

Peer Review File

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Reviewer A

Comment 1: For primary outcome, I suggested the risk of thrombosis in coronary artery is enough. The safety of dual anti-platelet drugs (aspirin plus clopidogrel) is considered as the secondary outcome.

Reply 1: Thanks for your advice, and we have revised the safety of dual anti-platelet drugs (aspirin plus clopidogrel) as the secondary outcome.

Changes in the text: We have modified our text as advised (see page 4, line127).

Comment 2: The evaluation of anti-thrombotic therapy is considered to using coronary computed tomography at 30d, 60d, 90d, 6mon, 9mon and 1y after discharge due to more scientific indicator.

Reply 2: Thanks for your advice. According to 2017 AHA scientific statement of KD, computed tomography (CT) can provide 3-dimensional visualization of the coronary arterial tree and may identify regions of stenoses more optimally than current cardiac magnetic resonance techniques, however, the radiation may limit its use when make serial studies. The time and frequency of CT use were determined according to the children's coronary arteries, medium or large CAAs of the KD patients were considered to use CT in the one-year follow-up.

Changes in the text: We modified as "Coronary computed tomography (CT) or coronary angiography will be made when the thrombosis is suspected or in the six-month during the course of the disease in this trial." (see page6, line172-174)

Comment 3: The different dosage of clopidogrel is according to CYP2C19 genotype. I think the protocol became no consistency of clopidogrel and bias developed. Perhaps, the dosage of clopidogrel is needed to be used the same dosage.

Reply 3: Thanks for your advice. It has been proved that the efficacy of clopidogrel is related to CYP2C19 genotype in clinical practice. If the same dosage of clopidogrel was used in patients with different genotype which leads to different efficacy, it will be hard to distinguish between the efficacy of clopidogrel or insufficient dosage. Therefore, in order to achieve precise treatment of clopidogrel, different dosage was given based on the genotype and platelet aggregability in this trial.

Changes in the text: We explained it in the revised version (page 7, line 207-213).

Comment 4: The exclusion criteria including KD children with small coronary artery aneurysm at the initial diagnosis is not suitable, because the coronary artery size might have the change after discharge.

Reply 4: Thanks for your advice, and we have added "6) KD patients with small CAAs at the diagnosis but extended to medium or large CAAs within one month of disease onset" in the inclusion criteria of RCT trial and excluded "KD children with

small coronary artery aneurysm” in the exclusion criteria of RCT trial.

Changes in the text: We have modified our text as advised (see page 6, line 184-185).

Comment 5: Z-score could be considered as the secondary outcome.

Reply 5: Thanks for your advice, and we have added “Measure the Z-score and compare the change of the Z-score of two groups in different time point of the one-year follow-up” in the secondary objectives and “the Z-score and compare the change of the Z-score of two groups” in the secondary outcome.

Changes in the text: We revised it as your advice (page4, line128-129 and page8, line248)

Reviewer B

Thank you for your application. Clearly a lot of thought and hard work has gone into this excellent project.

Summary: The role of dual anti-platelets in the setting of coronary artery aneurysms from Kawasaki Disease has not been defined. Recommendations for this therapy are largely based on expert opinion and data derived from the adult acute coronary syndrome population. Within this manuscript, the authors describe a randomised control trial to define the utility of DAPT in this setting.

A few points for improvement.

Comment 1: There are a few grammatical and spelling/word errors throughout the manuscript. I would suggest review by a native English speaker to correct these mistakes. For example, line 58 states "anticoagulant therapy", though clopidogrel and aspirin are in-fact anti-platelet agents.

Reply 1: We have invited a native English speaker to polish our paper as you advised.

Comment 2: There is inconsistency in the stated primary and secondary outcomes throughout the manuscript. In lines 61-62 and 115-119 there appears to be multiple primary outcomes compared to only one primary outcome in line 99. The authors should ensure that there is consistency throughout about the outcomes they wish to assess.

Reply 2: Thanks for your advice, and we modified the statements of the primary and secondary outcome throughout the manuscript to be consistent.

Changes in the text: We have modified our text as advised (see page 8, line242-270).

Comment 3: I suggest that the paragraph “Hypothesis to be tested” (Line 106-112) should be incorporated into the “Background” section of the document. Moreover, the hypothesis mentioned in line 97-99 is inconsistent with the hypothesis in 107-

112. Consistency is key.

Reply 3: Thanks for your advice, and we have incorporated “Hypothesis to be tested” (Line 106-112) into the “Background”.

