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Urinary albumin-to-creatinine ratio in patients with hypertension and risk of major cardiovascular events

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2025-003270).

To cite: Binding C, Elmegaard M, Anjum DZ, *et al*. Urinary albumin-to-creatinine ratio in patients with hypertension and risk of major cardiovascular events. *Open Heart* 2025;**12**:e003270. doi:10.1136/openhrt-2025-003270

Received 17 February 2025
Accepted 7 May 2025

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ABSTRACT

Introduction/aims Evaluation of urinary albumin-to-creatinine ratio (uACR) is a key component in the management of hypertension, yet there is a lack of data on the association between uACR and major cardiovascular events (MACEs) in large hypertensive cohorts, and it is also unknown how often uACR is measured among these patients.

We aimed to evaluate the usage of uACR in a nationwide population of patients with hypertension. Furthermore, we sought to assess the risk of cardiorenal events according to uACR, among patients with hypertension.

Methods We used Danish nationwide registries to identify patients who initiated antihypertensive treatment. The patients were grouped at treatment initiation according to uACR: normoalbuminuria, microalbuminuria, macroalbuminuria and no uACR measurement, and followed for 2 years, to evaluate the risk of a MACE, hospitalisation for heart failure (HF), 40% decline in estimated glomerular filtration rate (eGFR) and end-stage kidney disease (ESKD) according to uACR.

Results We included 144 644 patients, of whom 116 039 (80%) did not have their uACR evaluated at treatment initiation. Patients with macroalbuminuria comprised the greatest 2 year absolute risk of MACE (5.3%, 95% CI: 4.0% to 6.6%) and had a greater risk of MACE (HR: 2.02, 95% CI: 1.54 to 2.66), HF (HR: 1.99, 95% CI: 1.35 to 2.95), 40% decline in eGFR (HR: 4.81, 95% CI: 3.78 to 6.10) and ESKD (HR: 4.52, 95% CI: 3.00 to 6.82) compared with patients with normoalbuminuria. Increased risk of MACE, HF and 40% decline in eGFR among patients with macroalbuminuria was persistent across subgroups of eGFR 120–30 mL/min/1.73 m².

Conclusions In this real-world cohort, uACR was not regularly measured among patients initiating antihypertensive treatment. Nonetheless, the 2-year risks of cardiorenal events were considerably higher among patients with albuminuria compared with patients without.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Urinary albumin-to-creatinine has been linked to cardiorenal events in smaller cohorts, and evaluation of urinary albumin-to-creatinine ratio in patients with hypertension is endorsed in current international guidelines.

WHAT THIS STUDY ADDS

⇒ In a nationwide cohort of patients initiating antihypertensive treatment, albumin-to-creatinine ratio was not measured in 80% of patients, yet any degree of albuminuria was associated with an increased risk of cardiovascular and renal events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Evaluation of urinary albumin-to-creatinine ratio should be conducted much more frequently in patients initiating antihypertensive treatment as this could help risk stratify the patients.

⇒ Future research will need to investigate the impact of urinary albumin-to-creatinine ratio according to exact blood pressure to unveil potential high-risk patients.

INTRODUCTION

It is well known that hypertension is causally related to cardiovascular diseases (CVDs) and to the progression of kidney disease to end-stage kidney disease (ESKD). Prevention, detection, treatment and control of hypertension are therefore key when assessing cardiorenal risks among these patients.

Proteinuria is known to be strongly associated with hypertension and to increase in patients with poor antihypertensive control[1] and was recognised as an indicator for kidney disease as early as in the 1820s.[2] Newer studies have recommended urinary albumin-to-creatinine ratio (uACR) as the best assessment of proteinuria due to accuracy and reliability.[3 4] Albuminuria has also been shown to be a marker of stroke and of systemic congestion in patients with heart failure (HF), and uACR has been acknowledged as a parameter that ideally should be systematically evaluated in adults visiting primary health centres to assess the risk of cardiorenal diseases.[5–7]

Current international guidelines[8–10] have also addressed the importance of assessing

both uACR and estimated glomerular filtration rate (eGFR) among patients with hypertension to evaluate the cardiovascular and renal risk profile of these patients, yet few studies conducted on data from health databases suggest underusage of such screening methods.[11 12] Nonetheless, it is unknown whether uACR is regularly measured in a nationwide real-world cohort with universal healthcare access, and how different levels of uACR are associated with the risk of cardiorenal outcomes in a large nationwide cohort of patients with hypertension.

This study aimed to evaluate the usage of uACR among patients initiating antihypertensive treatment. Furthermore, we sought to investigate the risk of cardiovascular events and progression of kidney disease according to uACR level and kidney function.

METHODS

Study design and population

This was an observational cohort study using data from Danish nationwide registries. The conduction of the study and the study results were reported in conformation with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13]

Patients were included between 2014 and 2019 on the day they initiated antihypertensive treatments with either angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers or thiazides, if they had an available creatinine measurement within 1 year of treatment initiation.

