Supplementary Online Content

Roumie CL, Chipman J, Min JY, et al. Association of treatment with metformin vs sulfonylurea with major adverse cardiovascular events among patients with diabetes and reduced kidney function. *JAMA*. doi:10.1001/jama.2019.13206

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

eTable 1: Definitions of comorbid conditions based on codes in 720 days before reaching kidney threshold; Definitions of medications used are restricted to prescription fill in the 180 days before reaching kidney threshold

Covariate Condition	Inclusive conditions	Definition*
Malignancy	Cancer excluding non melanoma skin cancer	ICD 9- CM diagnosis codes:140.X-208.X (exclude 173) ICD10 diagnosis codes: C00* - C96*; D37* -D48*
Liver failure	End stage liver disease	ICD 9- CM diagnosis codes: 570.X- 573.X ICD10 diagnosis codes: K72*; K70.*; K73.*; K74.*; K76.*
Respiratory Failure	Respiratory failure/ Pulmonary Embolism/Hypertension	ICD 9- CM diagnosis codes: 518.81, 518.83, 518.84, 799.1, 415.X, 416.X ICD10 diagnosis codes: J96.*; R092; I26.9*; I27.*
Congestive Heart Failure	CHF (excluding post procedure-CHF)	ICD 9- CM diagnosis codes: 428.X, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 ICD10 diagnosis codes: I11.0, I13.0, I13.2, I50.9, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43
Cardiovascular disease	1. MI	ICD 9- CM diagnosis codes: 410.X, 412.X, 429.7X ICD10 diagnosis codes: I21*
	2. Obstructive coronary disease	ICD 9- CM diagnosis codes: 411.X, 413.X, 414.X ICD10 diagnosis codes: I24.*; I25.*; I20.* ICD9-CM procedure codes: 36.01, 36.02, 36.03, 36.05, 36.09, 36.10-36.19 CPT procedure codes: 33533-36, 33510-23, 33530, 92980-82,92984, 92995-6, 92974
	3. Peripheral artery disease or revascularization	ICD 9- CM diagnosis codes: 440.2X, 442.2, 443.1, 443.9, 445.0X ICD10 diagnosis codes: I70.2*; I72.*; I77.*; I73.9; I75.* ICD9-CM procedure codes:38.08-09, 38.18, 38.38, 38.39, 38.48, 38.49, 38.88, 38.89, 39.25, 39.29, 39.5, 84.1X CPT procedure codes: 35226,35256, 35286, 35351, 35355, 35371, 35372, 35381, 35454, 35456, 35459, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35646, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 34800, 34802-5
	4. Carotid revascularization	ICD9-CM procedure codes: 38.12, 38.11, 00.61, 00.63, 39.28 CPT procedure codes: 35301, 0005T, 0006T, 0007T, 0075T, 0076T, 37215, 37216 ICD10 procedure code: 031H0AG, 031H0JG, 031H0KG, 031H0ZG, 031J09G, 031J0AG, 031J0JG, 031J0KG,031H09G, 031J0ZG, 037H34Z, 037H3DZ, 037H3ZZ, 037H44Z, 037H4DZ, 037H4ZZ, 037J3DZ, 037J3ZZ, 037J44Z, 037J4DZ, 037J4ZZ, 037K34Z, 037K3DZ, 037K3ZZ, 037K4DZ, 037K4ZZ, 037L34Z, 037L3DZ, 037L3ZZ, 037L44Z, 037L4DZ, 037L4ZZ, 037M34Z, 037M3DZ, 037M3ZZ, 037M44Z, 037M4DZ, 037M4ZZ, 037N34Z, 037N3DZ, 037N3ZZ, 037N44Z, 037N4DZ, 037N4ZZ, 037P34Z, 037P3DZ, 037P3ZZ, 037P44Z, 037P4DZ, 037P4ZZ, 037Q34Z, 037Q3DZ, 037Q3ZZ, 037Q44Z, 037Q4DZ, 037Q4ZZ, 03CH0ZZ, 03CH3ZZ, 03CH4ZZ, 03CJ0ZZ, 03CJ3ZZ, 03CJ4ZZ, 03CK0ZZ, 03CK3ZZ, 03CK4ZZ, 03CL0ZZ, 03CL3ZZ, 03CL4ZZ, 03CM0ZZ, 03CM3ZZ, 03CM4ZZ, 037J34Z, 03CN0ZZ, 03CN3ZZ, 03CN4ZZ, 03CP0ZZ, 03CP3ZZ, 037K44Z, 03CP4ZZ, 03CQ0ZZ, 03CQ3ZZ, 03CQ4ZZ HCPCS procedure code: S2211
TIA		ICD 9- CM diagnosis codes: 435.X ICD10 diagnosis codes: G45.0; G45.1;G45.8; G45.9;I67.848

