

Title: *Comparative Effectiveness of Second Line Agents for the Treatment of Diabetes Type 2 in Preventing Kidney Function Decline*

Supplemental Material

Supplemental Figure 1: Distribution of Propensity Scores by Drug.

Supplemental Figure 2: Percent of Person-Time Exposed to Sulfonylureas, Insulin, and Metformin for the two Exposure Groups, Metformin + Insulin and Metformin + Sulfonylurea, Under the Persistent Exposure Not Required Conditions.

Supplemental Figure 3. Adjusted hazard ratios for the composite outcome of persistent reduction of baseline estimated glomerular filtration rate of 35% or end-stage renal disease among age, race, HbA1c, and proteinuria subgroups.

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Supplemental Table 3: Logistic Regression Model for the Probability of Intensifying with Metformin + Insulin.

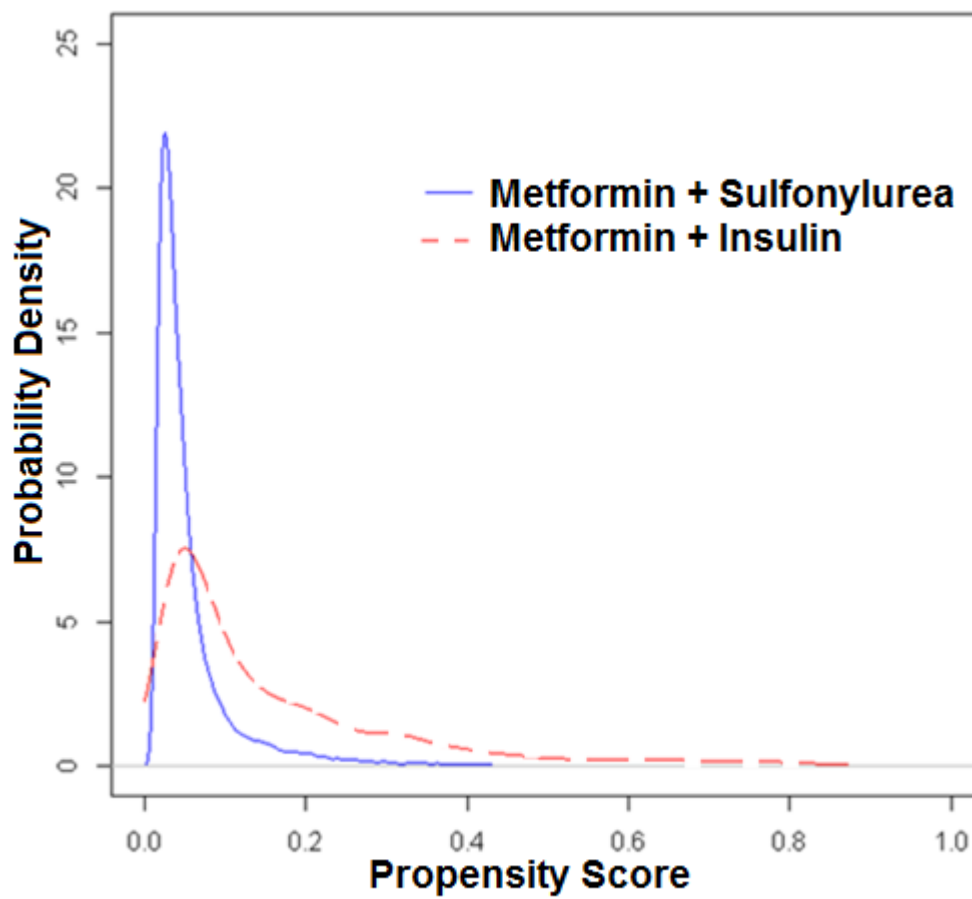
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Supplemental Table 5: Characteristics of the Full Cohort at the Time of Add on Therapy.

