Supplemental Materials

Supplemental Table 1. Specification and emulation of a target trial of rosuvastatin therapy (vs. atorvastatin therapy) and risk of hematuria and proteinuria using observational data

Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	Age≥18 years, between 2011 and 2019 No history of hematuria, proteinuria, rhabdomyolysis, or end-stage kidney disease No statin prescription within the past year At least 1 year of engagement with health system Baseline is defined as the initiation of treatment strategies	Same as for the target trial We used diagnostic codes and lab values (if available) to define hematuria, proteinuria, or rhabdomyolysis We used codes to define end-stage kidney disease We also required information on lab values and body mass index measured during the past year
Treatment strategies	(1) Initiation of rosuvastatin (2) Initiation of atorvastatin (active comparator) When clinically warranted during the follow-up, patients and providers decide whether to stop or switch therapy Baseline is defined as the statin initiation date (rosuvastatin or atorvastatin)	Same as for the target trial We defined the date statin initiation to be the first date of a prescription.
Treatment assignment	Individuals are randomly assigned to a strategy and will be aware of their assigned treatment group	We classified individuals according to the strategy that their data were compatible with at baseline and attempted to emulate randomization by inverse probability of treatment weighting
Outcome	Hematuria and proteinuria	Same as for the target trial
Follow-up	Starts at baseline and ends at the first occurrence of a study outcome, end-stage kidney disease, death, end of study follow-up (transfer out of the current health system or incomplete follow-up), whichever comes first	Same as for the target trial
Causal contrasts	Intention-to-treat effect	Observational analog of intention-to-treat effect
Statistical analysis	Intention-to-treat analyses Subgroup analyses by eGFR	Same as for the target trial

Supplemental Table 2. Codes for comorbidities, negative control outcome, and kidney failure with replacement therapy

Comorbidities	ICD-9 diagnostic codes	ICD-10 diagnostic codes	ICD-9 procedure codes	ICD-10 procedure codes	CPT	HCPCS
Hematuria[§]	599.7, 599.70, 599.71, 599.72	R31, R31.0, R31.1, R31.2, R31.21, R31.29, R31.9				
Proteinuria[§]	791.0	R80, R80.0, R80.1, R80.9, R80.8, R80.9				
Hypothyroidism	244	E02, E03, E89.0				
Diabetes	250	E10, E11, E13				
Hypertension	401-405	I10-I16				
Coronary artery disease	410, 411.8, 414, 36.1	I21-I25, 0210-0213				
Cerebrovascular disease	430-438, V12.54	I60-I69				
Heart failure	428	I50				
Urinary tract infection	595.0, 595.2, 595.89, 595.9, 599.0, 590.10, 590.11, 590.00, 590.01, 590.80	N30, N30.0, N30.00, N30.01, N30.2, N30.20, N30.21, N30.8, N30.80, N30.81, N30.9, N30.90, N30.91, N39.0, N10, N11.0, N11.1, N13.6				
Kidney failure with replacement therapy (KFRT)[¶]	585.5, 585.6, V42.0, V45.1*, V56*, 996.81	N18.5, N18.6, Z48.22, Z49*, Z91.15, Z94.0, Z99.2, T86.1*	39.95, 54.98, 55.69	0TY*, 5A1D*, 3E1M39Z	90920, 90921, 90924, 90925, 90935, 90937, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90989, 90993, 90997, 90999, 99512	G0257, G0317, G0317, G0318, G0319, G0323, G0327, S9339

[§]ICD codes were used only to exclude individuals from the study at baseline.
Underlined codes in KFRT are codes for kidney transplant.
[¶]KFRT is defined as kidney transplant with procedure codes or inpatient diagnosis codes, or chronic dialysis with ICD diagnosis code of stage V CKD or ESKD when there was a CPT, HCPSC and ICD codes of dialysis within 7 days later or CPT, HCPSC and ICD codes of dialysis when there were at least three dialysis codes lasted longer than a month and any two consecutive codes were within three months.
ICD, International Classification of Diseases; CPT, current procedural terminology; HCPCS, health system common procedure coding system

