Differential Cardiovascular and Renal Benefits of SGLT2 Inhibitors and GLP1 Receptor Agonists in Patients With Type 2 Diabetes Mellitus

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Original investigation

Keywords: diabetes mellitus, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, heart failure, renal outcomes

Posted Date: July 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-734897/v1

Abstract

Background: The differential benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) in cardiovascular or renal outcomes have not been fully investigated. This study sought to compare the real-world cardiovascular and renal outcomes between SGLT2i and GLP1RA in patients with type 2 diabetes.

Methods: Patients with diabetes prescribed SGLT2i or GLP1RA were retrospectively identified. Patients treated with antihyperglycemic medications other than SGLT2i or GLP1RA were used as a control group. After 2:1:3 propensity score matching among 24,752 eligible patients, 614 patients treated with SGLT2i, 307 patients treated with GLP1RA, and 921 control patients were analyzed. Primary outcomes were composite ischemic events (acute coronary syndrome, coronary revascularization, and stroke) and a composite of heart failure and renal events (hospitalization for heart failure, renal death, initiation of renal replacement therapy, and renal admission). Serial changes in laboratory findings according to medication use were compared.

Results: During a median 38.7 months of follow-up, the incidence of composite ischemic events tended to be lower in the GLP1RA group (annualized rate 0.82% per person-year) than in the other groups (1.68% per person-year in the SGLT2i group and 1.36% per person-year in the control group). The risk of a composite of heart failure and renal outcomes was significantly lower in the SGLT2i group than in the GLP1RA and control groups (0.86% per person-year, 2.33% per person-year, and 1.48% per person-year, respectively; SGLT2i vs. GLP1RA, hazard ratio [HR] 0.384, 95% confidence interval [CI] 0.194-0.763, p=0.006; SGLT2i vs. control, HR 0.426, 95% CI 0.242-0.751, p=0.003). The SGLT2i group had a slower decline in renal function over time compared to that in other groups.

Conclusions: SGLT2i showed more benefits in heart failure and renal outcomes, whereas GLP1RA tended to have more favorable ischemic outcomes. The observed differential benefit profiles of SGLT2i and GLP1RA may be applied to the selection of antidiabetic medication in clinical practice.

Introduction

Since the US Food and Drug Administration issued a requirement for the evaluation of cardiovascular safety of antihyperglycemic agents in 2008, cardiovascular and renal protective effects of diabetic medications, beyond their glucose-lowering abilities, have been emphasized. Whereas dipeptidyl peptidase-4 inhibitors (DPP4i) have failed to show benefits in cardiovascular and renal outcomes [1, 2], sodium glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated robust benefits in terms of cardiovascular outcomes in patients with type 2 diabetes, which were mainly derived from the prevention of heart failure (HF) and the delaying of kidney disease progression [3–7]. Glucagon-like peptide-1 receptor agonists (GLP1RA) have also demonstrated cardiovascular and survival benefits, with a reduced risk of atherosclerotic cardiovascular disease (ASCVD) [8, 9] and renal function decline [10]. Accordingly, recent guidelines on diabetes recommend SGLT2i and GLP1RA as preferable medications for patients who have a higher risk of HF, ASCVD, or kidney disease [11, 12]. In particular, SGLT2i are more preferable for patients with diabetes with predominate HF or chronic kidney disease (CKD), whereas SGLT2i and GLP1RA are equally recommended for patients with predominate ASCVD, based on recent trials conducted for each medication individually [12, 13]. However, data based on the direct comparison of SGLT2i and GLP1RA in terms of cardiovascular and renal outcomes are not yet available.

Therefore, this study sought to compare the real-world cardiovascular and renal outcomes of SGLT2i and GLP1RA in patients with type 2 diabetes.

Methods

Study population

This retrospective cohort study was conducted at Seoul National University Bundang Hospital (Seongnam, South Korea). Patients prescribed SGLT2i or GLP1RA from April 2009 to December 2020 were identified. Patients treated with antihyperglycemic medications other than SGLT2i or GLP1RA were used as a control group. Exclusion criteria were type 1 diabetes, short duration of medication use (< 3 months), low medication possession rate (< 75%) during follow-up, and simultaneous or sequential use of SGLT2i and GLP1RA. Among 24,752 eligible patients (5,103 patients treated with SGLT2i, 710 patients treated with GLP1RA, and 18,939 control patients), propensity score matching with a 2:1:3 ratio for clinical risk factors, laboratory findings, and medication use was performed. Finally, 614 patients treated with SGLT2i, 307 patients treated with GLP1RA, and 921 control patients were analyzed (Fig. 1).

The study protocol was approved by the institutional review board; given the retrospective nature of the study, the need for informed consent was waived.

