Supplemental Online Materials

Supplemental Table 1. ICD-9 and procedure (CPT) codes used to define prevalent comorbid conditions

Comorbid condition	ICD-9 code
Hypertension	401-405
Diabetes mellitus	250.x
Coronary artery disease	414.0, 414.8, 414.9
Angina	411, 413
Myocardial infarction	410-410.9, 412
PCI	36.03, 36.04, 36.06, 36.07, 36.09
CABG	36.10-36.17, 36.19
Congestive heart failure	428-428.9
Cerebrovascular disease	430-438
Peripheral arterial disease	440.0-440.9, 443, 443.x, 38.0, 38.1, 39.50, 39.22, 39.24, 39.25, 39.26, 39.28
Chronic lung disease	490-496, 500-505, 506.4
Dementia	290-290.9
Rheumatologic disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725
Liver disease	571.x, 572.x, 456.0-456.21
Malignancy	140-172.9, 174-195.8, 200-208.9, 196-199.1
HIV/AIDS	042, V08, 795.71
Depression	296.x
Procedure (CPT) codes used to define coronary interventions	
Procedure	**CPT code**
PCI	92980 92981 92982 92984 92985 92986 92987 92988 92989 92990 92991 92992 92993 92994 92995 92996
CABG	33510 33511 33512 33513 33514 33515 33516 33517 33518 33519 33521 33522 33523 33533 33534 33535 33536

Abbreviations: AIDS = acquired immunodeficiency syndrome; CABG = coronary artery bypass grafting; CPT = Current Procedural Terminology; HIV = human immunodeficiency virus; ICD = International Classification of Diseases; PCI = percutaneous coronary intervention

Supplemental Table 2. Area-based socio-economic indicators

The Area Health Resources Files (AHRF, http://ahrf.hrsa.gov/) system is issued by the National Center for Health Workforce Analysis, Bureau of Health Workforce, Health Resources and Services Administration.
Within the AHRF, we used select **2004 County Typology Codes** from the Economic Research Service (ERS), U.S. Department of Agriculture, www.ers.usda.gov. The 2004 County Typology Codes were developed for all 3,141 counties, county equivalents, and independent cities in the United States.

Indicators	Definition
Housing stress	30 percent or more of households had one or more of these housing conditions in 2000: lacked complete plumbing, lacked complete kitchen, paid 30 percent or more of income for owner costs or rent, or had more than 1 person per room.
Low-education	25 percent or more of residents 25 through 64 years old had neither a high school diploma nor General Education Development (GED) in 2000.
Low-employment	Less than 65 percent of residents 21 through 64 years old were employed in 2000.
Persistent poverty	20 percent or more of residents were poor as measured by each of the last 4 censuses: 1970, 1980, 1990 and 2000.

Supplemental Table 3. Summary of outcome variables of (A) incident CKD and (B) rapid eGFR decline overall and by 1-year fold UACR change categories

Characteristics	Total	1-year fold changes in UACR				
		>2 fold decrease	1.25-2 fold decrease	Stable	1.25-2 fold increase	>2 fold increase
(A) Incident CKD						
Patients, n	53,342	8,494	7,996	15,527	10,444	10,881
Follow-up, yrs	6.3 (4.2, 6.6)	6.2 (3.9, 6.6)	6.3 (4.4, 6.6)	6.3 (4.5, 6.7)	6.3 (4.3, 6.6)	6.2 (3.6, 6.6)
Events, n (%)	8,194 (15)	1,357 (16)	1,157 (15)	2,210 (14)	1,600 (15)	1,870 (17)
Incidence rate, 1000 person-yr	29.3 (28.7, 29.9)	30.9 (29.3, 32.5)	27.3 (25.8, 29.0)	26.6 (25.6, 27.8)	29.0 (27.6, 30.5)	33.9 (32.4, 35.5)
(B) Rapid eGFR decline						
Patients, n	56,440	9,341	8,475	16,244	10,888	11,492
Events, n (%)	6,512 (12)	1,189 (13)	903 (11)	1,635 (10)	1,196 (11)	1,589 (14)

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

Supplemental Table 4. Adjusted subhazard ratios of incident CKD associated with 1-year fold UACR changes in competing risk regression models with death as a competing event (*n* = 47,635)

