Supplemental Material

Table S1. Definitions of comorbid conditions and medications, on the basis of codes and prescriptions in 730 days before treatment intensification

Covariate Condition	Inclusive conditions	Definition*
Malignancy	Cancer excluding non melanoma skin cancer	ICD 9- CM diagnosis codes:140.X-208.X (exclude 173)
Liver/ Respiratory failure	1. End stage liver disease	ICD 9- CM diagnosis codes: 570.X- 573.X
	2. Respiratory failure	ICD 9- CM diagnosis codes: 518.81, 518.83, 518.84, 799.1, 415.X, 416.X
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, 425.X
Cardiovascular disease	1. MI	ICD 9- CM diagnosis codes:410.X, 412.X, 429.7X
	2. Obstructive coronary disease	ICD 9- CM diagnosis codes:411.X, 413.X, 414.X 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. TIA	ICD 9- CM diagnosis codes: 435.X
	4. Stroke	ICD 9- CM diagnosis codes: 430.X, 431.X. 434.X, 436.X
	5. Peripheral artery disease revascularization or amputation	ICD 9- CM diagnosis codes:440.2X, 442.2, 443.1, 443.9, 445.0X 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; 84.10-84.17 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
	6. 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 HCPCS procedure code: S2211
	7. Pentoxifylline & related drugs	Medications: Pentoxifylline, Cilostazol, Cyclandelate, Ethaverine HCL, Nicotinyl Alcohol Tartate, Papaverine, Tolazolin
Serious Mental illness	1. Dementia	ICD 9- CM diagnosis codes: 290.X, 291.2, 292.82, 294.1X, 331.0-331.1X, 331.82 Medications: Donepezil, Rivastigmine, Galantamine, Tacrine, Memantine
	2. Depression,	ICD 9- CM diagnosis codes: 311, 300.4, 296.2, 296.3, V79.0
	3. Schizophrenia,	ICD 9- CM diagnosis codes: 295.X
	4. Bipolar disorder	ICD 9- CM diagnosis codes: 296.0, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89
	5. Post traumatic stress disorder	ICD 9- CM diagnosis codes: 309.81
Cardiac valve disease		ICD 9- CM diagnosis codes: 394.X, 395.X, 396.X, 424.0, 424.1
Arrhythmia	1. Atrial fibrillation/flutter	ICD 9- CM diagnosis codes: 427.3X
	2. Arrhythmia and conduction disorder	ICD 9- CM diagnosis codes: 426.X, 427.X
Smoking		ICD 9- CM diagnosis codes:305.1, V15.82, 989.84 Medications: Varenicline tartrate, Nicotine Replacement therapy (gum, patch, lozenge)
COPD/ Asthma		ICD 9- CM diagnosis codes:491.X, 492.X, 493.X, 496.X, V17.5, V81.3
HIV		ICD 9- CM diagnosis codes: 042, 079.53, 795.71, V08 Medications: Zidovudine, Didanosine, Zalcitabine, Stavudine, Indinavir, Ritonavir, Saquinavir, Nevirapine, Nelfinavir, Delavirdine, Delavirdine, Abacavir, Amprenavir, Efavirenz, Lamivudine-Zidovudine, Ritonavir-Lopinavir, Abacavir-Lamivudine-Zidovudine
Parkinson's Disease		ICD 9- CM diagnosis codes: 332 Medications: Apokyn, Apomorphine, Carbidopa/levodopa, Entacapone, Pergolide, Pramipexole, Ropinirole, Rotigotine, Selegiline, Tolcapone, Zelapar, Azilect/Rasagiline, Emsam, Isocarboxazid, Phenelzine, Tranylcypromine
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
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

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
Other Antihypertensives			Doxazosin, Prazosin, Terazosin, Clonidine, Guanabenz, Guanfacine, Hydralazine, Methyldopa, Metyrosine, Reserpine, Minoxidil, Alfuzosin, Silodosin, Alseroxylon, Cryptenamine, Deserpidine, Diazoxide Guanethidine, Iloprost, 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 and Platelet inhibitors, not aspirin	1.	Anticoagulants	Warfarin, Argatroban, Bivalirudin, Dalteparin, Enoxaprin, Eptifibatide, Fondaparinux, Heparin, Lepirudin, Tirofiban, Tinzaparin, Reviparin, Nadroparin, Ardeparin, Certoparin, Dabigatran
	2.	Platelet Inhibitors	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; MI = myocardial infarction; TIA = transient ischemic attack If medications are combinations of 2 drug classes then a patient is recorded as using both medications.
* 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 in the 730 days before treatment intensification.