Outcomes

The time at which medication was started was defined as the index date. For clinical outcomes measurements, all-cause death, cardiovascular death, acute coronary syndrome, coronary revascularization, stroke, hospitalization for HF (HHF), and renal events (renal death, initiation of renal replacement therapy, and renal admission due to acute kidney injury or progression of CKD) were evaluated. The primary outcomes were a composite of ischemic events (acute coronary syndrome, coronary revascularization, and stroke) and a composite of HF and renal events. Additionally, composites of cardiovascular events (cardiovascular death, acute coronary syndrome, coronary revascularization, and stroke) and coronary events (acute coronary syndrome and coronary revascularization) were evaluated. Serial changes in glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDLc), creatinine, and glomerular filtration rate (GFR) levels were evaluated.

Statistical analysis

To adjust for imbalances in the baseline characteristics of patients in the SGLT2i, GLP1RA, and control groups, propensity score matching with a 2:1:3 ratio was performed using the nearest neighbor method, with following covariates: age, sex, smoking status, duration of diabetes, hypertension, dyslipidemia, CKD, atrial fibrillation, prior HF, prior coronary artery disease, prior myocardial infarction, prior stroke, heart rate, QRS duration, left ventricular hypertrophy; total cholesterol, LDLc, HbA1c, fasting glucose, serum creatinine, GFR, hemoglobin, proteinuria, serum albumin, and the use of aspirin, clopidogrel, statin, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, mineralocorticoid receptor antagonists, thiazide, loop diuretics, oral anticoagulants, insulin, metformin, sulfonylurea, alpha glucosidase inhibitors, and thiazolidinedione. The distribution of propensity scores and standardized mean differences were calculated to assess the strength of matching.

Categorical variables are presented as numbers with percentages, and continuous variables as means with standard deviations. Group comparisons were performed using the χ^2 test for categorical variables and analysis of

variance for continuous variables. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using the Cox proportional-hazards method. Two-sided p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Co., Armonk, NY, USA) and R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Baseline characteristics of the matched population are summarized in Table 1. The mean age was 55.2 ± 12.3 years, and 48.2% of patients were male. The mean duration of diabetes was 3.7 ± 4.4 years. Comorbidities, baseline laboratory findings, and medications (with the exception in the antihyperglycemic agents) were well-matched among the groups. In total, 49% of patients had hypertension, and 9.6% had CKD. Overall, atrial fibrillation was present in 3.6% of patients. The mean baseline HbA1c and serum creatinine levels were 7.9 ± 1.5% and 0.91 ± 0.53 mg/dL, respectively. Metformin was used in 83.9% of patients, and 32.7% of patients were insulin-dependent. Statin was used in 74.4% of patients.

Table 1
Baseline characteristics

	Total (n = 1,842)	SGLT2i (n = 614)	GLP1RA (n = 307)	Control (n = 921)	p
Clinical characteristics					
Age (years)	55.2 ± 12.3	55.6 ± 12.0	54.5 ± 13.0	54.8 ± 12.0	0.318
Male	888 (48.2%)	294 (47.9%)	156 (50.8%)	438 (47.6%)	0.601
Duration of diabetes (years)	3.7 ± 4.4	3.7 ± 4.3	3.9 ± 4.2	3.7 ± 4.6	0.804
Hypertension	897 (48.7%)	306 (49.8%)	153 (49.8%)	438 (47.6%)	0.619
Dyslipidemia	986 (53.5%)	329 (53.6%)	166 (54.1%)	491 (53.3%)	0.973
Chronic kidney disease	177 (9.6%)	57 (9.3%)	36 (11.7%)	84 (9.1%)	0.384
Atrial fibrillation	66 (3.6%)	25 (4.1%)	11 (3.6%)	30 (3.3%)	0.702
Prior heart failure	65 (3.5%)	23 (3.7%)	14 (4.6%)	28 (3.0%)	0.429
Prior coronary artery disease	195 (10.6%)	65 (10.6%)	36 (11.7%)	94 (10.2%)	0.602
Prior myocardial infarction	90 (4.9%)	33 (5.4%)	18 (5.9%)	39 (4.2%)	0.409
Prior stroke	132 (7.2%)	35 (5.7%)	20 (6.5%)	77 (8.4%)	0.125
Laboratory findings					
Hemoglobin (g/dL)	13.8 ± 1.9	13.8 ± 1.8	13.9 ± 1.8	13.8 ± 1.9	0.674
Albumin (g/dL)	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.596
Total cholesterol (mg/dL)	160.3 ± 42.2	158.5 ± 39.0	159.3 ± 44.0	161.7 ± 43.5	0.306
Triglycerides (mg/dL)	162.8 ± 143.3	162.7 ± 172.7	178.8 ± 147.8	158.8 ± 124.0	0.158
HDLc (mg/dL)	47.2 ± 12.0	46.7 ± 10.9	46.1 ± 12.2	47.8 ± 12.6	0.042
LDLc (mg/dL)	95.7 ± 34.2	94.9 ± 30.6	96.6 ± 34.3	95.9 ± 34.2	0.739
Fasting glucose (mg/dL)	152.7 ± 55.4	152.1 ± 50.5	151.6 ± 58.7	153.4 ± 57.4	0.840
Hemoglobin A1c (%)	7.9 ± 1.5	7.9 ± 1.3	7.9 ± 1.5	8.0 ± 1.6	0.597
Creatinine (mg/dL)	0.91 ± 0.53	0.88 ± 0.42	0.94 ± 0.50	0.92 ± 0.60	0.209
GFR (mL/min/1.73 m^2)	88.9 ± 24.3	89.3 ± 23.7	87.4 ± 26.1	89.1 ± 24.1	0.477
Medications					
Aspirin	545 (29.6%)	184 (30.0%)	93 (30.3%)	268 (29.1%)	0.895

