PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

PARIS Coronary Thrombosis Risk Score Combined With D-dimer to Guide New Oral Anticoagulant Antithrombotic Therapy in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention: Study protocol of the PRIDE-ACS trial

Authors

Jia, Sida; Song, Ying; Yuan, Deshan; Wang, Peizhi; Xu, Jingjing; Chen, Yan; Zhang, Ce; Zhao, Xueyan; Yuan, Jin-qing

VERSION 1 - REVIEW

Reviewer 1

Name Li, Qiuyu

Affiliation Center for Coronary Artery Disease, Beijing AnZhen Hospital, Capital Medical University, and Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, 100029,

Date 02-Aug-2024

COI None

This study aims to identify high ischemic risk ACS-PCI patients using D-dimer and the PARIS coronary thrombosis risk score. It investigates whether a 3-month low-dose rivaroxaban treatment on top of DAPT can reduce ischemic events without increasing bleeding risk, with MACCE as the primary endpoint.

Strengths

The study's design strengths include its multicenter, large-sample, prospective, and open-label structure, ensuring broad applicability and real-time relevance of the results. Combining rivaroxaban with standard DAPT aims to balance efficacy and safety, exploring the potential of low-dose rivaroxaban to reduce ischemic events without increasing bleeding risk. Overall, this RCT design effectively addresses common clinical issues and is a highly practical and meaningful study.

Major concerns:

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1. What is the rationale for combining D-dimer and the PARIS coronary thrombosis risk score? Have there been preliminary experiments or supporting literature? What is the basis for using a D-dimer baseline of 0.28 μg/ml as the threshold? Different centers might have varying methods and reference ranges for D-dimer testing. How will this be standardized across centers?

2. Although the authors have explained the use of clopidogrel instead of ticagrelor, I still have certain concerns. In clinical practice, some patients need ticagrelor, such as CYP2C19 poor metabolizers or those with multiple stents. Will these patients still be included with aspirin and clopidogrel or excluded from the study? If excluded, could this lead to selection bias and affect the outcomes? Additionally, it is recommended to include CYP2C19 genotyping in the baseline, as the metabolism of P2Y12 inhibitors might affect the outcome.

3. There might be differences in procedure and skill levels among PCI operators at different centers, potentially impacting outcomes like in-stent restenosis and thrombosis. Are there any selection criteria for the PCI operators? Please specify the criteria for selecting operators and the definition of PCI success for enrolled patients.

Minor concerns:

4. Please specify the methods for handling lost-to-follow-up patients and missing data.

5. It is recommended to exclude patients with conditions that might elevate D-dimer levels, such as aortic dissection, malignancies, and rheumatic diseases (e.g., vasculitis, SLE, Henoch-Schönlein purpura).

I hope these comments are helpful for improving the manuscript. Thank you for your contribution to this important area of research.

Reviewer	**2**
Name	**Katsikis, Athanasios**
Affiliation	**401 General Military Hospital of Athens, Cardiology**
Date	**12-Aug-2024**
COI	**None**

Overview

The designers of this RCT will essentially try to replicate the performance of the ATLAS-TIMI-51 trial, using however, a fixed, short-term duration of the low-dose of rivaroxaban that has been established as the dose of choice for the purpose of secondary prevention in ACS patients with no indication for anticoagulation. Although ATLAS-TIMI-51 was released more than 10 years ago, up to this day there are no new RCTs addressing the issue of low dose NOACs in ACS patients. Furthermore, the optimal long-term antithrombotic regimen in ACS patients who have undergone PCI remains unknown, despite extensive past and present research. This is very characteristically reflected on the fact that, ESC-NTEMI 2020 GLs provide a IIb recommendation for low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) in ACS patients with no prior stroke/TIA who are at high ischaemic and low bleeding risk, while ESC 2023 GLs for ACS provide no specific recommendations on the subject.

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The trial is worth conducting, in terms of providing more evidence for formatting recommendations for low dose rivaroxaban use in the population studied, but requires finetuning of its protocol, to stand a chance for fulfilling this purpose.

Major issues

Inclusion criteria

The focus is patients at high ischemic risk, while no bleeding risk assessment is performed. Strongly consider including a bleeding risk score (PRECISE-DAPT or ARC-HBR) on top of the PARIS score at baseline assessment, even if high-bleeding risk patients are not excluded for the purposes of maintaining the power calculations of the study. This will be particularly helpful for the interpretation of the results of the study.

End-points:

- There is no reference as to how the end-points will be defined. This is particularly relevant to the definition of MI. End-points are not defined in the Supplementary material/ Tables. Consult and most importantly include relevant ARC criteria (Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document – Circulation 2018 Jun 12;137(24):2635-2650).
- Since essentially all the end-points of the study are acute and will be mostly documented in the hospital-setting, what is the purpose of the regular follow-up clinic visits? I understand a potential role for τιμελυ detecting safety concerns, but I see no specific protocols for withdrawing patients from the study based on the data collected from the regular FU visits.
- How will the endpoints experienced by the patients at home or at hospitals not participating in the study be collected?
- Given that stent thrombosis definition includes ACS by default, what is the point and especially the feasibility of including ST as a separate end-point? Consider discarding it.
- Ischemic end-points include non-coronary events. Although stroke has been included in the end-points of ATLAS-TIMI 51, systemic embolism is a novel approach. Antiplatelet and anticoagulant treatment is valid for prevention of PAD-related events, but definition and documentation protocols for this very general term should be established, if it is to be used as an end-point.
- Ischemia-driven revascularization is directly related to residual ischemic disease after culprit vessel intervention. How will the researchers adjust for this potential confounder in the two groups formed? There are no angiographic data included in the scheduled data for acquisition…Also, how will patients deemed candidates for repeat PCI for severe residual CAD during the index PCI be handled. These patients usually undergo a staged procedure during the index hospitalization or shortly after and there is a need to define planned vs. unplanned PCI revascularization, if revascularization is going to be used as an endpoint.
- How will patients who are enrolled and subsequently undergo CABG be handled? For example, patient with 3VD, low EF and DM who undergoes culprit PCI because of STEMI or high risk NSTEMI. Will such a patient be excluded or censored if he/she subsequently undergoes CABG?

Power size calculations:

Researchers calculated a sample size of 3548 (1774 for each group) patients based on their assumptions. Regarding previous studies included in these assumptions, I see that these include the ATLAS-TIMI 51, but also two other trials in populations that I feel are not relevant to the present study. In ATLAS-TIMI-51, which used as a primary efficacy end point a composite of CV death, MI, or stroke, the respective rates were 8.9% and 10.7%. Given that the population of this study carries a higher ischemic risk than the ATLAS-TIMI-51, the quoted rates of 13% for the control group seem plausible, but not necessarily supported by hard evidence. Afterall, the authors themselves mention that residual ischemic risk in the ACS population undergoing PCI is between 5-10%. Can the authors indicate any specific study supporting a higher than 10% residual ischemic risk in contemporary ACS patients undergoing PCI?

Randomization

Authors mention the use of IWRS for the purpose of randomization with no further details. I would like to highlight the importance of addressing all the major factors that need to be balanced in the two groups of the study. Major, evidence based risk factors for future MACE in this population should be clearly defined by the authors before randomization and consideration should be given also to residual anatomic CAD after culprit PCI, especially if revascularization is used as an end-point. The latter is an aspect not addressed in ATLAS-TIMI-51, which nevertheless did not include revascularization as an end-point.

DDimers

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- What is the rationale for repeated measurements at 3, 6 and 12 months?
- From a diagnostic point of view, DD is a marker with high negative prognostic value and low specificity used predominately for the exclusion of pulmonary embolism or large vessel thrombosis/dissection in the ED population presenting with chest pain and/or shortness of breath. I understand that the authors aim as a side-benefit of the study to support the prognostic role of DD but I am concerned that there is no provision or mention in the eligibility criteria about the exclusion of other major causes associated with DD elevation.

Minor issues

The manuscript could benefit from a slight linguistic review, as several sentences require better wording. There is an occasional feeling, that patches of text from various different sources have been incorporated in the manuscript without the appropriate consideration for homogeneity (tenses, plural vs. singular, choice of words, text vs. bulleted format, etc) and overall linguistic standards. Examples include among others, lines 16-17 (p.6), lines 16-19 (p.7), lines 6-10 & 53-56 (p.34), numbers 6, 7 of inclusion criteria and numbers 20 & 22 of exclusion criteria.

The detailed description of the results of the trials included in the Discussion section, should be abbreviated and tailored to the nature of the present manuscript, which is reporting of a study design in ACS patients, not reporting of results of an original study in patients with either ACS or stable CAD. Discussion should focus more on what new this research will bring compared to current knowledge and why this will be important.

Reviewer	**3**
Name	**Yamaji, Kyohei**
Affiliation	**Kokura Memorial Hospital, Division of Cardiology**
Date	**17-Aug-2024**
COI	**No competing interests.**

The authors present the design of the PRIDE-ACS trial, which aims to assess the efficacy of a 3-month low-dose rivaroxaban regimen combined with standard DAPT in reducing ischemic events among high thrombotic risk ACS patients after PCI. This multi-center, open-label RCT will include approximately 4,000 patients with elevated PARIS coronary thrombosis scores and D-dimer levels. The primary outcome is Major Adverse Cardiovascular and Cerebrovascular Events (MACCE), and safety will be assessed based on BARC type 3 and 5 bleeding events.

The reviewer has the following specific concerns:

1. The authors specify that the regimen will include aspirin 75-100 mg daily for at least 3 days and clopidogrel 75 mg daily for at least 6 days prior to PCI. How will the study address the treatment of STEMI patients who have not received prior antiplatelet therapy and require primary PCI?

2. The choice of a β value of 0.20 may be considered too large given contemporary clinical research standards.

3. The modified intention-to-treat principle used in this study may introduce a risk of bias, as participants assigned to the triple antiplatelet therapy arm may be more likely to refuse participation.

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4. The rationale for including triple therapy should be discussed in the context of studies such as WOEST, RE-DUAL PCI, PIONEER AF-PCI, AUGUSTUS, and ENTRUST AF-PCI. Additionally, it is important to address that patients in this study do not have established indications for anticoagulation.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1
Major concerns:

1. What is the rationale for combining D-dimer and the PARIS coronary thrombosis risk score? Have there been preliminary experiments or supporting literature? What is the basis for using a D-dimer baseline of 0.28 μg/ml as the threshold? Different centers might have varying methods and reference ranges for D-dimer testing. How will this be standardized across centers?
Thank you for your comment. We have conducted preliminary analysis in a large cohort of Chinese patients undergoing PCI. We found D-dimer to be an independent predictor of long-term all-cause death and cardiac death. D-dimer (using 0.28 ug/mL as cutoff) significantly improves the predictive value of PARIS score over 5-year all-cause death and cardiac death. The abstract is published in JACC. 2023 Mar, 81 (8_Supplement) 1184, and the full text is now under review for publication. The threshold of 0.28 μg/ml was found in our previously published studies to be associated with increased 2-year all-cause mortality and cardiac mortality (Zhao X. et al. Ther Adv Chronic Dis 2020; 11: 2040622320904302.), as well as stent thrombosis (Zhao X. et al. European Heart Journal (2021) 42 (Supplement), 1281). In terms of testing methods of D-dimer, all centers recruiting patients are using the same measurement method as described in the methods section, eliminating the need for standardization.

2. Although the authors have explained the use of clopidogrel instead of ticagrelor, I still have certain concerns. In clinical practice, some patients need ticagrelor, such as CYP2C19 poor metabolizers or those with multiple stents. Will these patients still be included with aspirin and clopidogrel or excluded from the study? If excluded, could this lead to selection bias and affect the outcomes? Additionally, it is recommended to include CYP2C19 genotyping in the baseline, as the metabolism of P2Y12 inhibitors might affect the outcome.
Thank you for your recommendations. We agree that CYP2C19 metabolic traits would have an impact on the results, but we did not routinely test for CYP2C19 gentyping of all patients before enrollment. Patients who are on ticagrelor already does not meet eligibility of this study and therefore excluded. CYP2C19 genotyping is available in our institution, which can be included in the baseline for future analysis, but not in all participating centers.

3. There might be differences in procedure and skill levels among PCI operators at different centers, potentially impacting outcomes like in-stent restenosis and thrombosis. Are there any selection criteria for the PCI operators? Please specify the criteria for selecting operators and the definition of PCI success for enrolled patients.
Thank you for your question. In our institution, PCI operators are strictly selected by a committee of expert PCI operators. Qualifications will be given to the operators who meet specific standards on the number of years, number of cases, etc. Successful PCI is defined as achieving TIMI flow grade 3 in the target lesion after PCI.

Minor concerns:
4. Please specify the methods for handling lost-to-follow-up patients and missing data.
Thank you for your suggestion. Patients who are lost to follow-up will be censored at the last available contact. Missing values in the baseline will be imputed using single imputation or multiple imputation method as appropriate. These descriptions have now been added to the statistical analysis subsection.

5. It is recommended to exclude patients with conditions that might elevate D-dimer levels, such as aortic dissection, malignancies, and rheumatic diseases (e.g., vasculitis, SLE, Henoch-Schönlein purpura).
Thank you for your suggestion, the mentioned conditions that may cause elevated D-dimer levels are now added to exclusion criteria (Spplementary Table 1, exclusion criteria number 26)

Reviewer 2
Overview
The designers of this RCT will essentially try to replicate the performance of the ATLAS-TIMI-51 trial, using however, a fixed, short-term duration of the low-dose of rivaroxaban that has

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been established as the dose of choice for the purpose of secondary prevention in ACS patients with no indication for anticoagulation. Although ATLAS-TIMI-51 was released more than 10 years ago, up to this day there are no new RCTs addressing the issue of low dose NOACs in ACS patients. Furthermore, the optimal long-term antithrombotic regimen in ACS patients who have undergone PCI remains unknown, despite extensive past and present research. This is very characteristically reflected on the fact that, ESCNTEMI 2020 GLs provide a IIb recommendation for low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) in ACS patients with no prior stroke/TIA who are at high ischaemic and low bleeding risk, while ESC 2023 GLs for ACS provide no specific recommendations on the subject.
The trial is worth conducting, in terms of providing more evidence for formatting recommendations for low dose rivaroxaban use in the population studied, but requires finetuning of its protocol, to stand a chance for fulfilling this purpose.

