REVIEW

Costs and Healthcare Resource Use Associated with Risk of Cardiovascular Morbidity in Patients with Chronic Kidney Disease: Evidence from a Systematic Literature Review

Oliver Darlington · Carissa Dickerson · Marc Evans · Phil McEwan ·

Elisabeth Sörstadius · Daniel Sugrue · Heleen van Haalen ·

Juan Jose Garcia Sanchez

ABSTRACT

Introduction: The management of chronic kidney disease (CKD) costs in excess of $114 billion in the USA and £1.45 billion in the UK annually and is projected to increase alongside the increasing disease prevalence. The aim of this review was to evaluate the risks of cardiovascular (CV) morbidity, CV mortality or all-cause mortality based on KDIGO (Kidney Disease: Improving Global Outcomes) 2012 categorisations and estimate the additional costs and healthcare resource utilisation associated with CV morbidity linked to CKD severity in US and UK settings.

O. Darlington · C. Dickerson · P. McEwan ·
D. Sugrue
Health Economics and Outcomes Research Ltd.,
Cardiff, UK

M. Evans
Diabetes Resource Centre, Llandough Hospital,
Cardiff, UK

E. Sörstadius · H. van Haalen
Global Market Access and Pricing, AstraZeneca,
Mölndal, Sweden

J. J. Garcia Sanchez (✉)
Global Market Access and Pricing, AstraZeneca,
Cambridge, UK
e-mail: juanjose.garciasanchez@astrazeneca.com

Methods: A systematic literature review was conducted of studies reporting on the risk of CV morbidity, CV mortality or all-cause mortality characterised by CKD severity (published between January 2000 and September 2018). Additional costs and bed days associated with CKD severity in the USA and UK were estimated on the basis of median hazard ratios for CV morbidity risk at each CKD and albuminuria stage.

Results: Twenty-nine studies reported risk of adverse clinical outcomes based on KDIGO categorisations. Compared to stage 1 (or without) CKD, patients with stage 5 CKD and macroalbuminuria experienced a relative risk increase of 11.77–12.46 across all outcomes. Additional costs and bed days associated with stage 5 CKD and macroalbuminuria (versus stage 1 (or without) CKD) per 1000 patient years were US$3.93 million and 803 bed days and £435,000 and 1017 bed days, in the USA and UK, respectively.

Conclusion: Risks of adverse clinical outcomes increase with CKD and albuminuria severity and are associated with substantial additional costs and resource utilisation. Thus, early diagnosis and proactive management of CKD and its complications should be a priority for healthcare providers to alleviate the burden of CV morbidity and its management on healthcare resources.

Key Summary Points

Costs associated with the management of CKD are significant and are projected to rise alongside the increasing prevalence of CKD due to ageing populations and an increased prevalence of comorbidities

The aim of this study was to quantify the costs and impact on service delivery that CV morbidity associated with CKD—as categorised by KDIGO classification— imposes on healthcare providers in both US and UK settings

The risk of CV morbidity and the costs and bed days associated with its management increased substantially with CKD severity

Albuminuria was a significant driver of the health economic burden associated with the management of CKD-related CV morbidity; costs and bed days associated with managing a patient with macroalbuminuria are four to eight times greater than for a patient with normoalbuminuria at the same CKD stage

The results highlight the clinical and economic importance of early diagnosis and proactive management of CKD to reduce the risk of adverse clinical outcomes and their associated burden

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13360040.

INTRODUCTION

The prevalence of chronic kidney disease (CKD) is estimated to be 8–16% worldwide and continues to grow as a result of an ageing population and an increasing prevalence of comorbidities, including type 2 diabetes and hypertension [1–3]. Consequently, costs associated with the management of CKD are significant. US Medicare expenditure for combined CKD and end-stage renal disease (ESRD) exceeded US\$114 billion (£86 billion) in 2016 [4], and the National Health Service (NHS) in England spent an estimated US\$1.95 billion (£1.45 billion) on CKD in 2009–2010 [5]. The healthcare burden of CKD is projected to increase alongside increasing disease prevalence and, when combined with a shortage of kidney specialists [6], the need exists to prioritise services and manage resource utilisation efficiently.

CKD severity has traditionally been evaluated on the basis of estimated glomerular filtration rate (eGFR) decline; however, in 2012 KDIGO (Kidney Disease: Improving Global Outcomes) highlighted the importance of albuminuria in the evaluation and prognostication of CKD [7]. It is relatively well established in the literature that more advanced CKD is associated with poor outcomes [8, 9]; however, it remains uncertain how the magnitude of the risks of CV morbidity and mortality (CV and all-cause mortality) change as CKD progresses according to the KDIGO categorisation of both eGFR and albuminuria.

Although the cost and service delivery implications of the direct management of CKD are well characterised [5, 10], especially in patients with ESRD, there is a need to update costs and healthcare resource utilisation in line with KDIGO CKD categorisation. A better understanding of the costs associated with the management of CV morbidity as a result of CKD will better support healthcare resource planning according to level of risk and therefore aid overall service prioritisation.

