Supplementary material

Title: Urinary Albumin-to-Creatinine ratio in patients with hypertension – a real-world cohort study of more than 140,000 patients

Casper Binding MD (a,b,c), Mariam Elmegaard MD (a), Deewa Zahir Anjum MD (a), Nicholas Carlson MD PhD (d), Morten Schou MD PhD (a), Anders Nissen Bonde MD PhD (a,e)

a) Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte, 2900 Hellerup, Denmark.
b) Department of Cardiology, Aalborg University Hospital, 9000 Aalborg, Denmark
c) Department of Cardiology, Copenhagen University Hospital Amager and Hvidovre, 2650 Hvidovre, Denmark
d) Department of Nephrology, Copenhagen University Hospital Rigshospitalet, 2100 Copenhagen, Denmark
e) Department of Cardiology, Zealand University Hospital Roskilde, 4000 Roskilde, Denmark

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Methods

Study design

We used the latest available creatinine measurement and the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) to evaluate eGFR as recommended in the Kidney Disease Improving Global Outcome Guidelines due to accuracy (14, 15). The calculated eGFR was used to further subcategorise patients according to kidney function into the following groups: eGFR between 15 and 29 ml/min/1.73m², eGFR between 30 to 59 ml/min/1.73m², eGFR 60 to 89 ml/min/1.73m², and eGFR between 90 and 120 ml/min/1.73m².

Data sources

The Danish Civil Registration System holds information regarding birth, death, and sex(1); the Danish Income Statistics register covers income, and cohabitation status(2); the Danish National prescription Registry contains information on all redeemed prescriptions from the Danish pharmacies, which also includes drug dosages, strengths, and packaging of dispensed drugs tied to Anatomical Therapeutic Chemical codes (ATC-codes) (3); the Danish National Patient Register holds information regarding fees from tests performed at general practitioners, hospital contacts, date of admissions/discharges, and diagnosis codes using International Classification of Diseases 10 (ICD-10) codes (4); and the Danish Laboratory Database contains information regarding date, results, site of measurement, and a Nomenclature for Properties and Units (NPU) code from blood tests taken at hospitals and GPs, from four out of five major regions of Denmark (5).

Statistics

The analyses were evaluated on a 5% significance level, meaning that 95% confidence intervals in

relative risk analyses not containing 1.00, were considered statistically significant. To evaluate whether the effect of uACR status depended on eGFR, we calculated p-values for the interaction of eGFR on relative risks with each uACR-group.

To evaluate whether the effect of uACR status depended on eGFR, we calculated p-values for the interaction of eGFR on standardised absolute risks with each uACR-group. We conducted an additional analysis in which we censored patients discontinuing treatment to evaluate the effect of proteinuria if no patients discontinued treatment. We also stratified patients according to uACR below the microalbuminuria cut-off to evaluate the risk of cardiorenal events in this subgroup.

The Cox models were tested for proportional hazards and relevant interactions, and we found no violations of model assumptions.

SAS (version 9.4 for Windows, SAS Institute, Cary, and C) and R (version 3.6.1 for Windows, R foundation for statistical computing) were used to handle data management, statistical analysis, and the creation of figures.

Results

When censoring patients discontinuing antihypertensive treatment, the associated risks of MACE and heart failure were similar to those obtained in the main analysis (supplementary table 6). In an additional analysis, patients with uACR between 10-30 mg/g were found to have an increased risk of cardiovascular events compared to patients with uACR 1-10 mg/g (supplementary figure 2).

The risks of decline in kidney function and EKSD among patients not discontinuing, were similar to those presented in the main analysis (supplementary table 6). The estimated risk of renal events was higher among patients with uACR 10-30 mg/g compared to patients with 1-10 mg/g, yet these

results were not statistically significant (supplementary figure 2). Interaction analyses suggested no differences in risk of cardiovascular events according to uACR in subgroups of eGFR. The risk of renal events among patients with albuminuria compared to patients with normoalbuminuria however, seemed to differ according to eGFR level (Supplementary figure 2).

Supplementary figure Legends

Supplementary figure 1. Direct acyclic graphs

Direct acyclic graphs depicting the relationships between exposures, outcomes, and covariates incorporated in the statistical models.

Abbreviations: ASA: Acetylsalicylic acid. eGFR: Estimated glomerular filtrations rate. ESKD: End-stage kidney disease. MACE: Major cardiovascular events. NSAID: Non-steroid anti-inflammatory drugs. uACR: Urinary albumin-to-creatinine ratio

Supplementary figure 2. Risk of cardiorenal events according to urinary albumin-to-creatinine ratio levels below microalbuminuria cut-off

Risk of major cardiovascular events, heart failure, progression of kidney disease, and end-stage kidney disease according to urinary albumin-to-creatinine ratio levels below microalbuminuria cut-off.

Abbreviations: eGFR: Estimated glomerular filtrations rate. ESKD: End-stage kidney disease. MACE: Major cardiovascular events. Ref: Reference. uACR: Urinary albumin-to-creatinine ratio

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Supplementary table 1. Codes used to define the population.

