

SUPPLEMENTAL MATERIAL

Supplemental Table I.

A. Concept set definitions for drug exposures

<b>Category</b>	<b>RxNorm concept code</b>	<b>RxNorm concept name (active ingredient)*</b>
Metformin	6809	Metformin
Dipeptidyl peptidase 4 (DPP4) inhibitors	596554	Vildagliptin
	593411	Sitagliptin
	857974	Saxagliptin
	1100699	Linagliptin
	1368001	Alogliptin
Glucagon-like peptide-1 (GLP1) analogues	1991302	Semaglutide
	1440051	Lixisenatide
	475968	Liraglutide
	60548	Exenatide
	1551291	Dulaglutide
	1534763	Albiglutide
Thiazolidinediones	1991302	Semaglutide
	72610	Troglitazone
	84108	Rosiglitazone
Sulfonylureas	33738	Pioglitazone
	10635	Tolbutamide
	10633	Tolazamide
	4815	Glyburide
	25793	Gliquidone
	4821	Glipizide
	25789	Glimepiride
	4816	Gliclazide
	102846	Glibornuride
2404	Chlorpropamide	

	2068	Carbutamid
	173	Acetohexamide

\* all drugs containing the ingredient

B. Concept set definitions for defining study groups and outcomes. For each concept set, we used the hierarchies of corresponding vocabularies and obtained a list of all child concepts for each concept in the table. We used OMOP Standardized Vocabularies as a reference (<https://athena.ohdsi.org>).

Concept set	Concept code	Concept name	Vocabulary
Diabetes mellitus type II	44054006	Type 2 diabetes mellitus	SNOMED
Diabetes mellitus type I	46635009	Type 1 diabetes mellitus	SNOMED
Gestational diabetes	11687002	Gestational diabetes mellitus	SNOMED
Cardiac arrest	410429000	Cardiac arrest	SNOMED
Atrial fibrillation	49436004	Atrial fibrillation	SNOMED
Atrial flutter and supraventricular arrhythmia	72654001	Supraventricular arrhythmia	SNOMED
	5370000	Atrial flutter	SNOMED
Pacemaker or bradycardia	60423000	Sinus node dysfunction	SNOMED
	48867003	Bradycardia	SNOMED
	49710005	Sinus bradycardia	SNOMED
	C1786	Pacemaker, single chamber, rate-responsive (implantable)	HCPCS
	C2620	Pacemaker, single chamber, non rate-responsive (implantable)	HCPCS
	C2621	Pacemaker, other than single or dual chamber (implantable)	HCPCS
	C1785	Pacemaker, dual chamber, rate-responsive (implantable)	HCPCS
	C2619	Pacemaker, dual chamber, non rate-responsive (implantable)	HCPCS
	C1898	Lead, pacemaker, other than transvenous vdd single pass	HCPCS
	175135009	Introduction of cardiac pacemaker system via vein	SNOMED

	0JH835Z	Insertion of Pacemaker, Single Chamber Rate Responsive into Abdomen Subcutaneous Tissue and Fascia, Percutaneous Approach	ICD10PCS
	92960	Cardioversion, elective, electrical conversion of arrhythmia; external	CPT4
	233174007	Cardiac pacemaker procedure	SNOMED
Ventricular Tachycardia and Fibrillation	25569003	Ventricular tachycardia	SNOMED
	71908006	Ventricular fibrillation	SNOMED

\* SNOMED - Systematized Nomenclature of Medicine Clinical Terms; HCPCS - Healthcare Common Procedure Coding System; ICD10PCS - International Classification of Diseases, 10th Revision, Procedure Coding System; CPT4 - Current Procedural Terminology, 4th Edition.

Supplemental Table II. SNOMED concepts used as negative controls for p-value confidence interval calibration. Concepts and all their descendants within SNOMED hierarchy were used.

<b>SNOMED concept code</b>	<b>SNOMED concept name</b>
53726008	Acute conjunctivitis
15167005	Alcohol abuse
61582004	Allergic rhinitis
197480006	Anxiety disorder
13746004	Bipolar disorder
57406009	Carpal tunnel syndrome
13645005	Chronic obstructive lung disease
40055000	Chronic sinusitis
40275004	Contact dermatitis
22878006	Contusion of knee
64634000	Corneal opacity
80967001	Dental caries
79962008	Diffuse spasm of esophagus

17322007	Disease caused by parasite
25906001	Disorder of ear
41188003	Disorder of oral soft tissues
75860007	Disorder of pharynx
3441005	Disorder of sebaceous gland
32895009	Hereditary disease
111859007	Herpes zoster without complication
240532009	Human papilloma virus infection
40930008	Hypothyroidism
18070006	Impacted cerumen
400097005	Ingrowing nail
193462001	Insomnia
38214006	Internal hemorrhoids without complication
209565008	Lumbar sprain
200936003	Lupus erythematosus
46206005	Mood disorder
191736004	Obsessive-compulsive disorder
16001004	Otalgia
65363002	Otitis media
202882003	Plantar fasciitis
41256004	Presbyopia
69322001	Psychotic disorder
70076002	Rhinitis
31541009	Sarcoidosis
191567000	Schizoaffective schizophrenia
58214004	Schizophrenia
23056005	Sciatica
239815007	Solitary sacroiliitis

6020002	Tinea pedis
34713006	Vitamin D deficiency

Supplemental Table III. Number of patients before and after propensity score matching, number of events and mean follow-up for each outcome, comparing metformin and other anti-diabetic drugs; on-treatment.

	Target group	Comparator group	Before matching		After matching		Number of events		Mean follow-up, years	
			T	C	T	C	T	C	T	C
Atrial Fibrillation	Metformin	TZD	190,180	88,258	47,161	50,633	4,977	2,319	2.9	1.1
	Metformin	DPP4	190,180	99,050	53,550	59,530	5,532	2,925	2.6	1.1
	Metformin	GLP1	190,180	26,380	16,438	17,338	1325	1033	2.6	1.8
	Metformin	Sulfonylurea	190,180	241,917	96,125	136,144	9,242	10,054	2.7	1.5
Atrial flutter and supraventricular arrhythmia	Metformin	TZD	190,180	88,258	47,161	50,633	6,329	2,890	2.9	1.1
	Metformin	DPP4	190,180	99,050	53,550	59,530	6,828	3,622	2.6	1.1
	Metformin	GLP1	190,180	26,380	16,438	17,338	1716	1280	2.5	1.7
	Metformin	Sulfonylurea	190,180	241,917	96,125	136,144	11,581	12,353	2.7	1.5
Ventricular Tachycardia and Fibrillation	Metformin	TZD	190,180	88,258	47,161	50,633	53	17	3.1	1.1
	Metformin	DPP4	190,180	99,050	53,550	59,530	69	33	2.8	1.2
	Metformin	GLP1	190,180	26,380	16,438	17,338	26	12	2.7	1.8
	Metformin	Sulfonylurea	190,180	241,917	96,125	136,144	122	148	2.9	1.6
Bradycardia or pacemaker	Metformin	TZD	190,180	88,258	47,161	50,633	2,852	1,144	3.0	1.1
	Metformin	DPP4	190,180	99,050	53,550	59,530	3,260	1,714	2.7	1.1
	Metformin	GLP1	190,180	26,380	16,438	17,338	852	576	2.6	1.8
	Metformin	Sulfonylurea	190,180	241,917	96,125	136,144	5,342	5,398	2.8	1.5

Supplemental Table IV. Selected descriptive baseline patients characteristics for comparative effectiveness of first-line diabetes therapy; on-treatment.

IV.1. Selected descriptive baseline patient characteristics for comparative effectiveness of metformin (Mtf) vs sulfonylureas (Slfr).