Table S2. Details for the construction of the propensity score model

The pre-matching cohort was composed of all eligible persons who initiated metformin or sulfonylurea for diabetes and met the study's inclusion criteria. The matched cohort was formed by matching metformin users to sulfonylurea users with similar propensity scores. The propensity score (PS) is defined as the probability of sulfonylurea use, given a particular pattern of baseline covariates (Table 2). We estimated the PS using a logistic regression model in which the dependent variable was 1 for patients who used sulfonylurea and 0 for metformin users and used restricted cubic splines (3 knots) for continuous covariates in the model. The PS model is designed to be non-parsimonious and highly flexible to capture all observable confounding by indication. Indicator variables denoting missingness were included in the PS model, allowing the PS to balance missingness patterns between the exposures and control for potentially informative missingness. Multiply imputed PS model coefficients were aggregated using Rubin's rules and the aggregated model used to generate PS values. The PS model is displayed in Appendix Table 2. The PS model yielded a C statistic of 0.71. When used to facilitate matching, the success of the PS model is determined by the covariate balance achieved in the matched cohort. Table S1 and Figures S2 and S3 demonstrate the mean standardized differences before and after propensity score matching. Indicating good balance after matching, all standardized differences have an absolute value $\leq$ 0.1. An important condition for propensity score methods is that every cohort member have a nontrivial probability of having received either of the study therapies (positivity). Our matching procedure excluded sulfonylurea patients for whom very few similar metformin users existed. Unmatched sulfonylurea patients primarily were older, had higher number of co-morbidities and had a higher serum creatinine at the time of drug initiation (See Table S3 for characteristics of unmatched patients). The matching was performed on the log odds of the propensity scores using an 8:1 digit greedy match algorithm.

Logistic regression model for the probability of initiating Sulfonylurea (N=65,986 matches)

Characteristic	Odds Ratio	95% Confidence Intervals	
Comorbidities			
Malignancy	1.06	1.02	1.11
Liver/ respiratory failure	2.12	1.94	2.31
Congestive heart failure	1.60	1.53	1.67
Cardiovascular disease	1.02	0.99	1.04
Serious mental illness	0.98	0.95	1.01
Cardiac valve disease	1.04	0.96	1.12
Arrhythmia	1.02	0.98	1.06
Smoking	1.01	0.98	1.05
Chronic Obstructive Pulmonary Disease/ Asthma	1.01	0.98	1.05
HIV	1.66	1.45	1.91
Parkinsons	1.02	0.90	1.15
Indicators of health care utilization			
Hospitalized in last year (VA)	1.12	1.07	1.18
Hospitalized in last year (Medicare)	1.05	0.98	1.12
Hospitalized in last year (Medicaid)	0.92	0.72	1.17
Hospitalized in month of incident diabetes prescription (VA)	1.12	1.05	1.20
Hospitalized in month of incident diabetes prescription (Medicare)	1.21	1.11	1.31
Hospitalized in month of incident diabetes prescription (Medicaid)	1.11	0.76	1.61
Nursing Home encounter in last year	0.90	0.61	1.33
Number of medications	1.12	1.09	1.15
Outpatient Visits in past year	1.00	0.98	1.02
Medicare encounters in last year	0.92	0.90	0.94
Medicaid encounters in last year	1.11	1.05	1.17
Demographics			
Race Black	1.19	1.15	1.23
Race Other	1.11	1.06	1.17
Gender Female	0.54	0.50	0.57
Age	1.35	1.32	1.39
Incident therapy date	0.65	0.64	0.66
Clinical and laboratory			
HbA1c	1.09	1.08	1.11
Systolic Blood pressure	1.06	1.04	1.07

Diastolic Blood pressure	0.99	0.97	1.00
Body Mass Index	0.76	0.74	0.77
Low Density Lipoprotein	1.02	1.01	1.03
Creatinine	1.11	1.06	1.15
Estimated Glomerular Filtration Rate	0.80	0.77	0.83
Urine Protein negative	1.07	1.02	1.11
Urine Protein Trace or 1+	1.21	1.15	1.26
Proteinuria present at 2+,	1.26	1.17	1.36
Proteinuria present at 3+,	1.29	1.09	1.52
Proteinuria present at 4+	2.00	1.17	3.43
Medications			
ACE Inhibitors	0.98	0.96	1.00
ARBs	0.92	0.89	0.96
Calcium Channel Blockers	0.99	0.97	1.02
Beta Blockers	1.04	1.02	1.06
Thiazide and k sparing	0.97	0.95	0.99
Other Anti hypertensive medications	0.96	0.94	0.99
Statin lipid lowering agents	0.75	0.73	0.76
Non-statin lipid lowering agents	0.90	0.88	0.93
Anti-arrhythmics, digoxin and inotropes	1.15	1.07	1.23
Anticoagulant	1.05	1.01	1.10
Nitrates	1.12	1.09	1.16
Aspirin	0.97	0.95	1.00
Loop Diuretics	1.44	1.40	1.49
Antipsychotics	1.06	1.02	1.11
Oral glucocorticoids	1.03	0.99	1.06
Indicators of Missing covariates imputed			
HbA1c missing	0.97	0.94	1.00
LDL missing	1.08	1.05	1.11
Glomerular filtration rate missing	1.25	1.21	1.30
Blood pressure missing	0.93	0.85	1.03
BMI missing	1.23	1.14	1.33
Race missing	0.92	0.87	0.96
Urine protein testing missing	0.97	0.94	0.99
Location of care versus station 589			
Station 402	0.85	0.75	0.97
Station 405	0.84	0.71	1.00
Station 436	0.90	0.77	1.05
Station 437	1.83	1.59	2.12
Station 438	1.15	1.00	1.32
Station 442	0.72	0.58	0.89
Station 459	1.21	1.00	1.46
Station 460	1.00	0.87	1.16
Station 463	0.48	0.38	0.60
Station 501	0.92	0.81	1.04
Station 502	1.42	1.26	1.60
Station 503	1.30	1.13	1.49
Station 504	1.43	1.22	1.67
Station 506	0.98	0.85	1.14
Station 508	2.30	2.05	2.57
Station 509	1.12	0.97	1.30
Station 512	1.46	1.29	1.64
Station 515	1.16	1.00	1.34
Station 516	0.87	0.79	0.96
Station 517	1.12	0.94	1.33
Station 518	0.90	0.73	1.10
Station 519	1.82	1.53	2.16
Station 520	0.91	0.81	1.02
Station 521	0.63	0.56	0.72
Station 523	1.23	1.09	1.40
Station 526	1.04	0.88	1.25
Station 528	1.07	0.98	1.17
Station 529	2.30	1.93	2.74
Station 531	0.51	0.42	0.61
Station 534	0.75	0.66	0.86
Station 537	1.58	1.39	1.78
Station 538	2.27	1.94	2.66
Station 539	0.79	0.69	0.92