Population		
Hypertension	*Defined from treatment with anti-hypertensive drugs.*	Presence of: ATC: C03A, C08, C09A, C09B, C09C, C09D
Urinary albumin-to-creatinine ratio	*Defined from NPU code of uACR or NPU of u-albumin together with NPU of u-creatinine.*	NPU: 19661, 19676, 01808.
Estimated glomerular filtration rate	*Defined from NPU code of creatinine.*	NPU: 18016, 04998
Protein dipstick test	*Defined from NPU code and honorary fees from general practitioners.*	NPU: 04206, 14924 Protein dipstick test fee: 7101
Outcomes and comorbidities		
Major cardiovascular events	*Defined from diagnosis of stroke, acute myocardial infarction, or cardiovascular cause of death.*	ICD10: I63, I64, I74, G458, G459, I22. I10, I11, I13-I87, I95, I99, R00, R01, R03.
Heart failure	*Defined from hospitalization with primary diagnosis.*	ICD10: I50, I110, I130, I132.
End-stage kidney disease	*Defined from chronic dialysis, eGFR<15, and kidney transplantation.*	NCSP: KKAS, BJFD. NPU: 18016, 04998.
Atherosclerosis	*Defined from diagnosis.*	ICD10: I70
Vascular disease	*Defined from diagnosis.*	ICD10: I21-I25, I70.
Coagulopathy	*Defined from diagnosis.*	ICD10: I66-I69.
Atrial fibrillation	*Defined from diagnosis of atrial fibrillation*	ICD10: I48.
Chronic kidney disease	*Defined from diagnosis.*	ICD10: N02-N08, N11, N12, N14, N18, N19, N26, N158-N160, N162-N164, N168, Q612, Q613, Q615, Q619, E102, E112, E132, E142, I120, M300, M313, M319, M321B.
Chronic liver disease	*Defined from diagnosis of liver chronic liver disease, cirrhosis and hepatitis.*	ICD10: B15-B19, C22, D684C, I982, K70-K77, Q618A, Z944.
Major bleeding	*Defined from diagnosis of intracranial or intradural bleeding, major gastrointestinal bleeding, haemopericardium, respiratory or urinary tract bleeding, retroperitoneal bleeding, bleeding in the eye, and anaemia due to bleeding.*	ICD10: I312, N02, R31, R04, H313, H356, H431, H450, H052A, K228F, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K298A, K625, K638B, K638C, K661, K838F, K868G, K920, K921, K922, I850, I864A, S064, S065, S066, G951A, S368D, J942.
Stroke/thromboembolism	*Defined from diagnosis of ischemic stroke, transient ischemic attack, or systemic thromboembolism.*	ICD10: I63, I64, G458, G459, I74.
Alcohol abuse	*Defined from diagnosis.*	ICD10: L278A.
Chronic obstructive pulmonary disease	*Defined from diagnosis.*	ICD10: J44.
Diabetes type 1	*Defined from age and ATC-codes*	ATC: A10A and age < 18 years. ATC: A10A as monotherapy and age < 30 years.
Diabetes type 2	*Defined from diagnosis and ATC-codes*	ICD10: E11. ATC: A10 except women receiving monotherapy with A10BA02 and age <

		40 years.
Syncope	*Defined from diagnosis.*	ICD10: R559.
Heart failure	*Defined from diagnosis.*	ICD10: I50, I110, I130, I132.
Cancer	*Defined from diagnosis.*	ICD10: Presence of C.
Fracture	*Defined from diagnosis.*	ICD10: S321-S325, S42, S52, S62, S72.
Concomitant medication		
Glucocorticoids	*Defined from ATC codes.*	ATC: H02.
Acetylsalicylic acid (aspirin)	*Defined from ATC codes.*	ATC: B01AC06, N02BA01.
Non-steroidal anti-inflammatory drugs	*Defined from ATC codes.*	ATC: M01A without M01AX05.
Antiadrenergic agents	*Defined from ATC codes.*	ATC: C02A, C02B, C02C.
Beta-blockers	*Defined from ATC codes.*	ATC: C07A, C07B, C07C, C07D, C07F.
Statin	*Defined from ATC codes.*	ATC:C10AA01-C10AA08.
Hormone replacement therapy	*Defined from ATC codes.*	G03C, G03D, G03F, G03XC, G02BA03.
Digoxin	*Defined from ATC codes.*	ATC: C01AA
ADP-receptor blocker	*Defined from ATC codes.*	ATC: B01AC04, B01AC22, B01AC24
Renin-angiotensin-system inhibitors	*Defined from ATC codes.*	ATC:C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Loop diuretics	*Defined from ATC codes.*	ATC: C03C, C03EB.
Calcium channel blockers	*Defined from ATC codes.*	ATC: C08, C09BB, C09DB
Vitamin k antagonists	*Defined from ATC codes.*	ATC: B01AA
Direct oral anticoagulants	*Defined from ATC codes.*	ATC: B01AE07, B01AF01, B01AF02, B01AF03.

