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Albuminuria testing in hypertension and diabetes: An individual-participant data meta-analysis in a global consortium

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Disclosure

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

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Abstract

Albuminuria is an under-recognized component of chronic kidney disease (CKD) 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 non-diabetic adults with hypertension from the CKD 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 mmHg 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 CKD and initiation of treatment with cardiovascular and renal benefits.

Keywords

albuminuria testing; ACR; hypertension; diabetes; chronic kidney disease

Introduction

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 (ADA) all recommend blockade of the renin-angiotensin-aldosterone system (RAAS) with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-II-receptor blocker (ARB) 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 sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with and without diabetes.[7, 9] Therefore, early diagnosis of CKD 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 eGFR 30–60 ml/min/1.73 m^2.[7] Hypertension guidelines are inconsistent. The 2018 European Society of Cardiology/ European Society of Hypertension (ESC/ESH) 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 ACEI 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 (CKD-PC) 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-PC cannot share individual data with third parties, but will be able to facilitate communications with individual cohorts.

Study Design and Data Sources

The CKD-PC 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 two 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, non-fasting glucose ≥200 mg/dl, hemoglobin A1c (HbA1c) ≥6.5%, use of glucose-lowering medications, or self-reported diabetes. Hypertension was defined as blood pressure ≥140/90 mmHg or the use of antihypertensive medications. In clinical cohorts, the International Classification of Diseases (ICD) codes were used to define diabetes and hypertension (Appendix S1).

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 pre-selected two-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 two 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 two measurements during the follow-up period, with at least one within the 2–4 year window for the 3-year analysis and at least one within the 4–6 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 standard deviations (SDs) or medians and interquartile intervals (IQIs) 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/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/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 (BMI) (linear splines with a knot at 30 kg/m^2), and eGFR (linear splines with three knots at 90, 60, 45 ml/min/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 (i.e. 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 <.05.

Results

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

There were 31 diabetes subcohorts included in our analyses (Table 1 & 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/1.73 m^2 than those with eGFR ≥60 ml/min/1.73 m^2 (median, 48.6% vs. 28.1%, *p*-value<0.001) and not significantly different by RAAS inhibitor use (median, 35.2% vs. 30.0%, *p*-value=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 & 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/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/1.73 m^2 than those with eGFR ≥60 ml/min/1.73 m^2 (median, 35.3% vs. 18.0%, *p*-value<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 systolic blood pressure (odds ratio [95% CI] per 20 mmHg 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 systolic blood pressure 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–B).

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 (Table S6–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 non-diabetic participants with hypertension and baseline ACR <30 mg/g (Table S9–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 systolic blood pressure was a risk factor in diabetes but not in hypertension (Table S11). There was no difference in the association between systolic blood pressure 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 vs. predicted incidence at 3 and 5 years shown in Figure S2 and Figure 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 naïve participants, initiation of RAAS inhibitors in the year after ACR testing was substantially higher in people with ACR ≥30 mg/g compared to 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 more than 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 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.

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 to 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 ≥30 mg/g.[7] The only hypertension guideline that recommends

universal ACR testing (the ESC/ESH) 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 4.3–44.8%, 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 31–51% 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 mmHg; mean age, 36 years), whereas all participants in the hypertension subcohorts in our study had hypertension, and more than 50% were on antihypertensive medications (mean SBP, 134 mmHg; mean age, 62 years).[22]

Although discrimination of the developed risk prediction models was only modest, we utilized 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 non-diabetic 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 vs. 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 geographical 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 ICD 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 (e.g., biomarkers for early kidney damage).[25] We were 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 non-diabetic 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What is New?

- ACR (urine 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 ACR ≥30 mg/g (CKD 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 CKD-related complications, including sodium-glucose cotransporter-2 inhibitors, there is substantial opportunity to improve early diagnosis of CKD for better use of these agents in the population with diabetes or hypertension.