Supplemental Table 3. Inverse-probability-of-treatment weighted urine testing rates

Testing rates per 2-year, median (IQI)	Rosuvastatin group	Atorvastatin group
Hematuria, overall	0.6 (0, 2.0)	0.6 (0, 1.9)
≥60	0.6 (0, 1.9)	0.6 (0, 1.8)
30-59	0.8 (0, 2.2)	0.8 (0, 2.3)
<30	0.5 (0, 2.0)	0.5 (0, 2.1)
Proteinuria, overall	1.1 (0, 2.9)	1.1 (0, 2.8)
≥60	1.1 (0, 2.8)	1.1 (0, 2.7)
30-59	1.3 (0, 3.3)	1.3 (0, 3.3)
<30	1.0 (0, 3.1)	1.0 (0, 3.3)

IQI: interquartile interval

Supplemental Table 4. Comparison of patient characteristics between those included and excluded due to missing data

	Patients included	Patients excluded	SMD (%)
No. of cohorts	40	40	−
No. of participants	947,900	1,126,740	−
Age, mean (SD), years	60.1 (12.1)	62.1 (12.4)	-16.30
Women, No. (%)	451024 (47.6)	529085 (47.0)	1.25
Race/ethnicity, No. (%)			
Black	92323 (9.7)	113086 (10.0)	-0.99
Hispanic	37293 (3.9)	41914 (3.7)	1.12
White	767090 (80.9)	912205 (81.0)	-0.09
Other	51194 (5.4)	59535 (5.3)	0.52
Comorbidities, No. (%)			
Diabetes	279648 (29.5)	286419 (25.4)	9.17
Hypertension	636422 (67.1)	659999 (58.6)	17.76
Coronary artery disease	224396 (23.7)	349207 (31.0)	-16.42
Cerebrovascular disease	98602 (10.4)	150959 (13.4)	-9.22
Heart failure	59430 (6.3)	89764 (8.0)	-6.57
Hypothyroidism	147306 (15.5)	123324 (10.9)	13.68
Concomitant medications, No. (%)			
ACE inhibitors	211275 (22.3)	264634 (23.5)	-2.85
ARBs	100438 (10.6)	123801 (11.0)	-1.26
Aldosterone antagonists	13724 (1.4)	21119 (1.9)	-3.32
Other HTN meds	328160 (34.6)	450368 (40.0)	-11.07
SGLT2 inhibitors	7853 (0.8)	8190 (0.7)	1.16
DPP4 inhibitors	16193 (1.7)	21466 (1.9)	-1.47
GLP1RAs	8614 (0.9)	10116 (0.9)	0.12
Other oral DM meds	143350 (15.1)	150497 (13.4)	5.07
Insulin	42122 (4.4)	72946 (6.5)	-8.88
DOACs	13366 (1.4)	28111 (2.5)	-7.76
Warfarin	18362 (1.9)	31900 (2.8)	-5.82
Antiplatelets	57933 (6.1)	137016 (12.2)	-20.84
Cyclosporine	617 (0.1)	1860 (0.2)	-2.90
Itraconazole	180 (0.0)	77 (0.0)	1.09
Clarithromycin	540 (0.1)	921 (0.1)	-0.93
Protease inhibitors	399 (0.0)	436 (0.0)	0.17
Fibrates	24479 (2.6)	31637 (2.8)	-1.39
Niacin	4663 (0.5)	8775 (0.8)	-3.58
PCSK9 inhibitors	159 (0.0)	251 (0.0)	-0.39
Ezetimibe	11101 (1.2)	16406 (1.5)	-2.49

Supplemental Table 5. Results in the users of rosuvastatin or atorvastatin with at least two prescriptions

