PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of a standardized heart team protocol versus a guideline-based protocol on revascularization decision stability in stable complex coronary artery disease: rationale and design of a randomized trial of cardiology specialists using historic cases
AUTHORS	Ma, Hanping; Lin, Shen; Li, Xi; Yang, Wang; Xu, Bo; Zheng, Zhe

VERSION 1 – REVIEW

REVIEWER	William Wijns Onze Lieve Vrouw Hosp
REVIEW RETURNED	15-Jul-2022

GENERAL COMMENTS	The authors are set out to perform a randomized comparison between standardized protocol or guideline-based protocol for retrospective case discussion by heart teams. The study will be large involving 84 specialists, 26 hospitals, 12 heart teams and 480 retrospectively discussed patients. Primary endpoint will be decision stability but outcome metrics will be obtained as well from patient follow-up. The manuscript is well written although some sentences seem to be repeated twice or sometimes more. The methods are very well described and sufficient details are provided such that anyone who would like to implement the standardized heart team protocol will find all the needed information to allow for prompt local implementation. As such, this manuscript that describes the planned protocol will be a great resource and may contribute to a much improved process for heart team decisions. I only have minor remarks. It is stated that all patients have provided written informed consent for the study, which seems impossible given the retrospective design. Is it possible that the authors mean that all participating physicians have provided informed consent. How will you deal with actual treatment decisions that are not in keeping with the heart team recommendations in each randomization arm? How will these cases be adjudicated with respect to evaluation of the consistency of the decisions?

REVIEWER	Korakoth Towashiraporn Mahidol University, Her Majesty Cardiac Center
REVIEW RETURNED	28-Sep-2022

GENERAL COMMENTS	Thank you editor to invite me to review this interesting work and congratulation to all authors for such an excellent research protocol. I think this research protocol may need some minor revisions before

	publication. Please find my comments below.: 1. As the median SYNTAX score is 22.5. The median LVEF is 63% and only 4.3% of the population has LVEF of less than 40%. In addition, only 1.5% of the population has kidney impairment. As a result, the complexity of the lesion and the patient would not be appropriate to classify as "complex" CAD as described in the manuscript's title. 2. Please explain whether only cardiac surgeons are required to undergo the personality test and please give the information regarding the utilization of TIPI-C in clinical practice. Why were only cardiac surgeons with moderate TIPI-C only selected (page 11 line 50)? 3. For the inclusion criteria, how could the authors evaluate the proficiency in the clinical practice guidelines of the heart team specialist (page 9 table 1)? 4. Please explain the criteria "Capable for CTO PCI" for the interventional cardiologist (page 9 table 1). 5. Please explain why the non-interventional cardiologist only participates in the guideline-based group (not in the standardized protocol group). 6. Who would take responsibility for adjudicating the appropriate use criteria (the secondary outcome: Inappropriate decision rate: page 14 line33)? 7. Regarding the secondary outcome (page 14 line 9). Please explain why only the 1-year MACCEs rate should be the secondary outcome. Or do the authors aim to demonstrate the relation between the percentage agreement and the 1-year MACCEs rate? 8. Please give more information regarding the reference (unpublished data: page 16 line 32). 9. Please give more information regarding the reference ("the minimum estimate of the previous literature: page 16 line 37). 10. Because the heart team's decision does not affect the patient's actual treatment (page 24 line 37). Please explain how would the decision stability will be associated with 1-year MACCEs (page 4 line 55). As the decision does not lead to the actual treatment.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer #1

Comment 1: The manuscript is well written although some sentences seem to be repeated twice or sometimes more.

Response: Thanks for your comment. We have appealed to a native English-speaking colleague for assistance and polished up the manuscript for publication. The revised manuscript expression will be more native and readable.

Comment 2: It is stated that all patients have provided written informed consent for the study, which seems impossible given the retrospective design. Is it possible that the authors mean that all participating physicians have provided informed consent?

Response: We appreciate the comment. The cases discussed in this study are selected from a prospective registry of consecutive patients who underwent coronary angiography between August 2016 and August 2017. At the time of registry, all the registered patients provided written informed consent and agreed to use their data for subsequent approved cardiovascular-related medical research. All physicians and surgeons are prospectively enrolled and have provided written informed consent. To avoid confusion, we have revised the statement of participant informed consent as below (Line 252 to line 253 on page 8, line 306 to line 307 on page 10):

… All participating specialists have provided written informed consent for enrollment (Supplemental File 2).

…All cases provided written informed consent at the time of registration and agreed to use their data for subsequent approved cardiovascular-related medical research.…

Comment 3: How will you deal with actual treatment decisions that are not in keeping with the heart team recommendations in each randomization arm? How will these cases be adjudicated with respect to evaluation of the consistency of the decisions?

Response: Thanks for your comment and we apologize for your confusion. We assume that you thought our primary goal is to compare the actual treatment decisions with heart team decisions in different groups, and we explain it as follows:

The primary aim of this study is to evaluate the inter-team decision-making agreement in each randomization arm, without consideration of the actual treatment decisions, and the assumption is heart teams organized by the standardized protocol perform better on decision stability than the guideline-based group. While in further exploratory analysis, we will compare the heart team recommendations with the actual treatment decisions in all cases, and demonstrate whether 0adhering to heart team recommendations is associated with better outcomes.