Values are mean ± standard deviations or n (%).

Abbreviations: SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; DPP4i, dipeptidyl peptidate-4 inhibitors; GFR, glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; N/A, not available

	Total (n = 1,842)	SGLT2i (n = 614)	GLP1RA (n = 307)	Control (n = 921)	p
Clopidogrel	232 (12.6%)	75 (12.2%)	43 (14.0%)	114 (12.4%)	0.713
Statins	1371 (74.4%)	469 (76.4%)	233 (75.9%)	669 (72.6%)	0.209
Calcium channel blockers	654 (35.5%)	218 (35.5%)	112 (36.5%)	324 (35.2%)	0.918
Angiotensin converting enzyme inhibitors	70 (3.8%)	26 (4.2%)	12 (3.9%)	32 (3.5%)	0.743
Angiotensin receptor blocker	931 (50.5%)	311 (50.7%)	161 (52.4%)	459 (49.8%)	0.730
Beta blockers	336 (18.2%)	116 (18.9%)	63 (20.5%)	157 (17.0%)	0.345
Mineralocorticoid receptor antagonists	92 (5.0%)	29 (4.7%)	20 (6.5%)	43 (4.7%)	0.407
Thiazides	251 (13.6%)	80 (13.0%)	43 (14.0%)	128 (13.9%)	0.869
Loop diuretics	139 (7.5%)	48 (7.8%)	29 (9.4%)	62 (6.7%)	0.282
Direct oral anticoagulants	44 (2.4%)	19 (3.1%)	8 (2.6%)	17 (1.8%)	0.281
Insulin	602 (32.7%)	200 (32.6%)	107 (34.9%)	295 (32.0%)	0.657
Metformin	1546 (83.9%)	523 (85.3%)	253 (82.4%)	770 (83.6%)	0.520
DPP4i	1454 (78.9%)	354 (57.7%)	179 (58.3%)	921 (100.0%)	< 0.001
Sulfonylurea	1018 (55.3%)	340 (55.4%)	165 (53.7%)	513 (55.7%)	0.835
Thiazolidinedione	179 (9.7%)	52 (8.5%)	26 (8.5%)	101 (11.0%)	0.195
Types of SGLT2i					
Dapagliflozin	-	358 (58.3%)	-	-	N/A
Empagliflozin	-	235 (38.3%	-	-	N/A
Ertugliflozin	-	11 (1.8%)	-	-	N/A
Ipragliflozin	-	10 (1.6%)	-	-	N/A
Types of GLP1RA					
Dulaglutide	-	-	175 (57.0%)	-	N/A
Liraglutide	-	-	97 (31.6%)	-	N/A
Lixisenatide	-	-	23 (7.5%)	-	N/A

Values are mean ± standard deviations or n (%).

Abbreviations: SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; DPP4i, dipeptidyl peptidate-4 inhibitors; GFR, glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; N/A, not available

	Total (n = 1,842)	SGLT2i (n = 614)	GLP1RA (n = 307)	Control (n = 921)	p
Exenatide	-	-	12 (3.9%)	-	N/A

Values are mean ± standard deviations or n (%).

Abbreviations: SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; DPP4i, dipeptidyl peptidate-4 inhibitors; GFR, glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; N/A, not available

