Peer Review File

Article information: https://dx.doi.org/10.21037/cdt-23-349

Reviewer A

About the article entitled "Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on the top of Metformin in Patients with Diabetes and Acute Myocardial Infarction Short running title: Metformin combined with DPP4 inhibitors or sulfonylureas in AMI", I would suggest you my personal recommendations:

Comment 1: please, report the ameliorative effects of incretin therapy in patients with AMI, via significant reduction of MACEs and best clinical outcomes in the clinical setting on Non-ST-elevation myocardial infarction (NSTEMI; Diabetes Obes Metab. 2018 Mar;20(3):723-729. doi: 10.1111/dom.13122), and ST-elevation myocardial infarction (Diabetol Metab Syndr. 2018 Jan 3;10:1. doi: 10.1186/s13098-017-0304-3) in diabetic patients. Please discuss this pints, referring to these articles.

Reply 1:
Thank you for your comments. As you pointed out, we have added the recommended references and further addressed the relevant content in the Discussion section (page 12).

From:
Lastly, DPP4 inhibitors might inhibit atherosclerosis and proliferation of vascular smooth muscle cell.

To:
Lastly, DPP4 inhibitors might inhibit 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. 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.**

Comment 2: Please, consider the effects played by metformin on the endothelial dysfunction in patients with insulin resistance and without coronary obstructive stenosis (Diabetes Care. 2019 Oct;42(10):1946-1955. doi: 10.2337/dc18-2356), and the anti-infiammatory/anti-apoptotic effect played by metformin in pericoronary fat excised from pre-diabetic patients with acute myocardial infarction via the modulation of the expression of sodium-glucose cotransporter 2, leptin, and sirt6 levels (Biomedicines. 2021 Jul 28;9(8):904. doi: 10.3390/biomedicines9080904). In this case, we

could consider a pleiotropic effects played by metformin in the diabetic patients. Please discuss this point.

Reply 2:
Thank you for your comments. Following your recommendations, we have integrated the appropriate references and elaborated on the relevant content within the Discussion section (page 11).

From:
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. Both DPP4 inhibitors and MET have been shown to improve insulin resistance and attenuate myocardial injury caused by ischemia-reperfusion injury, and several studies have suggested that the combined therapy provided better outcomes than monotherapy with a reduction in CV outcomes and all-cause mortality rates.

To:
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. **It is crucial to examine the impact of metformin 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-glocose cotransporter 2, leptin, and sirt 6 levels.** Both DPP4 inhibitors and MET have been shown to improve insulin resistance and attenuate myocardial injury caused by ischemia-reperfusion injury, and several studies have suggested that the combined therapy provided better outcomes than monotherapy with a reduction in CV outcomes and all-cause mortality rates.

Comment 3: Again, please introduce the concept of best in-hospital glycemic control (Diabetes Res Clin Pract. 2021 Aug;178:108959. doi: 10.1016/j.diabres.2021), and peri-procedural glycemic control, as for the patients treated by PCI (Int J Cardiol. 2013 Oct 9;168(4):3954-62. doi: 10.1016/j.ijcard.2013.06.053), and its ameliorative implication on the clinical outcomes (MACEs reduction). Please fix this point.

Reply 3:
Thank you for pointing this out. We have adhered to your request by adding the specified references and discussing the pertinent content in the Introduction section (page 4).

From:
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. However, the CV effects of different glucose-lowering agents and of more intensive glucose control remain a matter of controversy.

To:

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. **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.** However, the CV effects of different glucose-lowering agents and of more intensive glucose control remain a matter of controversy.

Comment 4: Finally, I would suggest you to remember the positive effect exerted by incretins (as the GLP1-RA) on the MACEs reduction and reduction of hospitalization also for the case of subjects with advanced HF (Cardiovasc Diabetol. 2018 Oct 22;17(1):137. doi: 10.1186/s12933-018-0778-9). Indeed, form the current international guidelines the recommended incretin for patients with CVDs looks to be the GLP1-RA. Please fix this point.