We excluded patients with an eGFR above 120 or below 15 mL/min/1.73 m², patients younger than 30 years of age, patients older than 100 years of age, patients with prior HF diagnosis and patients with invalid registry coverage (ie, no registered income, no registered cohabitation status or invalid date of death).

The included patients were analysed according to whether they had a uACR measurement within 1 year prior to inclusion and grouped according to uACR: patients with normoalbuminuria (uACR below 30 mg/g), patients with microalbuminuria (uACR between 30 and 300 mg/g), patients with macroalbuminuria (uACR above 300 mg/g), and patients without any registered uACR measurement within 1 year prior to index.

More information about the study design can be found in the online supplemental material.

Data sources

At birth or immigration, Danish citizens are provided with a unique personal identification number used for documentation of person-specific information in nationwide registries.

We used the unique personal identification numbers to cross-link these registries, to include and evaluate patients on an individual level in the nationwide cohort. A more detailed description of the data sources can be found in the online supplemental material.

Comorbidities and concomitant medication

Comorbidities were based on ICD-10 codes from inpatient and outpatient contacts within 5 years prior to inclusion, and concomitant medication was defined using ATC codes and pharmacy prescriptions claimed within 180 days prior to baseline.

Type 2 diabetes was defined as patients discharged from hospital with a diagnosis of type 2 diabetes and patients in treatment with glucose-lowering medication, except female patients below 40 years of age receiving monotherapy with metformin as they were likely to be treated for polycystic ovarian syndrome. Cohabitation status was defined from the civil registration system as the number of adult residents on an address using the most recent cohabitation status prior to index, as done in previous studies.[14] Annual income was converted into an ordinal variable by dividing patients into four quartile groups according to annual earnings.

ICD-10, ATC and NPU codes used to define the population's comorbidities, concomitant medication and outcomes are listed in online supplemental table 1.

Outcomes

We assessed the usage of uACR measurements at baseline using the laboratory databases and the most recent uACR measurement within 1 year of index, if any measurement was registered. Patients were followed for 2 years or until the occurrence of an outcome, death, emigration or end of study period (31 December 2018).

The included patients were analysed according to three outcomes: major cardiovascular events (MACEs), consisting of hospital contacts with ICD-10 codes for non-fatal acute myocardial infarction, non-fatal stroke and cardiovascular death; HF, defined as a hospital contact with ICD-10 codes for HF; decline in eGFR, defined as a decline in eGFR of at least 40% compared with baseline eGFR; and ESKD, defined as patients receiving chronic dialysis, kidney transplantation and patients with an eGFR below 15 mL/min/1.73 m².

Statistics

Categorical variables were handled as counts and percentages, and continuous variables as medians and IQRs. Unadjusted absolute risks were evaluated using the Aalen-Johansen estimator to estimate the 2-year cumulative incidences of each outcome. Adjusted Cox regression analyses were used to calculate hazard ratios with 95% CIs. Standardised absolute risks were calculated using the G-formula.[15] In all analyses, death from all causes served as a competing risk, and the analyses were adjusted according to well-known positive predictors.

MACE was adjusted for age, sex, income, year of inclusion, cohabitation status, stroke, diabetes, vascular disease, eGFR level (in groups corresponding to chronic kidney disease stages) and statin use. HF was adjusted for age, sex, income, year of inclusion, cohabitation status, diabetes, vascular disease, treatment with diuretics, treatment with digoxin, eGFR level and treatment with

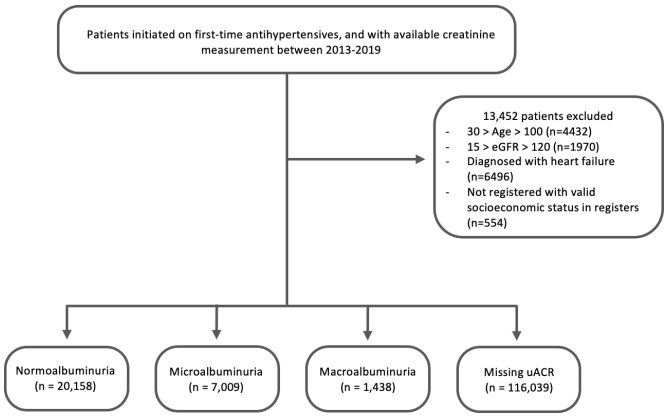

Figure 1 Selection of the study population. Flow chart depicting the inclusion and exclusion of patients. eGFR, estimated glomerular filtration rate. uACR, urinary albumin-to-creatinine ratio.

beta-blockers. 40% decline in eGFR and ESKD was adjusted for age, sex, income, year of inclusion, cohabitation status, diabetes, use of acetylsalicylic acid, eGFR level and treatment with non-steroid anti-inflammatory drugs. We performed interaction analysis to investigate whether the relative risk of cardiorenal events depended on eGFR for each primary outcome. Direct acyclic graphs were created to visualise the relationship between covariates included in the models (online supplemental figure 1).

