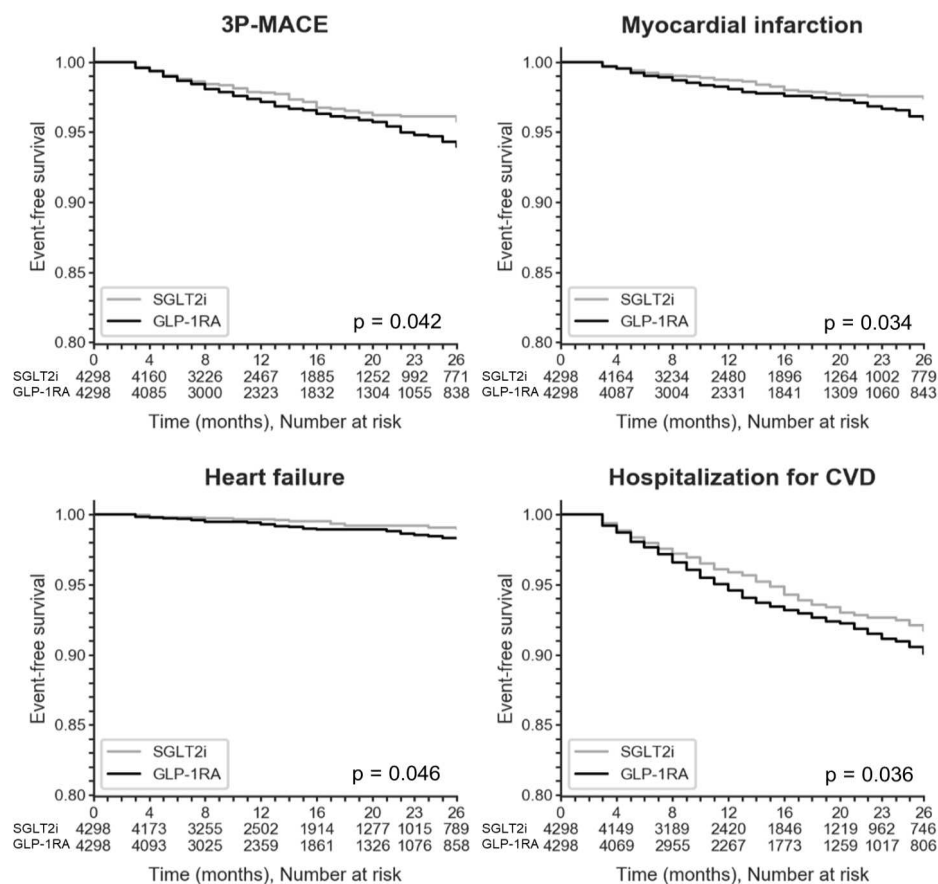1

Online Data Supplement

Figure S1. Kaplan-Meier curves. Comparison of event-free survival over time. Only outcomes associated with statistically significant log-rank test p-values ("p" in the Figure) are shown. MACE denotes major adverse cardiovascular events. 3P-MACE is a combination of all-cause death, myocardial infarction, stroke. Hospitalization for CVD refers to all hospitalization for cardiovascular causes. SGLT2i, SGLT-2 inhibitors. GLP-1RA, GLP-1 receptor agonists.

1

2

Figure S2. Subgroup analysis for the primary outcome. Results of Cox analysis on the primary outcome, after stratification according to the indicated variables. In the figure, "p int." refers to the interaction term (SGLT2i or GLP-1RA × stratification variable) in the adjusted model.