Major issues

Inclusion criteria
The focus is patients at high ischemic risk, while no bleeding risk assessment is performed. Strongly consider including a bleeding risk score (PRECISE-DAPT or ARC-HBR) on top of the PARIS score at baseline assessment, even if highbleeding risk patients are not excluded for the purposes of maintaining the power calculations of the study. This will be particularly helpful for the interpretation of the results of the study.
Thank you for your suggestion. Actually, the exclusion criteria has included almost all ARC-HBR major criteria. We agree that assessing bleeding risk through bleeding risk score is more precise. Since this is already an actively recruiting study, it is not appropriate to make significant changes to inclusion criteria at this stage. We will calculate PRECISE-DAPT score for patients enrolled in our study for better interpretation of the results.

End-points:
• There is no reference as to how the end-points will be defined. This is particularly relevant to the definition of MI. End-points are not defined in the Supplementary material/ Tables. Consult and most importantly include relevant ARC criteria (Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document – Circulation 2018 Jun 12;137(24):2635-2650).
Thank you for your suggestion. Detailed endpoint definition is now available in Supplementray Table 3.

• Since essentially all the end-points of the study are acute and will be mostly documented in the hospital-setting, what is the purpose of the regular follow-up clinic visits? I understand a potential role for τιμελυ detecting safety concerns, but I see no specific protocols for withdrawing patients from the study based on the data collected from the regular FU visits.
Thank you for your question. Safety is not the only reason for clinic visits. The regular clinic follow-ups are necessary for medical reasons including testing for coagulation function (including D-dimer), blood count, urinalysis, stool analysis, as well as for research purpose such as evaluating compliance, collecting unused study drug, etc. (Supplementary Table 2)

• How will the endpoints experienced by the patients at home or at hospitals not participating in the study be collected?
During informed consent, patients are told to contact investigators should they experience adverse events, and investigators will provide necessary help to aid in their treatment. Regular telephone follow-up will also record endpoints happened at home and other hospitals.

• Given that stent thrombosis definition includes ACS by default, what is the point and especially the feasibility of including ST as a separate end-point? Consider discarding it.
Thank you for your question. We agree that patients experiencing stent thrombosis events manifest as ACS, but not all ACS are caused by ST. The reasons for setting ST as an independent secondary endpoint is as follows: First, to assess the safety of PCI and stenting for high-ischemic risk patients; Second, to assess the efficacy of triple antiplatelet therapy in reducing ST events. We think it adds clinical value to our study results.

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• Ischemic end-points include non-coronary events. Although stroke has been included in the end-points of ATLASTIMI 51, systemic embolism is a novel approach. Antiplatelet and anticoagulant treatment is valid for prevention of PAD-related events, but definition and documentation protocols for this very general term should be established, if it is to be used as an end-point.

Thank you for your question. Systemic Embolism is defined as sudden loss of extremity and organ perfusion with clinical and objective evidence (See details and reference in the updated Supplementary Table 3).

• Ischemia-driven revascularization is directly related to residual ischemic disease after culprit vessel intervention. How will the researchers adjust for this potential confounder in the two groups formed? There are no angiographic data included in the scheduled data for acquisition…Also, how will patients deemed candidates for repeat PCI for severe residual CAD during the index PCI be handled. These patients usually undergo a staged procedure during the index hospitalization or shortly after and there is a need to define planned vs. unplanned PCI revascularization, if revascularization is going to be used as an endpoint.

Thank you for your questions. Revascularization was defined as ischemia-driven if it was associated with any of the following: Angiography Core Laboratory (ACL) reported QFR or field reported FFR ⩽ 0 80 or iFR ⩽ 0 89; Patients with ischemic symptoms or positive non-invasive functional tests, quantitative coronary angiography [QCA] showed stenosis ⩾50% in diameter; Patients with no ischemic symptoms or positive non-invasive functional tests with ⩾70% stenosis of lesion diameter by QCA. If patients are deemed necessary for repeat PCI for residual CAD, patients will be advised to either stay in the hospital until a repeat PCI is performed (usually within 1 week) or discharge and return for re-admission for planned repeat PCI after a certain amount of time. If a patient experience severe ischemic events before the planned repeat PCI, the repeat revascularization will still be considered ischmia-driven. That is to say, the majority of residual CAD after index culprit lesion PCI would be relatively stable and therefore not lead to unplanned ischemia-driven revascularization.

• How will patients who are enrolled and subsequently undergo CABG be handled? For example, patient with 3VD, low EF and DM who undergoes culprit PCI because of STEMI or high risk NSTEMI. Will such a patient be excluded or censored if he/she subsequently undergoes CABG?

Thank you for your questions. CABG candidates who underwent culprit PCI will be excluded if they are scheduled for a later CABG surgery, as the antithrombotic regimen will need to comply with surgical demand. Enrolled patients will be withdrawn from the study if CABG is performed and considered not ischemia-driven (which is rare) before the completion of our study. If the CABG surgery is considered ischemia-driven, the primary endpoint is met.

Power size calculations:

Researchers calculated a sample size of 3548 (1774 for each group) patients based on their assumptions. Regarding previous studies included in these assumptions, I see that these include the ATLAS-TIMI 51, but also two other trials in populations that I feel are not relevant to the present study. In ATLAS-TIMI-51, which used as a primary efficacy end point a composite of CV death, MI, or stroke, the respective rates were 8.9% and 10.7%. Given that the population of this study carries a higher ischemic risk than the ATLAS-TIMI-51, the quoted rates of 13% for the control group seem plausible, but not necessarily supported by hard evidence. Afterall, the authors themselves mention that residual ischemic risk in the ACS population undergoing PCI is between 5-10%. Can the authors indicate any specific study supporting a higher than 10% residual ischemic risk in contemporary ACS patients undergoing PCI?

Thank you for your question. Our sample size calculation is based on several contemporary trials as well as estimation from our own cohort of Chinese patients undergoing PCI. In addition to ATLAS TIMI-51 trial, the CREATIVE trial reported a 12-month MACE incidence of 13% in the control group (DAPT), and 6.8% in the experiment group (DAPT+cilostazol). See reference here: Tang YD, Wang W, Yang M, Zhang K, Chen J, Qiao S, Yan H, Wu Y, Huang X, Xu B, Gao R, Yang

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Y; CREATIVE Investigators. Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol Versus Standard Dual Antiplatelet in Patients With High Posttreatment Platelet Reactivity: Results of the CREATIVE Trial. Circulation. 2018 May 22;137(21):2231-2245.

Randomization

Authors mention the use of IWRS for the purpose of randomization with no further details. I would like to highlight the importance of addressing all the major factors that need to be balanced in the two groups of the study. Major, evidence based risk factors for future MACE in this population should be clearly defined by the authors before randomization and consideration should be given also to residual anatomic CAD after culprit PCI, especially if revascularization is used as an end-point. The latter is an aspect not addressed in ATLAS-TIMI-51, which nevertheless did not include revascularization as an end-point.

Thank you for your comments. We have now added text addressing major risk factors balanced by IWRS method (Methods section, Allocation and Interventions subsection, 2nd paragraph). Since planned revascularization is not an endpoint, which typically happens during the index hospital stay or after a relatively short period after index PCI, there is no need to address residual anatomic CAD after culprit PCI.

DDimers

• What is the rationale for repeated measurements at 3, 6 and 12 months?

Thank you for your question. Repeated measurement of D-dimer is carried out for the following reasons: First, for research purpose, to measure the effect of antithrombotic therapy and later investigate if the fluctuation of D-dimer levels are associated with ischemic events. Second, for medical purpose, as part of a routine check-up after PCI, to rule out potential DVT/PE.

• From a diagnostic point of view, DD is a marker with high negative prognostic value and low specificity used predominately for the exclusion of pulmonary embolism or large vessel thrombosis/dissection in the ED population presenting with chest pain and/or shortness of breath. I understand that the authors aim as a sidebenefit of the study to support the prognostic role of DD but I am concerned that there is no provision or mention in the eligibility criteria about the exclusion of other major causes associated with DD elevation.

Thank you for your questions. Major causes for D-dimer elevation is now added to the exclusion criteria (Supplementary Table 1, exclusion criteria number 26).

Minor issues

The manuscript could benefit from a slight linguistic review, as several sentences require better wording. There is an occasional feeling, that patches of text from various different sources have been incorporated in the manuscript without the appropriate consideration for homogeneity (tenses, plural vs. singular, choice of words, text vs. bulleted format, etc) and overall linguistic standards. Examples include among others, lines 16-17 (p.6), lines 16-19 (p.7), lines 6-10 & 53-56 (p.34), numbers 6, 7 of inclusion criteria and numbers 20 & 22 of exclusion criteria.

Thank you for your suggestion. We apologize for the linguistic errors and have made corresponding changes in the text listed above. We have reviewed the manuscript for linguistic errors to improve readability.

The detailed description of the results of the trials included in the Discussion section, should be abbreviated and tailored to the nature of the present manuscript, which is reporting of a study design in ACS patients, not reporting of results of an original study in patients with either ACS or stable CAD. Discussion should focus more on what new this research will bring compared to current knowledge and why this will be important.

Thank you for your suggestions. We have now abbreviated non-essential results of previous studies and kept those key study results closely related to the design of our study in the discussion. We hope this would better highlight the importance of our study design.

Reviewer 3

The reviewer has the following specific concerns:

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1. The authors specify that the regimen will include aspirin 75-100 mg daily for at least 3 days and clopidogrel 75 mg daily for at least 6 days prior to PCI. How will the study address the treatment of STEMI patients who have not received prior antiplatelet therapy and require primary PCI?
Thank you for your question. For STEMI patients not previously on antiplatelet therapy, they will be given a loading dose of DAPT, followed by the maintenance dose. However, if patients receive ticagrelor instead of clopidogrel as the P2Y12 inhibitor, they're not eligible for our study, as our study requires asipirin+clopidogrel as the baseline DAPT regimen (See Discussion Paragraph 5 for explanation). By the time a patient is eligible for inclusion, they must be symtomatically stablized for at least 1 day (after their loading dose of DAPT is given), so the choice of DAPT regimen would not be affected by our study.

2. The choice of a β value of 0.20 may be considered too large given contemporary clinical research standards.

Thank you for your question. Before setting the beta-value of statistical analysis, we consulted our statisticians and referred to several contemporary trials, including the CREATIVE trial (in which the beta-value is also 0.20), the 0.20 was finally adopted as suggested by the statisticians. If preferred by the editors, we can change the β value to a smaller value.

3. The modified intention-to-treat principle used in this study may introduce a risk of bias, as participants assigned to the triple antiplatelet therapy arm may be more likely to refuse participation.
Thank you for your suggestion. We agree that patients randomized to TAT group have a higher tendency of dropping out after informed consent, introducing a potential bias. We have changed modified intention-to treat principle to the standard intention to treat principle.

4. The rationale for including triple therapy should be discussed in the context of studies such as WOEST, RE-DUAL PCI, PIONEER AF-PCI, AUGUSTUS, and ENTRUST AF-PCI. Additionally, it is important to address that patients in this study do not have established indications for anticoagulation.
Thank you for your suggestions. First, in patients indicated for anticoagulation such as atrial fibrillation, the mentioned studies have investigated the efficacy and safety between different triple antiplatelet therapies and alternative antithrombotic regimens (dual pathway inhibition vs. low-dose rivaroxaban and DAPT). We agree that these studies are worthy to be mentioned in the context of our study on ACS PCI population. They have now been added to the second paragraph in the discussion part of our manuscript. Second, patients with clinical indication for PCI are excluded from our study according to the exclusion criteria number 20 (Supplementary Table 1).

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Li, Qiuyu**
Affiliation	**Center for Coronary Artery Disease, Beijing AnZhen Hospital, Capital Medical University, and Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, 100029,**
Date	**13-Oct-2024**
COI	

I have no further comment.

Reviewer	**2**
Name	**Katsikis, Athanasios**
Affiliation	**401 General Military Hospital of Athens, Cardiology**

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Date 30-Oct-2024

COI

Major issues

Inclusion criteria

C1: The focus is patients at high ischemic risk, while no bleeding risk assessment is performed. Strongly consider including a bleeding risk score (PRECISE-DAPT or ARC-HBR) on top of the PARIS score at baseline assessment, even if high bleeding risk patients are not excluded for the purposes of maintaining the power calculations of the study. This will be particularly helpful for the interpretation of the results of the study.

A1: Thank you for your suggestion. Actually, the exclusion criteria has included almost all ARC-HBR major criteria. We agree that assessing bleeding risk through bleeding risk score is more precise. Since this is already an actively recruiting study, it is not appropriate to make significant changes to inclusion criteria at this stage. We will calculate PRECISE-DAPT score for patients enrolled in our study for better interpretation of the results.

C2: It is slightly awkward that the authors are submitting a study design for review and approval, but have already started conducting the trial. Any RCT needs to be registered before data collection begins and I understand that the trial was registered quite some time ago (26 Nov 22) with ClinicalTrials.gov, but registration is best done through protocol publication. Nevertheless, PRECISE-DAPT score can still be calculated for all patients at baseline from the data that will be collected, as per the study's protocol. Based on the exclusion criteria of the study, almost all patients with very high bleeding risk (based on history of bleeding, active bleeding-predisposing conditions and significant derangements in bleeding-related biochemical parameters) as well as most high bleeding risk patients will be excluded. Still, formal, quantitative bleeding risk assessment of the patients that will be eventually enrolled will be greatly beneficial for the interpretation and clinical applicability of the results of the study. For example, a patient not falling under any of the exclusion criteria, with eGFR of 40 ml/min, Hb of 11,2 g/dl, and aged 65 years would have been well enrolled in the study, but would qualify for high bleeding risk based on a DAPT SCORE of 34. A significant proportion of such patients in the study, could either explain a potential failure to achieve the safety endpoint while achieving the primary efficacy endpoint or surprisingly show that the antithrombotic regimen used is both safe and effective regardless of baseline DAPT score, by means of DPAT stratified analysis. In conclusion, I strongly believe that DAPT score should be calculated for all patients retrospectively, secondary analyses of efficacy and safety endpoints based on DAPT score should be performed and the above should be mentioned in the Methods section.

