Original Article

Dipeptidyl peptidase-4 inhibitors versus sulfonylureas on the top of metformin in patients with diabetes and acute myocardial infarction

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Background: Recent trials have shown that both the extent of glycated hemoglobin reduction and the duration of enhanced glycemic control are major factors that may affect cardiovascular outcome results. We aimed to investigate the impact of metformin (MET) combined with dipeptidyl peptidase-4 (DPP4) inhibitors or sulfonylureas (SU) on long-term clinical outcomes in patients with acute myocardial infarction (AMI) and type 2 diabetes mellitus (DM).

Methods: This study was a prospective cohort trial. From November 2011 to December 2015, a total of 13,104 AMI patients were consecutively enrolled from the Korea AMI registry-National Institutes of Health. The patients were divided into the MET + DPP4 inhibitors group and the MET + SU group. The primary endpoint, major adverse cardiac events (MACE), was defined as the composite of all-cause death, recurrent myocardial infarction (MI), and any repeat revascularization up to 3-year follow-up. To adjust baseline potential confounders, an inverse probability weighting (IPTW) analysis was performed.

Results: Baseline well-matched two groups were generated (the MET + DPP4 inhibitors group, n=468 and the MET + SU group, n=468). During 3-year clinical follow-up, the cumulative incidence of MACE between the two groups was not significantly different after adjustment (16.8% for MET + DPP4 inhibitors group *vs.* 19.4% for MET + SU group, P=0.302). However, the MET + DPP4 inhibitors group was associated with reduced risk of MI [1.3% *vs.* 4.9%; hazard ratio (HR): 0.228, 95% confidence interval (CI): 0.090–0.580, P=0.001] than the MET + SU group.

Conclusions: In patients with AMI and type 2 DM, the use of MET combined with DPP4 inhibitors was associated with reduced incidence of recurrent MI than MET combined with SU during 3-year follow-up.

Keywords: Metformin (MET); dipeptidyl peptidase-4 inhibitors (DPP4i); sulfonylureas (SU); acute myocardial infarction (AMI); type 2 diabetes mellitus (type 2 DM)

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Introduction

Diabetes mellitus (DM) is an important modifiable risk factor for cardiovascular (CV) disease. DM is very common among patients with acute myocardial infarction (AMI), and these patients showed a 2-fold higher mortality rate than in those with normoglycemia (1,2). The recent trials showed that both the amplitude of reduction in glycated hemoglobin (HbA1c) and the duration of the intensification of glycemic control are major factors that may influence CV outcome results (3). Previous studies demonstrated that intensive in-hospital glycemic control and peri-procedural glycemic control in patients undergoing percutaneous coronary intervention (PCI) are associated with improved clinical outcomes (4,5). However, the CV effects of different glucose-lowering agents and of more intensive glucose control remain a matter of controversy (6).

The recent guidelines recommend that metformin (MET) should be the first-line therapy followed by various options for second-line treatment if adequate glycemic control is not achieved despite MET monotherapy (7,8). Although the newer therapies have been rapidly introduced and the treatment guidelines for type 2 DM are regularly updated based on new evidence (7), sulfonylureas (SU) such as glimepiride and dipeptidyl peptidase-4 (DPP4) inhibitors are the most commonly used second-line glucose-lowering agents in many countries (9). Several studies have suggested that the use of SU is associated with an increased risk for CV outcomes and all-cause mortality (10,11), in contrast, the use of DPP4 inhibitors in monotherapy or in combination has been shown to have neutral or slightly beneficial effects on CV outcomes (12-14). However, there are few data about the head-to-head comparison trials of the effectiveness of the MET-DPP4 inhibitors combination and the MET-SU combination on CV outcomes in type 2 DM patients with high CV risk such as AMI. Of note, the potential long-term benefits or risks were not assessed effectively.

Therefore, we investigated the impact of MET combined with DPP4 inhibitors (MET + DPP4 inhibitors group) or SU (MET + SU group) on 3-year clinical outcomes in patients with AMI and type 2 DM. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-349/rc).

Highlight box

Key findings

- The use of metformin (MET) combined with dipeptidyl peptidase-4 (DPP4) inhibitors in acute myocardial infarction (AMI) patients with type 2 diabetes mellitus (DM) was associated with significantly reduced incidence of recurrent myocardial infarction (MI) than that of MET combined with sulfonylureas (SU) during 3-year follow-up.

What is known and what is new?

- While SU were associated with higher risk of cardiovascular events and all-cause mortality, both monotherapy and combination therapy involving DPP4 inhibitors have demonstrated neural or beneficial effects on cardiovascular outcomes.
- The potential long-term benefits or risks of MET combined with DPP4 inhibitors in patients with AMI and type 2 DM were not assessed effectively.

What is the implication, and what should change now?

