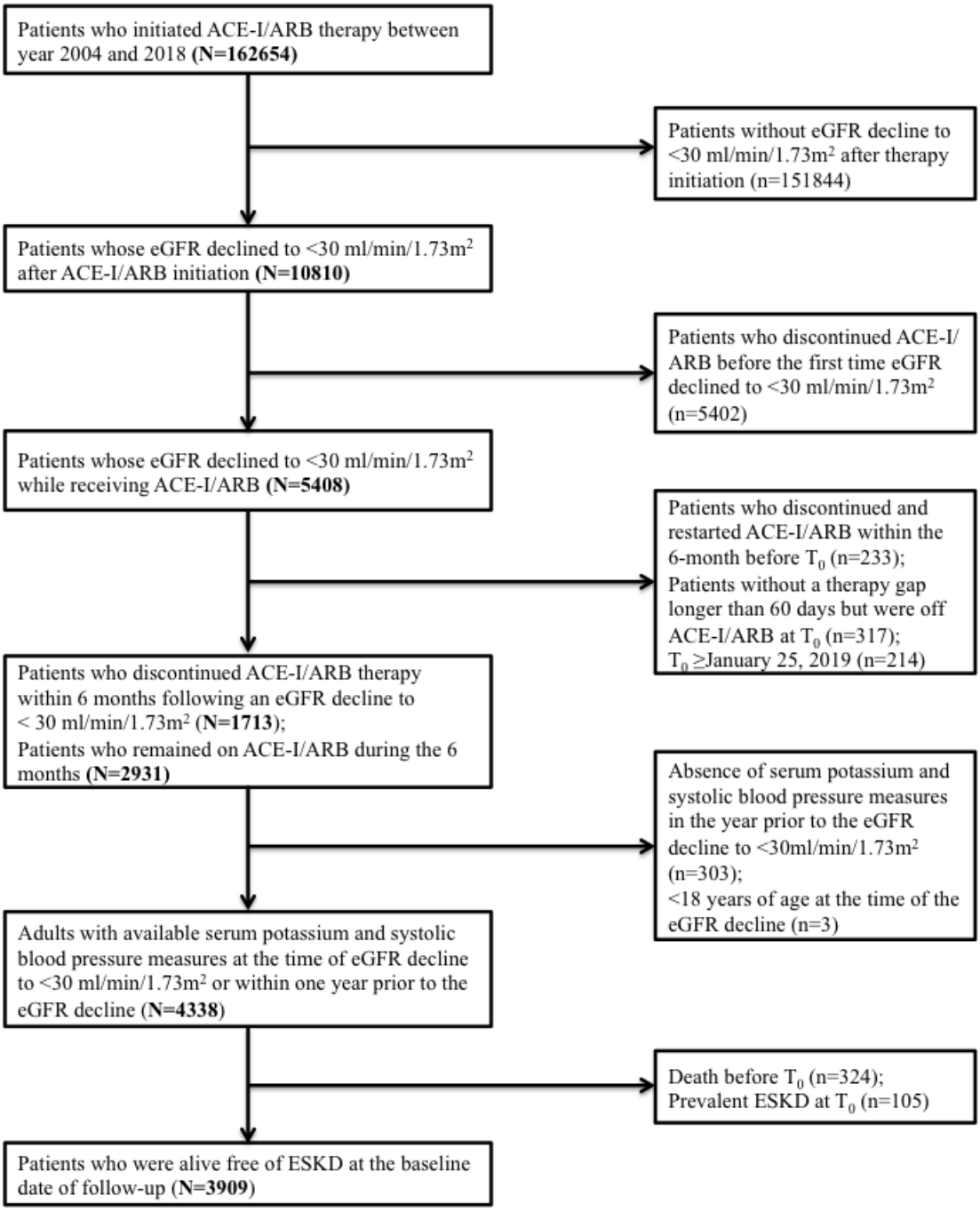
Supplementary Online Content

Qiao Y, Shin J-I, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. *JAMA Intern Med.* Published online March 9, 2020. doi:10.1001/jamainternmed.2020.0193