End-points:

C1: There is no reference as to how the end-points will be defined. This is particularly relevant to the definition of MI. End-points are not defined in the Supplementary material/ Tables. Consult and most importantly include relevant ARC criteria (Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document – Circulation 2018 Jun 12;137(24):2635-2650).

A1: Thank you for your suggestion. Detailed endpoint definition is now available in Supplementray Table 3.

C2: In the added Endpoint definition Table provided, please: Discard the term "in detail" everywhere that is used. Correct description of systemic embolism events to "Sudden loss of extremity OR organ perfusion with clinical and objective evidence". Remove MACCE definition from the Table, this term is defined by the individual components. Use brief descriptions, not only reference sources for stroke and MI. As far as MI concerns, the trial obviously refers to types 1-3 MIs. Include definition of unplanned IDR (which is the one to be used as an end-point) on top of IDR (see related comment below also).

C1: Since essentially all the end-points of the study are acute and will be mostly documented in the hospital-setting, what is the purpose of the regular follow-up clinic visits? I understand a potential role for

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timely detecting safety concerns, but I see no specific protocols for withdrawing patients from the study based on the data collected from the regular FU visits.
A1: Thank you for your question. Safety is not the only reason for clinic visits. The regular clinic follow- ups are necessary for medical reasons including testing for coagulation function (including D- dimer), blood count, urinalysis, stool analysis, as well as for research purpose such as evaluating compliance, collecting unused study drug, etc. (Supplementary Table 2)
C2: There is no description in the manuscript about how the interim results of the parameters measured will be used and no mention about potential impact of these results in the eligibility of the patients to continue the study protocol (p.e. what will be the fate of a patient who started with a baseline Hb of 13 g/dL and is discovered to have an Hb of 9g/dL at 3 months with no macroscopic bleeding?). The purposes for choosing to measure the parameters that will be measured should be briefly (namely) mentioned (safety checks for patients' premature withdrawal, secondary analyses of outcomes, logistic reasons, etc) especially if some of these parameters will be considered for secondary analyses of the outcomes (p.e degree of compliance, Hb changes).

C1: How will the endpoints experienced by the patients at home or at hospitals not participating in the study be collected?
A1: During informed consent, patients are told to contact investigators should they experience adverse events, and investigators will provide necessary help to aid in their treatment. Regular telephone follow-up will also record endpoints happened at home and other hospitals.
C2: A brief mention about handling of endpoint related events in non-study participating centers, in line with the reply to this comment, should be included in the manuscript.

C1: Given that stent thrombosis definition includes ACS by default, what is the point and especially the feasibility of including ST as a separate end-point? Consider discarding it.
A1: Thank you for your question. We agree that patients experiencing stent thrombosis events manifest as ACS, but not all ACS are caused by ST. The reasons for setting ST as an independent secondary endpoint is as follows: First, to assess the safety of PCI and stenting for high-ischemic risk patients; Second, to assess the efficacy of triple antiplatelet therapy in reducing ST events. We think it adds clinical value to our study results.
C2: In terms of the primary end-point individual components, there is absolutely no meaning in including both ST and MI/death, as the former is a subset of the latter and its inclusion will have no numerical effect. Please remove it from the primary endpoint. For the purposes of additional analyses based on ST, I agree with the rationale of including it as a secondary standalone endpoint, but if the authors are willing to go down this road, it is advised to opt for including all forms of ST (definite, probable, possible) in this endpoint and clarify that in the endpoints Table.

A1: Ischemic end-points include non-coronary events. Although stroke has been included in the end-points of ATLASTIMI 51, systemic embolism is a novel approach. Antiplatelet and anticoagulant treatment is valid for prevention of PAD-related events, but definition and documentation protocols for this very general term should be established, if it is to be used as an end-point.
C1: Thank you for your question. Systemic Embolism is defined as sudden loss of extremity and organ perfusion with clinical and objective evidence (See details and reference in the updated Supplementary Table 3).
C2: Addressed in previous comment.

C1: Ischemia-driven revascularization is directly related to residual ischemic disease after culprit vessel intervention. How will the researchers adjust for this potential confounder in the two groups formed? There are no angiographic data included in the scheduled data for acquisition…Also, how will patients deemed candidates for repeat PCI for severe residual CAD during the index PCI be handled. These patients usually undergo a staged procedure during the index hospitalization or shortly after and there is a need to define

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planned vs. unplanned PCI revascularization, if revascularization is going to be used as an endpoint.
A1: Revascularization was defined as ischemia-driven if it was associated with any of the following: Angiography Core Laboratory (ACL) reported QFR or field reported FFR ≤ 0 80 or iFR ≤ 0 89; Patients with ischemic symptoms or positive non-invasive functional tests, quantitative coronary angiography [QCA] showed stenosis ≥ 50% in diameter; Patients with no ischemic symptoms or positive non-invasive functional tests with ≥70% stenosis of lesion diameter by QCA. If patients are deemed necessary for repeat PCI for residual CAD, patients will be advised to either stay in the hospital until a repeat PCI is performed (usually within 1 week) or discharge and return for re-admission for planned repeat PCI after a certain amount of time. If a patient experience severe ischemic events before the planned repeat PCI, the repeat revascularization will still be considered ischmia-driven. That is to say, the majority of residual CAD after index culprit lesion PCI would be relatively stable and therefore not lead to unplanned ischemia-driven revascularization.
C2: Please re-read the comment and try to understand it. I did not ask for the definition of ischemia-driven revascularization (IDR), nor for the logistics of the care of the patients undergoing repeat procedures. Furthermore, authors provided a definition of IDR in the end-points Table that introduces further questions and concerns, as they now mention an Angiography Core Laboratory which was not included in the design of the former version of the manuscript. Actually, there is no information about baseline angiographic data collection at all, not to mention how these data will be handled in terms of functionally or anatomically significant residual stenoses. In general, IDR is considered as a weak endpoint and, when used, it is common practice to use unplanned IDR, instead of simply IDR. This practice, a most recent prime example of which can be found in the MULTISTARS AMI trial (DOI: 10.1056/NEJMoa2307823), simplifies end-point adjudication and reduces inhomogeneity of trial groups as far as revascularization concerns. I suggest that, if the authors insist on using IDR as an endpoint, to only use unplanned IDR in the composite, and clarify that any IDR triggered by the baseline angiographic results within a specific period after the culprit vessel index procedure (1-3 months) will not count as an end-point related event.

C1: How will patients who are enrolled and subsequently undergo CABG be handled? For example, patient with 3VD, low EF and DM who undergoes culprit PCI because of STEMI or high risk NSTEMI. Will such a patient be excluded or censored if he/she subsequently undergoes CABG?
A1: Thank you for your questions. CABG candidates who underwent culprit PCI will be excluded if they are scheduled for a later CABG surgery, as the antithrombotic regimen will need to comply with surgical demand. Enrolled patients will be withdrawn from the study if CABG is performed and considered not ischemia-driven (which is rare) before the completion of our study. If the CABG surgery is considered ischemia-driven, the primary endpoint is met.
C2: Part of this comment was addressed here, another part is discussed in the previous comment. Add a brief comment about the fate of the patients undergoing CABG after PCI in the main text or the eligibility criteria supplement.

Power size calculations:
C1: Researchers calculated a sample size of 3548 (1774 for each group) patients based on their assumptions. Regarding previous studies included in these assumptions, I see that these include the ATLAS-TIMI 51, but also two other trials in populations that I feel are not relevant to the present study. In ATLAS-TIMI-51, which used as a primary efficacy end point a composite of CV death, MI, or stroke, the respective rates were 8.9% and 10.7%. Given that the population of this study carries a higher ischemic risk than the ATLAS-TIMI-51, the quoted rates of 13% for the control group seem plausible, but not necessarily supported by hard evidence. After all, the authors themselves mention that residual ischemic risk in the ACS population undergoing PCI is between 5-10%. Can the authors indicate any specific study supporting a higher than 10% residual ischemic risk in contemporary ACS patients undergoing PCI?
A1: Thank you for your question. Our sample size calculation is based on several contemporary trials as well as estimation from our own cohort of Chinese patients undergoing PCI. In addition to ATLAS TIMI-51 trial, the CREATIVE trial reported a 12-month MACE incidence of 13% in the control group (DAPT), and

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6.8% in the experiment group (DAPT+cilostazol). See reference here: Tang YD, Wang W, Yang M, Zhang K, Chen J, Qiao S, Yan H, Wu Y, Huang X, Xu B, Gao R, Yang Y; CREATIVE Investigators. Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol Versus Standard Dual Antiplatelet in Patients With High Posttreatment Platelet Reactivity: Results of the CREATIVE Trial. Circulation. 2018 May 22;137(21):2231-2245.
A2: Although CREATIVE trial involved patients with confirmed low responsiveness to clopidogrel hence, not fully applicable to this study's population, in the broader sense it provides some support for a high of 13% as far as MACE concern in high ischemic risk populations in general. It will suffice.

Randomization
C1: Authors mention the use of IWRS for the purpose of randomization with no further details. I would like to highlight the importance of addressing all the major factors that need to be balanced in the two groups of the study. Major, evidence based risk factors for future MACE in this population should be clearly defined by the authors before randomization and consideration should be given also to residual anatomic CAD after culprit PCI, especially if revascularization is used as an end-point. The latter is an aspect not addressed in ATLAS-TIMI-51, which nevertheless did not include revascularization as an end-point.
A1: Thank you for your comments. We have now added text addressing major risk factors balanced by IWRS method (Methods section, Allocation and Interventions subsection, 2nd paragraph). Since planned revascularization is not an endpoint, which typically happens during the index hospital stay or after a relatively short period after index PCI, there is no need to address residual anatomic CAD after culprit PCI.
C2: Instead of adding this meaningless extra text regarding the IWRS (I suggest to keep the initial form of the text), authors should provide in the supplement, the parameters that they feel that need to be balanced among the two groups, as far as risk factors concern, along with a reference about this system's prior use, if available. The issue of planned PCI has been settled in previous comments.

DDimers
C1: What is the rationale for repeated measurements at 3, 6 and 12 months?
A1: Thank you for your question. Repeated measurement of D-dimer is carried out for the following reasons: First, for research purpose, to measure the effect of antithrombotic therapy and later investigate if the fluctuation of D-dimer levels are associated with ischemic events. Second, for medical purpose, as part of a routine check-up after PCI, to rule out potential DVT/PE.
C2: I am not aware of any literature supporting these rationales, which seem arbitrary at least. If the authors plan to perform secondary analyses using DD fluctuations, they should include this plan in the methods section, along with some kind of reference supporting a basis for using DD for anti-thorombotic efficacy monitoring. There is absolutely no indication for routinely measuring DD after PCI in asymptomatic patients to rule out DVT/PE.

C1: From a diagnostic point of view, DD is a marker with high negative prognostic value and low specificity used predominately for the exclusion of pulmonary embolism or large vessel thrombosis/dissection in the ED population presenting with chest pain and/or shortness of breath. I understand that the authors aim as a side benefit of the study to support the prognostic role of DD but I am concerned that there is no provision or mention in the eligibility criteria about the exclusion of other major causes associated with DD elevation.
A1: Thank you for your questions. Major causes for D-dimer elevation is now added to the exclusion criteria (Supplementary Table 1, exclusion criteria number 26).
C2: Comment properly addressed

Minor issues
C1: The manuscript could benefit from a slight linguistic review, as several sentences require better wording. There is an occasional feeling, that patches of text from various different sources have been incorporated in the manuscript without the appropriate consideration for homogeneity (tenses, plural vs. singular, choice of words, text vs. bulleted format, etc) and overall linguistic standards. Examples include

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among others, lines 16-17 (p.6), lines 16- 19 (p.7), lines 6-10 & 53-56 (p.34), numbers 6, 7 of inclusion criteria and numbers 20 & 22 of exclusion criteria.
A1: Thank you for your suggestion. We apologize for the linguistic errors and have made corresponding changes in the text listed above. We have reviewed the manuscript for linguistic errors to improve readability.
C2: Comment properly addressed

C1: The detailed description of the results of the trials included in the Discussion section, should be abbreviated and tailored to the nature of the present manuscript, which is reporting of a study design in ACS patients, not reporting of results of an original study in patients with either ACS or stable CAD. Discussion should focus more on what new this research will bring compared to current knowledge and why this will be important.
A1: Thank you for your suggestions. We have now abbreviated non-essential results of previous studies and kept those key study results closely related to the design of our study in the discussion. We hope this would better highlight the importance of our study design.
Comment properly addressed.

Reviewer	**3**
Name	**Yamaji, Kyohei**
Affiliation	**Kokura Memorial Hospital, Division of Cardiology**
Date	**18-Oct-2024**
COI	

While the authors have responded to my previous comments, they have not yet incorporated these changes into the revised manuscript. Specifically, there is still a lack of clarity regarding the inclusion of patients who have not received aspirin for at least 3 days and clopidogrel for at least 6 days. The authors should explicitly state whether such patients will be included in the study. Additionally, the manuscript should provide a detailed description of the protocol for managing STEMI patients who present without prior antiplatelet therapy and require urgent PCI.

Furthermore, while the authors have addressed the concern regarding the β-value, I continue to find a β-value of 0.20 to be too large. Although this decision will ultimately rest with the editors, I recommend that the authors reconsider adopting a lower β-value in line with current standards in clinical trials.

