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**Appendix Table 1: Definitions of comorbid conditions and medications, on the basis of codes and prescriptions in 730 days before treatment intensification**

<b>Covariate Condition</b>	<b>Inclusive conditions</b>	<b>Definition*</b>
<b>Malignancy</b>	Cancer excluding non melanoma skin cancer	ICD 9- CM diagnosis codes:140.X-208.X (exclude 173)
<b>Liver/ Respiratory failure</b>	<ol style="list-style-type: none"> <li>1. End stage liver disease</li> <li>2. Respiratory failure</li> </ol>	ICD 9- CM diagnosis codes: 570.X- 573.X ICD 9- CM diagnosis codes: 518.81, 518.83, 518.84, 799.1, 415.X, 416.X
<b>Congestive Heart Failure Cardiovascular disease</b>	<p>CHF (excluding post procedure-CHF)</p> <ol style="list-style-type: none"> <li>1. MI</li> <li>2. Obstructive coronary disease</li> <li>3. TIA</li> <li>4. Stroke</li> <li>5. Peripheral artery disease revascularization or amputation</li> <li>6. Carotid revascularization</li> <li>7. Pentoxifylline &amp; related drugs</li> </ol>	<p>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</p> <p>ICD 9- CM diagnosis codes:410.X, 412.X, 429.7X</p> <p>ICD 9- CM diagnosis codes:411.X, 413.X, 414.X</p> <p>ICD9-CM procedure codes: 36.01, 36.02, 36.03, 36.05, 36.09, 36.10-36.19</p> <p>CPT procedure codes: 33533-36, 33510-23, 33530, 92980-82,92984, 92995-6, 92974</p> <p>ICD 9- CM diagnosis codes: 435.X</p> <p>ICD 9- CM diagnosis codes: 430.X, 431.X, 434.X, 436.X</p> <p>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</p> <p>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</p> <p>ICD9-CM procedure codes: 38.12, 38.11, 00.61, 00.63, 39.28</p> <p>CPT procedure codes: 35301, 0005T, 0006T, 0007T, 0075T, 0076T, 37215, 37216</p> <p>HCPCS procedure code: S2211</p> <p>Medications: Pentoxifylline, Cilostazol, Cyclandelate, Ethaverine HCL, Nicotiny Alcohol Tartate, Papaverine, Tolazolin</p>
<b>Serious Mental illness</b>	<ol style="list-style-type: none"> <li>1. Dementia</li> <li>2. Depression,</li> <li>3. Schizophrenia,</li> <li>4. Bipolar disorder</li> <li>5. Post traumatic stress disorder</li> </ol>	<p>ICD 9- CM diagnosis codes: 290.X, 291.2, 292.82, 294.1X, 331.0-331.1X, 331.82</p> <p>Medications: Donepezil, Rivastigmine, Galantamine, Tacrine, Memantine</p> <p>ICD 9- CM diagnosis codes: 311, 300.4, 296.2, 296.3, V79.0</p> <p>ICD 9- CM diagnosis codes: 295.X</p> <p>ICD 9- CM diagnosis codes: 296.0, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89</p> <p>ICD 9- CM diagnosis codes: 309.81</p>

<b>Cardiac valve disease</b>		ICD 9- CM diagnosis codes: 394.X, 395.X, 396.X, 424.0, 424.1
<b>Arrhythmia</b>	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
<b>Smoking</b>		ICD 9- CM diagnosis codes:305.1, V15.82, 989.84 Medications: Varenicline tartrate, Nicotine Replacement therapy (gum, patch, lozenge)
<b>COPD/ Asthma</b>		ICD 9- CM diagnosis codes:491.X, 492.X, 493.X, 496.X, V17.5, V81.3
<b>HIV</b>		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
<b>Parkinson's Disease</b>		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
<b>Medications</b>		
<b>ACE Inhibitors or ARBs alone/combo</b>	ACE Inhibitors or ARBs alone/combo	Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, Candesartan, Eprosartan, Irbesartan, Losartan, Azilsartan, Olmesartan, Telmisartan, Valsartan
<b>Antipsychotics</b>	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
<b>Antihypertensives</b>	1. Beta-blockers	Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol Tartrate, Metoprolol Succinate, Propranolol, Penbutolol, Pindolol, Nadolol, Sotalol, Timolol, Nebivolol
	2. Calcium Channel Blockers	Amlodipine, Isradipine; Felodipine, Nifedipine, Nifedipine ER, Nicardipine; Diltiazem, Verapamil, Nimodipine; Nisoldipine; Bepridil, Amlodipine/Atorvastatin, Clevidipine Butyrate

	3. 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
	4. 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
<b>Anti-arrhythmics Digoxin and other inotropes</b>	1. Digoxin 2. Anti- Arrhythmics	Digoxin, Digitalis Adenosine, Amiodarone, Lidocaine, Flecainide, Ibutilide, , Procainamide, Propafenone, Ropafenone, Quinidine, Disopyramide, Verapamil, Dofetilide, Mexiletine, Moricizine, Tocainide
<b>Anticoagulants and Platelet inhibitors, not aspirin</b>	1. Anticoagulants 2. Platelet Inhibitors	Warfarin, Argatroban, Bivalirudin, Dalteparin, Enoxaprin, Eptifibatide, Fondaparinux, Heparin, Lepirudin, Tirofiban, Tinzaparin, Reviparin, Nadroparin, Ardeparin, Certoparin, Dabigatran Clopidogrel, Ticlopidine, Aspirin/Dipyridamole, Dipyridamole alone, Abciximab, Factor IX, Factor VIIa, Factor VIII, Prasugrel, Ticagrelor
<b>Lipid lowering drugs</b>	1. Statins 2. Non-Statins	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Rosuvastatin, Cerivastatin Pitavastatin, Lovastatin ER, Ezetimibe/Simvastatin, Lovastatin/Niacin, Amlodipine/Atorvastatin Cholestyramine, Colesevelam, Clofibrate, Colestipol, Niacin, Niacinamide, Fish Oil Concentrate, Omega 3 Fatty Acids, Gemfibrozil, Fenofibrate, Fenofibric Acid, Ezetimibe Omacor, Tricor/Fenofibrate, Ezetimibe/Simvastatin
<b>Nitrates</b>		Amyl Nitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Erythrityl Tetranitrate, Nitroglycerin (all forms--SA, Patch, SL, Ointment; Aerosol spray), Ranolazine
<b>Aspirin</b>		Aspirin, Aspirin/ Dipyridamole
<b>Loop Diuretics</b>		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.