Variable	Before PS adjustment			After PS adjustment		
	Mtf	Slfr	Standardized difference	Mtf	Slfr	Standardized difference
Age						
50-54	0.2%	0.1%	0.02	0.2%	0.2%	0.009
55-59	0.8%	0.5%	0.033	0.6%	0.6%	0.002
65-69	40.3%	31.8%	0.176	36.4%	36.8%	-0.009
70-74	25.0%	22.7%	0.055	24.7%	24.9%	-0.005
75-79	17.2%	18.6%	-0.039	18.7%	18.5%	0.004
80-84	9.8%	14.3%	-0.136	11.7%	11.4%	0.009
85-89	4.0%	7.8%	-0.164	4.9%	4.8%	0.007
90-94	0.9%	2.5%	-0.122	1.1%	1.1%	0.002
95-99	0.1%	0.4%	-0.059	0.1%	0.1%	-0.005
Gender						
Male	49.5%	52.8%	-0.065	51.1%	51.1%	0.001
Female	50.5%	47.2%	0.065	48.9%	48.9%	-0.001
Comorbidities						
Hypertensive Disorder	68.3%	68.8%	-0.01	67.7%	67.7%	-0.002
Coronary Artery Disease	19.3%	23.8%	-0.109	20.6%	20.3%	0.007
Heart Failure	4.2%	8.2%	-0.169	4.9%	4.8%	0.005
Valvular Heart Disease	7.4%	8.8%	-0.049	7.5%	7.5%	0.003
Hypothyroidism	10.4%	10.3%	0.005	10.8%	10.7%	0.003
Hyperparathyroidism	0.8%	0.7%	0.002	0.7%	0.7%	-0.002

Chronic kidney disorder	3.7%	13.3%	-0.349	4.5%	4.4%	0.008
Chronic obstructive lung disorder	7.8%	9.5%	-0.059	8.1%	8.1%	0.002
Asthma	5.7%	5.2%	0.023	5.3%	5.3%	0.002
<b>Drugs</b>						
Beta blockers	40.5%	44.9%	-0.087	41.8%	41.4%	0.007
Ca channel blockers	30.4%	34.2%	-0.082	31.4%	31.3%	0.002
ACE inhibitors	47.4%	49.0%	-0.032	48.4%	48.5%	-0.003
Anticoagulants	15.2%	19.7%	-0.118	16.4%	16.2%	0.007
sStatins	72.7%	69.9%	0.063	70.7%	70.9%	-0.003

IV.2. Selected descriptive baseline patient characteristics for comparative effectiveness of metformin (Mtf) vs dipeptidyl peptidase 4 inhibitors (DPP4).

Variable	Before PS adjustment			After PS adjustment		
	Mtf	DPP4	Standardized difference	Mtf	DPP4	Standardized difference
<b>Age</b>						
50-54	0.2%	0.1%	0.02	0.2%	0.1%	0.009
55-59	0.7%	0.5%	0.03	0.5%	0.5%	0.002
60-64	1.6%	1.4%	0.019	1.4%	1.4%	0.004
65-69	39.7%	34.3%	0.111	35.2%	35.2%	-0.001
70-74	25.0%	24.3%	0.014	24.5%	24.7%	-0.004
75-79	17.4%	17.9%	-0.014	17.9%	17.9%	-0.001
80-84	10.2%	12.6%	-0.076	12.3%	12.2%	0.005
85-89	4.2%	6.6%	-0.106	6.1%	6.0%	0.002
90-94	1.0%	1.9%	-0.081	1.7%	1.7%	-0.001
95-99	0.1%	0.3%	-0.046	0.2%	0.3%	-0.012
<b>Gender</b>						
Male	51.2%	51.4%	-0.004	50.3%	50.3%	-0.001
Female	48.8%	48.6%	0.004	49.7%	49.7%	0.001

Comorbidities						
Hypertensive Disorder	67.1%	71.9%	-0.103	70.6%	70.6%	-0.001
Coronary Artery Disease	19.4%	25.1%	-0.136	23.9%	23.6%	0.007
Heart Failure	4.3%	8.4%	-0.17	6.7%	6.6%	0.006
Valvular Heart Disease	7.1%	10.5%	-0.12	9.4%	9.5%	-0.003
Hypothyroidism	10.4%	12.3%	-0.061	12.0%	11.9%	0.003
Hyperparathyroidism	0.7%	0.9%	-0.021	0.8%	0.9%	-0.003
Chronic kidney disorder	3.8%	17.2%	-0.45	9.0%	8.9%	0.006
Chronic obstructive lung disorder	7.6%	9.4%	-0.064	8.9%	8.9%	-0.001
Asthma	5.3%	5.7%	-0.02	5.8%	5.8%	0.004
Drugs						
Beta blockers	40.8%	46.4%	-0.114	44.4%	44.4%	-0.002
Ca channel blockers	30.6%	35.3%	-0.102	33.5%	33.4%	0.002
ACE inhibitors	49.5%	44.9%	0.091	44.5%	45.1%	-0.01
Anticoagulants	15.4%	19.9%	-0.118	18.8%	18.6%	0.004
Statins	72.7%	75.0%	-0.052	73.9%	74.1%	-0.005

IV.3. Selected descriptive baseline patient characteristics for comparative effectiveness of metformin (Mtf) vs thiazolidinediones (TZD).

Variable	Before PS adjustment			After PS adjustment		
	Mtf	TZD	Standardized difference	Mtf	TZD	Standardized difference
Age						
50-54	0.2%	0.1%	0.016	0.2%	Mtf 1%	0.008
55-59	0.8%	0.5%	0.035	0.6%	0.5%	0.009
65-69	40.3%	33.1%	0.149	33.2%	33.3%	-0.003
70-74	24.6%	25.5%	-0.019	25.6%	25.6%	0.001



75-79	17.2%	19.1%	-0.05	19.3%	19.2%	0.002
80-84	10.0%	12.9%	-0.091	12.7%	12.6%	0.002
90-94	0.9%	1.6%	-0.055	1.4%	1.5%	-0.006
95-99	0.1%	0.2%	-0.025	0.2%	0.2%	-0.008
Gender						
Male	50.5%	57.9%	-0.15	56.7%	56.3%	0.009
Female	49.5%	42.1%	0.15	43.3%	43.7%	-0.009
Comorbidities						
Hypertensive Disorder	67.9%	63.1%	0.1	63.1%	63.3%	-0.003
Coronary Artery Disease	19.8%	20.9%	-0.029	21.1%	20.6%	0.011
Heart Failure	4.4%	5.0%	-0.028	4.6%	4.6%	0.003
Valvular Heart Disease	7.3%	7.3%	-0.001	7.4%	7.1%	0.009
Hypothyroidism	10.7%	8.4%	0.076	8.7%	8.7%	0.002
Hyperparathyroidism	0.7%	0.5%	0.022	0.6%	0.5%	0.002
Chronic kidney disorder	3.9%	12.4%	-0.317	7.5%	7.1%	0.016
Chronic obstructive lung disorder	7.8%	7.4%	0.016	7.4%	7.3%	0.003
Asthma	5.4%	4.3%	0.052	4.5%	4.4%	0.003
Drugs						
Beta blockers	41.3%	39.7%	0.033	39.8%	39.7%	0.003
Ca channel blockers	30.8%	31.6%	-0.019	31.0%	30.9%	0.002
ACE inhibitors	49.1%	49.5%	-0.011	49.0%	49.4%	-0.007
Anticoagulants	15.6%	17.8%	-0.058	17.7%	17.2%	0.012
Statins	72.5%	75.4%	-0.067	74.8%	74.6%	0.006

IV.4. Selected descriptive baseline patient characteristics for comparative effectiveness of metformin (Mtf) vs glucagon-like peptide 1 receptor agonists (GLP-1).