	1-year fold changes in UACR				
	>2 fold decrease	1.25-2 fold decrease	Stable	1.25-2 fold increase	>2 fold increase
Patients, n	7,603	7,121	13,926	9,272	9,713
Primary events, n (%)	1,267 (17)	1,080 (15)	2,074 (15)	1,488 (16)	1,759 (18)
Competing events (deaths), n (%)	1,263 (17)	1,165 (16)	2,101 (15)	1,523 (16)	1,827 (19)
SHR (95% CI)	0.82 (0.77–0.89)	0.93 (0.86–1.00)	1 [reference]	1.11 (1.04–1.19)	1.25 (1.17–1.33)

Data are adjusted for age, sex, race, baseline eGFR and log-transformed UACR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome), baseline body mass index, systolic BP, and diastolic BP, slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence.

*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

Abbreviations: BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate;RASi = renin-angiotensin system inhibitors; SHR = subhazard ratio; UACR = urinary albumin-to-creatinine ratio.

Supplemental Table 5. Associations of 1-year fold UACR changes with (A) incident CKD and (B) rapid eGFR decline with multiple imputations for missing data

	1-year fold changes in UACR				
	>2 fold decrease	1.25-2 fold decrease	Stable	1.25-2 fold increase	>2 fold increase
(A) Incident CKD (*n* = 53,342)					
HR (95% CI)	0.82 (0.77–0.88)	0.93 (0.86–1.00)	1 [reference]	1.11 (1.04–1.19)	1.28 (1.20–1.36)
(B) Rapid eGFR decline (*n* = 56,440)					
OR (95% CI)	0.88 (0.81–0.96)	097 (0.88–1.05)	1 [reference]	1.16 (1.07–1.26)	1.62 (1.50–1.75)

Data are adjusted for age, sex, race, baseline eGFR and log-transformed UACR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome), baseline body mass index, systolic BP, and diastolic BP, slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence.

*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

Abbreviations: BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; OR = odds ratio; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.

Supplemental Table 6. Associations of 1-year fold UACR changes with (A) incident CKD and (B) rapid eGFR decline with further adjustment for socioeconomic parameters and baseline serum albumin and total cholesterol

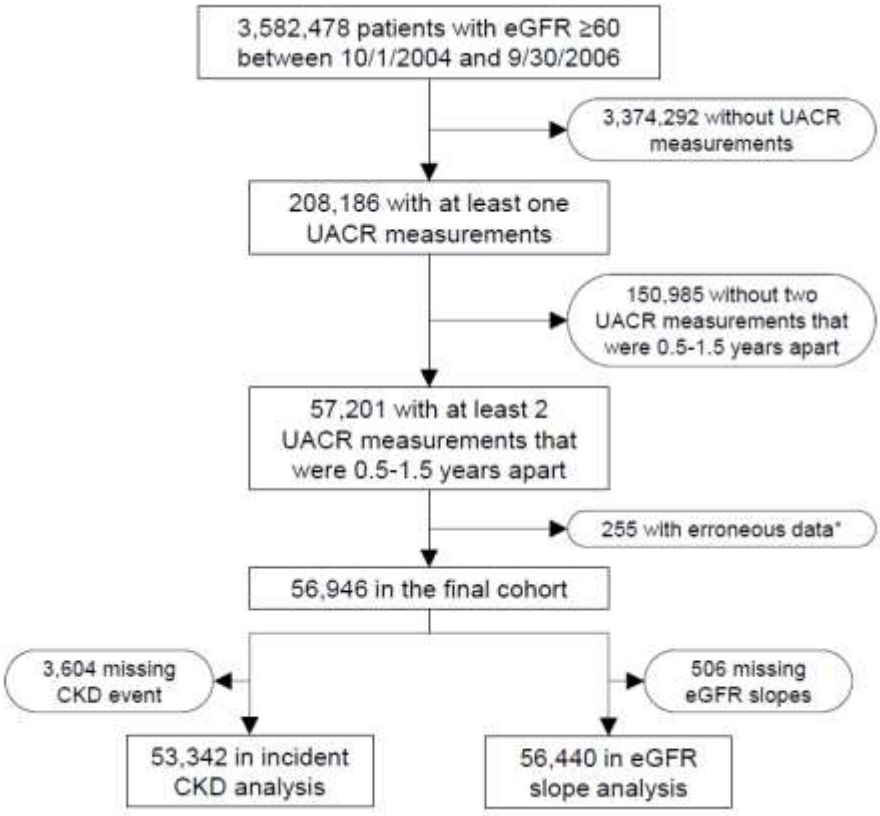
	1-year fold changes in UACR				
	>2 fold decrease	1.25-2 fold decrease	Stable	1.25-2 fold increase	>2 fold increase
(A) Incident CKD (*n* = 30,017)					
HR (95% CI)	0.86 (0.79–0.94)	0.92 (0.84–1.01)	1 [reference]	1.17 (1.07–1.27)	1.28 (1.18–1.39)
(B) Rapid eGFR decline (*n* = 32,385)					
OR (95% CI)	0.90 (0.80–1.02)	1.04 (0.92–1.18)	1 [reference]	1.27 (1.14–1.42)	1.74 (1.57–1.94)