## Appendix Table 2: Details for the construction of the propensity score model

### Propensity Score

The cohort was composed of a subset of all eligible persons who initiated metformin+ insulin or metformin+ sulfonylurea after using metformin monotherapy for diabetes. The matched cohort was formed by matching metformin+ insulin users to 5 metformin+ sulfonylurea users with similar propensity scores. The propensity score (PS) is defined as the probability of metformin+ insulin use, given a particular pattern of baseline covariates (Appendix Table 2). We estimated the PS using a logistic regression model in which the dependent variable was 1 for patients who used metformin+ insulin and 0 for metformin+ sulfonylurea users. The model was simple logistic regression, with a third degree polynomial term for continuous covariates and VISN of care in the model. Unlike a model being used for direct covariate adjustment, the PS model is designed to be non-parsimonious and highly flexible to capture any possible confounding by indication. Table 1 in the paper lists baseline covariates included. Missing covariate values were multiply imputed. We utilized indicator variables to denote missingness. These indicator variables were also included in the model to account for the potential that when a covariate was missing it was possibly informative. The patients' average PS from the imputation were used for matching. The PS model for the probability of being a metformin+ insulin user is displayed in Appendix Table 2. Two variables were particularly strongly related to addition of insulin over sulfonylurea. Insulin as add on therapy increased relative to sulfonylureas over time as reflected by odds ratios for fiscal years 2009 to 2011 relative to 2007. Insulin as add on therapy increased with increasing baseline creatinine as reflected by odds ratios for 1.3. The PS model yielded a C statistic of 0.77. When used to facilitate matching, the success of the PS model is determined by the covariate balance achieved in the matched cohort. Table 1 in the paper demonstrates the standardized difference in means before and after propensity score matching. Indicating good balance after matching, all standardized differences have an absolute value  $< 0.1$  with many  $\leq 0.01$ . An important condition for propensity score methods is that every cohort member have a nontrivial probability of having received either of the study therapies. Our 1:5 matching procedure excluded metformin+ insulin patients for whom very few similar metformin+ sulfonylurea users existed. This corresponds fairly closely to the region of Appendix Figure 1 where the probability of metformin+ insulin use surpasses that of the much more prevalent metformin+ sulfonylurea use. It includes primarily patients who had very high HbA1c (median 11.8%) at the time of intensification. The optimal matching algorithm selects the cohort with the smallest average difference in propensity scores between exposure groups. The matching was performed on the log odds of the propensity scores with a caliper equivalent to 0.15 on the probability scale.

## Logistic regression model for the probability of intensifying with Metformin+ Insulin

Characteristic	Odds Ratio	95% Confidence Intervals	
<b>Comorbidities</b>			
Malignancy	1.184	1.147	1.223
Liver/ respiratory failure	1.426	1.372	1.483
Congestive heart failure	0.929	0.896	0.964
Cardiovascular disease	1.080	1.055	1.105
Serious mental illness	1.026	1.004	1.048
Cardiac valve disease	0.917	0.866	0.972
Arrhythmia	0.873	0.845	0.902
Smoking	0.880	0.860	0.900
Chronic Obstructive Pulmonary Disease/ Asthma	1.094	1.068	1.121
HIV	1.722	1.545	1.920
Parkinsons	1.913	1.751	2.091
<b>Indicators of health care utilization</b>			
Hospitalized in last year	1.112	1.058	1.169
Recentness of hospitalization, months	1.055	1.026	1.085
Recentness of hospitalization, months <sup>2</sup>	0.982	0.975	0.989
Recentness of hospitalization, months <sup>3</sup>	1.002	1.002	1.003
Nursing Home encounter in last year	2.292	1.936	2.715
Outpatient Visits in past year	1.011	1.009	1.013
Outpatient Visits in past year <sup>2</sup>	1.000	1.000	1.000
Outpatient Visits in past year <sup>3</sup>	1.000	1.000	1.000
Medicare encounters in last year	1.539	1.504	1.574
Medicaid encounters in last year	1.806	1.736	1.879
<b>Demographics</b>			
Race_Black	1.091	1.062	1.120
Race_Other	0.866	0.829	0.906
gender_female	1.338	1.283	1.395
Age	0.981	0.979	0.983
Age <sup>2</sup>	1.000	1.000	1.000
Age <sup>3</sup>	1.000	1.000	1.000
Fiscal Year 2002_2003	0.974	0.923	1.027
Fiscal Year 2004	0.923	0.885	0.962
Fiscal Year 2005	0.953	0.919	0.989
Fiscal Year 2006	1.084	1.050	1.119
Fiscal Year 2008	1.684	1.632	1.737
Fiscal Year 2009	2.099	2.031	2.169
Fiscal Year 2010	2.401	2.315	2.491
Fiscal Year 2011	2.212	2.089	2.342
Time to intensification*, months	0.987	0.986	0.989
Time to intensification, months <sup>2</sup>	1.000	1.000	1.000