Variable		N. of Subjects		3P-MACE (HR & 95% CIs)	Hazard Ratio (CI)	p value	p. int
		SGLT2i	GLP-1RA				
Sex	female	1590	1587		0.61 (0.34 – 1.08)	0.090	0.352
	male	2708	2711		0.82 (0.63 – 1.08)	0.164	
Age	≥ 65	1922	2001		0.70 (0.51 – 0.97)	0.032	0.346
	< 65	2376	2297		0.90 (0.61 – 1.33)	0.590	
Cardiovascular disease	yes	786	759		0.70 (0.49 – 0.99)	0.049	0.420
	no	3512	3539		0.86 (0.61 – 1.21)	0.382	
Any insulin	yes	1226	1252		0.72 (0.49 – 1.06)	0.091	0.623
	no	3072	3046		0.81 (0.59 – 1.12)	0.208	
Statins	yes	2771	2772		0.75 (0.57 – 0.99)	0.045	0.630
	no	1527	1526		0.87 (0.51 – 1.48)	0.604	
Diuretics	yes	784	805		0.65 (0.42 – 0.99)	0.045	0.290
	no	3514	3493		0.86 (0.63 – 1.16)	0.323	

0.25   0.5   0.75 1.0 1.25   1.75

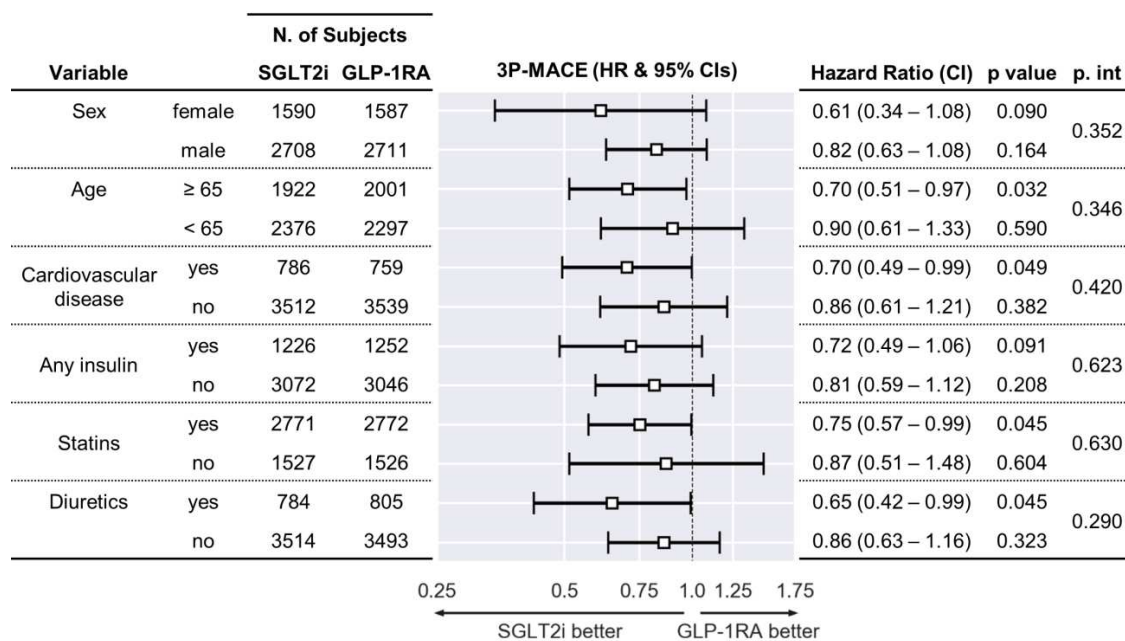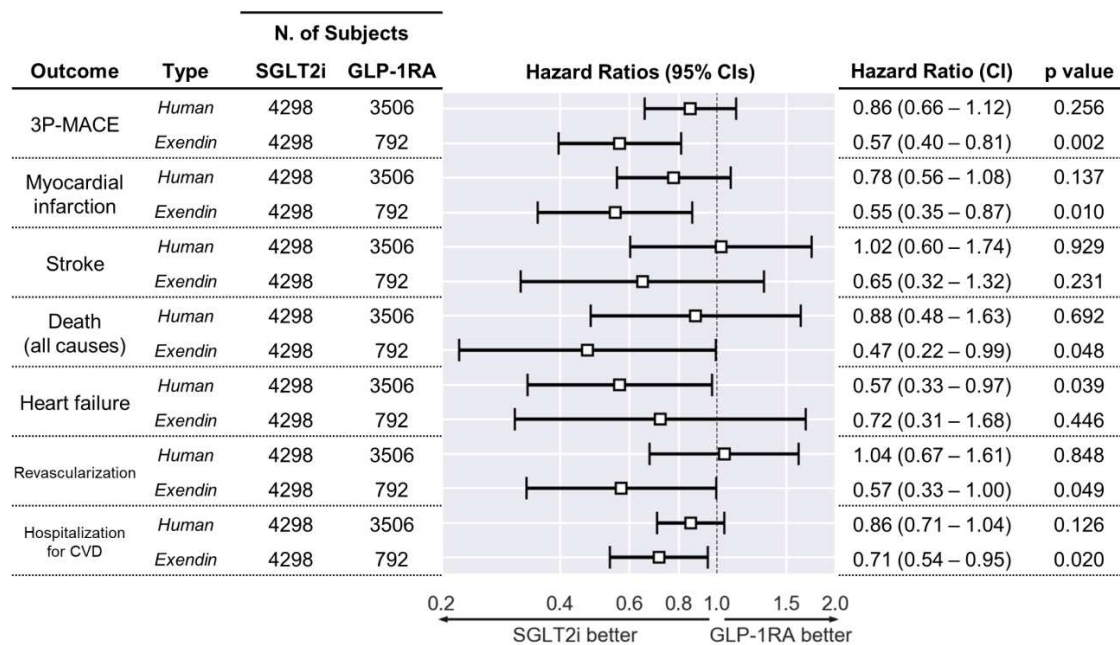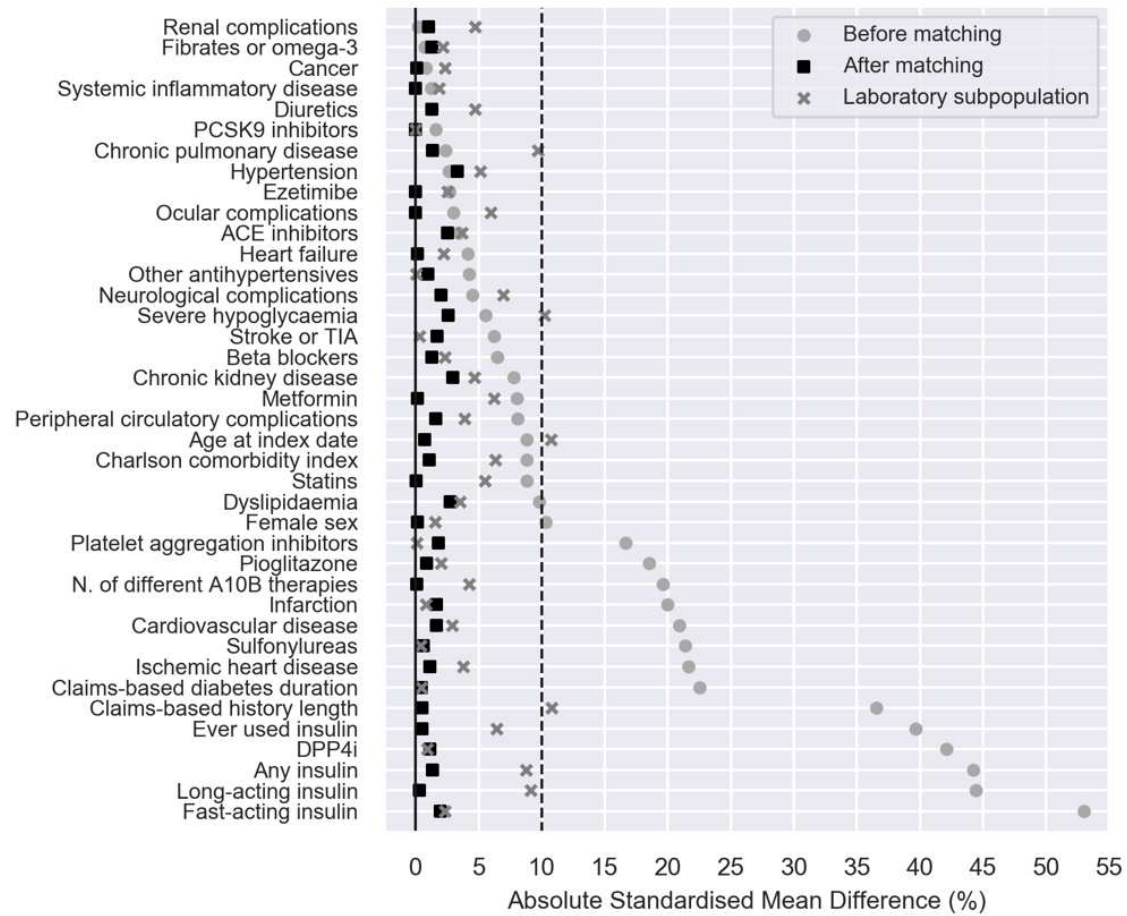← SGLT2i better   GLP-1RA better →

