

Supplemental material

Cardiovascular morbidity and mortality in patients with type 2 diabetes using novel antidiabetic medicines as add-on therapy: an observational real-world study

Zerovnik Spela, Kos Mitja, Locatelli Igor

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Description of the Slovenian healthcare system and data sources

Slovenian healthcare system

Slovenia has a Bismarck-type social health insurance system and provides compulsory health insurance for the entire Slovenian population. Compulsory health insurance fund is managed by the Health Insurance Institute of Slovenia (HIIS), which pays for healthcare services, including medicines. Some healthcare services (including some groups of medicines) are fully covered by compulsory health insurance, while others are only partially covered (the rest is covered by voluntary complementary health insurance). HIIS covers the full price of all antidiabetic medicines.

Data sources

Three healthcare databases obtained from the National Institute of Public Health (NIJZ) were used in this study, namely Outpatient Prescription Medicines Database, National Hospital Health Care Statistics Database and Causes of Death Registry. These databases contain data on all dispensed outpatient prescriptions, hospital admissions and deaths for the entire Slovenian population. The databases can be linked using a unique anonymous patient identifier.

1) *Outpatient Prescription Medicines Database*¹

This prescription claims database contains data on all dispensed outpatient prescriptions in Slovenia and serves as the basis for medicine reimbursement by the HIIS. The database does not include data on hospital-prescribed medicines, over-the-counter drugs and out-of-pocket prescriptions. Out-of-pocket prescriptions account for less than 1% of all outpatient prescriptions in Slovenia.

Patients can be followed within the database using unique anonymous patient identifier. The database contains information on dispensed drug coded using ATC (Anatomical Therapeutic Chemical) classification, date of prescription, amount of drug dispensed. It also contains information about the patient such as patient gender, year of birth and statistical region.

2) *National Hospital Health Care Statistics Database*²

The hospitalisation claims database contains information on all hospital admissions, main and admission diagnoses for the entire Slovenian population, date of hospital admission, concomitant diagnoses, patient gender, year of birth, therapeutic or diagnostic procedures performed in the hospital. Diagnoses are coded according to ICD-10-AM (International Classification of Diseases, 10th Revision, Australian Modification, Sixth Edition) as of 1 January 2013. Before that ICD-10 (Second Edition) was in use.

3) *Causes of Death Registry (CoD)*³

Causes of Death Registry contains information on the date of death, the underlying cause of death, and the external cause of death. The causes of death are coded according to ICD-10.

¹ Source: NIJZ, Outpatient Prescription Medicines Database.

² Source: NIJZ, National Hospital Health Care Statistics Database.

³ Source: NIJZ, Causes of Death Registry.

Table S1: ATC codes for the definition of exposure

Exposure	ATC codes
Dipeptidyl peptidase-4 inhibitors	A10BH01, A10BH02, A10BH03, A10BH04, A10BH05, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD13
Glucagon-like peptide-1 receptor agonists	A10BJ01, A10BJ02, A10BJ03, A10BJ04, A10BJ05, A10BJ06, A10AE54, A10AE56
Sodium-glucose co-transporter 2 inhibitors	A10BK01, A10BK02, A10BK03, A10BK04, A10BD15, A10BD20

