30.8,  $P = .8$ ) (Table 1).

## 2.2 | CVE and association with mortality

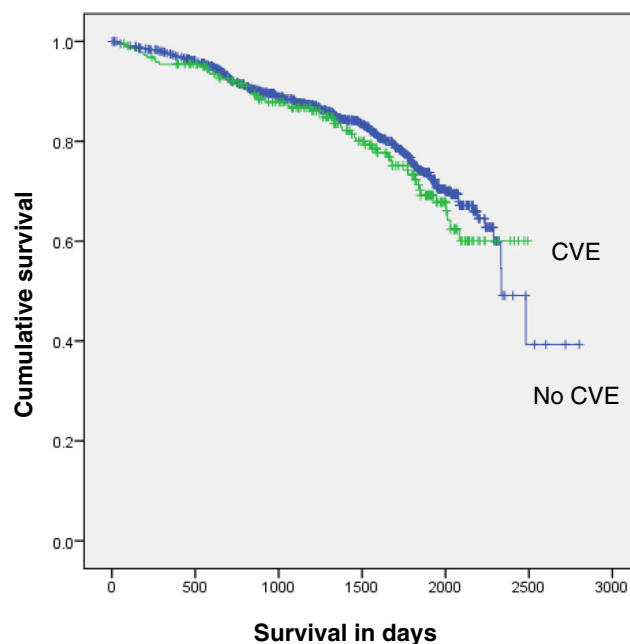
There were 87 deaths in the CVE group (87/222; 39%) compared with 197 in the non-CVE group (197/901; 22%), with significantly higher mortality in CKD participants (odd risk ratio 2.3; 95% CI 1.7-3.1;  $P < .01$ ). Kaplan Meier analysis was done using two different dates; one where the start date was the time of the CVE and second was using the start date as the time of entry into the registry. Kaplan Meier survival analysis using the CVE as the first date showed that the time to death was significantly shorter in participants with CVE compared with participants without CVE (Figure 2). The mean estimate survival in participants with CVE was 1901.2 days compared with 2259 days in those without CVE ( $P < .05$ ). Furthermore Kaplan Meier analysis using entry to registry as the first date revealed mean estimate survival in participants with CVE was 2166 days compared with 2867 days in those without CVE ( $P < .05$ ). Cox regression analysis revealed a hazard ratio of 1.69 (95% CI 1.31-2.17,  $P < .05$ ). Following adjustment for age, the association between CVE and mortality was still maintained ( $P = .03$ ). However, with multivariate cox regression analysis, following adjustment for other cardiovascular comorbidities such as diabetes, hypertension, stroke, heart failure and BMI, revealed there was no significant association between CVE and death ( $P = .37$ ) (Table 2). In addition Kaplan Meier analysing the association between survival and cause of CKD (non-diabetic vs diabetic) revealed no significant difference in mean estimate survival: 2671 days vs 2202 days ( $P = .239$ ).

## 2.3 | CVE and CKD progression

Participants with CVE had a lower baseline eGFR upon entry into the registry (Table 1). In order to assess the association between CVE and CKD progression, percentage annualized delta eGFR analysis was used  $T$  test analysis revealed no significant association between CVE and annualized percentage delta eGFR with percentage annualized delta eGFR of 15.3% (25) for participants without CVE compared with percentage annualized delta eGFR of 13.5% (22) ( $P = .9$ ) in participants with CVE. Furthermore, 23 participants (10%) in the CVE group progressed to KRT during the study period. In contrast, 47 participants (5%) in the non-CVE group (Table 1). Kaplan Meier analysis revealed no significant difference in progression to KRT between the two groups, with mean estimated survival of 2034 days and 2187 days in the CVE and non-CVE groups respectively ( $P = .4$ ) (Figure 3). Moreover, hazard ratio between progression to KRT and CVE was 0.851 which was not significant ( $P = .31$ ). In order to assess the association



**FIGURE 2** Kaplan Meier analysis of mortality (in days) of CKD.QLD (RBWH) participants with and without cardiovascular events (CVE)



**FIGURE 3** Kaplan Meier analysis of progression to kidney replacement therapy (in days) of CKD.QLD (RBWH) participants with and without cardiovascular events (CVE)

Comorbidity	B	SE	Wald	df	Sig.
Age	.056	0.006	82.288	1	.000
Body mass index	-.019	0.010	3.658	1	.056
Diabetes	-.242	0.126	3.680	1	.055
Hypertension	.032	0.156	0.043	1	.837
Stroke	-.101	0.170	0.348	1	.555
Heart failure	-.112	0.185	0.368	1	.544
Cardiovascular event	-.324	0.136	5.688	1	.017

**TABLE 2** Cox regression analysis between cardiovascular events and survival (adjusting for co-morbidities)

between annualized percentage delta eGFR on CVE, participants were placed into quartiles based on calculated delta eGFR. For those in the first quartile of delta eGFR, 22.5% experienced CVE compared with 24.1% in the fourth quartile having CVE, which was not statistically significant ( $P = .8$ ). In addition, the annualized percentage delta eGFR did not have an association with the cause of CKD, with 12% (SD 236.4) compared with 24.6% (SD 113.9) in non-diabetic nephropathy and diabetic nephropathy respectively ( $P = .49$ ). Furthermore, multivariate analysis with adjustment for cardiovascular risk factors as well as age revealed no significant association between CVE and ultimate commencement of KRT ( $P = .45$ ) (Table 2).