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Supplementary table 2. Selected baseline characteristics of the study population according to eGFR 120-60 (ml/min/1.73m^2)

	120 ≥ eGFR ≤ 90				90 > eGFR ≥ 60			
	Normo	**Micro**	**Macro**	**Missing**	**Normo**	**Micro**	**Macro**	**Missing**
Number of patients	9150	3328	534	51246	9892	2931	484	57388
ACEi (%)	3361 (36.7)	1550 (46.6)	284 (53.2)	13961 (27.2)	3236 (32.7)	1204 (41.1)	244 (50.4)	15286 (26.6)
ARB (%)	3202 (35.0)	1197 (36.0)	145 (27.2)	15589 (30.4)	3232 (32.7)	1029 (35.1)	150 (31.0)	16620 (29.0)
CC-Blockers (%)	1835 (20.1)	449 (13.5)	92 (17.2)	13095 (25.6)	2393 (24.2)	519 (17.7)	72 (14.9)	15842 (27.6)
Thiazides (%)	752 (8.2)	132 (4.0)	13 (2.4)	8601 (16.8)	1031 (10.4)	179 (6.1)	18 (3.7)	9640 (16.8)
Age, median [IQR]	54 [48, 61]	54 [47, 62]	52 [42, 59]	53 [46, 61]	67 [58,73]	68 [58,75]	61.5 [49,71]	66 [57,74]
Sex, male (%)	5695 (62.2)	1944 (58.4)	296 (55.4)	27021 (52.7)	5713 (57.8)	1709 (58.3)	303 (62.6)	29182 (50.9)
uACR, median [IQR]	10 [6,15]	60 [41,104]	603 [398,1130]	-	10 [6, 14]	61 [41,102]	691 [430, 1300]	-
Protein dipstick test (%)	3501 (38.3)	1419 (42.6)	285 (53.4)	10707 (20.9)	4027 (40.7)	1317 (44.9)	264 (54.5)	13169 (22.9)
eGFR, median [IQR]	99 [94,105]	101 [95,107]	102 [96,109]	99 [94,105]	80 [72,85]	79 [71,85]	77 [70,85]	79 [72,85]
Socioeconomics								
Living alone (%)	2698 (29.5)	1165 (35.0)	199 (37.3)	16681 (32.6)	2793 (28.2)	968 (33.0)	162 (33.5)	19005 (33.1)
Annal income								
1st quartile (highest) (%)	3059 (33.4)	863 (25.9)	126 (23.6)	15909 (31.0)	2545 (25.7)	622 (21.2)	108 (22.3)	14585 (25.4)
2nd quartile (%)	2462 (26.9)	892 (26.8)	144 (27.0)	13402 (26.2)	2506 (25.3)	673 (23.0)	125 (25.8)	13579 (23.7)
3rd quartile (%)	1943 (21.2)	842 (25.3)	120 (22.5)	11634 (22.7)	2662 (26.9)	850 (29.0)	115 (23.8)	14885 (25.9)
4th quartile (lowest) (%)	1686 (18.4)	731 (22.0)	144 (27.0)	10301 (20.1)	2179 (22.0)	786 (26.8)	136 (28.1)	14339 (25.0)
Comorbidities								
Vascular Disease (%)	684 (7.5)	221 (6.6)	39 (7.3)	3708 (7.2)	885 (8.9)	232 (7.9)	52 (10.7)	5402 (9.4)
Coagulopathy (%)	63 (0.7)	21 (0.6)	8 (1.5)	359 (0.7)	46 (0.5)	16 (0.5)	9 (1.9)	342 (0.6)
Atrial fibrillation (%)	155 (1.7)	66 (2.0)	13 (2.4)	1304 (2.5)	464 (4.7)	189 (6.4)	29 (6.0)	3336 (5.8)
Liver Disease (%)	134 (1.5)	85 (2.6)	18 (3.4)	957 (1.9)	105 (1.1)	54 (1.8)	8 (1.7)	729 (1.3)
Prior Bleeding (%)	589 (6.4)	251 (7.5)	64 (12.0)	4149 (8.1)	711 (7.2)	321 (11.0)	74 (15.3)	5200 (9.1)
Prior Stroke/TE (%)	319 (3.5)	86 (2.6)	23 (4.3)	2724 (5.3)	527 (5.3)	134 (4.6)	16 (3.3)	4136 (7.2)
Alcohol Abuse (%)	226 (2.5)	125 (3.8)	24 (4.5)	2049 (4.0)	151 (1.5)	58 (2.0)	16 (3.3)	1086 (1.9)
COPD (%)	219 (2.4)	102 (3.1)	23 (4.3)	1669 (3.3)	255 (2.6)	105 (3.6)	30 (6.2)	2202 (3.8)
Diabetes type 1 (%)	118 (1.3)	55 (1.7)	18 (3.4)	79 (0.2)	23 (0.2)	16 (0.5)	8 (1.7)	16 (0.0)
Diabetes Type 2 (%)	2632 (28.8)	1404 (42.2)	191 (35.8)	2873 (5.6)	1763 (17.8)	802 (27.4)	129 (26.7)	2000 (3.5)
Cancer (%)	385 (4.2)	165 (5.0)	26 (4.9)	3855 (7.5)	947 (9.6)	327 (11.2)	50 (10.3)	6932 (12.1)
Concomitant medication								
Glucocorticoids (%)	200 (2.2)	65 (2.0)	26 (4.9)	1774 (3.5)	269 (2.7)	83 (2.8)	26 (5.4)	2367 (4.1)
Aspirin (%)	745 (8.1)	247 (7.4)	36 (6.7)	2832 (5.5)	1169 (11.8)	321 (11.0)	57 (11.8)	4966 (8.7)
Loop diuretics (%)	68 (0.7)	47 (1.4)	25 (4.7)	577 (1.1)	162 (1.6)	69 (2.4)	34 (7.0)	1189 (2.1)
NSAID (%)	1536 (16.8)	537 (16.1)	75 (14.0)	9909 (19.3)	1266 (12.8)	384 (13.1)	63 (13.0)	8817 (15.4)
beta blockers (%)	774 (8.5)	244 (7.3)	35 (6.6)	3753 (7.3)	1296 (13.1)	372 (12.7)	46 (9.5)	5866 (10.2)
Statins (%)	2391 (26.1)	902 (27.1)	115 (21.5)	6206 (12.1)	2922 (29.5)	835 (28.5)	132 (27.3)	9715 (16.9)
Digoxin (%)	17 (0.2)	12 (0.4)	<3 (<0.6)	117 (0.2)	71 (0.7)	45 (1.5)	8 (1.7)	439 (0.8)