The primary aim of this study was to undertake a systematic literature review and meta-analysis to quantify the combined associations between eGFR and albuminuria and the

risks of CV morbidity, CV mortality and all-cause mortality in patients with CKD. We then aimed to utilise results from the meta-analysis to inform economic analyses to estimate the additional costs and bed days associated with the management of CV morbidity linked to advancing CKD and albuminuria in both US and UK settings.

METHODS

Systematic Literature Review

A systematic literature review was designed and conducted according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) checklist [11]. Inclusion criteria were defined prior to undertaking the literature searches. Searches were conducted across PubMed, Embase, The Cochrane Library and relevant conference proceedings from January 2000 to September 2018. Electronic search strategies for each database and a list of congresses are included in the Supplementary Material (Tables S1–S3). In addition, a grey literature search was performed to identify further studies that may have met the eligibility criteria and included relevant conference proceedings (Table S4), a free-text internet search and reference lists from relevant studies. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnote version X7. Titles and abstracts were independently assessed for eligibility by two reviewers [CD and Sukhvir Rai (Health Economics and Outcomes Research Ltd)]. Full texts of all potentially eligible studies (both open access and paywall-restricted) were retrieved and assessed against the Population-Intervention-Comparators-Outcomes-Study (PICOS) eligibility criteria (Table S5) independently by two reviewers. Any discrepancies between the two reviewers concerning eligibility were resolved by consensus.

Studies were included if they comprised adult patients with stages 2–5 CKD and reported the risk of CV morbidity, CV mortality or all-cause mortality characterised by both CKD and albuminuria stage. Advancing CKD was defined as worsening of either eGFR or albuminuria, or the worsening of combined eGFR and albuminuria. To align with KDIGO 2012 criteria, only studies that reported advancing CKD based on combined eGFR and albuminuria data were included in the main analysis; risks of CV morbidity, CV mortality and all-cause mortality based on the worsening of eGFR alone and albuminuria alone are included in the Supplementary Material (Tables S8 and S9). CV morbidity included CV disease (e.g. coronary heart disease and heart failure), cardiac or ischaemic events (e.g. myocardial infarction) and stroke. Patients receiving haemodialysis or peritoneal dialysis were not included in the analysis; studies specifically in patients with prior renal transplantation were not included; however, patients with prior transplantation may have been included in cohorts of included studies. Relative measures of risk [hazard ratios (HR) odds ratios (OR), incidence rate ratios (IRR), or relative risk (RR)] for CV morbidity, CV mortality and all-cause mortality were extracted to enable comparability of risk based on disease progression across studies. Meta-analyses were identified in the systematic review but were excluded from our meta-analysis. Studies that only assessed the impact of CKD of any severity in comparison with no CKD were excluded as this study aimed to characterise the impact of advancing CKD on outcomes. Studies conducted in child or adolescent patients and studies reported in languages other than English were also excluded, and searches were limited to publications from 2000 onwards to only capture contemporary data.

For analysis, categorical eGFR data were aligned with the corresponding CKD stage, where possible, as per KDIGO classification [7]. Albuminuria data were categorised as normoalbuminuria (normal to mildly increased), microalbuminuria (moderately increased) and macroalbuminuria (severely increased), based on the KDIGO 2012 classifications of urine albumin-to-creatinine ratio (UACR) less than

30 mg/g, 30–300 mg/g, and greater than 300 mg/g respectively. Those that reported data in alternative units (e.g. milligrams per millimole) were converted to milligrams per gram where possible. Extracted HRs and ORs were grouped according to eGFR and/or albuminuria category (based on KDIGO criteria) and further aligned as per the reference group. Associations were most frequently reported in terms of HR, and as such studies reporting the HR of CV morbidity, mortality or all-cause mortality associated with CKD stages 2, 3a, 3b, 4 and 5 in comparison with stage 1 or no CKD extracted. Extracted data were combined using a random-effects meta-analysis (R version 4.0.3) of log HRs with inverse variance weighting used for pooling, and all data are reported as mean HR (95% confidence interval), unless stated otherwise. To assess the impact of publication bias on the results of the meta-analysis, sensitivity analysis was conducted comparing the results of random- and fixed-effects meta-analysis and the exclusion of studies including fewer than 10,000 patients, and results displayed in a funnel plot.

For analysis exploring associations between renal impairment and adverse patient outcomes within comorbid subpopulations, HR and OR were pooled independently by CKD and albuminuria stage and the median and interquartile range (IQR) calculated to provide indicative measures of risk for each KDIGO category. All comparisons were based on data where stage 1 (or no) CKD and normoalbuminuria formed the reference groups. A subgroup analysis was also performed on patients according to baseline comorbidity.

A quality assessment was performed using the National Institute for Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Quality assessment was performed by one reviewer (CD) and checked by a second reviewer [Sukhvir Rai (Health Economics and Outcomes Research Ltd)]. Disagreements were resolved by consensus. Studies were not categorised by quality and no studies were excluded from the meta-analysis on the basis of the outcome of the quality assessment.

