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Appendix Table 5: Rates and adjusted hazard ratios (95% confidence intervals [CI]) for risk of cardiovascular disease or death (primary composite outcome) and cardiovascular events (secondary outcome) among the full cohort of new users of sulfonylureas compared to metformin, stratified by age, cardiovascular disease history and body mass index. Similar analyses for sample of 14.3% of patients with urine protein measurement, by proteinuria status.

Appendix Table 6: Rates and adjusted hazard ratios (95% confidence interval [CI]) for risk of cardiovascular disease or death (primary composite outcome) and cardiovascular events (secondary outcome) among those with complete covariates who are new users of sulfonylureas compared to metformin.

Appendix Table 7: Risk of cardiovascular disease (CVD) in the presence of an unobserved confounder with a relative hazard of 1.25 for CVD risk, and various prevalence levels of the confounder by exposure group. The bolded numbers correspond to the necessary differential prevalence of such a confounder by exposure group that could account for study results being the result of such confounding.

Appendix Table 8: Risk of cardiovascular disease (CVD) in the presence of an unobserved confounder with a relative hazard of 2.0 for CVD risk, and various prevalence levels of the confounder by exposure group. The bolded numbers correspond to the necessary differential prevalence of such a confounder by exposure group that could account for study results being the result of such confounding.

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Appendix Figure 1: Examination of the Proportional Hazards Assumption using Log -log survival plots
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- Panel C: Cohort with complete covariates

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Appendix Figure 3: Adjusted hazard ratios for cardiovascular disease (CVD) or death composite outcome and secondary outcome (CVD alone) among patients with cardiovascular disease (CVD); body mass index (BMI); and age subgroups.

* Cardiovascular disease (CVD) defined by diagnoses or procedure codes for myocardial infarction, coronary artery disease, transient ischemic attack, stroke, or surgical procedures for repair of peripheral or carotid artery disease in the baseline period.

†Results are also presented for a sample of patients (14.3%) tested for proteinuria and found positive or negative.

Appendix Table 1: Definitions of co-morbidities and medications, based on codes and prescriptions in 365 days prior to exposure

Condition or Drug Class	***Definition ****
Myocardial infarction	ICD- 9 diagnosis codes: 410 (acute MI), 412 (old MI), 429.7 (MI sequela)
Obstructive coronary artery disease	ICD-9 diagnosis codes: 411; 413 or 414.xx (angina) ICD-9 procedure codes associated with a hospital discharge: 36.01, 36.02, 36.03, 36.05, 36.09, 36.10-36.19, CPT codes: 33533-36, 33510-23, 30, 92980-82, 84, 92995-6 (coronary artery revascularization procedure) or prescription for a long acting nitrate
Transient Ischemic attack or Cerebrovascular Disease/ Stroke or carotid revascularization procedure	ICD-9 diagnosis codes: 435, 430.X; 431.X; 433.x1, 434 (excluding 434.x0), or 436, 433.1 ICD-9 procedure codes: 38.12 38.11, 00.61, 00.6339.28 or CPT 35301 or
Peripheral artery disease/ revascularization/ amputation	ICD- 9 diagnosis codes: 440.2, 443.1, 443.9, 442.2; 445.0 ICD-9 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 CPT 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) or prescription for pentoxifylline or cilostazol amputations 84.1X; 84.10 – 84.17
Rheumatic/ aortic/mitral valve disease	ICD-9 diagnosis codes:394, 395, 396, 424.0, 424.1)
Atrial fibrillation flutter	ICD-9 diagnosis code: 427.3
Smoking	ICD-9 diagnosis codes: 305.1, V15.82, 989.84 or prescription for varenicline tartrate or nicotine replacement therapy
COPD/ Emphysema/ Asthma	ICD-9 diagnosis codes: 496; 491.2; 491.21; 493.2; 492; 492.8; v81.3; 493; 493.1; 493.9; 493.8; V17.5; 493.82
ACE Inhibitors or ARBs	benazapril; captopril; enalapril; fosinopril; 2ipyrimido; moexipril; perindopril; quinapril; ramipril; trandolapril; candesartan; irbesartan; losartan; olmisartan; telmisartan; valsartan
Anti-arrhythmics	amiodarone; flecanide; ibutilide; procainimide; propofenone; quinidine disopyramide; dofetilide; mexiletine; moricizine; tocainide
Anticoagulants	warfarin; argatroban; bivalirudin; dalteparin; enoxaprin; eptifibatide, fondaparinux; heparin ; lepirudin; tirofiban tinzaparin
Antipsychotic medications	lithium; clozapine; haloperidol; loxipine; molindone; olanzipine; paliperidone; quetiapine fumerate; resperidone; aripiprazole; ziprasidone; chlorpromazine; fluphenazine; fluphenazine deconate; mesoridazine; perphenazine; thioridazine; thiothixene; trifluoperazine; triflupromazine
Beta-blockers	acebutolol; atenolol, betaxolol; bisoprolol, carvedilol, esmolol, labetalol, metoprolol tartrate, metoprolol succinate, propranolol, penbutolol pindolol nadolol; sotolol; timolol
Calcium Channel Blockers	amlodipine, isradipine; felodipine, nifedipine, nicardipine; diltiazem (regular and sa), verapamil (regular and sa) nimodipine; nisoldipine; bepridil; caduet
Digoxin	digoxin
Statin lipid lowering agents	atorvastatin; fluvastatin; lovastatin; simvastatin; rosuvastatin; lovastatin/niacin; ezetamibe/simvastatin;