Covariate Condition	Inclusive conditions	Definition*
Stroke		ICD 9- CM diagnosis codes: 430.X, 431.X. 434.X, 436.X
		ICD10 diagnosis codes: I67.89, I60.9, I61.9, I63.30, I63.40 , I63.50, I66.09, I66.19, I66.29, I66.9, I67.89
Serious Mental illness	1. Dementia	ICD 9- CM diagnosis codes: 290.X, 291.2, 292.82, 294.1X, 331.0-331.1X, 331.82
		ICD 10 diagnosis codes: F03.9;F01.5*; F10.27; F19.97; F02.80; F02.81; G30.9; G31.*
		Medications: Donepezil, Rivastigmine, Galantamine, Tacrine, Memantine Bethanechol, Ambenonium, Atomoxetine, Ergoloid Mesylates, Dihydrogenated Ergot, Neostigmine, Physostigmine, Pyridostigmine, Riluzole, Hydergine
	2. Depression,	ICD 9- CM diagnosis codes: 311, 300.4, 296.2, 296.3, V79.0
		ICD 10 diagnosis codes: F33.9, F34.1, F32.*
	3. Schizophrenia,	ICD 9- CM diagnosis codes: 295.X
		ICD 10 diagnosis codes: F20.*
	4. Bipolar disorder	ICD 9- CM diagnosis codes: 296.0, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89
		ICD 10 diagnosis codes: F30.* F31.*
	5. Post traumatic stress disorder	ICD 9- CM diagnosis codes: 309.81
		ICD 10 diagnosis codes: F43.10; F43.12
Cardiac valve disease		ICD 9- CM diagnosis codes: 394.X, 395.X, 396.X, 424.0, 424.1
		ICD 10 diagnosis codes: I05.*; I06.*; I08.*; I34.*; I35.*;
Arrhythmia	Atrial fibrillation/flutter	ICD 9- CM diagnosis codes: 427.3X
		ICD 10 diagnosis codes: I48.91, I48.92
Smoking		ICD 9- CM diagnosis codes:305.1, V15.82, 989.84
		ICD 10 diagnosis codes: F17.200, Z87.891, T65.211A, T65.212A, T65.213A, T65.214A, T65.221A, T65.222A, T65.223A, T65.224A, T65.292A, T65.293A, T65.294A
		Medications: Varenicline tartrate, Nicotine Replacement (gum, patch, lozenge)
COPD/ Asthma		ICD 9- CM diagnosis codes:491.X, 492.X, 493.X, 496.X, V17.5, V81.3
		ICD 10 diagnosis codes: J41.0, J41.1, J44.9, J44.1, J44.0, J41.8, J42-J43.9, J45.20, J45.22, J45.21, J45.990,J45.991, J45.909, J45.998, J45.902, J45.901, Z13.83
HIV		ICD 9- CM diagnosis codes: 042, 079.53, 795.71, V08
		ICD 10 diagnosis codes: B20.*; B97.35; Z21
Parkinson's Disease		ICD 9- CM diagnosis codes: 332
		ICD 10 diagnosis codes: G20; G21.*
		Medications: Apokyn, Apomorphine, Carbidopa/levodopa, Entacapone, Pergolide, Pramipexole, Ropinirole, Rotigotine, Selegiline, Tolcapone, Zelapar, Azilect/Rasagiline, Emsam, Isocarboxazid, Phenelzine, Tranylcypromine, Biperiden/Akineton, Comtan/Entacapone, Safinamide, Trihexyphenidyl
Urinary Tract / Kidney Infection		ICD 9- CM diagnosis codes: 590.*, 599.0*, 595.0
		ICD 10 diagnosis codes: N11.*; N39.* N30.*
Osteomyelitis		ICD 9- CM diagnosis codes: 730.*
		ICD 10 diagnosis codes: M86.1*; M86.2*; M86.6*; M86.9*; A02.24
Sepsis/Bacteremia		ICD 9- CM diagnosis codes: 995.91, 995.92, 038.*, 036.2, 790.7
		ICD 10 diagnosis codes: A41.9; R65.20; A41.*; A39.4; R78.81
Pneumonia		ICD 9- CM diagnosis codes: 480.*-486.*, 487.0
		ICD 10 diagnosis codes: J11.*; J12.*; J13.*; J14.*; J15.*;J16.*; J17.*; J18.*

Covariate Condition	Inclusive conditions	Definition*
Fractures (any)		ICD 9- CM diagnosis codes: 733.1*, 800.*-829.*, E887 ICD 10 diagnosis codes: M84.*; M80.*; S02; *; S12.*; S22.*; S32.*; S42.*; S52.*; S62.*; S72.*; S82.*; S92.*
Falls		ICD 9- CM diagnosis codes: E880.*, E881.*, E884.*, E885.9 ICD 10 diagnosis codes: Z98.8, W18.30XA,W18.49XA,W01.110A,W01.198A,W19.XXXA
Osteoporosis		ICD 9- CM diagnosis codes: 733.0* ICD 10 diagnosis codes: M81.*
Retinopathy		ICD 9- CM diagnosis codes: 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07 ICD 10 diagnosis codes: E08.311; E08.319; E08.3211; E08.3212; E08.3291; E08.3292; E08.3293; E08.3299; E08.3219; E08.3213; E08.3313; E08.3312; E08.3311; E08.3319; E08.3391; E08.3392; E08.3393; E08.3399; E08.3411; E08.3412; E08.3413; E08.3419; E08.3491; E08.3492; E08.3493; E08.3499; E08.3511; E08.3512; E08.3513; E08.3519; E08.3521; E08.3522; E08.3523; E08.3529; E08.3531; E08.3532; E08.3533; E08.3539; E08.3541; E08.3542; E08.3543; E08.3549; E08.3551; E08.3552; E08.3553; E08.3559; E08.3591; E08.3592; E08.3593; E08.3599; E11.311; E11.3491; E11.3492; E11.3493; E11.3499; E11.3591 ; E11.3592; E11.3593 ; E11.3599 ; E11.3591; E11.3592; E11.3593; E11.3599; E11.3291; E11.3292; E11.3293; E11.3299; E11.3391; E11.3392; E11.3393; E11.3399; E11.3491; E11.3492; E11.3493; E11.3499; E11.319
Amputations		ICD 9- CM diagnosis codes: V49.75; V49.76; V49.77 ICD 10 diagnosis codes: Z89.519; Z47.81; Z89.6*
Medications Antipsychotics	Atypical and typical antipsychotic medications	Lithium, Clozapine, Haloperidol, Loxapine, Lurasidone, Molindone, Olanzapine, Paliperidone, Quetiapine Fumerate; Risperidone, Aripiprazole, Asenapine, Ziprasidone, Chlorpromazine, Fluphenazine, Fluphenazine Deconate, Mesoridazine, Perphenazine, Thioridazine, Thiothixene; Trifluoperazine; Triflupromazine, Asenapine, Chlorprothixene, Iloperidone, Molindone, Promazine, Piperacetazine, Methotrimeprazine, Acetophenazine, Fazaclo/clozapine, Molindone
ACE Inhibitors alone/combination		Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril
ARBs alone/combination		Candesartan, Eprosartan, Irbesartan, Losartan, Azilsartan, Olmesartan, Telmisartan, Valsartan
Beta-blockers		Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol Tartrate, Metoprolol Succinate, Propranolol, Penbutolol, Pindolol, Nadolol, Sotalol, Timolol, Nebivolol
Calcium Channel Blockers		Amlodipine, Isradipine; Felodipine, Nifedipine, Nifedipine ER, Nicardipine; Diltiazem, Verapamil, Nimodipine; Nisoldipine; Bepridil, Amlodipine/Atorvastatin, Clevidipine Butyrate; Mibefradil
Thiazide diuretics/ Potassium sparing diuretics		Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Methyclothiazide, Trichlormethiazide, Metolazone, Indapamide, Eplerenone; Amiloride, Spironolactone, Triamterene, Hydrochlorothiazide/Triamterene, Hydrochlorothiazide/Spironolactone, Bendroflumethiazide, Benzthiazide, Cyclothiazide, Hydroflumethiazide, Polythiazide, Quinethazone

