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Astley, M.; Caskey, F.J.; Evans, M.; Torino, C.; Szymczak, M.; Drechsler, C.; ... ; EQUAL Study Investigators

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Original Article

The Forgotten Sex
gender disparities in kidney disease

ORIGINAL ARTICLE

The impact of gender on the risk of cardiovascular events in older adults with advanced chronic kidney disease

Megan Astley[1,2], Fergus J. Caskey[3], Marie Evans[4], Claudia Torino[5], Maciej Szymczak[6], Christiane Drechsler[7], Maria Pippias[3,8], Esther de Rooij[9], Gaetana Porto[10], Vianda S. Stel[1,11], Friedo W. Dekker[9], Christoph Wanner[7], Kitty J. Jager[1,11] and Nicholas C. Chesnaye[1,11]; the EQUAL study investigators

[1]Amsterdam UMC location University of Amsterdam, ERA Registry, Medical Informatics, Amsterdam, The Netherlands, [2]Amsterdam Public Health, Health Behaviours and Chronic Diseases and Methodology, Amsterdam, The Netherlands, [3]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK, [4]Renal Unit, Department of Clinical Intervention and Technology (CLINTEC), Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, [5]IFC-CNR, Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, Reggio Calabria, Italy, [6]Department of Nephrology and Transplantation Medicine, Wroclaw Medical University, Wroclaw, Poland, [7]Division of Nephrology, University Hospital of Würzburg, Würzburg, Germany, [8]North Bristol NHS Trust, Renal Unit, Bristol, UK, [9]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, [10]G.O.M., Bianchi Melacrino Morelli, Reggio Calabria, Italy and [11]Amsterdam Public Health Research Institute, Quality of Care, Amsterdam, The Netherlands

Correspondence to: Megan Astley; E-mail: m.e.astley@amsterdamumc.nl

ABSTRACT

Background. Patients with chronic kidney disease (CKD) are at a higher risk of major adverse cardiovascular events (MACE) compared with the general population, but gender differences in this risk, especially in older adults, are not fully known. We aim to identify gender differences in the risk of MACE in older European CKD patients, and explore factors that may explain these differences.

Methods. The European Quality study (EQUAL) is a prospective study on stage 4–5 CKD patients, ≥65 years old, not on dialysis, from Germany, Italy, the Netherlands, Poland, Sweden and the UK. Cox regression and cumulative incidence competing risk curves were used to identify gender differences in MACE risks. Mediation analysis was used to identify variables which may explain risk differences between men and women.

Results. A total of 417 men out of 1134 (37%) and 185 women out of 602 women (31%) experienced at least one MACE, over a follow-up period of 5 years. Women had an 18% lower risk of first MACE compared with men (hazard ratio 0.82; 95% confidence interval 0.69–0.97; $P = .02$), which was attenuated after adjusting for pre-existing cardiometabolic

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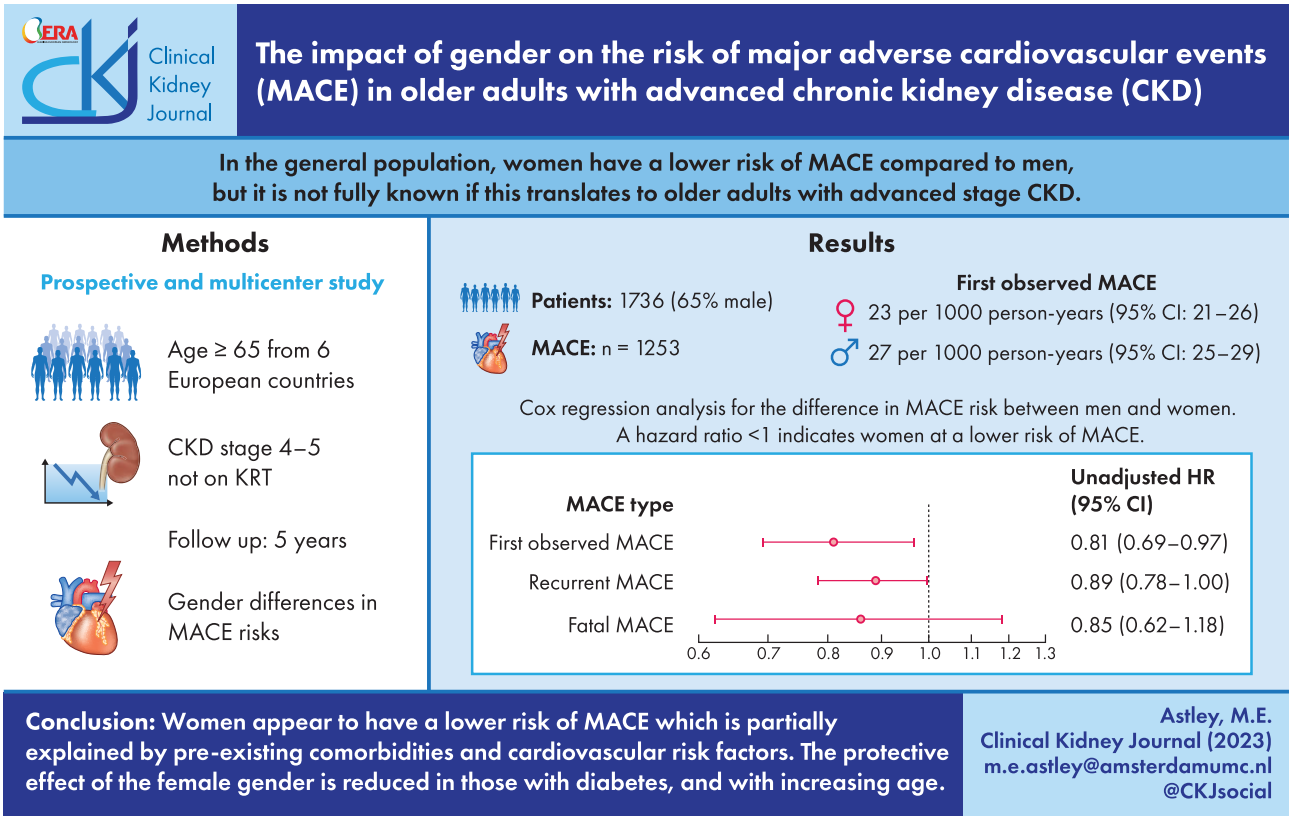
comorbidities and cardiovascular risk factors. There were no significant gender differences in the risk of recurrent MACE or fatal MACE. The risk difference in MACE by gender was larger in patients aged 65–75 years, compared with patients over 75 years.