Summary

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

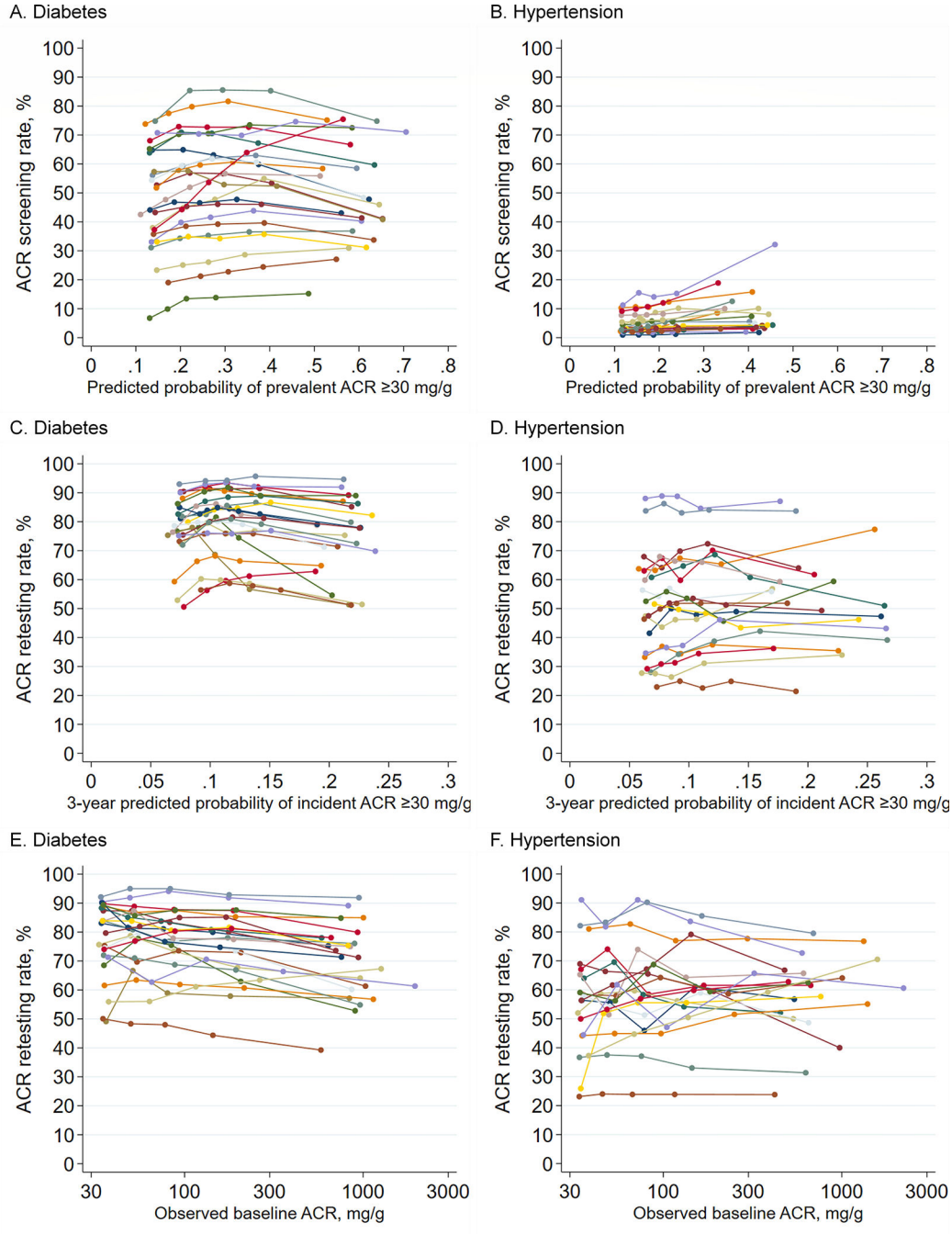

Figure 1. ACR screening rate at baseline and retesting rate among those who were tested at baseline in general population clinical cohorts.

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.

