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KIDNEY

Albuminuria Testing in Hypertension and Diabetes: An Individual-Participant Data Meta-Analysis in a Global Consortium

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ABSTRACT: Albuminuria is an under-recognized component of chronic kidney disease definition, staging, and prognosis. Guidelines, particularly for hypertension, conflict on recommendations for urine albumin-to-creatinine ratio (ACR) measurement. Separately among 1 344 594 adults with diabetes and 2 334 461 nondiabetic adults with hypertension from the chronic kidney disease Prognosis Consortium, we assessed ACR testing, estimated the prevalence and incidence of ACR ≥30 mg/g and developed risk models for ACR ≥30 mg/g. The ACR screening rate (cohort range) was 35.1% (12.3%–74.5%) in diabetes and 4.1% (1.3%–20.7%) in hypertension. Screening was largely unrelated to the predicted risk of prevalent albuminuria. The median prevalence of ACR ≥30 mg/g across cohorts was 32.1% in diabetes and 21.8% in hypertension. Higher systolic blood pressure was associated with a higher prevalence of albuminuria (odds ratio [95% CI] per 20 mm Hg in diabetes, 1.50 [1.42–1.60]; in hypertension, 1.36 [1.28–1.45]). The ratio of undetected (due to lack of screening) to detected ACR ≥30 mg/g was estimated at 1.8 in diabetes and 19.5 in hypertension. Among those with ACR <30 mg/g, the median 5-year incidence of ACR ≥30 mg/g across cohorts was 23.9% in diabetes and 21.7% in hypertension. Incident albuminuria was associated with initiation of renin-angiotensin-aldosterone system inhibitors (incidence-rate ratio [95% CI], diabetes 3.09 [2.71–3.53]; hypertension 2.87 [2.29–3.59]). In conclusion, despite similar risk of albuminuria to those with diabetes, ACR screening in patients with hypertension was low. Our findings suggest that regular albuminuria screening should be emphasized to enable early detection of chronic kidney disease and initiation of treatment with cardiovascular and renal benefits. **(*Hypertension*. 2021;78:1042–1052. DOI: 10.1161/HYPERTENSIONAHA.121.17323.)** • **Data Supplement**

Key Words: albuminuria ■ blood pressure ■ diabetes mellitus ■ hypertension ■ kidney ■ prevalence risk

Albuminuria, most commonly measured as urine albumin-to-creatinine ratio (ACR), is a key component of chronic kidney disease (CKD) definition, staging, and prognosis, including cardiovascular events and death.[1–5] The presence of pathological levels of albuminuria guides therapy: guidelines from the American Heart Association, Kidney Disease Improving Global Outcomes, and the American Diabetes Association all recommend blockade of the renin-angiotensin-aldosterone system (RAAS) with an ACE (angiotensin-converting enzyme) inhibitor or an ARB (angiotensin II-receptor blocker) for all patients with diabetes and ACR ≥30 mg/g and all patients with hypertension and ACR ≥300 mg/g.[6–8] Elevated levels of albuminuria are also an indication for SGLT2 (sodium-glucose cotransporter 2) inhibitors in patients with and without diabetes.[7,9] Therefore, early diagnosis of CKD

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Novelty and Significance

What Is New?

- Albumin-to-creatinine ratio screening rates are extremely low in both diabetes (35%) and hypertension (4%), and current testing is not targeted toward the highest-risk individuals. The predicted number of undetected albumin-to-creatinine ratio ≥30 mg/g (chronic kidney disease A2+) is nearly 2-fold and 20-fold of detected cases in diabetes and hypertension, respectively.

What Is Relevant?

- With an increasing number of effective therapies to prevent chronic kidney disease-related complications, including sodium-glucose cotransporter 2 inhibitors, there is substantial opportunity to improve early diagnosis of chronic kidney disease for better use of these agents in the population with diabetes or hypertension.

Summary

Despite similar risk of albuminuria to those with diabetes, albumin-to-creatinine ratio screening in patients with hypertension is low. Our findings suggest that regular albuminuria screening should be emphasized to enable early detection of chronic kidney disease and initiation of treatment with cardiovascular and renal benefits.

Nonstandard Abbreviations and Acronyms

ACR	albumin-to-creatinine ratio
ARB	angiotensin II-receptor blocker
CKD	chronic kidney disease
HbA1c	hemoglobin A1c
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure
SGLT2	sodium-glucose cotransporter 2

with ACR ≥30 mg/g (CKD stage A2+) is important to institute effective preventative therapies.

Despite significant advances in therapies for patients with albuminuria, guidelines conflict on the utility of albuminuria measurement. Major diabetes guidelines recommend annual ACR testing[7,10,11] with greater frequency in patients with estimated glomerular filtration rate (eGFR) 30 to 60 mL/min per 1.73 m^2.[7] Hypertension guidelines are inconsistent. The 2018 European Society of Cardiology/European Society of Hypertension guidelines recommend ACR screening for all patients with hypertension with annual ACR testing in patients with CKD.[12] The 2017 American College of Cardiology/American Heart Association guidelines and 2020 International Society of Hypertension guidelines recommend routine urine dipstick testing, noting that serial testing for ACR can add value as a part of optimal care.[6,13] In contrast, the 2013 American College of Physicians guideline recommends against routine testing or monitoring for albuminuria, including in adults with diabetes who are currently taking an ACE inhibitor or ARB.[14] Given the new treatments with cardiovascular and kidney benefits for patients with albuminuria, low rates of albuminuria screening may impede optimal treatment.

We used individual-participant data from multinational cohorts from the CKD Prognosis Consortium with the following goals separately in participants with diabetes and hypertension but no diabetes: (1) to estimate ACR testing rates, and to determine if high-risk patients for albuminuria are more likely to be tested; (2) to estimate the prevalence of ACR ≥30 mg/g; (3) to estimate the 5-year incidence of ACR ≥30 mg/g; and (4) to develop and utilize risk prediction models for ACR ≥30 mg/g to estimate the burden of undetected albuminuria.

METHODS

The data that support the findings of this study may be available from the corresponding author upon reasonable request. Under agreement with the participating cohorts, CKD Prognosis Consortium cannot share individual data with third parties but will be able to facilitate communications with individual cohorts.

Study Design and Data Sources

The CKD Prognosis Consortium is an open, collaborative research group that currently includes >80 participating cohorts worldwide, including both research cohorts, in which data were collected for clinical research, and clinical cohorts, in which data were collected in the course of routine clinical care.[15] To be included in this study, we required cohorts to include participants over the age of 18 years with repeated ACR measurement (Appendix S1). Because ACR availability is different between people with and without diabetes, cohorts were divided into 2 analytic sets: participants with diabetes (diabetes subcohorts) and participants without diabetes but with hypertension (hypertension subcohorts). A total of 31 cohorts had the requisite data, contributing as 31 diabetes subcohorts and 25 hypertension subcohorts. The diabetes and hypertension subcohorts were further split into development and validation. The Johns Hopkins Bloomberg School of Public Health Institutional Review Board approved this study.