- The combination of MET with DPP4 inhibitors may be considered for improving long-term cardiovascular outcomes in patients with AMI and type 2 DM.

Methods

Study population

The study participants were recruited from the Korea AMI Registry (KAMIR)-National Institutes of Health (NIH) registry. The previous publications (15,16) provide a comprehensive overview of the KAMIR study design, and additional registry details are available on the KAMIR website (http://www.kamir.or.kr). Essentially, the KAMIR study is a prospective, multicenter, observational cohort trial intended to reflect the "real world" clinical practices in a cohort of Korean AMI patients. It has been ongoing since November 2005, with the primary goal of investigating the current epidemiology and clinical outcomes of AMI in the Korean population. Over the period from November 2011 to December 2015, a total of 13,104 patients AMI patients have been consecutively enrolled in the nationwide KAMIR-NIH registry. The flow chart illustrates the

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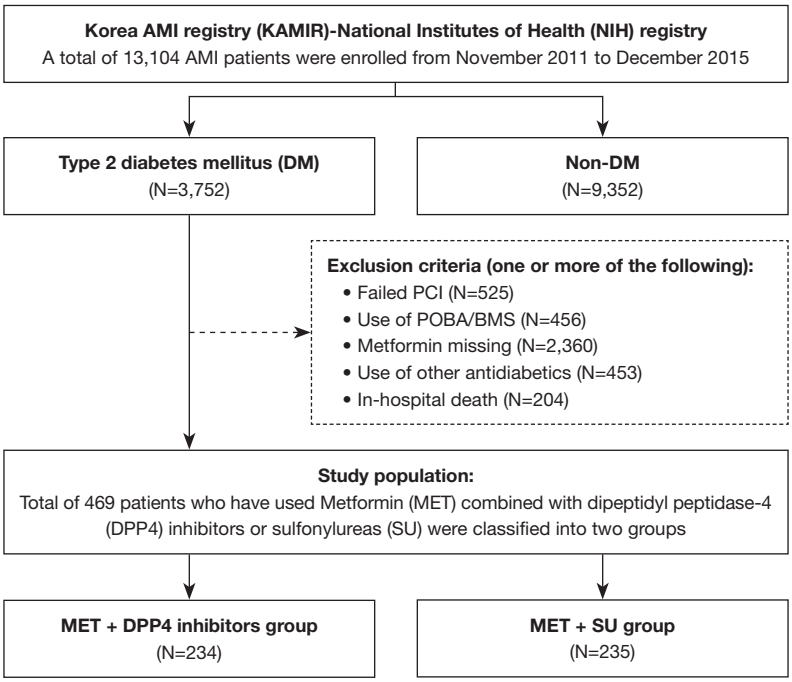

Figure 1 Flow chart of this study. PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; BMD, bare-metal stent.

procedural framework of the present study (*Figure 1*). Among the entire population, 3,752 patients had known DM history irrespective of treatment or newly diagnosed DM on admission. After the exclusion of those who had undergone failed PCI, those who had received PCI with a device other than drug-eluting stents (DES), those with missing MET data, those taking other glucose-lowering agents except MET combined with DPP4 inhibitors or SU at discharge and during follow-up period, and those who had in-hospital death, a total of 469 patients who have used MET combined with DPP4 inhibitors or SU according to the physician's discretion were classified into two groups; the MET + DPP4 inhibitors group (n=234) and the MET + SU group (n=235).

Data collection occurred through a web-based case report from at each collaborating center. The study protocol was approved by the Korea University Guro Hospital Institutional Review Board (IRB) under the #2016GR0740, and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (as revised in 2013). The other hospitals were informed and agreed with the study. Prior to enrollment, all patients furnished written informed consent. A comprehensive 3-year clinical follow-up was completed for all 469 participants, involving face-to-face interviews, telephone calls, or chart reviews.

PCI procedure and medical treatment

PCI was performed using a general standard PCI technique (17). PCI was proceeded through either the femoral or radial artery after an administration of unfractionated heparin (50–100 U/kg). All patients received loading doses of aspirin (200–300 mg) and other anti-platelets (ticagrelor 180 mg, prasugrel 60 mg or clopidogrel 300–600 mg as loading doses according to current guideline-based dual antiplatelet regimen) before PCI (18). DES were deployed after prior balloon angioplasty, and the use of anti-coagulation therapy during PCI was left to the discretion of the individual operator. Anti-ischemic therapy, comprising medications such as calcium channel blockers, beta-blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, and statins, was prescribed as deemed appropriate by the physician. The patients maintained dual anti-platelet therapy for at least one year.

Study definition and endpoint

DM was defined as either known DM for which patients received medical treatment (insulin or antidiabetics) or not, or newly diagnosed DM defined as an HbA1c level ≥6.5%, fasting plasma glucose (FPG) level ≥126 mg/dL

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(7.0 mmol/L), and/or random plasma glucose (RPG) level ≥200 mg/dL (11.1 mmol/L) according to the American Diabetes Association clinical practice recommendations (19).