	Unweighted no. of events/N		IPTW-IR (95% CI), per 1000 PYs		IPTW-IRD (95% CI), per 1000 PYs	IPTW-HR (95% CI)
	Rosuvastatin	Atorvastatin	Rosuvastatin	Atorvastatin		
Hematuria	4902/144470	19024/685551	9.2 (8.9, 9.5)	8.5 (8.4, 8.7)	0.68 (0.36, 1.0)	1.08 (1.04, 1.12)
Proteinuria	1638/144470	6254/685551	3.1 (3.0, 3.3)	2.7 (2.7, 2.8)	0.39 (0.20, 0.58)	1.15 (1.08, 1.22)

Abbreviations: IPTW, inverse-probability of treatment weight; IR, incidence rate; PYs, person-years; HR, hazard ratio; CI, confidence interval; IRD, incidence rate difference

Supplemental Table 6. As treated analysis: comparing rosuvastatin use vs. atorvastatin use, overall and across eGFR levels

	Unweighted no. of events/N		IPTW-IR (95% CI), per 1000 PYs		IPTW-IRD (95% CI), per 1000 PYs	P-for heterogeneity*	IPTW-HR (95% CI)	P-for heterogeneity*
	Rosuvastatin	Atorvastatin	Rosuvastatin	Atorvastatin				
Hematuria								
Overall	3726/152101	17779/795799	9.6 (9.2, 9.9)	8.9 (8.8, 9.1)	0.63 (0.25, 1.02)		1.07 (1.03, 1.11)	
eGFR						0.32		0.26
≥60	2970/130506	14229/687461	8.8 (8.4, 9.1)	8.2 (8.1, 8.4)	0.52 (0.12, 0.92)		1.06 (1.01, 1.11)	
30-59	705/20427	3324/102392	14.1 (13.0, 15.4)	13.1 (12.6, 13.5)	1.08 (-0.20, 2.35)		1.08 (0.98, 1.18)	
<30	51/1168	226/5946	25.6 (18.6, 36.0)	19.4 (17.0, 22.2)	6.16 (-2.50, 14.8)		1.30 (0.92, 1.83)	
Proteinuria								
Overall	1234/152101	5794/795799	3.3 (3.1, 3.5)	2.8 (2.8, 2.9)	0.41 (0.18, 0.64)		1.15 (1.07, 1.23)	
eGFR						0.04		0.16
≥60	789/130506	3783/687461	2.4 (2.2, 2.6)	2.1 (2.1, 2.2)	0.22 (0.0047, 0.43)		1.10 (1.01, 1.21)	
30-59	394/20427	1758/102392	8.3 (7.4, 9.3)	6.8 (6.4, 7.1)	1.5 (0.50, 2.5)		1.23 (1.09, 1.39)	
<30	51/1168	253/5946	25.5 (18.4, 36.4)	21.7 (19.1, 24.6)	3.9 (-5.1, 12.8)		1.18 (0.83, 1.68)	

IPTW-HRs were from stratified Cox proportional hazards regression models by cohort

*P-for heterogeneity in IRD across eGFR subgroups was estimated using fixed effects meta-analysis and P-for heterogeneity in HR was estimated using stratified