Variable	Before PS adjustment			After PS adjustment		
	Mtf	GLP-1	Standardized difference	Mtf	GLP-1	Standardized difference
Age						
50-54	0.2%	0.2%	-0.011	0.3%	0.2%	0.011
55-59	0.7%	1.3%	-0.058	1.1%	1.3%	-0.014
60-64	1.6%	2.5%	-0.063	2.8%	2.5%	0.019
65-69	39.3%	54.0%	-0.298	54.0%	53.5%	0.009
70-74	17.6%	11.0%	0.189	11.1%	11.4%	-0.009
75-79	10.2%	4.1%	0.239	3.9%	4.3%	-0.019
80-84	4.2%	1.0%	0.201	0.9%	1.0%	-0.012
85-89	0.9%	0.1%	0.115	0.2%	0.1%	0.021
90-94	0.2%	0.2%	-0.011	0.3%	0.2%	0.011
Gender						
Male	51.8%	49.1%	0.055	48.2%	48.7%	-0.01
Female	48.2%	50.9%	-0.055	51.8%	51.3%	0.01
Comorbidities						
Hypertensive Disorder	66.9%	73.2%	-0.137	71.6%	71.5%	0.002
Coronary Artery Disease	19.6%	22.7%	-0.075	22.4%	22.1%	0.008
Heart Failure	4.3%	5.5%	-0.056	5.5%	5.2%	0.013
Valvular Heart Disease	7.2%	7.8%	-0.024	7.5%	7.6%	-0.002
Hypothyroidism	10.2%	15.7%	-0.165	15.2%	14.5%	0.02
Hyperparathyroidism	0.7%	0.9%	-0.022	0.9%	0.9%	-0.003
Chronic kidney disorder	3.8%	14.5%	-0.376	4.3%	6.3%	-0.089
Chronic obstructive lung disorder	7.6%	7.9%	-0.012	7.9%	7.7%	0.007

Asthma	5.2%	7.2%	-0.082	7.0%	6.8%	0.009
Drugs						
Beta blockers	41.0%	43.4%	-0.049	42.9%	42.8%	0.002
Ca channel blockers	30.6%	31.8%	-0.025	31.3%	31.3%	0.001
ACE inhibitors	49.6%	44.8%	0.098	44.9%	45.4%	-0.009
Anticoagulants	15.5%	17.1%	-0.044	16.9%	16.8%	0.003
Statins	73.1%	77.6%	-0.105	77.0%	77.1%	-0.001

Supplemental Table V. Number of patients before and after propensity score matching, number of events and mean follow-up for each outcome, comparing metformin and other anti-diabetic drugs, intent-to-treat.

	Target group	Comparator group	Before matching		After matching		Number of events		Mean follow-up, years	
			T	C	T	C	T	C	T	C
Atrial Fibrillation	Metformin	TZD	190,180	88,258	79,807	86,244	12,487	12,860	4.2	3.7
	Metformin	DPP4	190,180	99,050	84,677	94,719	11,666	12,579	3.7	3.2
	Metformin	GLP1	190,180	26,380	23,600	24,895	2,638	2,561	3.5	3.0
	Metformin	Sulfonylurea	190,180	241,917	170,620	232,056	23,449	33,851	3.9	3.3
Atrial flutter and supraventricular arrhythmia	Metformin	TZD	190,180	88,258	79,807	86,244	15,645	15,853	4.1	3.6
	Metformin	DPP4	190,180	99,050	84,677	94,719	14,489	15,470	3.6	3.1
	Metformin	GLP1	190,180	26,380	23,600	24,895	3,355	3,209	3.4	3.0
	Metformin	Sulfonylurea	190,180	241,917	170,620	232,056	29,402	41,376	3.8	3.2
Ventricular Tachycardia and Fibrillation	Metformin	TZD	190,180	88,258	79,807	86,244	159	148	4.6	4.1
	Metformin	DPP4	190,180	99,050	84,677	94,719	173	148	4.0	3.4
	Metformin	GLP1	190,180	26,380	23,600	24,895	43	32	3.7	3.2
	Metformin	Sulfonylurea	190,180	241,917	170,620	232,056	298	442	4.2	3.6
Bradycardia or pacemaker	Metformin	TZD	190,180	88,258	79,807	86,244	7,865	7,610	4.4	3.9
	Metformin	DPP4	190,180	99,050	84,677	94,719	7,610	8,091	3.8	3.3
	Metformin	GLP1	190,180	26,380	23,600	24,895	1,847	1,653	3.6	3.1
	Metformin	Sulfonylurea	190,180	241,917	170,620	232,056	15,124	20,490	4.0	3.4

Supplemental Table VI. Estimated hazard ratios of arrhythmias among patients on metformin vs other anti-diabetic drugs. HR = hazard ratio with 95% confidence interval, intent-to-treat.

Outcome	DPP4		GLP-1		Sulfonylureas		TZD	
	HR	P-value	HR	P-value	HR	P-value	HR	P-value
Atrial Fibrillation	0.93 (0.90-0.96)	<0.01	0.95 (0.88-1.01)	0.12	0.91 (0.90-0.94)	<0.01	0.94 (0.92-0.97)	<0.01
Ventricular Tachycardia and Fibrillation	1.15 (0.86-1.51)	0.35	1.19 (0.65-2.21)	0.57	0.83 (0.70-1.00)	0.06	1.12 (0.85-1.47)	0.42
Bradycardia	0.94 (0.91-0.98)	<0.01	1.04 (0.95-1.14)	0.34	0.93 (0.91-0.96)	<0.01	1.00 (0.97-1.05)	0.67
Atrial flutter and supraventricular arrhythmia	0.94 (0.91-0.97)	<0.01	0.97 (0.92-1.03)	0.45	0.92 (0.90-0.93)	<0.01	0.95 (0.92-0.98)	<0.01

Supplemental Table VII. Number of patients before and after propensity score matching, number of events and mean follow-up for pairwise comparison of second-line diabetes therapy; on-treatment.

Outcome	Target group	Comparator group	Before matching		After matching		Number of events		Mean follow-up, years	
			T	C	T	C	T	C	T	C
Atrial Fibrillation	DPP4	GLP1	30,176	26,389	16,943	25,510	968	1,044	1.9	1.4
	DPP4	Sulfonylureas	30,176	24,772	14,585	25,013	810	1,031	1.5	1.4
	DPP4	TZD	30,176	9,793	7,861	19,969	309	819	1.5	1.4
	GLP1	Sulfonylureas	26,389	24,772	10,934	19,580	567	1,173	1.5	1.9
	GLP1	TZD	26,389	9,793	6,519	15,091	264	911	1.5	2.0
	TZD	Sulfonylureas	9,793	24,772	8,164	8,497	441	316	1.6	1.5

Ventricular Tachycardia and Fibrillation	DPP4	GLP1	30,176	26,389	16,943	25,510	10	7	2.0	1.4
	DPP4	Sulfonylureas	30,176	24,772	14,585	25,013	9	6	1.6	1.4
	DPP4	TZD	30,176	9,793	7,861	19,969	4	6	1.5	1.5
	GLP1	Sulfonylureas	26,389	24,772	10,934	19,580	6	10	1.6	2.0
	GLP1	TZD	26,389	9,793	6,519	15,091	4	11	1.5	2.1
	TZD	Sulfonylureas	9,793	24,772	8,164	8,497	5	5	1.7	1.5
Atrial flutter and supraventricular arrhythmia	DPP4	GLP1	30,176	26,389	16,943	25,510	1,224	1,348	1.9	1.4
	DPP4	Sulfonylureas	30,176	24,772	14,585	25,013	1,036	1,343	1.5	1.4
	DPP4	TZD	30,176	9,793	7,861	19,969	442	1,074	1.4	1.4
	GLP1	Sulfonylureas	26,389	24,772	10,934	19,580	735	1,486	1.5	1.9
	GLP1	TZD	26,389	9,793	6,519	15,091	363	1,144	1.5	2.0
	TZD	Sulfonylureas	9,793	24,772	8,164	8,497	581	459	1.6	1.4
Bradycardia or pacemaker	DPP4	GLP1	30,176	26,389	16,943	25,510	573	641	1.9	1.4
	DPP4	Sulfonylureas	30,176	24,772	14,585	25,013	447	611	1.6	1.4
	DPP4	TZD	30,176	9,793	7,861	19,969	211	483	1.5	1.5
	GLP1	Sulfonylureas	26,389	24,772	10,934	19,580	333	674	1.6	2.0
	GLP1	TZD	26,389	9,793	6,519	15,091	172	518	1.5	2.0
	TZD	Sulfonylureas	9,793	24,772	8,164	8,497	260	215	1.6	1.5

Supplemental Table VIII. Selected descriptive baseline patients characteristics for comparative effectiveness of second-line diabetes therapy; on-treatment.