Table 2
Clinical outcomes

	SGLT2i	GLP1RA	Control	SGLT2i vs. Control		GLP1RA vs. Control		SGLT2i vs. GLP1RA	
				HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
All-cause death	3 (0.5%)	1 (0.3%)	20 (2.2%)	0.370 (0.106–1.285)	0.118	0.262 (0.034–1.994)	0.196	NA	NA
Cardiovascular death	2 (0.3%)	0 (0.0%)	7 (0.8%)	0.690 (0.134–3.547)	0.657	NA	NA	NA	NA
Composite of ischemic events	29 (4.7%)	6 (2.0%)	49 (5.3%)	1.200 (0.750–1.922)	0.447	0.542 (0.230–1.276)	0.161	2.186 (0.905–5.280)	0.082
Acute coronary syndrome	16 (2.6%)	2 (0.7%)	23 (2.5%)	1.344 (0.703–2.570)	0.371	0.374 (0.087–1.602)	0.185	3.763 (0.863–16.403)	0.078
Coronary revascularization	12 (2.0%)	4 (1.3%)	39 (4.2%)	0.638 (0.330–1.260)	0.183	0.462 (0.163–1.310)	0.147	1.424 (0.459–4.418)	0.541
Stroke	8 (1.3%)	2 (0.7%)	9 (1.0%)	2.205 (0.807–6.026)	0.123	1.298 (0.268–6.299)	0.746	0.573 (0.329–7.464)	0.573
HHF	10 (1.6%)	10 (3.3%)	28 (3.0%)	0.635 (0.306–1.318)	0.223	1.347 (0.647–2.803)	0.426	0.456 (0.189–1.097)	0.080
Composite of renal events	7 (1.1%)	11 (3.6%)	46 (5.0%)	0.336 (0.150–0.753)	0.008	1.142 (0.581–2.248)	0.007	0.337 (0.128–0.886)	0.027
Renal death	1 (0.2%)	0 (0.0%)	3 (0.3%)	1.269 (0.100-16.117)	0.854	NA	NA	NA	NA

Values are n (%).

Abbreviations: SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1RA, Glucagon-like peptide 1 receptor agonists; HR, hazard ratio; CI, confidence interval; HHF, hospitalization for heart failure; RRT, renal replacement therapy

	SGLT2i	GLP1RA	Control	SGLT2i vs. Control		GLP1RA vs. Control		SGLT2i vs. GLP1RA	
				HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Initiation of RRT	5 (0.8%)	9 (2.9%)	11 (1.2%)	0.836 (0.286–2.442)	0.743	3.129 (1.276–7.674)	0.013	0.265 (0.089–0.793)	0.017
Renal admission	5 (0.8%)	7 (2.3%)	46 (5.0%)	0.246 (0.097–0.628)	0.003	0.758 (0.336–1.710)	0.758	0.394 (0.120–1.293)	0.124
Composite of HHF and renal events	15 (2.4%)	18 (5.9%)	68 (7.4%)	0.426 (0.242–0.751)	0.003	1.107 (0.651–1.881)	0.708	0.384 (0.194–0.763)	0.006
Composite of cardiovascular events	27 (4.4%)	6 (2.0%)	51 (5.5%)	1.078 (0.667–1.742)	0.758	0.511 (0.217–1.202)	0.124	2.112 (0.871–5.123)	0.098
Composite of coronary events	21 (3.4%)	4 (1.3%)	42 (4.6%)	1.003 (0.587–1.715)	0.991	0.410 (0.146–1.155)	0.092	2.492 (0.854–7.272)	0.095
Values are n (%).									
Abbreviations: SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1RA, Glucagon-like peptide 1 receptor agonists; HR, hazard ratio; CI, confidence interval; HHF, hospitalization for heart failure; RRT, renal replacement therapy									

Clinical outcomes

Patients were followed for a median of 38.7 months (interquartile range: 23.0 to 66.3 months). All-cause death occurred in 3 patients (annualized rate: 0.17% per person-year) in the SGLT2i group and 1 patient (0.13% per person-year) in the GLP1RA group; although these rates were lower than that in the control group (0.42% per person-year), the differences failed to reach statistical significance. There were no significant differences in cardiovascular death among the groups. Composite ischemic events occurred least frequently in the GLP1RA group (1.68% per person-year in the SGLT2i group; 0.82% per person-year in the GLP1RA group; and 1.36% per person-year in the control group), without significant differences. The risk of each component in the composite of ischemic events (acute coronary syndrome, coronary revascularization, and stroke) tended to be lower in the GLP1RA group than in the SGLT2i and control groups. The HHF annualized rate was 0.57% per person-year in the SGLT2i group, 1.29% per person-year in the GLP1RA group, and 0.59% per person-year in the control group, without significant differences. Renal events occurred least frequently in the SGLT2i group (0.40% per person-year), with a significantly lower risk than that in the GLP1RA (1.40% per person-year; HR 0.336, 95% CI 0.150–0.753; p = 0.008) and control groups (0.98% per person-year; HR 0.337, 95% CI 0.128–0.886; p = 0.027). The risk of a composite of HF and renal events was lower in the SGLT2i group (0.86% per person-year) than in the GLP1RA (2.33% per person-year; HR 0.384, 95% CI 0.194–0.763, p = 0.006) and control groups (1.48% per person-year, HR 0.426, 95% CI 0.242–0.751, p = 0.003).

However, no difference in a composite of HF and renal events was observed between the GLP1RA and control groups (HR 1.107, 95% 0.651–1.881, p = 0.708).

