Clinical Kidney Journal, 2023, vol. 16, no. 12, 2304–2308

https://doi.org/10.1093/ckj/sfad235
Advance Access Publication Date: 3 October 2023
Editorial Comment

The Forgotten Sex
gender disparities in kidney disease

EDITORIAL COMMENT

Cardiovascular disease in older women with CKD

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INTRODUCTION

Chronic kidney disease (CKD) is a significant global health concern. In 2019, 850 million individuals were recorded as having kidney impairment, and there is an expectation that by 2040 CKD will be the fifth leading cause of death worldwide [1]. Women are disproportionately affected, experiencing lower estimated glomerular filtration rate (eGFR) and greater prevalence of albuminuria when compared with men [2].

Patients with CKD, particularly those requiring kidney replacement therapy (KRT), have significantly reduced life expectancy when compared with age-matched individuals in the general population [3]. Excess mortality occurs across the full spectrum of CKD stages and those with a CKD diagnosis have a greater probability of dying than developing end-stage kidney disease [4].

Cardiovascular (CV) disease remains a leading cause of death in CKD patients, who experience a high burden of hypertension, diabetes and CV comorbidity [5]. CV disease burden begins early in CKD, with eGFR <60 mL/min/1.73 m^2 and albumin creatinine ratio 30 mg/g being associated with higher rates of CV mortality, independent of existing CV risk factors [6]. This risk increases with CKD progression, with 5 mL/min/1.73 m^2 deterioration in kidney function being associated with a 26% increased risk of CV death [7]. The CKD population is aging, with a mean age of 75 years described among a large pooled patient cohort [8]. The median age of prevalent CKD patients with eGFR $\leq$30 mL/min/1.73 m^2 in the UK is now 77.6 years [9]. Enhanced CV risk is particularly relevant to these patients, the majority of whom will never require KRT prior to death and who are as likely to experience a major adverse cardiovascular event (MACE) as they are to require KRT [10].

In their investigation of the role of gender in CV disease in older adults with CKD, Astley *et al.* focused on a patient group that is traditionally under-represented in the medical literature [11]. This editorial considers the burden of CV disease in CKD, with particular emphasis on gender disparities in diagnosis, treatment, outcomes and evidence-base. In keeping with Astley *et al.*, we elect to describe 'gender' differences, whilst acknowledging that sex and gender are distinct.

DEFINING CKD IN OLDER WOMEN

KDIGO guidelines recommend diagnosis and staging of CKD severity on the basis of measurement of GFR and albuminuria [12]. This mechanism for stratifying CKD has the potential to overestimate renal function in women, particularly when considering older women [11].

The Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) was used by Astley *et al.* [11] as a measurement of kidney function and is commonly used by clinicians for prognostication in CKD. However, the CKD-EPI study population under-represented older adults, with only 13% of participants $>$65 years and $<$2% of participants $>$75 years [13]. Women were also under-represented, constituting 43% of the total study group [14]. In a study of community-based older adults, CKD-EPI was demonstrated to overestimate kidney function in women, particularly at higher eGFR [15]. It is therefore likely that we have not yet captured the true burden of CKD in women globally.

Several mechanisms exist for GFR measurement, but measurement of the concentration of creatinine (eGFRcr) or cystatin C (eGFRcys) in serum are the most commonly used in clinical practice [16]. eGFRcr is an imperfect measure of kidney function, as serum creatinine concentrations are dependent on muscle cell turnover, and therefore vary with non-GFR determinants such as physical activity, muscle inflammation, catabolic states and dietary protein intake [16]. CKD accelerates physiological changes such as sarcopenia, systemic inflammation and protein malnutrition which contribute to the frailty phenotype in older adults [17]. While also influenced by non-GFR determinants such as inflammation and cardiometabolic disease, eGFRcys may be considered a more accurate method of GFR estimation [18].