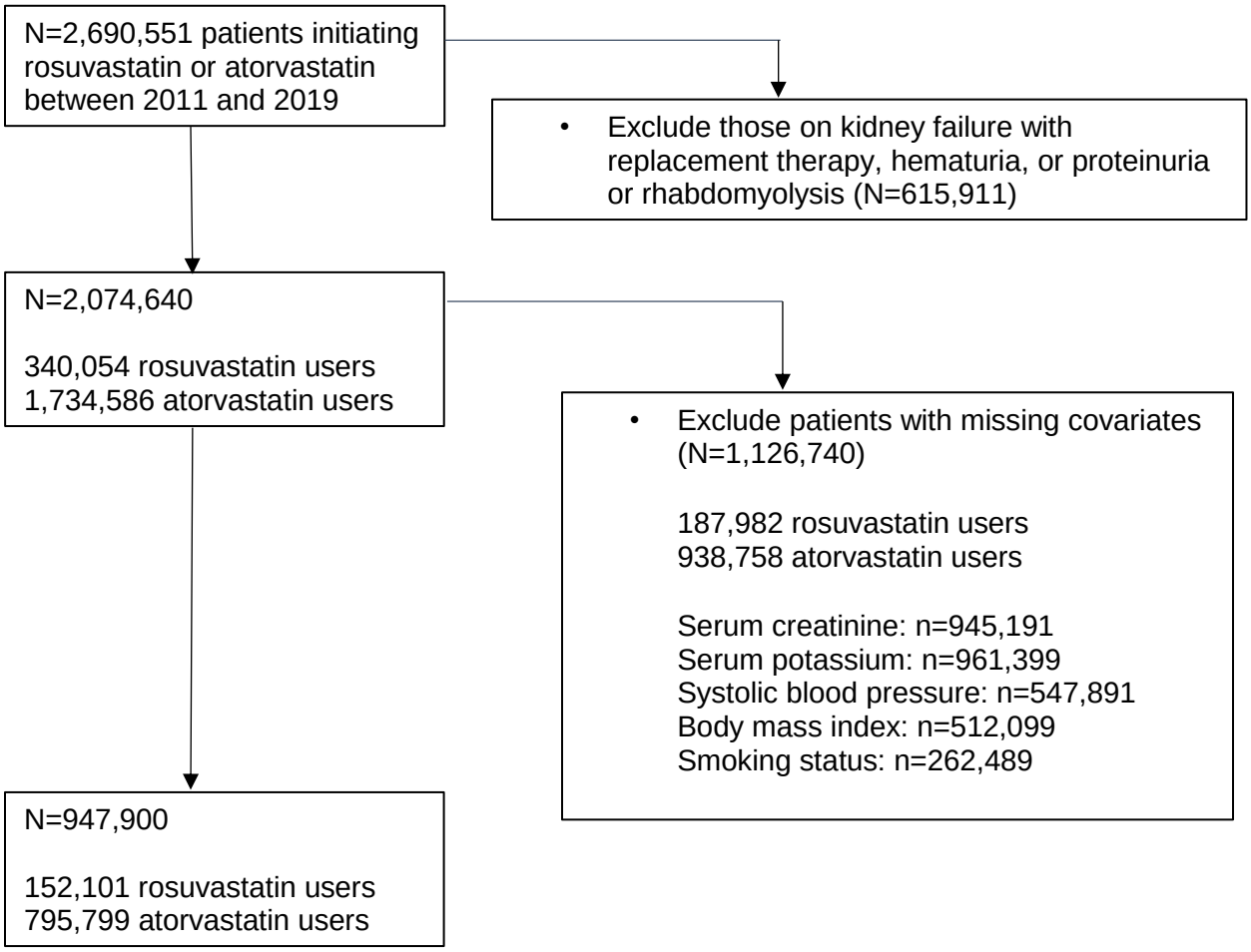
Cox models with interaction term between rosuvastatin use and eGFR category.

Abbreviations: eGFR, estimated glomerular filtration rate; IPTW, inverse-probability of treatment weight; IR, incidence rate; PYs, person-years; HR, hazard ratio; CI, confidence interval; IRD, incidence rate difference