Health Economic Analyses

The summarised risks of CV morbidity at each CKD and albuminuria stage obtained from the conducted systematic literature review were used to estimate the additional costs and hospitalisation requirements of CV morbidity associated with each CKD and albuminuria stage compared to stage 1 (or without) CKD. Relative risks derived from the results of the systematic review were used to estimate the additional risk of CV events with advancing CKD, which were then scaled to CKD population level figures based on prevalence data from the US Renal Data System [12], NHS England [13] and the UK Renal Registry [14], and population data reported by the US Census Bureau [15] and the UK Office for National Statistics [16]. Total costs and median length of hospital stay estimates associated with CV events were sourced from published literature for analysis conducted from a US perspective [17], and from NHS data [18] for UK analysis (Table S10 presents input costs and healthcare resource utilisation for each setting).

A baseline risk of coronary heart disease (CHD), ischaemic stroke or transient ischaemic attack (TIA) in patients without CKD was derived using the QRISK-3 risk equation, a validated risk equation developed on a large cohort of primary care patients in England to predict the incidence of CV disease [19]. Patient characteristics were aligned to the population of the Chronic Renal Insufficiency Cohort [20], an observational study that examined risk factors for the progression of CKD and CV disease to provide patient characteristics representative of a CKD population and allow the estimation of marginal risk associated with CKD alone. Any patient characteristics not reported were assumed to be equal to the QRISK-3 development cohort.

RESULTS

Systematic Literature Review

Study Characteristics

The literature search identified 4168 studies after the removal of duplicates. After titles and abstracts were reviewed, 3396 studies were excluded and the full texts for the remaining 772 studies were retrieved and reviewed in full (Fig. S1). A total of 314 studies met the inclusion criteria and reported associations between eGFR and/or albuminuria and the risk of CV morbidity, CV mortality or all-cause mortality, or included risk equations that included eGFR and/or albuminuria as predictive covariates for CV morbidity or mortality. Whilst the majority of included studies evaluated the risk of CV morbidity, CV mortality or all-cause mortality by either eGFR or albuminuria worsening alone, the primary focus of this analysis was on the 29 studies that assessed the risk of adverse clinical outcomes based on the combined associations between eGFR and albuminuria (Table 1).

Of these 29 studies, 26 were prospective observational cohort studies. Seven studies were undertaken in US populations, and eight in European populations, and sample sizes ranged from 531 to 1,128,310 patients. A quality assessment of the 29 included studies is included in Table S6. Furthermore, funnel plot analysis indicated the potential presence of publication bias (Fig. S2); however, there was consistency in results between the random- and fixed-effects meta-analysis between the sensitivity analysis which excluded studies with fewer than 10,000 patients (Table S11).

Risk of Adverse Clinical Outcomes with Advancing CKD

The risks of CV morbidity, CV mortality and all-cause mortality were strongly associated with more advanced CKD (Fig. 1; Table S7). The results of meta-analyses showed that across all outcomes, risk increased with CKD stage and increased further with the worsening of albuminuria. Compared to stage 1 (or without) CKD with normoalbuminuria the relative risks [mean HR (95% confidence interval)] of CV morbidity,

CV mortality and all-cause mortality were 2.58 (2.22–2.99), 3.10 (2.52–3.81) and 2.59 (2.40–2.81) respectively at stage 2 CKD with macroalbuminuria. Stage 5 CKD with macroalbuminuria was associated with further increases in the relative risks of CV morbidity, CV mortality and all-cause mortality of 11.82 (7.50–18.64), 12.46 (8.12–19.12) and 11.77 (9.66–14.36) respectively [versus stage 1 (or without) CKD with normoalbuminuria].

The presence of CV comorbidity at baseline was associated with a higher risk of all-cause mortality (Table 2). Based on eGFR categorisation alone (i.e. independent of albuminuria stage), the relative risks of all-cause mortality in patients with diabetes and stage 4 or 5 CKD were 6.42 and 9.49 respectively compared with 3.01 and 4.26 respectively across the entire cohort. The relative risks of all-cause mortality in patients with prior MI were also elevated compared to the entire cohort, at 4.82 and 5.21 at stages 4 and 5 CKD respectively. There was insufficient data available to evaluate the effect of baseline CV morbidity on all-cause mortality at different stages of albuminuria.

Health Economic Analyses

The increased risk of CV morbidity reported in patients with CKD translated into significant additional costs and bed days associated with its management in both US and UK settings (Table 3). Albuminuria was the largest driver of increased cost, with the additional cost of managing CV morbidity in patients with stage 2 CKD and macroalbuminuria (versus stage 1 (or without) CKD and normoalbuminuria) estimated to be $573,136 and £63,332 for the US and UK respectively per 1000 patient years. In patients with stage 5 CKD and macroalbuminuria, the estimated additional costs are $3,933,141 and £434,618 per 1000 patient years compared with stage 1 (or without) CKD and normoalbuminuria.