VIII.1. Selected descriptive baseline patient characteristics for comparative effectiveness of glucagon-like peptide 1 receptor agonists (GLP-1) vs dipeptidyl peptidase 4 inhibitors (DPP4).

Variable	Before PS adjustment			After PS adjustment		
	GLP-1	DPP4	Standardized difference	GLP-1	DPP4	Standardized difference
Age						
50-54	0.3%	0.2%	0.024	0.3%	0.2%	0.008
55-59	1.4%	0.7%	0.061	1.1%	1.0%	0.013

60-64	2.7%	1.7%	0.065	2.2%	2.2%	0.002
70-74	53.7%	46.5%	0.145	51.8%	52.1%	-0.006
75-79	26.0%	25.7%	0.007	26.1%	26.5%	-0.009
80-84	10.8%	14.8%	-0.118	12.2%	11.9%	0.008
85-89	4.0%	7.2%	-0.141	4.9%	4.6%	0.015
90-94	0.9%	2.5%	-0.119	1.2%	1.2%	0.006
Gender						
Male	50.1%	53.9%	-0.075	51.3%	51.0%	0.006
Female	49.9%	46.1%	0.075	48.7%	49.0%	-0.006
Comorbidities						
Hypertensive Disorder	72.7%	70.7%	0.045	71.9%	72.0%	-0.002
Coronary Artery Disease	22.4%	21.6%	0.021	21.1%	21.0%	0.003
Heart Failure	5.2%	4.5%	0.034	4.2%	4.4%	-0.008
Valvular Heart Disease	7.6%	8.4%	-0.031	7.4%	7.5%	-0.003
Hypothyroidism	15.0%	12.3%	0.079	13.7%	13.8%	-0.002
Hyperparathyroidism	0.9%	0.9%	-0.001	0.9%	1.0%	-0.005
Chronic kidney disorder	12.5%	4.6%	0.286	6.1%	6.3%	-0.012
Chronic obstructive lung disorder	7.8%	7.0%	0.03	6.9%	7.0%	-0.003
Asthma	6.9%	5.7%	0.046	6.2%	6.1%	0.001
Drugs						
Beta blockers	43.4%	40.0%	0.069	40.8%	40.9%	-0.002
Ca channel blockers	31.8%	30.8%	0.021	30.9%	30.6%	0.007
ACE inhibitors	46.8%	44.7%	0.043	46.0%	46.1%	-0.001
Anticoagulants	16.7%	15.7%	0.027	15.5%	15.6%	-0.003
Statins	78.4%	75.1%	0.079	76.8%	77.0%	-0.006

VIII.2. Selected descriptive baseline patient characteristics for comparative effectiveness of sulfonylureas (Slfr) vs dipeptidyl peptidase 4 inhibitors (DPP4).

Variable	Before PS adjustment			After PS adjustment		
	Slfr	DPP4	Standardized difference	Slfr	DPP4	Standardized difference
<b>Age</b>						
50-54	0.2%	0.2%	-0.001	0.2%	0.1%	0.014
55-59	0.7%	0.8%	-0.014	0.8%	0.8%	-0.004
60-64	1.6%	1.8%	-0.016	1.7%	1.6%	0.013
65-69	37.7%	47.3%	-0.194	42.7%	42.6%	0.003
70-74	25.9%	25.6%	0.008	26.2%	26.0%	0.006
75-79	18.3%	14.5%	0.104	16.0%	16.4%	-0.012
80-84	10.4%	6.9%	0.124	8.2%	8.6%	-0.017
85-89	4.3%	2.4%	0.107	3.3%	3.1%	0.008
90-94	0.8%	0.5%	0.037	0.8%	0.6%	0.016
95-99	0.1%	0.1%	0.015	0.1%	0.1%	0.018
<b>Gender</b>						
Male	54.8%	53.8%	0.02	53.6%	53.8%	-0.005
Female	45.2%	46.2%	-0.02	46.4%	46.2%	0.005
<b>Comorbidities</b>						
Hypertensive Disorder	64.6%	70.7%	-0.131	67.7%	66.9%	0.016
Coronary Artery Disease	20.4%	21.5%	-0.028	20.8%	20.6%	0.004
Heart Failure	4.6%	4.4%	0.007	4.6%	4.4%	0.007
Valvular Heart Disease	7.2%	8.4%	-0.043	7.5%	7.7%	-0.004
Hypothyroidism	8.1%	12.3%	-0.139	9.5%	9.5%	-0.001
Hyperparathyroidism	0.6%	0.9%	-0.037	0.7%	0.8%	-0.011
Chronic kidney disorder	3.9%	4.6%	-0.035	4.3%	4.1%	0.01

Chronic obstructive lung disorder	6.9%	7.0%	-0.001	6.8%	6.8%	0.003
Asthma	4.3%	5.7%	-0.067	4.7%	4.7%	-0.002
<b>Drugs</b>						
Beta blockers	39.4%	39.9%	-0.011	39.6%	39.6%	-0.001
Ca channel blockers	32.5%	30.8%	0.038	32.1%	32.2%	-0.001
ACE inhibitors	51.1%	44.4%	0.133	47.9%	48.1%	-0.002
Anticoagulants	16.8%	15.7%	0.031	16.0%	16.1%	-0.001
Statins	70.1%	75.3%	-0.118	72.1%	71.8%	0.007

VIII.3. Selected descriptive baseline patient characteristics for comparative effectiveness of sulfonylureas (Slfr) vs glucagon-like peptide 1 inhibitors (GLP-1).

Variable	Before PS adjustment			After PS adjustment		
	Slfr	GLP-1	Standardized difference	Slfr	GLP-1	Standardized difference
<b>Age</b>						
50-54	0.2%	0.3%	-0.028	0.2%	0.2%	-0.003
55-59	0.7%	1.3%	-0.068	1.0%	1.0%	-0.004
60-64	1.5%	2.7%	-0.081	2.2%	2.2%	-0.001
65-69	36.8%	53.7%	-0.343	48.2%	47.3%	0.019
70-74	26.0%	26.1%	-0.001	27.2%	27.1%	0.003
75-79	18.7%	10.9%	0.222	13.9%	14.4%	-0.017
80-84	10.7%	3.9%	0.261	5.6%	5.9%	-0.014
85-89	4.4%	0.9%	0.218	1.3%	1.6%	-0.02
90-94	0.9%	0.1%	0.109	0.2%	0.2%	0.008
<b>Gender</b>						
Male	54.7%	50.0%	0.094	51.1%	51.6%	-0.009
Female	45.3%	50.0%	-0.094	48.9%	48.4%	0.009
<b>Comorbidities</b>						
Hypertensive	64.6%	73.1%	-0.183	67.0%	66.4%	0.014