Covariate Definitions

In research cohorts, diabetes was defined as fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, HbA1c (hemoglobin A1c) ≥6.5%, use of glucose-lowering medications, or self-reported diabetes. Hypertension was defined as blood pressure ≥140/90 mm Hg

or the use of antihypertensive medications. In clinical cohorts, the *International Classification of Diseases* codes were used to define diabetes and hypertension (Appendix S1 in the Data Supplement).

Outcomes

We evaluated ACR testing at baseline in clinical cohorts, and prevalent ACR ≥30 mg/g among participants tested for baseline ACR in both research and clinical cohorts. Baseline was defined as the first visit with ACR measurement in research cohorts and in a preselected 2-year time window in clinical cohorts. We then evaluated incident ACR ≥30 mg/g at 3 or 5-years after baseline, requiring that the ACR ≥30 mg/g measurements be confirmed, with at least 2 ACR ≥30 mg/g at any time before the end of the relevant time window. Analyses for incident ACR ≥30 mg/g were restricted to participants with baseline ACR <30 mg/g and adequate follow-up testing, which was defined as at least 2 measurements during the follow-up period, with at least one within the 2 to 4 year window for the 3-year analysis and at least one within the 4 to 6 year window for the 5-year analysis if all values were <30 mg/g.

Statistical Analyses

We performed all analyses separately within diabetes and hypertension subcohorts. Baseline characteristics were summarized using means and SDs or medians and interquartile intervals for continuous variables and proportions for categorical variables. The proportion with available ACR measurements at baseline was estimated overall and by eGFR <60 mL/min per 1.73 m^2, as was the prevalence of ACR ≥30 mg/g among those with available baseline ACR measurements (overall, by baseline eGFR <60 mL/min per 1.73 m^2, and by RAAS inhibitor use). For those with baseline ACR <30 mg/g, we estimated 3- and 5-year cumulative incidence of ACR ≥30 mg/g, overall, by RAAS inhibitor use at baseline, and by RAAS inhibitor use at follow-up testing. Difference between strata was tested by nonparametric equality-of-medians tests.

Prediction models for prevalent ACR ≥30 mg/g as well as incident ACR ≥30 mg/g by 3- and 5- years were developed using multivariable logistic regression in each of the development cohorts and then by combining estimates using random-effects meta-analysis. Covariates included age, sex, systolic blood pressure (SBP), RAAS inhibitor use, other antihypertensive medication use, history of coronary artery disease and heart failure, body mass index (linear splines with a knot at 30 kg/m^2), and eGFR (linear splines with three knots at 90, 60, 45 mL/min per 1.73 m^2). For the diabetes subcohorts, we also included HbA1c, insulin use, and oral glucose-lowering medication use. Model discrimination was assessed by C statistics and model calibration by plotting quintiles of observed versus predicted risk within each cohort.

To understand sex differences in the associations between SBP and albuminuria, we fit a model with an interaction term between sex and SBP. To examine Black-White racial differences, we used the same approach in the 13 cohorts that have information on race and a sufficient number of Black participants (ie, the percentage of Black participants ≥5% and the number of Black participants ≥100).

To understand the burden of undetected ACR ≥30 mg/g among participants not tested for ACR at baseline, we applied the prediction model to participants without ACR testing in each cohort. To understand whether ACR testing during the baseline period (≥1 tests) and follow-up (≥2 tests) differed by risk status, we plotted proportion tested within quintiles of predicted risk of prevalent ACR ≥30 mg/g and 3-year incident ACR ≥30 mg. Among people who were tested at baseline and had ACR ≥30 mg/g, we examined whether ACR retesting differed by ACR levels at baseline.

To evaluate the association of ACR testing results with clinical action, we estimated the frequency and meta-analyzed incidence-rate ratio of RAAS inhibitor prescription within 1 year after follow-up ACR testing among people who were not using RAAS inhibitors at the time, stratified by previous RAAS inhibitor use (never/ever during the study period including baseline). All analyses were performed using Stata version 14 (StataCorp). Statistical significance was determined using a 2-sided test with a threshold *P* value of <0.05.

RESULTS

ACR Testing Rate and Prevalence of ACR ≥30 mg/g

There were 31 diabetes subcohorts included in our analyses (Table 1 and Table S1). In the 24 general population clinical cohorts, 35.1% had ACR tested during the 2-year baseline window (cohort range, 12.3%–74.5%; Table 2). ACR testing rate was slightly higher among participants with eGFR <60 mL/min/1.73 m^2 (mean, 36.9%). Median prevalence of ACR ≥30 mg/g was 32.1% (cohort range, 8.4%–56.0%). Prevalence of ACR ≥30 mg/g was higher among participants with eGFR <60 mL/min per 1.73 m^2 than those with eGFR ≥60 mL/min/1.73 m^2 (median, 48.6% versus 28.1%, *P*<0.001) and not significantly different by RAAS inhibitor use (median, 35.2% versus 30.0%, *P*=0.066; Table S2). Testing rate and prevalence were similar between the 23 development and 8 validation cohorts.

There were 25 hypertension subcohorts included in our analyses (Table 3 and Table S3). In the 20 general population clinical cohorts, 4.1% had ACR tested during the baseline window (cohort range, 1.3%–20.7%; Table 2). ACR testing rate was slightly higher among patients with eGFR <60 mL/min per 1.73 m^2 (mean, 6.2%). Median prevalence of ACR ≥30 mg/g was 21.8% (cohort range, 5.6%–43.4%). Prevalence of ACR ≥30 mg/g was higher among participants with eGFR <60 mL/min per 1.73 m^2 than those with eGFR ≥60 mL/min per 1.73 m^2 (median, 35.3% versus 18.0%, *P*<0.001; Table S2). Testing rate and prevalence were similar between the 18 development and 7 validation cohorts.

Prediction Model for Prevalent ACR ≥30 mg/g

Consistent risk factors for prevalent ACR included male sex, history of heart failure and coronary heart disease, obesity, lower eGFR, and higher SBP (odds ratio [95% CI] per 20 mm Hg in diabetes, 1.50 [1.42–1.60]; in hypertension, 1.36 [1.28–1.45]; Table S4). There was no difference in the association between SBP and prevalent albuminuria by sex or race. The prediction model of prevalent ACR ≥30 mg/g had a median (cohort range) C statistic of 0.706 (0.635–0.746) in validation cohorts in diabetes and 0.643

(0.605–0.710) in hypertension (Table S5). Calibration varied by cohort (Figure S1A and S1B).

ACR Screening Rate by Predicted Risk of Prevalent ACR ≥30 mg/g

Among participants with diabetes, ACR screening rates during the 2-year baseline period varied greatly across the different health systems and were largely not related to the predicted risk of prevalent ACR ≥30 mg/g (Figure 1A). Among participants with hypertension, ACR screening rates were uniformly low and largely unrelated to the predicted risk of prevalent ACR ≥30 mg/g (Figure 1B). Health systems that had high rates of screening in diabetes did not necessarily have high rates of screening in hypertension (correlation coefficient, 0.32; P=0.20).