Abbreviations: ACEi: Ace inhibitors, ARB: Angiotensin-II receptor blockers, CC-Blockers: Calcium channel blockers, COPD: Chronic obstructive pulmonary disease, eGFR: Estimated glomerular filtration rate, NSAID: Non-steroid anti-inflammatory drug. uACR: Urinary albumin-to-creatinine ratio. Normo, micro, and macro, refers to the degree of proteinuria from uACR measurement.

Supplementary table 3. Selected baseline characteristics of the study population according to eGFR 60-15 (ml/min/1.73m^2)

	60 > eGFR ≥ 30				30 > eGFR ≥ 15			
	Normo	**Micro**	**Macro**	**Missing**	**Normo**	**Micro**	**Macro**	**Missing**
Number of patients	1089	679	297	7129	27	71	123	276
ACEi (%)	317 (29.1)	264 (38.9)	131 (44.1)	1800 (25.2)	6 (22.2)	16 (22.5)	37 (30.1)	49 (17.8)
ARB (%)	286 (26.3)	186 (27.4)	66 (22.2)	1560 (21.9)	<3 (<11.1)	10 (14.1)	19 (15.4)	21 (7.6)
CC-Blockers (%)	348 (32.0)	182 (26.8)	84 (28.3)	2386 (33.5)	17 (63.0)	42 (59.2)	66 (53.7)	174 (63.0)
Thiazides (%)	138 (12.7)	47 (6.9)	16 (5.4)	1383 (19.4)	<3 (<11.1)	3 (4.2)	<3 (<2.4)	32 (11.6)
Age, median [IQR]	74 [68,80]	73 [64,79]	62 [51,73]	75 [68,82]	75 [69,79]	73 [63,78]	61 [48,72]	71 [59,79]
Sex, male (%)	563 (51.7)	412 (60.7)	192 (64.6)	3361 (47.1)	15 (55.6)	41 (57.7)	68 (55.3)	162 (58.7)
uACR, median [IQR]	10 [6,16]	70 [44,129]	803 [470,1690]	-	17 [11,22]	89 [55,168]	1030 [636,2170]	-
Protein dipstick test (%)	490 (45.0)	348 (51.3)	179 (60.3)	2094 (29.4)	13 (48.1)	29 (40.8)	71 (57.7)	113 (40.9)
eGFR, median [IQR]	54 [48,57]	52 [45, 57]	48 [39,55]	54 [48,57]	25 [23, 28]	23 [19,27]	23 [20,27]	24 [20,27]
Socioeconomics								
Living alone (%)	380 (34.9)	256 (37.7)	93 (31.3)	3087 (43.3)	16 (59.3)	21 (29.6)	53 (43.1)	122 (44.2)
Annual income								
1st quartile (highest) (%)	139 (12.8)	83 (12.2)	68 (22.9)	921 (12.9)	4 (14.8)	12 (16.9)	27 (22.0)	31 (11.2)
2nd quartile (%)	233 (21.4)	151 (22.2)	73 (24.6)	1334 (18.7)	5 (18.5)	18 (25.4)	21 (17.1)	47 (17.0)
3rd quartile (%)	349 (32.0)	201 (29.6)	80 (26.9)	2103 (29.5)	4 (14.8)	14 (19.7)	38 (30.9)	89 (32.2)
4th quartile (lowest) (%)	368 (33.8)	244 (35.9)	76 (25.6)	2771 (38.9)	14 (51.9)	27 (38.0)	37 (30.1)	109 (39.5)
Comorbidities								
Vascular Disease (%)	141 (12.9)	73 (10.8)	17 (5.7)	943 (13.2)	<3 (<11.1)	5 (7.0)	5 (4.1)	25 (9.1)
Coagulopathy (%)	8 (0.7)	6 (0.9)	6 (2.0)	68 (1.0)	<3 (<11.1)	<3 (<4.2)	<3 (<2.4)	5 (1.8)
Atrial fibrillation (%)	107 (9.8)	70 (10.3)	33 (11.1)	791 (11.1)	3 (11.1)	10 (14.1)	8 (6.5)	37 (13.4)
Liver Disease (%)	17 (1.6)	16 (2.4)	9 (3.0)	104 (1.5)	<3 (<11.1)	<3 (<4.2)	6 (4.9)	13 (4.7)
Prior Bleeding (%)	119 (10.9)	105 (15.5)	60 (20.2)	922 (12.9)	<3 (<11.1)	17 (23.9)	19 (15.4)	47 (17.0)
Prior Stroke/TE (%)	84 (7.7)	54 (8.0)	22 (7.4)	721 (10.1)	<3 (<11.1)	3 (4.2)	7 (5.7)	27 (9.8)
Alcohol Abuse (%)	3 (0.3)	14 (2.1)	6 (2.0)	146 (2.0)	<3 (<11.1)	5 (7.0)	7 (5.7)	15 (5.4)
COPD (%)	54 (5.0)	38 (5.6)	11 (3.7)	441 (6.2)	<3 (<11.1)	<3 (<4.2)	7 (5.7)	17 (6.2)
Diabetes type 1 (%)	<3 (<0.3)	3 (0.4)	<3 (<1.0)	<3 (<0.1)	<3 (<11.1)	<3 (<4.2)	<3 (<2.4)	<3 (<1.1)
Diabetes Type 2 (%)	168 (15.4)	171 (25.2)	42 (14.1)	283 (4.0)	7 (25.9)	16 (22.5)	16 (13.0)	23 (8.3)
Cancer (%)	132 (12.1)	124 (18.3)	44 (14.8)	1438 (20.2)	6 (22.2)	15 (21.1)	14 (11.4)	70 (25.4)
Concomitant medication								
Glucocorticoids (%)	50 (4.6)	28 (4.1)	22 (7.4)	436 (6.1)	<3 (<11.1)	6 (8.5)	8 (6.5)	16 (5.8)
Aspirin (%)	177 (16.3)	92 (13.5)	28 (9.4)	917 (12.9)	6 (22.2)	9 (12.7)	6 (4.9)	27 (9.8)
Loop diuretics (%)	64 (5.9)	56 (8.2)	43 (14.5)	477 (6.7)	9 (33.3)	12 (16.9)	26 (21.1)	51 (18.5)
NSAID (%)	129 (11.8)	95 (14.0)	41 (13.8)	977 (13.7)	<3 (<11.1)	8 (11.3)	18 (14.6)	31 (11.2)
beta blockers (%)	234 (21.5)	114 (16.8)	44 (14.8)	1108 (15.5)	7 (25.9)	13 (18.3)	19 (15.4)	43 (15.6)
Statins (%)	365 (33.5)	210 (30.9)	61 (20.5)	1386 (19.4)	4 (14.8)	17 (23.9)	20 (16.3)	36 (13.0)
Digoxin (%)	20 (1.8)	23 (3.4)	<3 (<1.0)	147 (2.1)	<3 (<11.1)	3 (4.2)	<3 (<2.4)	9 (3.3)

