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RESEARCH ARTICLE

Effects of sarpogrelate on microvascular complications with type 2 diabetes

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Abstract

Background Diabetes is a major cause of microvascular complications. Renin–angiotensin–aldosterone blockers have been known to have the benefits of delaying onset and progression of diabetic complications including nephropathy. *Objective* To evaluate the effect of sarpogrelate, an antiplatelet agent, on the new onset diabetic complications in patients with type 2 diabetes mellitus. *Setting* A 1108-bed tertiary university hospital in Korea. *Methods* A retrospective cohort study was conducted using electronic medical records between 2010 and 2015 in Korea. The study cohort of the propensity score matched patients with or without sarpogrelate was evaluated for the diabetic complications identified with the diagnosis codes in T2DM patients on the metformin based antidiabetic therapy. Nephropathy was further evaluated for progression of kidney function. *Main outcome measure* The incidence of composite microvascular complications included nephropathy, neuropathy, and retinopathy. *Results* The 1:2 propensity score matched 478 out of 14,440 patients were included in the final analysis with or without sarpogrelate (162 vs. 316 patients). The incidence of nephropathy, neuropathy, and retinopathy was 1.23% versus 5.38% (HR 0.21, 95% CI 0.05–0.92), 1.23% versus 4.43% (HR 0.26, 95% CI 0.06–1.14), and 6.17% versus 6.33% (HR 0.93, 95% CI 0.43–1.97) with sarpogrelate and without sarpogrelate, respectively. Changes in the estimated glomerular filtration rate and urine albumin creatinine ratio were not significantly different between the groups. *Conclusion* In Korean patients, sarpogrelate, an antiplatelet agent, was associated with reducing the incidence and progression of nephropathyin type 2 diabetes, but not associated with the composite endpoints including neuropathy and retinopathy.

Keywords Diabetic complications · Nephropathy · Neuropathy · Retinopathy · Sarpogrelate · Korea

Impacts on practice

- Combination of sarpogrelate with the metformin based antidiabetic therapy could be considered as a strategy to slow down progression of the renal disease in patients with type 2 diabetes.
- Sarpogrelate did not reduce other microvascular complications of neuropathy and retinopathy.

Introduction

The prevalence of diabetes mellitus (DM) is expected to increase worldwide from 451 million in 2017 to an estimated 693 million by 2045 along with a rising proportion of geriatric patients [1, 2]. DM is associated with macrovascular and microvascular complications, which are the leading causes of its mortality and morbidity [3]. As the number of

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complications increases, the risk of mortality also increases [4]. DM-associated complications increase the disease burden, mortality, and medical costs [4–6]. The microvascular complications in DM include nephropathy, neuropathy, and retinopathy [7]. Nephropathy is the most common complication that occurs in 20–40% of patients with DM. It can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation. Diabetic neuropathy, on the other hand, manifests with a variety of symptoms. Glycemic control can modestly delay the progression of nerve damage in DM, although it does not reverse any neuronal loss. Diabetic retinopathy, a common cause of loss of vision, is associated with different risk factors, such as duration of DM, poor glycemic control, nephropathy, hypertension, and dyslipidemia [8].

Several classes of drugs have shown benefits in delaying the onset or progression of DM-associated complications in addition to the control of blood glucose and blood pressure [9–12]. For nephropathy, angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) have proven benefits in delaying progression of chronic kidney disease (CKD) in patients with DM and hypertension [10–12]. Sodium-glucose cotransporter-2 inhibitors (SGLT-2I) have demonstrated to slow down the decline in glomerular filtration rate (GFR) in the EMPA-REG OUTCOME and CANVAS study [13, 14]. Dipeptidyl peptidase-4 inhibitors (DPP-4I) and glucagon-like peptide 1 (GLP-1) analogs have exhibited a reduction in the incidence of diabetic kidney disease in the LEADER and SUSTAIN-6 study [15, 16]. The mineralocorticoid receptor antagonist, finerenone has been shown to reduce albuminuria without causing hyperkalemia or altering renal functions [17].

No specific drugs are, however, identified for the prevention of complications of diabetic neuropathy and retinopathy. The current strategy for prevention of diabetic neuropathy and retinopathy is disease management with tight control of glucose and blood pressure. The drugs approved for diabetic neuropathic pain are pregabalin, duloxetine, tapentadol and topical capsaicin. Antidepressants, antiepileptics, and tramadol have been used although not approved for neuropathy. Photocoagulation surgery and anti-vascular endothelial factors (bevacizumab, ranibizumab, and aflibercept) can be also used for the treatment of diabetic retinopathy [8].

Sarpogrelate is a $5HT_2$ A receptor antagonist which can suppress platelet aggregation, thrombus formation, endothelial dysfunction, vasoconstriction, and vascular smooth muscle cell proliferation by multiple mechanisms. It has been used in patients with a peripheral vascular disease associated with DM or other diseases. It has 36 generic products available since it was approved in Korea in 1999, although it is not approved in the US and Canada. In Korea, it is also suggested to use sarpogrelate as an additional or alternate antiplatelet drug in patients with an aspirin allergy or patients receiving clopidogrel having a high risk of bleeding [18]. Studies have reported that sarpogrelate can reduce albuminuria in patients with DM having an early stage of diabetic nephropathy [19]. Several animal studies with sarpogrelate have revealed its mechanism of ameliorating diabetic nephropathy by reduction of renal fibrosis or inhibition of macrophage activity [20, 21]. We hypothesized that sarpogrelate may be beneficial for the prevention of complications associated with DM.