Additional information and description of the statistical approach used in supplementary analysis can be found in online supplemental material, statistics section.

Ethics

Only authorised personnel had access to the data used in the study. Ethical approval is not required for registry-based studies in Denmark, yet Danish and European legislation forbids further data sharing from this study.[16] Patient involvement was not possible in this nationwide cohort.

RESULTS

Study population and characteristics

We identified 158 096 patients who initiated antihypertensive treatment between 2013 and 2019 and who had a creatinine measurement within 1 year prior to index. Among these, we excluded 13 452 patients, leaving 144 644 patients in the study population (figure 1). Overall, 14% of the included patients had normoalbuminuria (uACR <30 mg/g), 5% had microalbuminuria (30≤uACR >300 mg/g), 1% had macroalbuminuria (uACR ≥300 mg/g) and 80% (116 039) of patients initiating antihypertensive treatment did not have their uACR evaluated at treatment initiation. Among the patients without uACR measurement, 22.5% were analysed with protein dipstick tests, resulting in 89 956 (62%) patients without any assessment of proteinuria within 1 year prior to treatment initiation (table 1). During the first year of follow-up, 54 688 (38%) patients were subjected to either uACR evaluation or protein dipstick test to assess kidney function. About 46% of the included patients were not subjected to either uACR measurement or protein dipstick test within index ±1 year. Patients with diabetes were more likely to have their uACR evaluated at index than patients without diabetes (table 1).

The median age was lowest among patients with macroalbuminuria (56, IQR: 46, 68). Male sex was predominant across all subgroups of patients regardless of proteinuria status.

As presented in table 1, patients with macroalbuminuria were more likely to have a lower annual income and to be living alone compared with patients with either microalbuminuria or normoalbuminuria and compared with patients with a missing uACR. Diagnoses of coagulopathy, atrial fibrillation, chronic liver disease, prior bleeding, alcohol abuse, chronic obstructive pulmonary disease and type 1 diabetes were all more frequent among patients with macroalbuminuria compared with patients with normoalbuminuria (table 1).

Baseline covariates and concomitant medication according to eGFR levels are presented in online supplemental tables 2 and 3.

Risk of cardiovascular events

Overall, patients with microalbuminuria had a greater 2-year risk of MACE (HR: 1.39, 95% CI: 1.17 to 1.64) and hospitalisation for HF (HR: 1.53, 95% CI: 1.19 to 1.98) compared with patients with normoalbuminuria. Patients with macroalbuminuria likewise had a significantly greater 2-year relative risk of MACE (HR: 2.02, 95% CI: 1.54 to 2.66) and HF (HR: 1.99, 95% CI: 1.35 to 2.95) compared with patients with normoalbuminuria (figure 2).

As shown in figure 2, patients with macroalbuminuria comprised the highest absolute 2-year risk of MACE (5.3%, 95% CI: 4.0% to 6.6%) and HF (1.9%, 95% CI: 1.2% to 2.5%) followed by patients with microalbuminuria.

The absolute 2-year risk of cardiovascular events increased as kidney function declined (figure 3). The absolute 2-year risk of MACE among patients with eGFR 59–30 mL/min/1.73 m² and macroalbuminuria was 8.7% (95% CI: 5.0% to 12.4%) compared with 4.7% (95% CI: 2.7% to 6.7%) among patients with macroalbuminuria and eGFR >90 mL/min/1.73 m² (online supplemental table 4).

The relative risk difference persisted among subgroups of kidney function, except among patients with eGFR 15–29 mL/min/1.73 m², among whom we found no statistically significant difference in relative risk of MACE or HF (online supplemental table 4). Interaction analyses suggested that the risk of cardiovascular events according to uACR depended on eGFR (p values for interaction <0.001) (figure 2).

Risk of kidney disease

As presented in figure 2, patients with macroalbuminuria had upwards of a fivefold risk of 40% decline in eGFR