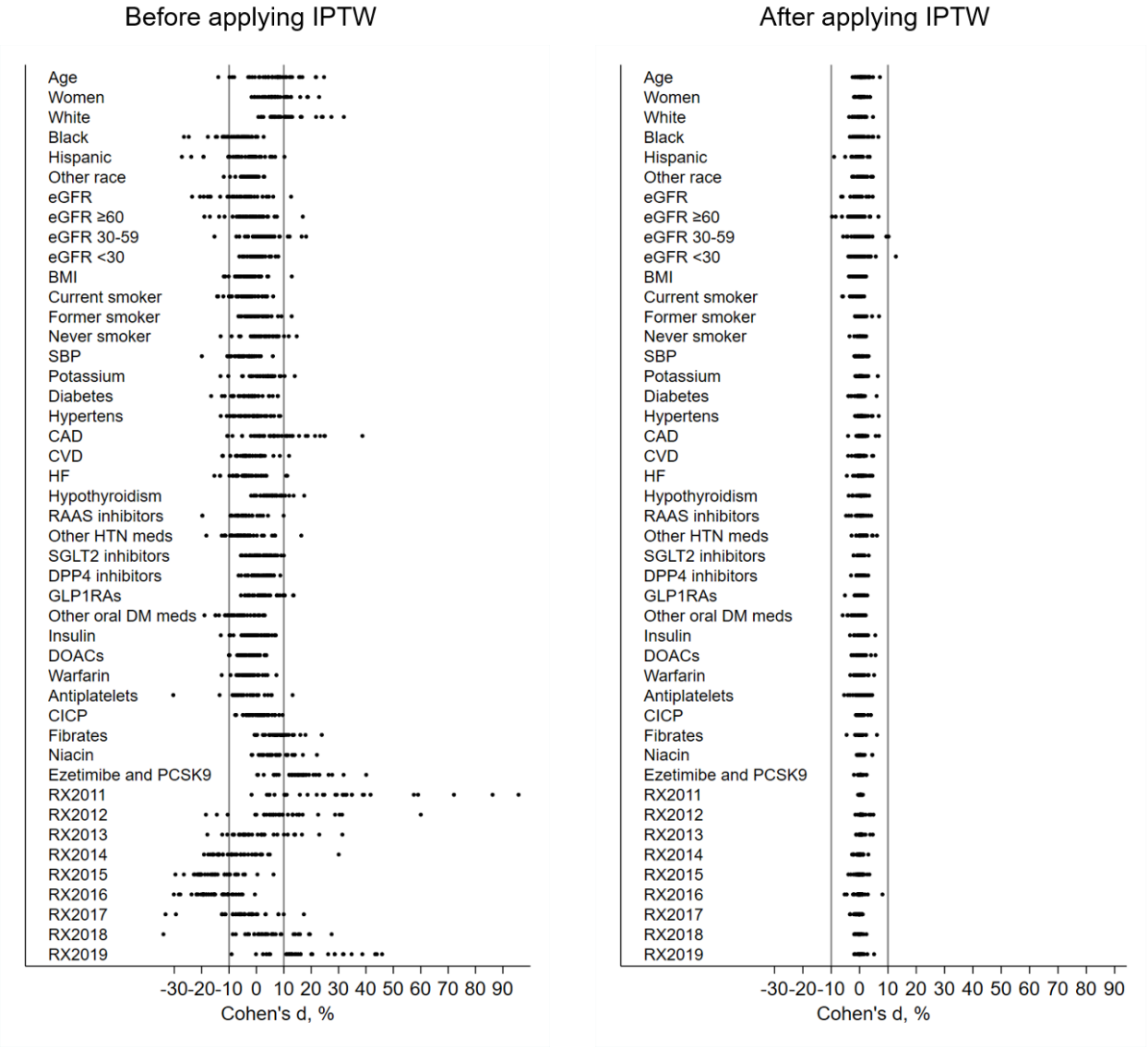
Supplemental Table 7. Risks of atherosclerotic cardiovascular disease associated with rosuvastatin versus atorvastatin across eGFR levels

	Unweighted no. of events/N		IPTW-IR (95% CI), per 1000 PYs		IPTW-HR (95% CI), rosuvastatin vs. atorvastatin	p for heterogeneity
	Rosuvastatin	Atorvastatin	Rosuvastatin	Atorvastatin		
Overall	2,151/105,508	12,100/56,1957	6.0 (5.6, 6.3)	5.9 (5.8, 6.0)	1.02 (0.96, 1.08)	
eGFR, ml/min/1.73 m^2						0.24
≥60	16,986/94,936	9,534/508,977	5.3 (5.0, 5.7)	5.1 (5.0, 5.2)	1.05 (0.98, 1.12)	
30-59	418/10,155	2,346/50,997	11.2 (10.0, 12.6)	12.9 (12.4, 13.5)	0.87 (0.77, 0.99)	
<30	37/417	220/1,983	30.3 (21.5, 44.0)	36.6 (32.0, 42.1)	0.83 (0.57, 1.22)	