### 3 | DISCUSSION

In this study we identified an association between CVE and increased mortality in this CKD cohort. However, we did not detect an association between CVE and rate of kidney function deterioration in the

CKD cohort. Our results add to current knowledge in understanding the complex interplay between kidney disease and cardiovascular disease.

Hypertension, diabetes and other cardiovascular risk factors such as ageing, hyperlipidaemia, obesity and smoking are consistently reported to be major contributors to kidney function impairment.<sup>24</sup> Moreover, previous studies established the synergistic relationship between CKD and CVE, attributed in part to overlapping risk factors.<sup>25-29</sup> The overlap is also seen at the mechanistic level. For example, CVE-induced upregulation of the renin angiotensin system and the sympathetic nervous system could in turn lead to increased mortality and worsening deterioration of the renal function amongst those with CKD.

The advent of CVE increased mortality in this CKD cohort. The CVE group had a higher prevalence of cardiovascular risk factors (Table 1). Following adjustment for such risk factors, CVE was not significantly associated with mortality in the CKD cohort. Observations from other studies, revealed that CVE occur up to 30 times more frequently in CKD cohorts as compared with the age-adjusted general

population.<sup>30</sup> This self-propagating cycle results in more participants with CKD stage 3 or 4 dying of CVE rather than progressing to end stage kidney disease (ESKD).<sup>31</sup> However, it is important to note that our results could be biased due to the shorter follow-up time in participants with CVE.

We did not find an association between CVE and rate of kidney functional deterioration. However, it is important to note that the participants with CVE had a lower baseline eGFR to begin with. Therefore, the renal deterioration in participants with CVE given the lower baseline eGFR could still be a significant association. Furthermore, the follow-up for participants with CVE as stated prior was lower, and this could have caused bias in the result. Nevertheless, these findings were unexpected given that previous studies have shown clear associations between CVE and progression to ESKD. However, the association was reported for outcomes of ESKD but not for pre-terminal kidney delta eGFR.<sup>32</sup> On the other hand, groups have reported an association between CVE and deteriorating proteinuria.<sup>33,34</sup> Some groups used coronary artery calcium scores as a correlate of vascular calcification to show an association with CVE and CKD progression. In our study, we used annualized delta eGFR to examine and analyse relationships with CKD progression. However, despite using both percentage annualized delta eGFR and ESKD as an outcome, we did not determine a significant association between CVE and CKD progression in multivariate analysis. Given there was no association between CVE and CKD, we tried to explore whether the type of diagnosis for CKD was associated with renal deterioration. However, there was no significant association between percentage annualized eGFR and diabetic and non-diabetic nephropathy.

The major strength of our study was that we used a large sample population from a well recorded registry. The database also included a variety of comorbid conditions enabling us to analyse the association by adjusting for multiple plausible confounders. Furthermore, we used delta eGFR to determine CKD progression which allowed analysis of relationships between CVE and kidney dysfunction progression in a pre-dialysis setting where the evidence is limited.

Our study also has limitations. Firstly, the study was performed in a single site in a metropolitan city. Therefore, the findings may not be applicable to a general population across both metropolitan and non-metropolitan settings. Moreover, there may be bias from unmeasured variables despite confounding for several variables described above. We included participants with CVE and non-CVE in the same analysis; however, we could not calibrate for the severity of the CVE and adjust for this in the analysis, for example triple vessel vs single artery coronary artery disease. In addition, we did not include information about heart failure, or medications such as renin angiotensin system inhibitors or statin which could have impacted on the results. Lastly, the follow-up time was only 6 years, precluding appreciation of kidney function deterioration and mortality over a slower course or longer period of time.

In summary, our single centre study demonstrated some sign for association between CVE and increased mortality in a CKD cohort. This is in keeping with published literature. However, there was no difference between CVE and rate of deterioration of kidney function in this CKD cohort. Studies using larger datasets from multiple sites

and longitudinally followed for longer periods will confirm, or dispute, our observations.

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## CONFLICT OF INTEREST

The authors declare no potential conflict of interests. The results presented in this paper have not been published previously in whole or part except in abstract format.

## AUTHOR CONTRIBUTIONS

Research idea and study design: Andrew Jeyaruban, Wendy Hoy and Andrew Mallett; Acquired data: Andrew Jeyaruban; Data analysis: Andrew Jeyaruban, Zaimin Wang and Jianzhen Zhang; Supervision: Wendy Hoy and Andrew Mallett; Draft writing: Andrew Jeyaruban, Wendy Hoy and Andrew Mallett. All authors interpreted the results, revised the draft and approved the final version of the manuscript.

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