Table 1 Selected baseline characteristics of the study population

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	No uACR
Number of patients	20158	7009	1438	116039
ACE inhibitors (%)	6920 (34.3)	3034 (43.3)	696 (48.4)	31096 (26.8)
Angiotensin receptor blockers (%)	6722 (33.3)	2422 (34.6)	380 (26.4)	33790 (29.1)
Calcium channel blockers (%)	4593 (22.8)	1192 (17.0)	314 (21.8)	31497 (27.1)
Thiazide diuretics (%)	1923 (9.5)	361 (5.2)	48 (3.3)	19656 (16.9)
Age, median (IQR)	61 (52, 70)	61 (52, 71)	56 (46, 68)	61 (51, 70)
Gender, male (%)	11986 (59.5)	4106 (58.6)	859 (59.7)	59726 (51.5)
uACR, median (IQR)	10 (6, 15)	61 (41, 105)	695(431, 1346)	–
Protein dipstick test (%)	8031 (39.8)	3113 (44.4)	799 (55.6)	26083 (22.5)
eGFR, median (IQR)	88 (77, 98)	89 (74, 100)	81 (55, 97)	88 (76, 98)
Socioeconomics				
Living alone (%)	5887 (29.2)	2410 (34.4)	507 (35.3)	38895 (33.5)
Annual income				
First quartile (highest) (%)	5747 (28.5)	1580 (22.5)	329 (22.9)	31446 (27.1)
Second quartile (%)	5206 (25.8)	1734 (24.7)	363 (25.2)	28362 (24.4)
Third quartile (%)	4958 (24.6)	1907 (27.2)	353 (24.5)	28711 (24.7)
Fourth quartile (lowest) (%)	4247 (21.1)	1788 (25.5)	393 (27.3)	27520 (23.7)
Comorbidities				
Vascular disease (%)	1712 (8.5)	531 (7.6)	113 (7.9)	10078 (8.7)
Coagulopathy (%)	117 (0.6)	44 (0.6)	24 (1.7)	774 (0.7)
Atrial fibrillation	729 (3.6)	335 (4.8)	83 (5.8)	5468 (4.7)
Chronic liver disease (%)	256 (1.3)	156 (2.2)	41 (2.9)	1803 (1.6)
Prior bleeding (%)	1420 (7.0)	694 (9.9)	217 (15.1)	10318 (8.9)
Stroke (%)	932 (4.6)	277 (4.0)	68 (4.7)	7608 (6.6)
Alcohol abuse (%)	380 (1.9)	202 (2.9)	53 (3.7)	3296 (2.8)
COPD (%)	530 (2.6)	247 (3.5)	71 (4.9)	4329 (3.7)
Diabetes type 1 (%)	142 (0.7)	74 (1.1)	29 (2.0)	97 (0.1)
Diabetes type 2 (%)	4570 (22.7)	2393 (34.1)	378 (26.3)	5179 (4.5)
Cancer (%)	1470 (7.3)	631 (9.0)	134 (9.3)	12295 (10.6)
Concomitant medication				
Glucocorticoids (%)	521 (2.6)	182 (2.6)	82 (5.7)	4593 (4.0)
Acetylsalicylic acid (%)	2097 (10.4)	669 (9.5)	127 (8.8)	8742 (7.5)
Loop diuretics (%)	303 (1.5)	184 (2.6)	128 (8.9)	2294 (2.0)
NSAID (%)	2933 (14.6)	1024 (14.6)	197 (13.7)	19734 (17.0)
Betablockers (%)	2311 (11.5)	743 (10.6)	144 (10.0)	10770 (9.3)
Statins (%)	5682 (28.2)	1964 (28.0)	328 (22.8)	17343 (14.9)
Digoxin (%)	110 (0.5)	83 (1.2)	13 (0.9)	712 (0.6)

eGFR, Estimated glomerular filtrations rate; NSAID, Non-steroid anti-inflammatory drugs; uACR, Urinary albumin-to-creatinine ratio.

(HR: 4.81, 95% CI: 3.78 to 6.10) and ESKD (HR: 4.52, 95% CI: 3.00 to 6.82) during follow-up compared with patients with normoalbuminuria. Patients with microalbuminuria had upwards of a twofold increased risk of a 40% decline in eGFR (HR: 1.76, 95% CI: 1.43 to 2.18) and ESKD (HR: 2.25, 95% CI: 1.50 to 3.37) compared with patients with normoalbuminuria.

The absolute 2-year risk of a 40% decline in eGFR and ESKD was highest among patients with macroalbuminuria (5.8%, 95% CI: 4.7% to 6.9% and 1.2%, 95% CI: 0.9% to 1.6%, respectively) (table 2 figure 2). Patients without uACR measurement at baseline had an absolute 2-year risk of a 40% decline in eGFR of 2.6% (95% CI: 2.5% to 2.7%) (figure 2).