Other lipid lowering agents	cholestyramine, colesevelam; clofibrate; colestipol, niacin, niacinamide, fish oil concentrate, omega 3 fatty acids, gemfibrozil, , fenofibrate, dextrothyroxine, fenofibric acid; ezetimibe
Thiazide and other diuretics, alone or in combination	chlorthiazide; chlorthalidone; hydrochlorothiazide; methyclothiazide; trichlormethiazide metolazone; indapamide; eplerenone; ameloride; sprinolactone; triamterene; hydrochlorothiazide /triamterene; hydrochlorothiazide/ spironolactone;
Nitrates	amyl nitrate; isosorbide dinitrate; isosorbide mononitrate; nitroglycerin (all forms—sustained action, patch, sublingual, ointment; aerosol spray); ranolazine
Aspirin	aspirin; aspirin/ dipyrimidole
Loop Diuretics	furosemide; ethacrynic acid ; bumetanide; torsemide
Other Antihypertensives	doxazosin, prazosin, terazosin, clonidine; guanabenz; guanfacine; hydralazine; methyldopa, metyrosine; reserpine; minoxidil
Platelet inhibitors, not aspirin	clopidogrel; ticlopidine; aspirin/ dipyrimidole; dipyrimidole alone

* Each co-morbidity defined as present if there was 1 specified inpatient or 2 specified outpatient codes separated by 30 days, or one specified procedure code or prescription for a medication defining that co-morbidity in the 365 days prior to initiating oral antidiabetic drug.

Propensity Score

We analyzed 2 cohorts. The first cohort was composed of all eligible persons who initiated either metformin or sulfonylurea monotherapy after 365 days with no exposure to medications for diabetes. The second cohort is a subset of the first and utilized propensity scores to match eligible metformin users to sulfonylurea users. The propensity score is defined as the probability of metformin use, given a particular pattern of baseline covariates. We estimated the propensity score using a logistic regression model in which the dependent variable was 1 for patients who used metformin at baseline and 0 for sulfonylurea users. The model was simple logistic regression, with a third degree polynomial term for continuous covariates and facility of care in the model. Appendix Table 1 and Table 1 in the paper list baseline covariates included. The model for the probability of being a metformin user is displayed in appendix table 2. Two variables were strongly related to metformin initiation. Metformin use increased relative to sulfonylureas over time as reflected by odds ratios for fiscal years 2004 to 2007. Metformin initiation decreased with increasing baseline creatinine as reflected by odds ratios for 0.54. Table 1 in the paper demonstrates the *P* values for metformin and sulfonylurea initiators before and after propensity score matching; after matching, few standardized differences are statistically significant, indicating good balance. Another important assumption for propensity score methods is that every cohort member has a nonzero probability of being either a sulfonylurea user or a metformin user. Any cohort members who must always receive a sulfonylurea or who could never receive a sulfonylurea would be excluded, because the relevant comparison is between persons who are eligible for either drug but who may or may not actually receive one or the other. We tested this assumption by reviewing the overlap in the distribution of the propensity scores in sulfonylurea and metformin initiators. As shown in Appendix Figure 1, this distribution differed slightly for users of metformin and sulfonylurea but the overlap was nearly complete. The model yielded a C statistic of 0.71.

Appendix Table 2: Odds ratios (95% confidence limits) of metformin compared to sulfonylurea initiation controlling for all variables in table.

Odds Ratio Estimates for Metformin use			
	Odds Ratio	**95% Confidence Limits**	
Co-morbidities			
Coronary disease or AMI	0.995	0.988	1.002
TIA stroke or carotid disease	0.901	0.892	0.910
Peripheral artery disease	0.931	0.921	0.942
Rheumatic/ aortic/mitral valve disease	1.055	1.030	1.081
Atrial fibrillation/ flutter	1.032	1.019	1.046
Smoking	1.014	1.007	1.021
COPD/ Emphysema/ Asthma	1.053	1.043	1.064
Medications			
Aspirin_365	1.041	1.035	1.047
ACEI_ARBS	1.023	1.019	1.027
AntiArrhythmics	0.825	0.809	0.842
Anticoagulants	0.946	0.936	0.956
Antipsychotics	0.938	0.931	0.945
BetaBlockers	0.980	0.976	0.985
CalciumChannelBlockers	0.992	0.987	0.997
Digoxin	0.875	0.866	0.884
Lipid lowering meds Statins	1.312	1.306	1.317
Lipid lowering meds NonStatins	1.069	1.063	1.076
Thiazide and Other Diuretics	1.070	1.065	1.075
Nitrates	0.895	0.888	0.903
LoopDiuretics	0.696	0.691	0.701
OtherAntihypertensives	0.995	0.990	1.001
Platelet Inhibitors nonaspirin	0.941	0.934	0.949
Demographics			