Supplemental Figure 1. Derivation of study population in 40 health care organizations (cohorts) in Optum Labs Data Warehouse



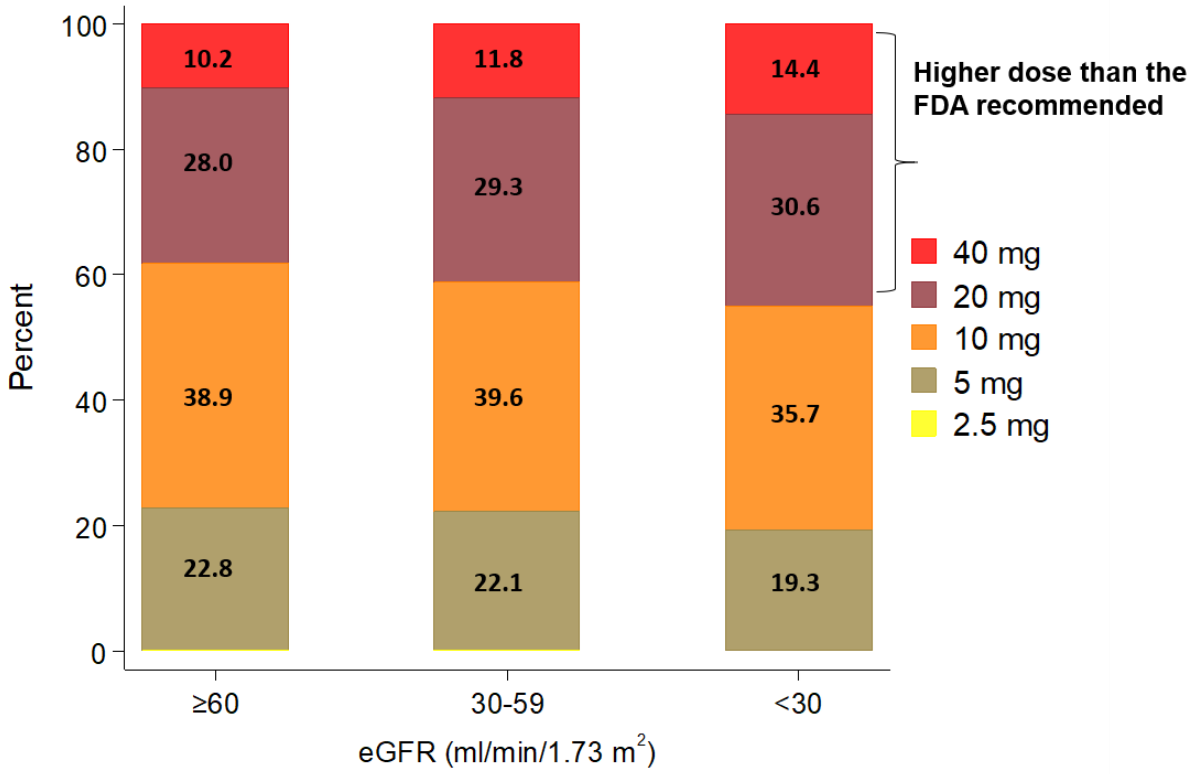
Supplemental Figure 2. Standardized mean differences (SMD) (%) across covariates in all individual cohorts



Each dot indicates an individual cohort.