Station 540	1.26	1.09	1.45
Station 541	0.95	0.87	1.05
Station 542	1.03	0.87	1.22
Station 544	1.61	1.45	1.79
Station 546	1.16	1.03	1.31
Station 548	3.19	2.87	3.55
Station 549	1.74	1.59	1.91
Station 550	1.73	1.51	1.98
Station 552	0.78	0.68	0.89
Station 553	1.48	1.29	1.71
Station 554	1.37	1.22	1.55
Station 556	0.88	0.74	1.04
Station 557	1.52	1.32	1.77
Station 558	0.89	0.78	1.01
Station 561	1.51	1.36	1.68
Station 562	2.10	1.79	2.46
Station 564	1.20	1.07	1.36
Station 565	1.03	0.91	1.16
Station 568	1.71	1.46	2.02
Station 570	2.91	2.55	3.33
Station 573	1.28	1.17	1.40
Station 575	1.02	0.80	1.29
Station 578	1.25	1.11	1.40
Station 580	1.25	1.14	1.38
Station 581	1.45	1.28	1.64
Station 583	0.80	0.70	0.90
Station 585	1.08	0.92	1.27
Station 586	1.57	1.40	1.75
Station 590	1.32	1.14	1.53
Station 593	1.70	1.50	1.92
Station 595	0.87	0.77	0.99
Station 596	0.79	0.68	0.90
Station 598	1.54	1.38	1.72
Station 600	0.80	0.70	0.92
Station 603	1.41	1.24	1.61
Station 605	1.67	1.49	1.87
Station 607	1.02	0.88	1.17
Station 608	0.86	0.72	1.02
Station 610	1.09	0.97	1.23
Station 612	1.95	1.76	2.17
Station 613	1.70	1.49	1.92
Station 614	1.27	1.13	1.43
Station 618	1.24	1.11	1.38
Station 619	1.67	1.47	1.90
Station 620	1.76	1.51	2.04
Station 621	0.89	0.78	1.01
Station 623	0.83	0.72	0.94
Station 626	1.06	0.97	1.17
Station 629	1.21	1.06	1.38
Station 630	0.81	0.71	0.93
Station 631	1.37	1.11	1.69
Station 632	0.95	0.82	1.09
Station 635	1.39	1.24	1.55
Station 636	1.08	0.98	1.18
Station 637	0.94	0.82	1.08
Station 640	1.02	0.91	1.16
Station 642	1.14	1.02	1.28
Station 644	1.84	1.64	2.06
Station 646	1.47	1.31	1.65
Station 648	2.11	1.88	2.36
Station 649	1.49	1.28	1.73
Station 650	0.66	0.56	0.77
Station 652	0.71	0.62	0.82
Station 653	1.09	0.92	1.29
Station 654	0.72	0.61	0.86
Station 655	0.92	0.78	1.07
Station 656	0.96	0.82	1.12
Station 657	1.50	1.37	1.64
Station 658	1.47	1.29	1.68
Station 659	1.61	1.44	1.81

Station 660	0.59	0.51	0.69
Station 662	0.80	0.68	0.95
Station 663	1.85	1.66	2.06
Station 664	0.53	0.46	0.61
Station 666	0.85	0.66	1.09
Station 667	0.84	0.74	0.95
Station 668	1.40	1.19	1.64
Station 671	0.94	0.85	1.04
Station 672	1.62	1.47	1.79
Station 673	1.62	1.48	1.77
Station 674	0.84	0.75	0.93
Station 675	2.08	1.73	2.50
Station 676	1.18	0.99	1.39
Station 678	2.02	1.78	2.29
Station 679	1.03	0.84	1.25
Station 687	0.70	0.58	0.85
Station 688	1.46	1.29	1.65
Station 689	1.05	0.94	1.18
Station 691	1.32	1.19	1.47
Station 692	0.40	0.31	0.50
Station 693	1.57	1.39	1.76
Station 695	1.11	0.99	1.26
Station 740	0	0	infinity
Station 756	0.61	0.52	0.72
Station 757	1.71	1.48	1.97