Response to reviewer #2

Comment 1: As the median SYNTAX score is 22.5. The median LVEF is 63% and only 4.3% of the population has LVEF of less than 40%. In addition, only 1.5% of the population has kidney impairment. As a result, the complexity of the lesion and the patient would not be appropriate to classify as "complex" CAD as described in the manuscript's title.

Response: We appreciate the comment and we acknowledge that the tile is inappropriately expressed. All cases in this study are **stable** complex CAD according to the National Cardiovascular Data Registry (NCDR) CathPCI criteria[1] (stable angina, no or silent myocardial ischemia) and angiographically confirmed 3-vessel disease or left main (3VD/LM) disease, for which the guidelines recommend to be discussed by the heart team and not be treated ad hoc.[2, 3] Previous heart team studies indicated that there are nearly 60%-68% ACS patients among complex CAD.[4-6] Thus, cases in our study might be less complicated with less comorbidity. To be more precise, we have revised the article title to “Effect of a standardized heart team protocol versus a guideline-based protocol on revascularization decision-making stability in **stable** complex coronary artery disease: rationale and design of a randomized trial”.

Reference:

[1] Registry C. NCDR CathPCI Registry v4.4 Coder's Data Dictionary [J].

[2] Head S J, Kaul S, Mack M J, et al. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease [J]. Eur Heart J, 2013, 34(32): 2510-2518. DOI:10.1093/eurheartj/eht059.

[3] Neumann F J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization [J]. Eur Heart J, 2018, DOI:10.1093/eurheartj/ehy394.

[4] Young M N, Kolte D, Cadigan M E, et al. Multidisciplinary Heart Team Approach for Complex Coronary Artery Disease: Single Center Clinical Presentation [J]. J Am Heart Assoc, 2020, 9(8): e014738. DOI:10.1161/JAHA.119.014738.
[5] Witberg G, Segev A, Barac Y D, et al. Heart Team/Guidelines Discordance Is Associated With Increased Mortality: Data From a National Survey of Revascularization in Patients With Complex Coronary Artery Disease [J]. Circ Cardiovasc Interv, 2021, 14(1): e009686. DOI:10.1161/CIRCINTERVENTIONS.120.009686.
[6] Patterson T, McConkey H Z R, Ahmed-Jushuf F, et al. Long-Term Outcomes Following Heart Team Revascularization Recommendations in Complex Coronary Artery Disease [J]. J Am Heart Assoc, 2019, 8(8): e011279. DOI:10.1161/JAHA.118.011279.

Comment 2: Please explain whether only cardiac surgeons are required to undergo the personality test and please give the information regarding the utilization of TIPI-C in clinical practice. Why were only cardiac surgeons with moderate TIPI-C only selected (page 11 line 50)?

Response: Thanks for your comment. There was evidence in our previous mixed method study [7] that personality affects decisions, but the extent of influence varies by specialist disciplines. Surgeons' and non-interventional cardiologists' decisions were more likely to be influenced by personality and specialists with moderate TIPI-10 score performed more stable in decision-making. In contrast, the decision was more stable in interventional cardiologists regardless of personality. Therefore, in the standardized protocol, we recommended the team, if possible, invite surgeons and non-interventional cardiologists with moderate personalities.

Reference:

[7] Ma H, Lin S, Li X, et al. Exploring optimal heart team protocol to improve decision-making stability for complex coronary artery disease: a sequential explanatory mixed method study [J]. Eur Heart J Qual Care Clin Outcomes, 2021, DOI:10.1093/ehjqcco/qcab074.

3. For the inclusion criteria, how could the authors evaluate the proficiency in the clinical practice guidelines of the heart team specialist (page 9 table 1)?

Response: We appreciate the comment. At the start of specialist enrollment, we invited all the potential participating specialists to complete a questionnaire about the latest high-level clinical

evidence and guideline recommendations on coronary revascularization. Only specialists with full marks are considered proficient in the clinical practice guidelines.

4. Please explain the criteria "Capable for CTO PCI" for the interventional cardiologist (page 9 table 1).

Response: Thanks for your comment. According to previous study [8] and experience in our center, the criteria “capable for CTO PCI” means the interventional cardiologists should be skilled in CTO PCI and have performed CTO PCI no less than 10 cases independently. For better understanding, we revised the specific criteria to “CTO PCI total volume ≥10”.

Reference:

[8] Young M N, Secemsky E A, Kaltenbach L A, et al. Examining the Operator Learning Curve for Percutaneous Coronary Intervention of Chronic Total Occlusions [J]. Circ Cardiovasc Interv, 2019, 12(8): e007877. DOI:10.1161/CIRCINTERVENTIONS.119.007877.

5. Please explain why the non-interventional cardiologist only participates in the guideline-based group (not in the standardized protocol group).