Abbreviations: IPTW, inverse-probability of treatment weight; eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; Hypertens, hypertension; CAD, coronary artery disease; CVD, cerebrovascular disease; HF, heart failure; RAAS inhibitors, renin-angiotensin-aldosterone system inhibitors (i.e., angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or aldosterone antagonists); HTN, hypertension; meds, medications; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitor; GLP1RAs, glucagon-like peptide-1 receptor agonists; DOACs, direct oral anticoagulants; CICP, cyclosporine, itraconazole, clarithromycin, and protease inhibitors; RX, baseline year (medication initiation year)

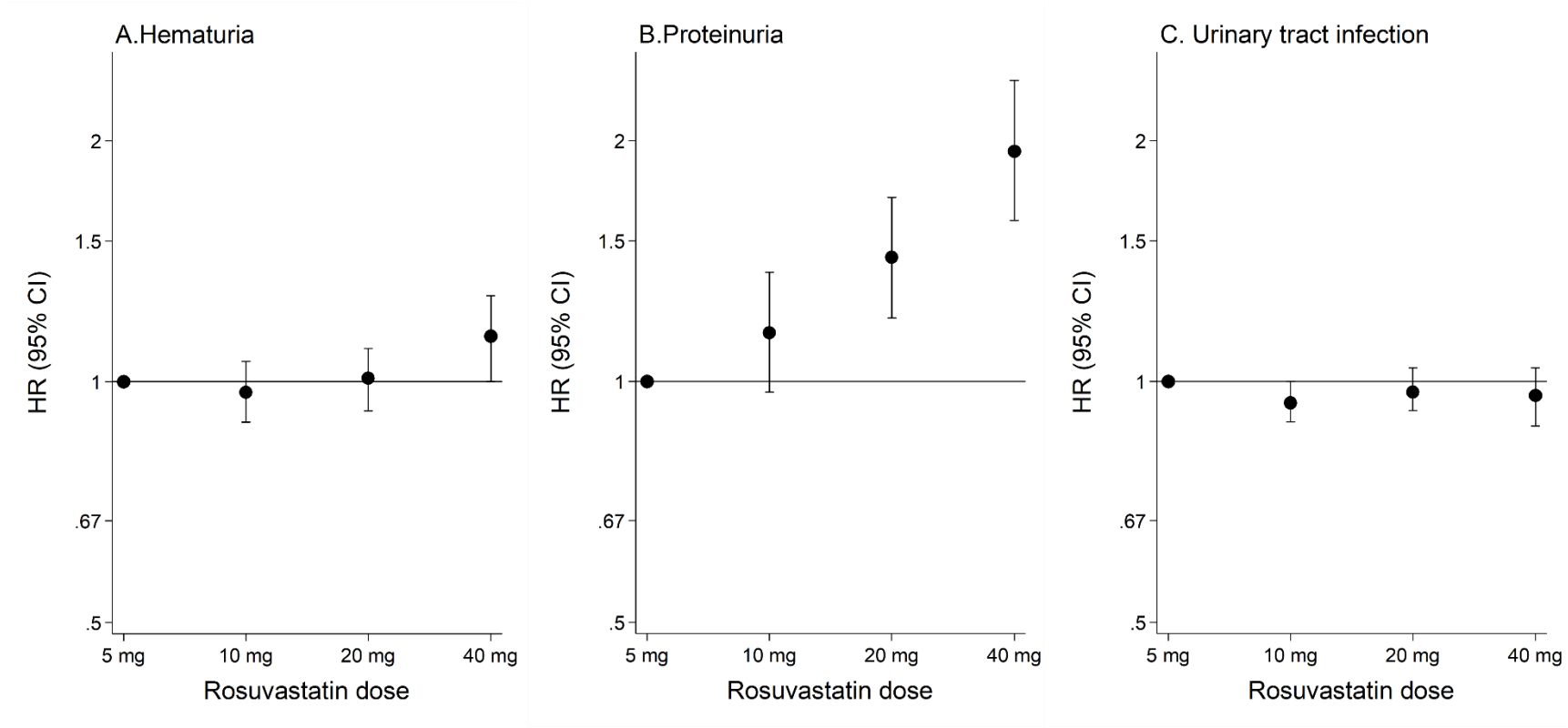
Supplemental Figure 3. Prescribed rosuvastatin dose by eGFR category after excluding individuals with recent heart failure or myocardial infarction or very high cholesterol value