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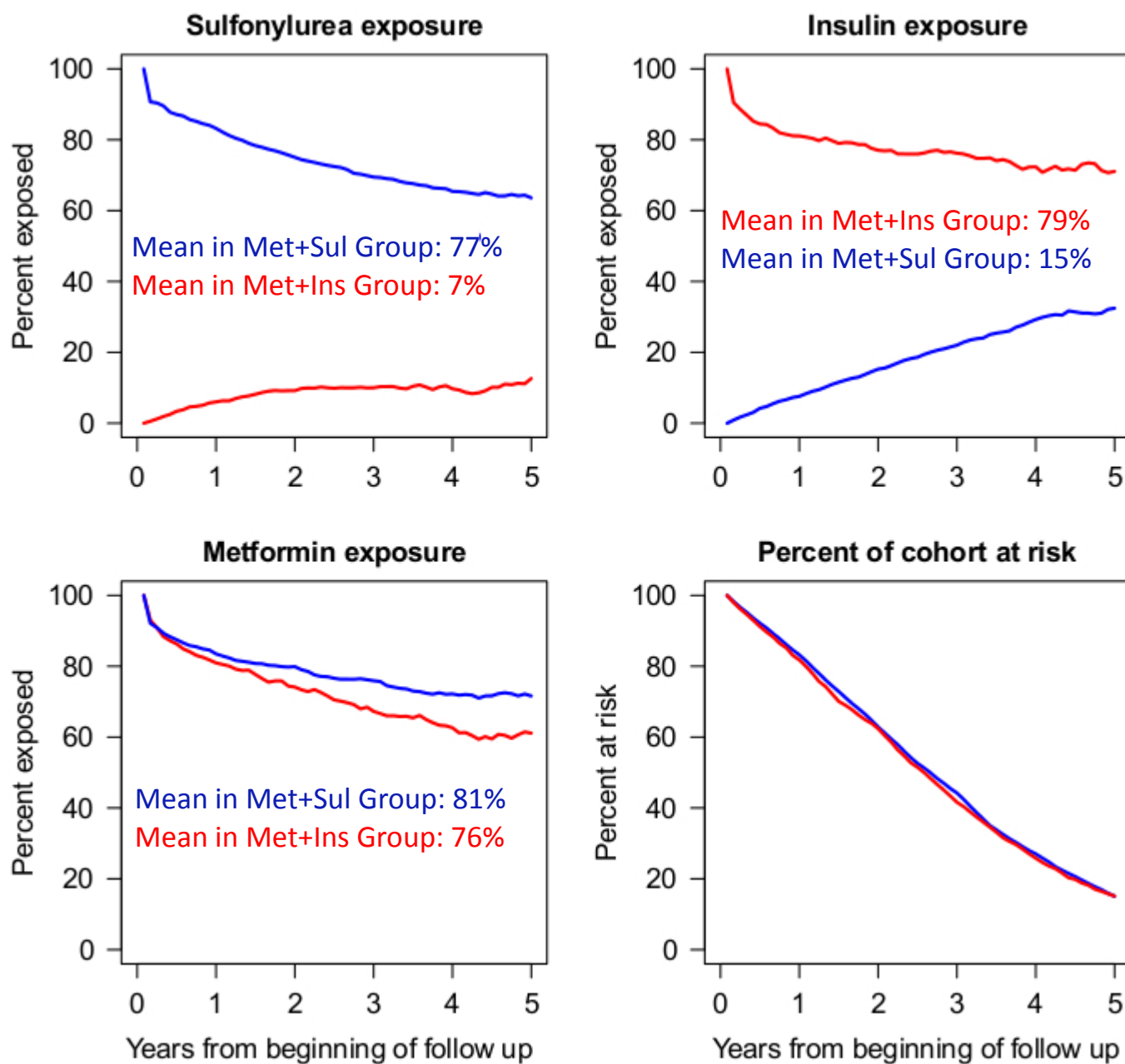
Supplemental Table 7: Characteristics of un-weighted propensity matched cohort remaining at risk 36 months after treatment intensification