Data are adjusted for the variables in model 4 (age, sex, race, baseline eGFR and log-transformed UACR, comorbidities [diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome], baseline body mass index, systolic BP, and diastolic BP, slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence) plus socioeconomic parameters (mean per capita income, marital status, service connected ness, housing stress, low education, low employment, and persistent poverty) and baseline serum albumin and total cholesterol.

*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

Abbreviations: BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; OR = odds ratio; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.

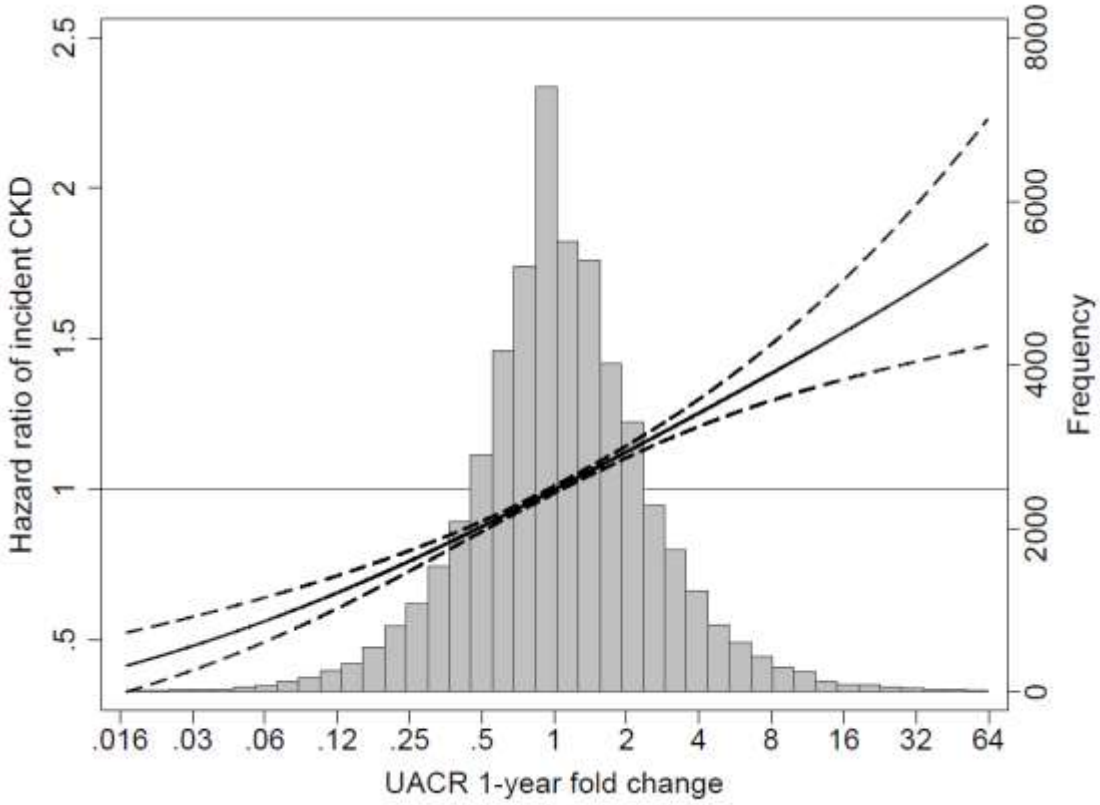
Supplemental Figure 1. Algorithm used to define study cohort



*Patients with the date of start of follow-up later than the date of last encounter or incident ESRD (*n* = 143) or those with an eGFR slope during follow-up of <-49 (0.1st percentile) or ≥33 (99.9th percentile) mL/min/1.73 m^2 per year (*n* = 112).