ACR, urine albumin-to-creatinine ratio

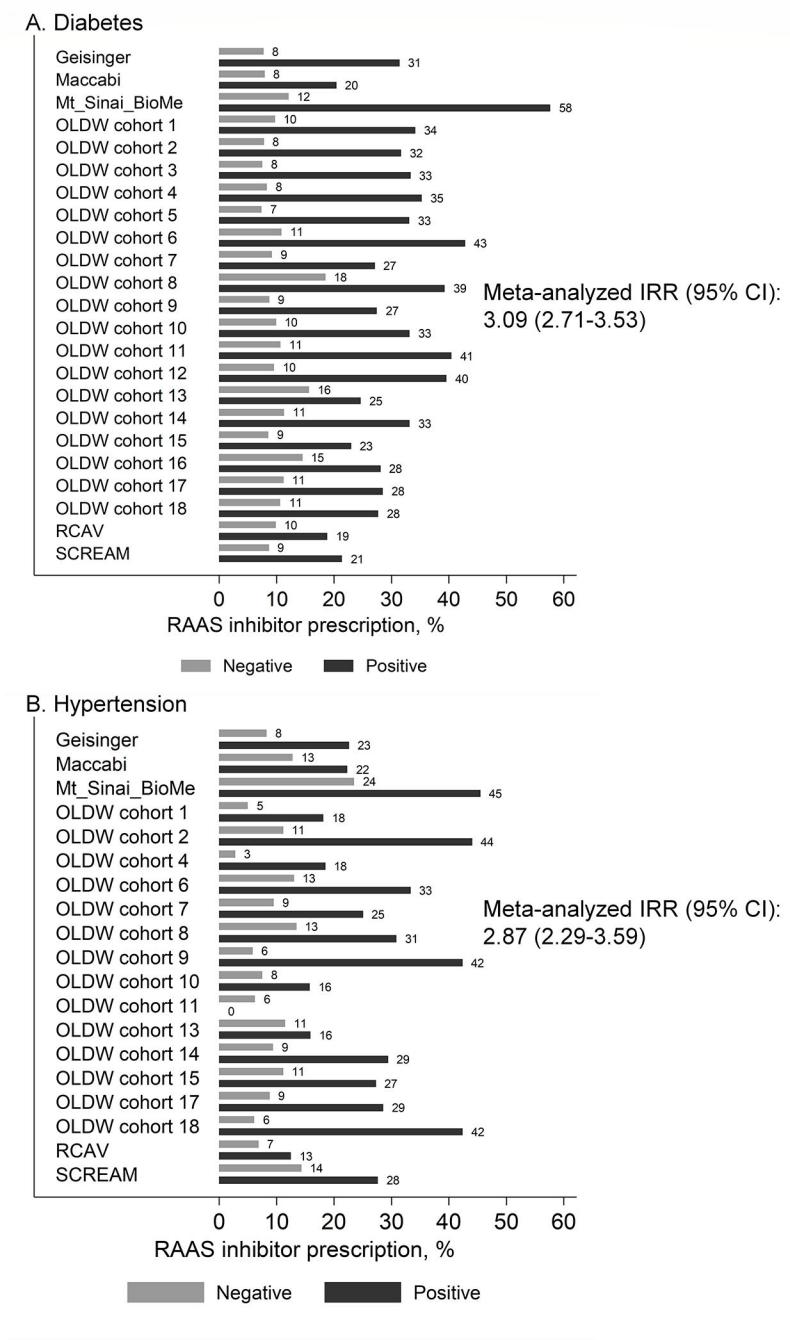

Figure 2. Comparison in initiation of RAAS inhibitors in the year after ACR testing by testing results (ACR <30 mg/g vs. ACR ≥30 mg/g) among RAAS inhibitor naïve participants.

(A) Diabetes; (B) Hypertension

ACR, urine albumin-to-creatinine ratio; RAAS, renin-angiotensin-aldosterone system; IRR, incidence rate ratio; CI, confidence interval

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Table 1.

Baseline characteristics of the participants with diabetes who were tested for ACR at baseline