Table S3. Characteristics of patients who did not match in 1 to 1 Propensity score matching

Characteristics of patients Excluded after PS matching	Sulfonylurea N=13,206	Metformin N=60,881
Age, median (IQR)	77 (69, 82)	60 (55, 67)
Male (%)	99	93
Race, (%)		
White	78	76
Black	14	11
Hispanic/ Other	5	4
Missing	0.7	10
HbA1c, % median (IQR)	7.0 (6.3, 8.0)	6.8 (6.2, 7.4)
Missing measurement, (%)	25	17
Low Density Lipoprotein mg/dL, median (IQR)	93 (74, 118)	100 (80, 124)
Missing measurement, (%)	40	20
Creatinine mg/dL, median (IQR)	1.2 (1.0, 1.4)	1.0 (0.9, 1.1)
Glomerular filtration rate ml/min, median (IQR)	62 (53, 77)	87 (76, 100)
Missing measurement, (%)	24	10
Proteinuria, (%) negative	41	53
Urine Protein Trace or 1+	13	8
Proteinuria present at 2+,	3	0.9
Proteinuria present at 3+,	0.7	0.2
Proteinuria present at 4+	0.1	0
Missing measurement, (%)	42	38
Systolic Blood pressure mm/Hg, median (IQR)	136 (122,150)	134 (124,144)
Diastolic Blood pressure mm/Hg, median (IQR)	72 (64, 80)	78 (70, 84)
Missing measurement, (%)	4	1
Body Mass Index (kg/meter^2), median (IQR)	27.9 (25.0, 31.2)	33.1 (29.7,37.4)
Missing measurement, (%)	6	2
Baseline Co-morbidities(%)‡		
Malignancy	9	4
Liver/ respiratory failure	4	0.3
HIV	1	0.1
Congestive heart failure	27	1
Cardiovascular disease	41	18
Serious mental illness	15	18
Smoking	10	12
Chronic Obstructive Pulmonary Disease	22	10
Cardiac valve disease	6	1
Arrhythmia	23	4
Parkinson's	1	0.3
Year N (%)		
2002-03	40	11
2004	22	15
2005	17	22
2006	12	26
2007	6	20
2008-2011 †	3	6
Use of Medications N (%)		
Angiotensin Converting Enzyme Inhibitors	55	53
Angiotensin II Receptor Blockers	7	8
Beta Blockers	52	37
Calcium Channel Blockers	30	22
Thiazide and potassium sparing diuretics	30	35
Non Selective alpha Blockers	19	13
Loop Diuretics	39	6
Other Anti hypertensive medications	28	22
Statin lipid lowering medications	49	69
Non Stain Lipid lowering medications	10	20
Anti-arrhythmics, digoxin and inotropes	5	1
Anticoagulants, platelet inhibitors	15	4
Nitrates	24	9
Aspirin	21	17
Antipsychotics	6	8
Oral Glucocorticoids	16	9
Indicators of health care utilization N (%)		
Hospitalized in last year (Veterans Health)	14	5
Hospitalized in last year (Medicare/Medicaid)	24	3
Hospitalized within 30 days (Veterans Health)	7	2
Hospitalized within 30 days (Medicare/Medicaid)	7	0.5

Nursing Home encounter in last year	0.1	0.03
Outpatient Visits in past year	6 (3, 10)	5 (3, 8)
Number Medications	11 (8,16)	9 (6, 14)
Medicare use in last year	48	20
Medicaid use in last year	29	5

Table S4. Description and Characteristics of the weighted analysis cohort

The weighted analyses were performed using inverse probability of treatment weights (IPTW). As opposed to a matched analysis which balances the baseline covariate distributions by selecting a subset of patients from each exposure, a weighted analysis balances the covariate distributions by assigning various weights to the patients in one exposure such that the weighted group now resembles the other group. When comparing metformin and sulfonylurea users, the sulfonylurea users were weighted so that their distribution of covariates resembled that of the metformin users. This was achieved by using stabilized IPTW such that metformin users receive a weight of 1 and sulfonylurea users a weight of $e_i/(1-e_i)$, where e_i is the probability of patient i receiving metformin given their covariates. This creates a pseudo-cohort that uses all of the eligible patients. In simple terms, the older, less healthy sulfonylurea users (who are over-abundant relative to metformin) are down-weighted to match the metformin distribution and the younger, healthier sulfonyurea users are up-weighted to match the metformin population. The sum of the metformin users' weights will equal the number of metformin users because they each received a weight of 1. The sum of the sulfonylurea users' weights will approximate the number of metformin users because the sulfonylurea users are being weighted to approximate that group. The sum will not equal the number of metformin users exactly because the IPTW rely on modeling the exposure and thus provide an approximate solution. Like with matching, the success of the weighting in achieving a well-balanced pseudo-cohort can be seen in the table of patient characteristics and plot of standardized differences. Also like matching, the weighted analysis may be used with or without additional direct covariate adjustment. The analysis that does not use additional covariate adjustment estimates the average sulfonylurea versus metformin effect in a population of metformin users - our control group. This is referred to as the average treatment effect among controls (ATC). In the metformin versus thiazolidinedione comparison, the smaller thiazolidinedione group could not be easily up-weighted to approximate the much larger metformin group; however, the metformin group could be easily down-weighted to approximate the thiazolidinedione users. Hence, we used the thiazolidinedione users as the stabilizing population and estimated the average treatment effect among the treated population (ATT).