Reviewer	**4**
Name	**Offorha, Bright Chiemezie**
Affiliation	**The University of Sheffield, School of Health and Related Research**
Date	**20-Nov-2024**

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COI **None**

Thank you for the opportunity to review this interesting paper. I commend the authors for their efforts and thoughtfulness. I have major concerns regarding the statistical aspects of the study. Generally, I would recommend that the investigators rely on any good statistical guideline like the ICH E9 (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf). Please find my comments and suggestions below:

1. Maintain consistency in using a "randomised controlled trial (RCT)" instead of a "randomised clinical trial." The latter is more appropriate since the study is controlled (i.e., has a control group) (line 50, page 5; throughout the manuscript).

2. Study setting and eligibility criteria: Specify what centres are, such as hospitals, care homes, primary care, community etc. Consider briefly stating the inclusion and exclusion criteria in the main body of the manuscript for complete reporting.

3. Allocation and Intervention: Consider separating this section into separate sections. It would be clearer to have randomisation and allocation as one section, and intervention and control as another. Regardless of the open nature of this trial, some elements of blinding can still be introduced to enhance the trial's validity. Start by ensuring that a different investigator, who is not involved with other aspects of the trial (like randomisation scheduling) conducts the allocation of treatments. The investigators should also consider making it impossible for the treatment allocator to know the next treatment allocation in advance (known as allocation concealment). Clearly state if this has been considered for reproducibility.

4. Randomisation and stratification: Elements of blinding/masking can also be introduced in the randomisation process by ensuring that the person in charge is not involved in other aspects of the trial. The randomisation schedule wasn't mentioned; this will also enhance blinding. How will the randomisation schedule be generated and handled? The investigators mentioned IWRS, more information should be provided regarding how it will handle the randomisation schedule. It is generally recommended (ICH E9) that for trials with many centres, randomisation (randomisation scheme) should be centre-specific (stratified randomisation) but allocation should be centrally conducted. This means that each centre will have a separate randomisation schedule. Also, the person handling the allocation should not have access to this schedule in advance, the next allocation should only be made known to the patient allocator after a patient has been recruited.

5. Outcomes: I think more information is needed regarding the outcomes in general and specifically the primary endpoint. I struggled to understand whether the primary endpoint was binary or time-to-event. This confusion also impacted the sample size/power calculation and statistical analysis.

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6. Sample size/power calculation: The content of this section points towards a power calculation rather than a sample size calculation. The investigator should reword this section to help readers grasp the message easily. I presume the primary endpoint is a time-to-event endpoint since Cox PH is proposed. However, the current sample size calculation does not reflect this, the investigator should consider revising the sample size/power calculation to match the sample size/power calculation for a time-to-event endpoint.

7. Statistical methods: Be specific on how missing data will be handled, multiple imputation is generally recommended (lines 17-19, page 8). The baseline covariates to be adjusted for in the adjusted models weren't mentioned. In a trial like this with many centres, it's more plausible that the centres would estimate different treatment effects - how will this be handled? In other words, how will the centre effect be addressed? Especially when randomisation is centre-specific (i.e., stratified), it is recommended to adjust for this effect. Finally, what is the alternative if the Cox PH assumption is violated?

8. Limitations: If the above concerns are addressed then the impact of the challenging nature of open-label design would have been minimised, which should be captured in the study's limitations.

VERSION 2 - AUTHOR RESPONSE

Reviewer: 1
Dr. Qiuyu Li, Center for Coronary Artery Disease, Beijing AnZhen Hospital, Capital Medical University, and Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, 100029,
Comments to the Author:

I have no further comment.

Reviewer: 3

Dr. Kyohei Yamaji, Kokura Memorial Hospital
Comments to the Author:
While the authors have responded to my previous comments, they have not yet incorporated these changes into the revised manuscript. Specifically, there is stillv a lack of clarity regarding the inclusion of patients who have not received aspirin for at least 3 days and clopidogrel for at least 6 days. The authors should explicitly state whether such patients will be included in the study. Additionally, the manuscript should provide a detailed description of the protocol for managing STEMI patients who present without prior antiplatelet therapy and require urgent PCI.

Response: Thank you for your suggestion. We have now revised the text in the first paragraph in Allocation and Interventions subsection of the Methods section to address the issues. "Patients who are not on long-term DAPT will still be eligible after receiving a loading dose, which contains aspirin 300 mg and clopidogrel 300 mg before PCI, followed by aspirin 75-100 mg and clopidogrel 75 mg orally once daily. For patients presenting as ST Elevation Myocardial Infarction indicated for urgent PCI but not previously on DAPT, they will be screened for eligibility after loading dose DAPT administration and stabilization of initial symptoms."

Furthermore, while the authors have addressed the concern regarding the β-value, I continue to find a β-value of 0.20 to be too large. Although this decision will ultimately rest

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with the editors, I recommend that the authors reconsider adopting a lower β-value in line with current standards in clinical trials.
Response: Thank you for your comments. We agree that reducing beta value would improve the credibility of our outcomes, so we have considered reducing beta value to 0.10 or 0.15. Nevertheless, after re-estimating the sample size, this will significantly increase the sample size required to meet the statistical power, which is not feasible based on the current volume of eligible patients.

Reviewer: 2

Dr. Athanasios Katsikis, 401 General Military Hospital of Athens
Comments to the Author:
Major issues
Inclusion criteria
C1: The focus is patients at high ischemic risk, while no bleeding risk assessment is performed. Strongly consider including a bleeding risk score (PRECISE-DAPT or ARC-HBR) on top of the PARIS score at baseline assessment, even if high bleeding risk patients are not excluded for the purposes of maintaining the power calculations of the study. This will be particularly helpful for the interpretation of the results of the study.
A1: Thank you for your suggestion. Actually, the exclusion criteria has included almost all ARC-HBR major criteria. We agree that assessing bleeding risk through bleeding risk score is more precise. Since this is already an actively recruiting study, it is not appropriate to make significant changes to inclusion criteria at this stage. We will calculate PRECISE-DAPT score for patients enrolled in our study for better interpretation of the results.
C2: It is slightly awkward that the authors are submitting a study design for review and approval, but have already started conducting the trial. Any RCT needs to be registered before data collection begins and I understand that the trial was registered quite some time ago (26 Nov 22) with ClinicalTrials.gov, but registration is best done through protocol publication. Nevertheless, PRECISE-DAPT score can still be calculated for all patients at baseline from the data that will be collected, as per the study's protocol. Based on the exclusion criteria of the study, almost all patients with very high bleeding risk (based on history of bleeding, active bleeding-predisposing conditions and significant derangements in bleedingrelated biochemical parameters) as well as most high bleeding risk patients will be excluded. Still, formal, quantitative bleeding risk assessment of the patients that will be eventually enrolled will be greatly beneficial for the interpretation and clinical applicability of the results of the study. For example, a patient not falling under any of the exclusion criteria, with eGFR of 40 ml/min, Hb of 11,2 g/dl, and aged 65 years would have been well enrolled in the study, but would qualify for high bleeding risk based on a DAPT SCORE of 34. A significant proportion of such patients in the study, could either explain a potential failure to achieve the safety endpoint while achieving the primary efficacy endpoint or surprisingly show that the antithrombotic regimen used is both safe and effective regardless of baseline DAPT score, by means of DPAT stratified analysis. In conclusion, I strongly believe that DAPT score should be calculated for all patients retrospectively, secondary analyses of efficacy and safety endpoints based on DAPT score should be performed and the above should be mentioned in the Methods section.
Response: Thank you for your suggestions. We agree that calculating PRECISE-DAPT score for all recruited patients is feasible and will be beneficial for results interpretation. Based on your suggestion, PRECISE-DAPT score will be calculated for all patients retrospectively for secondary analysis. We have added corresponding text as a new paragraph to the Statistical Methods subsection in the Methods section.
Additionally, PRECISE-DAPT score[11] will be calculated for all patients retrospectively for quantitative bleeding risk assessment. Secondary analysis of primary, secondary and safety endpoints will be performed based on PRECISE-DAPT score.

End-points:
C1: There is no reference as to how the end-points will be defined. This is particularly

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relevant to the definition of MI. End-points are not defined in the Supplementary material/ Tables. Consult and most importantly include relevant ARC criteria (Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document – Circulation 2018 Jun 12;137(24):2635-2650).
A1: Thank you for your suggestion. Detailed endpoint definition is now available in Supplementray Table 3.
C2: In the added Endpoint definition Table provided, please: Discard the term "in detail" everywhere that is used. Correct description of systemic embolism events to "Sudden loss of extremity OR organ perfusion with clinical and objective evidence". Remove MACCE definition from the Table, this term is defined by the individual components. Use brief descriptions, not only reference sources for stroke and MI. As far as MI concerns, the trial obviously refers to types 1-3 MIs. Include definition of unplanned IDR (which is the one to be used as an end-point) on top of IDR (see related comment below also).
Response: Thank you for your suggestions. We have now updated the Endpoint definition Table in the supplementary materials according to your suggestions. Additionally, we also removed NACE definition, which is also a combination of other endpoints. In terms of IDR, we apologize for the confusion, but we thought unplanned revascularization and IDR were the same thing. After reading the MULTISTARS AMI trial manuscript as you mentioned in a comment below, we realized "unplanned IDR" is the accurate word. Therefore, we have replaced IDR with unplanned IDR in throughout the manuscript to avoid any further confusion. The definition of unplanned IDR in our study is in line with the one used in MULTISTARS AMI trial.

C1: Since essentially all the end-points of the study are acute and will be mostly documented in the hospital-setting, what is the purpose of the regular follow-up clinic visits? I understand a potential role for timely detecting safety concerns, but I see no specific protocols for withdrawing patients from the study based on the data collected from the regular FU visits.
A1: Thank you for your question. Safety is not the only reason for clinic visits. The regular clinic follow- ups are necessary for medical reasons including testing for coagulation function (including D- dimer), blood count, urinalysis, stool analysis, as well as for research purpose such as evaluating compliance, collecting unused study drug, etc. (Supplementary Table 2)
C2: There is no description in the manuscript about how the interim results of the parameters measured will be used and no mention about potential impact of these results in the eligibility of the patients to continue the study protocol (p.e. what will be the fate of a patient who started with a baseline Hb of 13 g/dL and is discovered to have an Hb of 9g/dL at 3 months with no macroscopic bleeding?). The purposes for choosing to measure the parameters that will be measured should be briefly (namely) mentioned (safety checks for patients' premature withdrawal, secondary analyses of outcomes, logistic reasons, etc) especially if some of these parameters will be considered for secondary analyses of the outcomes (p.e degree of compliance, Hb changes).
Response: Thank you for your suggestion. We have now added a brief illlustration of how the measured parameters will be used according to your recommendation to the Participant Timeline subsection of the Methods section.

C1: How will the endpoints experienced by the patients at home or at hospitals not participating in the study be collected?
A1: During informed consent, patients are told to contact investigators should they experience adverse events, and investigators will provide necessary help to aid in their treatment. Regular telephone followup will also record endpoints happened at home and other hospitals.
C2: A brief mention about handling of endpoint related events in non-study participating centers, in line with the reply to this comment, should be included in the manuscript.
Response: Thank you for your suggestion. Corresponding text is now added to the Participant Timeline subsection of the Methods section.

C1: Given that stent thrombosis definition includes ACS by default, what is the point and

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especially the feasibility of including ST as a separate end-point? Consider discarding it.
A1: Thank you for your question. We agree that patients experiencing stent thrombosis events manifest as ACS, but not all ACS are caused by ST. The reasons for setting ST as an independent secondary endpoint is as follows: First, to assess the safety of PCI and stenting for high-ischemic risk patients; Second, to assess the efficacy of triple antiplatelet therapy in reducing ST events. We think it adds clinical value to our study results.
C2: In terms of the primary end-point individual components, there is absolutely no meaning in including both ST and MI/death, as the former is a subset of the latter and its inclusion will have no numerical effect. Please remove it from the primary endpoint. For the purposes of additional analyses based on ST, I agree with the rationale of including it as a secondary standalone endpoint, but if the authors are willing to go down this road, it is advised to opt for including all forms of ST (definite, probable, possible) in this endpoint and clarify that in the endpoints Table.
Response: Thank you for your suggestion. ST is now removed from the primary composite endpoint of MACCE (corresponding text change in the manuscript is in the Outcomes subsection of the Methods section). In secondary endpoints, ST remains a standalone endpoint, the definition of which (Definite, probable, possible) is already listed in the Supplementary Table 3.

C1: Ischemic end-points include non-coronary events. Although stroke has been included in the endpoints of ATLASTIMI 51, systemic embolism is a novel approach. Antiplatelet and anticoagulant treatment is valid for prevention of PAD-related events, but definition and documentation protocols for this very general term should be established, if it is to be used as an end-point.
A1: Thank you for your question. Systemic Embolism is defined as sudden loss of extremity and organ perfusion with clinical and objective evidence (See details and reference in the updated Supplementary Table 3).
C2: Addressed in previous comment.