Data source: Outpatient Prescription Medicines Database

Table S2: Definitions of baseline patient characteristics

Data source: Outpatient Prescription Medicines Database	
Characteristic	Definition
Duration of diabetes therapy	The number of days from the first dispensed prescription for antidiabetic medicine to the start date (Day 135 after the index date). The data were available as of 1 January 2009.
Antidiabetic medicines used in the past 135 days	At least one prescription for an antidiabetic medicine within the 135 days preceding start date
<i>Metformin</i>	ATC codes: A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25
<i>Sulphonylureas</i>	ATC codes: A10BB, A10BD02, A10BD04, A10BD06
<i>Repaglinide</i>	ATC codes: A10BX02, A10BD14
<i>Acarbose</i>	ATC codes: A10BF01, A10BD17
<i>Thiazolidinediones</i>	ATC codes: A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12
Insulin therapy in the past year	At least one prescription for insulin (ATC code: A10A) in the year preceding start date.
Concomitant therapy	At least one prescription for individual ATC code within the 135 days preceding start date.
<i>Anticoagulant</i>	ATC codes: B01AA, B01AE07, B01AF, B01AX05, B01AB04, B01AB05, B01AB06
<i>Platelet inhibitor</i>	ATC codes: B01AC
<i>Antiarrhythmic, cardiac glycoside or vasodilator</i>	ATC codes: C01
<i>Loop diuretic</i>	ATC codes: C03C, C03EB
<i>Thiazide and other diuretic</i>	ATC codes: C03A, C03B, C03EA, C07B, C07C, C07D, C08GA, C09BA, C09BX01, C09BX03, C09DA, C09DX01, C09DX03, C09DX06, C09DX07, C10BX13
<i>MRA</i>	ATC codes: C03D, C03E
<i>Beta blocker</i>	ATC codes: C07, C09BX02, C09BX04, C09DX05
<i>Calcium channel blocker</i>	ATC codes: C08G, C08C, C08D, C07FB, C09BB, C09BX01, C09BX03, C09BX04, C09DB, C09DX01, C09DX03, C09DX06, C09DX07, C10BX03, C10BX07, C10BX09, C10BX11, C10BX14
<i>ACE-inhibitor or ARB</i>	ATC codes: C09A, C09B, C09C, C09D, C10BX04, C10BX06, C10BX07, C10BX10, C10BX11, C10BX12, C10BX13, C10BX14, C10BX15, C10BX16, C10BX17
<i>Statin</i>	ATC codes: C10AA, C10BA, C10BX
<i>Other lipid modifying drug</i>	ATC codes: C10AB, C10AC, C10AD, C10AX, C10BA
<i>Antidepressant</i>	ATC codes: N06A
<i>Anxiolytic, hypnotic, or sedative</i>	ATC codes: N05B, N05C
<i>NSAID</i>	ATC codes: M01A
Data source: National Hospital Health Care Statistics Database	
Characteristic	Definition

Previous hospitalisations	At least one hospital admission due to specific cause in the year preceding start date.
<i>Hospital admission due to CV causes in the past year</i>	ICD-10-AM-AM codes: I00-I99
<i>Hospital admission due to CV causes (excluding HF) in the past year</i>	ICD-10-AM codes: I00-I99 (without I50)
<i>Hospital admission due to HF in the past year</i>	ICD-10-AM codes: I50
<i>Hospital admission due to MI in the past year</i>	ICD-10-AM codes: I21, I22
<i>Hospital admission due to stroke in the past year</i>	ICD-10-AM codes: I63, I64
<i>Hospital admission due to type 2 diabetes in the past year</i>	ICD-10-AM codes: E11
<i>Hospital admission with cancer as the main or concomitant diagnosis in the past five years</i>	ICD-10-AM codes: C00-C97

ACE - angiotensin-converting enzyme inhibitors; ARB - angiotensin II receptor blockers; ATC - Anatomical Therapeutic Chemical; CV - cardiovascular; HF - heart failure; ICD - International Classification of Diseases, 10th Revision, Australian Modification, Sixth Edition); MI - myocardial infarction; MRA - mineralocorticoid (aldosterone) receptor antagonists; NSAID - nonsteroidal anti-inflammatory drug

Table S3: Full covariate model for major adverse cardiovascular events in intention-to-treat analysis