The required bed days associated with CV morbidity also increased with CKD and albuminuria severity. Stage 2 CKD with macroalbuminuria was associated with an estimated additional 117 bed days per 1000 patient years

Table 1 Study characteristics of the subgroup of 29 studies that met the inclusion criteria and reported combined associations between eGFR, albuminuria and the risk of adverse clinical outcomes

Author	Year	Country	Study design	Setting	Sample size	Median eGFR (mL/min/1.73 m²)	CKD stages included (% of cohort)*					Follow-up (years)	Outcome definition
							2	3a	3b	4	5		
Alonso et al. [28]	2011	USA	Prospective observational cohort	Population	10,328	NR	59	5.5	5.5	1	NR	10.1	Atrial fibrillation
Amin et al. [29]	2013	USA	Prospective observational cohort	Population	42,761	NR	45	13	6	1	1	4.0	All-cause mortality
Berhane et al. [30]	2011	USA	Prospective observational cohort	Population	2420	110	8.8	1.3	1.3	0.6	NR	10.2	All-cause mortality
Blecker et al. [31]	2011	USA	Prospective observational cohort	Population	10,975	NR	62.4	8.1	1.3	NR	NR	8.3	Heart failure
Deo et al. [32]	2017	USA	Prospective observational cohort	Population	27,296	NR	44	7.3	1.2	1.2	1.2	6.1	Sudden cardiac death
Kovesdy et al. [33]	2013	USA	Prospective observational cohort	Database	298,875	NR	NR	NR	NR	NR	NR	5.0	All-cause mortality
Muntner et al. [34]	2011	USA	Prospective observational cohort	Population	24,350	NR	NR	NR	NR	NR	NR	4.5	All-cause mortality
Yuyun et al. [35]	2004	UK	Prospective observational cohort	Population	20,911	NR	NR	NR	NR	NR	NR	6.3	All-cause mortality, CV-specific mortality, CV events

Table 1 continued

Author	Year	Country	Study design	Setting	Sample size	Median eGFR (mL/min/1.73 m^2)	CKD stages included (% of cohort)*					Follow-up (years)	Outcome definition
							2	3a	3b	4	5		
Bruno et al. [36]	2007	Italy	Prospective observational cohort	Population	1565	NR	57.4	25.6	6.8	1.5	NR	11.0	CV-specific and all-cause mortality
Garofolo et al. [37]	2018	Italy	Prospective observational cohort	Secondary care (Outpatient)	774	95.2	3.4	0.94	0.94	0.94	0.94	8.3	All-cause mortality
Nerpin et al. [38]	2011	Sweden	Prospective observational cohort	Population	1113	75	NR	NR	NR	NR	NR	12.9	All-cause mortality
Sasso et al. [39]	2012	Italy	Prospective observational cohort	Secondary care (outpatient)	742	66	43.5	17.2	17.2	5.1	0.8	4.6	CV event
Solini et al. [40]	2012	Italy	Prospective observational cohort	Secondary care (outpatient)	15,773	NR	45	7.5	7.5	1	1	NR	CV disease
van der Velde et al. [41]	2010	The Netherlands	Prospective observational cohort	Population	8047	81	NR	NR	NR	NR	NR	7.0	CV event
Vlek et al. [42]	2008	The Netherlands	Prospective observational cohort	Primary and secondary care	2600	NR	NR	NR	NR	NR	NR	4.0	CV-specific mortality, all-cause mortality, CV event
Lim et al. [43]	2015	Singapore	Prospective observational cohort	Population	7098	NR	87.84	8.49	NR	NR	NR	4.3	Incident CV disease and all-cause mortality

Table 1 continued

Author	Year	Country	Study design	Setting	Sample size	Median eGFR (mL/min/1.73 m²)	CKD stages included (% of cohort)*					Follow-up (years)	Outcome definition
							2	3a	3b	4	5		
So et al. [44]	2006	Hong Kong	Prospective observational cohort	Secondary care (outpatient)	4421	91	37	5.2	5.2	1.6	0	3.3	Composite of CV mortality, angina, MI, stroke, revascularization, or HF
Wada et al. [45]	2014	Japan	Retrospective observational cohort	Secondary care (outpatient)	4,328	77	47.4	14.8	7.2	2.7	0.1	7.0	All-cause mortality and CV event
Wang et al. [46]	2017	China	Prospective observational cohort	Population	47,204	92	40.1	NR	NR	NR	NR	6.1	CV-specific and all-cause mortality
Wen et al. [47]	2008	Taiwan	Prospective observational cohort	Population	56,977	69	37.7	22.5	22.5	1.3	0.7	13.0	CV-specific and all-cause mortality
Yokoyama et al. [48]	2008	Japan	Cross-sectional	Primary and secondary care	3002	NR	NR	NR	5.8	5.8	5.8	NR	CV disease
Zhang et al. [49]	2015	China	Prospective observational cohort	Population	20,702	94	29.4	NR	NR	NR	NR	4.5	Stroke
Molnar et al. [50]	2017	Canada	Retrospective observational cohort	Database	736,666	84	NR	5.75	5.75	1.2	0.2	6.0	Incident atrial fibrillation