Conclusions. In a cohort of older adults with advanced CKD, women had lower risks of MACE. These risk differences were partially explained by pre-existing cardiometabolic comorbidities and cardiovascular risk factors.

GRAPHICAL ABSTRACT



Keywords: cardiovascular events, chronic kidney disease, gender differences, older adults, risk differences

INTRODUCTION

In the general population, the risk of major adverse cardiovascular events (MACE) is higher in men compared with women across most age groups [1], with women's risk of MACE lagging 10 years behind men's. After menopause this risk gap closes, with lifetime risks for some conditions being greater in women [2]. Furthermore, the magnitude of the effect of traditional risk factors may differ by gender [3] and women are also exposed to female-specific risk factors [4–6]. Women experience an under appreciation of their risk of cardiovascular disease (CVD), with evidence of gender differences in the diagnosis and treatment of MACE [7–9].

Gender differences in MACE risk found in the general population may not translate to the chronic kidney disease (CKD) population, where the difference in MACE risk between men and women often appears smaller [10]. Unlike younger CKD patients, older CKD patients are more likely to experience MACE than to progress to kidney failure [11–13]. Despite these age-related risks, few studies have directly assessed the risk of MACE in older CKD patients who are not yet on kidney replacement therapy (KRT). Comparisons among studies are challenging due to varying patient populations with regards to age, CKD stage or MACE definitions [14–18].

An understanding of the risk of MACE by gender may provide useful insights to help reduce the burden of CVD and improve gender-specific clinical management. Therefore, this study primarily aims to describe the gender-specific risk of first, recurrent and fatal MACE in a European population of advanced CKD patients over the age of 65 years. Secondly, to understand the mechanisms underlying these differences, we will explore demographic, cardiovascular and clinical factors that may explain any differences observed.

MATERIALS AND METHODS

Study design and population

The European Quality study (EQUAL study) is a prospective study on stage 4–5 CKD patients not yet on dialysis from Germany, Italy, the Netherlands, Poland, Sweden and the UK who were ≥65 years at inclusion. A full description of the study has been

previously published [19]. In brief, the EQUAL study includes patients who experienced an incident drop in estimated glomerular filtration rate (eGFR) ≤20 mL/min/1.73 m^2 in the last 6 months and were referred to a nephrologist. Patients were eligible when they were being followed in a nephrology clinic and excluded if their eGFR drop was due to an acute event or if they previously had KRT. For the current study, the follow-up period was from March 2012 to January 2022. Study visits were scheduled at 3- to 6-month intervals, and patients were followed until kidney transplantation, death, refusal for further participation, loss to follow-up or 5 years of follow-up. Initiation of dialysis did not exclude patients from follow-up. The study received approval by the Medical Ethics Committee or Institutional Review Boards of all participating centres. Written informed consent was obtained from all patients.

