

## Peer review file

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### Reviewer A

- Comment 1: I recommend that the authors read the instructions for authors carefully to modify their manuscript so that it can conform to the journal instructions. Especially, the abstract structure is quite different from the recent article from the Journal of Thoracic Disease.

- Reply 1: I agree with you. Following the journal instructions, I revised the abstract structure.

- Changes in the text: We have modified the text. (see page 4, line 61-73).

- Comment 2: This manuscript needs English language editing. And there are several typographical errors.

- Reply 2: Actually, before I submitted the manuscript, I have contacted with one of my American friend, who went through the manuscript with me to correct much language flaw.

- Changes in the text: We have modified the text.

- Comment 3: I am not sure if this is mandatory for the Journal of Thoracic Disease, but randomized controlled trial should be registered on the public website such as ClinicalTrials.gov before the enrollment of the first patient. The manuscript which is reporting the results of randomized controlled trial should contain the numbers from the website. The authors should present the registration number of this trial in the revised manuscript.

- Reply 3: I agree with you. Unfortunately, I did not register at ClinicalTrials.gov, but register at our hospital (Number CHCS052017), and got the permission of the Institutional Review Board of Changhai Hospital.

- Changes in the text: See page 7, line 133-135.

- Comment 4: In surgical technique, the SVG grafting technique needs more explanation. Was it aorto-coronary bypass, or was the saphenous vein used as a composite graft to LIMA?

- Reply 4: About the surgical technique, the LIMA was routinely anastomosed to the left anterior descending artery, and the SVG was anastomosed to other target vessels with aorto-coronary or sequential bypass.

- Changes in the text: We added some data of SVG grafting technique (see page 9, line 170-171).

- Comment 5: The explanation on sample size calculation should be presented.

- Reply 5: Sample size: According to previous studies, aspirin plus Ticagrelor has a venous graft occlusion rate of 13% one year after surgery. As for aspirin plus

Clopidogrel, the rate is 3.7%. We found that a 5% difference between 2 arms can be reliably detected under a power of 80%, if we have 170 venous grafts in each arm (significance level=0.05).

- Changes in the text: We added some data in page 9, line 166-170.

- Comment 6: In table 1, the patient disease category (left main, 2-vessel disease or 3-vessel disease / stable or unstable angina, non-ST-elevation myocardial infarction) should be presented.

- Reply 6: I agree with the reviewer that we should present the data. Actually, in our group we excluded the patient with single vessel disease. The candidates all had left main or multi-vessel disease.

- Changes in the text: We added some data in table 1 (see page 7, line 138-139, and page 17, line 335).

- Comment 7: In line 191, the numbers are slightly different from those found in Table 5.

- Reply 7: We have rechecked the data in line 191 and Table 5, and there were no mistakes.

- Changes in the text: No change.

## **Reviewer B**

- Comment 1: Title: I think your title could be sharper, you are presenting a great randomized trial but your title does not really invite to read on.

-Reply 1: Actually, the title was designed according to the journal instructions. Maybe, the Reviewer could give us some suggestions about the title.

- Changes in the text: No change.

- Comment 2: Page 6 line 92: why didn't you chose Prasugrel as DAPT regime? Please give us some explanation.

-Reply 2: In our hospital, we could not get Prasugrel. Ticagrelor and Clopidogrel were commonly used, additionally, these two drugs were priority recommended in the guideline.

- Changes in the text: No change.

- Comment 3: General: Did you exclude patients who were on preoperative DAPT? Please give some information.

-Reply 3: Yes, we excluded patients who needed for dual antiplatelet treatment pre-CABG, and the exclusion criteria was described in Clinical Study Protocol.

- Changes in the text: No change.

- Comment 4: General: In my opinion, the biggest drawback of your study is, that you did not include a sham group of patients only receiving an ASS single platelet therapy. on page 5 line 81 you mention that single ASS provides an 80-85% patency. In the

discussion, you explain that approximately 18% of SVG failed in one year. Which would result in 82% patency rate. The patency rates of ASS+Clopi are 91.0% and ASS-Tica 89.9%. It would have been greatly beneficial to have randomized data on ASS therapy. Please explain why you excluded those patients.

-Reply 4: Actually, according to guidelines as well as our experiences, there was no patient who only received aspirin at the first one year after CABG in our department. For 30 years, antiplatelet therapy has been the gold standard for preventing saphenous vein graft closure after CABG. Aspirin is recognized as the standard of care and is generally continued indefinitely given its benefit in preventing subsequent clinical events. But 2010 Canadian guideline and 2012 Society of Thoracic Surgeons guideline recommended that in patients undergoing CABG after ACS, dual antiplatelet drugs should be restarted and that may have secondary benefit of increasing early vein graft patency.

- Changes in the text: No change.

- Comment 5: Page 7 line 116: You are excluding patients receiving perioperative platelet therapy? Please give some explanations why you exclude those patients. Have you any strategies on platelet transfusion.

-Reply 5: We just excluded patients who needed for dual antiplatelet treatment pre-CABG. In most cases, they needed for urgent revascularization. In general, we would subcutaneous inject low molecular weight heparin(LMWH) before CABG procedures.

- Changes in the text: No change.

- Comment 6: Page 8 line 143: You included on-pump and off-pump CABG. As you probably know, CPB has a great influence on blood coagulation and platelet aggregation. Were there difference on SVG patency in your between on-pump and off-pump CABG please provide the data.