Time to intensification, months <sup>3</sup>	1.000	1.000	1.000
<b>Clinical and laboratory</b>			
HbA1c	1.276	1.268	1.284
HbA1c <sup>2</sup>	1.060	1.057	1.062
HbA1c <sup>3</sup>	0.994	0.993	0.994
Systolic Blood pressure	1.004	1.003	1.004
Systolic Blood pressure <sup>2</sup>	1.000	1.000	1.000
Systolic Blood pressure <sup>3</sup>	1.000	1.000	1.000
Diastolic Blood pressure	0.985	0.984	0.986
Diastolic Blood pressure <sup>2</sup>	1.000	1.000	1.000
Diastolic Blood pressure <sup>3</sup>	1.000	1.000	1.000
Body Mass Index	0.981	0.979	0.983
Body Mass Index <sup>2</sup>	1.002	1.002	1.002
Body Mass Index <sup>3</sup>	1.000	1.000	1.000
Low Density Lipoprotein	0.997	0.997	0.998
Low Density Lipoprotein <sup>2</sup>	1.000	1.000	1.000
Low Density Lipoprotein <sup>3</sup>	1.000	1.000	1.000
Creatinine	1.311	1.253	1.370
Creatinine <sup>2</sup>	1.062	0.980	1.151
Creatinine <sup>3</sup>	0.957	0.934	0.980
Urine Protein Trace or 1+	0.975	0.954	0.996
Proteinuria present at 2+,3+,4+	1.097	1.054	1.143
<b>Medications</b>			
ACE Inhibitors or ARBs	1.033	1.012	1.054
Anti hypertensive medications	1.002	0.981	1.024
Statin and non-statin lipid lowering agents	0.837	0.819	0.856
Anti-arrhythmics, digoxin and inotropes	1.320	1.245	1.400
Anticoagulant	1.135	1.104	1.168
Nitrates	1.062	1.031	1.095
Aspirin	1.026	1.004	1.047
Loop Diuretics	1.543	1.501	1.587
Antipsychotics	1.244	1.207	1.282
<b>Location of care</b>			
Service network_a	1.259	1.195	1.326
Service network_b	1.115	1.046	1.188
Service network_c	0.881	0.824	0.942
Service network_d	1.129	1.075	1.185
Service network_e	1.391	1.311	1.475
Service network_f	1.380	1.319	1.445
Service network_g	1.232	1.177	1.290
Service network_h	0.890	0.850	0.931
Service network_i	1.182	1.129	1.238
Service network_j	1.164	1.106	1.225
Service network_k	1.409	1.342	1.479
Service network_l	1.048	0.993	1.105

Service network_m	1.148	1.088	1.211
Service network_n	1.290	1.227	1.357
Service network_o	1.325	1.256	1.398
Service network_p	1.178	1.108	1.252
Service network_q	1.566	1.491	1.645
Service network_r	0.816	0.767	0.867
Service network_s	0.945	0.896	0.997
Service network_t	1.137	1.082	1.195
<b>Indicators of Missing covariates imputed</b>			
HbA1c missing	1.301	1.260	1.343
Blood pressure missing	0.924	0.860	0.992
BMI missing	1.184	1.110	1.263
LDL missing	1.202	1.170	1.235
Creatinine missing	1.021	0.991	1.052
Urine protein testing missing	0.991	0.970	1.012
Race missing	1.101	1.063	1.140

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\* Time to treatment intensification represents the time on metformin monotherapy. Because patients were free of all hypoglycemic medications for 180 days prior to starting metformin, time on metformin monotherapy approximates the length of time patients have had diabetes requiring treatment.