C1: Ischemia-driven revascularization is directly related to residual ischemic disease after culprit vessel intervention. How will the researchers adjust for this potential confounder in the two groups formed? There are no angiographic data included in the scheduled data for acquisition…Also, how will patients deemed candidates for repeat PCI for severe residual CAD during the index PCI be handled. These patients usually undergo a staged procedure during the index hospitalization or shortly after and there is a need to define planned vs. unplanned PCI revascularization, if revascularization is going to be used as an endpoint.
A1: Revascularization was defined as ischemia-driven if it was associated with any of the following: Angiography Core Laboratory (ACL) reported QFR or field reported FFR ≤ 0 80 or iFR ≤ 0 89; Patients with ischemic symptoms or positive non-invasive functional tests, quantitative coronary angiography [QCA] showed stenosis ≥ 50% in diameter; Patients with no ischemic symptoms or positive non-invasive functional tests with ≥70% stenosis of lesion diameter by QCA. If patients are deemed necessary for repeat PCI for residual CAD, patients will be advised to either stay in the hospital until a repeat PCI is performed (usually within 1 week) or discharge and return for re-admission for planned repeat PCI after a certain amount of time. If a patient experience severe ischemic events before the planned repeat PCI, the repeat revascularization will still be considered ischmia-driven. That is to say, the majority of residual CAD after index culprit lesion PCI would be relatively stable and therefore not lead to unplanned ischemiadriven revascularization.
C2: Please re-read the comment and try to understand it. I did not ask for the definition of ischemiadriven revascularization (IDR), nor for the logistics of the care of the patients undergoing repeat procedures. Furthermore, authors provided a definition of IDR in the end-points Table that introduces further questions and concerns, as they now mention an Angiography Core Laboratory which was not included in the design of the former version of the manuscript. Actually, there is no information about baseline angiographic data collection at all, not to mention how these data will be handled in terms of functionally or anatomically significant residual stenoses. In general, IDR is considered as a weak endpoint and, when used, it is common practice to use unplanned IDR, instead of simply IDR. This

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practice, a most recent prime example of which can be found in the MULTISTARS AMI trial (DOI: 10.1056/NEJMoa2307823), simplifies end-point adjudication and reduces inhomogeneity of trial groups as far as revascularization concerns. I suggest that, if the authors insist on using IDR as an endpoint, to only use unplanned IDR in the composite, and clarify that any IDR triggered by the baseline angiographic results within a specific period after the culprit vessel index procedure (1-3 months) will not count as an end-point related event.

Response: We apologize for the misunderstdanding. As addressed in a previous comment, we have replaced IDR with unplanned IDR in throughout the manuscript to avoid any further confusion. The definition of unplanned IDR in our study is now in line with the one used in MULTISTARS AMI trial.

C1: How will patients who are enrolled and subsequently undergo CABG be handled? For example, patient with 3VD, low EF and DM who undergoes culprit PCI because of STEMI or high risk NSTEMI. Will such a patient be excluded or censored if he/she subsequently undergoes CABG?

A1: Thank you for your questions. CABG candidates who underwent culprit PCI will be excluded if they are scheduled for a later CABG surgery, as the antithrombotic regimen will need to comply with surgical demand. Enrolled patients will be withdrawn from the study if CABG is performed and considered not ischemia-driven (which is rare) before the completion of our study. If the CABG surgery is considered ischemia-driven, the primary endpoint is met.

C2: Part of this comment was addressed here, another part is discussed in the previous comment. Add a brief comment about the fate of the patients undergoing CABG after PCI in the main text or the eligibility criteria supplement.

Response: Thank you for your suggestion. We have now added an exclusion criteria (number 26) with asterisk in the eligibility criteria supplement, which further explains their fate below the table.

Power size calculations:

C1: Researchers calculated a sample size of 3548 (1774 for each group) patients based on their assumptions. Regarding previous studies included in these assumptions, I see that these include the ATLAS-TIMI 51, but also two other trials in populations that I feel are not relevant to the present study. In ATLAS-TIMI-51, which used as a primary efficacy end point a composite of CV death, MI, or stroke, the respective rates were 8.9% and 10.7%. Given that the population of this study carries a higher ischemic risk than the ATLAS-TIMI-51, the quoted rates of 13% for the control group seem plausible, but not necessarily supported by hard evidence. After all, the authors themselves mention that residual ischemic risk in the ACS population undergoing PCI is between 5-10%. Can the authors indicate any specific study supporting a higher than 10% residual ischemic risk in contemporary ACS patients undergoing PCI?

A1: Thank you for your question. Our sample size calculation is based on several contemporary trials as well as estimation from our own cohort of Chinese patients undergoing PCI. In addition to ATLAS TIMI51 trial, the CREATIVE trial reported a 12-month MACE incidence of 13% in the control group (DAPT), and 6.8% in the experiment group (DAPT+cilostazol). See reference here: Tang YD, Wang W, Yang M, Zhang K, Chen J, Qiao S, Yan H, Wu Y, Huang X, Xu B, Gao R, Yang Y; CREATIVE Investigators. Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol Versus Standard Dual Antiplatelet in Patients With High Posttreatment Platelet Reactivity: Results of the CREATIVE Trial. Circulation. 2018 May 22;137(21):2231-2245.

C2: Although CREATIVE trial involved patients with confirmed low responsiveness to clopidogrel hence, not fully applicable to this study's population, in the broader sense it provides some support for a high of 13% as far as MACE concern in high ischemic risk populations in general. It will suffice.

Response: Thank you for your understanding. We agree that our power size calculation cannot be totally accurate, since it is difficult to find a published paper that fits exactly into the population of our current study.

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Randomization

C1: Authors mention the use of IWRS for the purpose of randomization with no further details. I would like to highlight the importance of addressing all the major factors that need to be balanced in the two groups of the study. Major, evidence based risk factors for future MACE in this population should be clearly defined by the authors before randomization and consideration should be given also to residual anatomic CAD after culprit PCI, especially if revascularization is used as an end-point. The latter is an aspect not addressed in ATLAS-TIMI-51, which nevertheless did not include revascularization as an endpoint.

A1: Thank you for your comments. We have now added text addressing major risk factors balanced by IWRS method (Methods section, Allocation and Interventions subsection, 2nd paragraph). Since planned revascularization is not an endpoint, which typically happens during the index hospital stay or after a relatively short period after index PCI, there is no need to address residual anatomic CAD after culprit PCI.

C2: Instead of adding this meaningless extra text regarding the IWRS (I suggest to keep the initial form of the text), authors should provide in the supplement, the parameters that they feel that need to be balanced among the two groups, as far as risk factors concern, along with a reference about this system's prior use, if available. The issue of planned PCI has been settled in previous comments.

Response: Thank you for your suggestion. Before randomization, patients' age and sex are entered into the system, so these two parameters are balanced between the groups. We have changed the text in the manuscript to the initial form, and added parameters that need to be balanced among the groups in the same subsection (since only 2 parameters are involved, we did not add another section in the supplemental materials). Since this is the first multicenter RCT reported by our team, we do not have prior experience of using this IWRS system

DDimers

C1: What is the rationale for repeated measurements at 3, 6 and 12 months?

A1: Thank you for your question. Repeated measurement of D-dimer is carried out for the following reasons: First, for research purpose, to measure the effect of antithrombotic therapy and later investigate if the fluctuation of D-dimer levels are associated with ischemic events. Second, for medical purpose, as part of a routine check-up after PCI, to rule out potential DVT/PE.

C2: I am not aware of any literature supporting these rationales, which seem arbitrary at least. If the authors plan to perform secondary analyses using DD fluctuations, they should include this plan in the methods section, along with some kind of reference supporting a basis for using DD for antithorombotic efficacy monitoring. There is absolutely no indication for routinely measuring DD after PCI in asymptomatic patients to rule out DVT/PE.

Response: Thank you for your suggestion. We have now added our plan of the secondary analysis (with reference of D-dimer being used as thrombus marker) to the 3rd paragraph of the Statistical Methods subsection of the Methods section.

C1: From a diagnostic point of view, DD is a marker with high negative prognostic value and low specificity used predominately for the exclusion of pulmonary embolism or large vessel thrombosis/dissection in the ED population presenting with chest pain and/or shortness of breath. I understand that the authors aim as a side benefit of the study to support the prognostic role of DD but I am concerned that there is no provision or mention in the eligibility criteria about the exclusion of other major causes associated with DD elevation.

A1: Thank you for your questions. Major causes for D-dimer elevation is now added to the exclusion criteria (Supplementary Table 1, exclusion criteria number 26).

C2: Comment properly addressed

Minor issues

C1: The manuscript could benefit from a slight linguistic review, as several sentences require better wording. There is an occasional feeling, that patches of text from various different sources have been incorporated in the manuscript without the appropriate consideration for homogeneity (tenses, plural vs. singular, choice of words, text vs. bulleted

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format, etc) and overall linguistic standards. Examples include among others, lines 16-17 (p.6), lines 16- 19 (p.7), lines 6-10 & 53-56 (p.34), numbers 6, 7 of inclusion criteria and numbers 20 & 22 of exclusion criteria.
A1: Thank you for your suggestion. We apologize for the linguistic errors and have made corresponding changes in the text listed above. We have reviewed the manuscript for linguistic errors to improve readability.
C2: Comment properly addressed

C1: The detailed description of the results of the trials included in the Discussion section, should be abbreviated and tailored to the nature of the present manuscript, which is reporting of a study design in ACS patients, not reporting of results of an original study in patients with either ACS or stable CAD. Discussion should focus more on what new this research will bring compared to current knowledge and why this will be important.
A1: Thank you for your suggestions. We have now abbreviated non-essential results of previous studies and kept those key study results closely related to the design of our study in the discussion. We hope this would better highlight the importance of our study design.
Comment properly addressed

Reviewer: 4

Dr. Bright Chiemezie Offorha, The University of Sheffield
Comments to the Author:
Thank you for the opportunity to review this interesting paper. I commend the authors for their efforts and thoughtfulness. I have major concerns regarding the statistical aspects of the study. Generally, I would recommend that the investigators rely on any good statistical guideline like the ICH E9 (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf). Please find my comments and suggestions below:

1. Maintain consistency in using a "randomised controlled trial (RCT)" instead of a "randomised clinical trial." The latter is more appropriate since the study is controlled (i.e., has a control group) (line 50, page 5; throughout the manuscript).
Response: Thank you for your suggestion. We have now changed all "randomized clinical trial" to "randomized controlled trial" throughour the manuscript.

2. Study setting and eligibility criteria: Specify what centres are, such as hospitals, care homes, primary care, community etc. Consider briefly stating the inclusion and exclusion criteria in the main body of the manuscript for complete reporting.
Response: Thank you for your suggestion. All centres involved are tertiary hospitals (provincial-level large centers with high annual capacity of PCI). We have now changed the first sentence of the Study Setting and Eligibility Criteria subsection to specify the type of centers involved. We have also added key inclusion and exclusion criteria to the same paragraph for complete reporting.

3. Allocation and Intervention: Consider separating this section into separate sections. It would be clearer to have randomisation and allocation as one section, and intervention and control as another. Regardless of the open nature of this trial, some elements of blinding can still be introduced to enhance the trial's validity. Start by ensuring that a different investigator, who is not involved with other aspects of the trial (like randomisation scheduling) conducts the allocation of treatments. The investigators should also consider making it impossible for the treatment allocator to know the next treatment allocation in advance (known as allocation concealment). Clearly state if this has been considered for reproducibility.
Response: Thank you for your suggestion. We have now separated the allocation and intervention as suggested. We have also added corresponding text describing independent allocation and allocation concealment (See Allocation and Randomization subsection of the Methods section).

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4. Randomisation and stratification: Elements of blinding/masking can also be introduced in the randomisation process by ensuring that the person in charge is not involved in other aspects of the trial. The randomisation schedule wasn't mentioned; this will also enhance blinding. How will the randomisation schedule be generated and handled? The investigators mentioned IWRS, more information should be provided regarding how it will handle the randomisation schedule. It is generally recommended (ICH E9) that for trials with many centres, randomisation (randomisation scheme) should be centre-specific (stratified randomisation) but allocation should be centrally conducted. This means that each centre will have a separate randomisation schedule. Also, the person handling the allocation should not have access to this schedule in advance, the next allocation should only be made known to the patient allocator after a patient has been recruited.

Response: Thank you for your comments.

First, regarding randomization schedule and IWRS, the IWRS independently generates and handles the randomization schedule, so that treatment allocation will not be known by any investigators in advance. Corresponding text has been added to the allocation and randomization subsection.

Second, regarding center-specific stratified randomization. All our patients are centrally randomized through IWRS system, so no center-specific stratified randomization is done. We acknowledge that center-specific randomization minimizes potential bias caused by different centers. Since this is an actively recruiting study, which has already recruited a fair amount of patients, it is not feasible to change randomization scheme at this point. On the other hand, all participating centres are large tertiary hospitals, the standard of PCI and post-PCI medical care are similar, which lowers potential center-based bias. We have now added this point to the limitation section.

Third, regarding the allocation of treatment. The allocation of treatment will be conducted by an independent investigator who will not be involved in other aspects of the trial, including randomization scheduling and patient follow-up. Corresponding text has been added to the allocation and randomization subsection.

5. Outcomes: I think more information is needed regarding the outcomes in general and specifically the primary endpoint. I struggled to understand whether the primary endpoint was binary or time-to-event. This confusion also impacted the sample size/power calculation and statistical analysis.

Response: Thank you for your question. Please refer to supplemental materials for the detailed definition of the endpoints. We apologize for the confusion. Although our endpoints are binary, we do record the time at which the endpoints happen. Time-to-event analysis including Kaplan-Meier survival analysis and Cox regression analysis will be conducted. We have now revised the Statistical Methods subsection accordingly.

6. Sample size/power calculation: The content of this section points towards a power calculation rather than a sample size calculation. The investigator should reword this section to help readers grasp the message easily. I presume the primary endpoint is a time-to-event endpoint since Cox PH is proposed. However, the current sample size calculation does not reflect this, the investigator should consider revising the sample size/power calculation to match the sample size/power calculation for a time-to-event endpoint.

Response: Thank you for your suggestion. We have now changed the subsection title from "Sample Size" to "Power Calculation", and reworded the content of this subsection accordingly. We have taken into account the time-to-event analysis during calculation of sample size. Now we have added expected duration of patient recruitment and length of follow-up to this subsection to reflect time-to-event based sample calculation.

7. Statistical methods: Be specific on how missing data will be handled, multiple imputation is generally recommended (lines 17-19, page 8). The baseline covariates to be adjusted for in the adjusted models weren't mentioned. In a trial like this with many centres, it's more plausible that the centres would estimate different treatment effects - how will this be handled? In other words, how will the centre effect be addressed? Especially when

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randomisation is centre-specific (i.e., stratified), it is recommended to adjust for this effect. Finally, what is the alternative if the Cox PH assumption is violated?

Response: Thank you for your suggestion.