Received: 18.7.2023; Editorial decision: 7.9.2023

In a dedicated study of older adults, Potok *et al*. demonstrated that the lower measurement of eGFRcr and eGFRcys provided a more accurate estimate of eGFR [19]. A discrepancy between eGFRcr and eGFRcys is commonly seen in older women, and there is evidence that using a combination of creatinine and cystatin C improves accuracy of GFR estimation in this circumstance [20].

There is a need for a greater body of evidence evaluating the quantification of CKD in women, in particular older women, to enable more accurate diagnosis and to inform prognostic conversations.

DEFINING MACE

How studies define MACE has a direct bearing on whether they capture the burden of CV disease in women with CKD. There is wide variation in the definition of MACE used within medical literature [21]. Studies most commonly include acute myocardial infarction and acute ischaemic stroke, and least commonly include heart failure [21]. This is directly relevant to older women, who experience higher mortality and hospitalization as a consequence of heart failure [22]. Inconsistencies in MACE measurement likely contribute to the inadequate characterization of MACE in older women with CKD.

Astley *et al*. used a broad definition to capture MACE which includes comorbidity or hospitalization as a result of cerebrovascular disease, coronary artery disease, peripheral vascular disease, arrhythmia and heart failure diagnoses [11]. Broad composite outcomes such as these are appealing as they reduce the study population size needed to demonstrate a significant event rate. This broad definition of MACE could also be viewed as inclusive of the group of older women with CKD that the study is aiming to characterize.

However, broad composite endpoints such as this have inherent flaws. Equal weighting is often given to each event type, meaning that studies have no ability to capture the relative impact or clinical significance of an event for patients [23]. Broad composite endpoints for MACE also draw comparison between events that are underpinned by different pathophysiological mechanisms. If the goal of clinical research is to reduce adverse healthcare outcomes for patients, then this makes translation of research into therapeutic intervention incredibly challenging.

Using a broad definition of MACE in observational epidemiological studies is therefore important in order to capture the burden of disease in women. However, a study that sought to improve female MACE outcomes would have to focus on the mechanisms of MACE that are directly relevant to women.

RISK FACTORS AND MECHANISMS OF MACE IN OLDER WOMEN

Diabetes and hypertension remain prominent causes of renal function decline and mortality in patients with CKD [4]. However, women with CKD are less likely to have features of the metabolic syndrome, with smaller waist circumference, lower cholesterol, less diabetes and lower systolic blood pressure than their male counterparts [7]. This suggests that alternative mechanisms may be relevant to the development of CV disease in women.

Socioeconomic factors such as smoking status, low income, access to healthy diet and exercise, and levels of depression are also important determinants of whether women develop cerebrovascular disease following menopause [24]. Globally, women are more likely to live in poverty with insecure access to nutrition, safe drinking water and basic healthcare resources [25]. Access to secondary and higher education is limited, meaning that many women participate in unpaid or low income employment, which limits financial autonomy and presents a significant barrier to accessing healthcare [25].

Ethnicity is an important determinant of CKD progression and CV risk factors. Women from Black and minority ethnic (BAME) groups have higher rates of diabetes, with earlier onset and poorer glycaemic control [26]. BAME groups are more likely to develop hypertension than white groups, with the Black population being least likely to achieve target blood pressure [27]. While women from white, Asian and Latino populations experience lower blood pressure readings than their male counterparts, this protective effect is lost for women in Black populations [28].

However, it is also likely that hormonal changes, and in particular declining oestrogen levels during peri-menopause, influence the risk of developing CV disease.

Pregnancy is an important event which influences female health across the lifespan, with higher parity being linked to increased MACE in post-menopausal women [24]. Pre-eclampsia and hypertensive disorders of pregnancy are common, affecting up to 10% of pregnancies globally, and these are also important risk factors for the lifetime development of CKD [29].

Women diagnosed with pre-eclampsia accrue risk factors that make CV disease more likely, such as dyslipidaemia and hypertension, and as a result they experience greater rates of CV mortality and morbidity. This heightened CV risk persists throughout the life course, with inequities being seen in women up to 95 years old [30]. This excess CV risk may be explained by abnormal vascular remodelling which contributes to premature vascular aging in women with pre-eclampsia [30].