Covariates	Major adverse cardiovascular events	
	Hazard ratio (95% CI)	p value
SGLT2i vs DPP-4i	0.67 (0.51-0.87)	0.003
GLP-1RA vs DPP-4i	0.65 (0.43-0.99)	0.043
Sex (female vs male)	0.74 (0.61-0.90)	0.003
Age	1.06 (1.04-1.07)	< 0.0005
Duration of diabetes (5 years or more vs less than 5 years)	1.48 (1.09-2.00)	0.012
Use of insulin (yes vs no)	1.37 (1.04-1.80)	0.027
T2D hospitalisation in the past year (yes vs no)	2.51 (1.59-3.97)	< 0.0005
CV hospitalisation in the past year (yes vs no)	1.59 (1.20-2.12)	0.001
Time of cohort entry†	0.95 (0.76-1.19)	0.666
Metformin (yes vs no)	0.77 (0.61-0.97)	0.027
Sulfonylureas (yes vs no)	0.92 (0.71-1.20)	0.558
Anticoagulants (yes vs no)	1.18 (0.88-1.57)	0.261
Platelet inhibitors (yes vs no)	1.25 (1.00-1.54)	0.046
Antiarrhythmics, cardiac glycosides or vasodilators (yes vs no)	1.20 (0.92-1.57)	0.178
Loop diuretics (yes vs no)	1.61 (1.26-2.06)	< 0.0005
Thiazides and other diuretics (yes vs no)	0.93 (0.74-1.15)	0.491
MRA (yes vs no)	1.32 (0.92-1.87)	0.127
Beta blockers (yes vs no)	1.29 (1.04-1.59)	0.018
Calcium channel blockers (yes vs no)	1.07 (0.87-1.31)	0.530
ACE-inhibitors or ARBs (yes vs no)	0.78 (0.61-0.99)	0.040
Statins (yes vs no)	0.59 (0.49-0.73)	< 0.0005
Other lipid modifying drugs (yes vs no)	1.02 (0.66-1.58)	0.930
Antidepressants (yes vs no)	1.07 (0.81-1.41)	0.624
Anxiolytic, hypnotic, or sedative (yes vs no)	1.10 (0.86-1.41)	0.442
NSAID (yes vs no)	1.24 (0.99-1.57)	0.066
Result of omnibus test (df)	418.82 (25 df)	

† from 30 June 2016 to 30 June 2018 versus from 30 June 2014 to 29 June 2016; ACE - angiotensin-converting enzyme inhibitors; ARB - angiotensin II receptor blockers; CV - cardiovascular; df - degrees of freedom; DPP-4i - dipeptidyl peptidase-4 inhibitor; GLP-1RA - glucagon-like peptide-1 receptor agonist; MACE - major adverse cardiovascular event; MRA - mineralocorticoid (aldosterone) receptor antagonists; NSAID - nonsteroidal anti-inflammatory drug; SGLT2i - sodium-glucose co-transporter 2 inhibitor; T2D - type 2 diabetes