2

Figure S3. Subgroup analysis stratified by type of GLP-1RA. Results of Cox analysis on the primary outcome, after stratification of GLP-1RA initiators according to whether they were on human- or exendin-based GLP-1RA

Outcome	Type	N. of Subjects SGLT2i	N. of Subjects GLP-1RA	Hazard Ratios (95% CIs)	Hazard Ratio (CI)	p value
3P-MACE	*Human*	4298	3506		0.86 (0.66 – 1.12)	0.256
	Exendin	4298	792		0.57 (0.40 – 0.81)	0.002
Myocardial infarction	*Human*	4298	3506		0.78 (0.56 – 1.08)	0.137
	Exendin	4298	792		0.55 (0.35 – 0.87)	0.010
Stroke	*Human*	4298	3506		1.02 (0.60 – 1.74)	0.929
	Exendin	4298	792		0.65 (0.32 – 1.32)	0.231
Death (all causes)	*Human*	4298	3506		0.88 (0.48 – 1.63)	0.692
	Exendin	4298	792		0.47 (0.22 – 0.99)	0.048
Heart failure	*Human*	4298	3506		0.57 (0.33 – 0.97)	0.039
	Exendin	4298	792		0.72 (0.31 – 1.68)	0.446
Revascularization	*Human*	4298	3506		1.04 (0.67 – 1.61)	0.848
	Exendin	4298	792		0.57 (0.33 – 1.00)	0.049
Hospitalization for CVD	*Human*	4298	3506		0.86 (0.71 – 1.04)	0.126
	Exendin	4298	792		0.71 (0.54 – 0.95)	0.020

0.2   0.4   0.6   0.8 1.0   1.5   2.0

SGLT2i better ← | → GLP-1RA better

4

Figure S4. Balance before and after matching. Visual representation of absolute standardised mean differences before and after PSM. The vertical, dashed line represents the 0.10 threshold.

5

Table S1. **Claims-based definition of study variables**. Each variable was defined as the presence of at least one of the claims-based indicators in the corresponding row. Medication names have been internally mapped 1:1 to ATC codes, exemptions from copayment to regional exemption codes.

Variable	ICD-9-CM Diagnosis Codes	ICD-9-CM Procedure Codes	Medications	Exemptions from Copayment
Hypertension	401-405		ACE inhibitors, diuretics, beta blockers, other antihypertensives	Hypertension
Dyslipidaemia			Statins, fibrates, omega 3, PCSK9 inhibitors, ezetimibe	Dyslipidaemia
Peripheral circulatory complications	440, 250.7	00.55, 38.48, 39.50, 39.52, 39.71, 39.90		
Myocardial Infarction	410-414			
Ischemic heart disease	410-414	00.66, 36.03, 36.06, 36.07, 36.10, 36.19		Ischemic heart disease
Stroke or TIA	431-436	00.61-00.65		Stroke or TIA
Heart failure	428			Heart failure
Cardiovascular disease	410-414, 428, 431-436, 440	00.55, 00.61-00.66, 36.03, 36.06, 36.07, 36.10, 36.19, 38.48, 39.50, 39.52, 39.71, 39.90		Ischemic heart disease, stroke or TIA, heart failure
Neurological complications	250.6			
Ocular complications	250.5			
Renal complications	250.4			
Chronic kidney disease	585-587			Chronic kidney disease