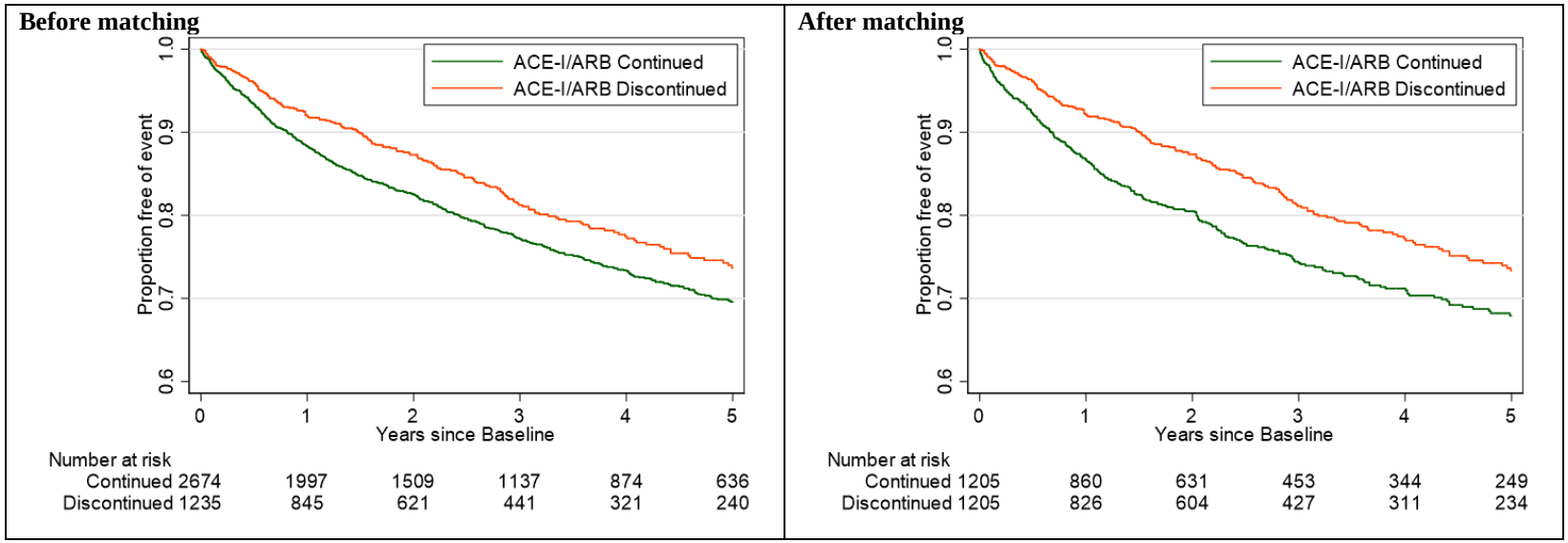
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Derivation of Study Population



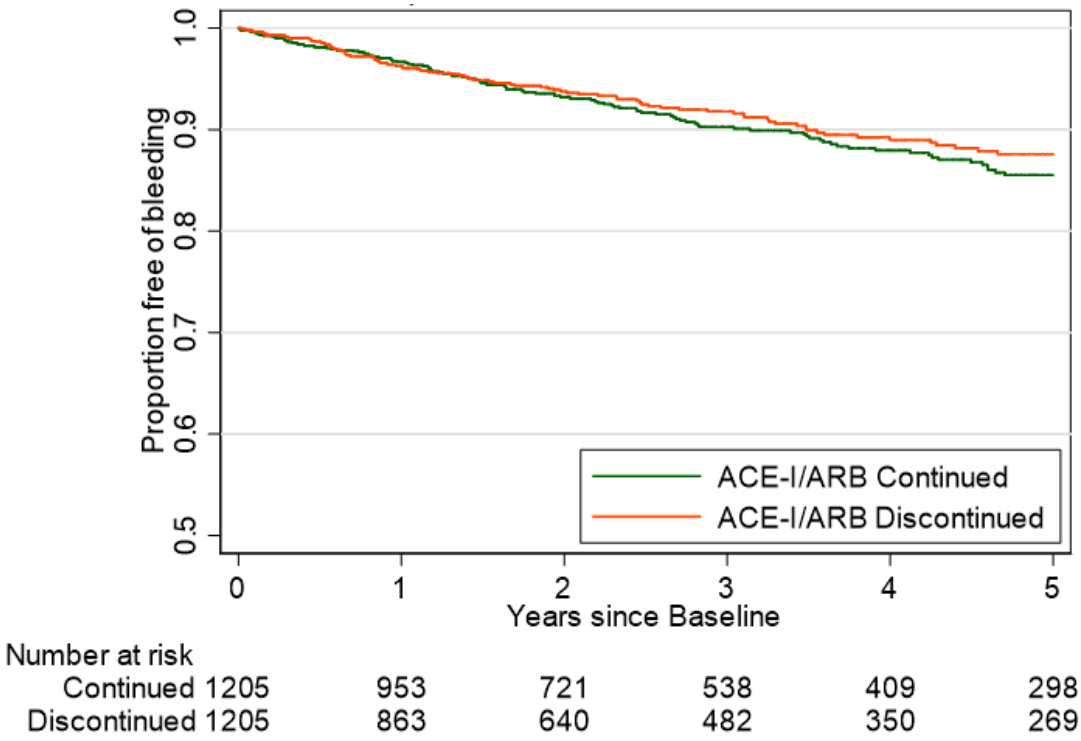
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate, ESKD, end-stage kidney disease