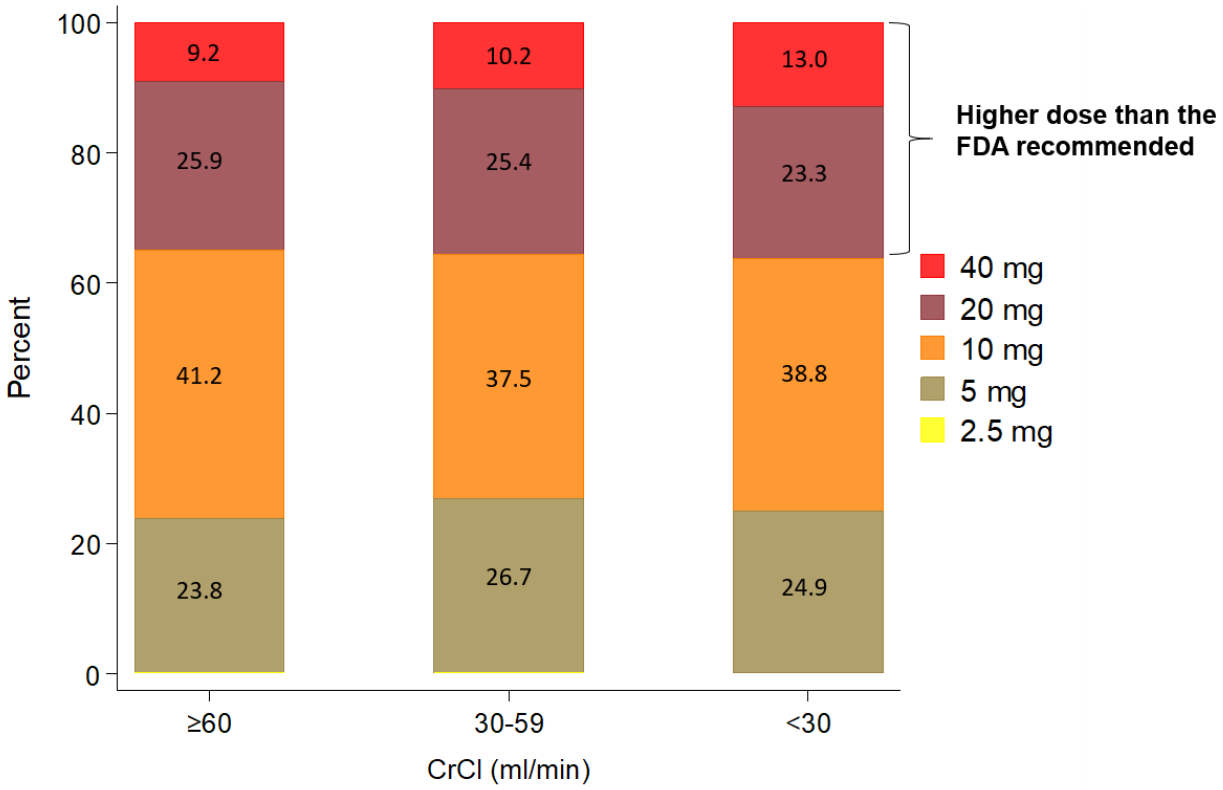
eGFR ≥60 ml/min/1.73 m^2, N=115,105; eGFR 30-59 ml/min/1.73 m^2, N=19,199, eGFR <30 ml/min/1.73 m^2, N=1,071

Abbreviations: eGFR, estimated glomerular filtration rate, FDA, the United States Food and Drug Administration

Supplemental Figure 4. Risks of outcomes comparing different doses of rosuvastatin among rosuvastatin users after excluding individuals with recent heart failure or myocardial infarction or very high cholesterol value



Supplemental Figure 5. Prescribed rosuvastatin dose by creatinine clearance category



CrCl ≥60 ml/min, N= 100,415; CrCl 30-59 ml/min, N=11,938, CrCl <30 ml/min, N=810

Abbreviations: CrCl, creatinine clearance, FDA, the United States Food and Drug Administration