5

6

Severe hypoglycaemia	250.3, 250.8, 250.10, 250.12			
Chronic pulmonary disease	491-496, 518.83, 518.84		Medications for obstructive airway diseases	Chronic pulmonary disease, asthma
Systemic inflammatory disease				Rheumatoid arthritis, systemic lupus erythematosus, connective tissue disease, Sjogren's syndrome, psoriasis, ankylosing spondylitis
Cancer				Cancer

7

Table S2. Baseline clinical characteristics before matching. Unless otherwise indicated, medication-related variables were calculated starting from 12 months before the index date. Pre-existing conditions were assessed with all available data up to the index date. SMD values reported as "<0.01" are, in fact, <0.01 and >-0.01.

	SGLT2i (N=7192)	GLP-1RA (N=5804)	SMD[*]	p value[**]
Demographics				
Age at index date (years)	63.2 (9.1)	62.4 (9.7)	0.09	<0.001
Female sex (%)	34.6	39.6	-0.10	<0.001
Claims-based history length[a] (months)	62.2 (11.5)	57.3 (15.5)	0.37	<0.001
Claims-based diabetes duration[b] (months)	126 (68.6)	111 (64.6)	0.23	<0.001
Risk factors				
Hypertension (%)	82.9	83.9	-0.03	0.146
Dyslipidaemia (%)	77.7	73.5	0.10	<0.001
Macrovascular complications				
Peripheral circulatory complications (%)	3.2	1.9	0.08	<0.001
Infarction (%)	12.4	6.5	0.20	<0.001
Ischemic heart disease (%)	18.8	11	0.22	<0.001
Stroke or TIA (%)	5.0	3.8	0.06	0.001
Heart failure (%)	3.5	2.7	0.04	0.022
Cardiovascular disease (%)	24.1	15.8	0.21	<0.001
Microvascular complications				
Neurological complications (%)	0.7	0.3	0.04	0.016
Ocular complications (%)	0.7	0.5	0.03	0.113
Renal complications (%)	0.4	0.4	<0.01	0.986
Chronic kidney disease (%)	1.3	2.3	-0.08	<0.001
Severe hypoglycaemia (%)	1.5	0.9	0.06	0.002
Comorbidities				
Chronic pulmonary disease (%)	34.1	33.0	0.02	0.185
Systemic inflammatory disease (%)	2.1	2.3	-0.01	0.516
Cancer (%)	10.5	10.8	-0.01	0.676
Charlson comorbidity index	0.6 (1.2)	0.5 (1.1)	0.09	<0.001
Glucose lowering medications				
No. of different A10B therapies[c]	2.2 (1.2)	2.4 (1.3)	-0.20	<0.001
Ever used insulin (%)	49.2	30	0.40	<0.001
Any insulin (%)	45.3	24.6	0.44	<0.001
Long-acting insulin (%)	44.4	23.6	0.44	<0.001
Fast-acting insulin (%)	31.7	10.4	0.53	<0.001
Metformin (%)	86.0	88.7	-0.08	<0.001
Sulfonylureas (%)	36.6	47.0	-0.21	<0.001
DPP4i (%)	21.0	39.8	-0.42	<0.001
Pioglitazone (%)	9.3	15.2	-0.18	<0.001
Other therapies				
ACE inhibitors (%)	70.9	72.4	-0.03	0.055
Diuretics (%)	19.3	19.8	-0.01	0.473
Beta blockers (%)	38.6	35.5	0.06	<0.001
Other antihypertensives (%)	7.7	8.9	-0.04	0.018
Statins (%)	67.8	63.7	0.09	<0.001
Fibrates or omega-3 (%)	12.9	12.6	0.01	0.713
PCSK9 inhibitors (%)	0.01	0	0.02	0.914
Ezetimibe (%)	4.4	3.9	0.03	0.141
Platelet aggregation inhibitors (%)	41.7	33.6	0.17	<0.001