Aim of the study

The aim of this retrospective cohort study was to investigate the effects of sarpogrelate with metformin-based antidiabetic therapy on microvascular complications including nephropathy, neuropathy, and retinopathy in patients with type 2 DM (T2DM).

Ethics approval

The study was approved by the Institutional Review Board (IRB) of Ajou University Hospital (AJIRB-MED-MDB-15-503). Informed consent from the study patients was waived as the patient records were de-identified when the data were provided by the clinical data warehouse of the hospital prior to the analyses.

Methods

Study design and data source

This was a retrospective observational cohort study using the electronic medical records of 1108-bed tertiary care, university-affiliated, teaching hospital between January 2010 and December 2015 in Korea. Our hospital has structured the clinical data warehouse (CDW) for the investigators to conduct clinical research and obtain real-world evidence. The Department of Medical Informatics provided the dataset with the data elements listed and defined for the purpose of the research following the methods approved by the IRB. The Department of Medical Informatics extracted the de-identified data from the CDW for the protection of confidentiality of the patients before the dataset was provided to us. All our study data at baseline and at follow-up were obtained from the CDW. We did not directly review the medical records of the individual patients. The database was available through clinical data research service of the Department of Medical Records.

Data regarding demographic characteristics, comorbidities, concomitant medications (obtained from prescription

records which included prescription date, brand name, generic name, days of supply, and route of administration), and clinical procedures were collected. Comorbidities prior to the index date were identified and Charlson comorbidity index score (CCI) was calculated for the year prior to the index date [23]. The concomitant medications used in the pre-index period were aspirin, ACEI/ARBs, beta blockers, calcium channel blockers, and statins. The laboratory tests included serum creatinine, urine albumin, and glycated hemoglobin (HbA1C).

Inclusion and exclusion criteria

The inclusion criteria for the study were patients aged ≥ 18 years, without any episode of hospitalization, diagnosed with T2DM [International Classification of Disease, 10th revision (ICD-10 codes, E11)], and who had continuously received metformin-based antidiabetics (ADM) or metformin-based antidiabetics plus sarpogrelate (ADMS) for a minimum of 30 days. The index date was defined as the date of initiation of metformin for ADM and the date of simultaneous initiation of sarpogrelate and metformin for ADMS. The pre-index period was 1 year prior to the index date. The follow-up period extended from the index date to 30 days after the end of treatment date. The end of treatment date was fixed as the terminal date of therapy with the study drug. Patients with a medication possession rate (MPR) of ≥ 80% were included in the study to reduce the impact on the outcomes that might not be identified during the follow-up period. MPR was defined as the ratio (A/B) of total prescription days (A) to the duration of the first to the last date of drug use during the follow-up period (B).

The outcomes in each group (ADM and ADMS) was assessed by the baseline estimated glomerular filtration rate (eGFR): the first group of patients (eGFR ≥ 60 mL/min/1.73 m^2) included CKD stage 1 (≥ 90 mL/min/1.73 m^2) and stage 2 (60–89 mL/min/1.73 m^2), while the second group of patients (eGFR < 60 mL/min/1.73 m^2) included CKD stage 3 (30–59 mL/min/1.73 m^2) and stage 4 (15–29 mL/min/1.73 m^2). The antidiabetic therapy was classified as monotherapy and combination therapy. The metformin combination therapy included DPP-4I, sulfonylureas (SU), and other drugs. The other antidiabetic drugs were meglitinide, alpha-glucosidase inhibitor, thiazolidinedione, SGLT-2 inhibitors, GLP-1 analogs, and insulin.

The exclusion criteria were patients receiving antiplatelet drugs other than aspirin or sarpogrelate for > 7 days during the follow up period, patients with a history of complications associated with DM (ICD 10 code, E11.2, N08.3, E11.4, E11.3, H36.0), severe disease state, during the pre-index period. The severe disease states included cancer (ICD-10 codes, C00–C75), chronic hepatic failure (ICD-10 codes, K72.1), renal failure (eGFR < 15 mL/min/1.75 m^2), and patients undergoing dialysis (ICD-10 codes, Z49.1, Z49.2) or renal transplantation (ICD-10 codes, Z94.0) (Fig. 1).