Ratio of Undetected to Detected ACR ≥30 mg/g at baseline

In the clinical cohorts, the median predicted prevalence of ACR ≥30 mg/g in participants without ACR measurements was 32.8% (cohort range, 25.1%–66.7%) in diabetes and 22.0% (cohort range, 17.9%–56.4%) in hypertension. The predicted prevalence in the untested group was similar to the observed prevalence in the tested group (33.1% [cohort range, 22.9%–56.0%] in diabetes; 22.3% [cohort range, 14.0%–43.4%] in hypertension, Table S2). The ratio (cohort range) of undetected to detected ACR ≥30 mg/g was 1.8 (0.2–7.6) in diabetes and 19.5 (0.8–78.3) in hypertension.

Incidence of ACR ≥30 mg/g at 3- and 5-Years

Among participants with diabetes and baseline ACR <30 mg/g (Tables S6 and S7), the median (cohort range) diabetes subcohort in the development studies had a 3-year incidence of ACR ≥30 mg/g of 12.8% (1.7%–33.3%) and a 5-year incidence of 23.9% (4.3%–44.8%). Incidence in the validation studies was similar (cohort range, 8.6%–26.5% at 3 years and 18.6%–29.3% at 5 years, respectively). Incidence was similar by RAAS inhibitor use at baseline and at follow-up testing (Table S8).

Among the nondiabetic participants with hypertension and baseline ACR <30 mg/g (Tables S9 and S10), the median (cohort range) hypertension subcohort in the development studies had a 3-year incidence of 14.8% (4.4%–21.3%) and a 5-year incidence of 21.7% (3.5%–31.7%). Incidence in the validation studies was similar (cohort range, 8.4%–22.8% at 3 years and 14.8%–35.4% at 5 years, respectively). Incidence was qualitatively similar by RAAS inhibitor use at baseline or at follow-up testing (Table S8).

Prediction Models for Incident ACR ≥30 mg/g

Consistent risk factors for the development of albuminuria over 3- and 5-years included older age, male sex, history of heart failure, and lower eGFR. Higher SBP was a risk factor in diabetes but not in hypertension (Table S11). There was no difference in the association between SBP and albuminuria by sex or race. The prediction model of 3- and 5-year incident ACR ≥30 mg/g had a median (cohort range) C statistic of 0.630 (0.618–0.676) and 0.634 (0.606–0.676) in validation cohorts in diabetes and 0.653 (0.571–0.728) and 0.655 (0.475–0.737) in hypertension (Table S12). Calibration varied by cohort, with observed versus predicted incidence at 3 and 5 years shown in Figures S2 and S3, respectively.

ACR Retesting Rate by Predicted Risk of Incident ACR ≥30 mg/g

Among participants with diabetes who were tested at baseline and had ACR <30 mg/g, ACR retesting rates were higher than baseline screening rates but remained variable across health systems and unrelated to the 3-year predicted risk of incident ACR ≥30 mg/g (Figure 1C). Similarly, ACR retesting rates were much higher than baseline screening rates in participants with hypertension, highly variable across health systems, and largely unrelated to the 3-year predicted risk of incident ACR ≥30 mg/g (Figure 1D). Health systems that had high rates of retesting in diabetes tended to have high rates of retesting in hypertension (correlation coefficient, 0.84; P<0.001). Among participants who were tested at baseline and had ACR ≥30 mg/g, ACR retesting rates were similar to those with baseline ACR <30 mg/g and largely unrelated to the ACR levels at baseline in both diabetes (Figure 1E) and hypertension (Figure 1F).

RAAS Inhibitor Initiation After ACR ≥30 mg/g

In RAAS inhibitor naive participants, initiation of RAAS inhibitors in the year after ACR testing was substantially higher in people with ACR ≥30 mg/g compared with those with ACR <30 mg/g (meta-analyzed incidence-rate ratio; diabetes, 3.09 [95% CI, 2.71–3.53]; hypertension, 2.87 [95% CI, 2.29–3.59]; Figure 2). Among participants with a history of RAAS inhibitor use during the study period but who were not taking a RAAS inhibitor at the time of ACR testing, a small difference in RAAS inhibitor prescription was observed in diabetes but not in hypertension (meta-analyzed incidence-rate ratio; diabetes, 1.10 [95% CI, 1.05–1.15]; hypertension 1.00 [95% CI, 0.94–1.07]; Figure S4).

DISCUSSION

In this study, spanning multiple international cohorts and including >3 million participants with diabetes or hypertension, we demonstrate extremely low ACR testing rates in diabetes (35.1%) and hypertension (4.1%) overall. Among tested participants, ACR ≥30

Table 1. Baseline Characteristics of the Participants With Diabetes Who Were Tested for ACR at Baseline