Changes in laboratory findings according to medications

Serial changes in HbA1c, LDLc, creatinine, and GFR levels at follow-up according to groups are shown in Fig. 3. Changes in HbA1c and LDLc levels did not significantly differ between groups. Despite comparable creatinine and GFR levels at baseline, the SGLT2i group showed a slower renal function decline over the follow-up period compared to that in the other groups. The control group showed higher creatinine and lower GFR levels compared to those in other groups during follow up.

Discussion

In this retrospective study of real-world patients, we compared the cardiovascular and renal outcomes between SGLT2i, GLP1RA, and other antihyperglycemic medications (as a control). The major findings are as follows. First, the risk of a composite of ischemic events tended to be lower in patients treated with GLP1RA than in patients treated with SGLT2i or control patients. Second, SGLT2i use was associated with a reduced risk of renal events and a composite of HF and renal events. Third, renal function assessed by serial changes in creatinine and GFR levels showed a slower decline in patients treated with SGLT2i than in patients treated with GLP1RA or control patients.

After rosiglitazone, a glucose-lowering agent, was found to increase the risk of myocardial infarction and cardiovascular death in patients with type 2 diabetes [14], concerns regarding the cardiovascular safety of antihyperglycemic agents arose, resulting in the regulatory requirement to evaluate the cardiovascular safety of new antidiabetic drugs. DPP4i, an incretin-based drug stimulating insulin secretion in pancreatic β cells by blocking the enzymatic degradation of GLP1 [15], did not show cardiovascular or renal benefits over placebo in cardiovascular outcome trials [1, 2, 16]. In contrast, SGLT2i proved its cardiovascular efficacy, especially in terms of preventing HF and CKD progression [3–5], and the benefits of GLP1RA were pronounced in preventing ASCVD [8, 9, 17, 18]. As the cardiovascular benefits of SGLT2i and GLP1RA have been widely proven in large-scaled studies, current guidelines have adopted a preferential strategy for the administration of SGLT2i and GLP1RA in patients with established ASCVD or at increased risk of cardiovascular disease. In particular, SGLT2i is recommended for patients with diabetes with predominate HF or CKD; for patients with established ASCVD or indicators of high ASCVD risk, the guidelines equally recommend SGLT2i and GLP1RA, while acknowledging that the level of evidence for a benefit in major adverse cardiac events is greater for GLP1RA [12, 13]. However, due to the lack of head-to-head comparison studies, potential differences in the benefit profiles of these two antidiabetic medications remained uncertain.

In the present study, we showed differential benefits in clinical outcomes between SGLT2i and GLP1RA. Composite ischemic events tended to occur less frequently in patients treated with GLP1RA than in patients treated with other drugs. Although statistical significance was not met in the present study, a lower risk of composite ischemic events was maintained continuously in the GLP1RA group during the follow-up period, resulting in a HR of 0.467 (95% CI 0.189–1.105; p = 0.082) in comparison to the SGLT2i group. Considering that serial changes in HbA1c and lipid profiles did not differ between groups, the lower risk of composite ischemic events in the GLP1RA group might be originated apart from the glucose lowering or lipid lowering effects. Previous animal and human studies have suggested that GLP1RA have an anti-inflammatory effect, targeting atherosclerosis [19, 20]. This direct vascular effect of GLP1RA might have contributed to the lower incidence of composite ischemic events in the present study.

In contrast, the risk of composite ischemic events in the SGLT2i group did not differ from that in the control group, suggesting that the cardiovascular benefits of SGLT2i are mainly derived from the prevention of HHF and renal events, rather than by the direct prevention of ischemic events. Indeed, a reduction in ischemic events other than cardiovascular death and HHF, such as myocardial infarction, acute coronary syndrome, and stroke, was not often observed in the landmark trials of SGLT2i. Additionally, according to a substudy of the DECLARE-TIMI 58 trial, dapagliflozin use reduced the risk of type 2 myocardial infarction (mismatch between myocardial oxygen supply and demand) but not type 1 myocardial infarction (plaque rupture and atherothrombosis) [21]. Although the overall cardiovascular benefits of SGLT2i demonstrated in the trials are considered robust, the present findings further support the previous trials in terms of relatively smaller benefits in ischemic events with SGLT2i compared to those with GLP1RA.