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

Supplemental Figure 2. Distribution of 1-year fold UACR changes and adjusted hazard ratio of incident CKD associated with 1-year fold UACR changes

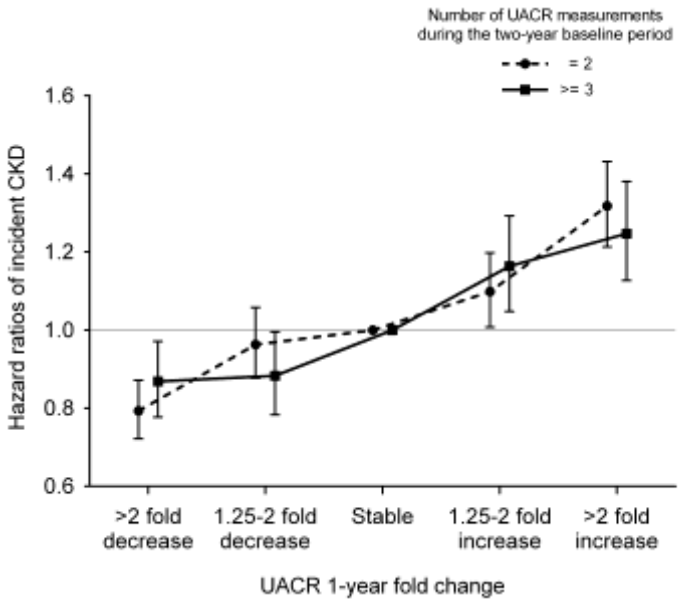


Solid and dashed lines represent hazard ratio and 95% CI, respectively.
A hazard reference ratio of 1 (solid horizontal line) and a histogram of observed values of 1-year fold UACR change are overlaid.
The x-axis shows levels of 1-year fold change in UACR, trimmed as 0.016- and 64-folds.
Data are adjusted for age, sex, race, baseline eGFR and log-transformed UACR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome), baseline body mass index, systolic BP, and diastolic BP, slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence.
*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

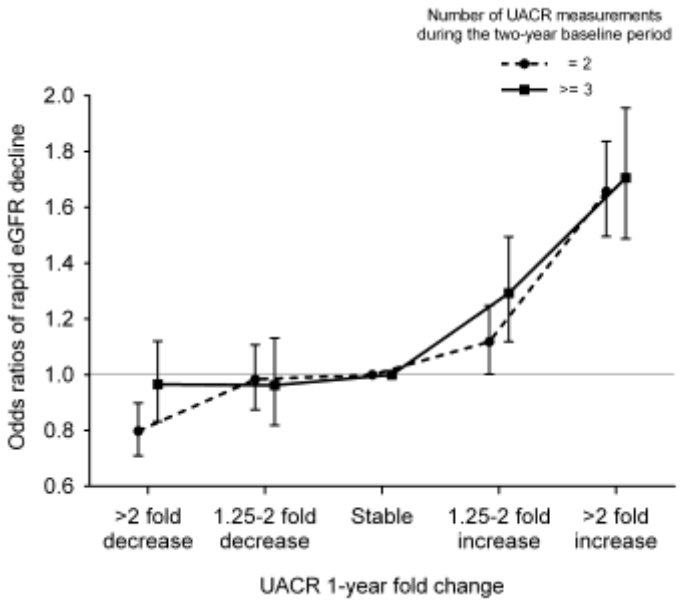
Abbreviations: BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.

Supplemental Figure 3. Association of 1-year fold UACR changes with (A) incident CKD and (B) rapid eGFR decline by number of UACR measurements during the two-year baseline period

(A)



(B)