Cohort (country)	N	Age, mean (SD), y	Women, No. (%)	SBP, mean (SD), mm Hg	Any HTN med use, No. (%)	RAAS inhibitor use, No. (%)	Other HTN med use, No. (%)
Development: research cohorts							
ADVANCE (multiple)	10542	66 (6)	4472 (42)	145 (21)	7884 (75)	4963 (47)	2921 (28)
Pima (United States)	454	36 (14)	217 (48)	126 (19)	98 (22)	69 (23)	29 (6)
PREVEND (Netherlands)	434	63 (10)	183 (42)	138 (20)	216 (52)	112 (26)	104 (25)
Rancho Bernardo (United States)	124	74 (12)	59 (48)	145 (22)	74 (60)	NA	74 (60)
ZODIAC (Netherlands)	1634	67 (12)	914 (56)	152 (24)	435 (27)	435 (27)	NA
Development: clinical cohorts							
Geisinger (United States)	26261	63 (14)	12605 (48)	128 (16)	20793 (79)	15897 (61)	15688 (60)
Maccabi (Israel)	44677	63 (13)	18575 (42)	134 (18)	30130 (67)	25156 (56)	21512 (48)
Mt Sinai BioMe (United States)	1490	59 (13)	994 (67)	132 (20)	1063 (71)	897 (60)	817 (55)
OLDW cohort 1 (United States)	16753	62 (13)	8234 (49)	126 (16)	9061(54)	5517 (33)	7358 (44)
OLDW cohort 2 (United States)	16014	62 (13)	8036 (50)	129 (16)	9924 (62)	7019 (44)	8022 (50)
OLDW cohort 3 (United States)	1055	58 (14)	563 (53)	134 (18)	326 (31)	232 (22)	227 (22)
OLDW cohort 4 (United States)	9718	63 (13)	4864 (50)	136 (21)	4305 (44)	2549 (26)	3380 (35)
OLDW cohort 5 (United States)	4120	61 (13)	1865 (45)	127 (16)	2384 (58)	1389 (34)	1991 (48)
OLDW cohort 6 (United States)	23168	63 (13)	11623 (50)	130 (17)	5793 (25)	3621 (16)	4687 (20)
OLDW cohort 7 (United States)	8988	61 (15)	4171 (46)	129 (17)	3957 (44)	2712 (30)	2976 (33)
OLDW cohort 8 (United States)	8080	59 (14)	4046 (50)	133 (19)	2702 (33)	1462 (18)	2191 (27)
OLDW cohort 9 (United States)	26318	60 (13)	12762 (48)	130 (17)	14716 (56)	10050 (38)	11437 (43)
OLDW cohort 10 (United States)	13591	61 (13)	6809 (50)	129 (17)	7618 (56)	5377 (40)	5866 (43)
OLDW cohort 11 (United States)	5389	63 (13)	2735 (51)	128 (17)	2477 (46)	1442 (27)	1950 (36)
OLDW cohort 12 (United States)	1142	53 (15)	634 (56)	132 (18)	276 (24)	154 (13)	216 (19)
OLDW cohort 13 (United States)	7084	62 (13)	3077 (43)	127 (16)	2649 (37)	1742 (25)	1971 (28)
SCREAM (Sweden)	9216	63 (15)	3604 (39)	NA	6221 (68)	4704 (51)	5008 (54)
West of Scotland (Scotland)	2451	68 (11)	1155 (47)	146 (25)	1082 (44)	707 (29)	820 (33)
Total	238703	62 (13)	112197 (47)	131 (18)	134184 (56)	96206 (40)	99245 (42)
Validation: research cohorts							
UK Biobank (UK)	23319	60 (7)	9001 (39)	143 (19)	12093 (52)	11309 (48)	784 (3)
Validation: clinical cohorts							
CURE-CKD (United States)	6881	62 (15)	3338 (49)	129 (17)	NA	NA	NA
OLDW cohort 14 (United States)	5949	65 (12)	3015 (51)	131 (17)	3742 (63)	2579 (43)	2845 (48)
OLDW cohort 15 (United States)	5363	58 (15)	2628 (49)	130 (16)	2092 (39)	1630 (30)	1419 (26)
OLDW cohort 16 (United States)	2856	60 (13)	1294 (45)	128 (15)	924 (32)	580 (20)	644 (23)
OLDW cohort 17 (United States)	40840	62 (13)	20474 (50)	130 (16)	22668 (56)	14918 (37)	17651 (43)
OLDW cohort 18 (United States)	7625	64 (14)	4006 (53)	129 (16)	4316 (57)	2606 (34)	3316 (43)
RCAV (United States)	136813	66 (11)	3806 (3)	132 (17)	96855 (71)	71301 (52)	74628 (55)
Total	206327	64 (12)	47562 (21)	133 (18)	142877 (69)	104947 (46)	101466 (44)

(*Continued*)

mg/g (which defines CKD stage A2+) was common, with a median prevalence of 32.1% in diabetes and 21.9% in hypertension. ACR testing was unrelated to the predicted risk of ACR ≥30 mg/g, suggesting that current albuminuria testing is not targeted toward the highest-risk individuals. Particularly in patients with hypertension, the burden of ACR ≥30 mg/g is likely far greater than currently recognized—by our estimates, undetected cases are nearly 20-fold higher than detected cases. The vast underdiagnosis of CKD in patients with hypertension has profound public health implications since an increasing number of effective therapies to prevent CKD-related complications are available.

Table 1. Continued

HbA1c, mean (SD), %	Insulin use, No. (%)	Oral DM med use, No. (%)	No. (%) of participants		BMI, mean (SD), Kg/m²	eGFR, mean (SD), mL/min per 1.73 m²	ACR ≥30 mg/g, No. (%)
			History of CHD	History of HF			
7.5 (1.5)	153 (1)	9445 (90)	1640 (16)	328 (3)	28 (5)	78 (17)	3235 (31)
9.0 (2.5)	57 (13)	109 (24)	NA	NA	35 (8)	121 (20)	211 (46)
NA	26 (6)	191 (46)	68 (16)	14 (3)	30 (5)	87 (17)	135 (31)
5.5 (1.4)	14 (11)	41 (33)	21 (17)	8 (6)	27 (5)	62 (18)	33 (27)
7.3 (1.3)	33 (2)	1303 (80)	176 (12)	NA	29 (5)	68 (17)	137 (8)
7.4 (1.6)	6404 (24)	17446 (66)	7026 (27)	2382 (9)	34 (8)	79 (25)	9364 (36)
7.6 (1.7)	5840 (13)	27389 (61)	9416 (21)	1773 (4)	31 (6)	83 (23)	25004 (56)
7.8 (2.0)	504 (34)	870 (58)	117 (8)	296 (20)	33 (8)	76 (26)	597 (40)
7.4 (1.6)	2689 (16)	7567 (45)	4625 (28)	1869 (11)	35 (8)	79 (23)	4531 (27)
7.4 (1.6)	3203 (20)	8620 (54)	3192 (20)	862 (5)	34 (8)	79 (24)	5132 (32)
7.7 (1.7)	211 (20)	337 (32)	159 (15)	46 (4)	33 (6)	83 (26)	268 (25)
7.5 (1.6)	958 (10)	3600 (37)	1941 (20)	501 (5)	35 (8)	77 (24)	2972 (31)
7.5 (1.7)	717 (17)	2312 (56)	790 (19)	259 (6)	34 (8)	79 (25)	1275 (31)
7.2 (1.5)	1794 (8)	4767 (21)	5911 (26)	2234 (10)	34 (8)	77 (23)	6694 (29)
7.3 (1.6)	1950 (22)	3429 (38)	1665 (19)	441 (5)	33 (8)	79 (25)	3134 (35)
7.6 (1.8)	1597 (20)	2583 (32)	1468 (18)	480 (6)	35 (9)	80 (26)	3011 (37)
7.5 (1.7)	6340 (24)	14268 (54)	5088 (19)	1621 (6)	33 (8)	82 (25)	8526 (32)
7.3 (1.7)	2938 (22)	7051 (52)	2794 (21)	1089 (8)	34 (8)	78 (23)	4496 (33)
7.2 (1.5)	685 (13)	2217 (41)	1475 (27)	745 (14)	34 (8)	72 (22)	2469 (46)
8.1 (1.9)	339 (30)	368 (32)	168 (15)	66 (6)	33 (8)	81 (24)	283 (25)
7.2 (1.6)	728 (10)	2603 (37)	1208 (17)	313 (4)	32 (7)	81 (22)	1906 (27)
6.8 (1.5)	4253 (46)	4276 (46)	1565 (17)	1306 (14)	NA	78 (26)	3858 (42)
8.1 (3.8)	305 (12)	579 (24)	453 (18)	153 (6)	32 (7)	43 (23)	933 (38)
7.4 (1.7)	41738 (17)	121371 (51)	50966 (21)	16786 (7)	33 (7)	79 (24)	88205 (37)
7.0 (1.3)	700 (3)	13096 (56)	2791 (12)	71 (0)	31 (6)	89 (17)	3535 (15)
7.5 (1.7)	NA	NA	788 (11)	294 (4)	32 (8)	77 (25)	2300 (33)
7.2 (1.4)	1037 (17)	3175 (53)	1371 (23)	297 (5)	33 (7)	74 (22)	1362 (23)
7.6 (1.5)	1224 (23)	2248 (42)	863 (16)	235 (4)	34 (8)	82 (25)	1864 (35)
7.5 (1.5)	398 (14)	891 (31)	483 (17)	135 (5)	34 (8)	82 (24)	1030 (36)
7.4 (1.6)	7345 (18)	22004 (54)	9820 (24)	3536 (9)	33 (8)	78 (23)	14606 (36)
7.1 (1.4)	1089 (14)	3258 (43)	1920 (25)	759 (10)	33 (7)	76 (23)	2340 (31)
7.3 (1.6)	23194 (17)	77157 (56)	48024 (35)	14545 (11)	32 (6)	77 (17)	41451 (30)
7.3 (1.6)	35264 (15)	122109 (53)	66060 (29)	19872 (9)	32 (7)	79 (19)	68487 (30)