Outcomes

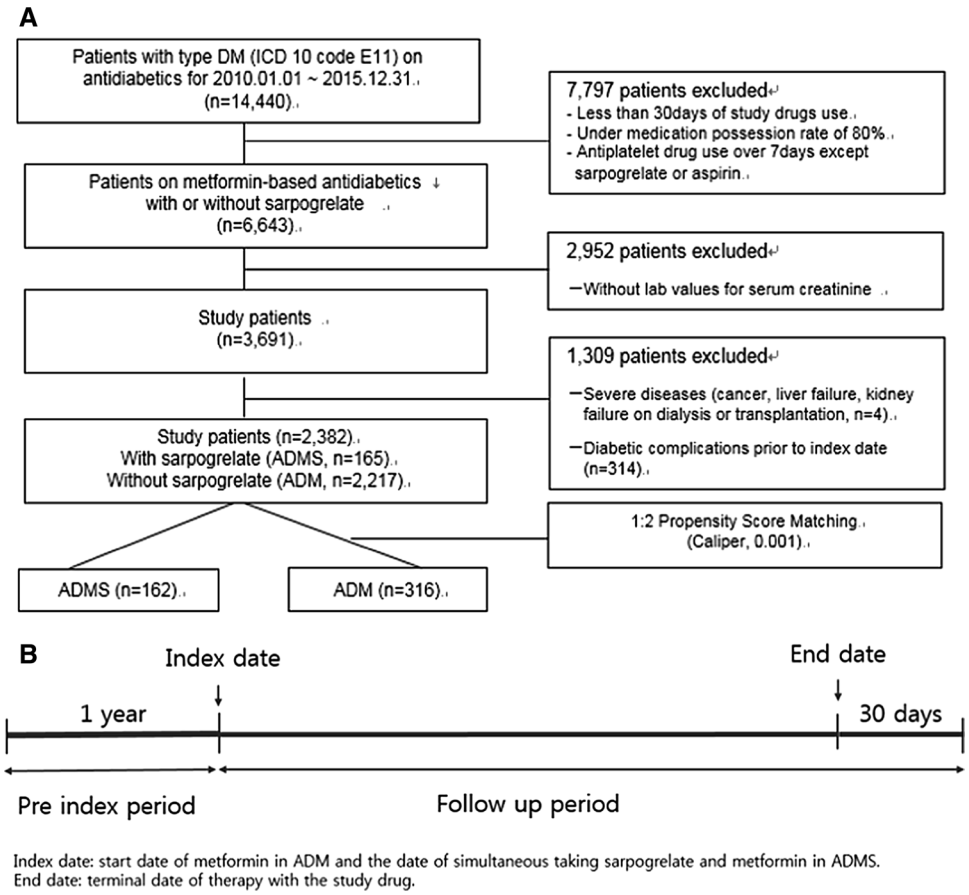
The primary outcome was defined as the first occurrence of composite diabetic microvascular complications including nephropathy (renal complications (E11.2) or glomerular disorders in DM (N08.3), neuropathy (neurological complications (E11.4), and retinopathy (ophthalmic complications (E11.3) or diabetic retinopathy (H36.0) as identified by the corresponding ICD-10 codes. The observation period for the clinical outcomes was from 30 days after the index date until 30 days after the end of treatment date.

The secondary outcomes were a reduction in eGFR and change in urine albumin-creatinine ratio (UACR). The eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) formula. The assessment of the progression of renal disease was performed by a reduction of 30%, 30–50%, and 50% of eGFR from the baseline values [22, 23]. The assessment for UACR was performed by its change from the baseline value: increase (> 2 times), minor change (2–0.5 times), or decrease (< 0.5 times) [24]. The date of the outcome was the earliest possible date of the reduction in eGFR or date of change of UACR from the baseline.

The safety assessment with the addition of sarpogrelate during the follow-up period included complications such as severe or life-threatening bleeding or minor events based on the GUSTO criteria [25]. Severe or life-threatening bleeding was classified as subarachnoid, intra-cerebral, or intracranial hemorrhage.

Statistical analysis

The baseline characteristics among the different groups were expressed as the mean ± standard deviation [(or median and inter-quartile range (IQR)] for the continuous variables or frequency with percentages for the categorical variables, as applicable. The continuous variables were compared by student's *t* test or one-way analysis of variance, and the categorical variables were compared by Chi squared test. Propensity score (PS) matching was applied using the caliper matching method at a fixed ratio of 1:2 (2 controls per study patient). The two groups were matched for covariates including age, sex, CCI, comorbidities (hypertension and hyperlipidemia), eGFR, and concomitant medications. These variables were considered to control the possible confounders of complications associated with DM [26]. The Kaplan–Meier method and log-rank test were used to evaluate the proportion of patients with preserved renal function with or without receiving sarpogrelate in the metformin-based antidiabetic therapy group. Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence



Index date: start date of metformin in ADM and the date of simultaneous taking sarpogrelate and metformin in ADMS.
End date: terminal date of therapy with the study drug.

Fig. 1 **a** Flow chart of the study population and **b** schematic description of the study design. ADMS, sarpogrelate and antidiabetic drugs with metformin; ADM, antidiabetic drugs with metformin

interval (CI). The PS-matched patients were further analyzed by Cox regression analysis with adjusted covariates including the potential confounders of CCI, ACEI/ARB, statin, DPP4-I, insulin, hypertension, and the number of antidiabetic drugs. The model was assessed for assumption of proportional hazards and log-linearity using the Schoenfeld residuals and the cumulative Martingale residual without violation [27, 28]. Subgroup analyses were performed according to the characteristics of the included patients. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 14,440 patients were screened between January 2010 and December 2015 and 2382 patients fulfilled the eligibility criteria. After PS matching (1:2 ratio), a cohort of 478 patients was finally included in the group with sarpogrelate (ADMS, n = 162) and without sarpogrelate (ADM, n = 316). The baseline characteristics of the PS-matched patients were comparable in terms of age, sex, and CCI score. Triple or higher combination therapy with metformin was administered in around 50% of the patients. Monotherapy or dual therapy with metformin were used in 22–31% of the patients. SU or DPP4-I were mainly used in combination with metformin. Insulin was used in around 10% of the patients. The frequency of comorbidities (hypertension and hyperlipidemia) was similar. The mean baseline eGFR with approximately 8 measurements over a maximum period of 5.4 years and the mean baseline UACR were comparable. The median follow-up period was 2.7 years (maximum 5.4 years, IQR 1.4–4.2 years). The concomitant medications (aspirin, ACEI/ARBs, beta blockers, calcium channel blockers, and statins) were similar in both the two groups. HbA1C was the only parameter which was higher in the ADMS group than the ADM group despite PS matching (Table 1, Supplement Table 1 and 2).