The key combined primary endpoint was major adverse cardiac events (MACE) as defined as the composite of all-cause death, recurrent MI, and any repeat revascularization. The key secondary endpoints were the occurrence of any clinical events such as all-cause death, recurrent MI, any repeat revascularization including surgical coronary artery bypass graft (CABG) or repeat PCI, target lesion failure (TLF), stent thrombosis (ST), and re-hospitalization due to heart failure (HF). All deaths were considered to be cardiac in origin unless a non-cardiac origin was definitely documented. Recurrent MI was defined as recurrent symptoms with new ST-segment elevation or re-elevation of cardiac markers to at least twice the upper limit of normal. Target lesion revascularization (TLR) was defined as repeat PCI within the index procedure stent or 5 mm edge. Target vessel revascularization (TVR) was defined as any repeat PCI or surgical CABG of any segment in the target vessel. Any repeat revascularization was defined as any repeat PCI or CABG of target vessel or non-target vessel. TLF was defined as the composite of clinically driven TLR, recurrent MI or cardiac death related to the target vessel. All participants were required to visit the outpatient department of cardiology at the end of the first month and then every six months after the PCI procedure, as well as whenever angina-like symptoms occurred.

Statistical analysis

For continuous variables, differences between the two groups were evaluated using the unpaired *t*-test or Mann-Whitney rank test. Data were expressed as mean ± standard deviations. For discrete variables, differences were expressed as counts and percentages and analyzed with the χ^2 or Fisher's exact test between two groups. To adjust for any potential confounders, an inverse probability weighting (IPTW) analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance: age, sex (male), body mass index, Killip class on admission, left ventricular ejection fraction, cardiovascular risk factors (e.g., hypertension, dyslipidemia, heart failure, cerebrovascular disease, prior CABG, prior MI, and prior PCI), co-medication treatment (e.g., aspirin, other anti-platelets, calcium channel blockers, beta-blockers, RAAS inhibitors, and statins), angiographic and procedural characteristics (e.g., target vessel, number of diseased vessels, lesion type, and DES type). Various clinical outcomes up to 3 years were estimated by the Kaplan-Meier analysis, and differences between the groups were compared with the log-rank test before and after IPTW. Binary logistic regression analysis was used to assess the hazard ratio (HR) of the MET + DPP4 inhibitors group compared to the MET + SU group in the IPTW population. For all analyses, a two-sided P<0.05 was considered statistically significant. All data were processed with SPSS (version 20.0, SPSS-PC, Inc. Chicago, IL, USA).

Results

Baseline clinical characteristics of the patients are shown in *Table 1*. The baseline clinical characteristics were balanced between the two groups. The angiographic and procedural characteristics and medications at discharge are presented in *Table 2*. The prescription rate of clopidogrel (63.2% *vs.* 74.5%, P=0.009) was lower in the MET + DPP4 inhibitors group than in the MET + SU group. However, this intergroup difference was well balanced after IPTW adjustment.

Table 3 and *Figure 2* show the cumulative incidences of major clinical outcomes during the 3-year follow-up. Before the adjustment, there was a trend toward lower cumulative incidence of MACE in the MET + DPP4 inhibitors group than in the MET + SU group (*Figure 2A*), but it did not show the significant difference between the two groups after IPTW adjustment (16.8% *vs.* 19.4%, P=0.302). There was no significant difference in all-cause death between the two groups, both before (*Figure 2B*) and after the adjustment. However, the cumulative incidences of recurrent MI (0.9% *vs.* 5.1%, P=0.007) (*Figure 2C*) and non-ST elevation MI (NSTEMI, 0.0 *vs.* 3.4%, P=0.007) were significantly lower in the MET + DPP4 inhibitors group before the adjustment. After IPTW adjustment, the incidences of recurrent MI [hazard ratio (HR): 0.228, 95% CI: 0.090–0.580, P=0.001] and NSTEMI (HR: 0.377, 95% CI: 0.094–1.504, P<0.001) in the MET + DPP4 inhibitors group were significantly lower than in the MET + SU group *(Figure 3)*. Although the cumulative incidences of any repeat revascularization (7.3% *vs.* 12.8%, P=0.05) (*Figure 2D*), TLR (1.7% *vs.* 5.1%, P=0.04), and TVR (3.0% *vs.* 8.5%, P=0.01) in the MET + DPP4 inhibitors group were significantly lower than in the MET + SU group, these differences between the two groups were not significant after IPTW adjustment.