Cohort (country)	N	Age, mean (SD), years	Women, No. (%)	SBP, mean (SD), mmHg	Any HTN med use, No. (%)	RAAS inhibitor use, No. (%)	Other HTN med use, No. (%)	HbA1c, mean (SD), %	Insulin use, No. (%)	Oral DM med use, No. (%)	No. (%) of participants		BMI, mean (SD), Kg/m^2	eGFR, mean (SD), ml/min/ 1.73 m^2	ACR ≥30 mg/g, No. (%)
											History of CHD	History of HF			
Development: research cohorts															
ADVANCE (multiple)	10542	66 (6)	4472 (42)	145 (21)	7884 (75)	4963 (47)	2921 (28)	7.5 (1.5)	153 (1)	9445 (90)	1640 (16)	328 (3)	28 (5)	78 (17)	3235 (31)
Pima (US)	454	36 (14)	217 (48)	126 (19)	98 (22)	69 (23)	29 (6)	9.0 (2.5)	57 (13)	109 (24)	NA	NA	35 (8)	121 (20)	211 (46)
PREVEND (Netherlands)	434	63 (10)	183 (42)	138 (20)	216 (52)	112 (26)	104 (25)	NA	26 (6)	191 (46)	68 (16)	14 (3)	30 (5)	87 (17)	135 (31)
Rancho Bernardo (US)	124	74 (12)	59 (48)	145 (22)	74 (60)	NA	74 (60)	5.5 (1.4)	14 (11)	41 (33)	21 (17)	8 (6)	27 (5)	62 (18)	33 (27)
ZODIAC (Netherlands)	1634	67 (12)	914 (56)	152 (24)	435 (27)	435 (27)	NA	7.3 (1.3)	33 (2)	1303 (80)	176 (12)	NA	29 (5)	68 (17)	137 (8)
Development: clinical cohorts															
Geisinger (US)	26261	63 (14)	12605 (48)	128 (16)	20793 (79)	15897 (61)	15688 (60)	7.4 (1.6)	6404 (24)	17446 (66)	7026 (27)	2382 (9)	34 (8)	79 (25)	9364 (36)
Maccabi (Israel)	44677	63 (13)	18575 (42)	134 (18)	30130 (67)	25156 (56)	21512 (48)	7.6 (1.7)	5840 (13)	27389 (61)	9416 (21)	1773 (4)	31 (6)	83 (23)	25004 (56)
Mt Sinai BioMe (US)	1490	59 (13)	994 (67)	132 (20)	1063 (71)	897 (60)	817 (55)	7.8 (2.0)	504 (34)	870 (58)	117 (8)	296 (20)	33 (8)	76 (26)	597 (40)
OLDW cohort 1 (US)	16753	62 (13)	8234 (49)	126 (16)	9061(54)	5517 (33)	7358 (44)	7.4 (1.6)	2689 (16)	7567 (45)	4625 (28)	1869 (11)	35 (8)	79 (23)	4531 (27)
OLDW cohort 2 (US)	16014	62 (13)	8036 (50)	129 (16)	9924 (62)	7019 (44)	8022 (50)	7.4 (1.6)	3203 (20)	8620 (54)	3192 (20)	862 (5)	34 (8)	79 (24)	5132 (32)
OLDW cohort 3 (US)	1055	58 (14)	563 (53)	134 (18)	326 (31)	232 (22)	227 (22)	7.7 (1.7)	211 (20)	337 (32)	159 (15)	46 (4)	33 (6)	83 (26)	268 (25)
OLDW cohort 4 (US)	9718	63 (13)	4864 (50)	136 (21)	4305 (44)	2549 (26)	3380 (35)	7.5 (1.6)	958 (10)	3600 (37)	1941 (20)	501 (5)	35 (8)	77 (24)	2972 (31)
OLDW cohort 5 (US)	4120	61 (13)	1865 (45)	127 (16)	2384 (58)	1389 (34)	1991 (48)	7.5 (1.7)	717 (17)	2312 (56)	790 (19)	259 (6)	34 (8)	79 (25)	1275 (31)
OLDW cohort 6 (US)	23168	63 (13)	11623 (50)	130 (17)	5793 (25)	3621 (16)	4687 (20)	7.2 (1.5)	1794 (8)	4767 (21)	5911 (26)	2234 (10)	34 (8)	77 (23)	6694 (29)