In the Cox regression analysis without covariate adjustments in the PS-matched patients, the incidence of occurrence of composite endpoints was 8.64% in the ADMS group and 14.24% in the ADM group (HR 0.55, 95% CI 0.30–1.01). The incidence of complications was not significantly different in all the CKD patients of different stages, although there was a trend of lower incidence of complications with sarpogrelate. In the ADMS and ADM groups, nephropathy was identified in 1.23% and 5.38% (HR 0.21, 95% CI 0.05–0.92) patients of all CKD stages, and 0% and

Table 1 Baseline characteristics of patients after propensity score matching

	All patients, PS matched			CKD Stage 1–2			CKD Stage 3–4		
	ADM (316)	ADMS (162)	*p*-value	ADM (233)	ADMS (118)	*p*-value	ADM (83)	ADMS (44)	*p*-value
Age, years (mean ± SD)	54.92 ± 11.41	55.21 ± 11.37	0.79	52.84 ± 10.92	52.77 ± 10.76	0.96	60.75 ± 10.78	61.72 ± 10.47	0.62
Age, n (%)			0.49			0.88			0.31
< 65 years	247 (78.16)	131 (80.86)		200 (85.84)	102 (86.44)		47 (56.63)	29 (65.91)	
≥ 65 years	69 (21.84)	31 (19.14)		33 (14.16)	16 (13.56)		36 (43.37)	15 (34.09)	
Male, n (%)	190 (60.13)	93 (57.41)	0.57	147 (63.09)	69 (58.47)	0.40	43 (51.81)	24 (54.55)	0.77
Pharmacotherapy, n (%)									
Monotherapy (metformin)	72 (22.78)	47 (29.01)	0.14	58 (24.89)	33 (27.97)	0.53	14 (16.87)	14 (31.82)	0.05
Dual therapy	99 (31.33)	41 (25.31)	0.08	69 (29.62)	32 (27.11)	0.05	30 (36.14)	9 (20.45)	0.88
Metformin and DPP-4I	45 (14.24)	11 (6.79)		30 (12.87)	8 (6.78)		15 (18.07)	3 (6.82)	
Metformin and SU	39 (12.34)	19 (11.73)		30 (12.87)	14 (11.86)		9 (10.84)	5 (11.36)	
Metformin and others	15 (4.75)	11 (6.79)		9 (3.86)	10 (8.47)		6 (7.23)	1 (2.27)	
Triple therapy or more	145 (45.89)	74 (45.68)	0.97	106 (45.49)	53 (44.92)	0.92	39 (46.99)	21 (47.73)	0.94
Follow-up period (years)									
Mean ± SD	2.74 ± 1.53	2.89 ± 1.49		2.80 ± 1.56	2.90 ± 1.50		2.57 ± 1.45	2.86 ± 1.47	
Median (q1–q3)	2.40 (1.4–4.3)	2.55 (1.70–4.50)		2.40 (1.40–4.40)	2.55 (1.70–4.50)		2.2 (1.50–3.90)	2.55 (1.75–4.50)	
CCI score									
Mean ± SD	1.81 ± 1.62	1.81 ± 1.52	0.99	1.81 ± 1.61	1.84 ± 1.51	0.88	1.82 ± 1.66	1.75 ± 1.56	0.82
Median (q1–q3)	3 (0–3)	3 (0–3)		3 (0–3)	3 (0–3)		3 (0–3)	3 (0–3)	
Comorbidities, n (%)									
Hypertension	37 (11.71)	19 (11.73)	0.99	23 (9.87)	11 (9.32)	0.87	14 (16.87)	8 (18.18)	0.85
Hyperlipidemia	40 (12.66)	17 (10.49)	0.49	28 (12.02)	12 (10.17)	0.61	12 (14.46)	5 (11.36)	0.63
eGFR (mL/min/1.73 m^2)									
Mean ± SD	68.72 ± 15.95	68.54 ± 13.21	0.89	75.48 ± 11.85	74.34 ± 10.07	0.37	49.76 ± 9.31	52.98 ± 6.15	0.04
Median (q1–q3)	68.87 (59.26–77.89)	68.34 (58.91–77.92)	0.89	73.05 (66.76–79.75)	73.54 (65.24–80.27)	0.37	53.01 (44.28–57.10)	55.05 (49.86–57.74)	0.04
UACR (n)	132	145		103	106		29	39	
Mean ± SD	135.8 ± 122.5	124.5 ± 134.8		140.3 ± 121	136.1 ± 145	0.82	119.9 ± 126.7	92.93 ± 93.05	0.32
Median (q1–q3)	108.39 (29.94–201.14)	84.94 (27.20–173.95)	0.47	117.73 (35.45–204.19)	88.80 (33.24–199.01)	0.82	79.63 (14.60–174.44)	75.85 (16.10–131.01)	0.32
HbA1C (%) (mean ± SD)	7.44 ± 1.25	8.20 ± 1.48	< 0.0001	7.43 ± 1.20	8.33 ± 1.47	< 0.0001	7.45 ± 1.38	7.84 ± 1.48	0.20
SBP (mmHg) (mean ± SD)	129.21 ± 17.72	124.80 ± 13.06	0.27	129.13 ± 18.60	122.06 ± 13.94	0.16	129.42 ± 15.56	131.67 ± 7.71	0.73
DBP (mmHg) (mean ± SD)	77.32 ± 11.45	75.23 ± 9.54	0.42	78.14 ± 12.20	73.80 ± 10.52	0.19	75.32 ± 9.15	78.83 ± 5.70	0.36
Concomitant medication, n (%)									
Aspirin	78 (24.68)	34 (20.99)	0.37	54 (23.18)	22 (18.64)	0.33	24 (28.92)	12 (27.27)	0.85
ACEI/ARB	116 (36.71)	62 (38.27)	0.74	89 (38.20)	45 (38.14)	0.99	27 (32.53)	17 (38.64)	0.49
Beta blocker	21 (6.65)	8 (4.94)	0.46	10 (4.29)	4 (3.39)	0.69	11 (13.25)	4 (9.09)	0.49