Supplemental Figure 1. Distribution of Propensity Scores by Drugs

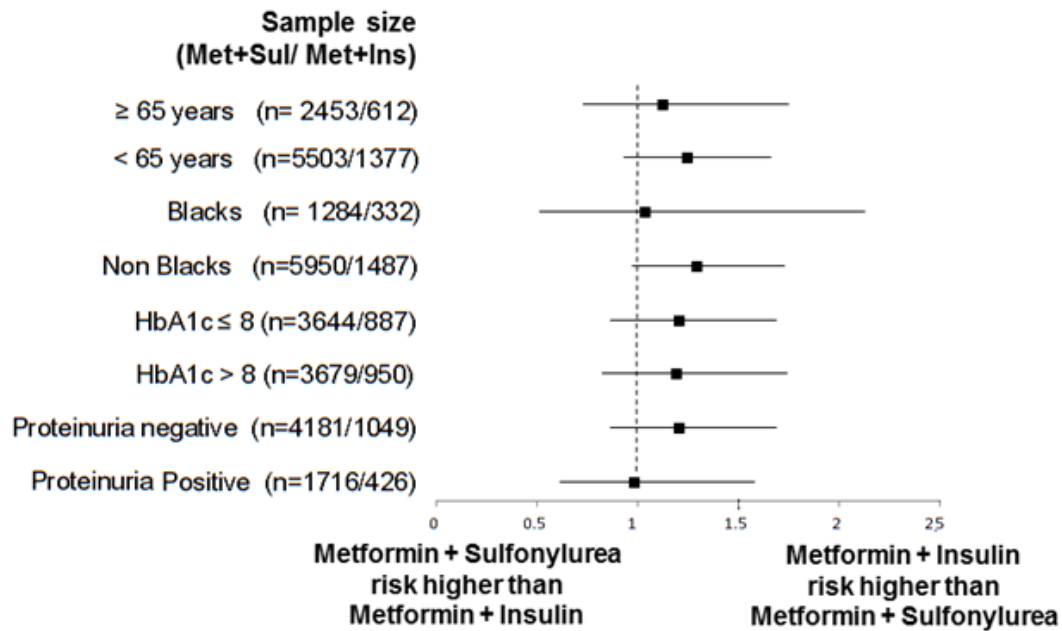


* Probability of using metformin + insulin

Supplemental Figure 2. Percent of Person-Time Exposed to Sulfonylureas, Insulin, and Metformin for the two Exposure Groups, Metformin + Insulin and Metformin + Sulfonylurea, Under the Persistent Exposure Not Required Conditions.



Supplemental Figure 3. Adjusted hazard ratios for the composite outcome of persistent reduction of baseline estimated glomerular filtration rate of 35% or end-stage renal disease among age, race, HbA1c, and proteinuria subgroups. Hazard ratios greater than 1 demonstrate an increased risk for composite outcome with the combination metformin plus insulin compared with the combination metformin plus sulfonylurea in the 1 to 4 match cohort.



Adjusted hazards were derived using Cox proportional hazard marginal structural model for time to the composite renal outcome, truncating weights at 5. Models were adjusted for : age, sex, race, fiscal year; physiologic variables (blood pressure, creatinine, HbA1c, low density lipoprotein levels [LDL] and body mass index [BMI] – baseline value was the measurement closest to the time of intensification); proteinuria categorized based on urine dipstick reading as negative, mild (trace or 1+) or heavy ($\geq 2+$)²⁷; indicators of healthcare utilization (number of outpatient visits, hospitalization during baseline, months from hospitalization to intensification; nursing home use); smoking; use of medications known to affect creatinine values (ACE inhibitors or ARBs, loop and thiazide diuretics), the presence of other co-morbidities and the location of care (Veterans Integrated Service Network [VISN]). All continuous variables were modeled as third degree polynomials.

Supplemental Table 1 Definitions of Outcomes

<i>Outcome</i>	<i>Definition</i>
1. GFR event	35% decrease in GFR noted on the second of 2 outpatient laboratory values. Requires change to be present on 2 outpatient GFR calculations between 3 and 12 months apart
2. ESRD	
a. eGFR <15 ml/min/1.73m ²	An outpatient laboratory measurement of eGFR <15 ml/min/1.73 m ² with confirmatory eGFR <15 or dialysis code at least 3 months and less than 12 months apart
b. dialysis	Either an inpatient and outpatient code or 2 outpatient codes for dialysis as the primary diagnosis (at least 3 months and less than 12 months apart) Codes include 1. ICD-9 diagnosis codes: 585.6; V56; V45.1 2. ICD 9 procedure codes: 399; 339; 955; 498 3. CPT4 codes: 90935, 90937, 90945, 90947, 909999, 90989, 90993, 90920, 90921, 90924, 90925, 90960, 90961, 90962, 90966, 90970, 99512
c. transplant	Either an inpatient and outpatient code for renal transplant as the primary diagnosis Codes include 1. ICD 9 diagnosis codes: 996.81; V42.0 2. ICD 9 procedure codes: 55.6, 55.61, 55.69 3. CPT codes: 50360, 50365, 50380

Supplemental Table 2

Definitions of Comorbid Conditions and Medications, on the Basis of Codes and 3 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, Nicotiny 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