First, regarding missing data and baseline covariates for adjusting, we have removed single imputation and kept multiple imputation method according to your recommendation. Baseline covariates to be adjusted for in the Cox regression models include age, gender, other risk factors (BMI, smoking), comorbidities (hypertension, diabetes, prior PCI, prior coronary artery bypass graft surgery, heart failure) and key results (including left ventricular ejection fraction, severity of coronary artery disease reflected by SYNTAX score), etc.

Second, regarding centre-related treatment effects. As addressed in a previous comment, our randomization is not center-stratified, we have added this point to the limitation part. However, since all centres involved are large tertiary hospitals, the standard of medical care are similar and according to contemporary guidelines, which lowers the difference in treatment effects across centres.

Third, time-dependent Cox regression model will be applicated when the Cox proportional hazards assumption was violated. We have now added this to the Statistical Methods subsection.

8. Limitations: If the above concerns are addressed then the impact of the challenging nature of open-label design would have been minimised, which should be captured in the study's limitations.

Response: Thank you for your suggestion. We agree our study cannot fully avoid potential bias related with open-label design, and have added corresponding text to the limitation part.

VERSION 3 - REVIEW

Reviewer	**2**
Name	**Katsikis, Athanasios**
Affiliation	**401 General Military Hospital of Athens, Cardiology**
Date	**10-Mar-2025**
COI	

Comments to the authors (C: Comment A: Authors answer)

Major issues

Inclusion criteria

C1: The focus is patients at high ischemic risk, while no bleeding risk assessment is performed. Strongly consider including a bleeding risk score (PRECISE-DAPT or ARC-HBR) on top of the PARIS score at baseline assessment, even if high bleeding risk patients are not excluded for the purposes of maintaining the power calculations of the study. This will be particularly helpful for the interpretation of the results of the study.

A1: Thank you for your suggestion. Actually, the exclusion criteria has included almost all ARC-HBR major criteria. We agree that assessing bleeding risk through bleeding risk score is more precise. Since this is already an actively recruiting study, it is not appropriate to make significant changes to inclusion criteria at this stage. We will calculate PRECISE-DAPT score for patients enrolled in our study for better interpretation of the results.

C2: It is slightly awkward that the authors are submitting a study design for review and approval, but have already started conducting the trial. Any RCT needs to be registered before data collection begins and I understand that the trial was registered quite some time ago (26 Nov 22) with ClinicalTrials.gov, but registration is best done through protocol publication. Nevertheless, PRECISE-DAPT score can still be calculated for all patients at baseline from the data that will be collected, as per the study's protocol. Based on the exclusion criteria of the study, almost all patients with very high bleeding risk (based on history of bleeding, active bleeding-predisposing conditions and significant derangements in bleedingrelated biochemical parameters) as well as most high bleeding risk patients will be

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excluded. Still, formal, quantitative bleeding risk assessment of the patients that will be eventually enrolled will be greatly beneficial for the interpretation and clinical applicability of the results of the study. For example, a patient not falling under any of the exclusion criteria, with eGFR of 40 ml/min, Hb of 11,2 g/dl, and aged 65 years would have been well enrolled in the study, but would qualify for high bleeding risk based on a DAPT SCORE of 34. A significant proportion of such patients in the study, could either explain a potential failure to achieve the safety endpoint while achieving the primary efficacy endpoint or surprisingly show that the antithrombotic regimen used is both safe and effective regardless of baseline DAPT score, by means of DPAT stratified analysis. In conclusion, I strongly believe that DAPT score should be calculated for all patients retrospectively, secondary analyses of efficacy and safety endpoints based on DAPT score should be performed and the above should be mentioned in the Methods section.
A2: Thank you for your suggestions. We agree that calculating PRECISE-DAPT score for all recruited patients is feasible and will be beneficial for results interpretation. Based on your suggestion, PRECISE-DAPT score will be calculated for all patients retrospectively for secondary analysis. We have added corresponding text as a new paragraph to the Statistical Methods subsection in the Methods section.
Additionally, PRECISE-DAPT score[11] will be calculated for all patients retrospectively for quantitative bleeding risk assessment. Secondary analysis of primary, secondary and safety endpoints will be performed based on PRECISE-DAPT score.
C3: Comment properly addressed (p.64, line 33), no further comments

End-points:
C1: There is no reference as to how the end-points will be defined. This is particularly relevant to the definition of MI. End-points are not defined in the Supplementary material/ Tables. Consult and most importantly include relevant ARC criteria (Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document – Circulation 2018 Jun 12;137(24):2635-2650).
A1: Thank you for your suggestion. Detailed endpoint definition is now available in Supplementray Table 3.
C2: In the added Endpoint definition Table provided, please: Discard the term "in detail" everywhere that is used. Correct description of systemic embolism events to "Sudden loss of extremity OR organ perfusion with clinical and objective evidence". Remove MACCE definition from the Table, this term is defined by the individual components. Use brief descriptions, not only reference sources for stroke and MI. As far as MI concerns, the trial obviously refers to types 1-3 MIs. Include definition of unplanned IDR (which is the one to be used as an end-point) on top of IDR (see related comment below also).
A2: Thank you for your suggestions. We have now updated the Endpoint definition Table in the supplementary materials according to your suggestions. Additionally, we also removed NACE definition, which is also a combination of other endpoints. In terms of IDR, we apologize for the confusion, but we thought unplanned revascularization and IDR were the same thing. After reading the MULTISTARS AMI trial manuscript as you mentioned in a comment below, we realized "unplanned IDR" is the accurate word. Therefore, we have replaced IDR with unplanned IDR in throughout the manuscript to avoid any further confusion. The definition of unplanned IDR in our study is in line with the one used in MULTISTARS AMI trial.
C3: End-points in Table 3 (p.42) are now better defined and referenced. In the text however, NACE is retained (p.62, line 52). This should be discarded. Furthermore, in the stroke definition, there is inadvertent text copied from the source of the definition ["164 (Stroke, not specified as haemorrhage or infarction), including cerebrovascular accident, excluding sequelae of stroke[3]] that needs fixing (parenthesis, number) while the description of the unplanned IDR lacks the word unplanned and repeats the definition. It should be changed to "Unplanned revascularization because of angina symptoms, new ischemic changes on electrocardiography (ECG), or signs of reversible myocardial ischemia on noninvasive imaging".

C1: Since essentially all the end-points of the study are acute and will be mostly documented in the hospital-setting, what is the purpose of the regular follow-up clinic visits? I understand a potential role for timely detecting safety concerns, but I see no specific protocols for withdrawing patients from the study based on the data collected from the regular FU visits.
A1: Thank you for your question. Safety is not the only reason for clinic visits. The regular clinic follow- ups are necessary for medical reasons including testing for coagulation function (including D- dimer), blood count, urinalysis, stool analysis, as well as for research purpose such as evaluating compliance, collecting unused study drug, etc. (Supplementary Table 2)
C2: There is no description in the manuscript about how the interim results of the parameters measured will be used and no mention about potential impact of these results in the eligibility of the patients to continue the study protocol (p.e. what will be the fate of a patient who started with a baseline Hb of 13 g/dL and is discovered to have an Hb of 9g/dL at 3 months with no macroscopic bleeding?). The purposes for choosing to measure the parameters

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that will be measured should be briefly (namely) mentioned (safety checks for patients' premature withdrawal, secondary analyses of outcomes, logistic reasons, etc) especially if some of these parameters will be considered for secondary analyses of the outcomes (p.e degree of compliance, Hb changes).
A2: Thank you for your suggestion. We have now added a brief illlustration of how the measured parameters will be used according to your recommendation to the Participant Timeline subsection of the Methods section.
C3: The authors have provided some rationale for repeated measurements of DD (p.64, line 38) specifically and other parameters in general (p.62, lines 13-27). Although the text added is not ideal, it will suffice.

C1: How will the endpoints experienced by the patients at home or at hospitals not participating in the study be collected?
A1: During informed consent, patients are told to contact investigators should they experience adverse events, and investigators will provide necessary help to aid in their treatment. Regular telephone followup will also record endpoints happened at home and other hospitals.
C2: A brief mention about handling of endpoint related events in non-study participating centers, in line with the reply to this comment, should be included in the manuscript.
A2: Thank you for your suggestion. Corresponding text is now added to the Participant Timeline subsection of the Methods section.
C3: Comment properly addressed (p.62, line 33), no further comments

C1: Given that stent thrombosis definition includes ACS by default, what is the point and especially the feasibility of including ST as a separate end-point? Consider discarding it.
A1: Thank you for your question. We agree that patients experiencing stent thrombosis events manifest as ACS, but not all ACS are caused by ST. The reasons for setting ST as an independent secondary endpoint is as follows: First, to assess the safety of PCI and stenting for high-ischemic risk patients; Second, to assess the efficacy of triple antiplatelet therapy in reducing ST events. We think it adds clinical value to our study results.
C2: In terms of the primary end-point individual components, there is absolutely no meaning in including both ST and MI/death, as the former is a subset of the latter and its inclusion will have no numerical effect. Please remove it from the primary endpoint. For the purposes of additional analyses based on ST, I agree with the rationale of including it as a secondary standalone endpoint, but if the authors are willing to go down this road, it is advised to opt for including all forms of ST (definite, probable, possible) in this endpoint and clarify that in the endpoints Table.
A2: Thank you for your suggestion. ST is now removed from the primary composite endpoint of MACCE (corresponding text change in the manuscript is in the Outcomes subsection of the Methods section). In secondary endpoints, ST remains a standalone endpoint, the definition of which (Definite, probable, possible) is already listed in the Supplementary Table 3.
C3: Comment properly addressed (p.41,Table 3 & p.62-Outcomes), no further comments

C1: Ischemic end-points include non-coronary events. Although stroke has been included in the endpoints of ATLASTIMI 51, systemic embolism is a novel approach. Antiplatelet and anticoagulant treatment is valid for prevention of PAD-related events, but definition and documentation protocols for this very general term should be established, if it is to be used as an end-point.
A1: Thank you for your question. Systemic Embolism is defined as sudden loss of extremity and organ perfusion with clinical and objective evidence (See details and reference in the updated Supplementary Table 3).
C2: Addressed in previous comment.

C1: Ischemia-driven revascularization is directly related to residual ischemic disease after culprit vessel intervention. How will the researchers adjust for this potential confounder in the two groups formed? There are no angiographic data included in the scheduled data for acquisition…Also, how will patients deemed candidates for repeat PCI for severe residual CAD during the index PCI be handled. These patients usually undergo a staged procedure during the index hospitalization or shortly after and there is a need to define planned vs. unplanned PCI revascularization, if revascularization is going to be used as an endpoint.
A1: Revascularization was defined as ischemia-driven if it was associated with any of the following: Angiography Core Laboratory (ACL) reported QFR or field reported FFR ≤ 0 80 or iFR ≤ 0 89; Patients with ischemic symptoms or positive non-invasive functional tests, quantitative coronary angiography [QCA] showed stenosis ≥ 50% in diameter; Patients with no ischemic symptoms or positive non-invasive functional tests with ≥70% stenosis of lesion diameter by QCA. If patients are deemed necessary for repeat PCI for residual CAD, patients will be advised to either

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stay in the hospital until a repeat PCI is performed (usually within 1 week) or discharge and return for re-admission for planned repeat PCI after a certain amount of time. If a patient experience severe ischemic events before the planned repeat PCI, the repeat revascularization will still be considered ischmia-driven. That is to say, the majority of residual CAD after index culprit lesion PCI would be relatively stable and therefore not lead to unplanned ischemiadriven revascularization.
C2: Please re-read the comment and try to understand it. I did not ask for the definition of ischemiadriven revascularization (IDR), nor for the logistics of the care of the patients undergoing repeat procedures. Furthermore, authors provided a definition of IDR in the end-points Table that introduces further questions and concerns, as they now mention an Angiography Core Laboratory which was not included in the design of the former version of the manuscript. Actually, there is no information about baseline angiographic data collection at all, not to mention how these data will be handled in terms of functionally or anatomically significant residual stenoses. In general, IDR is considered as a weak endpoint and, when used, it is common practice to use unplanned IDR, instead of simply IDR. This practice, a most recent prime example of which can be found in the MULTISTARS AMI trial (DOI: 10.1056/NEJMoa2307823), simplifies end-point adjudication and reduces inhomogeneity of trial groups as far as revascularization concerns. I suggest that, if the authors insist on using IDR as an endpoint, to only use unplanned IDR in the composite, and clarify that any IDR triggered by the baseline angiographic results within a specific period after the culprit vessel index procedure (1-3 months) will not count as an end-point related event.
A2: We apologize for the misunderstdanding. As addressed in a previous comment, we have replaced IDR with unplanned IDR in throughout the manuscript to avoid any further confusion. The definition of unplanned IDR in our study is now in line with the one used in MULTISTARS AMI trial.
C3: The definition of ischemia-driven revascularization is now given in the supplementary Table. Please apply the corrections mentioned regarding the description of the term in a previous comment and the issue will be fully settled.