Table 1 (continued)

	All patients, PS matched			CKD Stage 1–2			CKD Stage 3–4		
	ADM (316)	ADMS (162)	*p*-value	ADM (233)	ADMS (118)	*p*-value	ADM (83)	ADMS (44)	*p*-value
DHP-CCB	53 (16.77)	29 (17.90)	0.76	35 (15.02)	14 (11.86)	0.42	18 (21.69)	15 (34.09)	0.13
NDHP-CCB	11 (3.48)	4 (2.47)	0.55	7 (3.00)	4 (3.39)	0.84	4 (4.82)	–	0.14
Statin	54 (17.09)	30 (18.52)	0.70	45 (19.31)	24 (20.34)	0.82	9 (10.84)	6 (13.64)	0.64

PS matched, propensity score matched (age, sex, CCI, hypertension, hyperlipidemia, the level of baseline eGFR, aspirin, ACEI/ARB, statin); ADM, antidiabetic drugs with metformin; ADMS, sarpogrelate and antidiabetic drugs with metformin; CKD, chronic kidney disease; CKD stage 1–2, baseline eGFR ≥ 60; CKD stage 3–4 baseline eGFR < 60; SU, sulfonyl urea; DPP-4I, dipeptidyl peptidase-4 inhibitor; CCI, Charlson comorbidity Index (acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, paraplegia, HIV); eGFR, estimated glomerular filtration rate; UACR, urine albumin creatinine; ratio; HbA1C, Hemoglobin A1C; SBP, systolic blood pressures; DBP, diastolic blood pressure; TG, total cholesterol; ACEI, angiotensin-1 conversion enzyme Inhibitor; ARB, angiotensin-2 receptor blocker; DHP-CCB, dihydropyridine calcium channel blocker; NDHP-CCB, non-dihydropyridine calcium channel blocker

4.55% ($p = 0.01$) patients of CKD stage 1–2, respectively. The incidence of the other complications was not significantly different between the ADMS and ADM groups [1.23% and 4.43% (HR 0.26, 95% CI 0.06–1.14) for neuropathy and 6.17% and 6.33% (HR 0.93, 95% CI 0.43–1.97) for retinopathy, respectively]. In the PS-matched patients, the risk in the Cox regression analysis with covariate adjustments was not significantly different from the results obtained without covariate adjustments. The incidence of nephropathy was the only outcome which was significantly reduced in the ADMS group as compared to the ADM group (HR 0.23, 95% CI 0.05–0.99) (Table 2). The Kaplan–Meier analysis showed that the cumulative incidence of nephropathy was lower in the ADMS group as compared to the ADM group ($p = 0.04$) (Fig. 2).

The risk of composite complications was not significant in the subgroup analysis based on age, sex, and concomitant medications in the ADMS group as compared to the

Table 2 The number of new cases and hazards of complications associated with diabetes with or without sarpogrelate

	The number of new cases				HR (95% CI) ADMS vs. ADM	
	ADM, n	New cases, n (%)	ADMS, n	New cases, n (%)	PSM, unadjusted	PSM, adjusted[a]
Composite endpoints						
All CKD stages	316	45 (14.24)	162	14 (8.64)	0.55 (0.30–1.01)	0.60 (0.33–1.10)
Stage 1–2	233	32 (13.73)	118	9 (7.63)	0.51 (0.24–1.06)	0.49 (0.23–1.06)
Stage 3–4	83	13 (15.66)	44	5 (11.36)	0.66 (0.24–1.87)	0.89 (0.28–2.79)
Nephropathy						
All CKD stages	316	17 (5.38)	162	2 (1.23)	0.21 (0.05–0.92)*	0.23 (0.05–0.99)*
Stage 1–2	233	12 (4.55)	118	0 (0.00)	NA	NA
Stage 3–4	83	5 (6.02)	44	2 (4.55)	0.69 (0.13–3.54)	0.52 (0.06–4.83)
Neuropathy						
All CKD stages	316	14 (4.43)	162	2 (1.23)	0.26 (0.06–1.14)	0.30 (0.07–1.34)
Stage 1–2	233	13 (5.58)	118	1 (0.85)	0.14 (0.02–1.10)	0.16 (0.02–1.27)
Stage 3–4	83	1 (1.20)	44	1 (2.27)	1.80 (0.11–28.82)	2.17 (0.13–36.46)
Retinopathy						
All CKD stages	316	20 (6.33)	162	10 (6.17)	0.93 (0.43–1.97)	0.99 (0.46–2.15)
Stage 1–2	233	13 (5.58)	118	8 (6.78)	1.17 (0.49–2.84)	1.15 (0.47–2.82)
Stage 3–4	83	7 (8.43)	44	2 (4.55)	0.50 (0.10–2.42)	0.59 (0.11–3.07)