Characteristics	***Weighted Cohort primary exposure***		***Weighted Cohort with positive control***	
	Sulfonylurea Weighted N=125,362	***Metformin N=126,867***	***Metformin Weighted N=6967***	***Thiazolidinedione N=6945***
Age, median (IQR)	62 (56, 71)	62 (56, 71)	68 (59, 75)	67 (59, 75)
Male (%)	95	95	97	97
Race, (%)				
White	76	76	80	80
Black	12	13	10	10
Hispanic/ Other	4	4	7	7
Missing	7	7	3	3
HbA1c, % median (IQR)	6.9 (6.3, 7.6)	6.8 (6.3, 7.5)	6.6 (6.1, 7.3)	6.6 (6.0, 7.2)
Missing measurement, (%)	19	19	35	34
Low Density Lipoprotein mg/dL, median (IQR)	99 (79, 123)	99 (79, 123)	96 (77, 119)	97 (78, 121)
Missing measurement, (%)	25	25	37	36
Creatinine mg/dL, median (IQR)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.10 (0.9, 1.20)	1.10 (0.9, 1.20)
Glomerular filtration rate ml/min, median (IQR)	83.7 (71, 98)	83.7 (71, 99)	77 (64, 92)	76 (62, 91)
Missing measurement, (%)	14	14	28	28
Proteinuria, (%) negative	51	51	47	47
Urine Protein Trace or 1+	10	10	8	8
Proteinuria present at 2+,	1	1	1	1
Proteinuria present at 3+,	0	0	0	0
Proteinuria present at 4+	0	0	0	0
Missing measurement, (%)	38	39	43	43
Systolic Blood pressure mm/Hg, median (IQR)	135 (124,146)	135 (124, 146)	134 (123,145)	133 (122, 144)
Diastolic Blood pressure mm/Hg, median (IQR)	77 (70, 84)	77 (70, 84)	73 (66, 80)	73 (66, 80)
Missing measurement, (%)	2	2	6	5

Body Mass Index (kg/meter^2), median (IQR)	31.9 (28.5, 36.2)	32.0 (28.6, 36.2)	30.4 (27.2, 34.3)	30.5 (27.3, 34.0)
Missing measurement, (%)	3	3	7	6
Baseline Co-morbidities(%)‡				
Malignancy	5	5	6	6
Liver/ respiratory failure	1	1	1	1
HIV	0	0	0	0
Congestive heart failure	4	4	6	7
Cardiovascular disease	23	22	30	30
Serious mental illness	17	17	15	15
Smoking	12	12	8	8
Chronic Obstructive Pulmonary Disease	12	12	12	12
Cardiac valve disease	1	1	2	2
Arrhythmia	7	6	10	10
Parkinson's	1	0	1	1
Use of Medications N (%)				
Angiotensin Converting Enzyme Inhibitors	53	53	49	49
Angiotensin II Receptor Blockers	8	8	12	12
Beta Blockers	40	40	40	40
Calcium Channel Blockers	24	24	27	27
Thiazide and potassium sparing diuretics	32	33	28	28
Non Selective alpha Blockers	14	14	16	15
Loop Diuretics	10	10	16	16
Other Anti hypertensive medications	24	24	25	25
Statin Lipid lowering agents	64	64	64	64
Non Statin lipid Lowering agents	18	18	17	17
Anti-arrhythmics, digoxin and inotropes	2	1	3	2
Anticoagulants, platelet inhibitors	5	5	7	7
Nitrates	11	11	14	14
Aspirin	17	17	14	14
Antipsychotics	8	8	6	6
Oral Glucocorticoids	11	11	10	10
Indicators of health care utilization N (%)				
Hospitalized in last year (Veterans Health)	6	6	4	4
Hospitalized in last year (Medicare/Medicaid)	6	6	13	13
Hospitalized within 30 days (Veterans Health)	3	3	2	2
Hospitalized within 30 days (Medicare/ Medicaid)	1	1	2	2
Nursing Home encounter in last year	0	0	0	0
Outpatient Visits in past year	6 (3, 9)	6 (3, 9)	5 (3, 9)	5 (3, 9)
Number Medications	10 (7,14)	10 (7, 15)	10 (7, 14)	10 (7, 14)
Medicare use in last year	24	23	37	38
Medicaid use in last year	8	8	13	13

Table S5. Sensitivity Analyses evaluating the hazard of heart failure in first 180 days of use of Sulfonylurea versus Metformin and Thiazolidinedione versus Metformin, using new-user design and inverse probability treatment weighted analysis