Figure 3 shows that in cases of male, initial diagnosis

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Table 1 Baseline clinical characteristics

Variables	Crude population				IPTW			
	Metformin and		P value	S.diff	Metformin and		P value	S.diff
	DPP4i (n=234)	SU (n=235)			DPP4i (n=468)	SU (n=468)		
Sex, male	171 (73.1)	160 (68.1)	0.236	–0.60	325 (69.4)	336 (71.8)	0.430	0.28
Age, year	64.2±10.8	65.6±11.6	0.198	0.12	64.6±10.5	64.5±11.6	0.824	–0.01
Blood pressure, mmHg								
Systolic	130±26	127±25	0.231	–0.11	128±26	128±25	0.847	–0.01
Diastolic	79±16	77±15	0.077	–0.16	78±15	78±15	0.914	–0.01
Heart rate, beat per minutes	80±19	78±18	0.185	–0.12	79±19	79±18	0.853	–0.01
Body mass index, kg/m^2	24.2±3.6	24.1±2.9	0.743	–0.03	24.1±3.4	24.0±2.9	0.601	–0.03
LV ejection fraction, %	51.4±10.7	50.7±11.4	0.464	–0.07	51.2±10.7	50.8±11.2	0.605	–0.03
Final diagnosis								
STEMI	113 (48.3)	112 (47.7)	0.891	–0.09	218 (46.5)	215 (45.9)	0.868	–0.08
NSTEMI	121 (51.7)	123 (52.3)	0.891	0.09	251 (53.5)	253 (54.1)	0.868	0.07
Killip class								
I	173 (73.9)	174 (74.0)	0.978	0.01	356 (75.9)	355 (75.9)	0.985	–0.01
II	27 (11.5)	25 (10.6)	0.756	–0.27	48 (10.2)	50 (10.7)	0.822	0.14
III	17 (7.3)	18 (7.7)	0.871	0.14	30 (6.4)	29 (6.2)	0.893	–0.09
IV	17 (7.3)	18 (7.7)	0.871	0.14	35 (7.5)	34 (7.3)	0.900	–0.08
History of patients								
Hypertension	143 (61.1)	155 (66.0)	0.276	0.61	295 (63.0)	296 (63.2)	0.946	0.03
Dyslipidemia	50 (21.4)	35 (14.9)	0.069	–1.52	86 (18.4)	90 (19.2)	0.738	0.20
Prior CAD								
Myocardial infarction	13 (5.6)	23 (9.8)	0.085	1.53	30 (6.4)	35 (7.5)	0.515	0.41
Angina pectoris	21 (9.0)	23 (9.8)	0.763	0.27	40 (8.5)	41 (8.8)	0.899	0.08
Prior PCI	20 (8.5)	26 (11.1)	0.360	0.80	41 (8.7)	42 (9.0)	0.900	0.08
Prior CABG	1 (0.4)	4 (1.7)	0.372	1.24	2 (0.4)	5 (1.1)	0.287	0.74
Stroke	17 (7.3)	20 (8.5)	0.617	0.44	41 (8.8)	32 (6.8)	0.273	–0.69
Infarction	2 (0.9)	0	0.248	–1.31	2 (0.4)	0	0.499	–0.92
Hemorrhage	16 (6.8)	20 (8.5)	0.496	0.60	40 (8.5)	32 (6.8)	0.326	–0.62
Smoking								
Currently	93 (39.7)	83 (35.3)	0.322	–0.72	169 (36.0)	166 (35.5)	0.857	–0.09
Ex-smoker	47 (20.1)	49 (20.9)	0.837	0.17	104 (22.2)	100 (21.4)	0.751	–0.18
Serum glucose, mg/dL	230±93	233±93	0.754	0.03	227±97	235±96	0.225	0.08
HbA1c, %	7.8±1.5	7.8±1.6	0.984	0.00	8.0±1.7	7.9±1.6	0.408	–0.06

Data are presented as n (%) or mean ± standard deviation. IPTW, inverse probability weighting; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, sulfonylureas; S.diff, standardized mean difference; LV, left ventricular; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; HbA1c, glycated hemoglobin.

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Table 2 Angiographic, procedural characteristics and medications at discharge