Not surprisingly, SGLT2i use was associated with a decreased risk of renal events and a composite of HF and renal events, even though this was a small-sized retrospective study. Moreover, serial follow-up of the GFR level also showed a protective effect of SGLT2i on kidney function decline compared to that in the GLP1RA and control groups. Mechanisms of the effects of SGLT2i on HF and CKD progression are not yet clearly understood. However, the natriuresis and inhibition of tubuloglomerular feedback by SGLT2i seem to play a key role in preventing HF and delaying the progression of kidney disease [22]. Dedicated SGLT2i kidney outcome trials were stopped early due to the overwhelming efficacy of SGLT2i, confirming the benefits of SGLT2i on renal outcomes [23, 24]. Of note, in the present study, the GLP1RA group did not show a protective effect on renal events and serial change in GFR level. This might be due to the small sample size as well as the lack of specific renal outcomes, such as new-onset macroalbuminuria or doubling of the serum creatinine level. A meta-analysis showed that GLP1RA use reduced the occurrence of a broad kidney endpoint (including macroalbuminuria and changes in serum creatinine or GFR level), but not the risk of kidney outcomes excluding macroalbuminuria. Because we included renal death, initiation of renal replacement therapy and renal admission in the composite of renal events, the lack of benefits by GLP1RA in the present study does not preclude the potential renal benefits of GLP1RA. However, at the least, the present findings support the preference of SGLT2i for renal outcomes, compared to that with GLP1RA.

Although the findings of the present study are consistent with the results of landmark trials for each medication, and further support the current clinical recommendations regarding the preferred use of SGLT2i and GLP1RA, we acknowledge that our findings are based on a small retrospective cohort, and due to the limited number of events, the statistical significance was only modest. Additional studies with direct comparisons between SGLT2i and GLP1RA or population-based comparative studies would further clarify the differential benefit profile of these breakthrough medications. Furthermore, future studies are warranted to select the most appropriate antidiabetic medication according to the baseline risk for ASCVD, HF, or CKD.

Study limitations

First, this was a single-center retrospective study. Although propensity score matching was performed to overcome the imbalance in clinical characteristics, a possible bias according to the study design should be considered. Second, because of the small sample size of the current study, it was not possible to characterize the specific patient group that would benefit best from SGLT2i or GLP1RA. Third, we could not provide the mechanisms of action of SGLT2i and GLP1RA on the risk of ischemic, HF, and CKD outcomes. Future studies incorporating various biomarkers and hemodynamic findings would provide detailed results on the differences in the action mechanisms and clinical outcomes of these two medications.

Conclusions

SGLT2i showed more benefits in heart failure and renal outcomes, whereas GLP1RA tended to have more favorable ischemic outcomes. The observed differential benefit profiles of SGLT2i and GLP1RA may be applied for the appropriate selection of antidiabetic medication in clinical practice.

Abbreviations

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitors; GFR, glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; HF, heart failure; HHF, hospitalization for heart failure; LDLc, low-density lipoprotein cholesterol; SGLT2i, sodium-glucose cotransporter 2 inhibitors

Declarations

Ethics approval and consent to participate: The study protocol was approved by the institutional review board of Seoul National University Bundang Hospital; given the retrospective nature of the study, the need for informed consent was waived.

Consent for publication: Not applicable

Availability of data and materials: The de-identified data that support the findings of this study are available from the corresponding author upon reasonable request and appropriate permission from the institutional review board.

Competing interests: There are no conflicts of interest or competing interests to report.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions: CHK: data analysis and interpretation, writing – original draft; ICH: conceptualization, study design, data curation, data analysis and interpretation, writing – review and editing; CHA: data interpretation, writing – review and editing; YEY: writing – review and editing; GYC: writing – review and editing.