C1: How will patients who are enrolled and subsequently undergo CABG be handled? For example, patient with 3VD, low EF and DM who undergoes culprit PCI because of STEMI or high risk NSTEMI. Will such a patient be excluded or censored if he/she subsequently undergoes CABG?
A1: Thank you for your questions. CABG candidates who underwent culprit PCI will be excluded if they are scheduled for a later CABG surgery, as the antithrombotic regimen will need to comply with surgical demand. Enrolled patients will be withdrawn from the study if CABG is performed and considered not ischemia-driven (which is rare) before the completion of our study. If the CABG surgery is considered ischemia-driven, the primary endpoint is met.
C2: Part of this comment was addressed here, another part is discussed in the previous comment. Add a brief comment about the fate of the patients undergoing CABG after PCI in the main text or the eligibility criteria supplement.
A2: Thank you for your suggestion. We have now added an exclusion criteria (number 26) with asterisk in the eligibility criteria supplement, which further explains their fate below the table.
C3: Comment properly addressed, no further comments

Power size calculations:
C1: Researchers calculated a sample size of 3548 (1774 for each group) patients based on their assumptions. Regarding previous studies included in these assumptions, I see that these include the ATLAS-TIMI 51, but also two other trials in populations that I feel are not relevant to the present study. In ATLAS-TIMI-51, which used as a primary efficacy end point a composite of CV death, MI, or stroke, the respective rates were 8.9% and 10.7%. Given that the population of this study carries a higher ischemic risk than the ATLAS-TIMI-51, the quoted rates of 13% for the control group seem plausible, but not necessarily supported by hard evidence. After all, the authors themselves mention that residual ischemic risk in the ACS population undergoing PCI is between 5-10%. Can the authors indicate any specific study supporting a higher than 10% residual ischemic risk in contemporary ACS patients undergoing PCI?
A1: Thank you for your question. Our sample size calculation is based on several contemporary trials as well as estimation from our own cohort of Chinese patients undergoing PCI. In addition to ATLAS TIMI51 trial, the CREATIVE trial reported a 12-month MACE incidence of 13% in the control group (DAPT), and 6.8% in the experiment group (DAPT+cilostazol). See reference here: Tang YD, Wang W, Yang M, Zhang K, Chen J, Qiao S, Yan H, Wu Y, Huang X, Xu B, Gao R, Yang Y; CREATIVE Investigators. Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol Versus Standard Dual Antiplatelet in Patients With High Posttreatment Platelet Reactivity: Results of the CREATIVE Trial. Circulation. 2018 May 22;137(21):2231-2245.

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C2: Although CREATIVE trial involved patients with confirmed low responsiveness to clopidogrel hence, not fully applicable to this study's population, in the broader sense it provides some support for a high of 13% as far as MACE concern in high ischemic risk populations in general. It will suffice.
A2: Thank you for your understanding. We agree that our power size calculation cannot be totally accurate, since it is difficult to find a published paper that fits exactly into the population of our current study.

Randomization
C1: Authors mention the use of IWRS for the purpose of randomization with no further details. I would like to highlight the importance of addressing all the major factors that need to be balanced in the two groups of the study. Major, evidence based risk factors for future MACE in this population should be clearly defined by the authors before randomization and consideration should be given also to residual anatomic CAD after culprit PCI, especially if revascularization is used as an end-point. The latter is an aspect not addressed in ATLAS-TIMI-51, which nevertheless did not include revascularization as an endpoint.
A1: Thank you for your comments. We have now added text addressing major risk factors balanced by IWRS method (Methods section, Allocation and Interventions subsection, 2nd paragraph). Since planned revascularization is not an endpoint, which typically happens during the index hospital stay or after a relatively short period after index PCI, there is no need to address residual anatomic CAD after culprit PCI.
C2: Instead of adding this meaningless extra text regarding the IWRS (I suggest to keep the initial form of the text), authors should provide in the supplement, the parameters that they feel that need to be balanced among the two groups, as far as risk factors concern, along with a reference about this system's prior use, if available. The issue of planned PCI has been settled in previous comments.
A2: Thank you for your suggestion. Before randomization, patients' age and sex are entered into the system, so these two parameters are balanced between the groups. We have changed the text in the manuscript to the initial form, and added parameters that need to be balanced among the groups in the same subsection (since only 2 parameters are involved, we did not add another section in the supplemental materials). Since this is the first multicenter RCT reported by our team, we do not have prior experience of using this IWRS system
C3: The response of the authors to this comment (p.61, line 1-28) is particularly problematic and nearly alarming, as it makes me question not only if the authors understand the concept of the IWRS but also if they are using it correctly. In the usual practice of RCTs conduction, randomization is achieved by the use of interactive response technology, one form of it being the Interactive Web Response System. With this technology, a network-based central randomization system is used to complete the random allocation of subjects to control and treatment. Surprisingly, the authors mention the use of this system, which automatically and independently generates and handles the randomization schedule, and at the same time the allocation of treatment by an independent investigator, i.e manually. Furthermore, the text implies that the randomization will be based on only two variables, i,e age and gender. Despite my serious concerns about what is actually happening with the randomization process of this trial, I suggest to replace the text in lines 1-28 of page 61 with the following text: "Randomization of patients to the experiment or the control group at 1:1 ratio will be performed with the use of an Interactive Web Respond System (IWRS), which will independently generate and handle the randomization schedule and treatment allocation will not be known by any investigators in advance. Through the IWRS randomization process, all major risk factors for the end-point of the study (defined by the investigators of the trial) will be automatically balanced between the two groups".

DDimers
C1: What is the rationale for repeated measurements at 3, 6 and 12 months?
A1: Thank you for your question. Repeated measurement of D-dimer is carried out for the following reasons: First, for research purpose, to measure the effect of antithrombotic therapy and later investigate if the fluctuation of D-dimer levels are associated with ischemic events. Second, for medical purpose, as part of a routine check-up after PCI, to rule out potential DVT/PE.
C2: I am not aware of any literature supporting these rationales, which seem arbitrary at least. If the authors plan to perform secondary analyses using DD fluctuations, they should include this plan in the methods section, along with some kind of reference supporting a basis for using DD for antithorombotic efficacy monitoring. There is absolutely no indication for routinely measuring DD after PCI in asymptomatic patients to rule out DVT/PE.
A2: Thank you for your suggestion. We have now added our plan of the secondary analysis (with reference of D-dimer being used as thrombus marker) to the 3rd paragraph of the Statistical Methods subsection of the Methods section.
C3: The answer of the authors to this comment is covered in a previous comment and the issue is settled.

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C1: From a diagnostic point of view, DD is a marker with high negative prognostic value and low specificity used predominately for the exclusion of pulmonary embolism or large vessel thrombosis/dissection in the ED population presenting with chest pain and/or shortness of breath. I understand that the authors aim as a side benefit of the study to support the prognostic role of DD but I am concerned that there is no provision or mention in the eligibility criteria about the exclusion of other major causes associated with DD elevation.
A1: Thank you for your questions. Major causes for D-dimer elevation is now added to the exclusion criteria (Supplementary Table 1, exclusion criteria number 26).
C2: Comment properly addressed

Minor issues
C1: The manuscript could benefit from a slight linguistic review, as several sentences require better wording. There is an occasional feeling, that patches of text from various different sources have been incorporated in the manuscript without the appropriate consideration for homogeneity (tenses, plural vs. singular, choice of words, text vs. bulleted format, etc) and overall linguistic standards. Examples include among others, lines 16-17 (p.6), lines 16-19 (p.7), lines 6-10 & 53-56 (p.34), numbers 6, 7 of inclusion criteria and numbers 20 & 22 of exclusion criteria.
A1: Thank you for your suggestion. We apologize for the linguistic errors and have made corresponding changes in the text listed above. We have reviewed the manuscript for linguistic errors to improve readability.
C2: The need for an overall linguistic review still remains, as I mentioned to my comments to the Editor. The manuscript feels like a collection of patches hence, in terms of readability and grammar requires an overall linguistic review. Most characteristic examples of this problem include the following: p.60-lines 19,23,37,57 /p.62-line 29 /p.64-line 4, 42 (tenses, single vs. plural, etc)/p.68-line 30-38.. The Editor will be the final judge of whether the article is up to the linguistic standards of the journal.

C1: The detailed description of the results of the trials included in the Discussion section, should be abbreviated and tailored to the nature of the present manuscript, which is reporting of a study design in ACS patients, not reporting of results of an original study in patients with either ACS or stable CAD. Discussion should focus more on what new this research will bring compared to current knowledge and why this will be important.
A1: Thank you for your suggestions. We have now abbreviated non-essential results of previous studies and kept those key study results closely related to the design of our study in the discussion. We hope this would better highlight the importance of our study design.
C2: Comment properly addressed

VERSION 3 - AUTHOR RESPONSE

Comments to the authors (C: Comment A: Authors answer)

Major issues
Inclusion criteria
C1: The focus is patients at high ischemic risk, while no bleeding risk assessment is performed. Strongly consider including a bleeding risk score (PRECISE-DAPT or ARC-HBR) on top of the PARIS score at baseline assessment, even if high bleeding risk patients are not excluded for the purposes of maintaining the power calculations of the study. This will be particularly helpful for the interpretation of the results of the study.
A1: Thank you for your suggestion. Actually, the exclusion criteria has included almost all ARC-HBR major criteria. We agree that assessing bleeding risk through bleeding risk score is more precise. Since this is already an actively recruiting study, it is not appropriate to make significant changes to inclusion criteria at this stage. We will calculate PRECISE- DAPT score for patients enrolled in our study for better interpretation of the results.
C2: It is slightly awkward that the authors are submitting a study design for review and approval, but have already started conducting the trial. Any RCT needs to be registered before data collection begins and I understand that the trial was registered quite some time ago (26 Nov 22) with ClinicalTrials.gov, but registration is best done through protocol publication. Nevertheless, PRECISE-DAPT score can still be calculated for all patients at baseline from the data that will be collected, as per the study's protocol. Based on the exclusion criteria of the study, almost all patients with very high bleeding risk (based on history of bleeding, active bleeding-predisposing conditions and significant derangements in bleedingrelated biochemical parameters) as well as most high bleeding risk patients will be excluded. Still, formal, quantitative bleeding risk assessment of the patients that will be eventually enrolled will be greatly beneficial for the interpretation and clinical applicability of the results of the study. For example, a patient not falling under any of the exclusion criteria, with eGFR of 40 ml/min, Hb of 11,2

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g/dl, and aged 65 years would have been well enrolled in the study, but would qualify for high bleeding risk based on a DAPT SCORE of 34. A significant proportion of such patients in the study, could either explain a potential failure to achieve the safety endpoint while achieving the primary efficacy endpoint or surprisingly show that the antithrombotic regimen used is both safe and effective regardless of baseline DAPT score, by means of DPAT stratified analysis. In conclusion, I strongly believe that DAPT score should be calculated for all patients retrospectively, secondary analyses of efficacy and safety endpoints based on DAPT score should be performed and the above should be mentioned in the Methods section.
A2: Thank you for your suggestions. We agree that calculating PRECISE-DAPT score for all recruited patients is feasible and will be beneficial for results interpretation. Based on your suggestion, PRECISE-DAPT score will be calculated for all patients retrospectively for secondary analysis. We have added corresponding text as a new paragraph to the Statistical Methods subsection in the Methods section.
Additionally, PRECISE-DAPT score[11] will be calculated for all patients retrospectively for quantitative bleeding risk assessment. Secondary analysis of primary, secondary and safety endpoints will be performed based on PRECISE-DAPT score.
C3: Comment properly addressed (p.64, line 33), no further comments

End-points:
C1: There is no reference as to how the end-points will be defined. This is particularly relevant to the definition of MI. End-points are not defined in the Supplementary material/ Tables. Consult and most importantly include relevant ARC criteria (Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document – Circulation 2018 Jun 12;137(24):2635-2650).
A1: Thank you for your suggestion. Detailed endpoint definition is now available in Supplementray Table 3.
C2: In the added Endpoint definition Table provided, please: Discard the term “in detail” everywhere that is used. Correct description of systemic embolism events to “Sudden loss of extremity OR organ perfusion with clinical and objective evidence”. Remove MACCE definition from the Table, this term is defined by the individual components. Use brief descriptions, not only reference sources for stroke and MI. As far as MI concerns, the trial obviously refers to types 1-3 MIs. Include definition of unplanned IDR (which is the one to be used as an end-point) on top of IDR (see related comment below also).
A2: Thank you for your suggestions. We have now updated the Endpoint definition Table in the supplementary materials according to your suggestions. Additionally, we also removed NACE definition, which is also a combination of other endpoints. In terms of IDR, we apologize for the confusion, but we thought unplanned revascularization and IDR were the same thing. After reading the MULTISTARS AMI trial manuscript as you mentioned in a comment below, we realized “unplanned IDR” is the accurate word. Therefore, we have replaced IDR with unplanned IDR in throughout the

manuscript to avoid any further confusion. The definition of unplanned IDR in our study is in line with the one used in MULTISTARS AMI trial.
C3: End-points in Table 3 (p.42) are now better defined and referenced. In the text however, NACE is retained (p.62, line 52). This should be discarded. Furthermore, in the stroke definition, there is inadvertent text copied from the source of the definition [“164 (Stroke, not specified as haemorrhage or infarction), including cerebrovascular accident, excluding sequelae of stroke[3]] that needs fixing (parenthesis, number) while the description of the unplanned IDR lacks the word unplanned and repeats the definition. It should be changed to “Unplanned revascularization because of angina symptoms, new ischemic changes on electrocardiography (ECG), or signs of reversible myocardial ischemia on noninvasive imaging”.

A3: Thank you for your advice. We have now removed NACE in the manuscript text (Outcomes subsection of the Methods section). The texts in Supplementary Table 3 regarding the definition of stroke and unplanned IDR have now been fixed according to your suggestion.

C1: Since essentially all the end-points of the study are acute and will be mostly documented in the hospital-setting, what is the purpose of the regular follow-up clinic visits? I understand a potential role for timely detecting safety concerns, but I see no specific protocols for withdrawing patients from the study based on the data collected from the regular FU visits.

A1: Thank you for your question. Safety is not the only reason for clinic visits. The regular clinic follow- ups are necessary for medical reasons including testing for coagulation function (including D- dimer), blood count,

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urinalysis, stool analysis, as well as for research purpose such as evaluating compliance, collecting unused study drug, etc. (Supplementary Table 2)

C2: There is no description in the manuscript about how the interim results of the parameters measured will be used and no mention about potential impact of these results in the eligibility of the patients to continue the study protocol (p.e. what will be the fate of a patient who started with a baseline Hb of 13 g/dL and is discovered to have an Hb of 9g/dL at 3 months with no macroscopic bleeding?). The purposes for choosing to measure the parameters that will be measured should be briefly (namely) mentioned (safety checks for patients' premature withdrawal, secondary analyses of outcomes, logistic reasons, etc) especially if some of these parameters will be considered for secondary analyses of the outcomes (p.e degree of compliance, Hb changes).