Changes in the text: We have modified our text as advised (see page 4, line116-119).

Comment 4: I would recommend synthesising and combining “Statistical Analysis Plan”, “Analysis of the Primary Outcome” and “Analysis of Secondary Outcome” into one (much shorter) section.

Reply 4: Thanks for your advice, and we have synthesised and combined “Statistical Analysis Plan”, “Analysis of the Primary Outcome” and “Analysis of Secondary Outcome” into one section as “Statistical analysis plan”.

Changes in the text: We have modified our text as advised (see page 9-10, line311-326).

Comment 5: Primary and secondary outcomes are stated at multiple points throughout the text. They only need to be stated once.

Reply 5: Thanks for your advice, and we modified our paper that the primary and secondary outcomes are stated only once throughout the text.

Changes in the text: We have modified our text as advised (see page 8, line242-270).

Comment 6: It is a long manuscript. I would recommend trying your best to cut down the word count. Less is more and being comprehensive is key.

Reply 6: Thanks for your advice, and we have cut down the word count.

Comment 7: Your power calculation (resulting in a small sample size of 80) results from “preliminary experimental results” in line 311. Please elaborate on these preliminary results to support your power calculation. I personally don’t think that you have to include the formula for your power calculation in the manuscript (line 318).

Reply 7: Thanks for your advice, and we have added “for the Kawasaki disease patients with medium or large coronary artery aneurysm, 14 children were treated with aspirin and 6 of them developed thrombosis, 18 children were treated with aspirin plus clopidogrel and 3 of them developed thrombosis” and removed the formula in the manuscript in the Power and sample size.

Changes in the text: We have modified our text as advised (see page 9, line 292-302).

Overall, however, you have thought of a clinically relevant and interesting randomised trial to answer a question that no one has the answer to. This should be applauded.

Reviewer C

Thank you for the opportunity to review this exciting study protocol that measures the clinical effectiveness and safety of dual antiplatelet therapy in thromboprophylaxis. The protocol is nicely written and is concise. It has the potential to add incremental value to the growing body of evidence showing that dual antiplatelet therapy may be beneficial for patients with coronary artery aneurysm (CAA).

I have several major questions/concerns:

Comment 1: The authors state that the primary objective is to measure whether the effectiveness and safety of dual antiplatelet therapy in thromboprophylaxis. What is the effectiveness? Does that mean a reduction in the incidence of stenosis? If so, I think 1 year is too short of an observation period. Even in the literature cited by the authors (Ref.14,15,16), the incidence of stenosis within one year is minor.

Reply 1: Thanks for your advice, and the effectiveness of dual antiplatelet therapy was defined as the reduction of thrombosis formation in this trial. Mural thrombus formation in the early stage of KD does not result in coronary stenosis. We have added "If any enrolled children have medium or large coronary aneurysms after one year of observation, the follow-up period will be extended." in the time frame of the text.

Changes in the text: We have modified our text as advised (see page9, line 308-310).

Comment 2: What is the difference between the 1. of the primary objectives and the first part of 1. of the secondary objectives?

Reply 2: Thanks for your advice, and we modified the statements of the primary and secondary objectives throughout the manuscript to be consistent.

Changes in the text: We have modified our text as advised (see page 4-5, line120-141).

Comment 3: The authors include patients with medium CAAs. However, many reports have shown that only patients with giant CAAs developed stenosis (Ref 14-16, PMID: 29507955, etc.). With this study design, the authors may be able to evaluate the safety, but not the effect of suppressing stenosis.

Reply 3: Thanks for your advice, according to the 2017 AHA scientific statement of KD and related literatures, antiplatelet agents are considered to be standard in the management of KD patients with CAA. For patients with small CAA, monotherapy with low-dose ASA therapy is sufficient for prophylaxis of thrombosis. However, patients with medium and large or giant CAA, dual antiplatelet therapy, such as aspirin combined with a thienopyridine (eg, clopidogrel) was recommended in prophylaxis against coronary artery thrombosis. However, AHA scientific statement regarding antiplatelet therapy in KD with medium or giant CAAs relied on reasoning from retrospective studies, practices in atherosclerotic coronary artery disease and expert consensus (3). So

far it lacked of RCT evidences evaluating the effectiveness and safety of dual antiplatelet regimens for prophylaxis of coronary thrombosis in KD children with medium or giant CAAs.