Data collection, variable definition and outcomes

Data were collected on demographics, laboratory data, medication, physical examination, primary kidney disease and cardiovascular risk factors. We realize there is a difference between gender and sex, but we will use the term 'gender' throughout this manuscript based on guidelines from the US Institute of Medicine [20]. Data on pre-existing cardiovascular comorbid conditions were collected (definitions provided in Supplementary data, Table S1). eGFR was calculated from serum creatinine level standardized to isotope dilution mass spectrometry using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Urine albumin-to-creatinine ratio (uACR) was determined following routine 24-h urine collection or a single sample if 24-h urinary collection was unavailable. Primary kidney disease and causes of death were classified using the European Renal Association codes [21]. Hospitalization and comorbidity events were standardized into categories defined by the nephrologists from each country who are collaborating within the EQUAL study. MACE are defined as a comorbidity or hospitalization due to cerebrovascular disease, myocardial infarction, peripheral vascular disease, angina pectoris, arrhythmias, congestive heart failure, coronary artery disease, or death due to myocardial ischaemia and infarction, heart failure, cardiac arrest or cerebrovascular accident. A 'first MACE' refers to the first occurrence of a MACE after entering the study.

Statistical analysis

Baseline characteristics were presented as means with standard deviation (SD) for normally distributed continuous variables. Skewed continuous variables were presented as medians with interquartile range (IQR). Categories were presented as frequencies with percentages. uACR was log-transformed to improve normality. The rate of incident MACE was presented by gender. The cumulative incidence competing risk curve was used to visualize the probability of first MACE by gender in the presence of two competing events, non-MACE death and kidney transplantation, by gender. Cox proportional hazards models were used to determine the risk of first, recurrent and fatal MACE in men and women. As patients are censored when experiencing a non-MACE death or transplantation, the hazard ratio (HR) can be considered as cause-specific [22]. Proportional hazards assumptions were checked for each covariate and found to be fulfilled.

The difference method of mediation analysis [23] was performed to identify mediators, which are variables that do not qualify as confounders as they lie in the causal pathway and may therefore partially or fully explain a relationship between an exposure (gender) and outcome (MACE). The change in the gender HRs between the unadjusted and adjusted models (outlined in Supplementary data, Table S2) show the gender effect that is explained by the mediators. Variables were selected based on published research and advice from medical professionals. Analyses were performed using baseline observations of variables . Time-dependent variables used were eGFR, uACR, body mass index (BMI), systolic blood pressure, diastolic blood pressure, cholesterol, albumin, calcium, phosphate, potassium, haemoglobin and dialysis status.

For the recurrent event analysis, the Prentice, Williams and Peterson (PWP) gap time approach was used. This allows the start time for each event to be reset to zero after a previous event and for the effects of covariates to differ for subsequent MACE [24]. A cluster variable is also included to identify correlated events and a stratum variable representing the number of events per individual. We used the Multivariate Imputation by Chained Equations (MICE) package [25] to impute missing data using ten imputations (Supplementary data, Table S3). Missing data were considered missing at-random. All analyses were performed with SAS version 9.4 [26] and R version 3.4.1 [27].

Two subgroup analyses were carried out by stratifying on age at baseline (65–75 years old and >75 years old) and on the presence of diabetes at baseline. Patient characteristics per subgroup are provided in the Supplementary materials.

RESULTS

Patient characteristics

Among the 1736 EQUAL study participants, 1134 were men and 602 were women (Table 1). The mean age was 76 years for men and 77 years for women. A higher proportion of women were divorced, widowed or never married, compared with men. Women were more likely to have low or no education, while men were more likely to have high or intermediate education. Men had a higher prevalence of diabetes, peripheral vascular disease, prior myocardial infarction and angina pectoris. A larger proportion of men were current or ex-smokers compared with women. Over the follow-up period, 436 men (38% of men) and 154 women (26% of women) initiated dialysis.

MACE risk in men and women

Total follow-up time was 4916 years, with a median follow-up time of 3.8 years (IQR 2.5, 4.3). There were a total of 1253 incident MACE, of which 48% ($n = 600$) were first MACE. The proportion of type of first MACE by gender is presented in Fig. 1 and the median number of events is presented in Supplementary data, Fig. S1. The rate of first MACE was 23 per 1000 person-years (95% CI 21–26) in women compared with 27 per 1000 person-years (95% CI 25–29) in men. The rate of fatal MACE for women was 3 per 1000 person-years (95% CI 2–4) and 4 per 1000 person-years (95% CI 3–5) in men. The 1-year probability of experiencing first MACE was 18% (95% CI 16%–21%) for men and 14% (95% CI 12%–18%) for women. At 5 years, the probability of experiencing first MACE was 43% (95% CI 40%–47%) for men and 39% (95% CI 34%–44%) for women (Fig. 2). Women had an 18% lower crude risk of first MACE compared with men (HR 0.82; 95% CI 0.69–0.97; $P = .02$). Men and women had similar risks of recurrent MACE (HR 0.91; 95% CI 0.80–1.03; $P = .14$). Women had a lower risk of fatal MACE, but this did not reach statistical significance (HR 0.86; 95% CI 0.62–1.19; $P = .36$).

Table 1: Baseline characteristics of study participants with CKD stage 4–5 above 65 years of age within the EQUAL study cohort stratified by gender.