Covariate Condition	Inclusive conditions	Definition*
Other Antihypertensives		Doxazosin, Prazosin, Terazosin, Clonidine, Guanabenz, Guanfacine, Hydralazine, Methyldopa, Metyrosine, Reserpine, Minoxidil, Alfuzosin, Silodosin, Alseroxylon, Cryptenamine, Deserpidine, Diazoxide, Guanethidine, Mecamylamine, Pargyline, Rescinnamine, Trimethaphan Camsylate
Anti-arrhythmics Digoxin and other inotropes	1. Digoxin	Digoxin, Digitalis
	2. Anti- Arrythmics	Adenosine, Amiodarone, Lidocaine, Flecainide, Ibutilide, , Procainamide, Propafenone, Ropafenone, Quinidine, Disopyramide, Verapamil, Dofetilide, Mexiletine, Moricizine, Tocainide
Anticoagulants		Warfarin, Argatroban, Bivalirudin, Dalteparin, Enoxaprin, Eptifibatide, Fondaparinux, Heparin, Lepirudin, Tirofiban, Tinzaparin, Reviparin, Nadroparin, Ardeparin, Certoparin, Dabigatran
Platelet inhibitors, not aspirin		Clopidogrel, Ticlopidine, Aspirin/Dipyridamole, Dipyridamole alone, Abciximab, Factor IX, Factor VIIa, Factor VIII, Prasugrel, Ticagrelor
Statins		Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Rosuvastatin, Cerivastatin Pitavastatin, Lovastatin ER, Ezetimibe/Simvastatin, Lovastatin/Niacin, Amlodipine/Atorvastatin
Non-Statin lipid lowering drugs		Cholestyramine, Colesevelam, Clofibrate, Colestipol, Niacin, Niacinamide, Fish Oil Concentrate, Omega 3 Fatty Acids, Gemfibrozil, Fenofibrate, Fenofibric Acid, Ezetimibe Omacor, Tricor/Fenofibrate, Ezetimibe/Simvastatin
Nitrates		Amyl Nitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Erythrityl Tetranitrate, Nitroglycerin (all forms--SA, Patch, SL, Ointment; Aerosol spray), Ranolazine
Aspirin		Aspirin, Aspirin/ Dipyridamole
Loop Diuretics		Furosemide, Ethacrynic acid, Bumetanide, Torsemide

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; COPD = chronic obstructive pulmonary disease; CPT = Current Procedural Terminology; ICD-9- CM = International Classification of Diseases, Ninth Revision; ICD 10= International Classification of Diseases, Tenth Revision; MI = myocardial infarction; TIA = transient ischemic attack.

If medications are combinations of 2 drug classes then a patient is recorded as using both medications.

a Each co-morbid condition was defined as present if there was 1 specified inpatient or 2 specified outpatient codes separated by 30 days, or 1 specified procedure code or prescription for a medication defining that comorbid condition before reaching the creatinine threshold. Medications were searched in the pharmacy data using both generic and trade names.

eTable 2: Propensity Score and matching weights

The cohort was composed of all eligible persons who reached the kidney threshold and were using metformin or sulfonylurea for diabetes treatment. The weighted cohort was formed using matching weights, derived using propensity scores, and up or downweighting patients to more closely resemble each other. Table 1 in the paper lists baseline covariates included. For simplicity, Table 1 presents year of reaching kidney threshold, whereas date of reaching kidney threshold is treated as a continuous covariate in the model. Missing covariate values were multiply imputed and indicators for each variable's missingness was included to account for potential informative missingness. The propensity scores used to create the matching weights were obtained using the last imputed data set and a regression model whose coefficients are found by averaging the coefficient estimates of all the imputed data sets. The PS model is displayed below.

The weighted analysis balances the covariate distributions by assigning various weights to the patients in both exposure groups such that the weighted groups resemble each other group (average treatment effect in evenly matchable units [ATM]). When comparing metformin and sulfonylurea users, both the metformin and sulfonylurea users were weighted so that their distribution of covariates resembled each other and at least a small amount of data is used from each subject. An important condition for weighting and propensity score methods is that every cohort member have a nontrivial probability of having received either of the study therapies. Our weighting procedure down-weighted metformin patients for whom very few similar sulfonylurea users existed (**eFigure 2**). When used to facilitate a weighted cohort, the success of the model is determined by the ability to include all patients and the achievement of covariate balance in the weighted cohort. **eFigure 3** in the appendix demonstrates the standardized mean difference (SMD) before and after weighting. **Table 1** in the paper demonstrates that all SMD after weighting have an absolute value < 0.1. Matching weights yield approximately equal weighted sample sizes and a pseudo-matched cohort. Summaries of the matching weights, by group demonstrate that among sulfonylurea users the median weight is 1.0, mean weight is 0.855 and 90th percentile is 1.0. Among metformin users the median weight is 0.25, mean weight is 0.36 and 90th percentile is 0.952.

Note **eFigure 4** give the deviance for propensity score model as a measure of model fit.

	Chi-Square	d.f.
Demographics		
Age	448.6284	2
Gender	80.0880	1
Race	230.5030	2
Months from hypoglycemic start until kidney threshold	37.0795	2
Date reached kidney threshold	6711.5784	2
VISN of Care	411.6695	20
Clinical and Laboratory Variables		
BMI	34.8939	2
Systolic Blood Pressure mm/Hg	109.3335	2
Diastolic Blood Pressure mm/Hg	61.4275	2
Hemoglobin	192.4439	2
GFR	11.2857	2
GFR Historical	142.3088	2
Creatinine	4.4570	2
LDL_Cholesterol	38.3697	2
A1c	698.9043	2
urine_protein	41.2867	4
MACR	13.4030	3
Healthcare Utilization		
VA hospitalizations last year	3.2121	1
VA hospitalizations last 30 days	0.1011	1