Multiple countries included in ADVANCE (The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial): Australia, Canada, China, Czech Republic, Estonia, France, Germany, Hungary, India, Ireland, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Philippines, Poland, Russia, Slovakia, United Kingdom. ACR indicates urine albumin-to-creatinine ratio; BMI, body mass index; CHD, coronary heart disease; CURE-CKD, Center for Kidney Disease Research, Education, and Hope Study; DM, diabetes; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure; HTN, hypertension; med, medication; NA, not available; OLDW, OptumLabs Data Warehouse; PREVEND, Prevention of Renal and Vascular End-stage Disease Study; RAAS, renin-angiotensin-aldosterone system; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SBP, systolic blood pressure ; SCREAM, Stockholm CREAtinine Measurements Cohort; and ZODIAC, Zwolle Outpatient Diabetes project Integrating Available Care.

Both diabetes and hypertension are well established risk factors for albuminuria. Our study confirms these relationships and suggests a fairly similar prevalence of CKD Stage A2+ in patients with hypertension compared with those with diabetes. In contrast, guidelines for ACR screening differ between hypertension and diabetes, which may explain in part the extremely low rates of ACR screening in hypertension. Guidelines suggest uncertainty about the clinical implications of ACR ≥30 mg/g in this setting: whereas the quantification of ACR directly guides therapy in patients with diabetes, with a recommendation of RAAS inhibitor for those with ACR

Table 2. ACR Testing Rate at Baseline*

	Research cohorts	General population clinical cohorts		Referred CKD clinical cohort
Diabetes	All	All	eGFR <60 mL/min per 1.73 m^2	All
Number of cohorts	6	24	24	1
Number of participants	38 753	1 303 027	241 247	2814
Proportion (%), mean (cohort range)	94.2 (41.2–100)	35.1 (12.3–74.5)	36.9 (10.9–69.1)	88.3
Hypertension (without diabetes)				
Number of cohorts	4	20	20	1
Number of participants	222 874	2 109 486	320 329	2101
Proportion (%), mean (cohort range)	97.0 (29.5–99.5)	4.1 (1.3–20.7)	6.2 (1.8–31.7)	71.7

ACR indicates albumin-to-creatinine ratio; CKD, chronic kidney disease; and eGFR, estimated glomerular filtration rate.
*Baseline was defined as the first visit with ACR measurement in research cohorts and in a preselected 2-year time window in clinical cohorts.

≥30 mg/g.[7] The only hypertension guideline that recommends universal ACR testing (the European Society of Cardiology/European Society of Hypertension) states that "the presence of a specific manifestation of hypertension-mediated organ damage such as CKD is now considered less important for the selection of drug treatment" since RAAS inhibitors are recommended as initial therapy for most patients with hypertension.[12] However, we demonstrate the RAAS inhibitor use is relatively low, with only ≈40% of patients with diabetes or hypertension taking this class of medications at baseline. Furthermore, there are new classes of medications that may be indicated in patients with hypertension and albuminuria, such as SGLT2 inhibitors, suggesting a reexamination of screening recommendations.[16]

Our findings represent one of the first large-scale efforts to simultaneously characterize incidence of ACR ≥30 mg/g in diabetes and hypertension. The range of 5-year incidence in diabetes subcohorts was 4.3% to 44.8%, similar to a Swedish national diabetes register study and a single diabetes center study from Japan which had 19.9% and 8.3% of 5-year incidence of elevated albuminuria, respectively.[17,18] Small diabetes studies reported 31% to 51% of 9-year incidence.[19–21] Fewer studies are available to compare the 5-year incidence in our hypertension subcohorts (cohort range, 3.5%–35.4%). One US community-based cohort study of young adults reported an incidence of 8.1% over 15 years of follow-up.[22] However, most participants did not have hypertension and only 3% were on antihypertensive medications (mean SBP, 110 mm Hg; mean age, 36 years), whereas all participants in the hypertension subcohorts in our study had hypertension, and >50% were on antihypertensive medications (mean SBP, 134 mm Hg; mean age, 62 years).[22]

Although discrimination of the developed risk prediction models was only modest, we used this tool to better understand the real-world practice of ACR testing. ACR testing rates were not only low but also unrelated to risk, suggesting that albuminuria testing was not administered in a targeted fashion. Moreover, the predicted number of undetected ACR ≥30 mg/g was far greater than the number of detected cases, particularly among nondiabetic patients with hypertension (nearly 20-fold and 2-fold of detected cases in hypertension and diabetes, respectively). These results demonstrate substantial opportunity to improve early identification and monitoring of kidney disease, reinforcing the need for universal albuminuria screening in these high-risk patient populations. In keeping with clinical guidelines, we observed a higher RAAS inhibitor initiation in the presence versus absence of ACR ≥30 mg/g in both diabetes and hypertension. Thus, widespread use of ACR testing in clinical care for diabetes or hypertension can facilitate RAAS inhibitor prescription to patients who may benefit most. Early identification of increased albuminuria is also critical for better use of SGLT2 inhibitors for patients with and without diabetes.[9,23,24]

Strengths of this study include the large sample sizes of the study populations; the inclusion of both diabetes and hypertension subcohorts; the clinical and geographic diversity of the participants; and rigorous characterization of ACR testing by predicted risk of albuminuria. However, some limitations should also be acknowledged. There are potential sources of misclassification: from determining diabetes and hypertension status by International Classification of Diseases codes only in clinical cohorts; and from defining baseline albuminuria status by a single ACR level. By design, we were only able to measure prevalence and incidence of ACR ≥30 mg/g among participants who had adequate ACR measurements. We could not examine smoking, socioeconomic status, or duration of diabetes or hypertension as risk factors. The prediction models had only modest performance, likely due to stratification on diabetes, one of the strongest risk factors, and they may have performed better with the addition of more variables (eg, biomarkers for early kidney damage).[25] We were