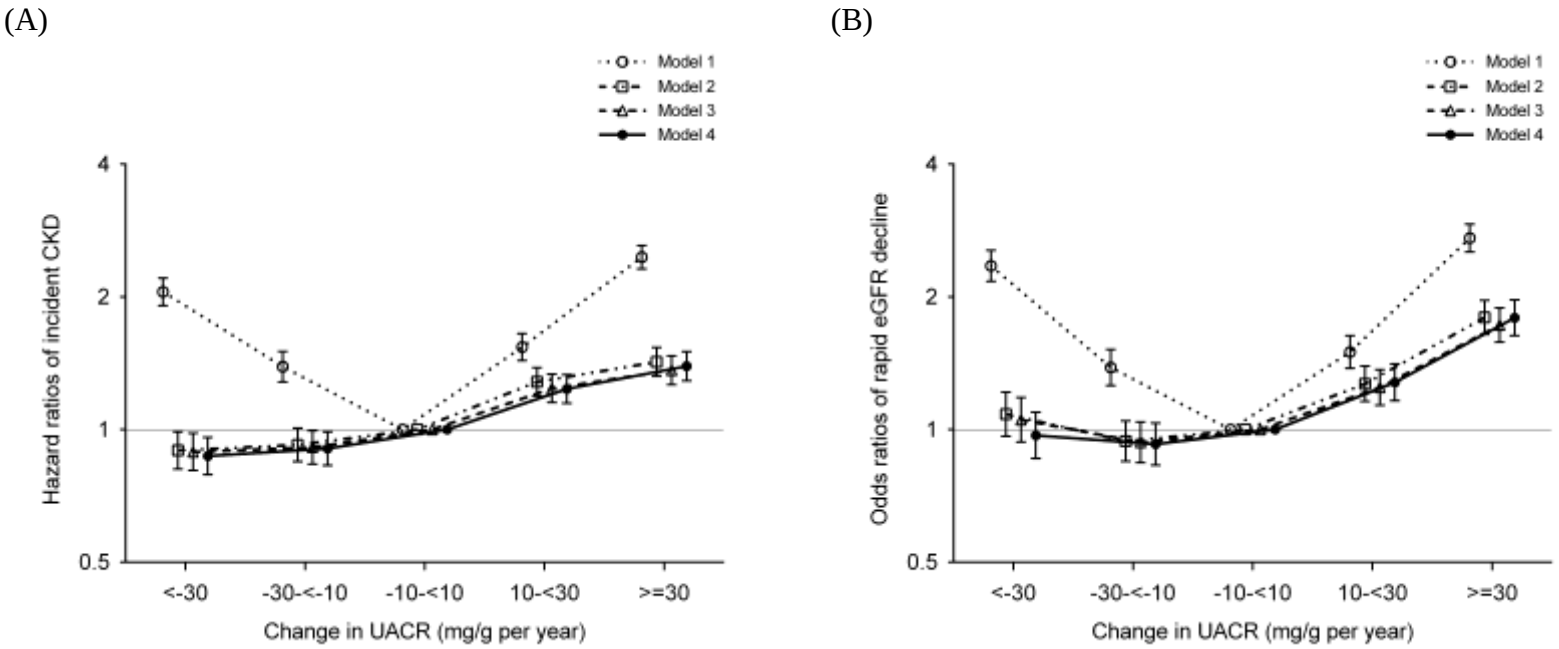
Data are adjusted for age, sex, race, baseline eGFR and log-transformed UACR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome), baseline body mass index, systolic BP, diastolic BP, and slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence.

*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

P for interaction = 0.25 and 0.14 for incident CKD and rapid eGFR decline, respectively.

Abbreviations: BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.

Supplemental Figure 4. Associations of UACR changes calculated by OLS regression model with (A) incident CKD and (B) rapid eGFR decline

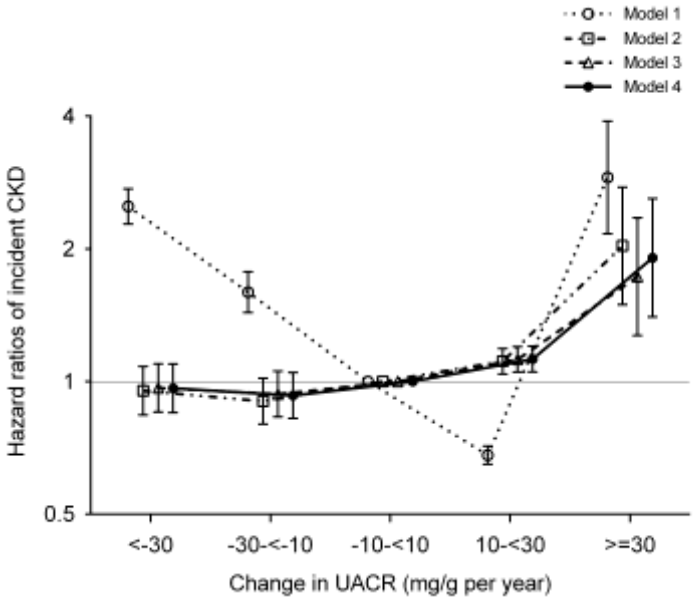


Models represent unadjusted association (model 1) and associations after adjustment for age, sex, race, and baseline eGFR and log-transformed UACR (model 2); model 2 variables plus comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome) (model 3); model 3 plus baseline body mass index, systolic BP, and diastolic BP, slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence (model 4).
The associations were estimated using Cox-proportional models (for incident CKD) and logistic regression models (for rapid eGFR decline).
*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