Table 1 continued

Author	Year	Country	Study design	Setting	Sample size	Median eGFR (mL/min/ 1.73 m²)	CKD stages included (% of cohort)*					Follow-up (years)	Outcome definition
							2	3a	3b	4	5		
Salles et al. [51]	2011	Brazil	Prospective observational cohort	Secondary care (outpatient)	531	77	35	14	14	5	0	4.9	CV-specific and all-cause mortality
Tonelli et al. [52]	2011	Canada	Prospective observational cohort	Secondary care (outpatient)	920,985	NR	64.9	8.7	1.8	0.4	0	2.9	All-cause mortality, acute MI, stroke or TIA
Clase et al. [53]	2011	Multinational	Prospective observational cohort	Secondary care (outpatient)	27,620	73	37.7	19	5	0.3	0.3	4.6	Composite of CV death, MI, stroke, or HF
Matsushita et al. [54]	2010	USA and the Netherlands	Prospective observational cohort	Population	1,128,310	NR	NR	NR	NR	NR	NR	7.9	CV-specific and all-cause mortality
Ninomiya et al. [55]	2009	Multinational	Pooled analysis from a randomised controlled trial	Secondary care (outpatient)	10,640	76	NR	NR	NR	NR	NR	4.0	Composite of CV disease and CV-specific death
Wang et al. [56]	2018	USA and China	Prospective observational cohort	Database	25,269	NR	NR	NR	NR	NR	NR	6.9	All-cause mortality

CKD chronic kidney disease, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *MI* myocardial infarction, *NR* not reported, *TIA* transient ischaemic attack, *UK* United Kingdom, *USA* United States of America

*All studies listed in this table reported combined associations between CKD and albuminuria stage and outcome; however, many did not report the proportions of patients at each CKD stage alone
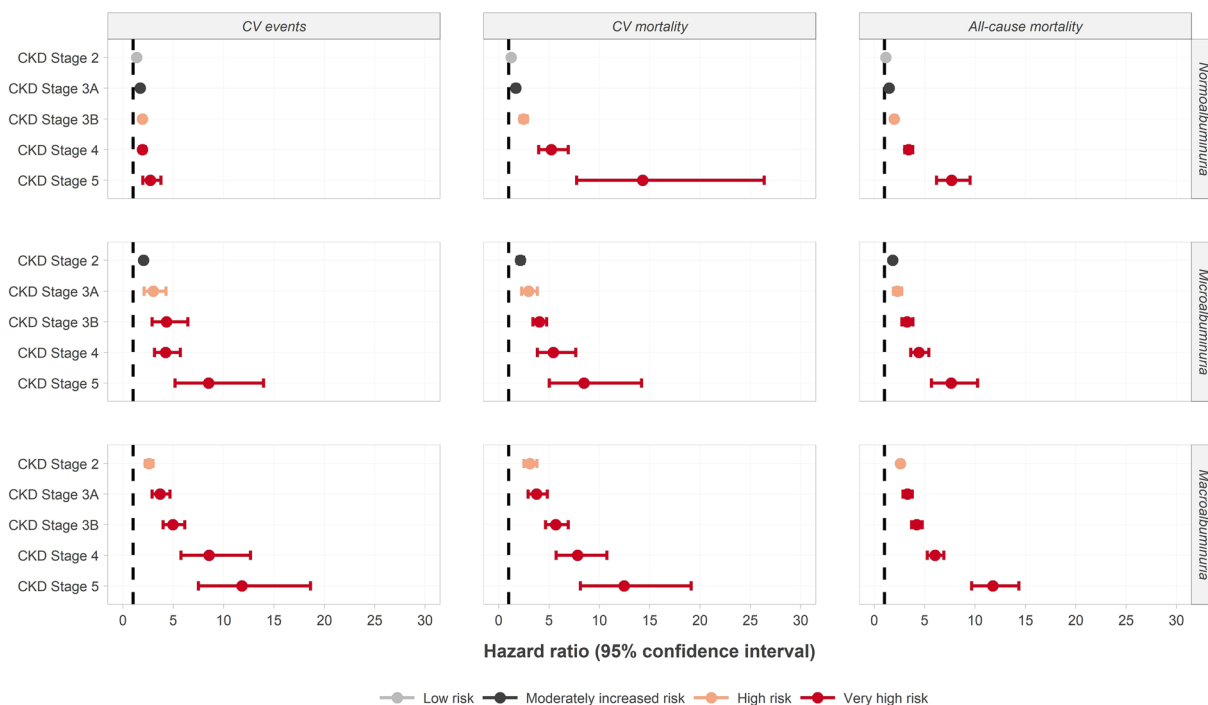
Fig. 1 Associations between eGFR (left axis), albuminuria (right axis) and the risk of cardiovascular events (first column), cardiovascular mortality (second column) and all-cause mortality (third column). Data are mean (95% CI) hazard ratios for the risk of outcome at each eGFR and albuminuria stage from the subgroup of 29 studies that met the inclusion criteria and reported combined associations between eGFR, albuminuria and the risk of adverse clinical outcomes. Risk is for each CKD and albuminuria stage vs. stage 1 (or without) CKD and normoalbuminuria. Increase in risk is vs. stage 1 (or without) CKD with normoalbuminuria