Table 3. Baseline Characteristics of the Participants With Hypertension (Without Diabetes) Who Were Tested for ACR at Baseline

Cohort (country)	N	Age, mean (SD), y	Women, No. (%)	SBP, mean (SD), mm Hg	Any HTN med use, No. (%)	RAAS inhibitor use, No. (%)	Other HTN med use, No. (%)	No. (%) of participants		BMI, mean (SD), Kg/m^2	eGFR, mean (SD), mL/min per 1.73 m^2	ACR ≥30 mg/g, No. (%)
								History of CHD	History of HF			
Development: research cohorts												
Pima (United States)	205	33 (15)	43 (21)	141 (15)	55 (27)	24 (18)	31 (15)	NA	0 (0)	36 (7)	119 (17)	31 (15)
PREVEND (Netherlands)	1917	61 (11)	844 (44)	143 (19)	1095 (62)	434 (23)	661 (37)	238 (12)	43 (2)	28 (4)	86 (17)	352 (18)
Rancho Bernardo (United States)	799	74 (10)	485 (61)	146 (20)	518 (65)	NA	518 (65)	78 (10)	28 (4)	25 (4)	63 (15)	120 (15)
Development: clinical cohorts												
Geisinger (United States)	5299	68 (15)	2938 (55)	130 (17)	4510 (85)	2884 (54)	3532 (67)	1287 (24)	397 (7)	31 (7)	66 (23)	1101 (21)
Maccabi (Israel)	18539	64 (13)	8410 (45)	137 (18)	14134 (76)	10494 (57)	10114 (55)	2713 (15)	409 (2)	30 (6)	80 (22)	7606 (41)
Mt Sinai BioMe (United States)	528	60 (13)	317 (60)	137 (22)	322 (61)	206 (39)	278 (53)	24 (5)	63 (12)	32 (9)	71 (27)	172 (33)
OLDW cohort 1 (United States)	858	66 (13)	503 (59)	131 (18)	558 (65)	252 (29)	501 (58)	184 (21)	78 (9)	32 (7)	70 (22)	185 (22)
OLDW cohort 2 (United States)	2684	62 (13)	1576 (59)	131 (18)	1914 (71)	1181 (44)	1680 (63)	491 (18)	142 (5)	32 (7)	75 (24)	579 (22)
OLDW cohort 4 (United States)	1490	63 (14)	751 (50)	150 (38)	757 (51)	313 (21)	660 (44)	285 (19)	97 (7)	31 (8)	63 (26)	563 (38)
OLDW cohort 6 (United States)	2200	61 (13)	1231 (56)	133 (18)	712 (32)	347 (16)	616 (28)	360 (16)	112 (5)	32 (7)	76 (23)	392 (18)
OLDW cohort 7 (United States)	1224	61 (14)	587 (48)	133 (18)	558 (46)	344 (28)	436 (36)	155 (13)	35 (3)	32 (7)	78 (22)	277 (23)
OLDW cohort 8 (United States)	2749	56 (13)	1500 (55)	141 (21)	1521 (55)	548 (20)	1408 (51)	382 (14)	96 (3)	34 (9)	82 (23)	613 (22)
OLDW cohort 9 (United States)	5910	60 (13)	2544 (43)	133 (18)	3985 (67)	2209 (37)	3405 (58)	952 (16)	226 (4)	31 (7)	77 (23)	1301 (22)
OLDW cohort 10 (United States)	2143	62 (13)	1114 (52)	134 (19)	1489 (70)	962 (45)	1221 (57)	346 (16)	107 (5)	32 (8)	77 (22)	416 (19)
OLDW cohort 11 (United States)	556	66 (13)	342 (62)	131 (19)	330 (59)	163 (29)	281 (51)	126 (23)	60 (11)	31 (7)	64 (23)	240 (43)
OLDW cohort 13 (United States)	2239	63 (13)	1136 (51)	130 (17)	1198 (54)	649 (29)	986 (44)	300 (13)	69 (3)	29 (6)	78 (20)	351 (16)
SCREAM (Sweden)	3803	65 (15)	1691 (44)	NA	3339 (88)	2208 (58)	2871 (75)	529 (14)	454 (12)	NA	68 (27)	1650 (43)
West of Scotland (Scotland)	1499	71 (13)	814 (54)	145 (25)	705 (47)	433 (29)	546 (36)	226 (15)	72 (5)	29 (8)	38 (18)	426 (28)
Total	54642	63 (14)	26826 (49)	135 (19)	37700 (69)	23651 (44)	29745 (55)	8676 (16)	2488 (5)	31 (7)	75 (24)	16375 (30)
Validation: research cohorts												
UK Biobank (UK)	213269	59 (7)	105697 (50)	153 (15)	57138 (27)	36818 (17)	20320 (10)	6243 (3)	128 (0)	28 (5)	89 (13)	12003 (6)
Validation: clinical cohorts												
CURE-CKD (United States)	2204	63 (15)	1107 (50)	132 (19)	NA	NA	NA	215 (10)	61 (3)	29 (6)	70 (26)	595 (27)
OLDW cohort 14 (United States)	957	67 (12)	460 (48)	133 (18)	674 (70)	415 (43)	566 (59)	202 (21)	48 (5)	31 (7)	68 (21)	134 (14)
OLDW cohort 15 (United States)	740	58 (14)	370 (50)	136 (19)	457 (62)	284 (38)	383 (52)	87 (12)	23 (3)	32 (7)	83 (24)	193 (26)
OLDW cohort 17 (United States)	6497	64 (13)	3482 (54)	134 (18)	4483 (69)	2459 (38)	3802 (59)	1222 (19)	316 (5)	31 (7)	74 (21)	1417 (22)
OLDW cohort 18 (United States)	1433	64 (14)	770 (54)	132 (16)	975 (68)	499 (35)	795 (55)	289 (20)	97 (7)	31 (7)	73 (22)	322 (22)
RCAV (United States)	21445	66 (12)	657 (3)	134 (17)	14785 (69)	7719 (36)	12190 (57)	6431 (30)	1606 (7)	30 (6)	77 (16)	4078 (19)
Total	246545	60 (9)	112543 (46)	151 (17)	78583 (32)	48202 (20)	38127 (15)	14689 (6)	2279 (1)	28 (5)	87 (15)	18742 (7)

ACR indicates albumin-to-creatinine ratio; BMI, body mass index; CHD, coronary heart disease; CURE-CKD, Center for Kidney Disease Research, Education, and Hope study eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; IQI, interquartile interval; med, medication; NA, not available; OLDW, OptumLabs Data Warehouse; PREVEND, Prevention of Renal and Vascular End-stage Disease Study; RAAS, renin-angiotensin-aldosterone system; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; SBP, systolic blood pressure; and SCREAM, Stockholm CREAtinine Measurements Cohort.