Abbreviations: ACEi: Ace inhibitors, ARB: Angiotensin-II receptor blockers, CC-Blockers: Calcium channel blockers, COPD: Chronic obstructive pulmonary disease, eGFR: Estimated glomerular filtration rate, NSAID: Non-steroid anti-inflammatory drug. uACR: Urinary albumin-to-creatinine ratio. Normo, micro, and macro, refers to the degree of proteinuria from uACR measurement.

Supplementary table 4. Unadjusted Absolute and Relative 2-year Risks of Major Cardiovascular events and Heart Failure, according to eGFR (ml/min/1.73m^2) and uACR.

Kidney function	Major cardiovascular events				Heart failure			
uACR	Events	Hazard ratios [95% CI]	Absolute risks, % (95% CI)	Absolute risk difference, % (95% CI)	Events	Hazard ratios (95% CI)	Absolute risks, % (95% CI)	Absolute risk difference, % (95% CI)
eGFR>90								
Normoalbuminuria	128	ref	1.8 (1.5 to 2.2)	ref	52	ref	0.7 (0.5 to 0.9)	ref
Microalbuminuria	68	1.48 [1.11-1.99]	2.6 (2.0 to 3.3)	0.9 (0.2 to 1.5)	31	1.65 [1.06-2.58]	1.1 (0.7 to 1.5)	0.4 (0.0 to 0.9)
Macroalbuminuria	20	2.67 [1.67-4.28]	4.7 (2.7 to 6.7)	2.9 (0.9 to 4.9)	10	3.28 [1.67-6.45]	2.2 (0.8 to 3.5)	1.5 (0.2 to 2.8)
Missing	1212	1.65 [1.38-1.98]	2.9 (2.8 to 3.1)	1.1 (0.8 to 1.5)	605	2.05 [1.54-2.72]	1.4 (1.3 to 1.5)	0.7 (0.5 to 0.9)
eGFR 60–89								
Normoalbuminuria	241	ref	3.2 (2.8 to 3.6)	ref	88	ref	1.1 (0.8 to 1.3)	ref
Microalbuminuria	99	1.38 [1.09-1.75]	4.4 (3.6 to 5.2)	1.2 (0.3 to 2.1)	37	1.42 [0.97-2.08]	1.5 (1.0 to 2.0)	0.4 (-0.1 to 1.0)
Macroalbuminuria	18	1.53 [0.95-2.47]	4.8 (2.6 to 7.0)	1.6 (-0.6 to 3.8)	9	2.09 [1.05-4.14]	2.2 (0.8 to 3.6)	1.1 (-0.3 to 2.5)
Missing	2044	1.41 [1.24-1.61]	4.5 (4.3 to 4.7)	1.3 (0.8 to 1.7)	1214	2.34 [1.89-2.91]	2.4 (2.3 to 2.6)	1.4 (1.1 to 1.6)
eGFR 30–59								
Normoalbuminuria	31	ref	3.8 (2.5 to 5.1)	ref	20	ref	2.2 (1.2 to 3.1)	ref
Microalbuminuria	44	2.27 [1.43-3.60]	8.3 (6.0 to 10.7)	4.5 (1.9 to 7.2)	25	1.98 [1.10-3.57]	4.2 (2.6 to 5.9)	2.1 (0.2 to 3.9)
Macroalbuminuria	19	2.41 [1.36-4.27]	8.7 (5.0 to 12.4)	4.9 (1.0 to 8.8)	11	2.08 [1.00-4.34]	4.4 (1.9 to 6.9)	2.2 (-0.5 to 4.9)
Missing	509	2.48 [1.73-3.57]	8.9 (8.1 to 9.6)	5.1 (3.6 to 6.6)	326	2.49 [1.59-3.92]	5.2 (4.6 to 5.7)	3.0 (1.9 to 4.1)
eGFR 15–29								
Normoalbuminuria	<3	ref	8.7 (0.0 to 20.1)	ref	<3	ref	4.0 (0.0 to 11.8)	ref
Microalbuminuria	<3	0.43 [0.06-3.05]	3.9 (0.0 to 9.1)	-4.8 (-17.3 to 7.6)	<3	0.41 [0.03-6.53]	1.7 (0.0 to 5.0)	-2.3 (-10.8 to 6.2)
Macroalbuminuria	5	0.57 [0.11-2.96]	5.2 (0.8 to 9.7)	-3.5 (-15.6 to 8.6)	<3	0.22 [0.01-3.49]	0.9 (0.0 to 2.7)	-3.1 (-11.1 to 4.9)