Cohort (country)	N	Age, mean (SD), years	Women, No. (%)	SBP, mean (SD), mmHg	Any HTN med use, No. (%)	RAAS inhibitor use, No. (%)	Other HTN med use, No. (%)	HbA1c, mean (SD), %	Insulin use, No. (%)	Oral DM med use, No. (%)	No. (%) of participants		BMI, mean (SD), Kg/m^2	eGFR, mean (SD), ml/min/ 1.73 m^2	ACR ≥30 mg/g, No. (%)
											History of CHD	History of HF			
OLDW cohort 7 (US)	8988	61 (15)	4171 (46)	129 (17)	3957 (44)	2712 (30)	2976 (33)	7.3 (1.6)	1950 (22)	3429 (38)	1665 (19)	441 (5)	33 (8)	79 (25)	3134 (35)
OLDW cohort 8 (US)	8080	59 (14)	4046 (50)	133 (19)	2702 (33)	1462 (18)	2191 (27)	7.6 (1.8)	1597 (20)	2583 (32)	1468 (18)	480 (6)	35 (9)	80 (26)	3011 (37)
OLDW cohort 9 (US)	26318	60 (13)	12762 (48)	130 (17)	14716 (56)	10050 (38)	11437 (43)	7.5 (1.7)	6340 (24)	14268 (54)	5088 (19)	1621 (6)	33 (8)	82 (25)	8526 (32)
OLDW cohort 10 (US)	13591	61 (13)	6809 (50)	129 (17)	7618 (56)	5377 (40)	5866 (43)	7.3 (1.7)	2938 (22)	7051 (52)	2794 (21)	1089 (8)	34 (8)	78 (23)	4496 (33)
OLDW cohort 11 (US)	5389	63 (13)	2735 (51)	128 (17)	2477 (46)	1442 (27)	1950 (36)	7.2 (1.5)	685 (13)	2217 (41)	1475 (27)	745 (14)	34 (8)	72 (22)	2469 (46)
OLDW cohort 12 (US)	1142	53 (15)	634 (56)	132 (18)	276 (24)	154 (13)	216 (19)	8.1 (1.9)	339 (30)	368 (32)	168 (15)	66 (6)	33 (8)	81 (24)	283 (25)
OLDW cohort 13 (US)	7084	62 (13)	3077 (43)	127 (16)	2649 (37)	1742 (25)	1971 (28)	7.2 (1.6)	728 (10)	2603 (37)	1208 (17)	313 (4)	32 (7)	81 (22)	1906 (27)
SCREAM (Sweden)	9216	63 (15)	3604 (39)	NA	6221 (68)	4704 (51)	5008 (54)	6.8 (1.5)	4253 (46)	4276 (46)	1565 (17)	1306 (14)	NA	78 (26)	3858 (42)
West of Scotland (Scotland)	2451	68 (11)	1155 (47)	146 (25)	1082 (44)	707 (29)	820 (33)	8.1 (3.8)	305 (12)	579 (24)	453 (18)	153 (6)	32 (7)	43 (23)	933 (38)
Total	238703	62 (13)	112197 (47)	131 (18)	134184 (56)	96206 (40)	99245 (42)	7.4 (1.7)	41738 (17)	121371 (51)	50966 (21)	16786 (7)	33 (7)	79 (24)	88205 (37)
Validation: research cohorts															
UK Biobank (UK)	23319	60 (7)	9001 (39)	143 (19)	12093 (52)	11309 (48)	784 (3)	7.0 (1.3)	700 (3)	13096 (56)	2791 (12)	71 (0)	31 (6)	89 (17)	3535 (15)
Validation: clinical cohorts															
CURE-CKD (US)	6881	62 (15)	3338 (49)	129 (17)	NA	NA	NA	7.5 (1.7)	NA	NA	788 (11)	294 (4)	32 (8)	77 (25)	2300 (33)
OLDW cohort 14 (US)	5949	65 (12)	3015 (51)	131 (17)	3742 (63)	2579 (43)	2845 (48)	7.2 (1.4)	1037 (17)	3175 (53)	1371 (23)	297 (5)	33 (7)	74 (22)	1362 (23)
OLDW cohort 15 (US)	5363	58 (15)	2628 (49)	130 (16)	2092 (39)	1630 (30)	1419 (26)	7.6 (1.5)	1224 (23)	2248 (42)	863 (16)	235 (4)	34 (8)	82 (25)	1864 (35)
OLDW cohort 16 (US)	2856	60 (13)	1294 (45)	128 (15)	924 (32)	580 (20)	644 (23)	7.5 (1.5)	398 (14)	891 (31)	483 (17)	135 (5)	34 (8)	82 (24)	1030 (36)
OLDW cohort 17 (US)	40840	62 (13)	20474 (50)	130 (16)	22668 (56)	14918 (37)	17651 (43)	7.4 (1.6)	7345 (18)	22004 (54)	9820 (24)	3536 (9)	33 (8)	78 (23)	14606 (36)