Mean centered age		0.991	0.991	0.991
Mean centered age^2		0.999	0.999	0.999
Mean centered age^3		1.000	1.000	1.000
gender_female		1.335	1.321	1.350
race_black		0.947	0.941	0.953
race_hispanic		0.829	0.818	0.841
race_other		0.910	0.901	0.918
Fiscal year_2004		1.135	1.128	1.142
Fiscal year_2005		1.349	1.340	1.358
Fiscal year_2006		1.608	1.597	1.618
Fiscal year_2007		2.020	2.007	2.034
Clinical and laboratory indicators				
Mean centered hga1c		0.855	0.854	0.857
Mean centered hga1c ^{2}		1.000	1.000	1.001
Mean centered hga1c ^{3}		1.001	1.001	1.001
Mean centered LDL		1.000	1.000	1.000
Mean centered LDL ^{2}		1.000	1.000	1.000
Mean centered LDL^3		1.000	1.000	1.000
Mean centered creatinine		0.537	0.528	0.546
Mean centered creatinine^2		0.022	0.021	0.023
Mean centered creatinine ^{3}		0.004	0.004	0.005
Mean centered Systolic		0.996	0.996	0.996
Mean centered Systolic^2		1.000	1.000	1.000
Mean centered Systolic^3		1.000	1.000	1.000
Mean centered Diastolic		1.002	1.001	1.002
Mean centered Diastolic^2		1.000	1.000	1.000
Mean centered Diastolic^3		1.000	1.000	1.000
Mean centered BMI		1.040	1.040	1.040
Mean centered BMI^2		0.999	0.999	0.999
Mean centered BMI ^{3}		1.000	1.000	1.000
Indicators of Healthcare Utilization				
Mean centered OutPtMeds		0.986	0.985	0.987
Mean centered OutPtMeds^2		0.999	0.999	0.999
Mean centered OutPtMeds^3		1.000	1.000	1.000
Mean centered OutPtVisits		1.001	1.000	1.001
Mean centered OutPtVisits^2		1.000	1.000	1.000
Mean centered OutPtVisits^3		1.000	1.000	1.000
Hospitalized in past year		0.854	0.847	0.861
Indicators of Missing Clinical Variables				
BMI missing		0.855	0.845	0.865
Creatinine missing		0.774	0.770	0.779
Diastolic missing		0.415	0.343	0.502
hga1c missing		0.945	0.940	0.949
LDL missing		0.914	0.910	0.918
Systolic missing		2.747	2.270	3.324
Race missing		1.157	1.147	1.167
VHA Medical Center				
VA station	402 vs 757	2.103	2.030	2.179
VA station	405 vs 757	1.953	1.875	2.035
VA station	436 vs 757	1.619	1.558	1.682
VA station	437 vs 757	0.908	0.875	0.943
VA station	438 vs 757	1.317	1.269	1.366
VA station	442 vs 757	1.858	1.771	1.950
VA station	459 vs 757	1.213	1.164	1.265
VA station	460 vs 757	1.592	1.535	1.650
VA station	463 vs 757	3.508	3.338	3.686
VA station	501 vs 757	1.771	1.712	1.833

VA station	502 vs 757	1.091	1.055	1.128
VA station	503 vs 757	1.422	1.371	1.475
VA station	504 vs 757	1.185	1.141	1.232
VA station	506 vs 757	1.564	1.507	1.624
VA station	508 vs 757	0.770	0.746	0.795
VA station	509 vs 757	1.395	1.344	1.448
VA station	512 vs 757	0.983	0.951	1.017
VA station	515 vs 757	1.367	1.318	1.418
VA station	516 vs 757	1.784	1.731	1.839
VA station	517 vs 757	1.557	1.493	1.623
VA station	518 vs 757	1.716	1.638	1.798
VA station	519 vs 757	0.835	0.802	0.871
VA station	520 vs 757	1.787	1.731	1.846
VA station	521 vs 757	2.533	2.449	2.621
VA station	523 vs 757	1.400	1.353	1.449
VA station	526 vs 757	1.389	1.331	1.449
VA station	528 vs 757	1.505	1.462	1.548
VA station	529 vs 757	0.595	0.571	0.620
VA station	531 vs 757	2.937	2.815	3.064
VA station	534 vs 757	2.362	2.280	2.446
VA station	537 vs 757	1.042	1.007	1.077
VA station	538 vs 757	0.629	0.605	0.654
VA station	539 vs 757	1.907	1.838	1.979
VA station	540 vs 757	1.377	1.327	1.429
VA station	541 vs 757	1.519	1.474	1.564
VA station	542 vs 757	1.623	1.557	1.692
VA station	544 vs 757	0.971	0.941	1.001
VA station	546 vs 757	1.309	1.267	1.353
VA station	548 vs 757	0.440	0.426	0.453
VA station	549 vs 757	0.848	0.824	0.873
VA station	550 vs 757	0.944	0.911	0.978
VA station	552 vs 757	1.846	1.781	1.913
VA station	553 vs 757	0.999	0.962	1.036
VA station	554 vs 757	1.041	1.008	1.076
VA station	556 vs 757	1.967	1.887	2.050
VA station	557 vs 757	1.186	1.142	1.231
VA station	558 vs 757	1.597	1.543	1.653
VA station	561 vs 757	1.010	0.979	1.042
VA station	562 vs 757	0.728	0.700	0.757
VA station	564 vs 757	1.477	1.429	1.526
VA station	565 vs 757	1.535	1.486	1.586
VA station	568 vs 757	0.896	0.861	0.932
VA station	570 vs 757	0.622	0.601	0.644
VA station	573 vs 757	1.227	1.192	1.263
VA station	575 vs 757	1.648	1.561	1.740
VA station	578 vs 757	1.296	1.254	1.339
VA station	580 vs 757	1.400	1.360	1.442
VA station	581 vs 757	1.010	0.976	1.045
VA station	583 vs 757	1.934	1.870	2.000
VA station	585 vs 757	1.334	1.282	1.387
VA station	586 vs 757	1.182	1.145	1.219
VA station	589 vs 757	1.494	1.452	1.537
VA station	590 vs 757	1.243	1.198	1.289
VA station	593 vs 757	0.841	0.814	0.869
VA station	595 vs 757	1.954	1.887	2.024
VA station	596 vs 757	2.140	2.061	2.221
VA station	598 vs 757	1.009	0.978	1.042