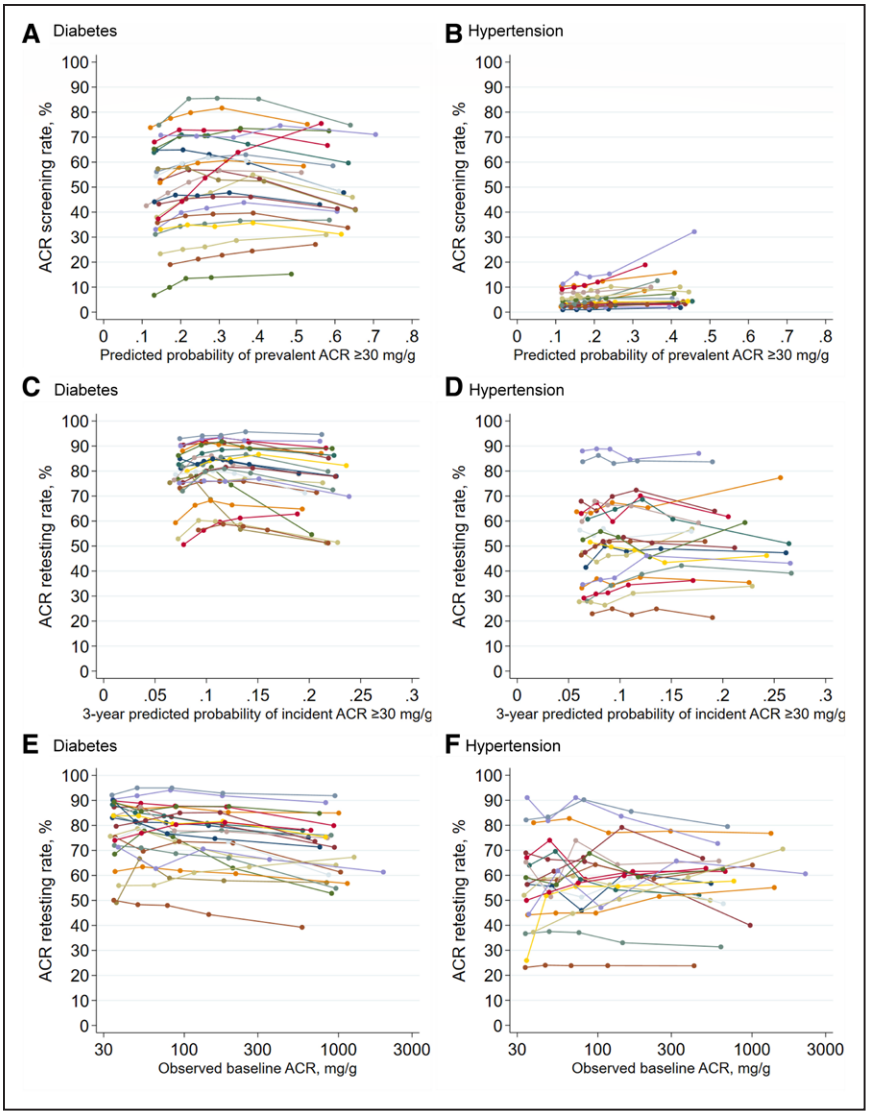

Figure 1. Urine albumin-to-creatinine ratio (ACR) screening rate at baseline and retesting rate among those who were tested at baseline in general population clinical cohorts. ACR screening rate (≥1 during 2-year baseline period) in (**A**) diabetes (N=1 303 027 in 24 cohorts) and (**B**) hypertension (N=2 109 486 in 20 cohorts) by the quintiles of cohort-specific predicted probability of prevalent ACR ≥30 mg/g. ACR retesting rate (≥2 during 4-years of follow-up) in (**C**) diabetes (N=280 918) and (**D**) hypertension (N=61 313) by the quintiles of cohort-specific 3-year predicted probability of incident ACR ≥30 mg/g among people who were tested at baseline and had ACR <30 mg/g. ACR retesting rate in (**E**) diabetes (N=148 473) and (**F**) hypertension (N=22 185) among people who were tested at baseline and had ACR ≥30 mg/g by the quintiles of cohort-specific observed ACR levels at baseline.

only able to examine Black-White racial differences in the associations between SBP and albuminuria in a subset of cohorts. Lastly, recent study showed that ACR testing rates varied across not only health care organizations but also practice sites in diabetes,[26] but we could not examine variation in ACR testing rates across provider types.

PERSPECTIVES

With the expanding armamentarium of effective therapies to prevent complications of elevated albuminuria, including SGLT2 inhibitors, early identification and monitoring of kidney disease is more important than ever. However, we demonstrate that real-world ACR testing is low, particularly among nondiabetic patients with hypertension, and testing was unrelated to predicted risk. Among those tested, albuminuria was common in both diabetes and hypertension. Thus, there are large swaths of the population with diabetes or hypertension with undiagnosed CKD. Our findings suggest that regular albuminuria screening should be emphasized for early detection of CKD and appropriate initiation of treatment with cardiovascular and kidney benefits.

ARTICLE INFORMATION

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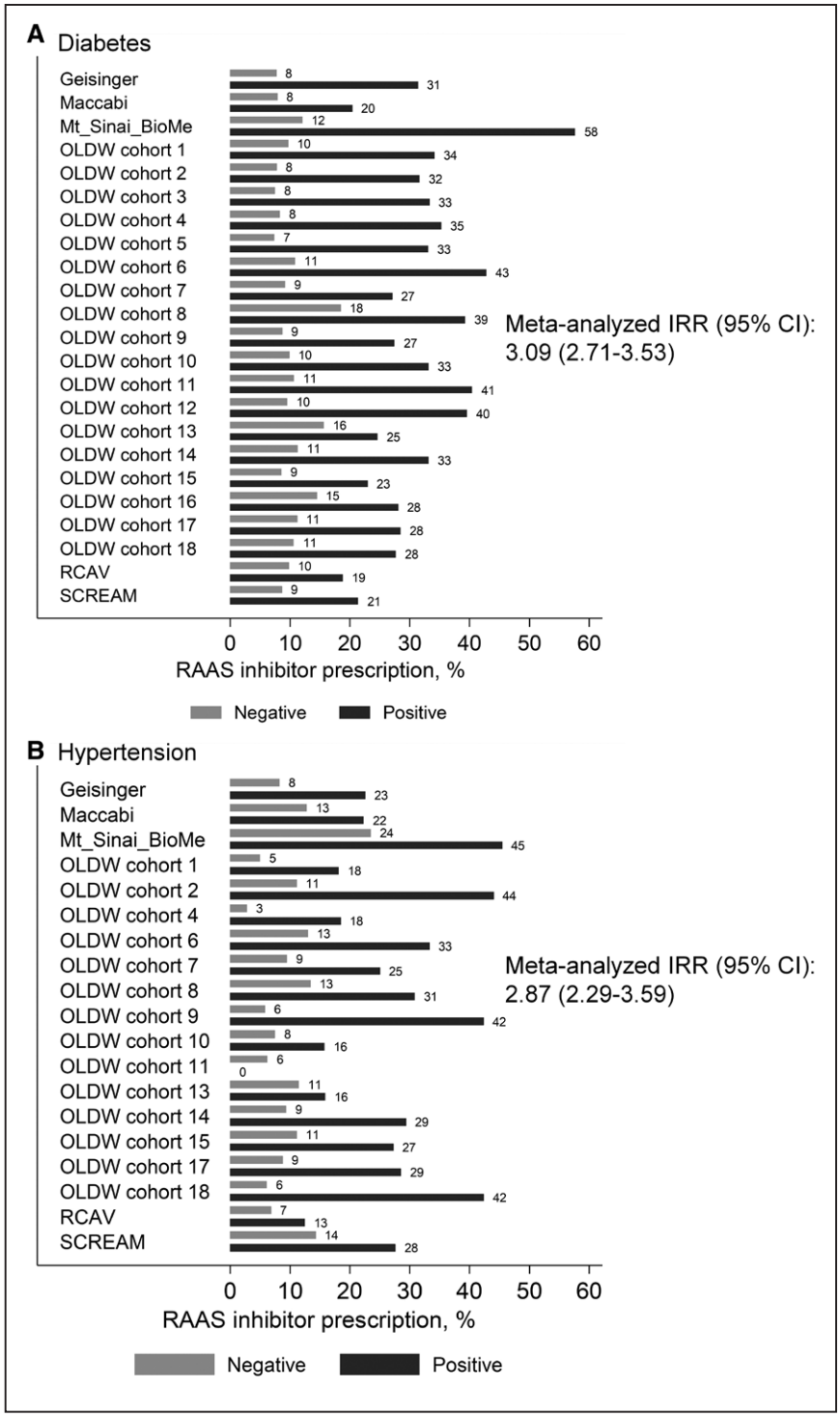