Appendix Table 3: Full Table of Patient Characteristics

<b>Characteristics</b>	<b>Full Cohort</b>			<b>Propensity matched Cohort</b>		
	<b>Metformin+ Sulfonylurea N=39,990</b>	<b>Metformin+ Insulin N=2948</b>	<b>St. Diff†</b>	<b>Metformin+ Sulfonylurea N=12180</b>	<b>Metformin+ Insulin N=2436</b>	<b>St. Diff†</b>
<b>Age*</b>	61 (56, 69)	60 (54, 67)	-0.13	60 (54, 68)	60 (55, 68)	0.02
<b>Male N (%)</b>	38345 (96)	2787 (95)	-0.07	11521 (95)	2315 (95)	0.02
<b>Race, N (%)</b>						
White	29458 (74)	2023 (69)	-0.11	8612 (71)	1726 (71)	0.00
Black	5161 (13)	571 (19)	0.19	2028 (17)	400 (16)	-0.01
Hispanic/ Other	1832 (5)	124 (4)	-0.02	512 (4)	111 (5)	0.02
Missing	3539 (9)	230 (8)	-0.04	1028 (8)	199 (8)	-0.01
<b>Time to intensification‡*</b>	18 (7, 34)	14 (5, 30)	-0.13	14 (6, 31)	14 (5, 30)	-0.01
<b>HbA1c, %*</b>	7.6 (7.0, 8.6)	8.5 (7.0,10.7)	0.54	8.1 (7.2, 9.9)	8.1 (6.9,9.9)	-0.07
Missing, N (%)	5470 (14)	573 (19)	0.17	2315 (19)	470 (19)	0.01
<b>Low Density Lipoprotein mg/dL*</b>	87 (70, 110)	87 (67, 113)	-0.02	86 (67, 110)	87 (67, 113)	0.02
Missing, N (%)	8492 (21)	851 (29)	0.19	3408 (28)	694 (28)	0.01
<b>Creatinine mg/dL*</b>	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	0.04	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	0.00
<b>Glomerular filtration rate ml/min*</b>	81 (70, 95)	82 (69, 100)	0.06	82 (70, 98)	82 (70, 98)	0.01
Missing, N (%)	5978 (15)	555 (19)	0.11	2372 (19)	468 (19)	-0.01
<b>Proteinuria, N(%)</b>	20909 (52)	1489 (50)		6044 (50)	1214 (50)	
negative						
trace through 4+	7468 (19)	615 (21)	0.01	2534 (20)	503 (20)	0.00
Missing, N (%)	11613 (29)	844 (29)	0.01	3602 (30)	719 (30)	0.00
<b>Systolic Blood pressure mm/Hg*</b>	132 (122, 143)	131 (120, 142)	-0.08	131 (120, 143)	131 (120, 142)	0.01
<b>Diastolic Blood pressure mm/Hg*</b>	77 (70, 84)	76 (68, 83)	-0.07	76 (68, 83)	76 (68, 84)	-0.01
Missing, N (%)	1689 (4)	187 (6)	0.10	788 (6)	159 (7)	0.00
<b>Body Mass Index (kilograms/meter<sup>2</sup>)*</b>	32.5(28.9,36.7)	32.4 (28.3, 37.0)	-0.04	32.3(28.6,37.0)	32.6(28.4,37.1)	0.00
Missing, N (%)	2098 (5)	236 (8)	0.12	961 (8)	191 (8)	0.00
<b>Baseline Co-morbidities N(%)§</b>						
Malignancy	3059 (8)	273 (9)	0.06	1115 (9)	223 (9)	0.00
Liver/ respiratory failure	1156 (3)	213 (7)	0.25	668 (5)	117 (5)	-0.04
HIV	125 (0.3)	24 (0.8)	0.09	69 (0.6)	14 (0.6)	0.00
Congestive heart failure	2222 (6)	306 (10)	0.21	1053 (9)	209 (9)	0.00
Cardiovascular disease	11849 (30)	1056 (36)	0.14	4125 (34)	825 (34)	0.00
Serious mental illness	11162 (28)	1028 (35)	0.15	3878 (32)	768 (32)	-0.01
Smoking	7719 (19)	685 (23)	0.10	2581 (21)	528 (22)	0.01
Chronic Obstructive Pulmonary Disease/ Asthma	6114 (15)	634 (22)	0.17	2378 (20)	481 (20)	0.01
Cardiac valve disease	766 (2)	84 (3)	0.07	296 (2)	62 (2)	0.01
Arrhythmia	3449 (9)	338 (11)	0.10	1274 (10)	255 (10)	0.00
Parkinson's	192 (0.5)	36 (1)	0.10	107 (0.9)	21 (0.9)	0.00
<b>Year N (%)</b>			0.14			-0.03
2002-03	1354 (3)	104 (3)		474 (4)	93 (4)	
2004	3047 (8)	191 (6)		837 (7)	171 (7)	
2005	4698 (12)	282 (10)		1171 (10)	250 (10)	
2006	6737 (17)	450 (15)		1848 (15)	379 (16)	
2007	7659 (19)	451 (15)		1895 (16)	401 (16)	

2008	6544 (16)	546 (19)		2209 (18)	428 (18)	
2009	5162 (13)	475 (16)		1915 (16)	369 (15)	
2010	3691 (9)	353 (12)		1463 (12)	275 (11)	
2011	1098 (3)	96 (3)		368 (3)	70 (3)	
<b>Use of Medications N (%)</b>						
ACE Inhibitors or ARBs	28685 (72)	2072 (70)	-0.03	8576 (70)	1727 (71)	0.01
Anti hypertensive medications	28945 (72)	2147 (73)	0.01	8894 (73)	1762 (72)	-0.02
Statin and non-statin lipid lowering agents	32206 (81)	2210 (75)	-0.14	9250 (76)	1858 (76)	0.01
Anti-arrhythmics, digoxin and other inotropes	569 (1)	78 (3)	0.10	274 (2)	57 (2)	0.01
Anticoagulants, platelet inhibitors	4603 (12)	482 (16)	0.15	1849 (15)	363 (15)	-0.01
Nitrates	3821 (10)	376 (13)	0.11	1472 (12)	297 (12)	0.00
Aspirin	9441 (24)	872 (30)	0.14	3411 (28)	666 (27)	-0.02
Loop Diuretics	4204 (11)	545 (18)	0.25	2022 (17)	395 (16)	-0.01
Antipsychotics	3254 (8)	405 (14)	0.20	1436 (12)	279 (11)	-0.01
<b>Indicators of health care utilization N(%)</b>						
Hospitalized in last year	5692 (14)	1023 (35)	0.57	3274 (27)	631 (26)	-0.03
Hospitalized in the 90 days prior to intensification	2286 (6)	679 (23)	0.06	1732 (14)	334 (14)	-0.02
Nursing Home encounter in last year	38 (0.1)	11 (0.4)	0.08	24 (0.2)	4 (0.2)	-0.01
Outpatient Visits in past year	6 (4, 10)	7 (4, 12)	0.15	7 (4, 12)	7 (4, 12)	-0.03
Medicare use in last year	11349 (28)	1066 (36)	0.17	4191 (34)	843 (35)	0.00
Medicaid use in last year	1046 (3)	202 (7)	0.25	590 (5)	122 (5)	0.01

\* Median and interquartile range reported ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker

†Standardized differences are the absolute difference in means or percent divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations. In the matched cohort all standardized differences were statistically insignificant except HbA1c at p=0.05.

‡Time to treatment intensification represents the median number of months on metformin monotherapy. It is an approximation of diabetes duration since patients were free of all hypoglycemic medications for 180 days prior to starting metformin.