	Chi-Square	d.f.
Medicare/ Medicaid hospitalizations last year	0.1741	1
Medicare/ Medicaid hospitalizations last 30 days	0.2730	1
Medicaid use	3.0689	1
Medicare Use	2.2603	1
Nursing Home Use	3.6494	1
Number of Outpatient visits	6.6576	2
Number of Outpatient medications	1.8145	2
Medicare Advantage	0.1585	1
Comorbidities		
Malignancy	7.5313	1
Liver_disease	179.3501	1
HIV	4.5331	1
CHF	126.6574	1
CVD	14.4706	1
Stroke	1.2396	1
TIA	0.1974	1
Serious_Mental_Illness	8.8581	1
Smoking	0.2823	1
Chronic Obstructive Pulmonary Disease	0.5353	1
Respiratory failure	0.8799	1
History of past Kidney disease	7.2666	1
Sepsis	3.1831	1
Pneumonia	8.8373	1
Arrhythmias	0.0161	1
Cardiac valve	0.0239	1
Parkinson	4.6249	1
Urinary Tract Infection	8.4451	1
Osteomyelitis	4.8452	1
Osteoporosis	0.0048	1
Falls	0.6541	1
Fractures	10.8701	1
Amputation	7.6348	1
Retinopathy	23.8684	1
Medications		
ACE	2.0984	1
ARB	5.9352	1
Beta Blocker	1.4165	1
Calcium Channel Blocker	0.2617	1
Thiazide diuretics	17.4713	1
Loop diuretics	117.4840	1
Other Antihypertensives	0.1820	1
Statins	248.2555	1
Non Statin lipid lowering medications	35.4201	1
Antiarrythmics	12.1575	1
Anticoagulants	0.4459	1
Nitrates	22.4636	1
Aspirin	0.1485	1

	Chi-Square	d.f.
Platelet Inhibitors Non aspirin	8.6273	1
Antipsychotics	2.7354	1
Oral Glucocorticoids	9.9919	1
Indicators of Missing Clinical Variables		
BMI_Missing	13.7566	1
Blood_Pressure_Missing	0.1771	1
hemoglobin_Missing	26.8750	1
GFR Historical	34.4951	1
LDL_Cholesterol_Missing	1.2188	1
A1c_Missing	48.1251	1

eTable 3: Subgroup analysis

	Metformin	Sulfonylurea	*P value for Interaction*
No Cardiovascular disease (N in weighted cohort)	16882	16931	
Composite Major Adverse Cardiovascular Events	537	723	
Person-Years	32164	33216	
Unadjusted Rate/1000 person-years (95% CI)	16.7 (15.4, 18.2)	21.8 (20.3, 23.4)	
Adjusted Hazard Ratio [a] (95% CI)	0.78 (0.70, 0.86)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-4.8 (-3.3, -6.1)		*p = 0.34*
Cardiovascular Disease (N in weighted cohort)	7797	7868	
Composite Major Adverse Cardiovascular Events	511	671	
Person-Years	13377	14547	
Unadjusted Rate/1000 person-years (95% CI)	38.2 (35.1, 41.6)	46.1 (42.8, 49.6)	
Adjusted Hazard Ratio [a] (95% CI)	0.83 (0.75, 0.92)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-7.9 (-4.0, -10.7)		
Age younger than 65 years (N in weighted cohort	7883	8034	
Composite Major Adverse Cardiovascular Events	178	258	
Person-Years	12791	13642	
Unadjusted Rate/1000 person-years (95% CI)	13.9 (12.0, 16.1)	18.9 (16.7, 21.3)	
Adjusted Hazard Ratio [a] (95% CI)	0.78 (0.66, 0.92)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-4.2 (-1.7, -5.7)		*p = 0.53*
Age 65 years and older (N in weighted cohort)	16796	16764	
Composite Major Adverse Cardiovascular Events	870	1136	
Person-Years	32751	34120	
Unadjusted Rate/1000 person-years (95% CI)	26.6 (24.9, 28.4)	33.3 (31.4, 35.3)	
Adjusted Hazard Ratio [a] (95% CI)	0.81 (0.75, 0.88)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-6.3 (-4.2, -7.9)		
Non-Black race (N in weighted cohort)	20644	20752	
Composite Major Adverse Cardiovascular Events	941	1240	
Person-Years	40274	41107	
Unadjusted Rate/1000 person-years (95% CI)	23.4 (21.9, 24.9)	30.2 (28.6, 31.9)	
Adjusted Hazard Ratio [a] (95% CI)	0.80 (0.74, 0.86)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-6.0 (-4.5, -7.4)		*p = 0.69*
Black race (N in weighted cohort)	4035	4047	
Composite Major Adverse Cardiovascular Events	107	154	
Person-Years	5268	6656	
Unadjusted Rate/1000 person-years (95% CI)	20.4 (16.9, 24.6)	23.1 (19.7, 27.0)	
Adjusted Hazard Ratio[b] (95% CI)	0.84 (0.67, 1.06)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-3.7 (-6.5, 1.6)		
eGFR ≥45 ml/min (N in weighted cohort)	22444	22578	*GFR spline terms*
Composite Major Adverse Cardiovascular Events	973	1262	
Person-Years	43072	440306	*eGFR*
Unadjusted Rate/1000 person-years (95% CI)	22.6 (21.2, 24.0)	28.5 (27.0, 30.1)	*p = 0.38*
Adjusted Hazard Ratio [a] (95% CI)	0.80 (0.74, 0.86)	Reference	*eGFR'*
Adjusted Incident Rate Difference[c] (95% CI)	-5.7 (-4.2, -7.0)		*p = 0.54*