The CV health of pregnant women has far-reaching implications for the health of the global population. Both CKD and hypertensive disorders of pregnancy increase the likelihood of adverse neonatal outcomes, such as low gestational weight and pre-term delivery. The consequence is higher incidences of CKD, hypertension and diabetes in future generations [2].

Incidence of MACE increases significantly post-menopause [22]. There is also increased CV risk demonstrated in women who undergo early menopause or premature ovarian failure [22]. This is further emphasized by studies demonstrating a long-term protective effect from myocardial infarction in women who commence hormone replacement therapy by the first year following menopause [31].

There is evidence that vascular remodelling and platelet activation are fundamental to the development of CV disease in women. Studies demonstrate that women have higher levels of platelet aggregation when compared with men, and have a diminished response to daily aspirin, a drug that is integral to MACE treatment pathways [32]. Women have different smooth muscle cell function and higher levels of vascular stiffness, which results in coronary artery disease that is diffuse and non-occlusive. This is in contrast to men who are more likely to develop vessel occlusion due to acute atherosclerotic plaque rupture [33]. This has important implications for the treatment options available to women, who derive less benefit from and develop a greater number of adverse bleeding events following percutaneous coronary intervention for non-ST elevation myocardial infarction [33].

Persistent systemic inflammation causes oxidative stress and endothelial dysfunction, and has been implicated in the development of atherosclerosis [34]. Women with CKD are more

likely to have elevated markers of systemic inflammation, such as C-reactive protein [7]. One explanation for this is higher levels of autoimmunity in women, who develop renal disease related to conditions such as systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis [29]. However, an inflammatory state can also be demonstrated in older adults with CKD. High levels of circulating pro-inflammatory cytokines are released in response to infection and uraemic toxins, and clearance declines with progression of renal dysfunction [35].

Systemic inflammation in older adults with CKD contributes to anaemia as a result of reduced effective iron absorption and utilization [34]. This is important, as low transferrin saturation is associated with an increased rate of MACE and increased mortality in patients with CKD, independent of whether anaemia is present [36]. High ferritin, which often represents systemic inflammation in patients with CKD, has also been associated with high mortality rates, though not specifically as a consequence of MACE [36].

Higher levels of systemic inflammation may explain recent UK Biobank data analysis showing that lower eGFRcys/eGFRcys-cr was associated with excess risk of stroke in women when compared with men, whereas lower eGFRcr was associated with equal stroke risk in both genders [37]. This study highlights that women and men may require different approaches to CV and cerebrovascular risk stratification.

CONSEQUENCES OF MACE FOR OLDER WOMEN

Astley *et al*. found that female gender became less protective against CV disease in older adults with CKD, particularly over 75 years of age [11]. When the entire life course is considered, men and women share a very similar absolute risk of developing CV disease [38]. The nature of this CV disease burden differs between genders, and for women the majority of risk is accrued in old age as a consequence of stroke [38].

Astley *et al*. describe similar rates of fatal MACE between older men and women with CKD [11]. However, older women who survive a CV insult are likely to have an additional burden of significant morbidity and change in functional status. Cerebrovascular disease is an important cause of excess mortality for older women, but it also causes significant functional impairment. When compared with age-matched men, women >75 years old experience poorer return to baseline physical function, greater levels of fatigue and higher reported depression and anxiety symptoms [39].

In addition, older adults with CKD are more likely to develop frailty than the general population [40]. The frailty syndrome may further disadvantage older women with CKD by predisposing them to longer inpatient admissions and a higher likelihood of discharge to long-term care following a stroke [41]. There are also gender disparities seen in access to evidence-based stroke treatments, with women 13% less likely to undergo treatment with intravenous thrombolysis, despite similar post-treatment benefits when compared with men [40].

These negative health outcomes are not confined to stroke, with older women reporting greater levels of physical limitation, social isolation and poorer health-related quality of life with coronary artery disease when compared with men [42].