Disorder						
Coronary Artery Disease	20.4%	22.5%	-0.05	20.9%	20.5%	0.01
Heart Failure	4.6%	5.2%	-0.027	4.5%	4.4%	0.006
Valvular Heart Disease	7.3%	7.7%	-0.015	7.1%	6.9%	0.009
Hypothyroidism	8.1%	15.0%	-0.22	10.1%	9.7%	0.011
Hyperparathyroidism	0.6%	0.9%	-0.037	0.7%	0.7%	0.003
Chronic kidney disorder	3.9%	12.5%	-0.319	5.9%	5.7%	0.012
Chronic obstructive lung disorder	6.9%	7.8%	-0.033	6.8%	6.8%	0.003
Asthma	4.3%	6.9%	-0.112	5.2%	4.8%	0.018
Drugs						
Beta blockers	39.3%	43.4%	-0.082	40.5%	40.5%	0.001
Ca channel blockers	32.7%	31.8%	0.019	32.2%	31.8%	0.009
ACE inhibitors	51.1%	46.4%	0.095	49.2%	49.7%	-0.009
Anticoagulants	16.9%	16.8%	0.003	16.1%	16.2%	-0.003
Statins	69.8%	78.5%	-0.2	74.9%	74.0%	0.02

VIII.4. Selected descriptive baseline patient characteristics for comparative effectiveness of sulfonylureas (Slfr) vs thiazolidinediones (TZD).

Variable	Before PS adjustment			After PS adjustment		
	Slfr	TZD	Standardized difference	Slfr	TZD	Standardized difference
Age						
50-54	0.2%	0.2%	0.002	0.2%	0.2%	0.011
55-59	0.7%	0.7%	-0.002	0.8%	0.6%	0.028
60-64	1.6%	1.6%	-0.005	2.0%	1.6%	0.029
65-69	37.8%	43.8%	-0.123	42.7%	42.7%	0.001
70-74	18.3%	16.1%	0.058	16.3%	16.6%	-0.007

75-79	10.3%	7.7%	0.093	7.5%	8.1%	-0.02
80-84	4.2%	2.6%	0.089	2.7%	2.8%	-0.009
85-89	0.8%	0.5%	0.038	0.7%	0.6%	0.021
90-94	0.2%	0.2%	0.002	0.2%	0.2%	0.011
Gender						
Male	54.6%	60.6%	-0.121	60.1%	59.4%	0.016
Female	45.4%	39.4%	0.121	39.9%	40.6%	-0.016
Comorbidities						
Hypertensive Disorder	64.5%	62.4%	0.044	63.7%	62.9%	0.016
Coronary Artery Disease	20.4%	18.0%	0.06	18.2%	18.0%	0.004
Heart Failure	4.6%	3.2%	0.071	3.4%	3.3%	0.005
Valvular Heart Disease	7.2%	6.6%	0.023	6.7%	6.8%	-0.005
Hypothyroidism	8.1%	8.0%	0.006	8.2%	8.0%	0.009
Hyperparathyroidism	0.6%	0.5%	0.02	0.6%	0.4%	0.022
Chronic kidney disorder	3.9%	3.6%	0.015	3.5%	3.7%	-0.012
Chronic obstructive lung disorder	6.9%	6.7%	0.007	6.8%	6.8%	-0.002
Asthma	4.3%	4.2%	0.006	4.4%	4.4%	0.003
Drugs						
Beta blockers	39.3%	35.0%	0.089	34.9%	35.7%	-0.017
Ca channel blockers	32.5%	28.4%	0.089	27.8%	29.0%	-0.025
ACE inhibitors	51.0%	47.3%	0.076	46.1%	47.1%	-0.019
Anticoagulants	16.8%	14.4%	0.064	14.7%	14.5%	0.008
Statins	70.1%	76.9%	-0.154	76.6%	75.8%	0.018

VIII.5. Selected descriptive baseline patient characteristics for comparative effectiveness of thiazolidinediones (TZD) vs dipeptidyl peptidase 4 inhibitors (DPP4).

Variable	Before PS adjustment			After PS adjustment		
	TZD	DPP4	Standardized difference	TZD	DPP4	Standardized difference
Age						
55-59	0.7%	0.8%	-0.012	0.6%	0.8%	-0.028
60-64	1.6%	1.8%	-0.014	1.7%	1.6%	0.005
65-69	43.9%	47.4%	-0.07	43.5%	43.9%	-0.009
70-74	26.7%	25.5%	0.026	26.7%	27.2%	-0.011
75-79	16.0%	14.4%	0.045	16.2%	15.8%	0.012
80-84	7.7%	6.9%	0.03	7.9%	7.6%	0.011
85-89	2.7%	2.4%	0.017	2.7%	2.4%	0.016
90-94	0.5%	0.5%	-0.002	0.6%	0.4%	0.019
Gender						
Male	60.4%	53.5%	0.14	59.0%	59.9%	-0.018
Female	39.6%	46.5%	-0.14	41.0%	40.1%	0.018
Comorbidities						
Hypertensive Disorder	62.6%	70.9%	-0.176	63.5%	62.4%	0.023
Coronary Artery Disease	18.0%	21.6%	-0.089	18.2%	18.4%	-0.003
Heart Failure	3.2%	4.5%	-0.064	3.4%	3.6%	-0.009
Valvular Heart Disease	6.7%	8.4%	-0.065	6.9%	6.8%	0.004
Hypothyroidism	8.0%	12.4%	-0.144	8.3%	8.4%	-0.004
Hyperparathyroidism	0.4%	0.9%	-0.063	0.4%	0.7%	-0.028
Chronic kidney disorder	3.6%	4.6%	-0.049	3.8%	3.4%	0.02
Chronic obstructive lung disorder	6.7%	6.9%	-0.009	6.9%	6.6%	0.01
Asthma	4.2%	5.7%	-0.07	4.4%	4.3%	0.003

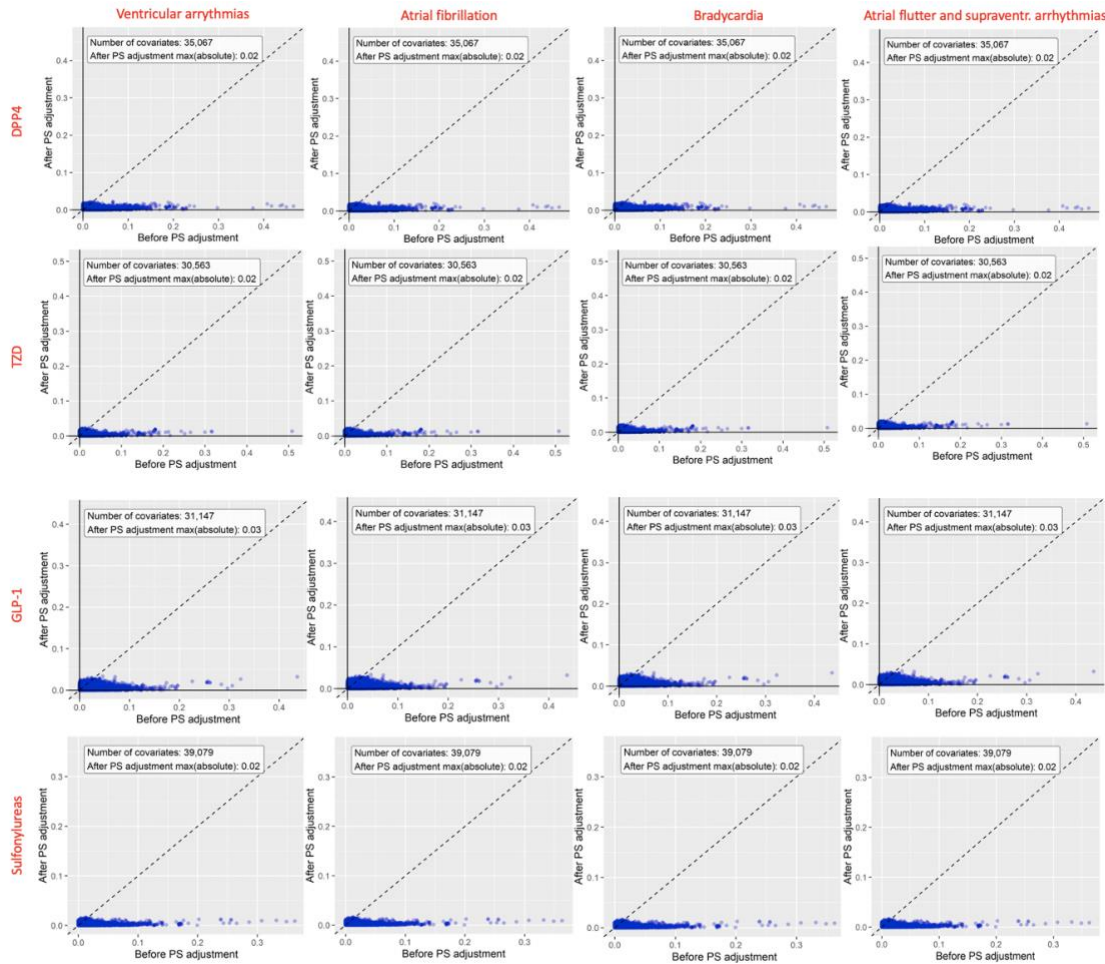
Drugs						
Beta blockers	35.2%	39.9%	-0.099	36.1%	35.9%	0.004
Ca channel blockers	28.6%	30.8%	-0.049	29.0%	29.3%	-0.006
ACE inhibitors	47.7%	44.7%	0.061	46.6%	46.5%	0.001
Anticoagulants	14.5%	15.8%	-0.034	14.8%	14.5%	0.007
Statins	76.8%	75.2%	0.037	76.4%	76.3%	0.001