|	Metformin	Sulfonylurea	P value for Interaction
eGFR 30-45 ml/min (N in weighted cohort)	1903	1886	
Composite Major Adverse Cardiovascular Events	65	115	
Person-Years	2178	2968	
Unadjusted Rate/1000 person-years (95% CI)	29.9 (23.6, 37.9)	38.7 (32.3, 46.3)	
Adjusted Hazard Ratio[b] (95% CI)	0.79 (0.59, 1.04)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-8.1 (-13.2, 1.9)		
eGFR<30ml/min (N in weighted cohort)	332	334	
Composite Major Adverse Cardiovascular Events	10	17	
Person-Years	292	488	
Unadjusted Rate/1000 person-years (95% CI)	33.6 (18.3, 61.1)	34.3 (21.5, 54.5)	
Adjusted Hazard Ratio[b] (95% CI)	0.82 (0.25, 2.72)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-6.2 (-16.1, 93.7)		
Serum Creatinine greater than FDA threshold	4806	4892	
Composite Major Adverse Cardiovascular Events	125	229	
Person-Years	5733	7779	
Unadjusted Rate/1000 person-years (95% CI)	21.9 (18.4, 26.0)	29.5 (26.0, 33.5)	
Adjusted Hazard Ratio[b] (95% CI)	0.74 (0.61, 0.90)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-7.7 (-3.4, -10.1)		p=0.46
eGFR<60 ml/min with Serum Creatinine below FDA threshold	19873	19907	
Composite Major Adverse Cardiovascular Events	923	1164	
Person-Years	39809	39983	
Unadjusted Rate/1000 person-years (95% CI)	23.2 (21.8, 24.7)	29.1 (27.5, 30.8)	
Adjusted Hazard Ratio[b] (95% CI)	0.81 (0.75, 0.88)	Reference	
Adjusted Incident Rate Difference[c] (95% CI)	-5.5 (-3.7, -6.9)		

[a] Cox Proportional Hazards model for time to event. Adjusted for demographics, clinical information derived from the electronic health record, comorbidities, use of medications and health care utilization (see Supplemental table 1). All continuous variables were modeled as restricted cubic splines.

[b] Reduced model to allow for convergence All covariates in above model except VISN of care regrouped into regions and model excluded comorbidities with small numbers (HIV, history of Kidney disease, Osteomyelitis, Osteoporosis, Falls, Sepsis, Parkinson's, Amputation and Retinopathy)

[c] The decrease in the number of events per 1000 person-years of metformin use compared with sulfonylurea use among patients with reduced kidney function. The adjusted rate difference is estimated by multiplying the unadjusted incident rate for sulfonylurea by the adjusted hazard ratio minus 1. Confidence bounds are calculated using the respective bounds from the hazard ratio.

eFigure 1 Study Design Schematic

Main analysis: Comparison of metformin versus sulfonylurea initiators who reached the kidney threshold, and continued their original regimen, persistent exposure on the original regimen is required to remain in follow-up. Gaps (red bars) of up to 90 days are allowed for medication refill after reaching kidney threshold. Patients begin follow-up at the kidney threshold and are censored at addition of another diabetes treatment or no medication refill for 90 days.
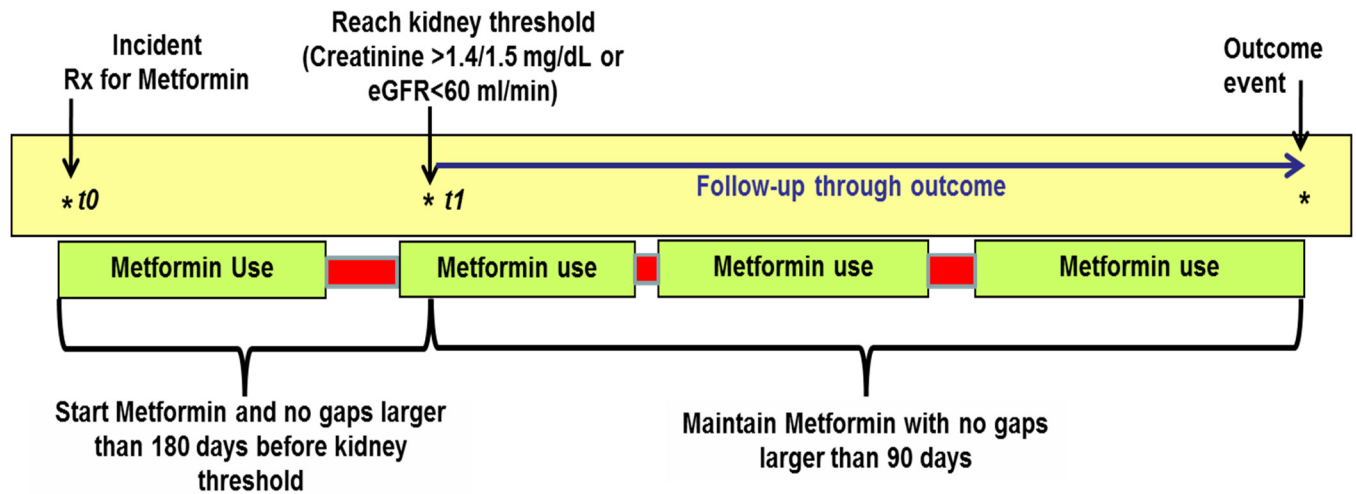
Sensitivity Analysis: Comparison of metformin versus sulfonylurea initiators who reached the kidney threshold, persistent exposure on the original regimen is not required to remain in follow-up. In this approach patients are analyzed as users of their regimen regardless of switching, stopping or additions (akin to intent to treat analysis). The resultant exposure misclassification, if non-differential would bias to null effect between treatment regimens.
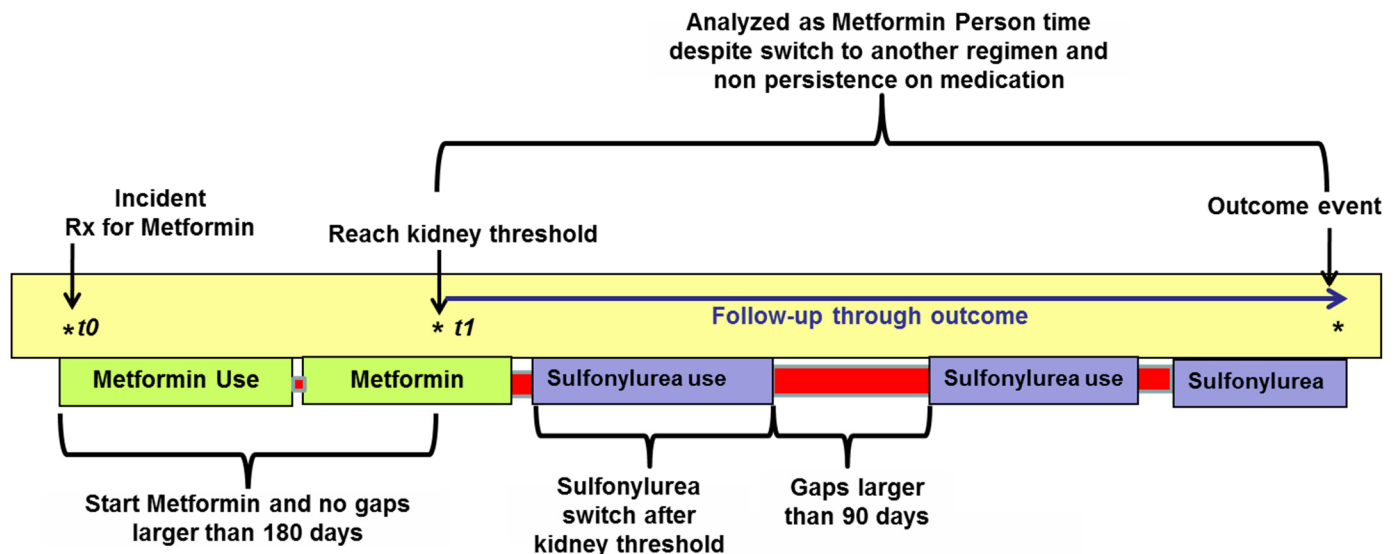
eFigure 2 Distribution of logit of propensity scores by drug