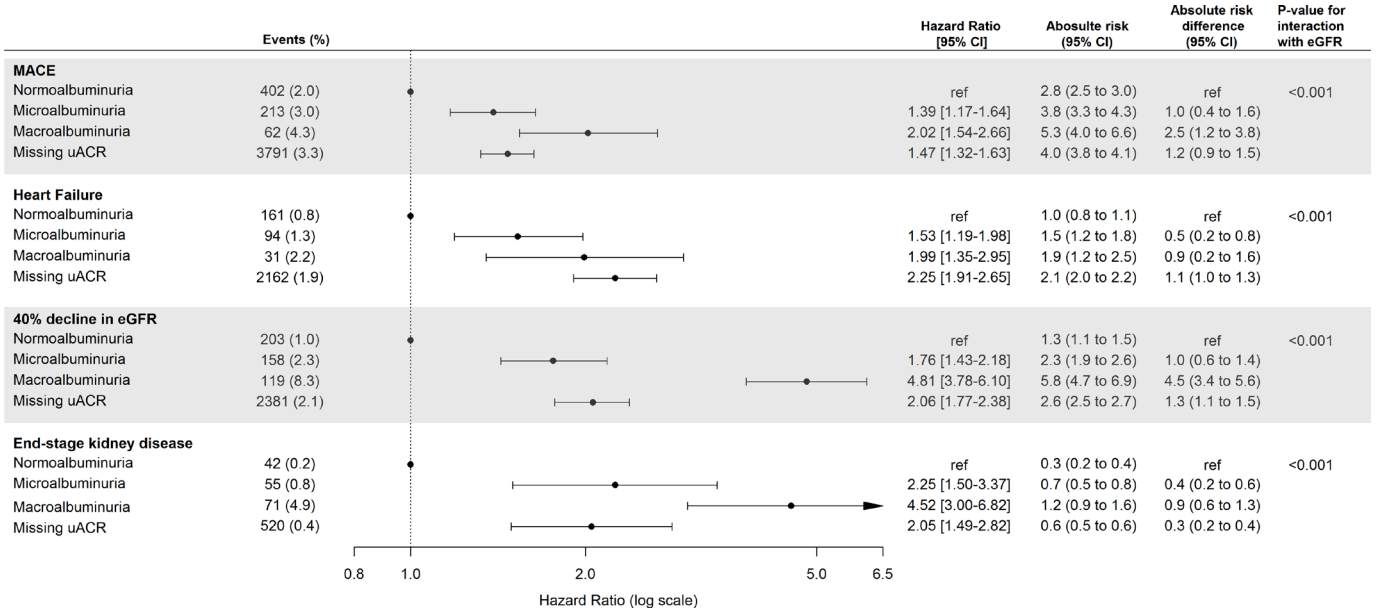

Figure 2 Standardised absolute and relative 2-year risks of MACEs, HF, 40% decline in kidney function and end-stage kidney disease. MACE was adjusted for age, sex, income, index year, living alone, prior stroke, diabetes type 1 and type 2, vascular disease, eGFR and treatment with statins. HF was adjusted for age, sex, income, index year, living alone, diabetes type 1 and type 2, treatment with renin angiotensin inhibitors, loop diuretics, digoxin, or beta blockers, eGFR and vascular disease. Decline in eGFR and ESKD was adjusted for age, sex, income, index year, living alone, diabetes type 1 and type 2, treatment with acetylsalicylic acid, treatment with non-steroid anti-inflammatory drugs and eGFR. eGFR, estimated glomerular filtration rate; HF, heart failure; MACE, major cardiovascular event; uACR, urinary albumin-to-creatinine ratio.

When evaluating the risk of renal events according to kidney function, the relative 2-year risk difference was greatest among patients with eGFR 89–60 mL/min/1.73 m², among whom patients with macroalbuminuria had a noticeably higher 2-year relative risk of a 40% decline in eGFR (HR: 5.65, 95% CI: 3.70 to 8.64) and ESKD (HR: 12.54, 95% CI: 5.92 to 26.56) compared with patients with normoalbuminuria (online supplemental table 5). The risk of renal outcomes according to uACR differed across subgroups of eGFR (p values for interaction <0.001) (figure 2). The standardised absolute 2-year risk of a 40% decline in eGFR and ESKD increased as kidney function declined, with the highest absolute 2-year risks found among patients with eGFR 29–15 mL/min/1.73 m² (figure 4). Patients with macroalbuminuria comprised the highest absolute 2-year risk of renal events across all eGFR levels (figure 4).

Additional results from supplementary analysis are found in the online supplemental material.

DISCUSSION

This study was the first to investigate nationwide registries and laboratory databases in the assessment of uACR and the associated risk of cardiorenal events. The overall analysis showed that the risk of MACE, HF, 40% decline in eGFR and ESKD increased among patients with elevated uACR compared with patients with normalised uACR, and that elevated levels of proteinuria increased the risk of cardiorenal event independently of eGFR level among patients with eGFR 30–120 mL/min/1.73 m². Furthermore, our study revealed that the majority of patients initiating antihypertensive treatment did not have their kidney function assessed by uACR or protein dipstick tests within 1 year prior to treatment initiation.