COPD/ Asthma HIV		Medications: Varenicline tartrate, Nicotine Replacement therapy (gum, patch, lozenge) ICD 9- CM diagnosis codes:491.X, 492.X, 493.X, 496.X, V17.5, V81.3 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 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
Parkinson's Disease		
Medications ACE Inhibitors or ARBs alone/combo	ACE Inhibitors or ARBs alone/combo	Benazapril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, Candesartan, Eprosartan, Irbesartan, Losartan, Azilsartan, Olmesartan, Telmisartan, Valsartan
Antipsychotics	Atypical and typical antipsychotic medications	Lithium, Clozapine, Haloperidol, Loxipine, 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
Antihypertensives	1. Beta-blockers 2. Calcium Channel Blockers 3. Thiazide diuretics/ Potassium sparing diuretics 4. Other Antihypertensives	Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol Tartrate, Metoprolol Succinate, Propranolol, Penbutolol, Pindolol, Nadolol, Sotolol, Timolol, Nebivolol Amlodipine, Isradipine; Felodipine, Nifedipine, Nifedipine ER, Nicardipine; Diltiazem, Verapamil, Nimodipine; Nisoldipine; Bepridil, Amlodipine–Atorvastatin, Clevidipine Butyrate, Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Methyclothiazide, Trichlormethiazide, Metolazone, Indapamide, Eplerenone; Amelioride, Spironolactone, Triamterene, Hydrochlorothiazide/Triamterene, Hydrochlorothiazide/Spironolactone, Bendroflumethiazide, Benzthiazide, Cyclothiazide, Hydroflumethiazide, Methyclothiazide, Trichlormethiazide, Metolazone, Indapamide, Polythiazide, Quinethazone 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-arrhythmic Digoxin and other inotropes	1. Digoxin 2. Anti- Arrhythmic	Digoxin, Digitalis Adenosine, Amiodarone, Lidocaine, Flecainide, Ibutilide, Pacerone, Procainamide, Rhythmol, Propafenone, 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

Lipid lowering drugs	2. Platelet Inhibitors	Clopidogrel, Ticlopidine, Aspirin/ Dipyrimidole, Dipyrimidole alone, Abciximab, Factor IX, Factor VIIa, Factor VIII, Prasugrel, Ticagrelor
	1. Statins	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Rosuvastatin, Cerivastatin, Pitavastatin, Lovastatin ER, Ezetimibe/Simvastatin, Lovastatin /Niacin
	2. Non Statins	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, Erythryl Tetranitrate Nitroglycerin (all forms--SA, Patch, SL, Ointment; Aerosol spray), Ranolazine
Aspirin		Aspirin, Aspirin/ Dipyrimidole
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

* 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.

Supplemental Table 3. Logistic regression model for the probability of intensifying with Metformin + Insulin

Characteristics	Odds Ratio 95% Confidence Interval
Comorbidities	
Malignancy	1.292 (1.249, 1.337)
Liver/respiratory failure	1.623 (1.558, 1.691)
Congestive Heart Failure	1.000 (0.961, 1.040)
Cardiovascular disease	1.092 (1.064, 1.120)
Cardiac valve disease	0.916 (0.862, 0.975)
Arrhythmia	0.915 (0.883, 0.949)
Smoking	0.891 (0.870, 0.914)
COPD/Asthma	1.155 (1.125, 1.185)
HIV	1.710 (1.524, 1.919)
Demographics	
Race Black	1.064 (1.033, 1.095)
Race Other	0.938 (0.893, 0.985)
Gender female	1.396 (1.335, 1.460)
Age*	0.990 (0.989, 0.992)
Age_2	1.000 (1.000, 1.000)
Age_3	1.000 (1.000, 1.000)
Fiscal year 2002-2003	0.985 (0.925, 1.049)
Fiscal year 2004	0.868 (0.827, 0.911)
Fiscal year 2005	0.897 (0.861, 0.935)
Fiscal year 2006	1.031 (0.994, 1.069)
Fiscal year 2008	1.722 (1.665, 1.781)
Fiscal year 2009	2.060 (1.987, 2.135)
Fiscal year 2010	2.367 (2.275, 2.463)
Fiscal year 2011	2.255 (2.120, 2.398)
Time to intensification*, Month	0.987 (0.985, 0.988)
Time to intensification*, Month_2	1.000 (1.000, 1.000)
Time to intensification*, Month_3	1.000 (1.000, 1.000)
Clinical and Laboratory	
Creatinine*	1.216 (1.154, 1.280)
Creatinine_2	1.053 (0.968, 1.146)