Reply 4:
In compliance with your comments, we have included the requested references and made mention of the associated content in the Discussion section (page 12).

From:
Lastly, DPP4 inhibitors might inhibit atherosclerosis and proliferation of vascular smooth muscle cell.

To:
Lastly, DPP4 inhibitors might inhibit 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. 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.**

Comment 5: Please include a full description of study inclusion and exclusion criteria.

Reply 5:
Thank you for your request. We have provided a more detailed description of the inclusion and exclusion criteria in the Methods section (page 5). Additionally, we have incorporated the relevant information into modified Figure 1.

From:
The flow chart shows the present study scheme (*Figure 1*). Of 9,853 patients who underwent successful percutaneous coronary intervention (PCI) with second generation drug-eluting stents (DES), 2,679 patients had known DM history irrespective of treatment or newly diagnosed DM on admission. After the exclusion of patients with other glucose-lowering agents except MET combined with DPP4 inhibitors or SU at discharge and during follow-up period, a total of 469 patients who have

used MET combined with DPP4 inhibitors or SU were classified into two groups; the MET+DPP4 inhibitors group (n = 234) and the MET+SU group (n = 235).

To:

The flow chart shows the present study scheme (*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 metformin 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 were classified into two groups; the MET+DPP4 inhibitors group (n = 234) and the MET+SU group (n = 235).

Comment 6: Please include a full description of study population anti-platelets and anti-ischemic therapy.

Reply 6:

According to your suggestion, we have provided a more detailed explanation of the anti-platelets and anti-ischemic therapy in the Methods section (page 6).

From:

All patients received loading doses of aspirin (200-300 mg) and other anti-platelets (ticagrelor, prasugrel or clopidogrel according to current guideline-based dual antiplatelet regimen) before PCI. 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. The patients maintained dual anti-platelet therapy for at least one year.

To:

All patients received loading doses of aspirin (200-300 mg) and other anti-platelets (ticagrelor **180mg**, prasugrel **60mg** or clopidogrel **300-600 mg as loading doses** according to current guideline-based dual antiplatelet regimen) before PCI. 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.

Comment 7: Discuss the follow-up time and the phases of clinical visits.

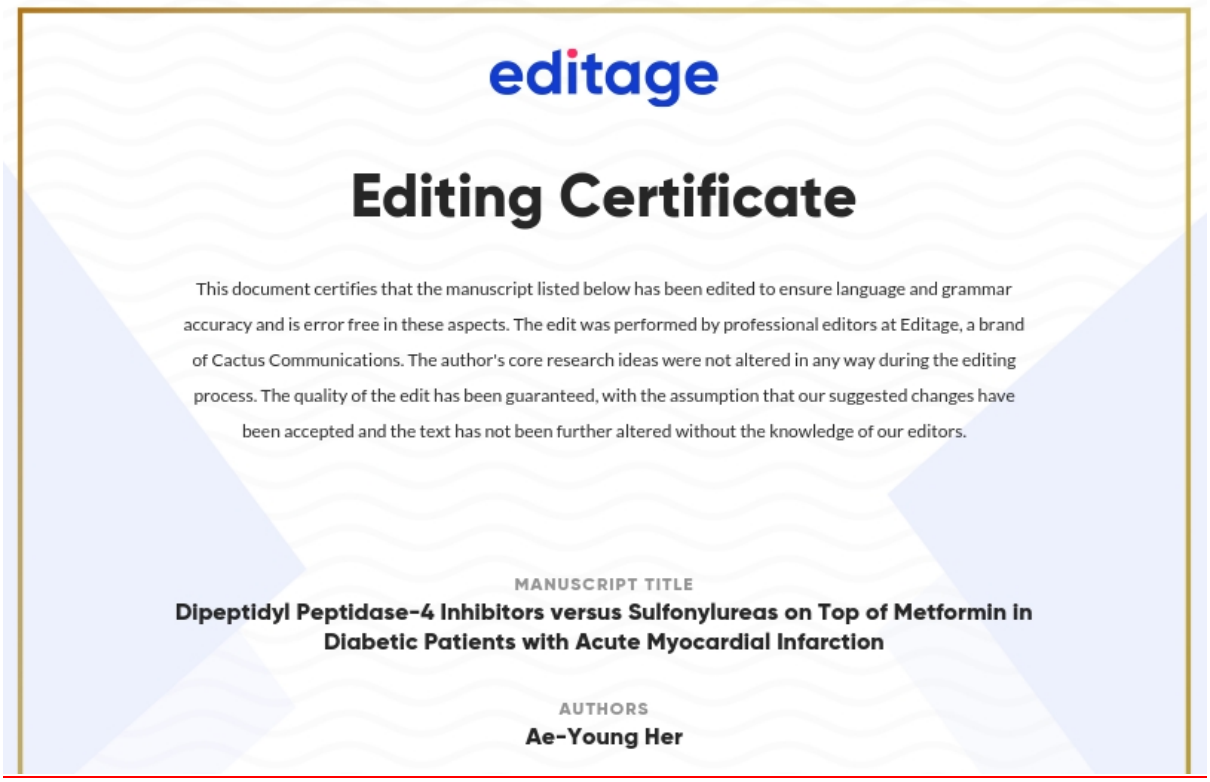
Thank you for your comment. We have already addressed your request in the Methods section on page 7.