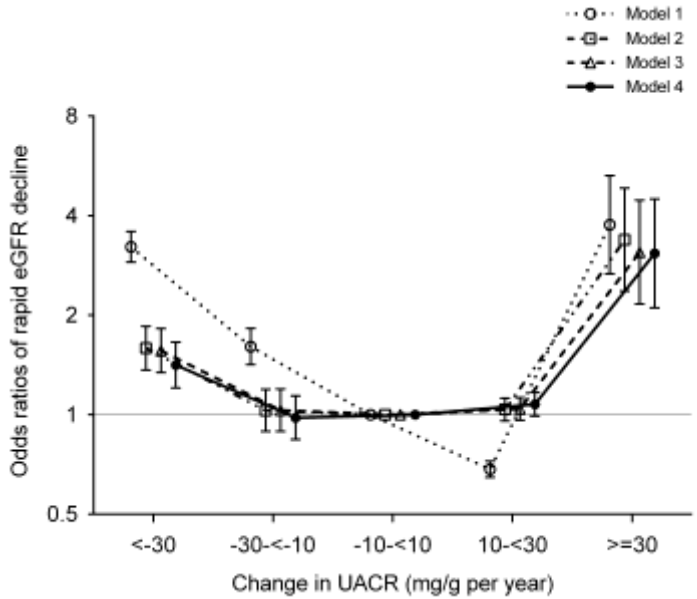
Abbreviations: BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; OLS = ordinary least-squares; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.

Supplemental Figure 5. Associations of UACR changes calculated by linear mixed-effects model with (A) incident CKD and (B) rapid eGFR decline

(A)



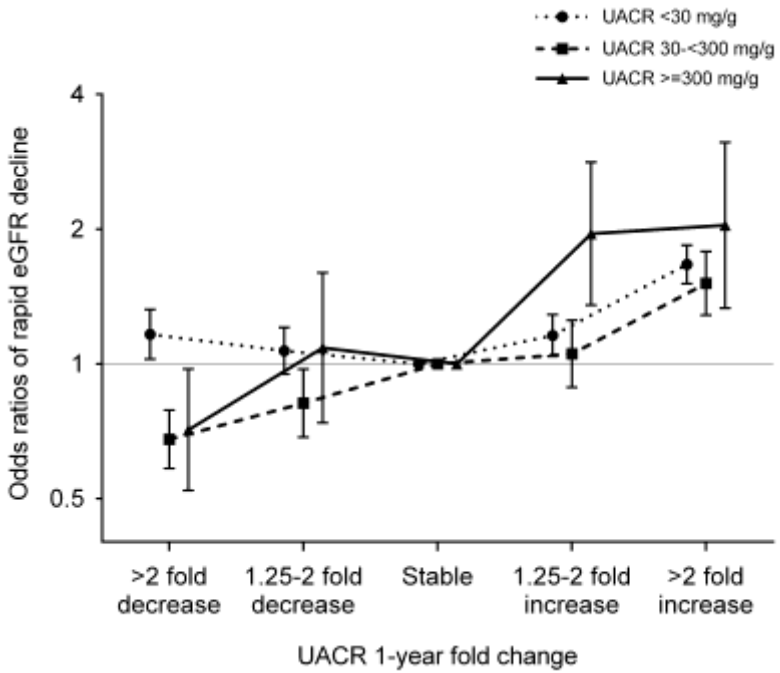
(B)



Models represent unadjusted association (model 1) and associations after adjustment for age, sex, race, and baseline eGFR and log-transformed UACR (model 2); model 2 variables plus comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome) (model 3); model 3 plus baseline body mass index, systolic BP, and diastolic BP, slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence (model 4).
The associations were estimated using Cox-proportional models (for incident CKD) and logistic regression models (for rapid eGFR decline).
*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

Abbreviations: BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.