Variables	Crude population				IPTW			
	Metformin and		P value	S.diff	Metformin and		P value	S.diff
	DPP4i (n=234)	SU (n=235)			DPP4i (n=468)	SU (n=468)		
Angiographic and procedural characteristics								
Infarct-related artery								
LAD	113 (48.3)	98 (41.7)	0.152	–0.98	217 (46.4)	211 (45.1)	0.694	–0.19
LCx	37 (15.8)	39 (16.6)	0.818	0.19	73 (15.6)	79 (16.9)	0.585	0.33
RCA	77 (32.9)	93 (39.6)	0.133	1.11	168 (35.8)	169 (36.1)	0.926	0.05
Left main	7 (3.0)	5 (2.1)	0.554	–0.54	11 (2.3)	9 (1.9)	0.655	–0.29
Multi-vessel disease	129 (55.1)	143 (60.9)	0.209	0.75	272 (58.0)	262 (56.0)	0.534	–0.27
Drug-eluting stents								
Everolimus	125 (53.4)	131 (55.7)	0.613	0.32	256 (54.6)	252 (53.8)	0.821	–0.10
Zotarolimus	2 (0.9)	1 (0.4)	0.623	–0.54	2 (0.4)	2 (0.4)	>0.999	0.00
Biolimus A9	47 (20.1)	37 (15.7)	0.220	–1.03	88 (18.8)	94 (20.1)	0.609	0.30
Sirolimus	7 (3.0)	6 (2.6)	0.773	–0.26	13 (2.8)	12 (2.6)	0.844	–0.13
Paclitaxel	0	1 (0.4)	>0.999	0.92	0	1 (0.2)	>0.999	0.65
Number of stent	1.20±0.43	1.21±0.45	0.935	0.01	1.22±0.47	1.21±0.45	0.918	–0.01
Stent diameter, mm (max)	3.12±0.44	3.09±0.42	0.375	–0.08	3.08±0.44	3.08±0.42	0.869	0.01
Stent diameter, mm (mean)	3.08±0.42	3.06±0.41	0.524	–0.06	3.04±0.42	3.05±0.41	0.657	0.03
Total stent length, mm	30.4±13.7	30.3±14.6	0.919	–0.01	30.8±13.9	30.6±14.1	0.828	–0.01
Discharge medication								
Aspirin	232 (99.1)	234 (99.6)	0.623	0.04	466 (99.4)	466 (99.6)	>0.999	0.02
Clopidogrel	148 (63.2)	175 (74.5)	0.009	1.36	331 (70.7)	345 (73.7)	0.307	0.35
Prasugrel	33 (14.1)	20 (8.5)	0.056	–1.66	50 (10.7)	42 (9.0)	0.380	–0.55
Cilostazol	24 (10.3)	38 (16.2)	0.059	1.63	68 (14.5)	60 (12.8)	0.447	–0.46
Ticagrelor	51 (21.8)	40 (17.0)	0.191	–1.08	85 (18.1)	82 (17.5)	0.810	–0.14
Ca-channel blockers	16 (6.8)	13 (5.5)	0.557	–0.53	29 (6.2)	37 (7.9)	0.303	0.65
Beta-blockers	206 (88.0)	207 (88.1)	0.986	0.01	419 (89.3)	414 (88.5)	0.669	–0.09
RAAS inhibitors	195 (83.3)	204 (86.8)	0.291	0.38	400 (85.5)	408 (87.2)	0.447	0.18
Statin	218 (93.2)	220 (93.6)	0.843	0.05	439 (93.6)	439 (93.8)	0.900	0.02

Data are presented as n (%) or mean ± standard deviation. IPTW, inverse probability weighting; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, sulfonylureas; S.diff, standardized mean difference; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; RAAS, renin-angiotensin-aldosterone system.

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Table 3 Various clinical outcomes after acute myocardial infarction up to 3 years follow-up

Variables	Crude population			IPTW		
	Metformin and		P value	Metformin and		P value
	DPP4i (n=234)	SU (n=235)		DPP4i (n=468)	SU (n=468)	
MACE	32 (13.7)	48 (20.4)	0.052	79 (16.8)	91 (19.4)	0.302
Target lesion failure	13 (5.6)	23 (9.8)	0.085	38 (8.1)	43 (9.2)	0.554
Total death	15 (6.4)	18 (7.7)	0.597	26 (5.6)	35 (7.5)	0.233
Cardiac death	9 (3.8)	9 (3.8)	0.993	17 (3.6)	18 (3.9)	0.858
Non-cardiac death	6 (2.6)	9 (3.8)	0.436	9 (1.9)	16 (3.4)	0.154
Myocardial infarction	2 (0.9)	12 (5.1)	0.007	6 (1.3)	23 (4.9)	0.001
STEMI	2 (0.9)	4 (1.7)	0.685	6 (1.3)	8 (1.7)	0.587
NSTEMI	0	8 (3.4)	0.007	0	15 (3.2)	<0.001
Revascularization	17 (7.3)	30 (12.8)	0.047	51 (10.9)	56 (12.0)	0.608
CABG	0	1 (0.4)	>0.999	0	2 (0.4)	0.499
PCI	17 (7.3)	29 (12.3)	0.065	51 (10.9)	54 (11.5)	0.756
TLR	4 (1.7)	12 (5.1)	0.043	21 (4.5)	21 (4.5)	0.994
TVR	7 (3.0)	20 (8.5)	0.010	27 (5.8)	36 (7.7)	0.237
Non-TVR	10 (4.3)	10 (4.3)	0.992	24 (5.1)	20 (4.3)	0.537
Stent thrombosis	1 (0.4)	3 (1.3)	0.623	2 (0.4)	5 (1.1)	0.451
Re-hospitalization due to HF	8 (3.4)	8 (3.4)	0.993	15 (3.2)	14 (3.0)	0.855

Data are presented as incidence (%). IPTW, inverse probability weighting; DPP4i, dipeptidyl peptidase-4 inhibitors; SU, sulfonylureas; MACE, major adverse cardiac events; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVR, target vessel revascularization; HF, heart failure.

of ST-segment elevation MI (STEMI), history of hypertension, or no history of dyslipidemia, the use of MET + DPP4 inhibitors over MET + SU may have benefits to reduce recurrent MI in patients with AMI and type 2 DM.