VA station	600 vs 757	1.788	1.727	1.850
VA station	603 vs 757	1.278	1.234	1.323
VA station	605 vs 757	0.961	0.930	0.991
VA station	607 vs 757	1.543	1.488	1.600
VA station	608 vs 757	1.761	1.688	1.838
VA station	610 vs 757	1.496	1.447	1.547
VA station	612 vs 757	0.655	0.636	0.674
VA station	613 vs 757	0.959	0.927	0.993
VA station	614 vs 757	1.193	1.155	1.233
VA station	618 vs 757	1.371	1.328	1.414
VA station	619 vs 757	1.061	1.026	1.098
VA station	620 vs 757	0.965	0.929	1.002
VA station	621 vs 757	2.083	2.010	2.158
VA station	623 vs 757	1.924	1.858	1.993
VA station	626 vs 757	1.457	1.413	1.501
VA station	629 vs 757	1.390	1.342	1.439
VA station	630 vs 757	1.683	1.625	1.742
VA station	631 vs 757	1.085	1.035	1.137
VA station	632 vs 757	1.896	1.826	1.969
VA station	635 vs 757	1.073	1.040	1.108
VA station	636 vs 757	1.556	1.511	1.603
VA station	637 vs 757	1.740	1.678	1.804
VA station	640 vs 757	1.593	1.541	1.647
VA station	642 vs 757	1.260	1.220	1.302
VA station	644 vs 757	0.802	0.777	0.828
VA station	646 vs 757	1.037	1.005	1.071
VA station	648 vs 757	0.723	0.700	0.746
VA station	649 vs 757	1.016	0.979	1.055
VA station	650 vs 757	2.548	2.446	2.654
VA station	652 vs 757	2.189	2.112	2.268
VA station	653 vs 757	1.420	1.364	1.478
VA station	654 vs 757	1.909	1.829	1.992
VA station	655 vs 757	1.703	1.637	1.771
VA station	656 vs 757	1.580	1.519	1.644
VA station	657 vs 757	1.109	1.077	1.142
VA station	658 vs 757	1.104	1.066	1.143
VA station	659 vs 757	1.057	1.024	1.092
VA station	660 vs 757	2.693	2.594	2.796
VA station	662 vs 757	1.767	1.698	1.839
VA station	663 vs 757	0.660	0.640	0.680
VA station	664 vs 757	2.227	2.150	2.307
VA station	666 vs 757	2.071	1.959	2.188
VA station	667 vs 757	1.714	1.656	1.773
VA station	668 vs 757	1.075	1.033	1.118
VA station	671 vs 757	1.779	1.726	1.834
VA station	672 vs 757	1.028	0.997	1.060
VA station	673 vs 757	0.963	0.935	0.991
VA station	674 vs 757	1.881	1.823	1.942
VA station	675 vs 757	0.671	0.640	0.703
VA station	676 vs 757	1.181	1.135	1.229
VA station	678 vs 757	0.700	0.676	0.724
VA station	679 vs 757	1.552	1.480	1.627
VA station	687 vs 757	2.065	1.975	2.159
VA station	688 vs 757	1.303	1.261	1.346
VA station	689 vs 757	1.400	1.355	1.446
VA station	691 vs 757	1.107	1.074	1.141
VA station	692 vs 757	3.828	3.630	4.036

VA station	693 vs 757	0.989	0.957	1.023
VA station	695 vs 757	1.378	1.332	1.425
VA station	756 vs 757	2.356	2.265	2.450

Appendix Table 3: Baseline characteristics of patients with complete covariates by antidiabetic drug