in the USA and 148 in the UK versus stage 1 (or without) CKD and normoalbuminuria. Patients with stage 5 CKD and macroalbuminuria require an estimated additional 803 and 1017 bed days per 1000 patient years for the management of CV morbidity in the USA and UK respectively versus stage 1 (or without) CKD and normoalbuminuria.

At a population level, total estimated additional annual costs and bed days required for the management of CV morbidity varied according to the prevalence of each CKD stage and albuminuria level. In the USA, patients with stage 5 CKD with macroalbuminuria only make up 0.2% of the total CKD population but account for 4% of additional estimated costs and bed days associated with management (i.e. $169.3 million and 34,564 bed days annually). In the UK, patients with stage 5 CKD and macroalbuminuria make up 2% of the CKD

population but account for 17% of additional estimated costs and bed days associated with its management (i.e. £31.0 million and 72,616 bed days annually). Furthermore, in the USA, although patients with stage 2 CKD with normoalbuminuria make up 75% of the CKD population (versus 33% in the UK), they only account for 43% of the additional annual estimated costs and bed days. There was insufficient data to explore the impact of comorbidities on additional costs and bed days due to CV morbidity in these patients.

DISCUSSION

The objectives of this systematic literature review were to evaluate the risk of CV morbidity, CV mortality and all-cause mortality in patients with CKD at each eGFR and

Table 2 Associations between baseline comorbidity, CKD stage and all-cause mortality

	Entire cohort	Baseline comorbidity			
		Diabetes	Hypertension	MI	Stroke*
Stage 2 CKD	1.11 (1.03–1.18)	1.27 (0.92–1.29)	1.14 (0.91–1.37)	1.21 (1.13–1.36)	OR 1.02 (0.96–1.26)
Stage 3a CKD	1.54 (1.43–1.67)	1.23 (1.23–1.23)	1.23 (1.23–1.23)	1.56 (1.54–2.05)	OR 1.71 (1.03–2.40)
Stage 3b CKD	2.22 (1.80–2.73)	1.40 (1.40–1.40)	1.40 (1.40–1.40)	1.99 (1.98–2.00)	OR 1.17 (1.17–1.17)
Stage 4 CKD	3.01 (2.40–3.76)	6.42 (5.19–9.50)	3.51 (2.62–3.54)	4.82 (4.11–5.83)	OR 3.62 (2.84–3.79)
Stage 5 CKD	4.26 (3.21–5.63)	9.49 (9.49–9.49)	–	5.21 (3.88–6.54)	–

Data are median (interquartile range; IQR) hazard ratios from all 323 studies that met the inclusion criteria and reported associations between CKD stage and all-cause mortality. Risks are for each CKD stage vs. stage 1 (or without) CKD
CKD chronic kidney disease, *MI* myocardial infarction, *OR* odds ratio
*There were no studies identified that reported the risk of all-cause mortality with advancing CKD in patients with prior stroke as hazard ratios; therefore, data from one study that reported risk as odds ratios [OR: median (IQR)] is presented

albuminuria stage (according to KDIGO categorisations [7]), and to quantify the cost and healthcare resource utilisation implications associated with the management of CV morbidity in CKD in both US and UK settings. In total, 29 studies reported on the risk of adverse clinical outcomes based on the combined relationship between eGFR and albuminuria stage as per KDIGO categorisation.

In 2012, KDIGO published guidelines on the evaluation and management of CKD [7]. Earlier KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines [21] focused on eGFR alone to categorise CKD and quantify patient risk and did not account for variations in albuminuria. KDIGO 2012 highlighted the importance of albuminuria to aid in the identification of higher-risk patients and recommended the measurement of urinary protein alongside eGFR to better evaluate CKD. Of the 29 studies included in this review, 10 were published from 2013 onwards. Of those, only six reported eGFR and albuminuria as per KDIGO categorisation, and indicates that further research is required to ensure that risk of adverse outcomes at each CKD and albuminuria stage can be accurately evaluated.

Across all outcomes, risk increased with eGFR decline and increased further with the worsening of albuminuria; even at the same level of renal function, worsening of albuminuria could increase the risk of CV morbidity, CV mortality or all-cause mortality by over fourfold. An increase in the risk of adverse outcomes was apparent even in patients with early-stage CKD. Patients with stage 2 CKD with normoalbuminuria had up to 36% increases in the risk of adverse clinical outcomes, increasing up to threefold for those with stage 2 CKD and macroalbuminuria; the risk increased 12-fold in patients with stage 5 CKD and macroalbuminuria.