§Definitions of comorbidities available in Supplemental Table 1

Appendix Table 4: Characteristics of cohort of patients on metformin monotherapy initiating sulfonylurea or insulin (follow-up beginning at intensification and continuing through the first 180 days), before and after propensity score matching

<b>Characteristics</b>	<b>Full Cohort</b>			<b>Propensity matched Cohort</b>		
	<b>Metformin+ Sulfonylurea N=62472</b>	<b>Metformin+ Insulin N=5647</b>	<b>St. Diff†</b>	<b>Metformin+ Sulfonylurea N=23965</b>	<b>Metformin+ Insulin N=4793</b>	<b>St. Diff‡</b>
<b>Age *</b>	62 (57, 71)	62 (55, 70)	-0.08	62 (55, 71)	62 (56, 71)	0.00
<b>Male, %</b>	96	95	-0.04	95	95	0.01
<b>Race %</b>						
White	74	70	-0.10	71	71	0.01
Black	14	19	0.16	17	17	-0.00
Hispanic/ Other	5	5	0.00	5	5	0.01
Missing	8	7	-0.04	7	7	-0.01
<b>Time to intensification, months‡*</b>	16 (7, 33)	13 (5, 30)	-0.10	14 (5, 31)	14 (5, 31)	-0.01
<b>HbA1c, % *</b>	7.5 (6.8, 8.4)	7.8 (6.6, 10.1)	0.41	7.9 (6.9, 9.6)	7.7 (6.6, 9.6)	-0.06
Missing, %	15	21		21	21	-0.02
<b>Low Density Lipoprotein mg/dL*</b>	88 (69, 110)	87 (66, 112)	-0.03	87 (67, 112)	87 (67, 112)	0.01
Missing, %	23	31	0.16	30	30	-0.01
<b>Creatinine mg/dL*</b>	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	-0.04	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.00
<b>Glomerular filtration rate ml/min*</b>	79(64, 93)	81 (66, 98)	0.14	81 (66, 97)	80 (66, 96)	-0.00
Missing, %	16	20	0.11	21	20	-0.03
<b>Proteinuria, % negative</b>	52	49	0.07	49	49	0.00
trace through 4+	19	23	0.07	22	22	0.00
Missing %	29	28	-0.02	29	29	-0.01
<b>Systolic Blood pressure mm/Hg*</b>	132 (121, 142)	130 (119, 142)	-0.09	130 (120, 142)	130 (120,142)	-0.01
<b>Diastolic Blood pressure mm/Hg, median (IQR)</b>	76 (68, 83)	75 (67, 83)	-0.06	75 (67, 82)	75 (67, 83)	-0.01
Missing, %	5	9	0.15	9	8	-0.03
<b>Body Mass Index (kg/m<sup>2</sup>)*</b>	32.0(28.4,36.3)	31.4(27.3,36.0)	-0.10	31.7(27.9,36.3)	31.7(27.7,36.3)	-0.01
Missing %	6	12	0.17	10	10	-0.03
<b>Co-morbidities %§</b>						
Malignancy	9	13	0.12	12	12	0.01
Liver/ respiratory failure	4	11	0.35	7	7	0.03
HIV	0.4	0.8	0.07	0.6	0.6	0.00
Congestive heart failure	8	14	0.24	12	13	0.04
Cardiovascular disease	33	41	0.18	40	40	0.02
Serious mental illness	27	36	0.20	33	33	0.00
Smoking	19	24	0.13	22	22	0.01
Chronic Obstructive Pulmonary Disease/ Asthma	17	25	0.22	22	22	0.01
Cardiac valve disease	2	3	0.07	3	3	0.02
Arrhythmia	11	15	0.15	14	15	0.02
Parkinson's	0.5	1	0.10	1	1	0.00
<b>Year N (%)</b>						
2002-03	4	3	-0.03	3	4	0.02
2004	8	6	-0.07	6	7	0.01
2005	12	10	-0.06	10	10	0.02
2006	17	15	-0.04	15	15	0.00
2007	19	16	-0.07	16	16	0.00
2008	15	18	0.08	17	17	-0.01
2009	12	14	0.08	14	14	-0.00
2010	8	10	0.07	11	10	-0.03
2011	6	7	0.05	7	7	-0.01
<b>Use of Medications %</b>						

ACE Inhibitors/ARBs	73	71	-0.05	71	71	0.02
Anti hypertensive medications	76	76	0.00	75	75	0.00
Statin and non-statin lipid lowering agents	81	75	-0.15	76	76	0.00
Anti-arrhythmics, digoxin	7	10	0.14	9	9	0.00
Anticoagulants, platelet inhibitors	14	21	0.19	19	19	0.01
Nitrates	12	16	0.11	15	15	0.01
Aspirin	23	30	0.16	28	28	0.01
Loop Diuretics	14	24	0.29	21	21	0.01
Antipsychotics	9	14	0.20	12	12	-0.00
<b>Indicators of health care utilization %</b>						
Hospitalized in last year	17	44	0.69	33	35	0.06
Hospitalized in prior 90 days	8	32	0.84	20	24	0.10
Nursing Home encounter	0.1	0.7	0.15	0.3	0.3	-0.01
Outpatient Visits	6 (4, 11)	7 (4, 13)	0.21	7 (4, 12)	7 (4, 12)	0.01
Medicare use	32	41	0.20	39	39	0.00
Medicaid use	3	8	0.32	5	6	0.02

\* Median and interquartile range reported ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker

† Standardized differences are the absolute difference in means or percent divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations. All P values in the unmatched cohort demonstrated statistically significant differences at  $p < 0.001$ . In the matched cohort all standardized differences were statistically insignificant except HbA1c, congestive heart failure, and past history of hospitalization at  $p < 0.05$ .