VIII.6. Selected descriptive baseline patient characteristics for comparative effectiveness of thiazolidinediones (TZD) vs glucagon-like peptide 1 receptor agonists (GLP-1).

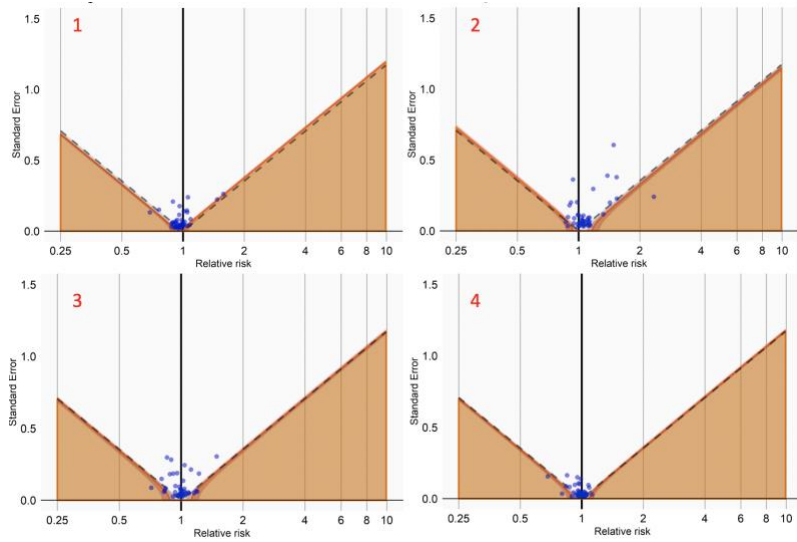
Variable	Before PS adjustment			After PS adjustment		
	TZD	GLP-1	Standardized difference	TZD	GLP-1	Standardized difference
Age						
50-54	0.1%	0.3%	-0.031	0.2%	0.2%	-0.008
55-59	0.6%	1.3%	-0.074	0.7%	0.8%	-0.022
60-64	1.5%	2.7%	-0.079	1.8%	2.0%	-0.017
65-69	43.0%	53.6%	-0.212	46.8%	46.6%	0.005
70-74	26.7%	26.2%	0.013	27.4%	27.3%	0.004
75-79	16.6%	10.9%	0.167	15.0%	14.9%	0.001
80-84	7.9%	3.9%	0.17	6.1%	6.3%	-0.007
85-89	2.7%	0.9%	0.134	1.6%	1.7%	-0.008
90-94	0.5%	0.1%	0.078	0.4%	0.2%	0.042
Gender						
Male	60.6%	49.9%	0.216	57.1%	58.1%	-0.019
Female	39.4%	50.1%	-0.216	42.9%	41.9%	0.019
Comorbidities						
Hypertensive Disorder	62.4%	73.1%	-0.23	63.7%	62.7%	0.02
Coronary Artery Disease	13.6%	17.3%	-0.102	14.2%	13.8%	0.01

Heart Failure	3.3%	5.2%	-0.095	3.5%	3.4%	0.007
Valvular Heart Disease	6.6%	7.7%	-0.042	6.6%	6.5%	0.005
Hypothyroidism	7.8%	15.0%	-0.228	8.8%	8.5%	0.011
Hyperparathyroidism	0.5%	1.0%	-0.053	0.6%	0.6%	-0.01
Chronic kidney disorder	3.6%	12.5%	-0.331	4.4%	4.3%	0.006
Chronic obstructive lung disorder	6.8%	7.8%	-0.039	6.7%	6.5%	0.007
Asthma	4.2%	6.9%	-0.117	4.6%	4.6%	0.003
Drugs						
Beta blockers	35.1%	43.4%	-0.172	36.9%	36.6%	0.006
Ca channel blockers	28.5%	31.8%	-0.073	29.0%	29.1%	-0.003
ACE inhibitors	47.1%	46.4%	0.013	46.7%	47.1%	-0.007
Anticoagulants	14.5%	16.8%	-0.062	15.0%	15.0%	-0.002
Statins	76.4%	78.4%	-0.048	76.8%	76.5%	0.005