Discussion

The main findings of this study are: (I) the cumulative incidence of MACE was similar between the two groups (MET + DPP4 inhibitors group *vs.* MET + SU group); (II) the cumulative incidence of recurrent MI was significantly lower in the MET + DPP4 inhibitors group than in the MET + SU group in patients with AMI and type 2 DM during 3-year follow-up. This analysis of Korean national registry data demonstrated that the use of MET combined with DPP4 inhibitors in patients with AMI and type 2 DM resulted in lower incidence of 3-year recurrent MI rates compared to MET combined with SU such as glimepiride.

SU have been used the common add-on second-line agents combined with MET, mainly because of their relatively lower cost and strong hypoglycemic effect. Several studies have reported that they have been associated with an increased risk of hypoglycemia, weight gain, and CV risks compared with other glucose-lowering agents (20-22). On the contrary, previous meta-analyses evaluating the safety of SU as a group or in combination with MET did not show higher risk of mortality or CV events (23,24). However, in direct comparisons with DPP4 inhibitors showed by other meta-analyses, SU were associated with significant increase in the incidence of CV events (25,26). Zhang *et al.* showed that DPP4 inhibitors were associated with 47% less CV events compared with SU (25). Morgan *et al.* demonstrated that MET-SU combination therapy was associated with an increased risk for MACE and all-cause mortality (HR:

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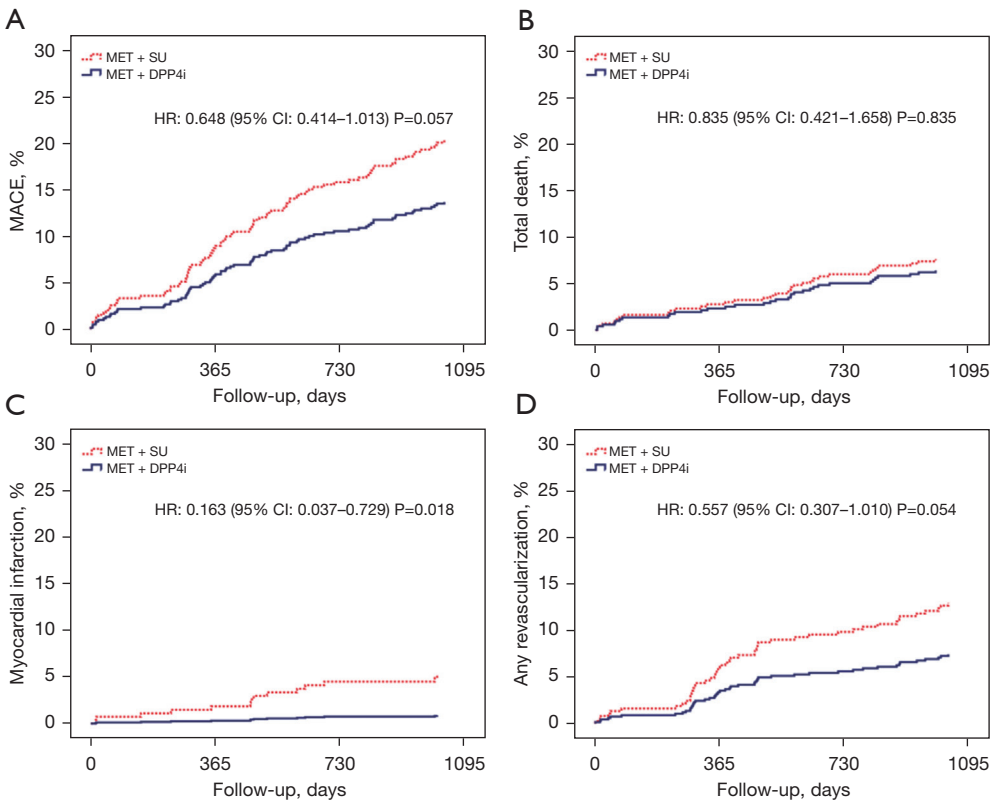

Figure 2 The cumulative incidences of clinical outcomes according to MET combined with DPP4 inhibitors and MET combined with SU at 3-year follow-up using Kaplan-Meier analyses in crude population: (A) major adverse cardiac events, (B) all-cause death, (C) recurrent myocardial infarction, (D) any repeat revascularization. MACE, major adverse cardiac events; MET, metformin; SU, sulfonylureas; DPP4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; CI, confidence interval.