Changes in the text: We have explained this point in the background in the text (see page 4, line 108-116).

Comment 4: The incidence of medium and giant CAAs is fairly low (Ref 3, PMID: 32454114, etc.). Is it feasible to complete the recruitment within the set research period?

Reply 4: Thanks for your advice, and we gave an explanation as follows: The morbidity of KD in Beijing region was 40.9 and 55.1 per 100 000 children under 5 years old in 2000 and 2004, respectively, and approximately 20.6% of patients with CAAs. Studies have shown that the incidence of KD has been on the rise in recent years. What is more, this is a multi-center study included 5 medical centers, which has the highest number of cardiovascular disease admissions in the region. Based on these reasons, we think it is feasible to complete the recruitment within the set research period.

Comment 5: The authors use the Z-value calculation system of Boston Children's hospital. Is the population of normal children for which the calculation system was created a good approximation of the population for which this study will be conducted? If they do not approximate, then this system for Z-score calculation cannot be used.

Reply 5: Thanks for your advice. The Z-value calculation system of Boston Children's hospital in the study of McCrindle et al. is more suitable for the American children. We changed the Z-value calculation system from Boston to Kobayashi system which derived from Japanese children whose demographic characteristics is a good approximation of the population for which this study will be conducted.

Changes in the text: We have modified our text as advised (see page 8, line260-261).

Comment 6: The authors confirm the CYP2C19 genotype, and decide on clopidogrel doses. The authors should describe the details of the genetics test. Also, what is the protection of genetic information, and how is genetic counseling conducted?

Reply 6: Thanks for your advice. We provided the details of CYP2C19 genotype test in the text and added "In order to reduce the clinical adverse events after clopidogrel was used, CYP2C19 gene detection has become a common detection method to guide clinical treatment. CYP2C19 genotypes are detected by sequencing method and gene chip generally. Detection of CYP2C19 genotypes can be used to individualize clopidogrel, which is of great significance to reduce cardiovascular mortality" in the discussion. We complied with the legal protection of genetic information in our country, and genetic counseling was conducted by

professional pharmacist.

Changes in the text: We provided the details of CYP2C19 genotype test in the text (see page 12, line 401-405).

Comment 7: The authors state “improves inflammatory conditions of KD patients”. I agree Clopidogrel may reduce inflammation. Please briefly add the evidence that the authors chose this as the objective, either here or in Discussion.

Reply 7: Thanks for your advice. 2017 AHA scientific statement of KD mentioned that KD arteriopathy included 3 pathological processes of which the second process is a subacute/chronic vasculitis characterized by an asynchronous infiltration of lymphocytes, plasma cells, and eosinophils with fewer macrophages that begins in the first 2 weeks after fever onset but can continue for months to years in a small subset of patients. Based on this pathological finding, we chose clopidogrel improving inflammatory conditions of KD patients as the objective in order to take advantage of the its dual effects with anti-platelet and anti-inflammatory.

Changes in the text: We have modified our text as advised (see page 10-11, line349-356).

Minor point:

Comment 8: How does the pediatrician diagnose gastrointestinal ulcers?

Reply 8: Gastrointestinal Endoscopy is the gold standard for the diagnosis of gastrointestinal ulcer. In this study, when the child's condition was not suitable for gastrointestinal endoscopy in the acute stage of KD, suspected diagnosis was made by the medical history and clinical symptoms, such as hematochezia, melena, hematemesis and other gastrointestinal symptoms.

Comment 9: The authors should also mention the report of Low et al., although it is a retrospective study. (PMID: 32697954 DOI: 10.1016/j.ijcard.2020.07.022)

Reply 9: Thanks for your advice, and we added “Low et al. reviewed KD patients with a medium to large CAAs receiving combination thromboprophylactic therapy (dual or triple therapy with ASA, clopidogrel, and low molecular weight heparin (LMWH) or warfarin), and concluded that the overall bleeding risk was lower in KD patients receiving combination thromboprophylaxis than single drug (17).” in the discussion.

Changes in the text: We have modified the text as advised (see page 11, line383-387).

Comment 10: References are not listed in a consistent manner.

Reply 10: We have listed references in a consistent manner in the revised version.