Characteristic	***Metformin N=63,584***	***Sulfonylurea N=35,199***	***Standardized differences †***
Age, median (IQR)	63 (56, 71)	67 (58, 76)	0.3
Male (%)	95	97	0.09
Race, (%)			
White	81	80	0.01
Black	13	13	0
Hispanic/ Other	6	6	0.01
HbA1c, % median (IQR)	7.0 (6.4, 7.8)	7.2 (6.6, 8.1)	0.16
Low Density Lipoprotein (mg/dL) mg/dL, median (IQR)	102 (81, 127)	101 (80, 126)	0.03
Creatinine mg/dL, median (IQR)	1.0 (0.9,1.2)	1.1 (0.9, 1.3)	0.32
Systolic Blood pressure mm/Hg, median (IQR)	134 (124, 144)	135 (124,145)	0.06
Diastolic Blood pressure mm/Hg, median (IQR)	76 (70, 83)	75 (68, 82)	0.09
Body Mass Index (kilograms/meter^2), median (IQR)	32.0 (28.5, 36.2)	30.4 (27.2, 34.4)	0.27
Number of Medications median (IQR)	5 (3, 8)	5 (3, 8)	0.04
Outpatient visits, median (IQR)	5 (3, 8)	5 (3, 8)	0
Hospitalized (%)	7	8	0.04
Baseline Co-morbidities (%)*			
Myocardial infarction /coronary disease	22	26	0.1
Stroke/ transient ischemic attack or carotid revascularization	9	11	0.07
Peripheral artery disease	3	4	0.05
Smoking	11	10	0.07
Obstructive pulmonary disease/ Emphysema	9	10	0.03
Atrial Fibrillation/ Flutter	3	5	0.08
Fiscal year			
2003	11	16	0.13
2004	17	21	0.11
2005	21	23	0.04
2006	25	22	0.07
2007	26	18	0.19
Use of Medications (%)			
ACE Inhibitors or ARBs	61	62	0.01
Beta-blockers	39	40	0.04
Calcium Channel Blockers	24	26	0.06
Other Antihypertensives	16	19	0.06
Statin lipid lowering agents	66	62	0.09
Other lipid lowering agents	14	13	0.03
Anti-arrhythmics	1	1	0.05
Anticoagulants	5	6	0.07
Antipsychotic medications	8	7	0.02
Digoxin	3	5	0.12

Thiazide and other diuretics	34	32	0.03
Loop Diuretics	9	13	0.13
Nitrates	12	15	0.09
Aspirin	19	20	0.01
Platelet inhibitors	7	9	0.07

* Definitions of co-morbidities and medications available in Appendix Table 1

† Standardized differences are the absolute difference in means or percents divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations. All P values for the comparison of metformin and sulfonylurea users were statistically significant at P<0.001, except outpatient visits p=0.016, ACE/ARB p=0.08; aspirin use p=0.15

Appendix Table 4: Yearly unadjusted incidence rates, unadjusted incidence rate difference, and adjusted incidence rate difference with 95% confidence intervals [CI] for cardiovascular disease or death (primary composite outcome) among propensity matched cohort of new users of sulfonylureas compared to metformin.

	Year 1		Year 2		Year 3		Year 4		Year 5	
Persistent Exposure required*	***Met***	***Sul.***	***Met***	***Sul.***	***Met***	***Sul.***	***Met***	***Sul.***	***Met***	***Sul.***
Number at risk	80648	80648	33418	29502	16887	14118	7976	6185	3297	2301
Person Years	51344	47979	24248	20848	11966	9658	5381	3984	1857	1272
Cardiovascular events or death	726	739	296	305	129	159	69	56	16	25
Unadjusted rate/1000 person-years, (95%CI)	14.1 (13.2,15.2)	15.4 (14.3,16.5)	12.2 (10.9,13.7)	14.6 (13.1,16.4)	10.8 (9.1,12.8)	16.4 (14.1,19.2)	12.8 (10.1,16.2)	14.0 (10.8,18.2)	8.6 (5.3, 14.0)	19.7 (13.3,28.9)
Unadjusted incidence rate difference (95% CI)	1.3 (-0.2, 2.8)		2.4 (0.3, 4.6)		5.7 (2.6, 8.9)		1.2 (-3.4, 6.2)		11.0 (2.8, 20.8)	
Adjusted incidence rate difference, † (95%CI)	2.3 (1.1, 3.5)		1.9 (1.0, 3.0)		1.7 (0.9, 2.7)		2.1 (1.0, 3.2)		1.4 (0.7, 2.2)	
Persistent exposure not required‡										
Number at risk	80648	80648	65655	64757	47552	45982	30413	29104	16391	15513
Person Years	74364	73730	56584	55155	38755	37097	23273	22070	10189	9523
Cardiovascular events or death	1199	1379	916	1023	629	760	415	419	167	212
Unadjusted rate/1000 person-years, (95%CI)	16.1 (15.2,17.0)	18.7 (17.7,19.6)	16.2 (15.2,17.3)	18.5 (17.5,19.7)	16.2 (15.0,17.5)	20.5 (19.1,22.0)	17.8 (16.2,19.6)	19.0 (17.3,20.9)	16.4 (14.1,19.0)	22.2 (19.5,25.4)
Unadjusted rate difference (95% CI)	2.6 (1.2, 3.9)		2.4 (0.8, 3.9)		4.3 (2.3, 6.2)		1.2 (-1.3, 3.6)		5.9 (2.0, 9.8)	
Adjusted incidence rate difference , † (95%CI)	3.2 (2.4, 4.2)		3.2 (2.4, 4.2)		3.3 (2.4, 4.2)		3.6 (2.7, 4.6)		3.3 (2.5, 4.3)	

* Primary analysis considers patients persistent on incident regimen until they do not have oral antidiabetic medications for 90 days.