This is attributable at least in part to difficulty engaging women in evidence-based treatments. Women are less likely than men to be taking secondary prevention medications as prescribed at 12-month follow-up post-myocardial infarction [43]. This results in higher rates of readmission, event recurrence and death [44].

Participation in cardiac rehabilitation has been extensively shown to provide morbidity and mortality benefits following acute myocardial infarction. Women are less likely to be referred for cardiac rehabilitation, particularly those from areas of socioeconomic deprivation, older women and those from minority ethnic groups [44]. However, attendance at cardiac rehabilitation remains poor even for those women who are referred, when compared with male counterparts [44].

REPRESENTATION OF OLDER WOMEN IN CKD RESEARCH

Over the past 30 years there has been poor inclusion of women in CKD trials in comparison with the burden of CKD that they experience [45]. This is a finding shared across CV research, where women in the >65-year-old age group are particularly underrepresented [46].

This is important, as the exclusion of women from clinical research directly impacts their ability to access high-quality healthcare resource. Women have restricted access to medications and are less likely to be referred for investigations that have been trialled in predominantly male patient groups [47]. For the CKD population this likely contributes to the disparity in access to KRT and kidney transplantation experienced by women globally [2].

Socioeconomic deprivation prevents women from participating in clinical trials through factors such as reduced access to transport, inflexible working patterns and employment insecurity [48]. With higher rates of hypertension, diabetes and obesity, women from low income backgrounds are precisely the women who are most likely to derive benefit from CV and CKD research.

Women experience an additional caregiver burden often not shared by men, and responsibilities for unpaid family care pose a barrier to participation in studies which usually require in-person visits and operate during conventional office working hours [49]. This is particularly problematic for women from minority ethnic groups [49]. For those motivated to include women in clinical trials, provision of financial remuneration, transport and childcare can enhance recruitment and retention [49].

The way in which women make decisions about participation in research is also important. Perception of study investigators, particularly building a trusting relationship, are valued highly [49]. Women are less likely to pursue careers in clinical research [50], and it seems likely that this lack of female leadership and visibility contributes to hesitance of women to participate in clinical trials. Furthermore, there is a scarcity of women in clinical academic leadership positions, with women accounting for only 10% of clinical trial leadership committees [48], and this will inevitably result in research trials that are less oriented towards female health.

Despite having high levels of engagement in healthcare services and a wealth of potential healthcare data available, evidence focused on the improvement of health outcomes for older adults is lacking [51]. This is particularly true for older adults >85 years, those with a dementia diagnosis and those living in residential care [52]. The majority of older adults in residential care are women, and they have complex polypharmacy, interacting comorbidities and a range of care needs [53]. The systematic exclusion of these women from clinical research means that there is a paucity of literature available to clinicians to guide holistic investigation and treatment decisions.

CONCLUSIONS

As a consequence of lower GFR, higher albuminuria and longer life-expectancy, women experience a greater burden of CKD than men, have similar lifetime risk of CV disease, and have a greater loss to their survival advantage with CKD when compared with men. Astley *et al*. have sought to capture the impact of CV disease in a group of patients who are consistently excluded from the medical literature. They have described a burden of CV morbidity and mortality that is accrued by older women with CKD. However, this observational study has not fully depicted the serious adverse consequences of non-fatal MACE for these women, such as loss of functional independence and reduced quality of life. We are in urgent need of a robust body of evidence that allows appropriate risk stratification, timely investigation, accurate diagnosis and targeted treatment of MACE in women with CKD. Research that is truly focused on women's health goals must promote inclusivity and address the numerous barriers to participation that limit recruitment and retention of women in clinical trials. Furthermore, CV trials must be developed with outcomes that reflect the mechanistic differences in the development of MACE between men and women.

CONFLICT OF INTEREST STATEMENT

K.I.S. is member of the *CKJ* editorial board.

(See related article by Astley et al. The impact of gender on the risk of cardiovascular events in older adults with advanced chronic kidney disease. *Clin Kidney J* (2023) 16: 2396–2404.)

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Received: 18.7.2023; Editorial decision: 7.9.2023