From:

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.

Comment 8: Improve English form of the text.

It is with regret that our paper was submitted after undergoing English language professionally edited by "Editage".



editage

Editing Certificate

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MANUSCRIPT TITLE

Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on Top of Metformin in Diabetic Patients with Acute Myocardial Infarction

AUTHORS

Ae-Young Her

Comment 9: Improve quality of figures and tables.

Following your advice, we have raised the quality of the figures and tables.

Comment 10: Is possible to see a survival curve for primary (and secondary) study outcomes in the study cohorts?

As you pointed out, we have added the survival curves for primary and secondary outcomes on *Figure 2* and in the Results section and Figure legends, we have made mention of these (page 8-9, 23). Furthermore, the previous *Figure 2* has been renamed to *Figure 3*.

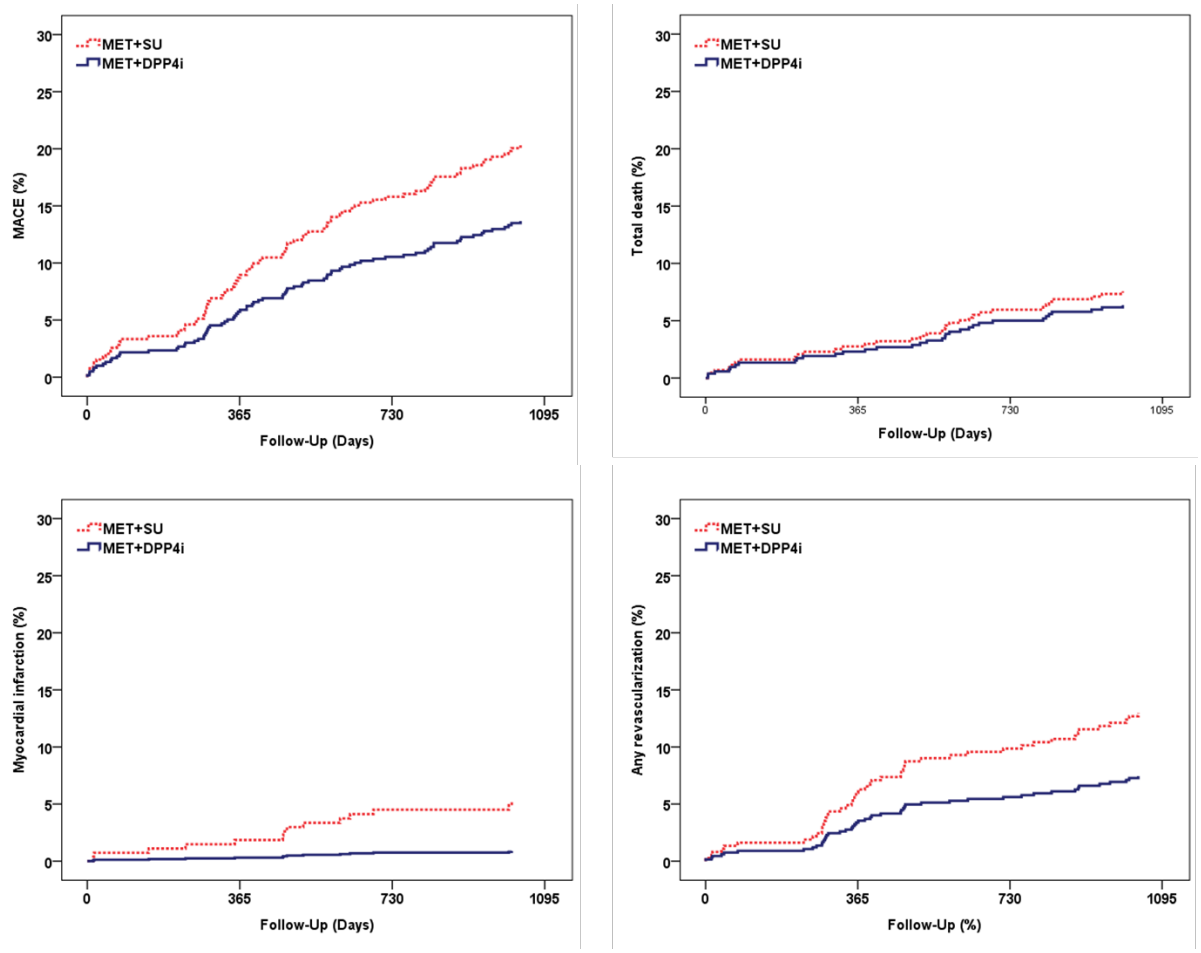
From:
Table 3 shows the cumulative incidences of major clinical outcomes during the 3-year follow-up. Before the adjustment, there was a trend toward lower cumulative incidence of MACE in the MET+DPP4 inhibitors group than in the MET+SU group, but it did not show the significant

difference between the two groups after IPTW adjustment (16.8% vs. 19.4%, P = 0.302). However, the cumulative incidences of recurrent MI (0.9 vs. 5.1%, P = 0.007) 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 (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. Although the cumulative incidences of any repeat revascularization (7.3 vs. 12.8%, P = 0.047), TLR (1.7 vs. 5.1%, P = 0.043), and TVR (3.0 vs. 8.5%, P = 0.010) 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.

To:

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 (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. Although the cumulative incidences of any repeat revascularization (7.3 vs. 12.8%, P = 0.047) **(*Figure 2D*)**, TLR (1.7 vs. 5.1%, P = 0.043), and TVR (3.0 vs. 8.5%, P = 0.010) 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 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.



From:

Figure 2. 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.

To:

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.

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.

Reviewer B

The study namely “Title: Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylureas on the top of Metformin in Patients with Diabetes and Acute Myocardial Infarction” is interesting, particularly for applying in Asian populations in low and middle income countries. However, the study population were enrolled before the current 2023 ESC guidelines for management of CVD in patients with DM which recommended to prescribe SGLT2i and GLP-1A firstly and Metformin in addition. It may add as one limitation. The conclusion of this study is based on secondary objective that should be aware for the interpretation.

We appreciate your opinion and concur with your points. Therefore, we have included the relevant content in the Limitation section (page 13) as you suggested.

From:
Finally, because this study population was composed of a single race of Korean, our findings should be confirmed in different races and ethnic groups.

To:
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.**