eFigure 2. Cumulative Incidence of Hyperkalemia, by ACE-I/ARB Discontinuation Status



Abbreviations**:** ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

eFigure 3. Cumulative Incidence of Bleeding, by ACE-I/ARB Discontinuation Status in the Propensity-Score Matched Sample



Number at risk						
Continued	1205	953	721	538	409	298
Discontinued	1205	863	640	482	350	269

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

eTable 1. Diagnosis and Procedure Codes Used to Define End-Stage Kidney Disease (ESKD)

Code system	Codes
Current Procedural Terminology (CPT)	90919-90999
Healthcare Common Procedure Coding System (HCPCS)	G0308-G0327, G0257, Q4081
International classification of disease, 9th edition, clinical modification (ICD-9-CM)	39.95, 54.98, 55.69, V56x, 585.5, 585.6, V42.0, 996.81
International classification of disease, 10th edition, clinical modification (ICD-10-CM)	5A1Dx, 3E1M39Z, 0TYx, Z49x, N18.5, N18.6, Z94.0, T86.1x

Note: The symbol "x" at the end of a code represents any characters. ESKD date was the earlier date of kidney transplant and dialysis. Kidney transplant date and dialysis date were both obtained from the US Renal Data System (USRDS), which covered through 7/31/2018. For the period after 7/31/2018, kidney transplant was coded as the date of ICD procedure codes of kidney transplant, or the first date of ICD diagnosis codes of kidney transplant in inpatient or problem list when there were at least another two ICD diagnosis codes of kidney transplant in other encounters within one year if procedure codes were not present. Similarly, for dialysis after 7/31/2018, it was defined as the date of ICD diagnosis code of stage V chronic kidney disease or ESKD when there was a CPT, HCPSC and ICD codes of dialysis within 7 days later, or the date of the first CPT, HCPSC and ICD codes of dialysis when there were at least three dialysis codes that covered longer than a month with intervals between any two consecutive codes within three months.

eTable 2. International Classification of Disease, 9th and 10th Editions, Clinical Modification (ICD-9-CM, ICD-10-CM) Used to Define Disease Conditions

Disease Conditions	ICD-9-CM codes	ICD-10-CM codes
Diabetes	250.x	E10.x, E11.x, E13.x
Congestive heart failure	428.x	I50.x
Coronary artery disease	410.x, 411.0, 411.8x, 412, 414.x, 36.1x	I21.x, I22.x, I23.x, I24.x, I25.x
Stroke	43x, V12.54	I6x
Cancer	14x-20x	Cx
Bleeding	531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 456.0, 456.20, 530.7, 530.82, 578x, 455.2, 455.5, 455.8, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 593.81, 599.7x, 626.8, 626.2, 626.6, 430, 431, 432x, 852.0x, 852.2x, 852.4x, 853.0x, 423.0, 459.0, 568.81, 719.1x, 784.7, 784.8, 786.3x	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.01, K29.21, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, I85.01, I85.11, K22.6, K22.8, K92.0, K92.1, K92.2, K64.4, K64.8, K57.11, K57.13, K57.31, K57.33, K66.1, K62.5, K55.21, R31.9, R31.0, R31.29, N93.8, N92.0, N92.1, I60.9, I61.9, I62.1, I62.00, I62.9, S06.6X0A, S06.6X1A, S06.6X2A, S06.6X3A, S06.6X4A, S06.6X5A, S06.6X6A, S06.6X7A, S06.6X8A, S06.6X9A, S06.5X0A, S06.5X1A, S06.5X2A, S06.5X3A, S06.5X4A, S06.5X5A, S06.5X6A, S06.5X7A, S06.5X8A, S06.5X9A, S06.4X0A, S06.4X1A, S06.4X2A, S06.4X3A, S06.4X4A, S06.4X5A, S06.4X6A, S06.4X7A, S06.4X8A, S06.4X9A, S06.360A, S06.361A, S06.362A, S06.363A, S06.364A, S06.3605A, S06.366A, S06.367A, S06.368A, S06.369A, I31.2, R58, K66.1, M25.00, M25.019, M25.029, M25.039, M25.049, M25.059, M25.069, M25.073, M25.076, M25.08, R04.0, R04.1, R04.2, R04.9, R04.89
Acute kidney injury	584.x	N17.x