1.71, 95% CI: 1.28–2.29) compared to the MET-DPP4 inhibitors combination (27). Furthermore, the combination of MET and SU was associated with increased mortality in comparison with SU alone (28).

DPP4 inhibitors inhibit the enzyme that degrades 2 gut-derived incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and stimulate insulin secretion and reduce glucagon secretion (29). DPP4 inhibitors have progressively replaced SU in many countries because they are not associated with hypoglycemia or weight gain, and have a relatively good safety profile (30,31). Hypoglycemia and weight gain among SU users may be associated with an increased CV risk (32). In animal experimental model, DPP4 inhibitors were shown to reduce infarct size and attenuate left ventricular dysfunction and remodeling via the GLP-1 receptor-protein kinase A pathway in the post-MI settings (33-35).

Recently, the major prospective clinical trials have investigated the various uses and CV outcomes of DPP4 inhibitors in diabetic patients. In EXAMINE (the CV outcomes study of alogliptin in patients with acute coronary syndrome and type 2 DM), SAVOR-TIMI 53 (the saxagliptin assessment of vascular outcomes in patients with DM-thrombolysis in MI), and TECOS (the sitagliptin CV outcome study), no significant differences were observed about the incidence of MACE, MI, stroke, CV mortality, and all-cause mortality between DPP4 inhibitors or matched placebo (13,36,37). Therefore, the favorable cardiac and vascular impacts observed in animal models using DPP4 inhibitors did not find validation in clinical investigations, including CV outcome trials. These trials only demonstrated non-inferiority when compared to a placebo.

However, the results of present study were that the use of MET combined with DPP4 inhibitors in patients with AMI and type 2 DM resulted in lower incidence of 3-year recurrent MI rates and did not show higher risk of MACE, mortality or other clinical events compared to MET combined with SU. Our results also showed that the

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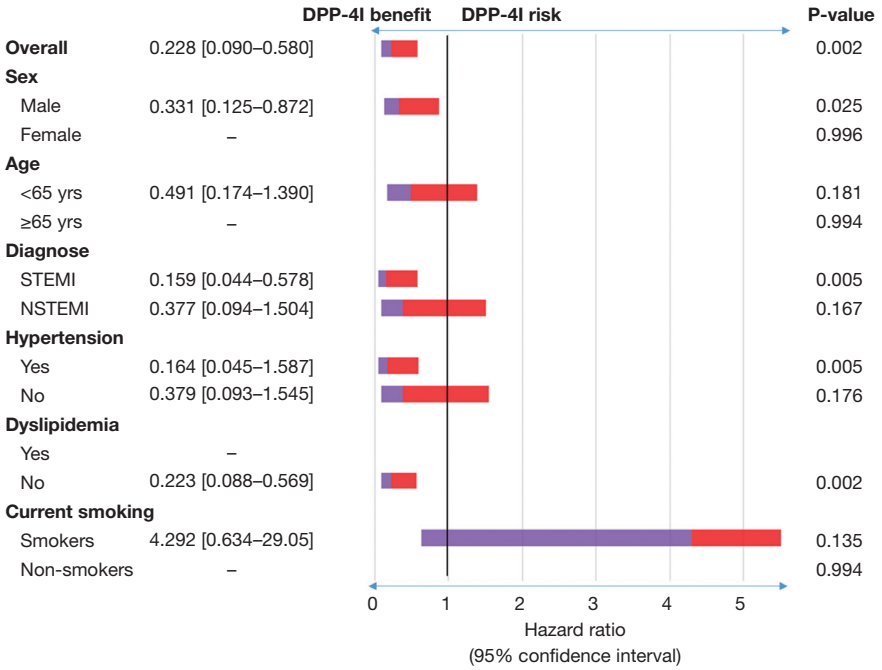

Figure 3 Subgroup analysis for impact of MET combined with DPP4 inhibitors compared to MET combined with SU such as glimepiride on recurrent MI at 3-year follow-up by binary regression hazard ratio analysis in IPTW population. Blue and red colors are the range of the lower and upper limits of 95 % CI respectively. DPP4i, dipeptidyl peptidase-4 inhibitors; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; MET, metformin; SU, sulfonylureas; MI, myocardial infarction; IPTW, inverse probability weighting; CI, confidence interval.