Missing	26	1.39 [0.33-5.86]	11.7 (7.4 to 15.9)	2.9 (-9.0 to 14.9)	17	1.80 [0.24-13.49]	7.0 (3.7 to 10.2)	2.9 (-5.6 to 11.4)

Abbreviations: CI: Confidence interval, eGFR: Estimated glomerular filtrations rate, uACR: Urinary albumin-to-creatinine ratio.

Supplementary table 5. Unadjusted Absolute and Relative 2-year Risks of decline in eGFR and end-stage kidney disease, according to eGFR (ml/min/1.73m^2) and uACR.

Kidney function	40% decline in eGFR				End-stage kidney disease			
uACR	Events	Hazard ratios [95% CI]	Absolute risks, % (95% CI)	Absolute risk difference, % (95% CI)	Events	Hazard ratios [95% CI]	Absolute risks, % (95% CI)	Absolute risk difference, % (95% CI)
eGFR>90								
Normoalbuminuria	62	ref	0.8 (0.6 to 1.1)	ref	11	ref	0.2 (0.1 to 0.3)	ref
Microalbuminuria	40	1.80 [1.21-2.68]	1.5 (1.1 to 2.0)	0.7 (0.2 to 1.2)	7	1.78 [0.69-4.59]	0.3 (0.1 to 0.5)	0.1 (-0.1 to 0.4)
Macroalbuminuria	15	4.21 [2.39-7.39]	3.5 (1.7 to 5.2)	2.6 (0.9 to 4.3)	<3	3.09 [0.69-13.95]	0.5 (0.0 to 1.2)	0.3 (-0.4 to 1.0)
Missing	665	1.88 [1.45-2.43]	1.6 (1.5 to 1.7)	0.7 (0.5 to 1.0)	91	1.43 [0.76-2.67]	0.2 (0.2 to 0.3)	0.1 (0.0 to 0.2)
eGFR 60–89								
Normoalbuminuria	102	ref	1.3 (1.1 to 1.6)	ref	18	ref	0.3 (0.1 to 0.4)	ref
Microalbuminuria	60	2.01 [1.46-2.76]	2.6 (2.0 to 3.3)	1.3 (0.6 to 2.0)	12	2.24 [1.08-4.66]	0.6 (0.2 to 0.9)	0.3 (0.0 to 0.6)
Macroalbuminuria	27	5.65 [3.70-8.64]	7.1 (4.6 to 9.7)	5.8 (3.2 to 8.4)	11	12.54 [5.92-26.56]	3.1 (1.3 to 4.8)	2.8 (1.0 to 4.6)
Missing	1207	1.99 [1.62-2.43]	2.6 (2.4 to 2.7)	1.3 (1.0 to 1.5)	200	1.84 [1.13-2.97]	0.5 (0.4 to 0.5)	0.2 (0.1 to 0.3)
eGFR 30–59								
Normoalbuminuria	32	ref	3.8 (2.5 to 5.1)	ref	7	ref	0.9 (0.2 to 1.5)	ref
Microalbuminuria	41	2.04 [1.29-3.24]	7.5 (5.3 to 9.7)	3.7 (1.2 to 6.3)	19	4.31 [1.81-10.25]	3.7 (2.1 to 5.3)	2.8 (1.1 to 4.5)
Macroalbuminuria	35	4.41 [2.73-7.12]	15.4 (10.7 to 20.0)	11.6 (6.8 to 16.4)	16	9.07 [3.73-22.05]	7.4 (3.9 to 10.9)	6.6 (3.0 to 10.1)
Missing	433	2.06 [1.44-2.94]	7.4 (6.7 to 8.1)	3.6 (2.2 to 5.1)	153	3.28 [1.54-6.99]	2.7 (2.3 to 3.1)	1.8 (1.1 to 2.6)
eGFR 15–29								
Normoalbuminuria	7	ref	30.0 (12.1 to 47.9)	ref	6	ref	25.7 (8.4 to 43.0)	ref
Microalbuminuria	17	1.03 [0.42-2.47]	29.3 (17.7 to 40.8)	-0.7 (-21.8 to 20.3)	17	1.19 [0.47-3.03]	29.1 (17.6 to 40.6)	3.4 (-17.2 to 24.0)
Macroalbuminuria	42	1.49 [0.67-3.32]	40.0 (30.7 to 49.4)	10.0 (-9.9 to 29.9)	42	1.76 [0.75-4.13]	40.2 (30.8 to 49.6)	14.5 (-5.0 to 34.0)
Missing	76	1.17 [0.54-2.54]	31.9 (26.0 to 37.9)	1.9 (-16.7 to 20.6)	76	1.38 [0.60-3.17]	32.1 (26.1 to 38.1)	6.4 (-11.8 to 24.6)