	Overall	Males	Females
Number of subjects, *N* (%)	1736	1134 (65.3)	602 (34.7)
Age, years (SD)	76 (6.7)	76 (6.5)	77 (7.1)
Primary kidney disease, *N* (%)			
Glomerular disease	159 (9.3)	117 (10.4)	42 (7.1)
Tubulo-interstitial disease	146 (8.5)	80 (7.1)	66 (11.2)
Diabetes mellitus	351 (20.6)	244 (21.8)	107 (18.2)
Hypertension	613 (35.9)	391 (34.9)	222 (37.8)
Other/unknown	439 (25.7)	288 (25.7)	151 (25.7)
Marital status, *N* (%)			
Married	890 (64.4)	689 (75.7)	201 (42.7)
Divorced	100 (7.2)	58 (6.4)	42 (8.9)
Widowed	333 (24.1)	133 (14.6)	200 (42.5)
Never married	58 (4.2)	30 (3.3)	28 (5.9)
One or more children, yes, *N* (%)	1177 (88.4)	778 (88.5)	399 (88.1)
Education level, *N* (%)			
None/low	426 (30.8)	243 (26.7)	183 (38.7)
Intermediate	678 (49.0)	457 (50.2)	221 (46.7)
High	210 (15.2)	169 (18.6)	41 (8.7)
Other/unknown	69 (5.0)	41 (4.5)	28 (5.9)
eGFR (mL/min/1.73 m^2), mean (SD)[a]	17.3 (5.51)	17.0 (5.46)	17.8 (5.57)
uACR (mg/g), median (IQR)	38.2 (9.6, 145.5)	44.5 (12.0, 152.5)	24.8 (8.0, 121.4)
Diabetes[b], yes, *N* (%)	716 (42.5)	496 (44.9)	220 (37.9)
Chronic heart failure, yes, *N* (%)	299 (18.3)	203 (19.0)	96 (16.9)
Cerebrovascular disease, yes, *N* (%)	258 (15.4)	171 (15.5)	87 (15.2)
Peripheral vascular disease, yes, *N* (%)	288 (17.4)	211 (19.4)	77 (13.4)
Myocardial infarction, yes, *N* (%)	294 (17.4)	229 (20.7)	65 (11.2)
Angina pectoris, yes, *N* (%)	246 (14.8)	186 (17.1)	60 (10.5)
Left ventricular hypertrophy, yes, *N* (%)	365 (24.3)	258 (26.1)	107 (20.8)
Atrial fibrillation, yes, *N* (%)	307 (18.4)	199 (18.3)	108 (18.8)
Hypertension, yes, *N* (%)	1463 (89.1)	958 (89.0)	505 (89.4)
Coronary artery disease, yes, *N* (%)	452 (27.4)	351 (32.4)	101 (17.9)
BMI (kg/m^2), mean (SD)	28.4 (5.35)	28.2 (4.87)	28.8 (6.16)
Charlson comorbidity index, mean (SD)	7.13 (1.88)	7.24 (1.93)	6.91 (1.77)
Systolic blood pressure (mmHg), mean (SD)	142.7 (22.04)	143.2 (21.65)	141.9 (22.76)
Diastolic blood pressure (mmHg), mean (SD)	73.9 (11.26)	74.0 (11.34)	73.6 (11.12)
Smoking status, *N* (%)			
Current smoker	120 (8.7)	82 (9.0)	38 (8.0)
Ex-smoker	748 (54.1)	584 (64.2)	164 (34.7)
Never	514 (37.2)	243 (26.7)	271 (57.3)
Cholesterol (mmol/L), mean (SD)	4.54 (1.29)	4.35 (1.19)	4.90 (1.39)
Albumin (g/dL), mean (SD)	37.71 (5.88)	37.65 (5.91)	37.83 (5.84)
Calcium (mmol/L), mean (SD)	2.30 (0.16)	2.28 (0.16)	2.33 (0.16)
Phosphate (mmol/L), mean (SD)	1.30 (0.31)	1.29 (0.32)	1.31 (0.30)
Potassium (mmol/L), mean (SD)	4.64 (0.60)	4.67 (0.61)	4.60 (0.59)
Haemoglobin (mmol/L), mean (SD)	7.20 (0.93)	7.26 (0.96)	7.09 (0.88)
Polypharmacy (>10 medications), yes, *N* (%)	663 (38.2)	439 (38.7)	224 (37.2)
Psychological comorbidities, yes, *N* (%)	113 (6.7)	60 (5.4)	53 (9.2)
Use of RAS-acting agents, yes, *N* (%)	125 (7.2)	80 (7.1)	45 (7.5)
Use of beta blockers, yes, *N* (%)	40 (2.3)	21 (1.9)	19 (3.2)
Use of angiotensin receptor blockers, yes, *N* (%)	59 (3.4)	32 (2.8)	27 (4.5)
Use of angiotensin-converting enzyme, yes, *N* (%)	46 (2.6)	28 (2.5)	18 (3.0)
Use of statins, yes, *N* (%)	93 (5.4)	64 (5.6)	29 (4.8)
Use of diuretics, yes, *N* (%)	154 (8.9)	97 (8.6)	57 (9.5)

Values are presented as median (IQR), frequency (%) or mean (SD) as appropriate.
[a]Estimated GFR calculated using CKD-EPI.
[b]Defined as both a history of diabetes mellitus or diabetes mellitus as cause of primary kidney disease, either Type I or Type II diabetes mellitus.
RAS, renin–angiotensin system.