incidences of any repeat revascularization (7.3% *vs.* 12.8%, P=0.05), TLR (1.7% *vs.* 5.1%, P=0.04), and TVR (3.0% *vs.* 8.5%, P=0.01) in the MET + DPP4 inhibitors group were significantly lower, although they had no statistical significance after IPTW adjustment. The major differences of our present study comparing other published CV outcome trials of DPP4 inhibitors were that the duration of studies (3-year follow-up) and head-to-head comparison of MET combined therapy of DPP4 inhibitors and SU. Given the relatively short durations of other trials (1–2 years), the variance in hyperglycemia exposure between the groups was insufficient to detect any notable differences in CV outcomes, particularly among diabetic patients with pre-existing advanced CV disease (3). Cowley *et al.* showed a trend toward reduced incidence of CV outcomes in MET-treated patients contrasting with a trend for an increase in MACE in patients not receiving MET (38). It is crucial to examine the impact of MET on endothelial dysfunction in diabetic patients, and we have to consider its anti-inflammatory and anti-apoptotic effects on pericoronary fat from pre-diabetic AMI patients, achieved by modulating sodium-glucose cotransporter 2, leptin, and sirt 6 levels (39,40). DPP4 inhibitors and MET have both demonstrated efficacy in enhancing insulin resistance and mitigating myocardial injury resulting from ischemia-reperfusion injury. Some studies propose that the combined therapy yields superior outcomes compared to monotherapy, resulting in decreased CV events and all-cause mortality rates (41-44). Thus, it was considered that MET may act as a moderator or facilitator of DPP4 inhibitors for improving CV outcomes. This suggests that the decreased CV risks of MET combined with DPP4 inhibitors observed in this study may possibly be the results of the MET-SU combination reference group. Furthermore, it can be assumed that a negative interaction with MET could be partly responsible for the increase of CV risk with SU.

Finally, the beneficial effects of DPP4 inhibitors in patients with AMI pose several potential explanations, despite the absence of a definitive mechanism outlining the CV benefits of DPP4 inhibitors. One possible mechanism involves the potential of DPP4 inhibitors to diminish reperfusion injury by protecting mitochondrial

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function (45). They have demonstrated an ability to enhance the activity of reperfusion injury salvage kinase, thereby reducing reperfusion injury originating from cardiac tissue damage and associated arrhythmias (46,47). Furthermore, in patients with DM experiencing ischemia/reperfusion injury, DPP4 inhibitors exhibit the capacity to rescue cardiac mitochondrial dysfunction, diminish reactive oxygen species production, and alleviate oxidative stress (45,48). Lastly, DPP4 inhibitors may exert an inhibitory effect on atherosclerosis and proliferation of vascular smooth muscle cell. Previous studies have shown that GLP-1 based therapies, including both endogenous (DPP4 inhibitors) and exogenous (incretin: GLP-1 agonist) treatments, have anti-inflammatory effects that may reduce the progression of atherosclerosis. It was reported that they were associated with reduced MACE as well as improved clinical outcomes in patients with NSTEMI and STEMI (49-51). In addition, GLP-1 based therapies have a positive impact on reducing MACE and hospitalizations, even in advanced heart failure, and current guidelines recommend them as the preferred choice for patients with cardiovascular disease (52).

The strengths of this study include that the duration of studies (3-year follow-up) and head-to-head comparison of MET combined therapy of DPP4 inhibitors and SU compared to other studies. Since the duration of other studies was relatively too short and the designs of those were not direct comparison of medications, the results of other studies showed less reliability and validity than our study. This analysis of Korean national registry data demonstrated that the use of MET combined with DPP4 inhibitors in AMI patients with type 2 DM was associated with lower incidence of 3-year recurrent MI rates compared to MET combined with SU such as glimepiride.

The present study has some limitations. First, because this study was multicenter national prospective observational registry and was focused on assessing, whether there were differences in effectiveness between the two most commonly used combination therapies (MET-DPP4 inhibitors and MET-SU) in patients with AMI, these results can be applied to patients who have same characteristics as inclusion criteria. Second, the clinical impact of MET-DPP4 inhibitors and MET-SU combination therapy were compared based on medications at discharge. Thus, the dose of medications, long-term adherence, discontinuation, and incidence of adverse events were not available in this study. Third, because this study population was composed of a single race of Korean, our findings should be confirmed in different races and ethnic groups. Finally, while it is a significant limitation that this study enrolled patients prior to the recent guidelines, it is believed to hold valuable implications, particularly in the context of the Asian populations in low and middle-income countries.

Conclusions

The use of MET combined with DPP4 inhibitors in AMI patients with type 2 DM was associated with significantly reduced incidence of recurrent MI than that of MET combined with SU such as glimepiride during 3-year follow-up.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-349/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study protocol was approved by the Korea University Guro Hospital Institutional Review Board (IRB) (#2016GR0740) and was conducted according to the ethical guidelines of the Declaration of Helsinki (as revised in 2013). The other hospitals were informed and agreed with the study. Prior to enrollment, the written informed consent was obtained from all patients.

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