Note: The symbol “x” at the end of a code represents any characters.

eTable 3. Baseline Characteristics of Patients With ≥40% eGFR Decline

Baseline Characteristics	Pre-matching (N=4251)			Post-matching (N=2320)		
	Discontinued (N=1189)	Control (N=3062)	Standardized mean difference	Discontinued (N=1160)	Control (N=1160)	Standardized mean difference
Age, mean (SD), years	68.9 (13.2)	66.4 (13.2)	0.185	68.8 (13.1)	68.0 (13.1)	0.059
eGFR[a], mean (SD), ml/min/1.73m^2	29.4 (13.5)	37.7 (13.1)	0.626	29.8 (13.4)	30.5 (12.5)	0.059
Potassium[a], mean (SD), mEq/L	4.7 (0.8)	4.5 (0.6)	0.313	4.7 (0.8)	4.6 (0.7)	0.060
Systolic blood pressure[a], mean (SD), mmHg	122.3 (21.4)	124.9 (20.1)	0.123	122.5 (21.4)	122.8 (20.9)	0.014
Number of outpatient visits[b], mean (SD)	7.1 (5.7)	6.7 (4.9)	0.080	7.1 (5.7)	7.1 (5.2)	0.007
Female, N (%)	641 (53.9)	1809 (59.1)	0.104	632 (54.5)	658 (56.7)	0.045
Black race, N (%)	20 (1.7)	92 (3.0)	0.087	20 (1.7)	15 (1.3)	0.035
Coronary artery disease[c], N (%)	458 (38.5)	1091 (35.6)	0.060	445 (38.4)	440 (37.9)	0.009
Congestive heart failure[c], N (%)	331 (27.8)	667 (21.8)	0.141	319 (27.5)	333 (28.7)	0.027
Diabetes[c], N (%)	557 (46.9)	1501 (49.0)	0.044	545 (47.0)	537 (46.3)	0.014
History of stroke[c], N (%)	197 (16.6)	480 (15.7)	0.024	193 (16.6)	198 (17.1)	0.012
Statin use, N (%)	656 (55.2)	1877 (61.3)	0.124	644 (55.5)	638 (55.0)	0.010
Beta-blocker use, N (%)	642 (54.0)	1618 (52.8)	0.023	631 (54.4)	635 (54.7)	0.007
Antiplatelet agent use, N (%)	463 (38.9)	1134 (37.0)	0.039	450 (38.8)	441 (38.0)	0.016
Hospitalization[b], N (%)	19 (1.6)	69 (2.3)	0.048	19 (1.6)	23 (2.0)	0.026
Nephrology visit[b], N (%)	126 (10.6)	221 (7.2)	0.119	120 (10.3)	121 (10.4)	0.003
Calendar year, N (%)						
2004-2008	158 (13.3)	538 (17.6)	0.119	157 (13.5)	164 (14.1)	0.017
2009-2013	443 (37.3)	1120 (36.6)	0.014	432 (37.2)	446 (38.5)	0.025
2014-2019	588 (49.5)	1404 (45.9)	0.072	571 (49.2)	550 (47.4)	0.036

[a] Most recent measure within the year before eGFR declined to below 30 ml/min/1.73m^2
[b] Assessed during the one-year window before baseline
[c] Any time before baseline
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate

eMethods. Target Trial Emulation

As a sensitivity analysis, we used a target trial emulation technique allowing for the inclusion of the patients who died or developed ESKD during the six months after the eGFR decline to below 30 ml/min/1.73m^2. In this method, T_0 was considered the day after eGFR declined below 30 ml/min/1.73m^2. All eligible patients were duplicated and assigned to either the strategy of ACE-I/ARB continuation or discontinuation within 6 months. At each 30-day increment after T_0, patients were assessed for compliance with the assigned treatment strategy. Those who deviated from the assigned treatment strategy were censored. For example, if a patient assigned to the continuation arm was not on ACE-I/ARB therapy at day 60, he would be censored at that time. To account for the selection bias potentially introduced by censoring, we applied time-varying weighting by the inverse probability of remaining on the assigned treatment strategy (i.e., remaining uncensored). Weights were determined using a pooled logistic regression model restricted to the first six months of follow-up with discontinuation as the outcome. The model included all baseline covariates, month and its quadratic term, and time varying covariates including eGFR, serum potassium level, systolic blood pressure, history of stroke, diabetes, congestive heart failure, coronary artery disease, hospitalization status, the number of outpatient encounters, and whether a patient had a nephrology visit during the one year prior to the beginning of each monthly interval, and concurrent use of statin, antiplatelet agents, and beta-blockers. Weights were truncated at the 99.5th percentile. Then, we estimated the association of ACE-I/ARB discontinuation with death, MACE, and ESKD using pooled logistic regression. Outcome models included an indicator variable for the assigned treatment strategy, month of follow-up and its quadratic term, and all the baseline covariates. 95% CIs of the HRs were estimated using a nonparametric bootstrap with 500 samples.

eResults. Sensitivity Analyses

Using the Fine-Gray method accounting for the competing risk of death, ACE-I/ARB discontinuation was not significantly associated with increased risk of ESKD (sHR: 1.11 [95% CI: 0.81-1.53]). Using the target trial emulation method in which patients were not required to survive free of ESKD for six months after eGFR dropped below 30 ml/min/1.73m^2, we detected similar associations of ACE-I/ARB discontinuation with mortality (HR: 1.59 [95% CI: 1.43-1.79]), MACE (HR: 1.51 [95% CI: 1.36-1.69]), and ESKD (HR: 1.26 [95% CI: 0.99-1.65]), adjusted for baseline covariates.

Excluding patients with hypotension or hyperkalemia at the time of the eGFR decline yielded a subsample of 1028 and 2447 patients in the discontinuation and non-discontinuation group, respectively. In the propensity-score matched cohort of 2052 patients, we found substantively similar associations of ACE-I/ARB discontinuation with mortality (HR: 1.38 [95% CI: 1.18-1.61]), MACE (HR: 1.32 [95% CI: 1.14-1.52]), and ESKD (HR: 1.36 [95% CI: 0.94-1.98]).

In another sensitivity analysis limited only to patients who had been on ACE-I/ARB for at least six months at the time of the eGFR decline to below 30 ml/min/1.73m^2, we identified 992 and 2281 patients from the discontinuation and non-discontinuation group, respectively. Based on the propensity-score matched sample of 1940 patients, we found similar patterns as ACE-I/ARB discontinuation appeared to be associated with higher risks of mortality (HR: 1.30 [95% CI: 1.11-1.53]) and MACE (HR: 1.29 [95% CI: 1.11-1.51]), but not significantly different risk of ESKD (HR: 1.22 [95% CI: 0.82-1.80]).

Excluding people with apparent stage 2 acute kidney injury at the time of eGFR decline to below 30 ml/min/1.73m^2, we yielded 925 and 2343 patients from the discontinuation and non-discontinuation group, respectively. Based on the propensity-score matched sample of 1830 patients, we also found ACE-I/ARB discontinuation was associated with higher risks of mortality (HR: 1.34 [95% CI: 1.15-1.57]) and MACE (HR: 1.33 [95% CI: 1.15-1.55]), but not ESKD (HR: 1.04 [95% CI: 0.73-1.49]).

Excluding people with a history of cancer at the time of eGFR decline to below 30 ml/min/1.73m^2 yielded a sample of 930 and 2082 and individuals from the discontinuation and non-discontinuation group, respectively. Based on the propensity-score matched sample of 1802 patients, ACE-I/ARB discontinuation was associated with higher risks of mortality (HR: 1.49 [95% CI: 1.24-1.78]) and MACE (HR: 1.43 [95% CI: 1.21-1.69]) but not ESKD (HR: 1.40 [95% CI: 0.98-2.00]).

Among the 1217 individuals with an eGFR decline to below 20 ml/min/1.73m^2 while on ACE-I/ARB therapy, 572 discontinued ACE-I/ARB within six months of the eGFR decline and the remaining 645 did not. A total of 514 (90%) individuals in the discontinuation group were successfully matched to controls, resulting in a total of 1028 individuals in the propensity-score matched sample. Similarly, ACE-I/ARB discontinuation was associated with a higher risk of mortality (HR: 1.34 [95% CI: 1.10-1.64]), MACE (HR: 1.27 [95% CI: 1.05-1.53]), but not ESKD (HR: 1.27 [95% CI: 0.89-1.82]), adjusted for baseline covariates in the propensity-score matched sample.