Weighted Analysis	*Metformin*	*Sulfonylurea Weighted**	*Metformin Weighted**	*Thiazolidinedione*
N at risk†	166397	163995	10200	10164
Heart failure hospitalization or cardiovascular death	624	915.9	72.7	125
Person Years	80031.8	78299.2	4881.9	4872.4
Unadjusted Rate/1000 person-years	7.8 (7.2, 8.4)	11.7 (11.0, 12.5)	14.9 (11.9, 18.7)	25.7 (21.6, 30.6)
Adjusted Hazard Ratio (95% CI)	**Reference**	**1.50 (1.35, 1.66)**	**Reference**	**1.72 (1.36, 2.18)**
Heart failure emergency department visit, hospitalization or cardiovascular death	769	1138.3	88.7	141
Person Years	79994.7	78240.8	4877.3	4869.8
Unadjusted Rate/1000 person-years	9.6 (9.0, 10.3)	14.5 (13.7, 15.4)	18.2 (14.8, 22.3)	29 (24.6, 34.0)
Adjusted Hazard Ratio (95% CI)	**Reference**	**1.51 (1.37, 1.66)**	**Reference**	**1.59 (1.28, 1.98)**

*****For the weighted analysis comparing sulfonylurea to metformin, the sulfonylurea population is weighted by their characteristics to more closely resemble the younger and healthier metformin population. For the weighted analysis comparing thiazolidinedione to metformin, the metformin population is weighted by their characteristics to more closely resemble the older population. Refer to Table S4 for details.

† The N at risk for the analysis of the first 180 days is larger then for the primary analysis cohort because it includes all patients from the primary unmatched cohort and also includes people who were excluded during the 180 day lag period for being non persistent; not having a full 180 days of follow-up; those who died; or were censored for reaching the threshold creatinine.

Table S6. Analysis of sensitivity to unmeasured confounding[1]

We evaluated the risk of heart failure in the presence of an unobserved confounder with a relative hazard of 2.3 for heart failure risk, and various prevalence levels of the confounder by exposure group. The primary analysis yielded a greater risk of heart failure with sulfonylurea use over metformin use; HR (95% CI): 1.32 (1.21, 1.43). The bolded numbers correspond to the necessary differential prevalence of such a confounder between exposure groups 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	1.32 (1.21,1.43)	1.49 (1.37,1.62)	1.66 (1.53,1.80)	1.84 (1.68,1.99)	2.01 (1.84,2.17)	2.17 (2.00,2.36)
	0.1	1.17 (1.07,1.27)	1.32 (1.21,1.43)	1.47 (1.35,1.60)	1.62 (1.49,1.76)	1.78 (1.63,1.92)	1.93 (1.77,2.09)
	0.2	**1.05 (0.96,1.14)**	1.18 (1.09,1.28)	1.32 (1.21,1.43)	1.46 (1.34,1.58)	1.59 (1.46,1.73)	1.73 (1.59,1.87)
	0.3	**0.95 (0.87,1.03)**	**1.07 (0.98,1.16)**	1.2 (1.10,1.30)	1.32 (1.21,1.43)	1.44 (1.32,1.56)	1.57 (1.44,1.70)
	0.4	**0.87 (0.80,0.94)**	**0.98 (0.90,1.06)**	1.09 (1.00,1.19)	1.21 (1.11,1.31)	1.32 (1.21,1.43)	1.43 (1.31,1.55)
	0.5	**0.80 (0.73,0.87)**	**0.90 (0.83,0.98)**	**1.01 (0.92,1.09)**	1.11 (1.02,1.21)	1.22 (1.12,1.32)	1.32 (1.21,1.43)

The observed risk of prior heart failure history with the primary outcome was an HR of 2.3. For an unmeasured confounder of this strength to tip the primary finding of this paper into statistical non-significance, it would need to be independent of the observed covariates and 17% more prevalent among sulfonylurea users if the prevalence among metformin users was 0%. If the prevalence in metformin users was between 20-50%, it would need to be 21-27% **more** prevalent. If the prevalence in metformin users was 70%, an unmeasured confounder of this strength could not tip the analysis into statistical non-significance. Due to the heterogeneous prescribing practices in the VHA during the study period, selection bias of this degree was not observed. There were no differences in prevalence of this magnitude among the observed covariates in the full (pre-matching) cohort (Table 1).

Figure S1. Study Design Schematic

Below is an example patient who initiated Metformin after having 180 days free of any antidiabetic drug. Sulfonylurea and Thiazolidinedione person time are tracked in the same manner.
Main analysis:
Persistent exposure required: Gaps (red bars) of up to 90 days are allowed in order to refill the regimen. Patients are censored at addition of another drug or no medication refills within 90 days.
Sensitivity analyses:
Persistent exposure not required: In this approach patients are analyzed as users of their incident prescribed regimen regardless of switching, stopping or additions (akin to intent to treat analysis)
First 180 days: This person time has a high likelihood of exposure misclassification and was excluded in above two analyses. This analysis of the first 180 days includes both those that do and don't refill their prescriptions as well as those who make other regimen changes, such as switching regimens and stopping medications. The resultant exposure misclassification, if non-differential would make it harder to show differences between treatment regimens.