† The adjusted incidence rate difference is the excess in the number of events per 1000 person years of sulfonylurea use compared to the number of events per 1000 person years of metformin use. The difference is calculated as the incidence rate among metformin users*(adjusted HR -1). The HRs used in each calculation is derived from the respective models presented in Table 2.

‡Persistent exposure not required analysis- In which patients remain in their exposure group, regardless of persistence on drug therapy, until outcome or end of the study.

Appendix Table 5: Incidence rates and adjusted hazard ratios (95% confidence intervals [CI]) for risk of cardiovascular disease or death (primary composite outcome) and cardiovascular events (secondary outcome) among full cohort of new users of sulfonylureas compared to metformin, stratified by history of CVD, age, and BMI. Similar analyses for sample of patients (14.3%) with urine protein measurement, by proteinuria status. Each analysis considers patients persistent on incident regimen until they do not have OAD medications for 90 days.

	Metformin	***Sulfonylurea***
History of CVD*	***N=40,577***	***N=30,366***
Cardiovascular or death rate /1000 person-years (95% CI)	17.1 (16.0, 18.3)	28.7 (27.0, 30.6)
Adjusted Hazard ratio† (95% CI)	Reference	1.26 (1.14, 1.39)
Cardiovascular event rate /1000 person-years (95% CI)	13.7 (12.7, 14.8)	20.8 (19.3, 22.4)
Adjusted Hazard ratio † (95% CI)	Reference	1.16 (1.05, 1.30)
No history of CVD*	***N=114,448***	***N=68,299***
Cardiovascular or death rate /1000 person-years (95% CI)	7.9 (7.5, 8.4)	13.3 (12.5, 14.2)
Adjusted Hazard ratio † (95% CI)	Reference	1.17 (1.06, 1.29)
Cardiovascular event rate /1000 person-years (95% CI)	6.1 (5.7, 6.6)	10.0 (9.4, 10.9)
Adjusted Hazard ratio † (95% CI)	Reference	1.15 (1.03, 1.28)
65 years old and older	***N=64,009***	***N=54,055***
Cardiovascular or death rate /1000 person-years (95% CI)	15.9 (15.0, 16.8)	24.6 (23.4, 25.9)
Adjusted Hazard ratio † (95% CI)	Reference	1.18 (1.09, 1.28)
Cardiovascular event rate /1000 person-years (95% CI)	12.9 (12.1, 13.7)	18.5 (17.5, 19.6)
Adjusted Hazard ratio † (95% CI)	Reference	1.13 (1.03, 1.24)
Less than 65 years old	***N=91,016***	***N=44,610***
Cardiovascular or death rate /1000 person-years (95% CI)	6.1 (5.6, 6.6)	9.4 (8.5, 10.3)
Adjusted Hazard ratio † (95% CI)	Reference	1.28 (1.13, 1.46)
Cardiovascular event rate /1000 person-years (95% CI)	4.4 (4.0, 4.8)	6.6 (5.8, 7.4)
Adjusted Hazard ratio † (95% CI)	Reference	1.24 (1.06, 1.44)
BMI $\geq$30 kg/m^2	***N=92,429***	***N=46,033***
Cardiovascular or death rate /1000 person-years (95% CI)	8.3 (7.8, 8.9)	13.6 (12.6, 14.7)
Adjusted Hazard ratio † (95% CI)	Reference	1.24 (1.12, 1.37)
Cardiovascular event rate /1000 person-years (95% CI)	6.4 (6.0, 6.9)	10.5 (9.6, 11.4)
Adjusted Hazard ratio † (95% CI)	Reference	1.20 (1.07, 1.34)
BMI <30 kg/m^2	***N=62,596***	***N=52,632***
Cardiovascular or death rate /1000 person-years (95% CI)	13.6 (12.8, 14.5)	22.6 (21.3, 23.8)
Adjusted Hazard ratio † (95% CI)	Reference	1.18 (1.06, 1.30)
Cardiovascular event rate /1000 person-years (95% CI)	10.8 (10.1, 11.6)	16.3 (15.3, 17.4)

Adjusted Hazard ratio † (95% CI)	Reference	1.11 (0.99, 1.24)
Tested positive for proteinuria (≥30 mg/g)	***N=4580***	***N=2979***
Cardiovascular or death rate /1000 person-years (95% CI)	13.8 (10.8, 17.7)	20.0 (15.2, 26.2)
Adjusted Hazard ratio † (95% CI)	Reference	1.13 (0.74, 1.73)
Cardiovascular event rate /1000 person-years (95% CI)	10.0 (7.5, 13.4)	15.6 (11.4, 21.2)
Adjusted Hazard ratio † (95% CI)	Reference	1.11 (0.67, 1.83)
Tested Negative for proteinuria (<30mg/g)	***N=19,302***	***N=9564***
Cardiovascular or death rate /1000 person-years (95% CI)	8.3 (7.2, 9.6)	12.7 (10.7, 15.1)
Adjusted Hazard ratio † (95% CI)	Reference	1.05 (0.84, 1.33)
Cardiovascular event rate /1000 person-years (95% CI)	7.0 (6.0, 8.2)	10.3 (8.4, 12.4)
Adjusted Hazard ratio † (95% CI)	Reference	1.02 (0.78, 1.32)

* Cardiovascular disease (CVD) defined by diagnoses or procedure codes for myocardial infarction, coronary artery disease, transient ischemic attack, stroke, or surgical procedures for repair of peripheral or carotid artery disease in the baseline period.