Creatinine_3	0.961 (0.936, 0.984)
Urine protein trace	0.966 (0.944, 0.990)
Urine protein positive	1.002 (0.957, 1.049)
HbA1c*	1.208 (1.199, 1.217)
HbA1c_2	1.080 (1.077, 1.083)
HbA1c_3	0.992 (0.992, 0.993)
Systolic blood pressure	1.001 (1.000, 1.002)
Systolic blood pressure	1.000 (1.000, 1.000)
Systolic blood pressure	1.000 (1.000, 1.000)
Diastolic blood pressure	0.988 (0.987, 0.990)
Diastolic blood pressure	1.000 (1.000, 1.000)
Diastolic blood pressure	1.000 (1.000, 1.000)
Body mass index	0.981 (0.979, 0.964)
Body mass index	1.002 (1.002, 1.002)
Body mass index	1.000 (1.000, 1.000)
Low Density Lipoprotein	0.997 (0.997, 0.977)
Low Density Lipoprotein	1.000 (1.000, 1.000)
Low Density Lipoprotein	1.000 (1.000, 1.000)
Medications	
ACE Inhibitors or ARBs	1.036 (1.012, 1.059)
Other anti-hypertensive medications	1.004 (0.980, 1.028)
Statin and no-Statin lipid lowering agents	0.850 (0.829, 0.872)
Anti-arrhythmic, digoxin and other inotropes	1.290 (1.210, 1.374)
Anticoagulants	1.290 (1.210, 1.374)
Nitrates	1.031 (0.997, 1.066)
Aspirin	1.023 (1.000, 1.047)
Loop diuretics	1.537 (1.490, 1.586)
Antipsychotics	1.241 (1.201, 1.283)
Indicators of health care utilization	
Hospitalized in the prior year	1.213 (1.141, 1.289)
Recentness of hospitalization	1.023 (0.991, 1.056)
Recentness of hospitalization	0.994 (0.986, 1.002)
Recentness of hospitalization	1.001 (1.001, 1.002)

Nursing home utilization in the prior year	1.982 (1.603, 2.452)
Number of outpatients visits in the prior year	1.009 (1.006, 1.011)
Number of outpatients visits in the prior year	1.000 (1.000, 1.000)
Number of outpatients visits in the prior year	1.000 (1.000, 1.000)
Location of care	
VISN_1	1.102 (1.041, 1.167)
VISN_2	1.051 (0.982, 1.125)
VISN_3	0.862 (0.802, 0.927)
VISN_4	0.991 (0.937, 1.048)
VISN_5	1.249 (1.168, 1.336)
VISN_6	1.293 (1.230, 1.358)
VISN_7	1.194 (1.136, 1.255)
VISN_8	0.752 (0.716, 0.791)
VISN_9	1.102 (1.048, 1.159)
VISN_10	1.123 (1.063, 1.186)
VISN_11	1.428 (1.356, 1.504)
VISN_12	0.854 (0.802, 0.909)
VISN_15	1.067 (1.006, 1.131)
VISN_17	1.133 (1.072, 1.198)
VISN_18	1.138 (1.074, 1.206)
VISN_19	1.230 (1.150, 1.316)
VISN_20	1.500 (1.424, 1.580)
VISN_21	0.585 (0.543, 0.631)
VISN_22	0.842 (0.796, 0.891)
VISN_23	0.987 (0.934, 1.042)
Indicators of missing covariates that were inputted	
HbA1c missing	1.289 (1.239, 1.341)
Systolic blood pressure missing	0.827 (0.744, 0.919)
BMI missing	1.305 (1.204, 1.416)
LDL missing	1.145 (1.111, 1.180)
Urine protein testing missing	1.023 (1.000, 1.180)

Supplemental Table 4. Logistic regression models for the probability of censoring and the probability of death throughout the follow-up period

Characteristics	Odds Ratio 95% Confidence Interval	
	Probability of death	Probability of Censoring
Comorbidities		
Malignancy	2.795 (2.521, 3.100)	1.027 (0.995, 1.059)
Liver/respiratory failure	2.319 (2.073, 2.593)	1.009 (0.972, 1.048)
Congestive Heart Failure	1.190 (1.049, 1.350)	1.089 (1.050, 1.130)
Cardiovascular disease	1.118 (0.997, 1.254)	1.139 (1.112, 1.167)
Cardiac valve disease	1.524 (1.312, 1.770)	1.139 (1.038, 1.204)
Arrhythmia	1.083 (0.966, 1.214)	1.010 (1.139, 1.043)
Smoking	1.261 (1.135, 1.401)	1.041 (1.010, 1.065)
COPD/Asthma	1.333 (1.197, 1.485)	1.010 (1.017, 1.036)
HIV	0.908 (0.481, 1.714)	0.830 (0.740, 1.065)
Demographics		
Race Black	0.967 (0.816, 1.146)	1.035 (1.006, 1.065)
Race Other	0.638 (0.455, 0.894)	1.128 (1.074, 1.184)
Gender female	0.895 (0.664, 1.207)	1.150 (1.101, 1.200)
Age*	1.023 (1.013, 1.033)	1.006 (1.004, 1.008)
Age_2	1.000 (0.999, 1.000)	1.000 (1.000, 1.000)
Age_3	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Fiscal year 2002-2003	0.956 (0.721, 1.268)	0.586 (0.549, 0.626)
Fiscal year 2004	0.812 (0.666, 0.990)	0.565 (0.538, 0.594)
Fiscal year 2005	1.098 (0.928, 1.299)	0.689 (0.661, 0.718)
Fiscal year 2006	0.856 (0.734, 0.997)	0.778 (0.751, 0.807)
Fiscal year 2008	0.982 (0.844, 1.143)	1.244 (1.204, 1.285)
Fiscal year 2009	1.014 (0.851, 1.208)	1.955 (1.888, 2.024)
Fiscal year 2010	0.877 (0.677, 1.137)	4.161 (4.001, 4.327)
Fiscal year 2011	0.611 (0.250, 1.494)	28.693 (26.631, 30.914)
Time to intensification*, Month	0.989 (0.983, 0.955)	1.034 (1.033, 1.036)