Supplemental Figure 6. Association of 1-year fold UACR changes with rapid eGFR decline by baseline UACR levels



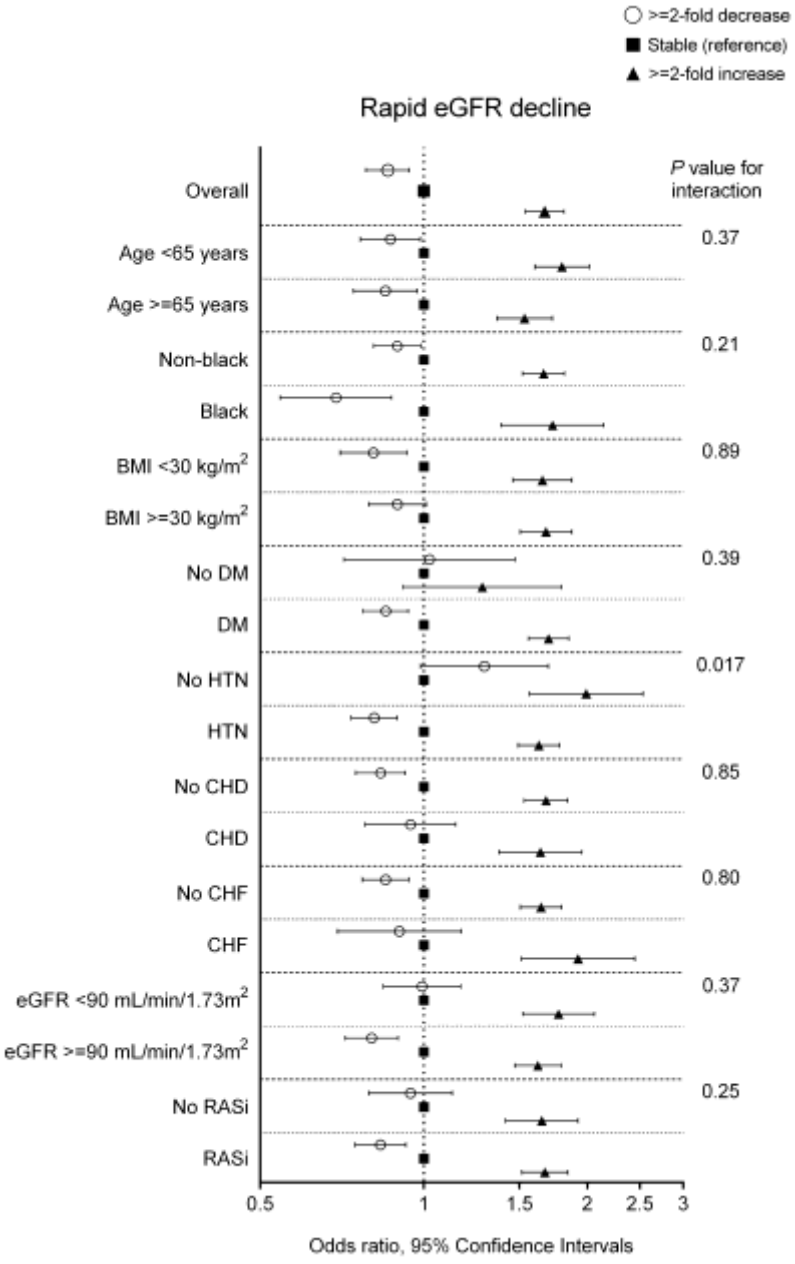
Data are adjusted for age, sex, race, baseline eGFR and log-transformed UACR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome), baseline body mass index, systolic BP, diastolic BP, and slopes of systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence.

*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

P for interaction <0.001

Abbreviations: BP = blood pressure; eGFR = estimated glomerular filtration rate; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.

Supplemental Figure 7. Association of 1-year fold UACR changes with rapid eGFR decline in predefined subgroups



RASi indicates patients with any exposure to RASi between the first and last UACR measurement during the two-year baseline period.
Data are adjusted for age, sex, race, baseline eGFR and log-transformed UACR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and human immunodeficiency virus/acquired immunodeficiency syndrome), baseline body mass index, systolic BP, and diastolic BP, slopes of

systolic BP and eGFR, use of statins and non-opioid analgesics at baseline, RASi treatment status*, and RASi adherence.

*Four categories based on RASi use at the dates of the first and last UACR measurements during the baseline period (i.e., use at both, either, or neither dates).

Abbreviations: BP = blood pressure; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension; RASi = renin-angiotensin system inhibitors; UACR = urinary albumin-to-creatinine ratio.