† Cox Proportional Hazards model for time to CVD with sandwich variance estimate clustered by VA medical center. Adjusted for age, sex, race, fiscal year of cohort entry, physiologic variables closest to cohort entry (blood pressure, creatinine, glycated hemoglobin [HbA1c], low density lipoprotein levels [LDL] and body mass index [BMI]), indicators of healthcare utilization (number of outpatient visits and active medications, hospitalization during baseline [yes/no]), smoking, selected medications indicative of CVD and presence of co-morbidities (myocardial infarction; obstructive coronary disease or prescription for a long acting nitrate; stroke/ transient ischemic attack; atrial fibrillation/ flutter; mitral/ aortic or rheumatic heart disease; asthma/obstructive pulmonary disease; procedures for carotid/ peripheral artery revascularization or bypass or lower extremity amputation—available in Appendix Table 1). All continuous variables were modeled as third degree polynomials.

Appendix table 6: Rates and adjusted hazard ratios (95% confidence interval [CI]) for risk of cardiovascular disease or death (primary composite outcome) and cardiovascular events (secondary outcome) among those with complete covariates who were new users of sulfonylureas compared to metformin.

Persistent exposure required*	***Metformin N=63,584***	***Sulfonylurea N=35,199***
Cardiovascular events or death	755	626
Person Years	75,137	37,791
Rate/1000 person-years	10.0 (9.4, 10.8)	16.6 (15.3, 17.9)
Adjusted Hazard ratio † (95% CI)	Reference	1.19 (1.07, 1.34)
Cardiovascular events	602	493
Rate/1000 person-years	8.0 (7.4, 8.7)	13.0 (11.9, 14.2)
Adjusted Hazard ratio † (95% CI)	Reference	1.18 (1.03, 1.33)
Persistent exposure not required‡		
Cardiovascular events or death	1919	1865
Person Years	147,331	87,740
Rate/1000 person-years	13.0 (12.5, 13.6)	21.3 (20.3, 22.2)
Adjusted Hazard ratio † (95% CI)	Reference	1.19 (1.11, 1.27)
Cardiovascular events	1293	1191
Rate/1000 person-years	8.8 (8.3, 9.3)	13.6 (12.8, 14.4)
Adjusted Hazard ratio † (95% CI)	Reference	1.14 (1.05, 1.24)

* Primary analysis considers patients persistent on incident regimen until 90 days without drug.

† Cox Proportional Hazards model for time to CVD with Sandwich variance estimate. Adjusted for age, sex, race, fiscal year of cohort entry, physiologic variables closest to cohort entry (blood pressure, creatinine, glycated hemoglobin [HbA1c], low density lipoprotein levels [LDL] and body mass index [BMI]), indicators of healthcare utilization (number of outpatient visits and active medications, hospitalization during baseline [yes/no]), smoking, selected medications indicative of CVD and presence of co-morbidities (myocardial infarction; obstructive coronary disease or prescription for a long acting nitrate; stroke/ transient ischemic attack; atrial fibrillation/ flutter; mitral/ aortic or rheumatic heart disease; asthma/obstructive pulmonary disease; procedures for carotid/ peripheral artery revascularization or bypass or lower extremity amputation—available in Appendix Table 1). All continuous variables were modeled as third degree polynomials.

‡ Persistent exposure not required analysis-patients remain in their exposure group, regardless of persistence on drug therapy, until outcome or end of the study.

Appendix table 7: Risk of cardiovascular disease (CVD) in the presence of an unmeasured confounder with a hazard ratio of 1.25 for CVD*, and various prevalence levels of the confounder by exposure group. The bolded numbers indicate the hazard ratios that correspond to the necessary differential prevalence of such a confounder by exposure group that could account for study results being the result of such confounding.