Time to intensification*, Month_2	1.000 (1.000, 1.001)	1.000 (1.000, 1.000)
Time to intensification*, Month_3	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Clinical and Laboratory		
Creatinine*	0.780 (0.634, 0.960)	1.667 (1.586, 1.752)
Creatinine_2	1.808 (1.502, 2.176)	1.460 (1.331, 1.600)
Creatinine_3	0.913 (0.884, 0.943)	0.902 (0.873, 0.931)
Urine protein trace	1.850 (1.667, 2.053)	0.988 (0.966, 1.011)
Urine protein positive	2.786 (2.346, 3.308)	1.147 (1.097, 1.200)
HbA1c*	0.961 (0.918, 1.005)	1.266 (1.257, 1.276)
HbA1c_2	1.016 (1.003, 1.030)	0.998 (0.994, 1.001)
HbA1c_3	1.000 (0.998, 1.002)	0.999 (0.998, 0.999)
Systolic blood pressure	0.994 (0.990, 0.998)	1.002 (1.001, 1.003)
Systolic blood pressure	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Systolic blood pressure	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Diastolic blood pressure	0.999 (0.992, 1.007)	1.001 (0.999, 1.003)
Diastolic blood pressure	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Diastolic blood pressure	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Body mass index	0.943 (0.935, 0.952)	1.001 (0.998, 1.003)
Body mass index	1.003 (1.002, 1.004)	1.000 (1.000, 1.001)
Body mass index	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Low Density Lipoprotein	0.996 (0.994, 0.998)	1.001 (1.001, 1.001)
Low Density Lipoprotein	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Low Density Lipoprotein	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Medications		
ACE Inhibitors or ARBs	0.832 (0.751, 0.922)	0.793 (0.776, 0.810)
Other anti-hypertensive medications	0.871 (0.771, 0.984)	0.781 (0.763, 0.799)
Statin and no-Statin lipid lowering agents	0.807 (0.719, 0.906)	0.608 (0.594, 0.623)

Anti-arrhythmic, digoxin and other inotropes	1.170 (0.939, 1.459)	0.986 (0.921, 1.054)
Anticoagulants	0.992 (0.885, 1.111)	0.964 (0.934, 0.995)
Nitrates	0.832 (0.724, 0.955)	1.087 (1.05, 1.127)
Aspirin	0.623 (0.555, 0.701)	0.918 (0.897, 0.939)
Loop diuretics	1.244 (1.105, 1.401)	0.937 (0.908, 0.967)
Indicators of health care utilization		
Hospitalized in the prior year	0.682 (0.447, 1.041)	1.032 (0.954, 1.117)
Recentness of hospitalization	1.396 (1.177, 1.655)	1.083 (1.045, 1.123)
Recentness of hospitalization	0.920 (0.889, 0.952)	0.989 (0.980, 0.997)
Recentness of hospitalization	1.007 (1.005, 1.009)	1.001 (1.000, 1.001)
Nursing home utilization in the prior year	6.178 (3.769, 10.126)	1.516 (1.123, 2.046)
Number of outpatients visits in the prior year	1.000 (0.989, 1.011)	1.004 (1.002, 1.006)
Number of outpatients visits in the prior year	1.000 (1.000, 1.001)	1.000 (1.000, 1.000)
Number of outpatients visits in the prior year	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
Location of care		
VISN_1	0.586 (0.433, 0.793)	0.864 (0.818, 0.912)
VISN_2	1.720 (1.256, 2.354)	0.890 (0.832, 0.952)
VISN_3	1.101 (0.821, 1.478)	0.870 (0.808, 0.936)
VISN_4	1.301 (1.017, 1.665)	0.896 (0.848, 0.947)
VISN_5	0.839 (0.594, 1.186)	0.961 (0.898, 1.027)
VISN_6	1.091 (0.858, 1.387)	0.955 (0.910, 1.003)
VISN_7	1.164 (0.916, 1.477)	0.999 (0.951, 1.049)
VISN_8	0.993 (0.787, 1.254)	0.985 (0.939, 1.033)
VISN_9	1.097 (0.870, 1.383)	0.930 (0.886, 0.977)
VISN_10	1.335 (1.045, 1.706)	0.954 (0.903, 1.008)