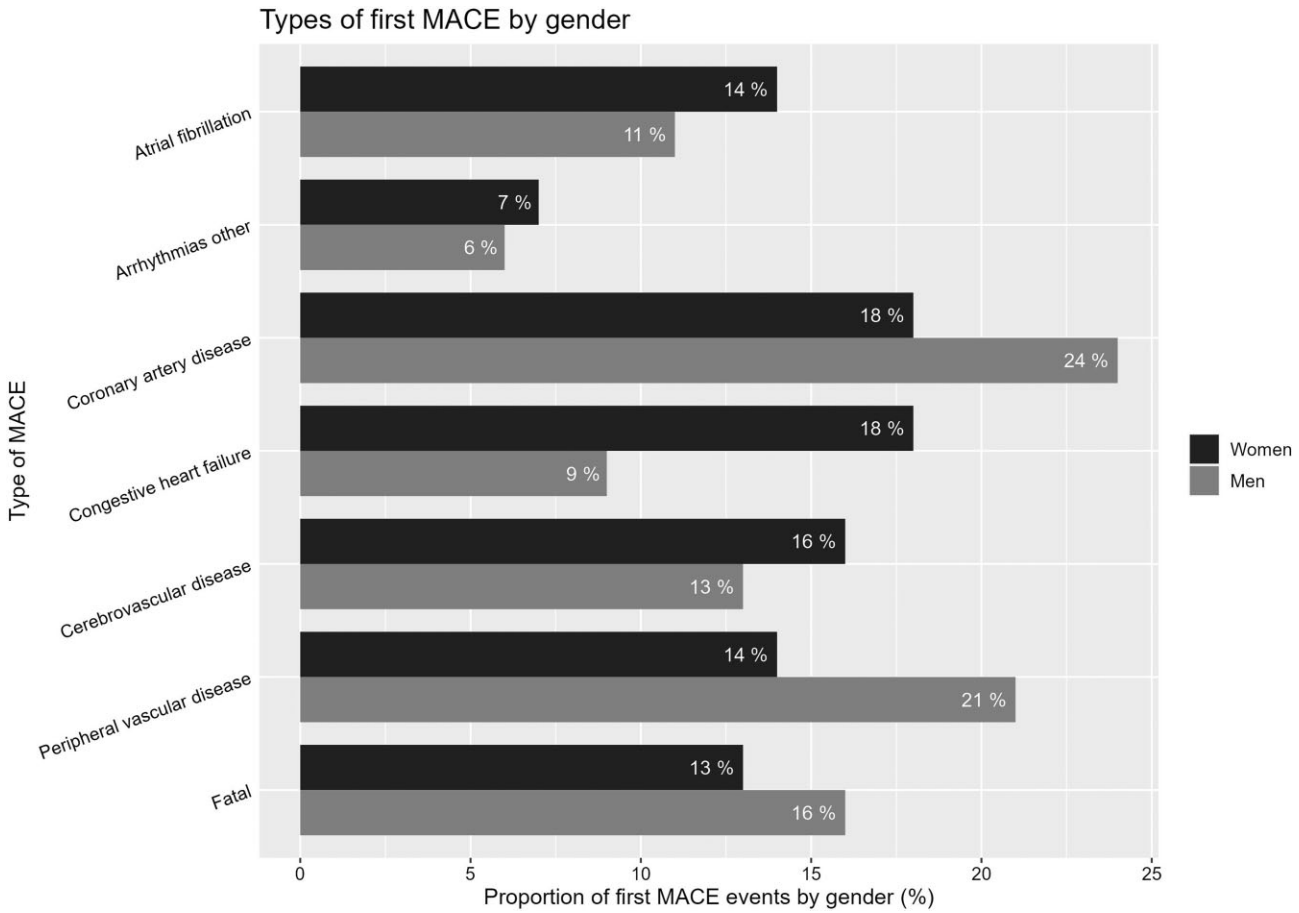


Figure 1: Proportion of causes of first MACE experienced by men and women with CKD stage 4–5 older than 65 years of age within the EQUAL study over a 5-year follow-up period.