The additional costs and bed day provision associated with the management of CV morbidity in patients with CKD are substantial in the UK, but are significantly higher in the USA. These differences are likely driven by the greater cost of healthcare in the USA compared with the UK and reflect differences in per capita costs of healthcare between the two countries [US\$4018 (£2989) per person in the UK in 2017 vs. US\$10,398 (£7736) per person in the USA] [22].

Whilst micro- and macroalbuminuria (at any CKD stage) are less prevalent than normoalbuminuria in the overall CKD population—13% and 24% of all patients with CKD in the USA and UK respectively—the cost and healthcare resource burden associated with the management of CKD-related CV morbidity in these patients is significant compared to those with normoalbuminuria. At a patient level, the

Table 3 Additional annual cost and bed days associated with CHD, ischaemic stroke and TIA in patients with advancing CKD and albuminuria based on KDIGO 2012 criteria in US and UK CKD populations

Marginal cost of CV morbidity associated with CKD

		Estimate per 1,000 patient years			Population estimate		
		Normoalbuminuria	Microalbuminuria	Macroalbuminuria	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
United States	CKD Stage 2	$132,341	$379,088	$573,136	$1,910,998,294	$525,652,292	$82,212,680
	CKD Stage 3a	$258,566	$727,651	$972,087	$445,076,228	$278,338,598	$139,439,770
	CKD Stage 3b	$338,108	$1,202,908	$1,438,688	$161,664,767	$230,066,013	$137,580,493
	CKD Stage 4	$339,534	$1,174,121	$2,743,120	$21,105,079	$56,140,098	$196,741,612
	CKD Stage 5	$628,504	$2,725,672	$3,933,141	$3,005,164	$52,130,719	$169,255,245

		Estimate per 1,000 patient years			Population estimate		
		Normoalbuminuria	Microalbuminuria	Macroalbuminuria	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
United Kingdom	CKD Stage 2	£14,624	£41,890	£63,332	£16,723,995	£4,600,217	£719,480
	CKD Stage 3a	£28,572	£80,407	£107,417	£31,800,908	£19,887,425	£9,963,038
	CKD Stage 3b	£37,361	£132,923	£158,977	£12,272,963	£17,465,721	£10,444,579
	CKD Stage 4	£37,519	£129,742	£303,119	£1,587,335	£4,222,354	£14,797,139
	CKD Stage 5	£69,451	£301,191	£434,618	£550,775	£9,554,324	£31,020,472

Marginal bed days due to CV morbidity associated with CKD

		Estimate per 1,000 patient years			Population estimate		
		Normoalbuminuria	Microalbuminuria	Macroalbuminuria	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
United States	CKD Stage 2	27.0	77.4	117.0	390,244	107,343	16,789
	CKD Stage 3a	52.8	148.6	198.5	90,889	56,839	28,475
	CKD Stage 3b	69.0	245.6	293.8	33,013	46,982	28,095
	CKD Stage 4	69.3	239.8	560.2	4,310	11,464	40,177
	CKD Stage 5	128.3	556.6	803.2	614	10,646	34,564

		Estimate per 1,000 patient years			Population estimate		
		Normoalbuminuria	Microalbuminuria	Macroalbuminuria	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
United Kingdom	CKD Stage 2	34.2	98.1	148.3	39,149	10,769	1,684
	CKD Stage 3a	66.9	188.2	251.5	74,442	46,554	23,322
	CKD Stage 3b	87.5	311.2	372.1	28,730	40,885	24,450
	CKD Stage 4	87.8	303.7	709.6	3,716	9,884	34,638
	CKD Stage 5	162.6	705.1	1017.4	1,289	22,366	72,616

Colours are based on KDIGO 2102 categories: Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk. Increase in cost is vs. stage 1 (or without) CKD with normoalbuminuria

KDIGO kidney disease: improving global outcomes, *CKD* chronic kidney disease

additional costs and bed days associated with managing a patient with macroalbuminuria are four to eight times greater than for a patient with normoalbuminuria at the same CKD stage. At a population level, 42% and 66% of estimated additional costs and bed days in the USA and UK respectively that are required to manage CV morbidity in patients with CKD are consumed by those with micro- or macroalbuminuria.

Given this substantial increase in cost and healthcare resource utilisation associated with the management of CV morbidity in micro- and macroalbuminuria and in latter-stage CKD, it should be a priority of healthcare providers to avoid patients reaching macroalbuminuria and advanced stage CKD through early identification of the disease and proactive management—especially in patients with more rapidly advancing disease—to slow CKD and albuminuria progression. Any reduction in the number of patients reaching latter-stage CKD has the potential to alleviate the burden of CV morbidity and its impact on healthcare resources.