VISN_11	0.810 (0.619, 1.059)	0.947 (0.901, 0.997)
VISN_12	0.379 (0.259, 0.556)	0.881 (0.829, 0.938)
VISN_15	0.784 (0.599, 1.025)	0.946 (0.893, 1.001)
VISN_17	0.823 (0.595, 1.138)	0.950 (0.900, 1.003)
VISN_18	1.068 (0.801, 1.424)	0.960 (0.907, 1.015)
VISN_19	0.870 (0.616, 1.228)	0.909 (0.852, 0.970)
VISN_20	0.943 (0.741, 1.200)	0.857 (0.814, 0.902)
VISN_21	0.858 (0.589, 1.251)	0.979 (0.913, 1.051)
VISN_22	1.074 (0.818, 1.409)	0.996 (0.942, 1.054)
VISN_23	1.008 (0.785, 1.294)	0.847 (0.803, 0.894)
Indicators of missing covariates that were inputted		
HbA1c missing	1.316 (1.020, 1.699)	1.180 (1.099, 1.266)
Systolic blood pressure missing	0.501 (0.303, 0.831)	0.995 (0.851, 1.164)
BMI missing	2.172 (1.501, 3.142)	1.341 (1.182, 1.523)
LDL missing	1.218 (1.017, 1.457)	1.153 (1.099, 1.208)
Creatinine missing post cohort entry	0.644 (0.463, 0.895)	1.033 (0.980, 1.087)
Urine protein testing missing	1.267 (1.140, 1.409)	0.991 (0.970, 1.014)

*Notice that imputed creatinine was used only in this study to calculate the probability of remaining uncensored.

Supplemental Table 5. Characteristics of the full cohort at the time of add on therapy

Characteristics	Full Cohort		Standardized differences
	Metformin + Sulfonylurea N=34012	Metformin + Insulin N=2393	
Age , median (IQR)*	61 (56, 68)	60 (54, 67)	0.16
Male %	96	94	0.09
Race , %			
White	74	69	0.12
Black	13	19	0.19
Other/Unknown	5	4	0.02
eGFR , ml/ min median (IQR)	81 (68, 96)	82 (67, 100)	0.08
Urine protein measurement available , %	64	67	0.06
	43	41	0.04
Proteinuria in the tested group , %			
Creatinine , mg/dL, median (IQR)	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	0.02
Systolic blood pressure , mmHg median(IQR)	132 (122,143)	131 (120, 142)	0.10
Diastolic blood pressure , mmHg median(IQR)	77 (70, 84)	76 (68, 84)	0.06
HbA1c , % median (IQR)	7.8 (7.0, 8.5)	8.5 (7.0, 10.7)	0.59
Body mass index (kg/m ²), median (IQR)	33 (29, 37)	32 (28, 37)	0.04
Baseline use of medications			
ACEI or ARBs, % †	72	71	0.02
Loop Diuretics, %	10	19	0.26
Statins, %	82	77	0.13
Anti-hypertensive drugs, %	73	73	0.01
Months to additional therapy , median (IQR)	18 (8,34)	17 (7, 34)	0.11
Baseline Co-morbidities (%)			
Cardiovascular Disease	30	36	0.08
Malignancy	8	10	0.09
Liver or respiratory failure	3	8	0.29
Congestive Heart Failure	6	11	0.23
HIV	0	1	0.09
Arrhythmias	9	12	0.12
Smoking	20	25	0.11

COPD/Asthma	16	23	0.20
Indicators of health care utilization			
Hospitalizations in the prior year (%)	14	37	0.63
Outpatients visit in the last year, % median (IQR)	6 (4, 10)	8 (4, 13)	0.26
Nursing home utilization in the prior year (%)	0.1	0.3	0.06
Calendar year			0.17
2002	0	0	
2003	3	3	
2004	7	6	
2005	11	9	
2006	16	13	
2007	19	15	
2008	17	20	
2009	14	17	
2010	10	13	
2011	3	4	

* IQR interquartile range

† ACEI angiotensin converting enzyme inhibitors, ARB angiotensin receptor blocker

Supplemental Table 6: Characteristics of un-weighted propensity matched cohort remaining at risk 12 months after treatment intensification