Acknowledgements: None

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Figures

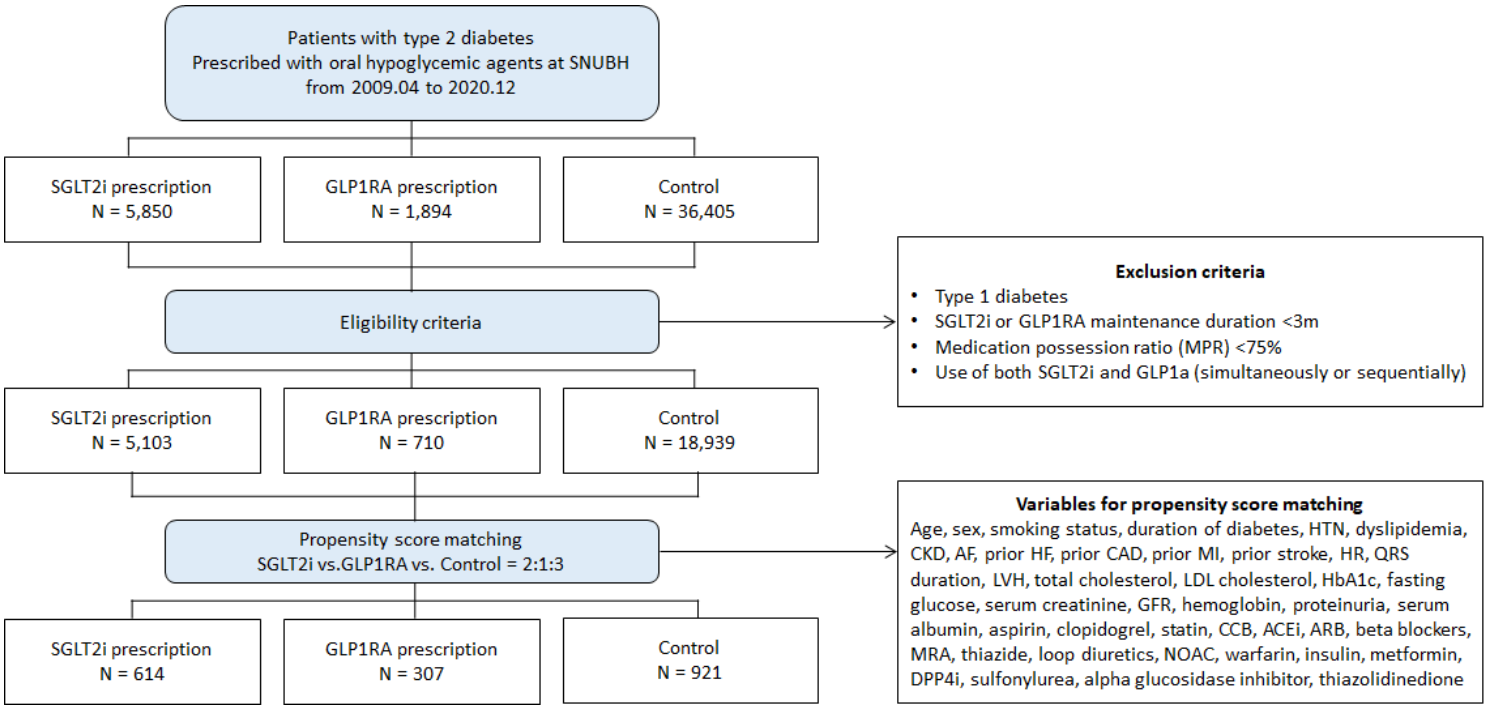

Figure 1

Study flow

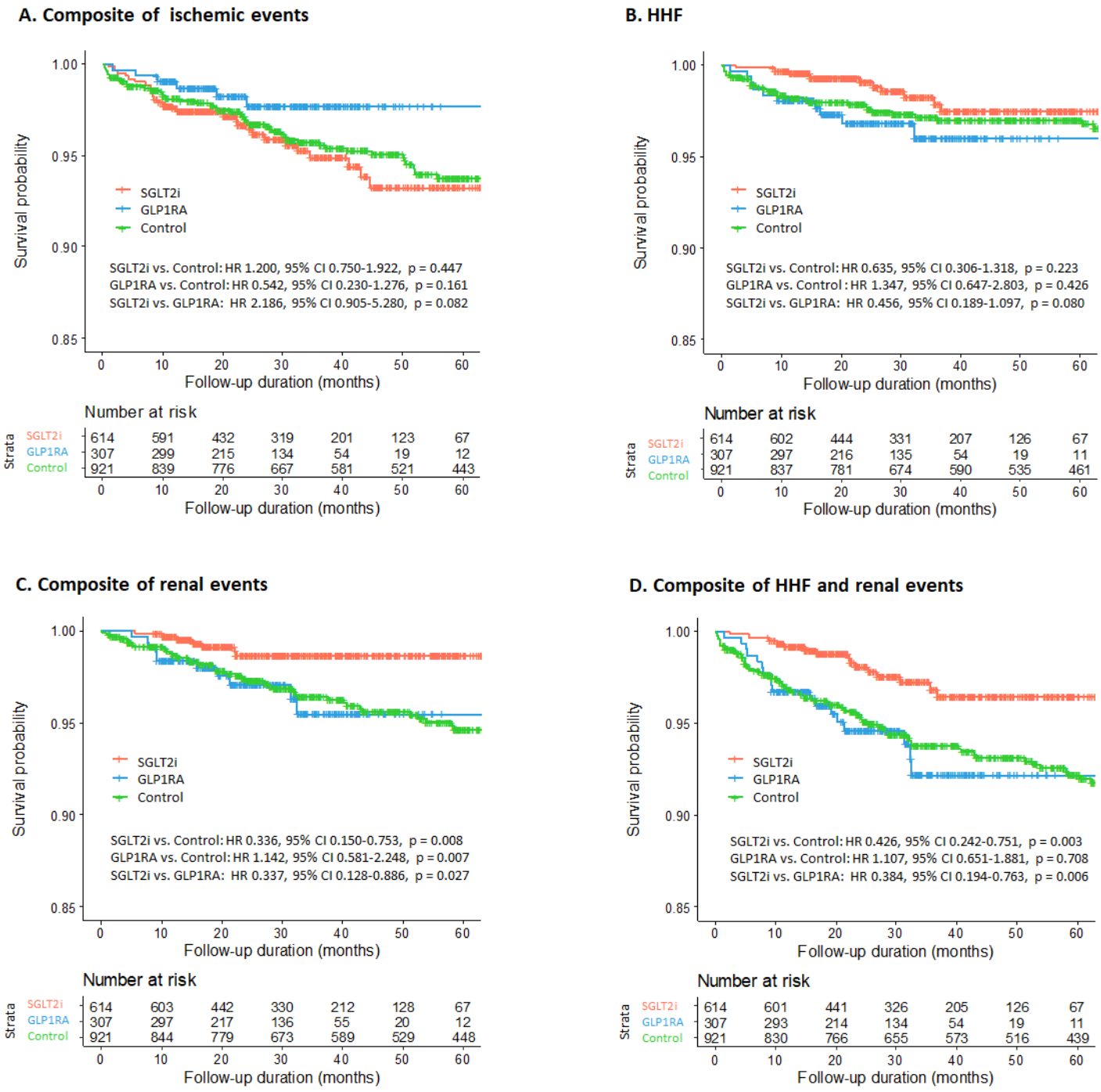