PSM, propensity score matched (age, sex, CCI, hypertension, hyperlipidemia, the level of baseline eGFR, aspirin, ACEI/ARB, statin); ADM, antidiabetic drugs with metformin; ADMS, sarpogrelate and antidiabetic drugs with metformin; CKD, chronic kidney disease; stage 1–2, baseline eGFR ≥ 60; stage 3–4 baseline eGFR < 60; nephropathy, type 2 diabetes mellitus with renal complications (E11.2) or glomerular disorders in DM (N08.3); neuropathy, type 2 diabetes mellitus with neurological complications (E11.4); retinopathy, type 2 diabetes mellitus with ophthalmic complications (E11.3) or diabetic retinopathy (H36.0); HR, hazard ratio; CI, confidence interval; NA, NA = not assessable due to zero incidence in the ADMS; b adjusted, CCI-sum, ACEI/ARB, statin, hypertension, DPP4-I, insulin, number of anti-diabetic drugs

* Statistically significant

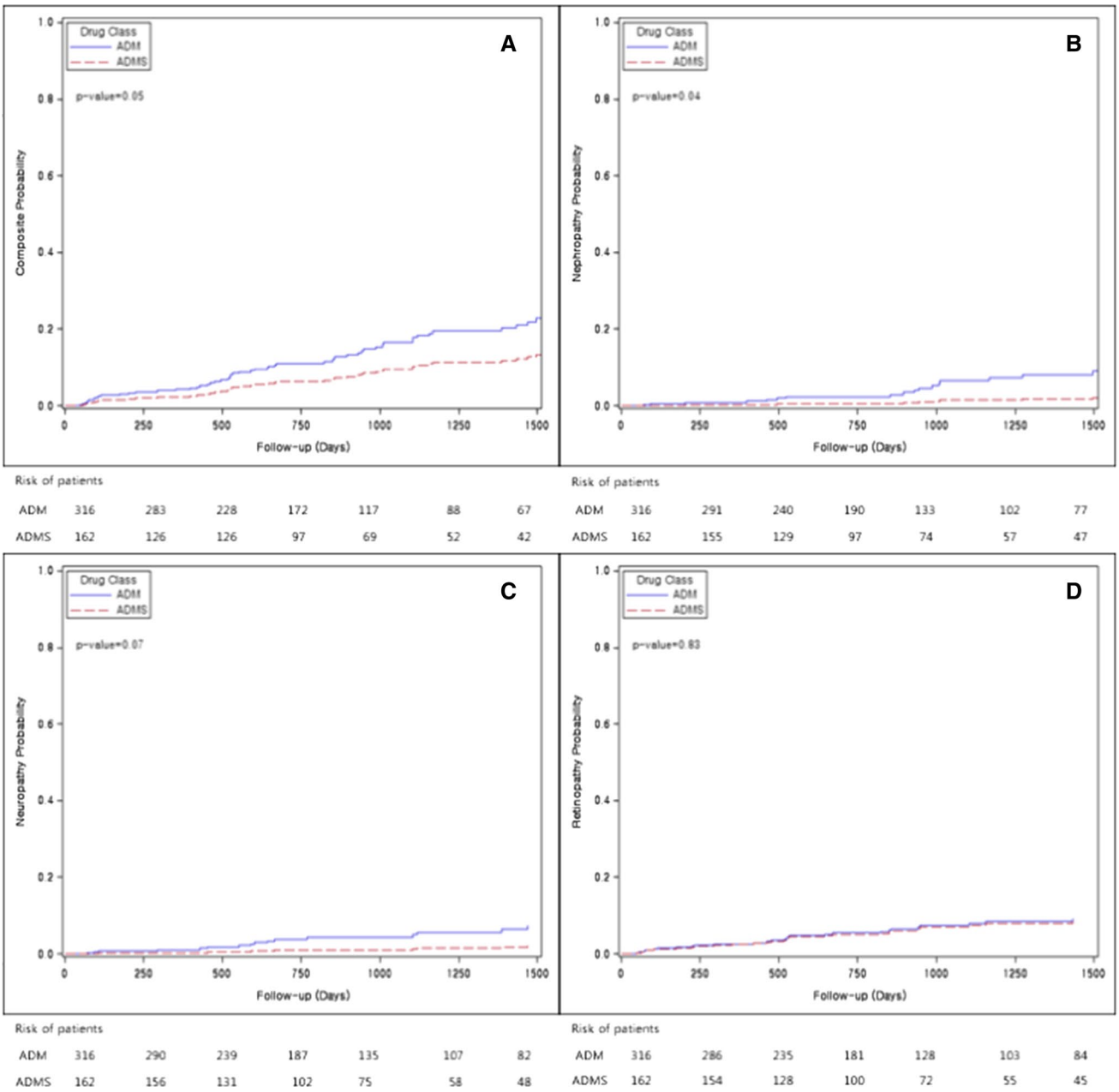


Fig. 2 Kaplan–Meier curve for cumulative incidence of microvascular complications. **a** Composite complications, **b** nephropathy, renal complications (E11.2) or glomerular disorders in DM (N08.3), **c** neuropathy, neurological complications (E11.4), **d** retinopathy, ophthalmic complications (E11.3) or diabetic retinopathy (H36.0); ADM, antidiabetic drugs with metformin; ADMS, sarpogrelate and antidiabetic drugs with metformin; *p* value, Log-rank test

ADM group. The risk of composite endpoints was lower in patients receiving combination therapy with ≥3 more antidiabetic drugs and patients receiving SU (Fig. 3). The change in eGFR was not significant across the different CKD stages. eGFR reduction was greater in CKD stage 3–4 than CKD stage 1–2 in both the ADM and ADMS groups. The Kaplan–Meier survival analysis did not show any significant difference in the time required for 30% eGFR reduction between both the groups ($p=0.24$) (Supplement Table 3 and Fig. 1). The change in UACR was also not significant across the different groups in respect to the changes from the baseline value between the ADM and ADMS groups (increase by 12.88% and 15.86%, minor change of 84.09% vs. 80.69%, and decrease by 3.03% and 3.45%, respectively) ($p=0.76$) (Supplement Table 4).