Mediation analysis for first MACE, recurrent MACE and fatal MACE

We explored various models to identify potential mediators which may partially or fully explain the lower risk of MACE in women (Table 2). Gender HRs adjusted for individual mediators are presented in Supplementary data, Table S4. Women remained at a significantly lower risk of first MACE after adjustment for demographic factors, and at a non-significantly lower risk after adjustment for socioeconomic factors and kidney function. With the addition of cardiometabolic comorbidities, women had an 8% lower risk (HR 0.92; 95% CI 0.76–1.10; $P = .36$), which remained similar with the addition of traditional CVD risk factors (HR 0.93; 95% CI 0.76–1.13; $P = .44$) and non-traditional CVD risk factors (HR 0.92; 95% CI 0.76–1.12; $P = .42$). The addition of mediators had little effect on the gender HR for recurrent or fatal MACE (Table 2). Time-dependent adjustment for dialysis status slightly reduced the HR for both first MACE (HR 0.84; 95% CI 0.71–1.00; $P = .05$) and fatal MACE (HR 0.86; 95% CI 0.62–1.29; $P = .33$). When censoring individuals at dialysis initiation, the hazard ratio for first, recurrent and fatal MACE was similar to the main results (Supplementary data, Table S5). The inclusion of time-dependent variables (Supplementary data, Table S6) had little effect on the results.

MACE risk in men and women by age group

Patient characteristics by age group (65–75 years old and >75 years old) are provided in Supplementary data, Table S7. In patients 65–75 years old, women had a non-significant 25% lower risk of first MACE compared with men (HR 0.75; 95% CI 0.57–1.00; $P = .05$) which was only a 15% lower risk in the >75 group (HR 0.85; 95% CI 0.68–1.06; $P = .15$). Conversely, in patients 65–75 years old, women and men had similar risks of recurrent MACE (HR 0.90; 95% CI 0.74–1.10; $P = .32$), whereas in those >75 years old women had a 18% lower risk (HR 0.82; 95% CI 0.70–0.97; $P = .02$). In those aged 65–75 years, we found no significant gender difference in the risk of fatal MACE (HR 1.33; 95% CI 0.78–2.26; $P = .28$), whereas in the >75 years group, women had a 39% lower risk of fatal MACE (HR 0.61; 95% CI 0.40–0.93; $P = .02$).

MACE risk in men and women by diabetes status

Summary characteristics for patients with (DM) and without diabetes (non-DM) at baseline are found in Supplementary data, Table S8. The gender difference in the risk of first MACE was similar in patients with DM (HR 0.81; 95% CI 0.63–1.04; $P = .09$) and without DM (HR 0.83; 95% CI 0.64–1.07; $P = .14$). The risk of