Figure 2

Survival curves

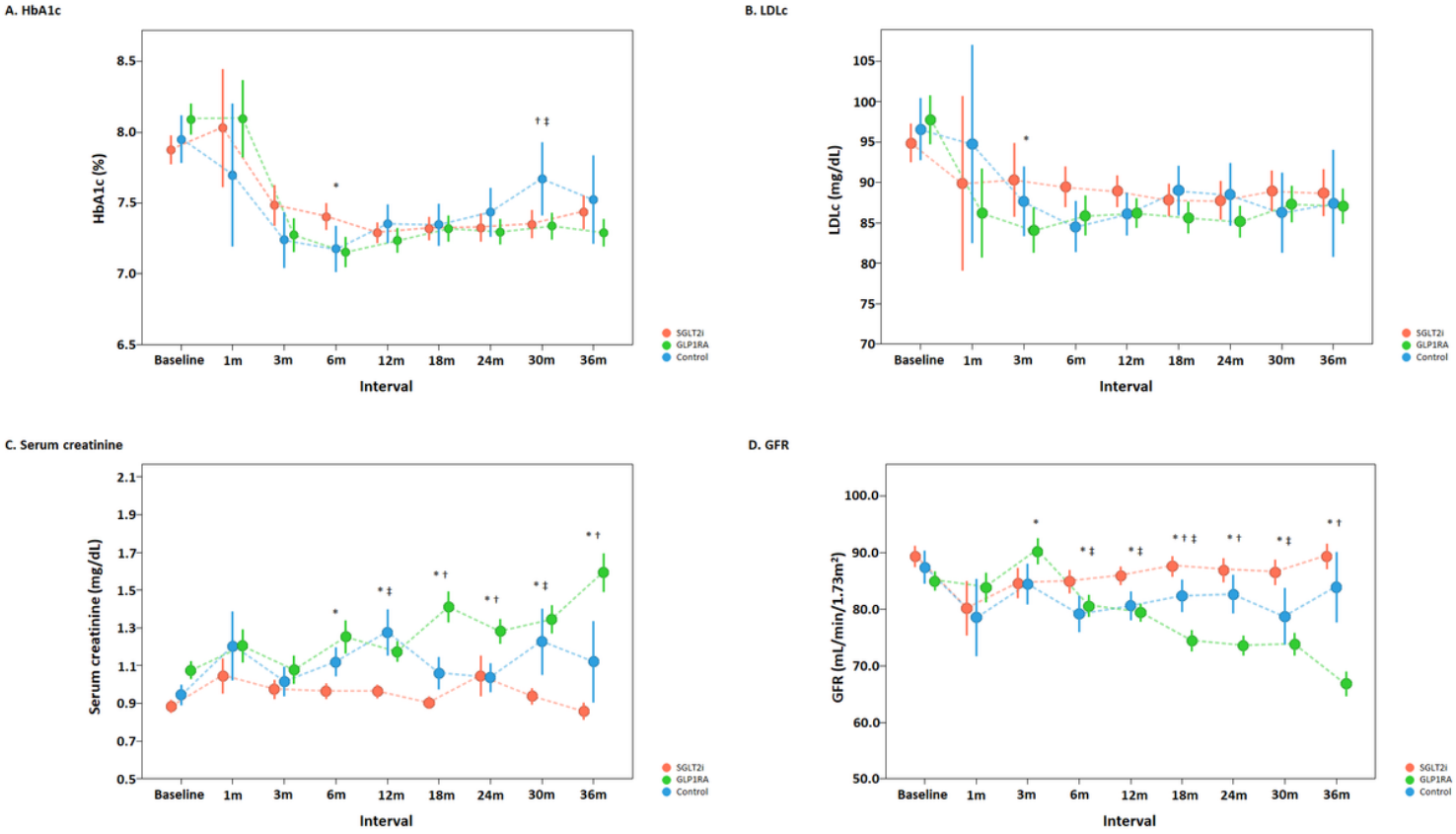

Figure 3

Changes in laboratory findings according to treatment groups

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