Abbreviations: CI: Confidence interval, eGFR: Estimated glomerular filtrations rate, uACR: Urinary albumin-to-creatinine ratio.

Supplementary table 6. Standardized Absolute and Relative 2-year Risks of Major Cardiovascular Events, Heart Failure, and End-stage Kidney Disease when censoring at treatment discontinuation.

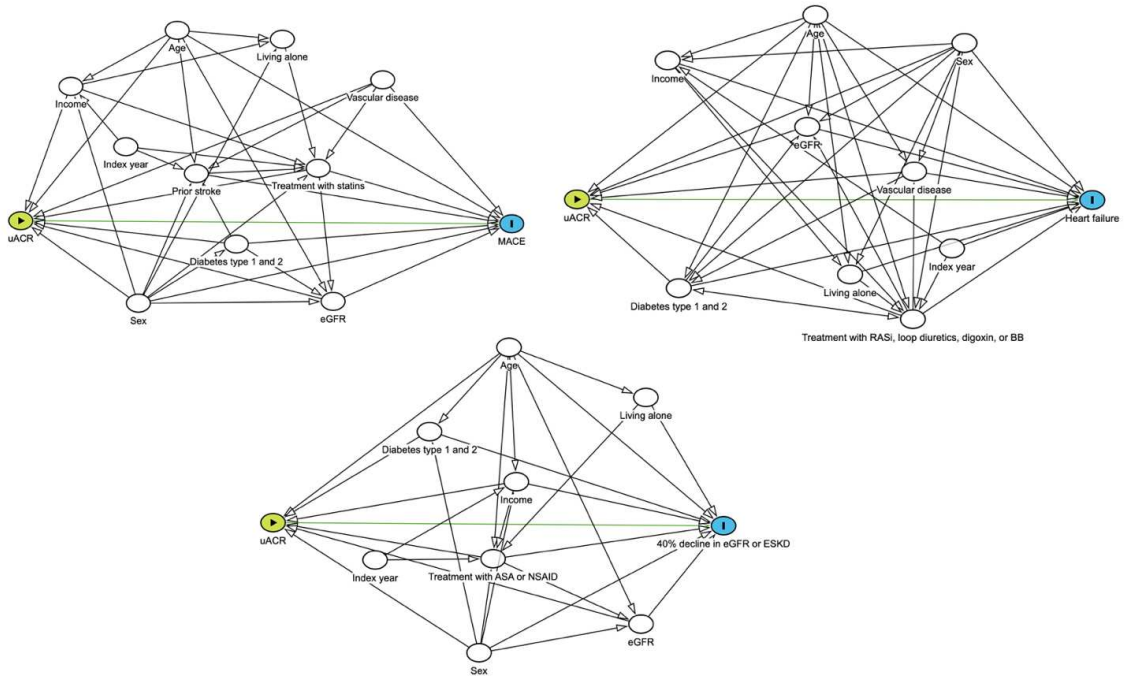
	Events (% of patients)	Hazard ratios (95% CI)	Absolute risk (95%CI)	Absolute risk-difference (95%CI)
MACE				
Normoalbuminuria	284 (1.4)	ref	2.7 (2.4 to 3.0)	ref
Microalbuminuria	128 (2.0)	1.19 [0.96-1.46]	3.2 (2.6 to 3.7)	0.4 (-0.2 to 1.1)
Macroalbuminuria	39 (2.7)	1.79 [1.28-2.52]	4.5 (3.2 to 5.9)	1.8 (0.4 to 3.2)
Missing uACR	2514 (2.3)	1.41 [1.24-1.60]	3.7 (3.5 to 3.8)	0.9 (0.6 to 1.3)
Heart Failure				
Normoalbuminuria	125 (0.8)	ref	0.9 (0.7 to 1.0)	ref
Microalbuminuria	65 (1.2)	1.40 [1.04-1.90]	1.2 (0.9 to 1.5)	0.3 (0.0 to 0.7)
Macroalbuminuria	26 (2.1)	2.52 [1.64-3.87]	2.1 (1.3 to 2.9)	1.2 (0.4 to 2.1)
Missing uACR	1750 (2.1)	2.47 [2.05-2.97]	2.1 (2.0 to 2.2)	1.2 (1.0 to 1.4)
40% decline in eGFR				
Normoalbuminuria	52 (0.3)	ref	0.5 (0.3 to 0.6)	ref
Microalbuminuria	56 (0.9)	2.23 [1.52-3.25]	1.0 (0.8 to 1.3)	0.6 (0.3 to 0.9)
Macroalbuminuria	54 (4.0)	5.75 [3.85-8.57]	2.5 (1.8 to 3.2)	2.0 (1.3 to 2.7)
Missing uACR	992 (0.9)	3.30 [2.49-4.38]	1.5 (1.4 to 1.6)	1.0 (0.8 to 1.2)
ESKD				
Normoalbuminuria	25 (0.1)	ref	0.3 (0.2 to 0.4)	ref
Microalbuminuria	34 (0.5)	2.13 [1.27-3.59]	0.5 (0.4 to 0.7)	0.3 (0.1 to 0.5)
Macroalbuminuria	43 (3.0)	3.50 [2.07-5.93]	0.8 (0.5 to 1.1)	0.5 (0.3 to 0.8)
Missing uACR	330 (0.3)	2.23 [1.47-3.36]	0.5 (0.5 to 0.6)	0.3 (0.2 to 0.4)