		Prevalence of unmeasured confounder* in Metformin users					
Prevalence of unmeasured confounder* in Sulfonylurea users		0.0	0.1	0.2	0.3	0.4	0.5
	0.0	1.21 (1.13, 1.30)	1.24 (1.16, 1.33)	1.27 (1.19, 1.37)	1.30 (1.22, 1.40)	1.33 (1.24, 1.43)	1.36 (1.27, 1.46)
	0.1	1.18 (1.10, 1.27)	1.21 (1.13, 1.30)	1.24 (1.16, 1.33)	1.27 (1.19, 1.36)	1.30 (1.21, 1.40)	1.33 (1.24, 1.43)
	0.2	1.15 (1.08, 1.24)	1.18 (1.10, 1.27)	1.21 (1.13, 1.30)	1.24 (1.16, 1.33)	1.27 (1.18, 1.36)	1.30 (1.21, 1.39)
	0.3	1.13 (1.05, 1.21)	1.15 (1.08, 1.24)	1.18 (1.10, 1.27)	1.21 (1.13, 1.30)	1.24 (1.16, 1.33)	1.27 (1.18, 1.36)
	0.4	1.10 (1.03, 1.18)	1.13 (1.05, 1.21)	1.15 (1.08, 1.24)	1.18 (1.10, 1.27)	1.21 (1.13, 1.30)	1.24 (1.16, 1.33)
	0.5	1.08 (1.00, 1.16)	1.10 (1.03, 1.18)	1.13 (1.06, 1.21)	1.16 (1.08, 1.24)	1.18 (1.11, 1.27)	1.21 (1.13, 1.30)
	0.6	**1.05 (0.98, 1.13)**	1.08 (1.01, 1.16)	1.10 (1.03, 1.19)	1.13 (1.06, 1.22)	1.16 (1.08, 1.24)	1.18 (1.11, 1.27)
	0.7	**1.03 (0.96, 1.11)**	**1.056 (0.99, 1.13)**	1.08 (1.01, 1.16)	1.11 (1.03, 1.19)	1.13 (1.06, 1.22)	1.16 (1.08, 1.24)
	0.8	**1.01 (0.94, 1.08)**	**1.034 (0.97, 1.11)**	**1.06 (0.99, 1.14)**	1.08 (1.01, 1.16)	1.11 (1.04, 1.19)	1.13 (1.06, 1.22)
	0.9	**0.99 (0.92, 1.06)**	**1.012 (0.95, 1.09)**	**1.04 (0.97, 1.11)**	**1.06 (0.99, 1.14)**	1.09 (1.02, 1.17)	1.11 (1.04, 1.19)
	1.0	**0.97 (0.90, 1.04)**	**0.99 (0.93, 1.07)**	**1.02 (0.95, 1.09)**	**1.04 (0.97, 1.12)**	**1.06 (0.99, 1.14)**	1.09 (1.02, 1.17)

* Unmeasured confounder could be a proposed confounder that was not included in our models or a confounder that was likely underreported in our cohort such as tobacco use.

Appendix table 8: Risk of cardiovascular disease (CVD) in the presence of an unmeasured confounder with a hazard ratio of 2.0 for CVD, and various prevalence levels of the confounder by exposure group. The bolded numbers indicate the hazard ratios that correspond to the necessary differential prevalence of such a confounder by exposure group that could account for study results being the result of such confounding.

		Prevalence of unmeasured confounder* in Metformin users					
Prevalence of unmeasured confounder* in Sulfonylurea users		0.0	0.1	0.2	0.3	0.4	0.5
	0.0	1.21 (1.13, 1.30)	1.331 (1.24,1.43)	1.452 (1.36,1.56)	1.573 (1.47,1.69)	1.694 (1.58,1.82)	1.815 (1.70,1.95)
	0.1	1.10 (1.03,1.18)	1.21 (1.13, 1.30)	1.32 (1.23,1.42)	1.43 (1.34,1.54)	1.54 (1.44,1.66)	1.65 (1.54,1.77)
	0.2	**1.01 (0.94, 1.08)**	1.109 (1.04,1.19)	1.21 (1.13, 1.30)	1.31 (1.22,1.41)	1.412 (1.32,1.52)	1.512 (1.41,1.63)
	0.3	0.931 (0.87,1.00)	**1.024 (0.96,1.10)**	1.117 (1.04,1.20)	1.21 (1.13, 1.30)	1.303 (1.22,1.40)	1.396 (1.30,1.50)
	0.4	0.86 (0.81,0.93)	**0.95 (0.89,1.02)**	**1.04 (0.97,1.11)**	1.12 (1.05,1.21)	1.21 (1.13, 1.30)	1.30 (1.21, 1.39)
	0.5	0.81 (0.75, 0.87)	0.89 (0.83, 0.95)	**0.97 (0.90, 1.04)**	**1.05 (0.98, 1.13)**	1.13 (1.06, 1.21)	1.21 (1.13, 1.30)
	0.6	0.76 (0.71, 0.81)	0.83 (0.78, 0.89)	0.91 (0.85, 0.98)	**0.98 (0.92, 1.06)**	**1.06 (0.99, 1.14)**	1.13 (1.06,1.22)
	0.7	0.71 (0.66, 0.77)	0.78 (0.73, 0.84)	0.85 (0.80, 0.92)	0.93 (0.86, 0.99)	**1.00 (0.93, 1.07)**	**1.07 (1.00,1.15)**
	0.8	0.67 (0.63, 0.72)	0.74 (0.69, 0.79)	0.81 (0.75, 0.87)	0.87 (0.82, 0.94)	**0.94 (0.88, 1.01)**	**1.01 (0.94, 1.08)**
	0.9	0.64 (0.59, 0.68)	0.70 (0.65, 0.75)	0.76 (0.71, 0.82)	0.83 (0.77, 0.89)	0.89 (0.83, 0.96)	**0.96 (0.89, 1.03)**
	1.0	0.61 (0.56, 0.65)	0.67 (0.62, 0.72)	0.73 (0.68, 0.78)	0.79 (0.74, 0.85)	0.85 (0.79, 0.91)	0.91 (0.85, 0.98)

* Unmeasured confounder could be a proposed confounder that was not included in our models or a confounder that was likely underreported in our cohort such as tobacco use.