There were four minor bleeding events and no major bleeding events. Three episodes of vitreous hemorrhage (H43.1) occurred in one patient in the ADMS group

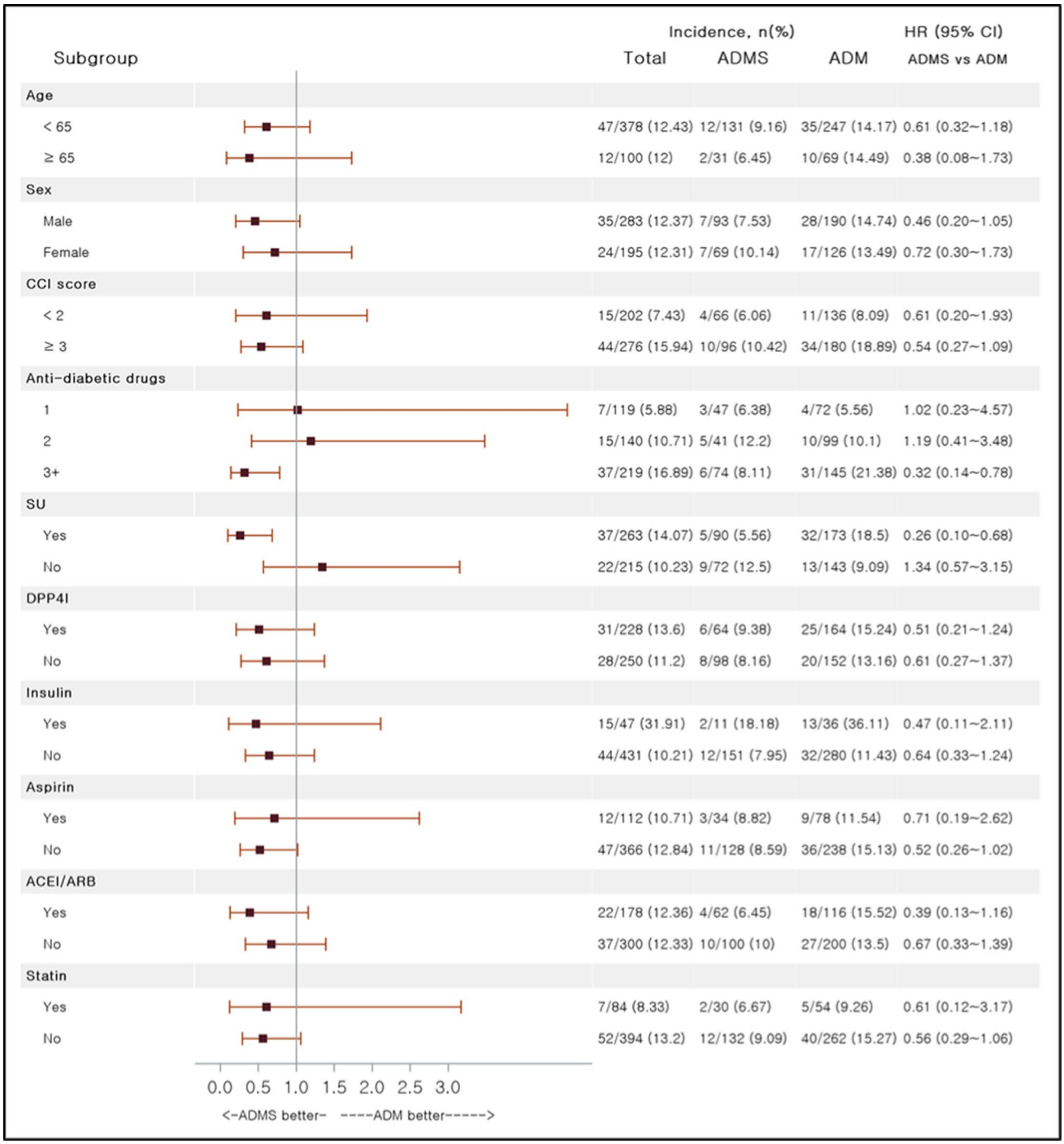


Fig. 3 Hazard ratio (ADMS vs. ADM) of composite end points by subgroup patients. ADM, antidiabetic drugs with metformin; ADMS, sarpogrelate and antidiabetic drugs with metformin; HR, hazard ratio; CI, confidence interval; DPP-4I, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; ACEI/ARB, angiotensin-1 conversion enzyme inhibitor/angiotensin-2 receptor blocker

and two patients of CKD stage 3–4 in the ADM group. Hemorrhage in the optic nerve sheath (H47.0) occurred in one patient of CKD stage 3–4 in the ADMS group. There was no difference in the risk of bleeding between the two groups (HR 1.88, 95% CI 0.25–13.38) (Supplement Table 5).