Cohort (country)	N	Age, mean (SD), years	Women, No. (%)	SBP, mean (SD), mmHg	Any HTN med use, No. (%)	RAAS inhibitor use, No. (%)	Other HTN med use, No. (%)	HbA1c, mean (SD), %	Insulin use, No. (%)	Oral DM med use, No. (%)	No. (%) of participants		BMI, mean (SD), Kg/m^2	eGFR, mean (SD), ml/min/ 1.73 m^2	ACR ≥30 mg/g, No. (%)
											History of CHD	History of HF			
OLDW cohort 18 (US)	7625	64 (14)	4006 (53)	129 (16)	4316 (57)	2606 (34)	3316 (43)	7.1 (1.4)	1089 (14)	3258 (43)	1920 (25)	759 (10)	33 (7)	76 (23)	2340 (31)
RCAV (US)	136813	66 (11)	3806 (3%)	132 (17)	96855 (71)	71301 (52)	74628 (55)	7.3 (1.6)	23194 (17)	77157 (56)	48024 (35)	14545 (11)	32 (6)	77 (17)	41451 (30)
Total	206327	64 (12)	47562 (21)	133 (18)	142877 (69)	104947 (46)	101466 (44)	7.3 (1.6)	35264 (15)	122109 (53)	66060 (29)	19872 (9)	32 (7)	79 (19)	68487 (30)

ACR, urine albumin-to-creatinine ratio; SD, standard deviation; SBP, systolic blood pressure; RAAS, renin-angiotensin-aldosterone system; HTN, hypertension; HbA1c, hemoglobin A1c; DM, diabetes; CHD, coronary heart disease; HF, heart failure; eGFR, estimated glomerular filtration rate; IQI, interquartile interval; BMI, body mass index; NA, not available; med, medication; Multiple countries included in ADVANCE: Australia, Canada, China, Czech Republic, Estonia, France, Germany, Hungary, India, Ireland, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Philippines, Poland, Russia, Slovakia, United Kingdom

Table 2.

ACR testing rate at baseline*

	Research cohorts	General population clinical cohorts		Referred CKD clinical cohort
Diabetes	All	All	eGFR <60 ml/min/1.73 m^2	All
Number of cohorts	6	24	24	1
Number of participants	38,753	1,303,027	241,247	2,814
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

*Baseline was defined as the first visit with ACR measurement in research cohorts and in a pre-selected two-year time window in clinical cohorts

ACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate

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Table 3.

Baseline characteristics of the participants with hypertension (without diabetes) who were tested for ACR at baseline

Cohort (country)	N	Age, mean (SD), years	Women, No. (%)	SBP, mean (SD), mmHg	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/ 1.73 m^2	ACR ≥30 mg/g, No. (%)
								History of CHD	History of HF			
Development : research cohorts												
Pima (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	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 (US)	2239	63 (13)	1136 (51)	130 (17)	1198 (54)	649 (29)	986 (44)	300 (13)	69 (3)	29 (6)	78 (20)	351 (16)

Cohort (country)	N	Age, mean (SD), years	Women, No. (%)	SBP, mean (SD), mmHg	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/ 1.73 m^2	ACR ≥30 mg/g, No. (%)
								History of CHD	History of HF			
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 (US)	2204	63 (15)	1107 (50)	132 (19)	NA	NA	NA	215 (10)	61 (3)	29 (6)	70 (26)	595 (27)
OLDW cohort 14 (US)	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 (US)	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 (US)	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 (US)	1433	64 (14)	770 (54)	132 (16)	975 (68)	499 (35)	795 (55)	289 (20)	97 (7)	31 (7)	73 (22)	322 (22)
RCAV (US)	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, urine albumin-to-creatinine ratio; SD, standard deviation; SBP, systolic blood pressure; RAAS, renin-angiotensin-aldosterone system; HTN, hypertension; CHD, coronary heart disease; HF, heart failure; eGFR, estimated glomerular filtration rate; IQI, interquartile interval; BMI, body mass index; NA, not available; med, medication