Table S4: Final covariate models for all outcomes in on-treatment analyses

	MACE	Cardiovascular death	Heart failure	All cause death
Covariates	<i>HR (95% CI) p value</i>			
SGLT2i vs DPP-4i	0.71 (0.49-1.02) 0.065	0.43 (0.24-0.80) 0.007	0.54 (0.30-0.99) 0.047	0.69 (0.48-0.99) 0.045
GLP-1RA vs DPP-4i	0.55 (0.30-1.02) 0.058	0.26 (0.08-0.86) 0.027	1.45 (0.79-2.65) 0.229	0.33 (0.16-0.70) 0.004
Sex (female vs male)	0.79 (0.59-1.05) 0.102	0.91 (0.60-1.39) 0.669	1.31 (0.86-1.99) 0.211	0.76 (0.57-1.00) 0.052
Age	1.05 (1.03-1.07) < 0.0005	1.08 (1.05-1.10) < 0.0005	1.03 (1.01-1.06) 0.008	1.08 (1.06-1.10) < 0.0005
Duration of diabetes therapy (5 years or more vs less than 5 years)	2.54 (1.43-4.49) 0.001	3.26 (1.31-8.09) 0.011	> 0.1*	1.67 (1.06-2.64) 0.027
Use of insulin (yes vs no)	1.49 (1.01-2.20) 0.042	1.85 (1.06-3.22) 0.030	> 0.1*	1.45 (0.98-2.13) 0.062
T2D hospitalisation in the past year (yes vs no)	1.46 (0.60-3.58) 0.405	2.35 (0.85-6.46) 0.099	2.96 (1.07-8.17) 0.036	2.32 (1.21-4.47) 0.012
CV hospitalisation in the past year (yes vs no)	1.68 (1.11-2.55) 0.014	1.67 (0.97-2.86) 0.064	NA	1.70 (1.17-2.47) 0.005
HF hospitalisation in the past year (yes vs no)	NA	NA	2.09 (1.01-4.33) 0.048	NA
CV hospitalisation (excluding HF) in the past year (yes vs no)	NA	NA	1.66 (0.97-2.85) 0.064	NA
Hospitalisation due to/with cancer in the past five years† (yes vs no)	NA	NA	NA	2.08 (1.40-3.10) < 0.0005
Time of cohort entry†	> 0.2*	> 0.1*	> 0.1*	> 0.2*
Sulfonylureas (yes vs no)	> 0.2*	> 0.1*	> 0.1*	> 0.2*
Metformin (yes vs no)	0.78 (0.56-1.09) 0.148	> 0.1*	0.67 (0.43-1.06) 0.086	> 0.2*
Anticoagulants (yes vs no)	1.33 (0.88-2.03) 0.180	> 0.1*	2.98 (1.77-5.01) < 0.0005	1.35 (0.93-1.96) 0.120
Platelet inhibitors (yes vs no)	1.43 (1.04-1.96) 0.028	> 0.1*	2.00 (1.26-3.18) 0.003	1.42 (1.05-1.91) 0.023
Antiarrhythmics, cardiac glycosides or vasodilators (yes vs no)	1.43 (0.99-2.06) 0.057	1.96 (1.24-3.09) 0.004	1.55 (0.99-2.42) 0.057	1.37 (0.98-1.92) 0.063
Loop diuretics (yes vs no)	1.98 (1.42-2.77) < 0.0005	2.68 (1.73-4.16) < 0.0005	3.66 (2.30-5.83) < 0.0005	2.23 (1.64-3.02) < 0.0005
Thiazides and other diuretics (yes vs no)	> 0.2*	> 0.1*	> 0.1*	> 0.2*
MRA (yes vs no)	> 0.2*	> 0.1*	2.95 (1.81-4.80) < 0.0005	1.35 (0.87-2.08) 0.176
Beta blockers (yes vs no)	> 0.2*	> 0.1*	> 0.1*	> 0.2*
Calcium channel blockers (yes vs no)	> 0.2*	> 0.1*	> 0.1*	> 0.2*
ACE-inhibitors or ARBs (yes vs no)	0.66 (0.48-0.90) 0.009	0.65 (0.42-1.01) 0.057	> 0.1*	0.75 (0.56-1.02) 0.070
Statins (yes vs no)	0.61 (0.46-0.82) 0.001	> 0.1*	> 0.1*	0.69 (0.52-0.91) 0.008
Other lipid modifying drugs (yes vs no)	1.64 (0.96-2.83) 0.073	> 0.1*	> 0.1*	1.56 (0.87-2.78) 0.134
Antidepressants (yes vs no)	> 0.2*	> 0.1*	> 0.1*	1.41 (0.99-2.03) 0.060

	MACE	Cardiovascular death	Heart failure	All cause death
Covariates	<i>HR (95% CI) p value</i>			
Anxiolytic, hypnotic, or sedative (yes vs no)	> 0.2*	1.51 (0.95-2.41) 0.081	> 0.1*	> 0.2*
NSAID (yes vs no)	> 0.2*	> 0.1*	> 0.1*	1.26 (0.91-1.76) 0.166
Result of omnibus test (df)	<i>215.56 (16 df)</i>	<i>198.43 (12 df)</i>	<i>253.93 (13 df)</i>	<i>373.97 (19 df)</i>

ACE - angiotensin-converting enzyme inhibitors; ARB - angiotensin II receptor blockers; CV - cardiovascular; df - degrees of freedom; DPP-4i - dipeptidyl peptidase-4 inhibitor; GLP-1RA - glucagon-like peptide-1 receptor agonist; HF - heart failure; HR - hazard ratio; MACE - major adverse cardiovascular event; MRA - mineralocorticoid (aldosterone) receptor antagonists; NA - not applicable; NSAID - nonsteroidal anti-inflammatory drug; SGLT2i - sodium-glucose co-transporter 2 inhibitor; T2D - type 2 diabetes

* removal probability for stepwise backward selection based on Wald test was set to 0.2 for MACE and all-cause death and to 0.1 for cardiovascular death and heart failure, therefore, covariates with p values of 0.2 (0.1) or greater were excluded from the model and their respective hazard ratios were not calculated.

† from 30 June 2016 to 30 June 2018 versus from 30 June 2014 to 29 June 2016.