Studies included in this systematic review were conducted across a broad population of patients with CKD, with approximately one-third conducted in higher-risk patient cohorts, including patients with diabetes, hypertension, prior MI or stroke, amongst others. Risks of all-cause mortality based on worsening eGFR in the subgroups of patients with baseline comorbidity tended to be higher than across the entire

cohort, with patients with diabetes at highest risk. Therefore, it would be prudent for healthcare providers to both prioritise CKD screening in patients with comorbidities to ensure early identification of CKD, and ensure optimal management of CKD in those already diagnosed to slow progression and thus reduce the already elevated risk of morbidity and early mortality in those with more advanced disease.

The major strength of this systematic literature review is the applicability of the findings across a wide CKD population. Approximately one third of the studies included were conducted in higher-risk patient cohorts and the remaining were based on general population cohorts, many of which included patients with significant comorbidity. However, this study is not without limitations. There was significant heterogeneity in the categorisation of eGFR and albuminuria across studies and many did not align with KDIGO categories, preventing their inclusion in the overall analysis. There is also potential for publication bias to impact the generalisability of the results; if fewer studies with non-significant outcomes are published, it could result in an overestimation of the level of risk associated with more advanced CKD. Whilst the funnel plot of included studies indicated the potential presence of publication bias, this is thought to be primarily as a result of the inclusion of large observational studies, and the clinical demographics of the CKD population rather than the presence of significant publication bias, as high-risk patients, such as those with stage 5 CKD, make up a comparatively small proportion of the overall CKD population. This conclusion was supported by consistency in results between the random- and fixed-effects meta-analysis and also the sensitivity analysis which excluded studies with fewer than 10,000 patients. There is also the potential that these findings are confounded as a result of significant differences in patient characteristics (including comorbidities such as type 2 diabetes, heart failure etc.) between different KDIGO categorisations; however, many of the included studies adjusted results for relevant patient characteristics and there is a well-established causal relationship between renal impairment and the incidence of adverse clinical outcomes in patients with CKD.

In addition, this analysis has only addressed risk at absolute eGFR/albuminuria stages, whereas risk is also linked to the rate of eGFR decline/albuminuria rise. Future research could explore the risk of adverse clinical outcomes based on the rate of CKD progression and delve deeper into the role that comorbidities such as diabetes or heart failure play in the risk of adverse clinical outcomes. Furthermore, the economic analysis in this manuscript focused only on the additional costs and bed days associated with the management of CV morbidity associated with CKD; there are further costs (e.g. monitoring and treatment costs) that also need to be considered when evaluating the full economic burden of CKD. Additionally, costs associated with CV morbidity in the USA setting were derived in a population of patients with type 2 diabetes rather than CKD; however, costs represent the per-event cost associated with the incidence of CV events and as such costs are likely to be representative of other comorbid populations.

Lastly, the quality of our analysis is limited by the availability of source data to inform our cost and bed day estimations. During this analysis, we noted significant differences in the prevalence of stage 2 CKD with normoalbuminuria in US and UK (75% vs. 33% respectively) CKD populations, likely due to the availability of data rather than significant differences in clinical practice and the diagnosis of early-stage CKD. Indeed, epidemiological data to inform US estimates was sourced from the US Renal Data System [4] which includes both diagnosed and potentially undiagnosed patients with CKD. Given our outcome of interest was CV morbidity and CV events will happen in both diagnosed and undiagnosed patients, the US Renal Data System data are relevant; however, these differences between US and UK data indicate that the true number of patients with earlier-stage CKD in the UK may be underestimated.

Safe and effective therapies to slow the rate to CKD progression are essential to reduce the cost and healthcare resource burden of CV morbidity in CKD. Treatment options to delay

CKD progression have previously been limited to renin–angiotensin–aldosterone system inhibitors, despite considerable residual risk of disease progression. However, following the observation that sodium–glucose co-transporter 2 (SGLT2) inhibitors demonstrated a reduced risk of CV and renal events in patients with type 2 diabetes [23–25], this class of drug is now being studied in CKD populations. Dapagliflozin has recently been evaluated in patients with and without type 2 diabetes in the DAPA-CKD study [26]. Dapagliflozin was associated with reductions in the risk of kidney failure, CV mortality, or hospitalisation for heart failure, and prolonged survival in patients with CKD with or without type 2 diabetes [27], potentially signalling a new class of therapy for patients with CKD, regardless of diabetes status.

In conclusion, the results of this systematic review and meta-analysis demonstrate that CKD (with or without albuminuria) is associated with poor patient outcomes even from an early stage. The risks increased with more advanced disease and the highest risk of CV morbidity, CV mortality and all-cause mortality was observed consistently in patients with stage 5 CKD with macroalbuminuria. The additional costs and bed days associated with management of the associated CV morbidity in patients with CKD are substantial and increase with disease severity. Early diagnosis and proactive management of CKD is important to be able to slow CKD progression, and reduce the risk of adverse clinical outcomes in patients with CKD. More effective management of the disease may result in a reduced healthcare, societal and patient burden of CKD.

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