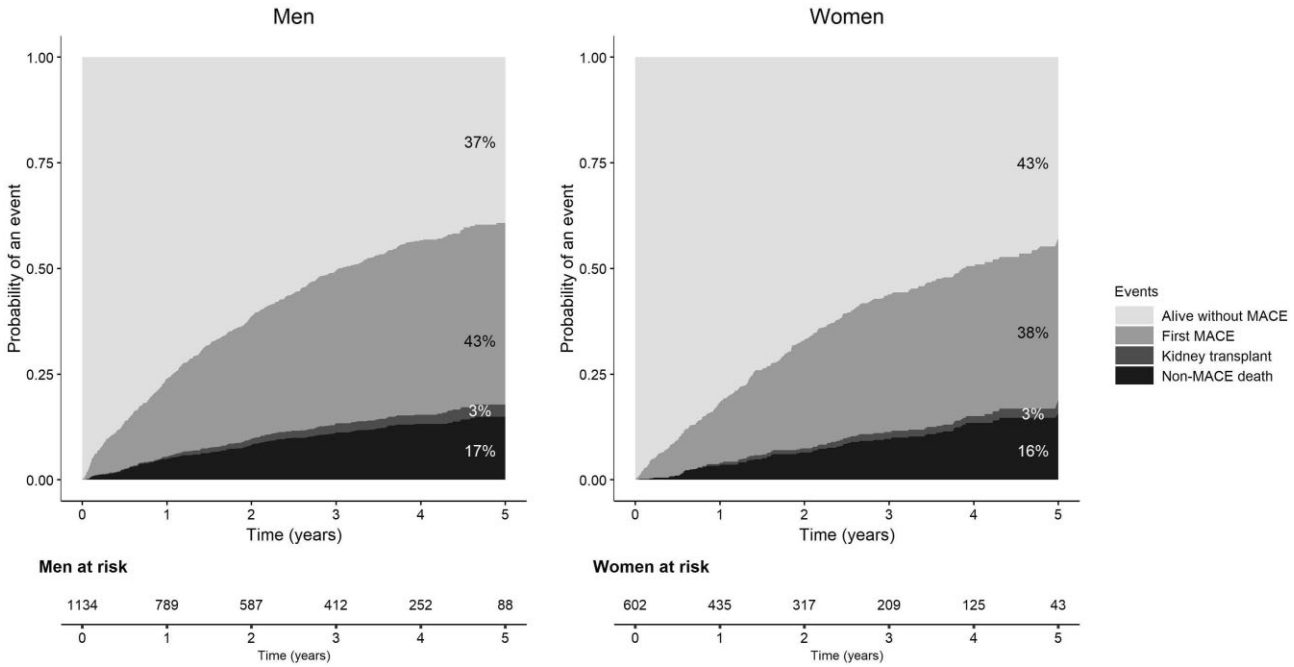


Figure 2: Cumulative incidence competing risk curves for the risk of first MACE in men and women over 65 years old with CKD stage 4–5 and the competing risk of non-MACE death. The category 'First MACE' includes both non-fatal and fatal MACE. The category 'Alive without MACE' includes subjects who were censored or did not have a MACE. 'Kidney transplant' includes patients who received a kidney transplant before having a MACE or non-MACE death. 'Non-MACE death' is death due to any condition not listed within our MACE definition. The at-risk tables provide an overview of the subjects at risk over the 5-year follow-up period.

recurrent MACE did not differ between men and women by diabetic status (DM HR 0. 90; 95% CI 0.75–1.07; $P = .23$, non-DM HR 0. 87; 95% CI 0.73–1.04; $P = .12$). Men and women with DM had a non-significant difference of fatal MACE (HR 0.77; 95% CI 0.48–1.24; $P = .28$), whereas in the non-DM group there was a similar risk (HR 0.95; 95% CI 0.59–1.52; $P = .82$).

DISCUSSION

An understanding of MACE risk by gender is vital for reducing the gender-specific burden of MACE and improving the gender-specific clinical management in CKD. This study characterized the impact of gender on the risk of MACE within a European cohort of advanced CKD patients aged 65 years and over. Overall, women had a lower risk of first MACE, whereas the risk of recurrent and fatal MACE was more similar. In older adults in the general population without CKD, similar differences in the risk of MACE by gender have been found [28].

Adjusting for pre-existing cardiometabolic comorbidities and cardiovascular risk factors reduced the difference in MACE risk between men and women, suggesting that these factors may be responsible for a part of this disparity. Gender differences also varied by age group, indicating converging MACE risks with increasing age.

In agreement with our findings, a meta-analysis in CKD stage 3–4 found that men had a 45% increased risk of both fatal and non-fatal cardiovascular events compared with women, even after adjustment for pre-existing traditional cardiovascular risk factors [16]. The Chronic Renal Insufficiency Cohort Study (CRIC) study found in individuals >51 years old, women had a 22%–44% lower risk of MACE [18]. Similarly, the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD) found women to have a 34% lower risk of MACE than men [15]. Compared with our results, these studies observed larger differences in the risk of MACE between men and women, which may be attributed to the inclusion of younger individuals and individuals in earlier stages of CKD. Others have shown women to experience a steeper increase in MACE risk with declining eGFR [14, 17], suggesting that the gender effect is likely modified by disease progression. In dialysis patients, the risk of MACE remains lower in women [29–31], although Carrero *et al*. found women may have a similar risk of cardiovascular mortality compared with men [32]. The Swedish Renal Registry–CKD also found the gender difference in cardiovascular mortality risk to disappear in individuals with stage 5 CKD [33]. Taken together, this suggests the seemingly protective effect of female gender, seen in both the general population and earlier CKD stages, is reduced with CKD progression and especially in those on dialysis.

Men and women share traditional cardiovascular risk factors but their prevalence and effect on cardiovascular risks has been shown to differ by gender. We found that adjustment for pre-existing cardiometabolic comorbidities and traditional and non-traditional CVD risk factors attenuated the MACE risk difference by gender. Similarly, the KNOW-CKD study found the gender risk difference to lower from a 66% to a 45% higher risk in men after adjustment for cardiovascular risk factors [15]. The CRIC study found that adjustment for traditional risk factors in patients with an eGFR <30 mL/min/1.73 m^2 reduced the gender risk difference for heart failure and fatal MACE, but not for atherosclerotic events [18]. Nevertheless, these findings suggest gender differences in MACE risks are likely explained by traditional risk factors in individuals with late-stage CKD.

The MACE risk difference by gender seems to narrow with increasing age, although the mechanisms underlying these converging risks, especially in the CKD population, remain largely unclear. It has been hypothesized that endogenous estrogens provide a cardio-protective effect in women, but production of

Table 2: Mediation analysis for the effect of gender on first, recurrent and fatal MACE in patients with CKD stage 4–5 older than 65 years of age.