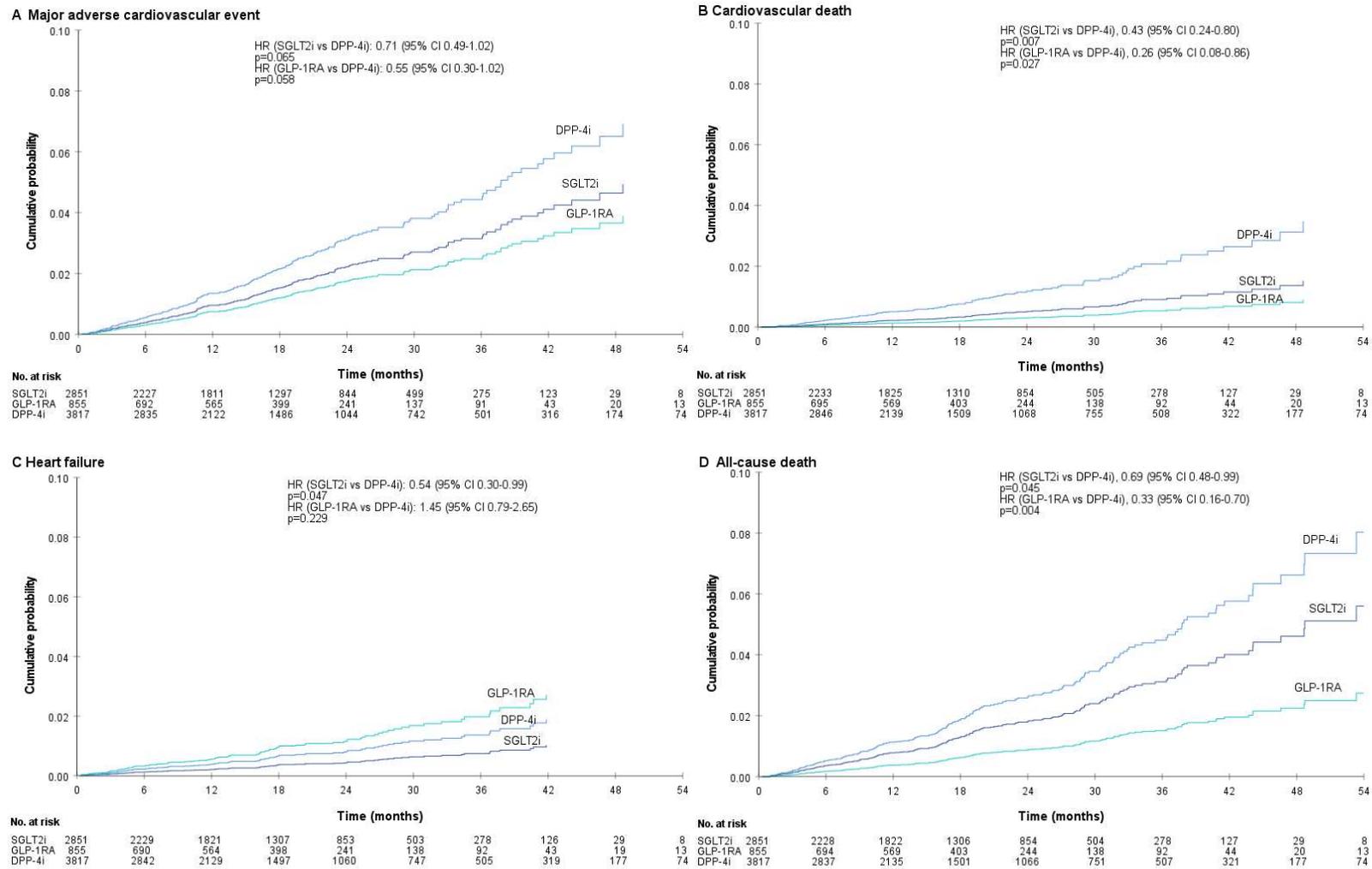


Figure S1: Cumulative probability of (A) major adverse cardiovascular events, (B) cardiovascular death, (C) heart failure, and (D) all-cause death in patients initiating DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors at mean values of all included covariates for on-treatment analyses