‡ Time to treatment intensification represents the time on metformin monotherapy. It represents an approximation of the duration of diabetes since patients were free of all hypoglycemic medications for 180 days prior to starting metformin

§ Definitions of comorbidities available in Supplemental Table 1

Appendix Table 5: Event rates and adjusted hazard with 95% confidence intervals for risk of first hypoglycemic event and recurrent hypoglycemic event using sensitivity analysis.

<b>Sensitivity Analyses</b>	<b>Metformin+ Sulfonylurea</b>	<b>Metformin+ Insulin</b>
<b>Sensitivity to outcome definitions, N at risk</b>	12,180	2,436
<b>Hypoglycemia hospitalization, emergency visit or blood glucose &lt; 50mg/dl</b>		
<i>Composite hypoglycemic first event*</i>	231	65
Person Years	19274	4005
Unadjusted Rate/1000 person-years	12 (10.5, 13.6)	16.2 (12.7, 20.6)
Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.38 (1.04, 1.83)</b>
<i>Composite hypoglycemic recurrent events</i>	275	78
Person Years	19593	4070
Unadjusted Rate/1000 person-years	14.0 (12.5, 15.8)	19.2 (15.4, 23.9)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.42 (1.05, 1.91)</b>
<i>Persistent Exposure Not Required</i>		
<i>Composite hypoglycemic first event*</i>	561	148
Person Years	37155	7328
Unadjusted Rate/1000 person-years	15.1 (13.9, 16.4)	20.2 (17.2, 23.7)
Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.38 (1.15, 1.66)</b>
<i>Composite hypoglycemic recurrent events</i>	733	240
Person Years	38248	7654
Unadjusted Rate/1000 person-years	19.2 (17.8, 20.6)	31.4 (27.7, 35.5)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.71 (1.35, 2.17)</b>
<b>Hospitalization or emergency department visit*</b>		
<i>Hypoglycemic first event</i>	114	27
Person Years	19446	4043
Unadjusted Rate/1000 person-years	5.9 (4.9, 7.0)	6.7 (4.6, 9.7)
Adjusted Hazard Ratio† (95% CI)	Reference	1.19 (0.77, 1.83)
<i>Hypoglycemic recurrent events</i>	125	32
Person Years	19593	4070
Unadjusted Rate/1000 person-years	6.4 (5.4, 7.6)	7.9 (5.6, 11.1)
Adjusted Hazard Ratio† (95% CI)	Reference	1.29 (0.83, 2.02)
<i>Persistent Exposure Not Required</i>		
<i>Hypoglycemic first event</i>	313	83
Person Years	37661	7486
Unadjusted Rate/1 000 person-years	8.3 (7.4, 9.3)	11.1 (9.0, 13.7)

Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.41 (1.10, 1.80)</b>
<i>Hypoglycemic recurrent events</i>	377	116
Person Years	38248	7654
Unadjusted Rate/1000 person-years	9.9 (8.9, 10.9)	15.2 (12.7, 18.1)
Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.62 (1.21, 2.17)</b>
<b><i>Sensitivity to exposure definitions</i></b>		
<b><i>First 180 days of use ‡</i></b> N at risk in matched cohort	23,965	4,793
<i>Composite hypoglycemic first event</i>	472	1.36130
Person Years	11601	2282
Unadjusted Rate/1000 person-years	40.7 (37.2, 44.4)	57.0 (48.2, 67.2)
Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.36 (1.12, 1.66)</b>
<i>Composite hypoglycemic recurrent events</i>	525	147
Person Years	11702	2313
Unadjusted Rate/1000 person-years	44.9 (41.3, 48.8)	63.6 (54.3, 74.2)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.37 (1.12, 1.69)</b>

\* Analysis requires persistence on metformin; patients are censored after 90 days without metformin in hand. Persistent Exposure not required analysis does not require persistence on regimen or refills within 90 days. Patients can add another regimen or stop.

† Adjusted analyses derived from Cox proportional hazards model for time to outcome for matched cohort, adjusted for all baseline covariates included in propensity score model except for service network of care

‡ Analysis checks for susceptible patients who intensify regimen and are at highest risk of adverse event in the first 180 days of use when exposure status remains uncertain. All potential patients start follow-up at treatment intensification and followup time ends at 180 days post intensification. Analyses do not require persistence on regimen or refills within 90 days. Patients can add another regimen or stop.

Appendix table 6: Event rates and adjusted hazard with 95% confidence intervals for risk of first hypoglycemic event and recurrent hypoglycemic event by subgroups.