Figure 2. Comparison in initiation of renin-angiotensin-aldosterone system (RAAS) inhibitors in the year after urine albumin-to-creatinine ratio (ACR) testing by testing results (ACR <30 mg/g vs ACR ≥30 mg/g) among RAAS inhibitor naive participants.
A, Diabetes and (**B**) hypertension. IRR indicates incidence-rate ratio; OLDW, OptumLabs Data Warehouse; RCAV, Racial and Cardiovascular Risk Anomalies in CKD Cohort; and SCREAM, Stockholm CREAtinine Measurements Cohort.

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Disclosures

All authors will complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

APPENDIX

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REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. Kdigo 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Intern Suppl.* 2013;3:1–150.
2. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001;286:421–426. doi: 10.1001/jama.286.4.421
3. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation.* 2004;110:32–35. doi: 10.1161/01.CIR.0000133312.96477.48
4. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375:2073–2081. doi: 10.1016/S0140-6736(10)60674-5
5. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J; Chronic Kidney Disease Prognosis Consortium. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int.* 2011;80:93–104. doi: 10.1038/ki.2010.531
6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension.* 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065
7. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes-2021. *Diabetes Care.* 2021;44:S151–S167. doi: 10.2337/dc21-S011
8. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int.* 2021;99(3S):S1–S87. doi: 10.1016/j.kint.2020.11.003
9. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383:1436–1446. doi: 10.1056/NEJMoa2024816
10. International Diabetes Federation. Recommendations for managing type 2 diabetes in primary care. 2017. www.idf.org/managing-type2-diabetes
11. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, et al; ESC Scientific Document Group. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J.* 2020;41:255–323. doi: 10.1093/eurheartj/ehz486
12. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339
13. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, et al. 2020 International Society of Hypertension Global Hypertension practice guidelines. *Hypertension.* 2020;75:1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026
14. Qaseem A, Hopkins RH Jr, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2013;159:835–847. doi: 10.7326/0003-4819-159-12-201312170-00726
15. Matsushita K, Ballew SH, Astor BC, Jong PE, Gansevoort RT, Hemmelgarn BR, Levey AS, Levin A, Wen CP, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Cohort profile: the chronic kidney disease prognosis consortium. *Int J Epidemiol.* 2013;42:1660–1668. doi: 10.1093/ije/dys173
16. Wheeler DC, Stefánsson BV, Jongs N, Chertow GM, Greene T, Hou FF, McMurray JJV, Correa-Rotter R, Rossing P, Toto RD, et al; DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol.* 2021;9:22–31. doi: 10.1016/S2213-8587(20)30369-7
17. Afghahi H, Cederholm J, Eliasson B, Zethelius B, Gudbjörnsdottir S, Hadimeri H, Svensson MK. Risk factors for the development of albuminuria and renal impairment in type 2 diabetes–the Swedish National Diabetes Register (NDR). *Nephrol Dial Transplant.* 2011;26:1236–1243. doi: 10.1093/ndt/gfq535
18. Takagi M, Babazono T, Uchigata Y. Differences in risk factors for the onset of albuminuria and decrease in glomerular filtration rate in people with type 2 diabetes mellitus: implications for the pathogenesis of diabetic kidney disease. *Diabet Med.* 2015;32:1354–1360. doi: 10.1111/dme.12793
19. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch Intern Med.* 1998;158:998–1004. doi: 10.1001/archinte.158.9.998
20. Forsblom CM, Groop PH, Ekstrand A, Tötterman KJ, Sane T, Saloranta C, Groop L. Predictors of progression from normoalbuminuria to microalbuminuria in NIDDM. *Diabetes Care.* 1998;21:1932–1938. doi: 10.2337/diacare.21.11.1932
21. Murussi M, Baglio P, Gross JL, Silveiro SP. Risk factors for microalbuminuria and macroalbuminuria in type 2 diabetic patients: a 9-year follow-up study. *Diabetes Care.* 2002;25:1101–1103. doi: 10.2337/diacare.25.6.1101
22. Peralta CA, Bibbins-Domingo K, Vittinghoff E, Lin F, Fornage M, Kopp JB, Winkler CA. APOL1 genotype and race differences in incident albuminuria and renal function decline. *J Am Soc Nephrol.* 2016;27:887–893. doi: 10.1681/ASN.2015020124
23. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380:2295–2306. doi: 10.1056/NEJMoa1811744
24. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2021. *Diabetes Care.* 2021;44:S111–S124. doi: 10.2337/dc21-S009
25. Fox CS, Gona P, Larson MG, Selhub J, Tofler G, Hwang SJ, Meigs JB, Levy D, Wang TJ, Jacques PF, et al. A multi-marker approach to predict incident CKD and microalbuminuria. *J Am Soc Nephrol.* 2010;21:2143–2149. doi: 10.1681/ASN.2010010085
26. Stempniewicz N, Vassalotti JA, Cuddeback JK, Ciemins E, Storfer-Isser A, Sang Y, Matsushita K, Ballew SH, Chang AR, et al. Chronic kidney disease testing among primary care patients with type 2 diabetes across 24 U.S. Health Care Organizations. *Diabetes Care.* 2021; doi: 10.2337/dc20-2715