Discussion

T2DM leads to various complications in multiple organs. As the severity index of complications associated with DM increases from 2 to 5 or more, the risk of mortality increases

from 1.90 to 7.18 times [4]. Prevention and treatment of complications are critical in patients with DM to improve the quality of life, and to prevent morbidity and mortality.

In our study, the benefits of sarpogrelate were limited to the progression of nephropathy in the early stages of CKD. Reduction of other microvascular complications was not observed with sarpogrelate when used with metformin-based antidiabetic therapy. Metformin-based antidiabetic therapy (ADM) was used as a control to evaluate the additional effects of sarpogrelate on the complications associated with DM because the practice guidelines recommend metformin as the first-line therapy in T2DM [29]. Addition of sarpogrelate with ADM has shown beneficial effects on kidney functions in the DM patients.

Diabetic nephropathy is one of the most frequent microvascular complications with a prevalence of 40% in T2DM patients [30, 31]. Patients with DM and nephropathy have a higher risk of cardiovascular morbidity [32]. Antiplatelet drugs, either aspirin or clopidogrel, are recommended to prevent primary or secondary atherosclerotic cardiovascular diseases in DM [7, 29]. Sarpogrelate, an antiplatelet agent with multiple mechanisms is used in patients with DM in Korea. Many studies have reported the beneficial effects of sarpogrelate in diabetic kidney disease. Sarpogrelate may reduce albuminuria in patients with DM in the early stage of diabetic nephropathy [19]. It has been shown to prevent the progression of renal fibrosis through multiple pathways in a mouse model of tubulointerstitial injury [20]. A recent animal study suggested a new mechanism by which sarpogrelate acts in diabetic nephropathy. In an animal model of proximal tubular inflammation and fibrosis with hyperglycemia, sarpogrelate was found to be beneficial in diabetic kidney disease by inhibiting macrophage activities and by anti-inflammatory actions [21]. For change in eGFR, a reduction of 30 or 40% eGFR from the baseline value has been suggested as a surrogate endpoint for the assessment of nephroprotective effects of drugs, such as renin-angiotensin system inhibitors in CKD [22, 23].

The beneficial effects of sarpogrelate on microvascular complications in the subgroup analyses were found to be similar across the different groups based on age, gender, comorbidity, and concomitant medications. In Korea, the prevalence of hypertension and hyperlipidemia are 62.5% and 49.5% in patients with DM [33, 34]. ACEIs and ARBs are recommended as the drug of choice in patients with DM and hypertension as they provide beneficial effects on the progression of nephropathy [35–38]. Among the antidiabetic drugs, DPP-4I have been reported to reduce microalbuminuria and development or exacerbation of diabetic nephropathy [39–41]. In this study, there was, however, no significant difference in the risk of complications in patients with or without receiving ACEI/ARB, DPP-4I, or statin therapy. As SGLT-2I were licensed in Korea in 2017, the effects of SGLT-2I on renal function could not be evaluated in this study. Sarpogrelate reduced the risk of complications in patients receiving ≥ 3 antidiabetic drugs and SU, while it showed a marginal benefit in patients without aspirin use. This study excluded patients receiving other antiplatelet drugs for > 7 days except for aspirin or sarpogrelate. This indicated that sarpogrelate could be used as an alternate antiplatelet drug in patients with an aspirin allergy. In our study, aspirin was used in about 20–29% of the patients with or without sarpogrelate administration. Although the risk of bleeding was low, caution is required when using a combination of sarpogrelate and aspirin due to an increased risk of bleeding.

This retrospective cohort study had several limitations in terms of complete data acquisition. The data extraction for the cohort of DM patients and identification of the complications of DM were based on the ICD-10 codes. The outcomes based on ICD-10 codes could be wrongly estimated because of coding errors. The frequency and interval of blood tests were different for each patient. We could not obtain complete information with regard to smoking status, body mass index, genetic information, diet, and activity, which may affect the complications of DM. The duration of DM was assessed based on the duration of use of drugs for DM as the exact time of diagnosis was not clearly identified in the visit records of the tertiary hospitals. HBA1c and blood pressure at baseline was included to evaluate their impact on the outcomes, but data at the end of the study was not fully available for all the patients. Blood pressure checked during each clinic visit in the follow-up period was not recorded in the clinical data warehouse for the outpatients who were included in this study. The patients with any episode of hospitalizations were also excluded while evaluating the change in kidney function to eliminate bias due to acute kidney injury from glomerulonephritis, computed tomography contrast, non-steroidal anti-inflammatory drugs (NSAIDS), or intravenous antibiotics. The over-the-counter use of NSAIDs could not be assessed as the electronic medical records did not contain the data on the actual use of NSAIDs, and hence, the use of NSAIDS could not be completely ruled out. Analysis of complications was also based on eGFR and urine albumin for renal function in the only available subjects. The lack of comprehensive clinical data might have influenced PS matching, which could affect the study results and reduce the study power. The benefits of sarpogrelate on the complications of diabetes was limited to nephropathy in the early CKD stages. The impact on the composite endpoints including neuropathy and retinopathy was not demonstrated with the use of sarpogrelate. In terms of the complexity involved in evaluating the complications associated with DM with various risk factors and disease management, the effects of sarpogrelate should be investigated with more robustly designed studies and complete data set including a sufficient number of patients.

Conclusion

Metformin-based antidiabetic therapy with sarpogrelate may reduce the incidence of diabetic nephropathy and progression of nephropathy in patients with T2DM. The use of sarpogrelate, an antiplatelet drug, can have a beneficial effect on the progression of renal complications in DM.

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