-Reply 6: There had no differences of graft patency between on-pump and off-pump CABG (Odds Ratio 1.07,95%CI 0.49-2.46, P=0.81) .

- Changes in the text: We added some data (see page 22, Table 5).

- Comment 7: Page 11 line 189: Were there any differences in the patency rates of particular anastomosis? Please provide data.

-Reply 7: There had no differences of graft patency between on-pump and off-pump CABG (Odds Ratio0.86, 95%CI 0.249-2.81, P=0.77).

- Changes in the text: We added some data (see page 22, Table 5).

## **Reviewer C**

- Comment 1: Was the study registered in the clinical trials registry? If so, such information should be given.

- Reply 1: I agree with you. Unfortunately, I did not register at ClinicalTrials.gov, but register at our hospital (Number CHCS052017) , and got the permission of the Institutional Review Board of Changhai Hospital.

- Changes in the text: See page 7, line 133-135.

- Comment 2: How was the sample size determined?

- Reply 2: Sample size: According to previous studies, aspirin plus Ticagrelor has a venous graft occlusion rate of 13% one year after surgery. As for aspirin plus Clopidogrel, the rate is 3.7%. We found that a 5% difference between 2 arms can be reliably detected under a power of 80%, if we have 170 venous grafts in each arm(significance level=0.05).

- Changes in the text: We added some data in page 9, line 166-170.

- Comment 3: I see no description of the trial design

-Reply 3: Actually, the trial design was described in Clinical Study Protocol.

- Changes in the text: No changes.

- Comment 4: How was the randomization performed?

-Reply 4: Patient eligibility will be established before treatment randomization. Patients will be enrolled/randomized strictly sequentially, as patients become eligible for enrolment/randomization. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study. After providing informed consent, patients who are consistent with the inclusion and exclusion criteria will be randomly assigned to one of the three treatment groups. The randomization will be performed by a computer equally for the two treatment regimens. Randomization numbers will be assigned strictly sequentially as subjects become eligible for randomization. When a subject is allocated to a specified randomization number, the corresponding code envelope will be opened to identify the allocated treatment regimen. The information was described in Clinical Study Protocol.

- Changes in the text: No changes.

- Comment 5: What other concomitant medication was used in both groups? Statin therapy is also associated with improved graft patency.

-Reply 5: We agree with the reviewer. According to the guidelines, Statin, as the secondary prevention strategy, was used to prevent adverse cardiovascular events and death in our department.

- Changes in the text: We added some data (see page 6, line 116-118).

- Comment 6: The primary outcome was incidence of graft occlusion at one year assessed by MSCT, how was the graft quality graded? I see no mention of the method in the manuscript. Was it according to Fitzgibbon and colleagues? If so, such information should be mentioned.

-Reply 6: Graft patency was defined according to FitzGibbon criteria. Contrast filling

of the grafts, anastomoses, and coronary arteries beyond the graft were considered in each assessment. FitzGibbon grade A indicates that the graft is patent with  $\leq 50\%$  stenosis; FitzGibbon grade B indicates that the extent of graft stenosis is  $>50\%$  but not occluded; and FitzGibbon grade O indicates total occlusion of the graft without contrast filling. The information was described in Clinical Study Protocol.

- Changes in the text: We added some data (see page 10, line 185-191).

- Comment 7: As for secondary outcomes, the authors defined MACCE as incidence of cardiovascular mortality, nonfatal MI or nonfatal stroke. The authors did not define cardiovascular mortality as well as nonfatal MI or nonfatal stroke. Although cardiovascular mortality is used as an outcome in studies, all-cause mortality is considered the most robust and unbiased index in cardiovascular research because no adjudication is required, thus avoiding inaccurate or biased documentation and clinical assessments. Whereas nonfatal MI is an inappropriate endpoint and the difference between a fatal and a nonfatal MI is often the result of chance factors.... nevertheless, these endpoints should be defined.

-Reply 7: We agree with the reviewer. Actually, this information was described in in Clinical Study Protocol (see CSP page 15-17).

- Changes in the text: No changes.

- Comment 8: The authors in this study focused mainly on graft patency among different CYP2C19 phenotype groups however this was not a prespecified endpoint in the study design.

-Reply 8: We agree with the reviewer. Different CYP2C19 phenotype was not a prespecified endpoint. Theoretically, some individuals may be less responsive to clopidogrel than others, because clopidogrel is a prodrug activated by several enzymes, including CYP2C19 and common genetic variation in CYP2C19 alters enzyme activity. So we just used this study data to subanalyse the association between the CYP2C19 genotype and DAPT responsiveness, and demonstrated that there was no significant association of genotypes with graft patency for up to 1 year after elective CABG surgery.

- Changes in the text: No changes.

- Comment 9: What was the incidence of perioperative MI in both groups?

-Reply 9: The incidence of perioperative MI was described in table3, showing 1.4% in AT group and 1.3% in AC group.

- Changes in the text: No changes.

- Comment 10: Safety measure defined as bleeding events should be defined according to Bleeding Academic Research Consortium (BARC) definition

-Reply10: In our study, the incidence of bleeding events, classified by the following TIMI criteria. This information was described in in Clinical Study Protocol (see CSP page 14-15).

- Changes in the text: No changes.