<b><i>Persistent Exposure required*</i></b>	<b><i>Metformin+ Sulfonylurea</i></b>	<b><i>Metformin+ Insulin</i></b>
<b>Age less than 65 years (N)</b>	8270	1654
<i>Composite hypoglycemic first event</i>	300	73
Person Years	13023	2815
Unadjusted Rate/1000 person-years	23.0 (20.6, 25.8)	25.9 (20.7, 32.5)
Adjusted Hazard Ratio† (95% CI)	Reference	1.17 (0.90, 1.52)
<i>Composite hypoglycemic recurrent events</i>	374	97
Person Years	13491	2912
Unadjusted Rate/1000 person-years	27.7 (25.1, 30.6)	33.3 (27.4, 40.5)
Adjusted Hazard Ratio † (95% CI)	Reference	1.26 (0.95, 1.67)
<b>Age 65 years and older (N)</b>	3910	782
<i>Composite hypoglycemic first event</i>	166	48
Person Years	5899	1104
Unadjusted Rate/1000 person-years	28.1 (24.2, 32.7)	43.4 (32.9, 57.2)
Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.49 (1.06, 2.10)</b>
<i>Composite hypoglycemic recurrent events</i>	211	62
Person Years	6101	1158
Unadjusted Rate/1000 person-years	34.6 (30.3, 39.5)	53.5 (42.0, 68.0)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.56 (1.10, 2.23)</b>
<b>Estimated glomerular filtration rate <math>\geq</math>60 ml/min (N)</b>	8682	1759
<i>Composite hypoglycemic first event</i>	328	84
Person Years	13807	2903
Unadjusted Rate/1000 person-years	23.8 (21.3, 26.4)	28.9 (23.4, 35.7)
Adjusted Hazard Ratio† (95% CI)	Reference	1.22 (0.95, 1.56)
<i>Composite hypoglycemic recurrent events</i>	407	110
Person Years	14289	2998
Unadjusted Rate/1000 person-years	28.5 (25.9, 31.3)	36.7 (30.5, 44.0)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.33 (1.03, 1.72)</b>
<b>Estimated glomerular filtration rate &lt;60 ml/min (N)</b>	3498	677
<i>Composite hypoglycemic first event</i>	138	37
Person Years	5115	1016

Unadjusted Rate/1000 person-years	27.0 (22.9, 31.8)	36.4 (26.5, 49.8)
Adjusted Hazard Ratio† (95% CI)	Reference	1.44 (0.98, 2.11)
<i>Composite hypoglycemic recurrent events</i>	178	49
Person Years	5303	1071
Unadjusted Rate/1000 person-years	33.6 (29.0, 38.8)	45.8 (34.8, 60.0)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.50 (1.01, 2.23)</b>
<b>Not hospitalized in 90 days before intensification (N)</b>	10448	2102
<i>Composite hypoglycemic first event</i>	370	105
Person Years	16323	3402
Unadjusted Rate/1000 person-years	22.7 (20.5, 25.1)	30.9 (25.6, 37.2)
Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.41 (1.13, 1.77)</b>
<i>Composite hypoglycemic recurrent events</i>	470	133
Person Years	16847	3544
Unadjusted Rate/1000 person-years	27.9 (25.5, 30.5)	37.5 (31.8, 44.3)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.44 (1.14, 1.83)</b>
<b>Hospitalized in 90 days before intensification (N)</b>	1732	334
<i>Composite hypoglycemic first event</i>	96	16
Person Years	2599	516
Unadjusted Rate/1000 person-years	36.9 (30.3, 44.9)	31.0 (19.2, 49.8)
Adjusted Hazard Ratio† (95% CI)	Reference	0.82 (0.46, 1.46)
<i>Composite hypoglycemic recurrent events</i>	115	26
Person Years	2746	526
Unadjusted Rate/1000 person-years	41.9 (35.0, 50.0)	49.4 (34.0, 71.4)
Adjusted Hazard Ratio † (95% CI)	Reference	1.17 (0.66, 2.06)
<b>Glyburide as reference (N)</b>	5006	2436
<i>Composite hypoglycemic first event</i>	228	121
Person Years	8443	3919
Unadjusted Rate/1000 person-years	27.0 (23.8, 30.9)	30.9 (25.9, 36.8)
Adjusted Hazard Ratio† (95% CI)	Reference	1.19 (0.95, 1.49)
<i>Composite hypoglycemic recurrent events</i>	290	159
Person Years	8796	4070
Unadjusted Rate/1000 person-years	33.0 (29.4, 36.9)	39.1 (33.5, 45.5)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.28 (1.00, 1.63)</b>
<b>Glipizide/ Glimepiride as reference (N)</b>	7174	2436



<i>Composite hypoglycemic first event</i>	238	121
Person Years	10479	3919
Unadjusted Rate/1000 person-years	22.7 (20.0, 25.7)	30.9 (25.9, 36.8)
Adjusted Hazard Ratio† (95% CI)	Reference	<b>1.40 (1.12, 1.75)</b>
<i>Composite hypoglycemic recurrent events</i>	295	159
Person Years	10797	4070
Unadjusted Rate/1000 person-years	27.3 (24.4, 30.6)	39.1 (33.5, 45.5)
Adjusted Hazard Ratio † (95% CI)	Reference	<b>1.49 (1.18, 1.63)</b>

\* Analysis requires persistence on metformin; patients are censored after 90 days without metformin in hand.

† Adjusted analyses derived from Cox proportional hazards model for time to outcome for matched cohort, adjusted for all baseline covariates included in propensity score model except for service network of care