A2: Thank you for your suggestion. We have now added a brief illlustration of how the measured parameters will be used according to your recommendation to the Participant Timeline subsection of the Methods section.
C3: The authors have provided some rationale for repeated measurements of DD (p.64, line 38) specifically and other parameters in general (p.62, lines 13-27). Although the text added is not ideal, it will suffice.

C1: How will the endpoints experienced by the patients at home or at hospitals not participating in the study be collected?
A1: During informed consent, patients are told to contact investigators should they experience adverse events, and investigators will provide necessary help to aid in their treatment. Regular telephone followup will also record endpoints happened at home and other hospitals.

C2: A brief mention about handling of endpoint related events in non-study participating centers, in line with the reply to this comment, should be included in the manuscript.
A2: Thank you for your suggestion. Corresponding text is now added to the Participant Timeline subsection of the Methods section.

C3: Comment properly addressed (p.62, line 33), no further comments

C1: Given that stent thrombosis definition includes ACS by default, what is the point and especially the feasibility of including ST as a separate end-point? Consider discarding it.
A1: Thank you for your question. We agree that patients experiencing stent thrombosis events manifest as ACS, but not all ACS are caused by ST. The reasons for setting ST as an independent secondary endpoint is as follows: First, to assess the safety of PCI and stenting for high-ischemic risk patients; Second, to assess the efficacy of triple antiplatelet therapy in reducing ST events. We think it adds clinical value to our study results.

C2: In terms of the primary end-point individual components, there is absolutely no meaning in including both ST and MI/death, as the former is a subset of the latter and its inclusion will have no numerical effect. Please remove it from the primary endpoint. For the purposes of additional analyses based on ST, I agree with the rationale of including it as a secondary standalone endpoint, but if the authors are willing to go down this road, it is advised to opt for including all forms of ST (definite, probable, possible) in this endpoint and clarify that in the endpoints Table.

A2: Thank you for your suggestion. ST is now removed from the primary composite endpoint of MACCE (corresponding text change in the manuscript is in the Outcomes subsection of the Methods section). In secondary endpoints, ST remains a standalone endpoint, the definition of which (Definite, probable, possible) is already listed in the Supplementary Table 3.

C3: Comment properly addressed (p.41,Table 3 & p.62-Outcomes), no further comments

C1: Ischemic end-points include non-coronary events. Although stroke has been included in the endpoints of ATLASTIMI 51, systemic embolism is a novel approach. Antiplatelet and anticoagulant treatment is valid for prevention of PAD- related events, but definition and documentation protocols for this very general term should be established, if it is to be used as an end-point.

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A1: Thank you for your question. Systemic Embolism is defined as sudden loss of extremity and organ perfusion with clinical and objective evidence (See details and reference in the updated Supplementary Table 3).
C2: Addressed in previous comment.

C1: Ischemia-driven revascularization is directly related to residual ischemic disease after culprit vessel intervention. How will the researchers adjust for this potential confounder in the two groups formed? There are no angiographic data included in the scheduled data for acquisition...Also, how will patients deemed candidates for repeat PCI for severe residual CAD during the index PCI be handled. These patients usually undergo a staged procedure during the index hospitalization or shortly after and there is a need to define planned vs. unplanned PCI revascularization, if revascularization is going to be used as an endpoint.

A1: Revascularization was defined as ischemia-driven if it was associated with any of the following: Angiography Core Laboratory (ACL) reported QFR or field reported FFR ≤ 0 80 or iFR ≤ 0 89; Patients with ischemic symptoms or positive non-invasive functional tests, quantitative coronary angiography [QCA] showed stenosis ≥ 50% in diameter; Patients with no ischemic symptoms or positive non-invasive functional tests with ≥70% stenosis of lesion diameter by QCA. If patients are deemed necessary for repeat PCI for residual CAD, patients will be advised to either stay in the hospital until a repeat PCI is performed (usually within 1 week) or discharge and return for re-admission for planned repeat PCI after a certain amount of time. If a patient experience severe ischemic events before the planned repeat PCI, the repeat revascularization will still be considered ischmia-driven. That is to say, the majority of residual CAD after index culprit lesion PCI would be relatively stable and therefore not lead to unplanned ischemiadriven revascularization.

C2: Please re-read the comment and try to understand it. I did not ask for the definition of ischemiadriven revascularization (IDR), nor for the logistics of the care of the patients undergoing repeat procedures. Furthermore, authors provided a definition of IDR in the end-points Table that introduces further questions and concerns, as they now mention an Angiography Core Laboratory which was not included in the design of the former version of the manuscript. Actually, there is no information about baseline angiographic data collection at all, not to mention how these data will be handled in terms of functionally or anatomically significant residual stenoses. In general, IDR is considered as a weak endpoint and, when used, it is common practice to use unplanned IDR, instead of simply IDR. This practice, a most recent prime example of which can be found in the MULTISTARS AMI trial (DOI: 10.1056/NEJMoa2307823), simplifies end-point adjudication and reduces inhomogeneity of trial groups as far as revascularization concerns. I suggest that, if the authors insist on using IDR as an endpoint, to only use unplanned IDR in the composite, and clarify that any IDR triggered by the baseline angiographic results within a specific period after the culprit vessel index procedure (1-3 months) will not count as an end-point related event.

A2: We apologize for the misunderstdanding. As addressed in a previous comment, we have replaced IDR with unplanned IDR in throughout the manuscript to avoid any further confusion. The definition of unplanned IDR in our study is now in line with the one used in MULTISTARS AMI trial.
C3: The definition of ischemia-driven revascularization is now given in the supplementary Table. Please apply the corrections mentioned regarding the description of the term in a previous comment and the issue will be fully settled.

A3: Thank you for your comments, the corrections have been made in response to the previous comment.

C1: How will patients who are enrolled and subsequently undergo CABG be handled? For example, patient with 3VD, low EF and DM who undergoes culprit PCI because of STEMI or high risk NSTEMI. Will such a patient be excluded or censored if he/she subsequently undergoes CABG?

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C2: Part of this comment was addressed here, another part is discussed in the previous comment. Add a brief comment about the fate of the patients undergoing CABG after PCI in the main text or the eligibility criteria supplement.
A2: Thank you for your suggestion. We have now added an exclusion criteria (number 26) with asterisk in the eligibility criteria supplement, which further explains their fate below the table.

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C1: Researchers calculated a sample size of 3548 (1774 for each group) patients based on their assumptions. Regarding previous studies included in these assumptions, I see that these include the ATLAS-TIMI 51, but also two other trials in populations that I feel are not relevant to the present study. In ATLAS-TIMI-51, which used as a primary efficacy end point a composite of CV death, MI, or stroke, the respective rates were 8.9% and 10.7%. Given that the population of this study carries a higher ischemic risk than the ATLAS-TIMI-51, the quoted rates of 13% for the control group seem plausible, but not necessarily supported by hard evidence. After all, the authors themselves mention that residual ischemic risk in the ACS population undergoing PCI is between 5-10%. Can the authors indicate any specific study supporting a higher than 10% residual ischemic risk in contemporary ACS patients undergoing PCI?
A1: Thank you for your question. Our sample size calculation is based on several contemporary trials as well as estimation from our own cohort of Chinese patients undergoing PCI. In addition to ATLAS TIMI51 trial, the CREATIVE trial reported a 12-month MACE incidence of 13% in the control group (DAPT), and 6.8% in the experiment group (DAPT+cilostazol). See reference here: Tang YD, Wang W, Yang M, Zhang K, Chen J, Qiao S, Yan H, Wu Y, Huang X, Xu B, Gao R, Yang Y; CREATIVE Investigators. Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol Versus Standard Dual Antiplatelet in Patients With High Posttreatment Platelet Reactivity: Results of the CREATIVE Trial. Circulation. 2018 May 22;137(21):2231-2245.
C2: Although CREATIVE trial involved patients with confirmed low responsiveness to clopidogrel hence, not fully applicable to this study's population, in the broader sense it provides some support for a high of 13% as far as MACE concern in high ischemic risk populations in general. It will suffice.
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C1: Authors mention the use of IWRS for the purpose of randomization with no further details. I would like to highlight the importance of addressing all the major factors that need to be balanced in the two groups of the study. Major, evidence based risk factors for future MACE in this population should be clearly defined by the authors before randomization and consideration should be given also to residual anatomic CAD after culprit PCI, especially if revascularization is used as an end-point. The latter is an aspect not addressed in ATLAS-TIMI-51, which nevertheless did not include revascularization as an endpoint.
A1: Thank you for your comments. We have now added text addressing major risk factors balanced by IWRS method (Methods section, Allocation and Interventions subsection, 2nd paragraph). Since planned revascularization is not an endpoint, which typically happens during the index hospital stay or after a relatively short period after index PCI, there is no need to address residual anatomic CAD after culprit PCI.
C2: Instead of adding this meaningless extra text regarding the IWRS (I suggest to keep the initial form of the text), authors should provide in the supplement, the parameters that they feel that need to be balanced among the two groups, as far as risk factors concern, along with a reference about this system's prior use, if available. The issue of planned PCI has been settled in previous comments.
A2: Thank you for your suggestion. Before randomization, patients' age and sex are entered into the system, so these two parameters are balanced between the groups. We have changed the text in the manuscript to the initial form, and added parameters that need to be balanced among the groups in the same subsection (since only 2 parameters are involved, we did not add another section in the supplemental materials). Since this is the first multicenter RCT reported by our team, we do not have prior experience of using this IWRS system

C3: The response of the authors to this comment (p.61, line 1-28) is particularly problematic and nearly alarming, as it makes me question not only if the authors understand the concept of the IWRS but also if they are using it correctly. In the usual practice of RCTs conduction, randomization is achieved by the use of interactive response technology, one form of it being the Interactive Web Response System. With this technology, a network-based central randomization system is used to complete the random allocation of subjects to control and treatment.

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Surprisingly, the authors mention the use of this system, which automatically and independently generates and handles the randomization schedule, and at the same time the allocation of treatment by an independent investigator, i.e manually. Furthermore, the text implies that the randomization will be based on only two variables, i,e age and gender. Despite my serious concerns about what is actually happening with the randomization process of this trial, I suggest to replace the text in lines 1-28 of page 61 with the following text: "Randomization of patients to the experiment or the control group at 1:1 ratio will be performed with the use of an Interactive Web Respond System (IWRS), which will independently generate and handle the randomization schedule and treatment allocation will not be known by any investigators in advance. Through the IWRS randomization process, all major risk factors for the end-point of the study (defined by the investigators of the trial) will be automatically balanced between the two groups".

A3: Thank you for your advice, we have now replaced the corresponding text according to your suggestion.

DDimers
C1: What is the rationale for repeated measurements at 3, 6 and 12 months?
A1: Thank you for your question. Repeated measurement of D-dimer is carried out for the following reasons: First, for research purpose, to measure the effect of antithrombotic therapy and later investigate if the fluctuation of D-dimer levels are associated with ischemic events. Second, for medical purpose, as part of a routine check-up after PCI, to rule out potential DVT/PE.
C2: I am not aware of any literature supporting these rationales, which seem arbitrary at least. If the authors plan to perform secondary analyses using DD fluctuations, they should include this plan in the methods section, along with some kind of reference supporting a basis for using DD for antithorombotic efficacy monitoring. There is absolutely no indication for routinely measuring DD after PCI in asymptomatic patients to rule out DVT/PE.
A2: Thank you for your suggestion. We have now added our plan of the secondary analysis (with reference of D-dimer being used as thrombus marker) to the 3rd paragraph of the Statistical Methods subsection of the Methods section. C3: The answer of the authors to this comment is covered in a previous comment and the issue is settled.

C1: From a diagnostic point of view, DD is a marker with high negative prognostic value and low specificity used predominately for the exclusion of pulmonary embolism or large vessel thrombosis/dissection in the ED population presenting with chest pain and/or shortness of breath. I understand that the authors aim as a side benefit of the study to support the prognostic role of DD but I am concerned that there is no provision or mention in the eligibility criteria about the exclusion of other major causes associated with DD elevation.

A1: Thank you for your questions. Major causes for D-dimer elevation is now added to the exclusion criteria (Supplementary Table 1, exclusion criteria number 26).
C2: Comment properly addressed

Minor issues
C1: The manuscript could benefit from a slight linguistic review, as several sentences require better wording. There is an occasional feeling, that patches of text from various different sources have been incorporated in the manuscript without the appropriate consideration for homogeneity (tenses, plural vs. singular, choice of words, text vs. bulleted format, etc) and overall linguistic standards. Examples include among others, lines 16-17 (p.6), lines 16- 19 (p.7), lines 6-10 & 53-56 (p.34), numbers 6, 7 of inclusion criteria and numbers 20 & 22 of exclusion criteria.
A1: Thank you for your suggestion. We apologize for the linguistic errors and have made corresponding changes in the text listed above. We have reviewed the manuscript for linguistic errors to improve readability.
C2: The need for an overall linguistic review still remains, as I mentioned to my comments to the Editor. The manuscript feels like a collection of patches hence, in terms of readability and grammar requires an overall linguistic review. Most characteristic examples of this problem include the following: p.60-lines 19,23,37,57 /p.62-line 29 /p.64-line 4, 42 (tenses, single vs. plural, etc)/p.68-line 30-38.. The Editor will be the final judge of whether the article is up to the linguistic standards of the journal.

A2: Thank you for your suggestion. We have made linguistic corrections in the locations mentioned to improve readability.

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C1: The detailed description of the results of the trials included in the Discussion section, should be abbreviated and tailored to the nature of the present manuscript, which is reporting of a study design in ACS patients, not reporting of results of an original study in patients with either ACS or stable CAD. Discussion should focus more on what new this research will bring compared to current knowledge and why this will be important.

A1: Thank you for your suggestions. We have now abbreviated non-essential results of previous studies and kept those key study results closely related to the design of our study in the discussion. We hope this would better highlight the importance of our study design.
C2: Comment properly addressed

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