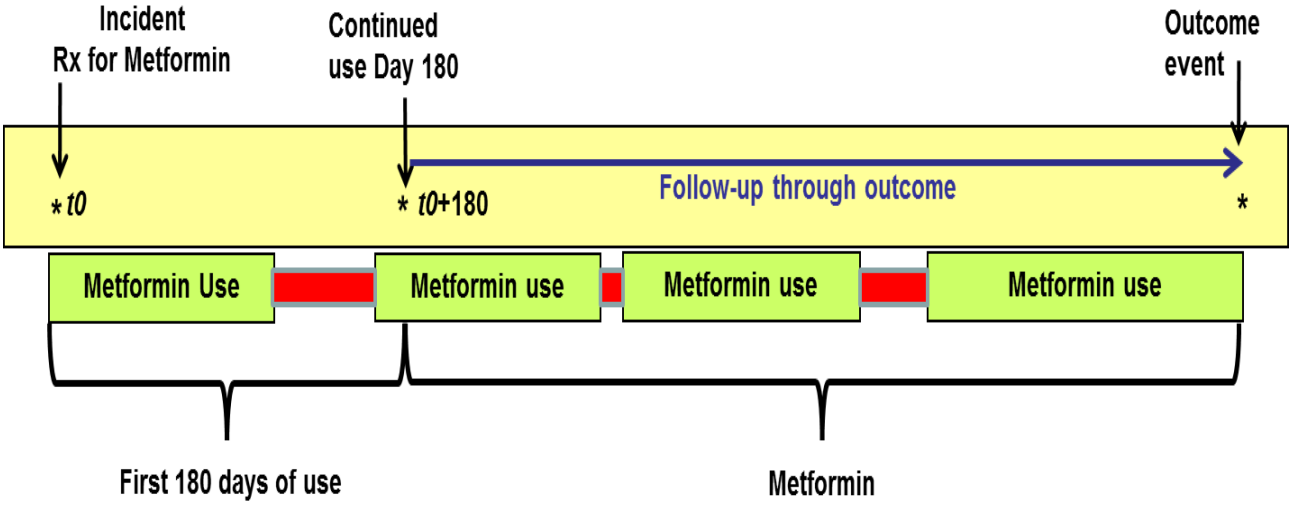


Figure S2. Distribution of Propensity Scores by drug

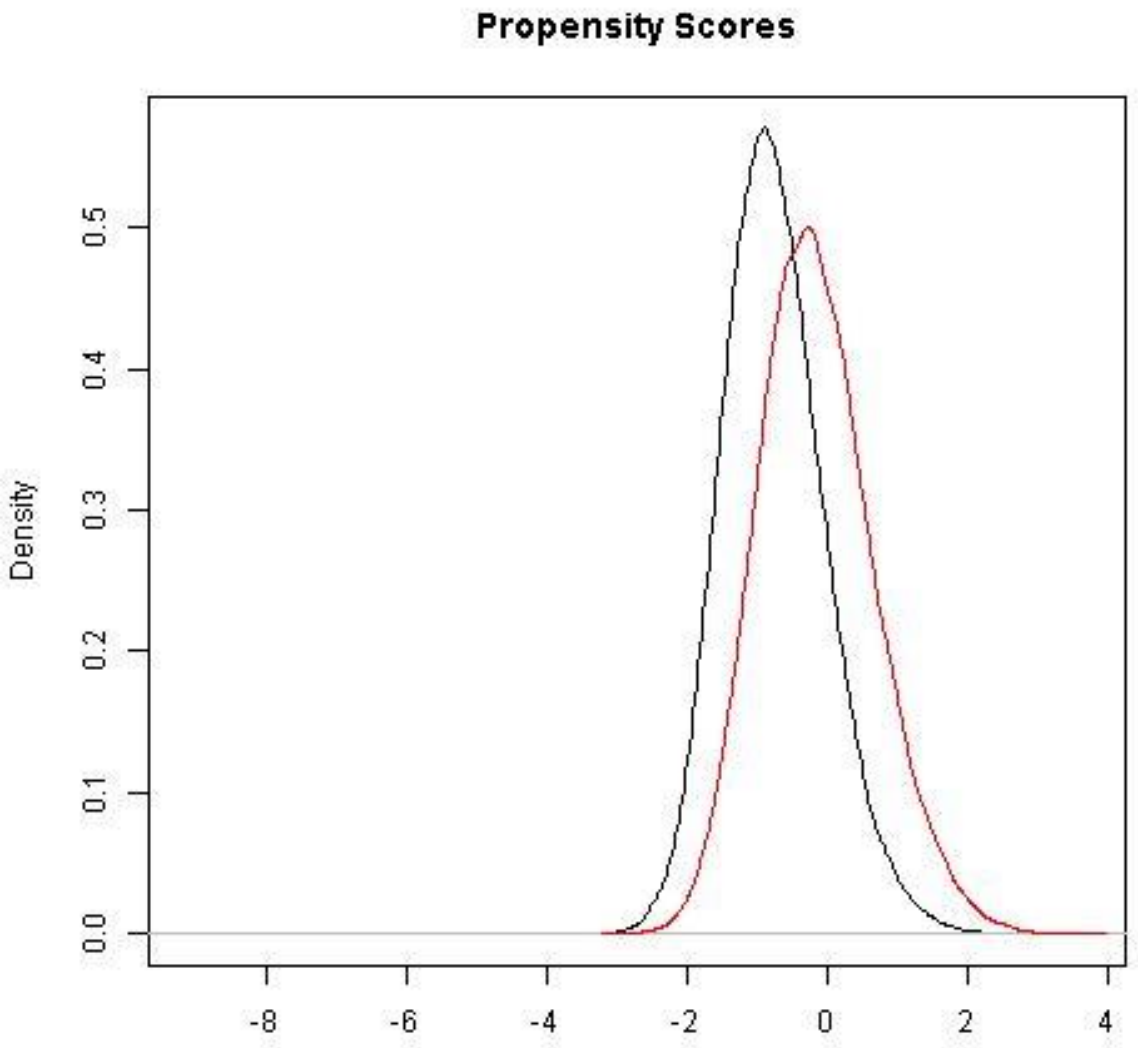
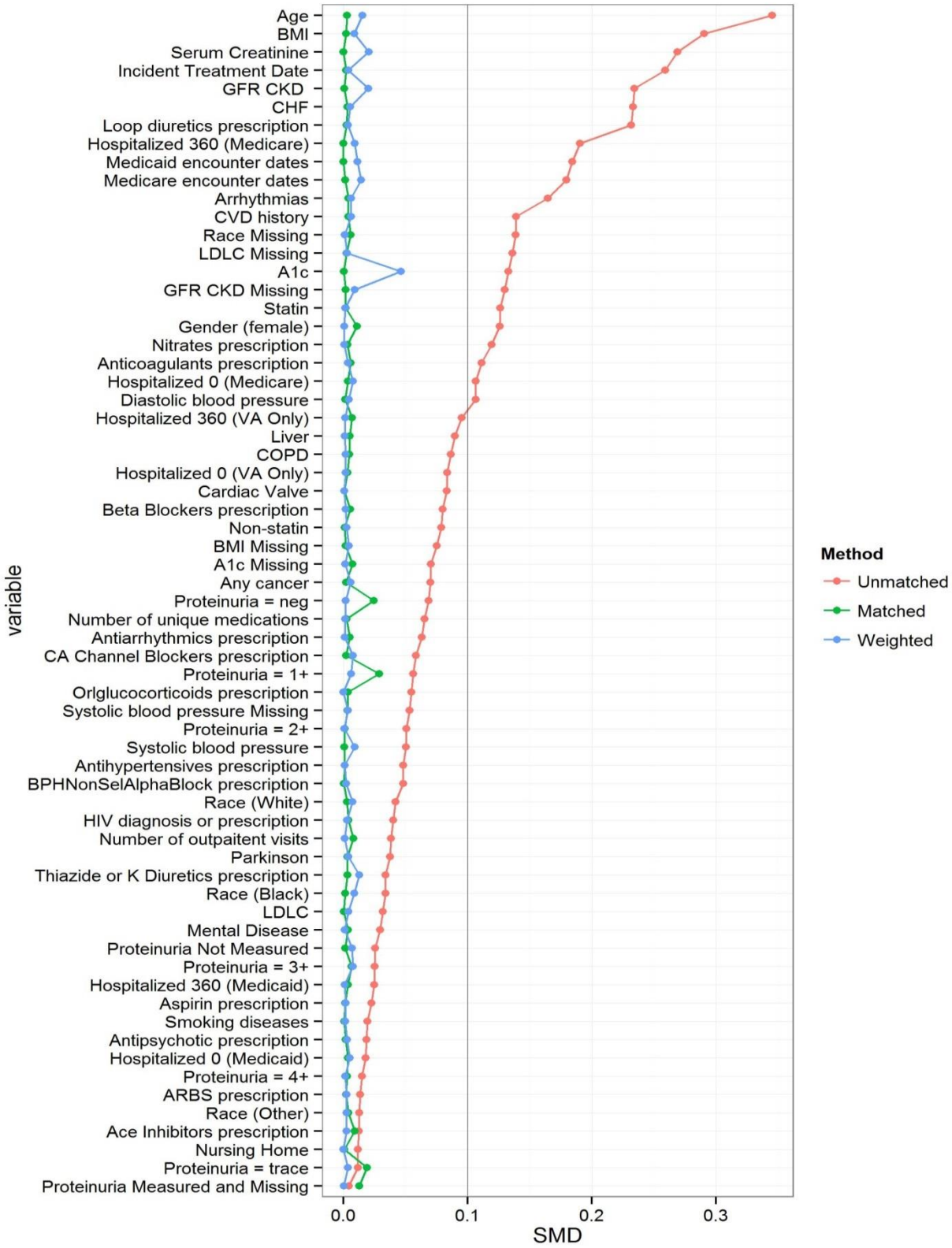


Figure S3. Mean Standardized difference plot comparing metformin versus sulfonylurea



Supplemental References:

1. Schneeweiss S, Glynn RJ, Tsai EH, Avorn J, Solomon DH. Adjusting for unmeasured confounders in pharmacoepidemiologic claims data using external information: the example of COX2 inhibitors and myocardial infarction. *Epidemiology*. 2005;16:17-24.

2. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011;46:399-424.

3. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661-79.