Appendix Figure 1: Study design Schematic

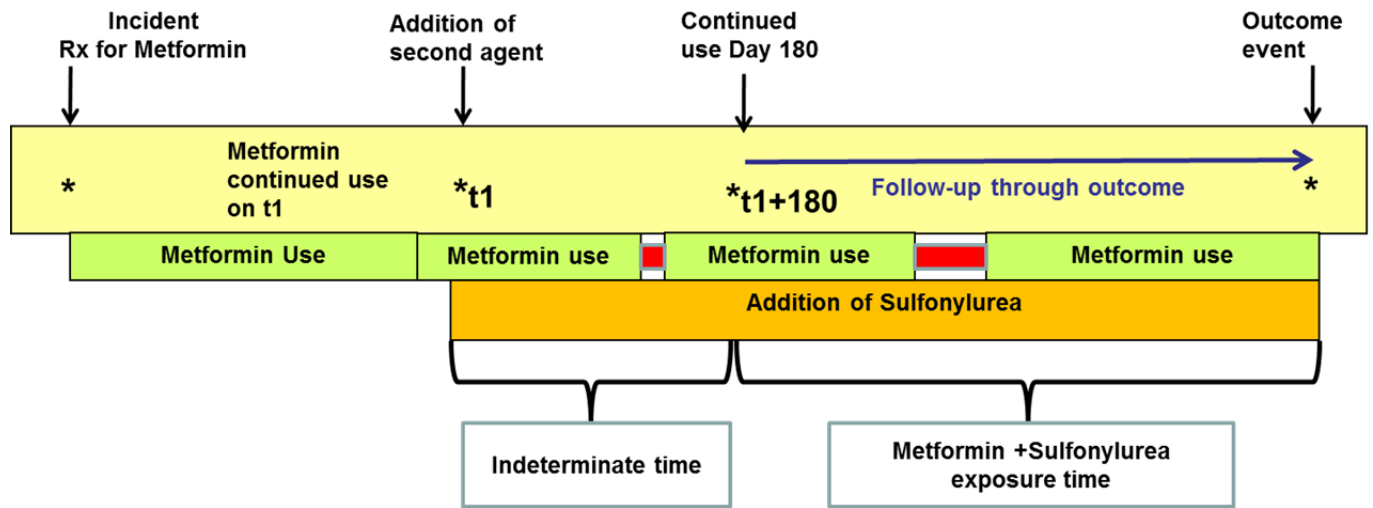
**Main analysis:**

**Persistent exposure required :** Gaps (red bars) of up to 90 days are allowed in order to refill the intensified regimen. Patients are censored at addition of third drug or no medication refills within 90 days

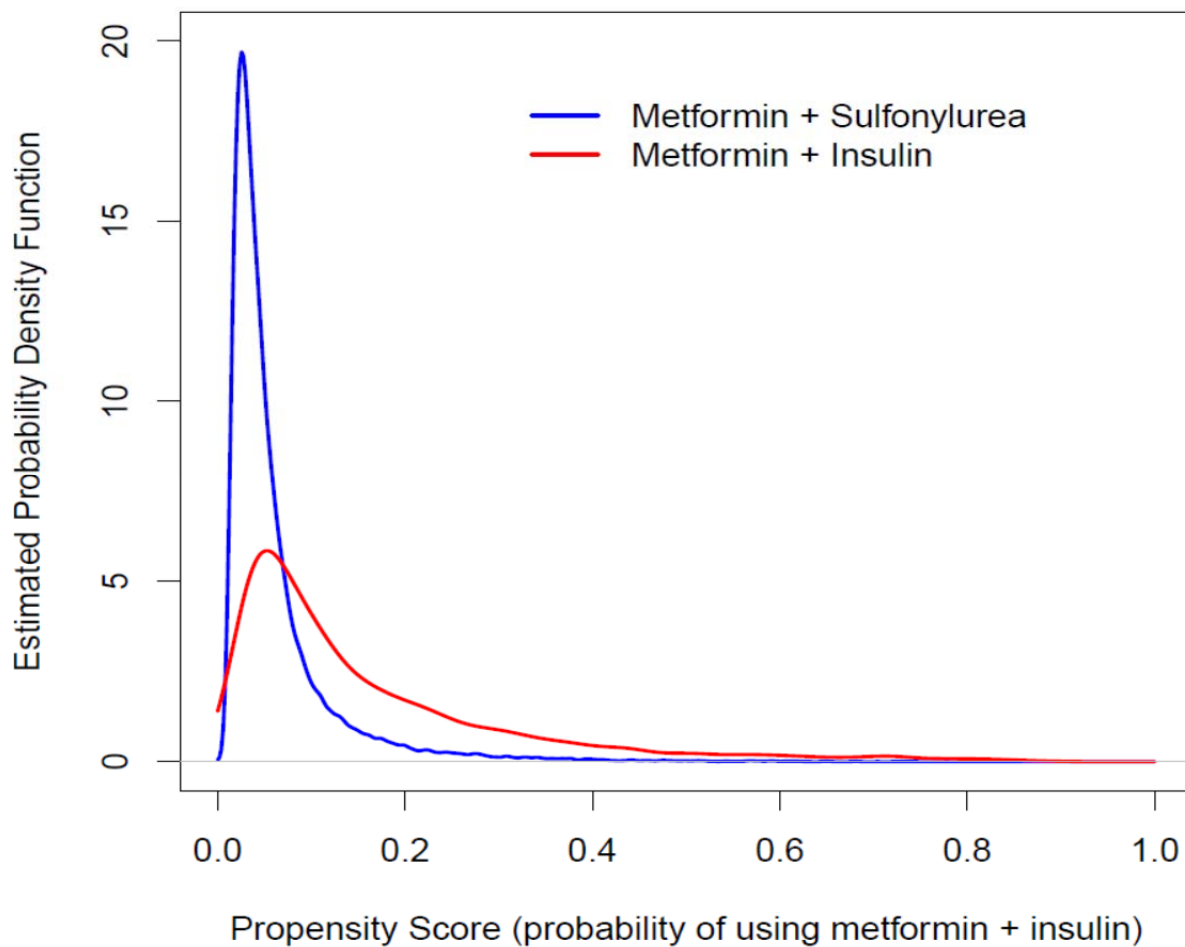
**Sensitivity analyses:**

**Persistent exposure not required:** In this approach patients are analyzed as users of their intensified regimen regardless of switching, stopping or additions (akin to an intent to treat analysis)

**Early effects of intensification:** Follow-up begins at t1 and is restricted to the first 180 day period (labeled indeterminate time on graphic)



Appendix Figure 2: Distribution of propensity scores by drug



Appendix Figure 3: Adjusted hazard with 95% confidence intervals for risk of first hypoglycemic event and recurrent hypoglycemic event for main outcome definition and sensitivity outcome definitions.