Present international guidelines suggest evaluation of uACR at initiation of antihypertensive treatment and continuous yearly measurements to establish the degree of kidney damage and to assess the risk of CVDs.[5 8 9] This corresponds well with findings in our study considering the greater risk of MACE, HF, decline in eGFR and ESKD among patients with high uACR. Yet, our study revealed that uACR was not regularly evaluated among patients starting antihypertensive treatment. As hypertension is a well-known predictor of reduced kidney function and cardiovascular events, and as evaluation of albuminuria has been recognised as having the potential to improve cardiorenal outcomes, the findings mentioned above could infer considerable issues in the risk profiling of hypertensive patients.[5 8 17 18]

The usage of albuminuria screening has been assessed in few prior studies conducted on data from healthcare databases. In cohorts of patients with hypertension and diabetes, the prevalence of uACR screening was estimated to be around 35% and to be even lower in patients with hypertension alone.[11 12] The results presented in this study confirm this trend as diabetes was more frequent among patients with measured uACR than among patients without. Moreover, this study revealed that despite universal healthcare access, the screening rate in a nationwide cohort was not considerately higher as

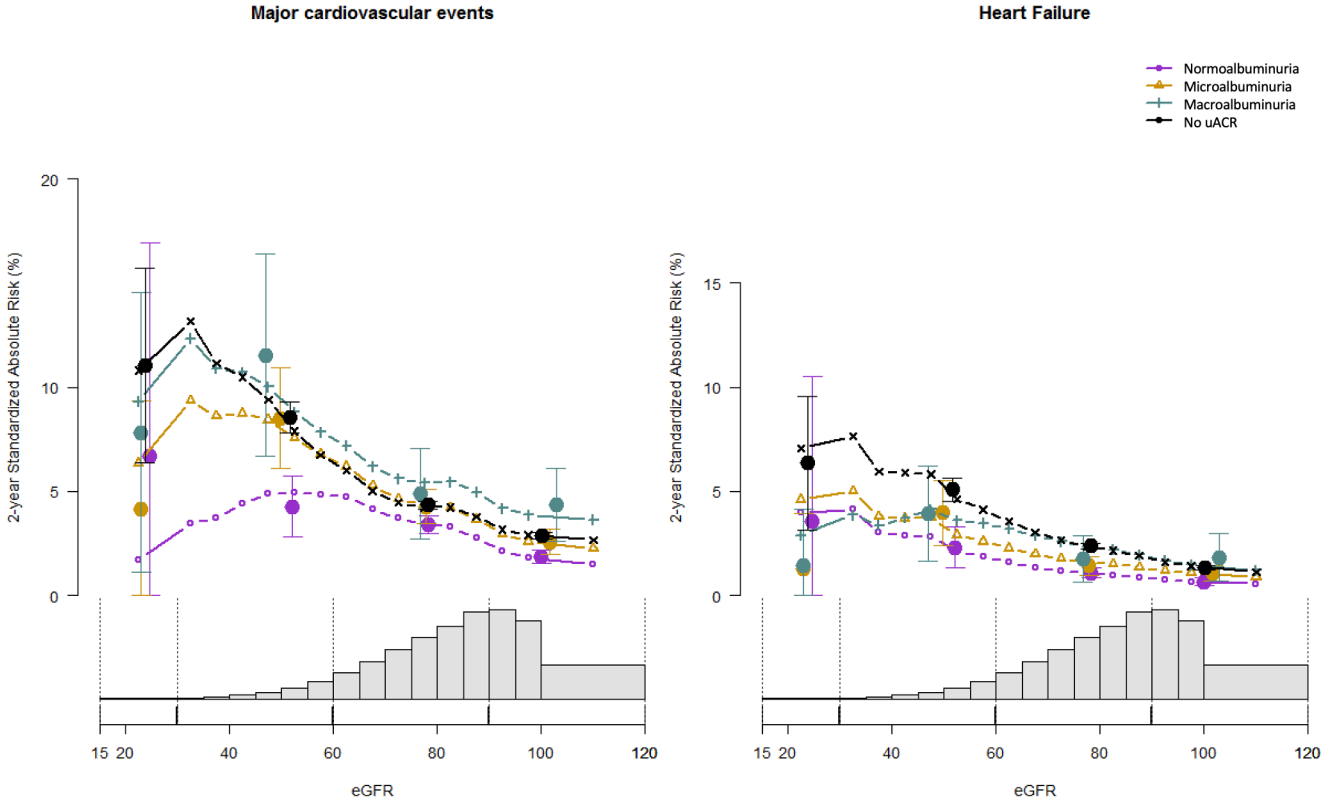

Figure 3 Absolute risk of MACEs and heart failure according to eGFR and uACR. Standardised absolute risks according to continuous eGFR. The larger dots represent grouped estimates (ie, eGFR 15–30, eGFR 30–59, eGFR 60–89, eGFR 90–120 mL/min/1.73m^2) with 95% CIs. MACE was adjusted for age, sex, income, index year, living alone, prior stroke, diabetes type 1 and type 2, vascular disease and treatment with statins. HF was adjusted for age, sex, income, index year, living alone, diabetes type 1 and type 2, treatment with renin angiotensin inhibitors, loop diuretics, digoxin, or beta blockers and vascular disease. All grouped estimates were adjusted for eGFR in addition to already applied adjustments. eGFR, estimated glomerular filtration rate; MACE, major cardiovascular event; uACR, urinary albumin-to-creatinine ratio.