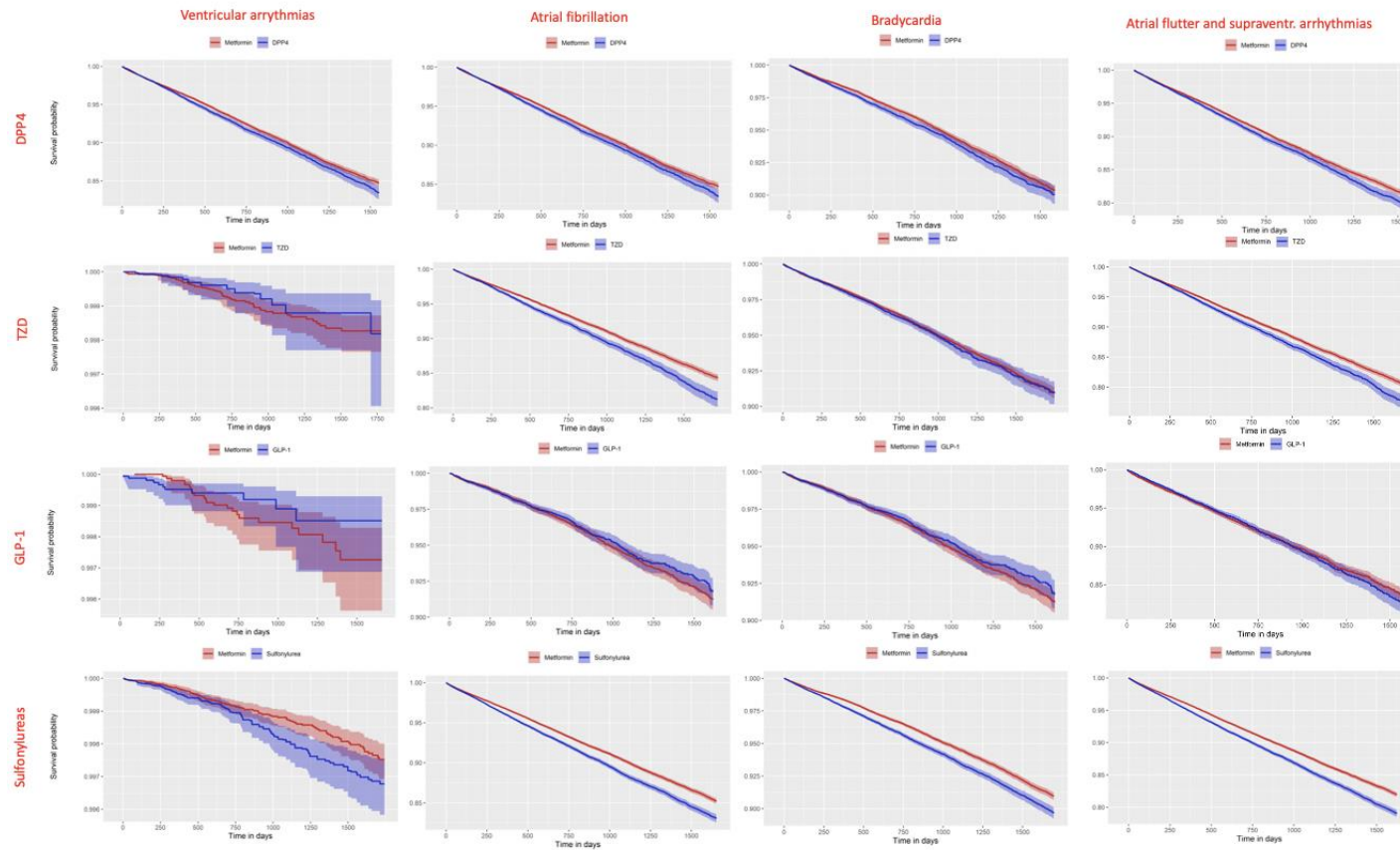
Supplemental Figure I. Covariate balance (standardized difference of mean) before and after propensity score matching for each drug comparison and outcome, comparing metformin and other antidiabetic drugs (sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 analogues); on-treatment.



Supplemental Figure II. Empirical calibration plots where estimates below the dashed line in gray area (small area above the orange area) have  $p < 0.05$  using traditional p-value calculation, comparison of first-line anti-diabetic therapy; on-treatment. 1 – metformin vs DPP4, 2 – metformin vs GLP1, 3 – metformin vs TZD, 4 – metformin vs sulfonylureas. Estimates in the orange area have  $p < 0.05$  using calibrated p-value calculation.

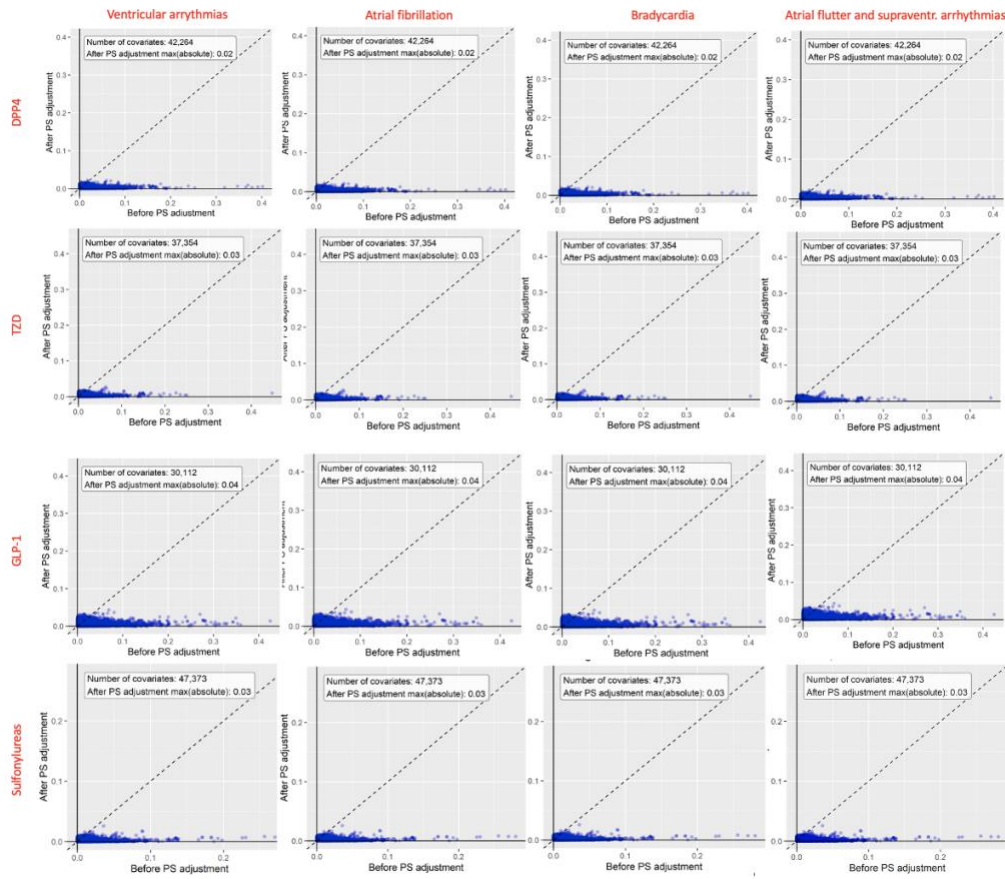


Supplemental Figure III. Kaplan-Meier plots of outcome-free survival for each drug comparison and outcome, comparing metformin and other antidiabetic drugs (sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 analogues); on-treatment. The Kaplan-Meier curves are shown with CI shading.