[*] Standardised mean differences (positive if SGLT2i greater). [**] Chi-squared test for categorical variables (expressed as %), Mann-Whitney test otherwise. [a] time interval between the first available claim and the index date. [b] time interval between the first claim or exemption from co-payment indicating diabetes and the index date. [c] computed using all available data up to the index date.

7

Table S3. Change in intermediate effectiveness parameters. Clinical-laboratory data of patients with available values at baseline and during follow-up. Data are reported as mean (standard deviation). SBP, systolic blood pressure. DBP, diastolic blood pressure. *p<0.05 vs. baseline. #p<0.05 vs. SGLT2i. ^p<0.05 vs. SGLT2i adjusted for baseline imbalance.

Variable	SGLT2i			GLP-1RA		
	Baseline	**Follow-up**	**Change**	**Baseline**	**Follow-up**	**Change**
Fasting glucose, mg/dl	169.7 (47.7)	148.8 (37.7)*	-21.0 (49.8)	161.6 (44.8)#	147.8 (45.5)*	-13.8 (53.7)#
HbA1c, %	8.0 (1.0)	7.6 (0.9)*	-0.4 (1.0)	7.8 (0.9)#	7.3 (0.9)*	-0.5 (1.0)^
SBP, mm Hg	142.4 (20.3)	137.1 (18.2)*	-5.3 (20.3)	143.3 (18.1)	141.1 (19.5)*	-2.2 (20.6)#
DBP, mm Hg	81.7 (10.2)	79.8 (10.3)*	-1.9 (10.3)	81.3 (10.1)	80.6 (10.4)	-0.7 (10.9)
Total cholesterol, mg/dl	168.8 (37.0)	162.2 (35.3)*	-6.6 (32.3)	169.2 (34.9)	160.2 (33.7)*	-9.0 (31.0)
HDL cholesterol, mg/dl	47.9 (14.4)	49.5 (13.0)*	1.6 (9.7)	48.6 (13.0)	48.0 (12.5)	-0.6 (8.1)#
LDL cholesterol, mg/dl	93.8 (33.4)	87.2 (30.7)*	-6.6 (28.2)	93.0 (30.7)	84.3 (28.6)*	-8.6 (26.6)
Triglycerides, mg/dl	134.5 (56.7)	128.3 (53.2)*	-6.2 (50.8)	138.2 (56.1)	140.0 (58.3)	1.8 (50.9)#

Table S4. Adverse events. Results of Cox analysis on adverse events, and corresponding event rates (calculated /1000 person-years). HR are calculated for SGLT2i vs. GLP-1RA. GUTI, genitourinary tract infections.

	SGLT2i		GLP-1RA		Total		HR (CI)	p value
	Events	Event rate	Events	Event rate	Events	Event rate		
GUTI	4	0.76	2	0.39	6	0.57	1.91 (0.35 – 10.41)	0.456
Fournier's gangrene	0	0.00	0	0.00	0	0.00	N/A	N/A
Bone fracture	26	4.92	23	4.44	49	4.68	1.10 (0.63 – 1.93)	0.73
Diabetic ketoacidosis	1	0.19	1	0.19	2	0.19	0.97 (0.06 – 15.56)	0.985
Acute renal disease	13	2.46	23	4.44	36	3.44	0.55 (0.28 – 1.09)	0.086
Amputation	10	1.89	6	1.16	16	1.53	1.59 (0.58 – 4.37)	0.37
Pancreatitis	4	0.76	2	0.39	6	0.57	1.98 (0.36 – 10.81)	0.43
Pancreatic cancer	9	1.7	6	1.16	15	1.43	1.45 (0.52 – 4.08)	0.48