Propensity Scores - Unmatched
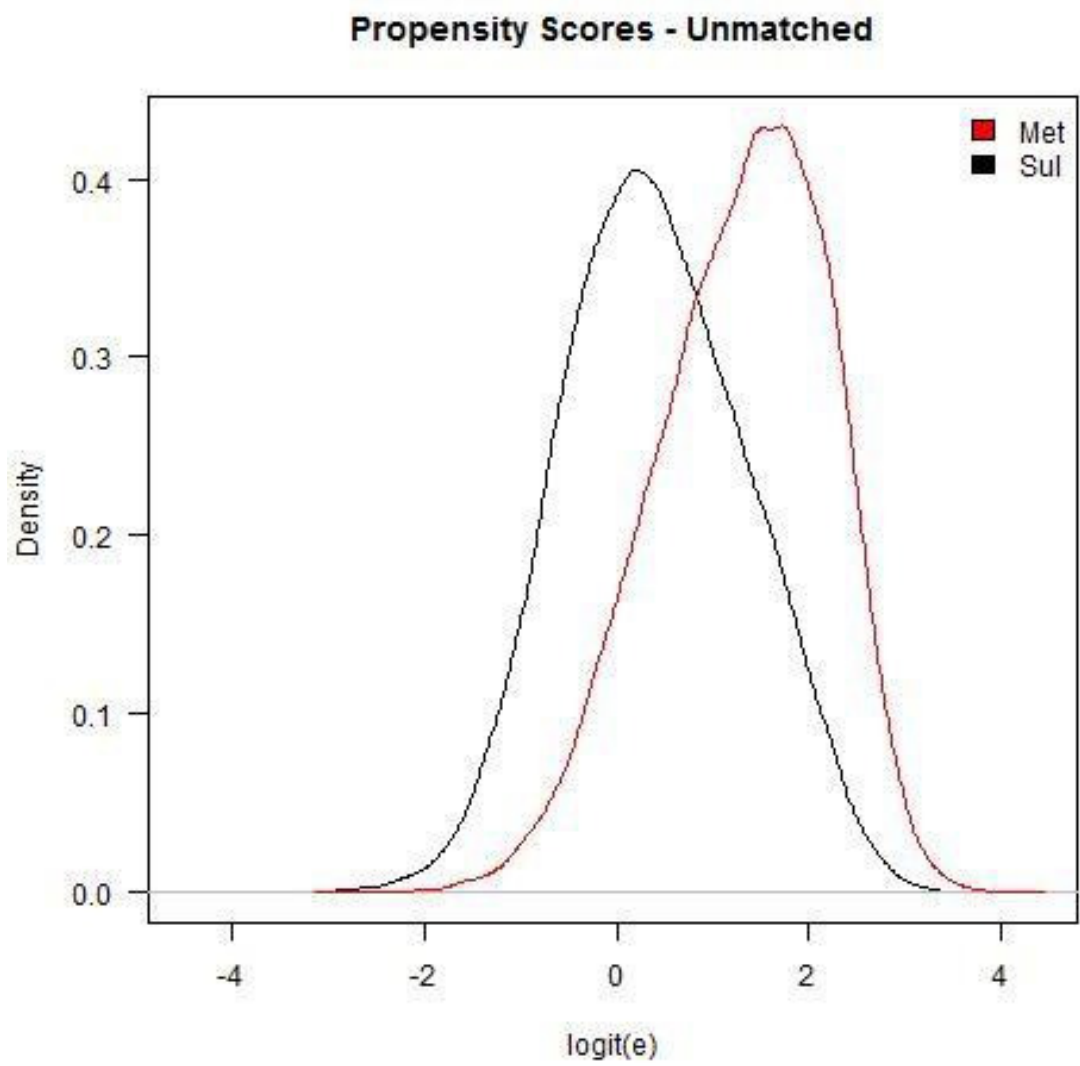
eFigure 3: Standardized Mean differences (SMD) comparing metformin versus sulfonylurea before and after weighting the cohort
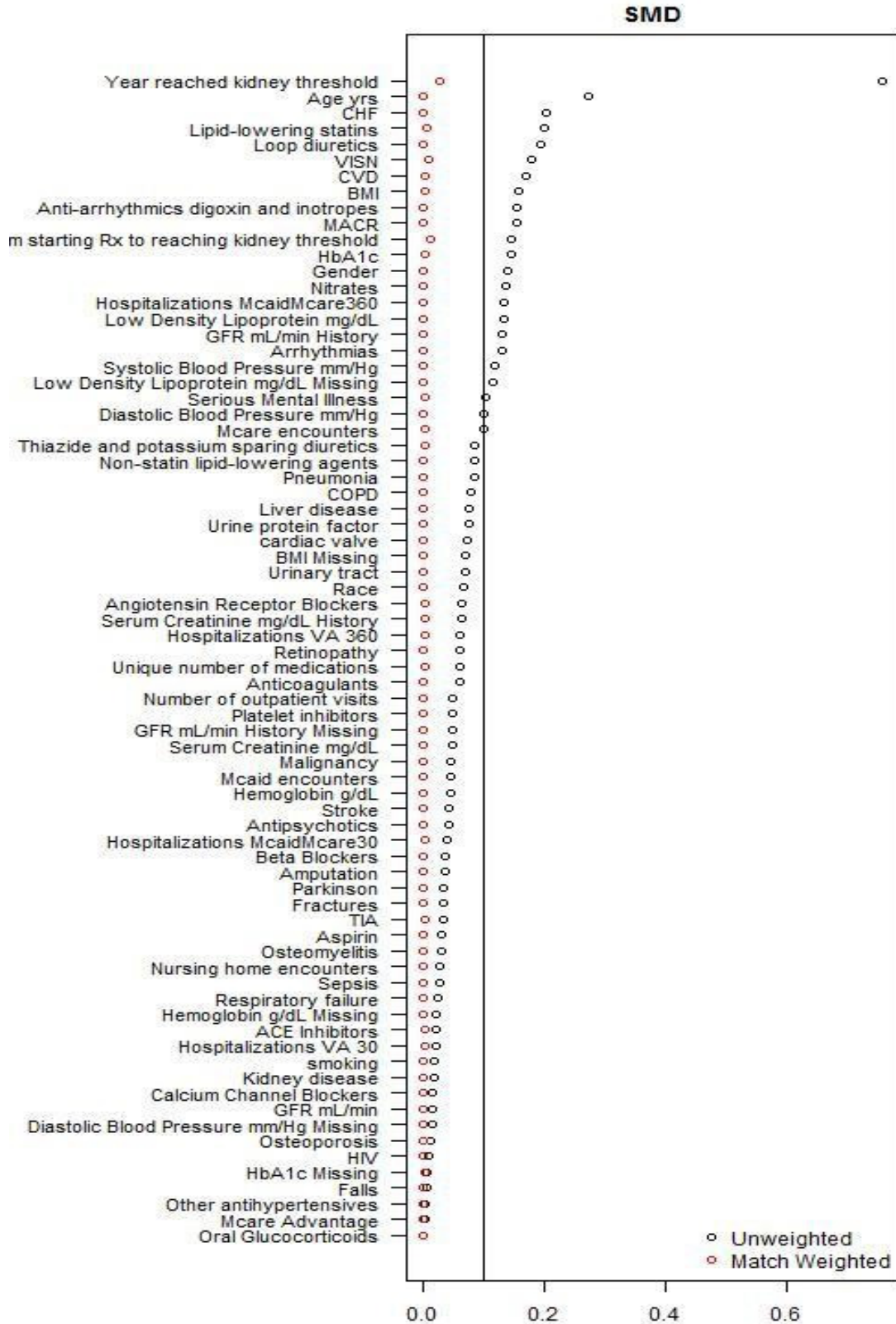
eFigure 4: Deviance of baseline covariates from the Propensity Score Model, relative contribution of each covariate in predicting exposure group.