80% of the included patients did not have their uACR evaluated.

Prior findings revealed that any degree of albuminuria was a risk factor for cardiovascular events in patients with and without diabetes and that the risk increased with uACR, starting below the microalbuminuria cut-off.[17] This correlates with the findings presented in this study as patients with uACR between 10 and 30 mg/g were found to be at increased risk of cardiovascular events. This could reflect a dose–response-like relationship between uACR and the risk of cardiovascular events starting below the microalbuminuria cut-off. This study also found that the proportion of patients living alone and with the lowest annual income was higher among patients with macroalbuminuria compared with patients with normoalbuminuria and microalbuminuria, reflecting the socioeconomic differences between the patient groups.

The use of both eGFR and uACR in terms of cardiovascular and renal risk assessment has been highlighted in several studies identifying the markers as supplementary and improving risk classification.[19–21] In a prior meta-analysis, eGFR less than 60 mL/min/1.73 m^2 and uACR above 10 mg/g were found to be independent predictors of cardiovascular mortality.[19] Patients included in the present study were subcategorised according to eGFR level, and the associated risk of cardiorenal events increased among patients with high levels of albuminuria compared with patients with lower levels of albuminuria and corresponding eGFR level between 30 and 120 mL/min/1.73 m^2. Findings like these suggest that the risk of cardiovascular and renal events should be quantified with both uACR and eGFR as they were both found to be independent predictors.

The results from our study showed that albuminuria was associated with an increased risk of cardiorenal outcomes independent of eGFR level among patients with eGFR between 30 and 120 mL/min/1.73 m^2, yet albuminuria was not regularly evaluated among patients initiating hypertensive treatment. Even though diabetes was more common among patients being tested for albuminuria in this study, the subgroup of patients without uACR comprised 5179 (4.5%) patients with diabetes type 2. Moreover, patients without uACR measurement were more likely to be suffering from cancer and to be treated with non-steroid anti-inflammatory drugs and less likely to have protein dipstick test performed than patients with measured uACR. Risk of cardiovascular and renal events was also higher among patients without uACR measurement compared with patients with normoalbuminuria. This suggests that the current approach to screening