MACE was adjusted for age, sex, income, index year, living alone, prior stroke, diabetes type-1 and type-2, vascular disease, prior heart failure diagnosis, eGFR, and treatment with statins. HF was adjusted for age, sex, income, index year, living alone, diabetes type-1 and type-2, prior heart failure diagnosis, 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, prior heart failure diagnosis, and eGFR.

Abbreviations: CI: Confidence interval, eGFR: Estimated glomerular filtrations rate, uACR: Urinary albumin-to-creatinine ratio.

Supplementary figure 1. Direct acyclic graphs

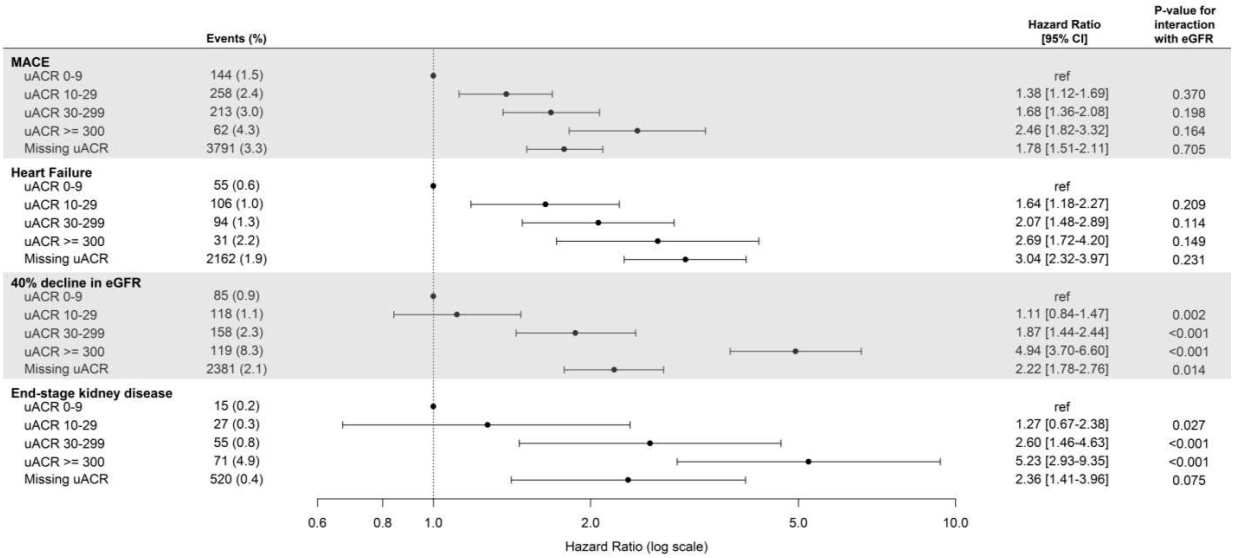
Direct acyclic graphs depicting the relationships between exposures, outcomes, and covariates incorporated in the statistical models.



Abbreviations: ASA: Acetylsalicylic acid. eGFR: Estimated glomerular filtrations rate. ESKD: End-stage kidney disease. MACE: Major cardiovascular events. NSAID: Non-steroid anti-inflammatory drugs. uACR: Urinary albumin-to-creatinine ratio.

Supplementary figure 2. Risk of cardiorenal events according to urinary albumin-to-creatinine ratio levels below microalbuminuria cut-off

Risk of major cardiovascular events, heart failure, progression of kidney disease, and end-stage kidney disease according to urinary albumin-to-creatinine ratio levels below microalbuminuria cut-off.



Abbreviations: eGFR: Estimated glomerular filtrations rate. ESKD: End-stage kidney disease. MACE: Major cardiovascular events. Ref: Reference. uACR: Urinary albumin-to-creatinine ratio.