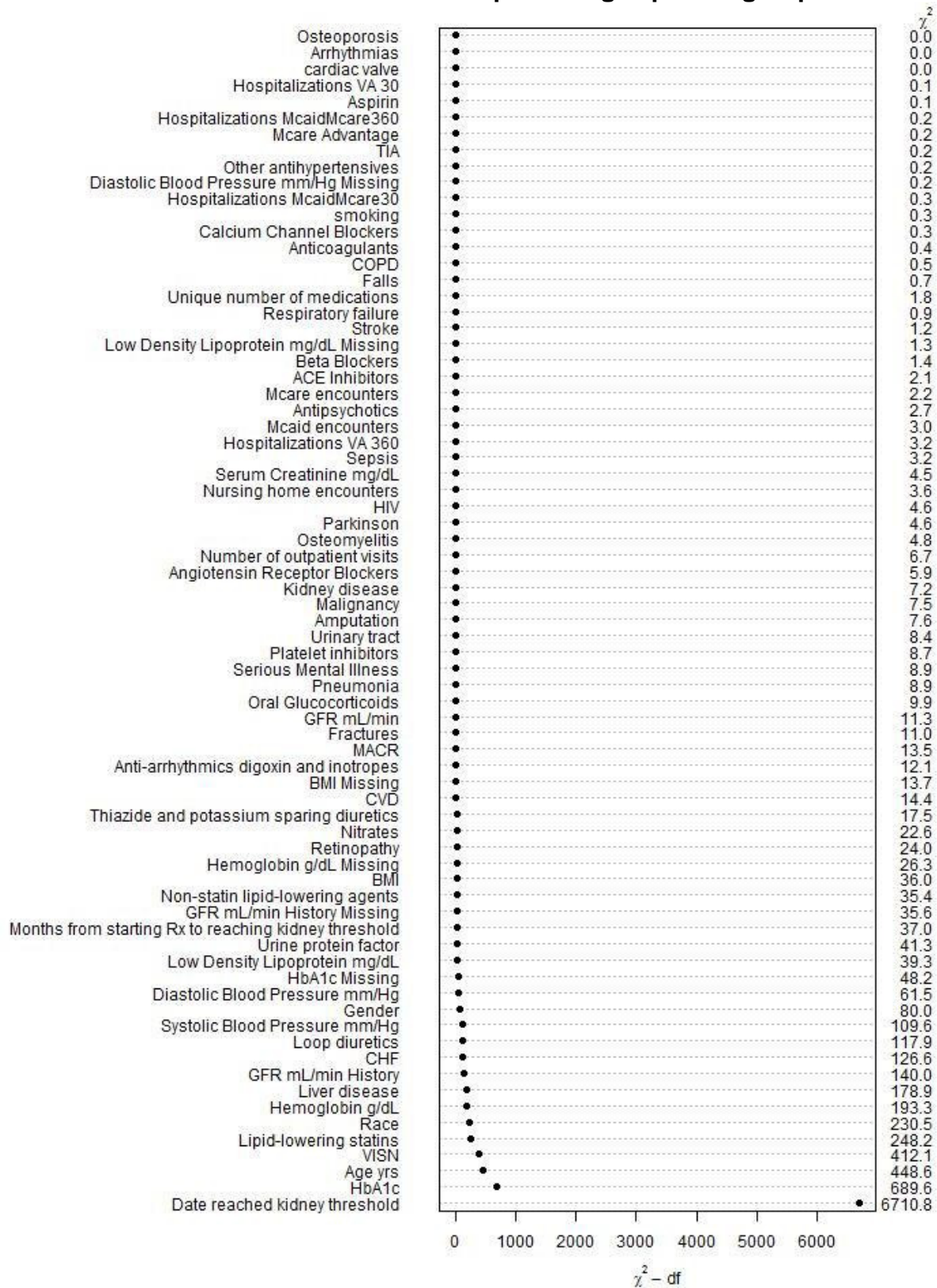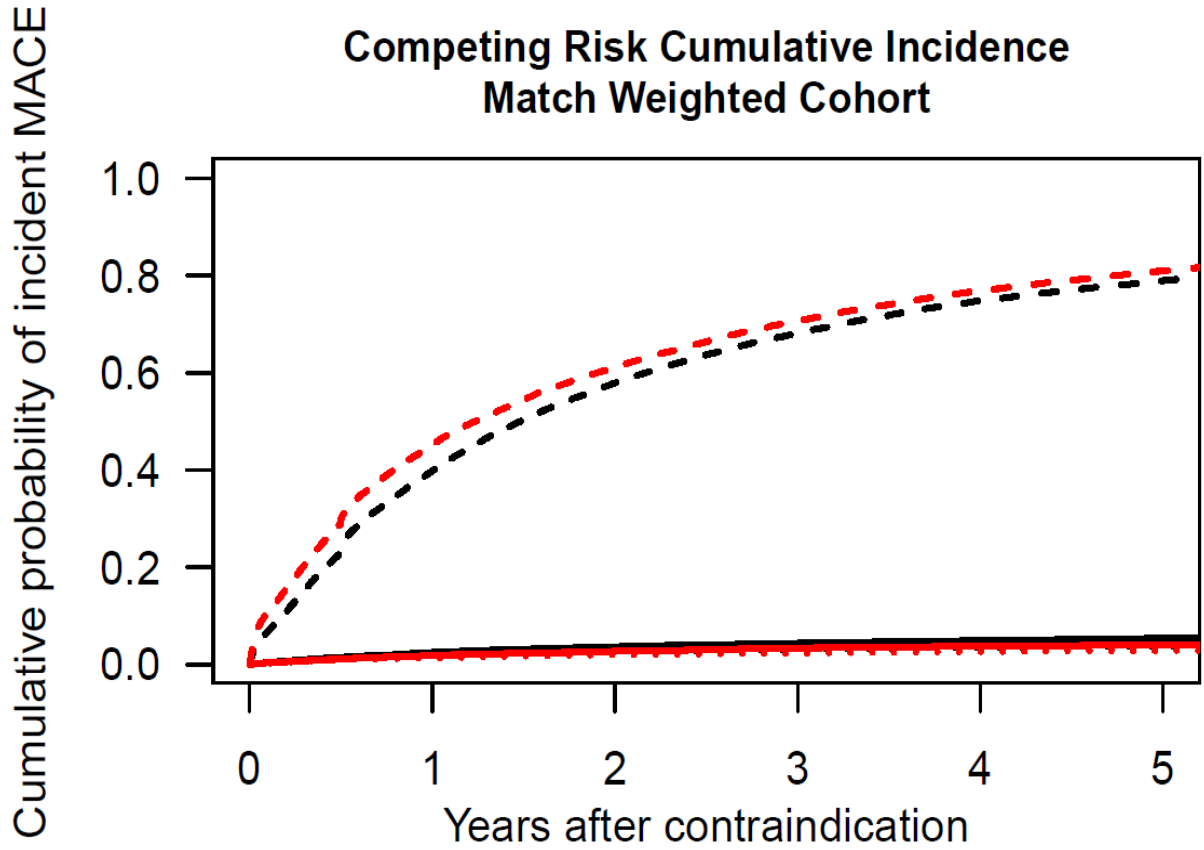| Covariate	χ^2
Osteoporosis	0.0
Arrhythmias	0.0
cardiac valve	0.0
Hospitalizations VA 30	0.1
Aspirin	0.1
Hospitalizations McaidMcare360	0.2
Mcare Advantage	0.2
TIA	0.2
Other antihypertensives	0.2
Diastolic Blood Pressure mm/Hg Missing	0.2
Hospitalizations McaidMcare30	0.3
smoking	0.3
Calcium Channel Blockers	0.3
Anticoagulants	0.4
COPD	0.5
Falls	0.7
Unique number of medications	1.8
Respiratory failure	0.9
Stroke	1.2
Low Density Lipoprotein mg/dL Missing	1.3
Beta Blockers	1.4
ACE Inhibitors	2.1
Mcare encounters	2.2
Antipsychotics	2.7
Mcaid encounters	3.0
Hospitalizations VA 360	3.2
Sepsis	3.2
Serum Creatinine mg/dL	4.5
Nursing home encounters	3.6
HIV	4.6
Parkinson	4.6
Osteomyelitis	4.8
Number of outpatient visits	6.7
Angiotensin Receptor Blockers	5.9
Kidney disease	7.2
Malignancy	7.5
Amputation	7.6
Urinary tract	8.4
Platelet inhibitors	8.7
Serious Mental Illness	8.9
Pneumonia	8.9
Oral Glucocorticoids	9.9
GFR mL/min	11.3
Fractures	11.0
MACR	13.5
Anti-arrhythmics digoxin and inotropes	12.1
BMI Missing	13.7
CVD	14.4
Thiazide and potassium sparing diuretics	17.5
Nitrates	22.6
Retinopathy	24.0
Hemoglobin g/dL Missing	26.3
BMI	36.0
Non-statin lipid-lowering agents	35.4
GFR mL/min History Missing	35.6
Months from starting Rx to reaching kidney threshold	37.0
Urine protein factor	41.3
Low Density Lipoprotein mg/dL	39.3
HbA1c Missing	48.2
Diastolic Blood Pressure mm/Hg	61.5
Gender	80.0
Systolic Blood Pressure mm/Hg	109.6
Loop diuretics	117.9
CHF	126.6
GFR mL/min History	140.0
Liver disease	178.9
Hemoglobin g/dL	193.3
Race	230.5
Lipid-lowering statins	248.2
VISN	412.1
Age yrs	448.6
HbA1c	689.6
Date reached kidney threshold	6710.8

$\chi^2 - df$

eFigure 5: Aalen–Johansen cumulative incidence demonstrating Major Adverse Cardiovascular Events with the competing risks of non-persistence and death from non-cardiovascular cause in weighted cohort

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