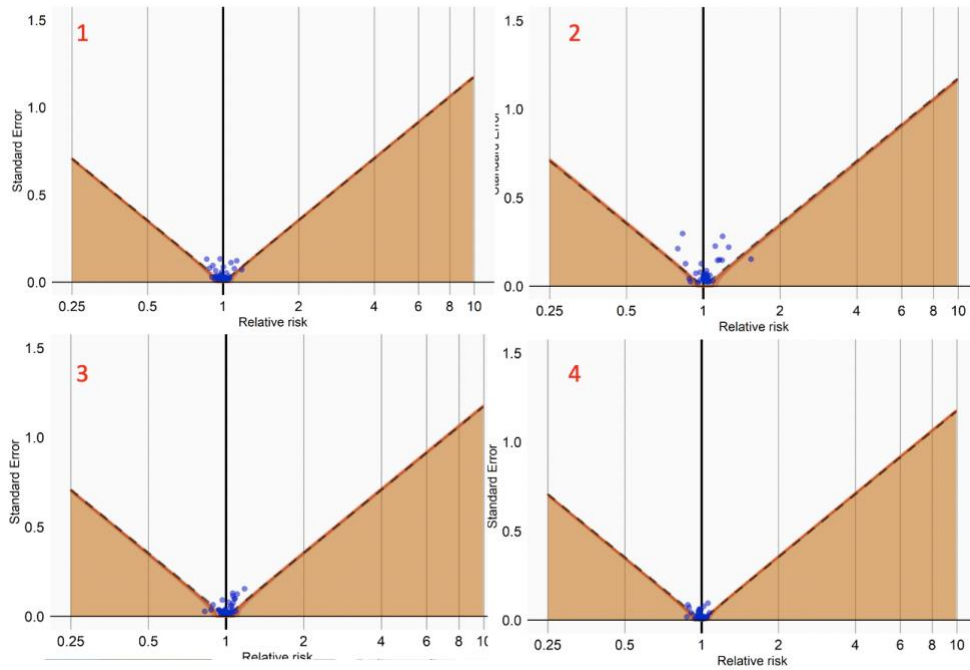




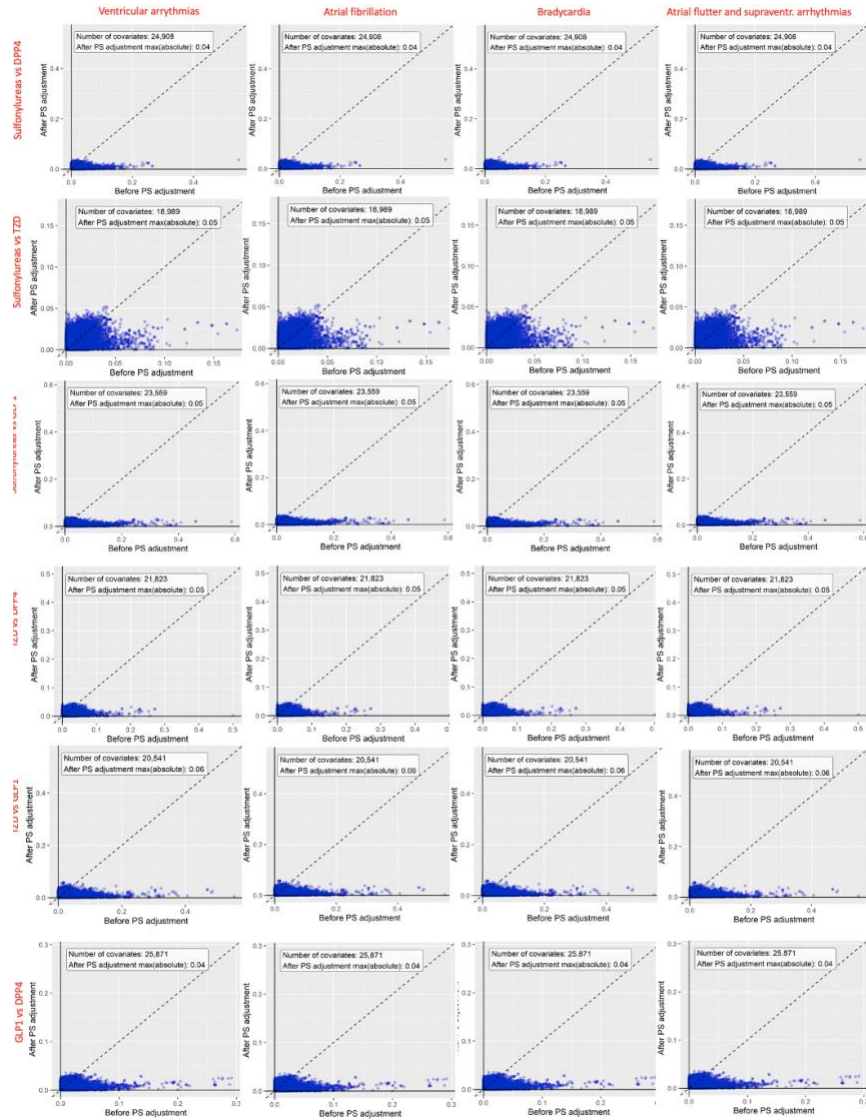
Supplemental Figure IV. Covariate balance (standardized difference of mean) before and after propensity score matching for each drug comparison and outcome, comparing metformin and other antidiabetic drugs (sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 analogues), intent-to-treat.



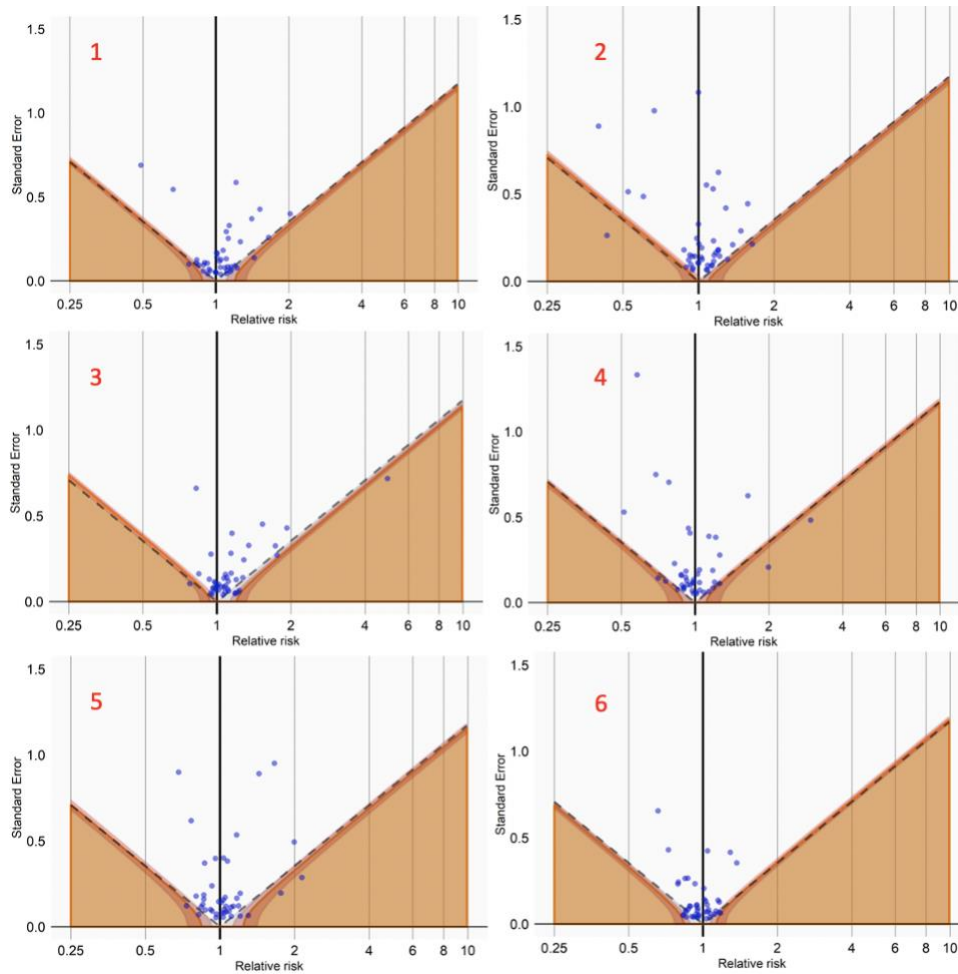
Supplemental Figure V. Empirical calibration plots where estimates below the dashed line in gray area (small area above the orange area) have  $p < 0.05$  using traditional p-value calculation, comparison of first-line anti-diabetic therapy, intent-to-treat analysis. 1 – metformin vs DPP4, 2 – metformin vs GLP1, 3 – metformin vs TZD, 4 – metformin vs sulfonylureas. Estimates in the orange area have  $p < 0.05$  using calibrated p-value calculation.



Supplemental Figure VI. Covariate balance (standardized difference of mean) before and after propensity score matching for each drug comparison and outcome, pairwise comparison of combo-therapy with metformin; on-treatment.



Supplemental Figure VII. Empirical calibration plots where estimates below the dashed line in gray area have  $p < 0.05$  using traditional p-value calculation, pairwise comparison of combo-therapy with metformin; on-treatment. 1 – sulfonylureas vs DPP4, 2 – sulfonylureas vs TZD, 3 – sulfonylureas vs GLP1, 4 – TZD vs DPP4, 5 – TZD vs GLP1, 6 – GLP1 vs DPP4. Estimates in the orange area have  $p < 0.05$  using calibrated p-value calculation.



Supplemental Figure VIII. Kaplan-Meier plots of outcome-free survival for each drug comparison and outcome, pairwise comparison of combo-therapy with metformin; on-treatment. The Kaplan-Meier curves are shown with CI shading.