Characteristics	Remaining in cohort at 1 year	
	Metformin+ Sulfonylurea N= 4451	Metformin+ Insulin N= 1095
Age , median (IQR)	60.56 (54.46, 66.98)	59.9 (54.5, 65.7)
Male N (%)	4201 (94)	1404 (95)
Race , N (%)		
White	3231 (73)	793 (72)
Black	649 (15)	162 (15)
Hispanic/ Other	165 (4)	37 (3)
Time to intensification †, months median (IQR)	19 (8, 34)	18 (8, 34)
HbA1c , % median (IQR)	8.0 (7.1, 9.7)	8.1 (6.9, 10.0)
Missing measurement, N (%)	319 (7)	92 (8)
Creatinine mg/dL, median (IQR)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
Glomerular filtration rate ml/min, median (IQR)	82.6 (70.48, 97.19)	82 (68.7, 99.6)
Proteinuria ,		
Negative	2363 (53)	595 (54)
Mild (trace or +1)	756 (17)	190(17)
Moderate	147 (3)	37(3)
Missing measurement, N (%)	1185 (27)	273(25)
Systolic Blood pressure mm/Hg, median (IQR)	131 (121, 141)	131(120,141)
Diastolic Blood pressure mm/Hg, median (IQR)	76 (69, 83)	76(68,83)
Missing measurement, N (%)	70 (2)	15(1)
Body Mass Index (kilograms/meter ²), median (IQR)	32.5 (28.8, 37.2)	32.9 (28.9, 37.7)
Missing measurement, N (%)	113 (2)	24 (2)
Low Density Lipoprotein mg/dL, median (IQR)	85 (67, 108)	87 (67, 112)
Missing measurement, N (%)	713 (16)	184 (17)

Baseline Co-morbidities N(%)‡		
Malignancy	422(9)	84(8)
Liver/ respiratory failure	238 (5)	49(4)
HIV	29(0.5)	9 (0.8)
Congestive heart failure	352 (8)	83 (8)
Cardiovascular disease	1470(33)	365 (33)
Serious mental illness	1477 (33)	356 (33)
Smoking	969 (22)	253(23)
Chronic Obstructive Pulmonary Disease/Asthma	892 (20)	230 (21)
Cardiac valve disease	97 (2)	19 (2)
Arrhythmia	445(10)	104 (9)
Parkinson's	38(1)	8 (0.7)

Supplemental Table 7: Characteristics of un-weighted propensity matched cohort remaining at risk 36 months after treatment intensification

Characteristics	Remaining in cohort at 3 years	
	Metformin+ Sulfonylurea N= 1277	Metformin+ Insulin N= 333
Age , median (IQR)	60.10 (54.47, 66.78)	59.12 (53.93, 64.51)
Male N (%)	1215 (95)	315 (95)
Race , N (%)		
White	951 (74)	241 (72)
Black	170 (13)	55 (17)
Hispanic/ Other	41 (3)	8 (2)
Time to intensification †, months median (IQR)	13 (6, 24)	14 (6, 27)
HbA1c , % median (IQR)	7.7 (6.9, 9.4)	8.0 (6.8, 10.1)
Missing measurement, N (%)	130 (10)	30 (9)
Creatinine mg/dL, median (IQR)	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)
Glomerular filtration rate ml/min, median (IQR)	82.0 (70.7, 95.1)	81.3 (69.9, 96.6)
Proteinuria ,		
Negative	699 (55)	181 (54)
Mild (trace or +1)	196 (15)	48 (14)
Moderate	32 (3)	13 (4)
Missing measurement, N (%)	350 (27)	91 (27)
Systolic Blood pressure mm/Hg, median (IQR)	130 (120, 140)	132 (122,142)
Diastolic Blood pressure mm/Hg, median (IQR)	75 (68, 82)	76 (69, 84)
Missing measurement, N (%)	26 (2)	6 (2)
Body Mass Index (kilograms/meter ²), median (IQR)	32.6 (28.9, 37.3)	33.3 (29.4, 37.7)
Missing measurement, N (%)	33 (3)	8 (2)
Low Density Lipoprotein mg/dL, median (IQR)	87 (67, 110)	85 (64, 108)
Missing measurement, N (%)	285 (22)	71 (21)

Baseline Co-morbidities N(%)‡		
Malignancy	107 (8)	23 (7)
Liver/ respiratory failure	55 (4)	16 (5)
HIV	3 (0)	6 (2)
Congestive heart failure	92 (7)	19 (6)
Cardiovascular disease	417 (33)	102 (31)
Serious mental illness	385 (30)	102 (31)
Smoking	236 (18)	73 (22)
Chronic Obstructive Pulmonary Disease/Asthma	229 (18)	67 (20)
Cardiac valve disease	27 (2)	6 (2)
Arrhythmia	117 (9)	24 (7)
Parkinson's	11 (1)	0 (0)