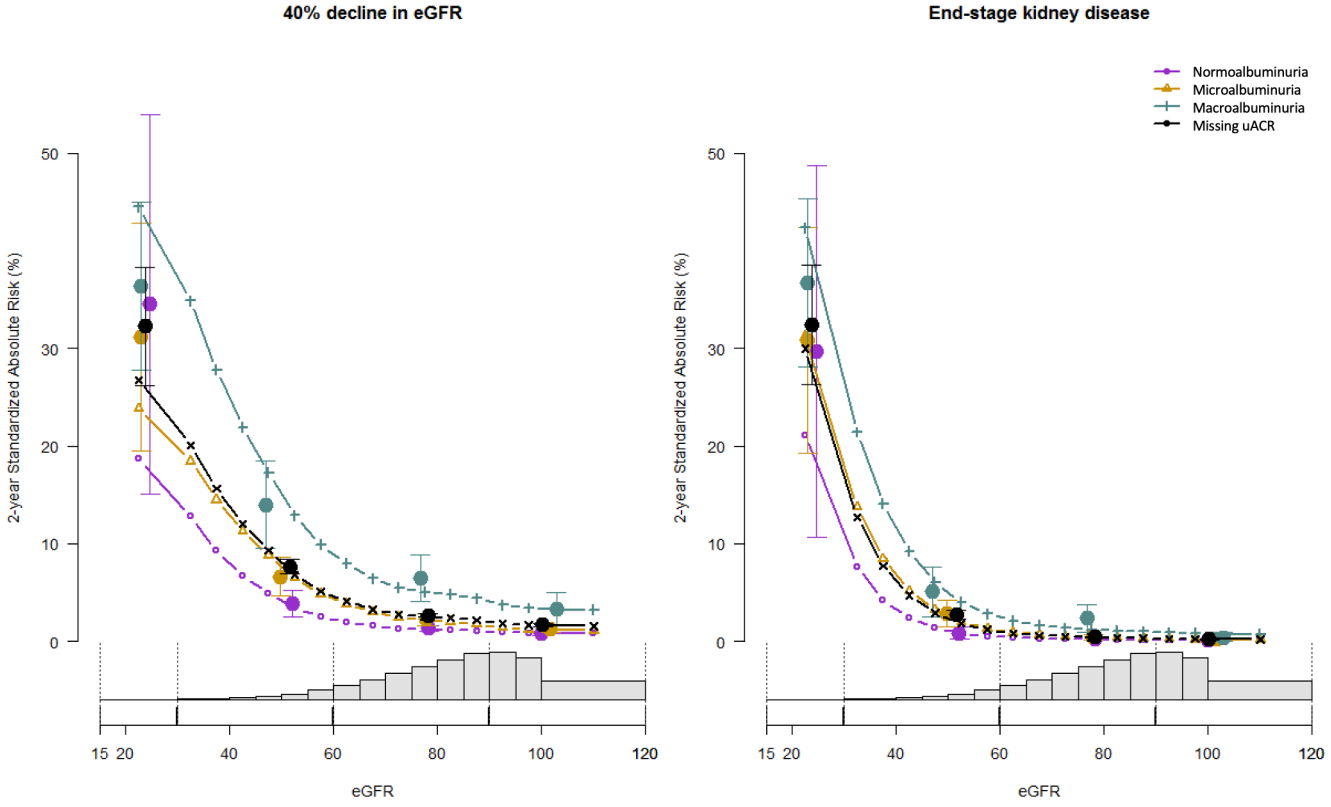

Figure 4 Absolute risk of decline in eGFR and ESKD according to eGFR and uACR. Standardised absolute risks according to continuous eGFR. The larger dots represent grouped estimates (ie, eGFR 15–30, eGFR 30–59, eGFR 60–89, eGFR 90–120 mL/min/1.73 m^2) with 95% CIs. Decline in eGFR and ESKD was adjusted for age, sex, income, index year, living alone, diabetes type 1 and type 2, treatment with acetylsalicylic acid and treatment with non-steroid anti-inflammatory drugs. All grouped estimates were adjusted for eGFR in addition to already applied adjustments. eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio.

does not always include high-risk patients, and that albuminuria was not evaluated with either protein dipstick or uACR in a substantial proportion of patients. Whether this was caused by lack of knowledge from healthcare professionals or because patients were evaluated by eGFR is not known, yet as this study showed, eGFR measurements should not stand alone in risk evaluation of hypertensive patients.

Further research regarding the usage of uACR during follow-up and evaluation of risk factors associated with different uACR levels is warranted.

Strengths and limitations

This study comprised real-world nationwide data, with no exclusions based on social or insurance status and no loss to follow-up.

The diagnosis codes used in this study to define the study population and to define the outcomes have previously been well validated.[22] Furthermore, this study was carried out with data from laboratory databases which are usually not available in large-scale registry-based studies.

This study did not have available creatinine measurements from the entire Danish population; however, we have previously found our data to be representative of the nationwide cohort in similar settings, and we found no indication of selection bias.[23] Furthermore, test results from urine protein dipstick tests performed at general practitioners were identified using the general practitioners' invoice claims to the healthcare regions. This could result in tests not being identified and thereby overestimation of the number of patients without protein dipstick test. Nonetheless, we believe that the number of tests that are omitted due to this is low, as the general practitioners are being funded by the healthcare region based on these invoice claims. Furthermore, urine protein dipstick tests do not provide a specific measurement for proteinuria, and several studies have found the sensitivity of urine protein dipstick tests with low level results to be low, which is why it is recommended to evaluate kidney function by urine spot tests.[8] The subgroup of patients with eGFR 29–15 mL/min/1.73 m^2 contained few patients. This could limit the clinical interpretation, and the results presented in this subgroup should be considered with caution.

We sought to minimise the risk of residual confounding by adjusting our analyses for variables known to affect the outcomes; however, confounders might have persisted due to variables not available in the datasets (eg, smoking, diet composition and physical training). Future studies incorporating such variables could help clarify how they interact with the outcomes evaluated in this study.

Additionally, research exploring the risk of cardiorenal events according to continuous blood pressure among patients with hypertension could help assess the association further.

CONCLUSIONS

Albuminuria was not evaluated regularly among patients initiating antihypertensive treatment. Nonetheless, patients with macroalbuminuria comprised the highest risks of cardiovascular and renal outcomes, and both patients with microalbuminuria and patients with macroalbuminuria were found to have a greater 2-year relative risk of cardiorenal outcomes, compared with patients with normalised uACR. This could result in high-risk patients not being identified.

Contributors All authors participated in developing the hypothesis and study design. CB wrote the first and successive drafts of the manuscript. MS, NC, ANB and CB defined the exposures and outcomes. All authors contributed to the study concept, interpretation of data, analysis of data and revision of the manuscript with important scientific feedback or additional data acquisition. CB and ANB had full access to the data and take full responsibility for the integrity of the data management and the accuracy of the data analysis. CB is responsible for the overall content as guarantor. The corresponding author, CB, attests that all listed authors meet authorship criteria as stated by the International Committee of Medical Journal Editors (IMCJE), and that no others meeting the criteria have been omitted from the list of authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The use of data for the study was approved by the Capital Region of Denmark (ref no. P-2019-191) in conformation with General Data Protection Regulation (GDPR).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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