Model	First MACE	Recurrent MACE	Fatal MACE
Model 1 (unadjusted)	0.82 (0.69–0.97, P = .02)	0.89 (0.78–1.00, P = .05)	0.84 (0.61–1.16, P = .30)
Model 2 (+ demographics)	0.81 (0.68–0.97, P = .02)	0.87 (0.77–0.99, P = .03)	0.80 (0.58–1.10, P = .17)
Model 3 (+ socioeconomic status)	0.84 (0.70–1.01, P = .06)	0.91 (0.80–1.04, P = .18)	0.81 (0.58–1.14, P = .24)
Model 4 (+ kidney function)	0.84 (0.70–1.01, P = .07)	0.92 (0.80–1.05, P = .20)	0.82 (0.59–1.16, P = .26)
Model 5 (+cardiometabolic comorbidities)	0.92 (0.76–1.10, P = .36)	0.98 (0.85–1.13, P = .78)	0.89 (0.63–1.26, P = .52)
Model 6 (+ traditional cardiovascular risk factors)	0.93 (0.76–1.13, P = .44)	0.98 (0.85–1.13, P = .78)	0.90 (0.62–1.29, P = .55)
Model 7 (+ non-traditional cardiovascular risk factors)	0.92 (0.76–1.12, P = .42)	0.97 (0.84–1.12, P = .67)	0.84 (0.58–1.21, P = .34)

HRs represent the difference in risk of MACE in women compared with men. An HR <1 suggests women have a lower risk than men. The difference between the HR from the unadjusted model and mediator-adjusted HR represents the proportion of the effect that is explained by the mediators included in the model.
Model 1: only gender included.
Model 2: Model 1 + age at baseline + primary kidney disease.
Model 3: Model 2 + marital status + one or more children + education level.
Model 4: Model 3 + eGFR + log-transformed uACR.
Model 5: Model 4 + diabetes + chronic heart failure + cerebrovascular disease + peripheral vascular disease + myocardial infarction + angina pectoris + left ventricular hypertrophy + atrial fibrillation + hypertension + coronary artery disease.
Model 6: Model 5 + BMI + systolic blood pressure + diastolic blood pressure + smoking status + cholesterol.
Model 7: Model 6 + albumin + calcium + phosphate + potassium + haemoglobin.

these hormones decreases after menopause [34]. This may explain why younger populations of CKD patients still retain gender differences after adjustment for traditional risk factors but older populations do not. An alternative explanation for changes in MACE risk in ageing women has been suggested by The Framingham Heart Study, which found that cardiovascular risk factors affect the age of menopause onset, and not the reverse. Therefore, the underlying cardiovascular risk factors that accumulate with age may be responsible for worsening MACE risks, and menopause onset is just a result of these cardiovascular risk factors [35].

In the general population, women have a lower risk of MACE compared with men but diabetes seems to remove the female advantage with regards to CVD outcomes [28–30, 36, 37]. Here we found no effect modification by diabetes on the risk of first MACE by gender. In agreement with our results, the CRIC and KNOW-CKD studies found no significant interaction between diabetes and gender on the risk of MACE in the CKD population [15, 18]. Nonetheless, a meta-analysis by Fox *et al*. [31] found that in end-stage kidney disease, diabetes increased cardiovascular mortality risk to a larger magnitude in women than men, with similar findings reported by Carrero *et al*. [32]. As the protective effect of female gender is already reduced with CKD progression, especially in those on dialysis, the additional presence of diabetes in women may further reduce their advantage. Overall, it seems that in CKD patients, diabetes disproportionately affects adverse outcomes more in women than in men, and perhaps even more so for those on dialysis.

This study has several strengths including the provision of MACE risks in an underrepresented population, older CKD patients with stage 4–5 CKD. We used data from six European countries, allowing for a better generalizability of results within Europe. Also, we had access to detailed laboratory measurements which were used longitudinally in adjusted models. Finally, we minimized the risk of survivor bias by prospectively including patients when eGFR dropped below the pre-defined level of 20 mL/min/1.73 m^2. Our study is also subject to several limitations. The power of this study was limited by the study sample size and number of events, thus our subgroup analyses should be interpreted cautiously. Although we included a selection of clinical and comorbidity variables in our analyses, we could not account for gender differences in the diagnosis and treatment of MACE, access to care, or certain behavioural factors known to differ by gender. As our population of CKD stage 4–5 patients offers a short observation of a more lengthy disease trajectory, MACE risks in men and women are likely to vary in earlier stages of CKD. Furthermore, we lack the dates of previous MACE prior to entering the study, and our definition of first MACE refers to the first observed MACE after study entry.

In conclusion, we found that in elderly patients with stage 4–5 CKD in Europe, women have a lower risk of MACE than men. The gender risk difference was partially explained by pre-existing cardiometabolic comorbidities and cardiovascular risk factors. In line with the current literature, our results support the notion that the protective effect of female gender is reduced with CKD progression and increasing age, and by diabetes. Further research may focus on using biomarkers to explore the physiological mechanisms by which risk factors affect the relationship between gender and MACE risk, which may help implement individualized prevention strategies and improve gender-specific management.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

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LIST OF EQUAL STUDY INVESTIGATORS:

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to privacy laws, such as the General Data Protection Regulation (GDPR).

(See related article by Radley et al. Cardiovascular disease in older women with CKD. *Clin Kidney J* (2023) 16: 2304–2308.)

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