Response: We appreciate the comment. There was evidence in our previous mixed method study [7] that non-interventional cardiologists may be an unstable factor in decision-making and are indispensable in the routine heart team. They could be invited only if necessary. Thus, the standardized heart team protocol recommends the non-interventional cardiologist could not be routinely included in the team. While in the coronary revascularization guideline [3], a heart team comprising cardiac surgeons, interventional cardiologists, and non-interventional cardiologists is recommended. As a result, the non-interventional cardiologist only participates in the guideline-based group instead of the standardized protocol group.

Reference:

[3] Neumann F J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization [J]. Eur Heart J, 2018, DOI:10.1093/eurheartj/ehy394.

[7] Ma H, Lin S, Li X, et al. Exploring optimal heart team protocol to improve decision-making stability for complex coronary artery disease: a sequential explanatory mixed method study [J]. Eur Heart J Qual Care Clin Outcomes, 2021, DOI:10.1093/ehjqcco/qcab074.

6. Who would take responsibility for adjudicating the appropriate use criteria (the secondary outcome: Inappropriate decision rate: page 14 line33)?

Response: Thanks for your comment. Two investigators who do not participate in data collection will take responsibility for reviewing the team decisions and adjudicating the decision appropriateness independently. Any disputes will be settled via review by a third investigator, with decision by consensus. To be more understandable, we revised the manuscript regarding the details of appropriateness adjudication as below: (Line 437 to line 440 on page 15)

(3) Inappropriate decision rate: the final heart team recommendations will be adjudicated for appropriateness using the American College of Cardiology (ACC) /American Association for Thoracic Surgery (AATS) /American Heart Association (AHA) 2017 Appropriate Use Criteria (AUC) and the Chinese AUC for coronary revascularization for each case. Two investigators who do not participate in data collection will take responsibility for reviewing the team decisions and adjudicating the decision appropriateness independently. Any disputes will be settled via review by a third investigator, with decision by consensus.

7. Regarding the secondary outcome (page 14 line 9). Please explain why only the 1-year MACCEs rate should be the secondary outcome. Or do the authors aim to demonstrate the relation between the percentage agreement and the 1-year MACCEs rate?

Response: We appreciate the comment. As for the follow-up time of the outcome, only 1-year MACCEs have been recorded in the registry database. To explore the clinical implication of the standardized protocol, we will compare the actual treatment decision with the heart team decision, and cases will be classified as heart team decision agreement /discordant. We will further explore the association between heart team decision adherence and 1-year clinical outcome.

8. Please give more information regarding the reference (unpublished data: page 16 line 32).

Response: Thanks for your comment. In our previous study [7], we established four heart teams based on guideline recommendations and made revascularization decisions for 101 stable complex CAD cases. The implementation process is accordant with the guideline-based protocol in this study, and heart team decisions were compared for all cases. In the *post-hoc* analysis, the overall percent agreement (OPA) is estimated to be 66.3%, which serves as the reference rate of the guideline-based group in the present study.

Reference:

[7] Ma H, Lin S, Li X, et al. Exploring optimal heart team protocol to improve decision-making stability for complex coronary artery disease: a sequential explanatory mixed method study [J]. Eur Heart J Qual Care Clin Outcomes, 2021, DOI:10.1093/ehjqcco/qcab074.

9. Please give more information regarding the reference ("the minimum estimate of the previous literature: page 16 line 37).

Response: We appreciate the comment. Our study assumes that the standardized heart team protocol performs better than the guideline-based protocol on decision-making stability. For sample size calculation, the OPA of each randomization arm is needed. However, there is no data on inter-team decision stability in the standardized group. Thus, we assume that the inter-team agreement in the standardized group is similar to or no better than the reproducibility rate of the guideline-based group. After the literature review, we found the reproducibility rate ranged from 76% to 80%[9, 10]. Less effect size is associated with a larger sample size. For sake of conservation, we use the minimum estimate of the reproducibility rate as the OPA of the standardized group.

Reference:

[9] Pavlidis A N, Perera D, Karamasis G V, et al. Implementation and consistency of Heart Team decision-making in complex coronary revascularisation [J]. Int J Cardiol, 2016, 206(37-41. DOI:10.1016/j.ijcard.2016.01.041.
[10] Long J, Luckraz H, Thekkudan J, et al. Heart team discussion in managing patients with coronary artery disease: outcome and reproducibility [J]. Interact Cardiovasc Thorac Surg, 2012, 14(5): 594-598. DOI:10.1093/icvts/ivr157.

10. Because the heart team's decision does not affect the patient's actual treatment (page 24 line 37). Please explain how would the decision stability will be associated with 1-year MACCEs (page 4 line 55). As the decision does not lead to the actual treatment.

Response: Thanks for your comment. Prior data showed that 18.1% of the overall decision-making for stable angina patients was classified as inappropriate based on single disciplinary decisions, especially among patients undergoing PCI [11]. Qualified heart teams perform more evidence-based and neutral in revascularization decision-making [12], which leads to increased stability and appropriateness in decision-making [7]. In addition, appropriate revascularization is associated with improved 1-year outcomes in patients with appropriate indications and has no benefit in those with uncertain or inappropriate indications. [13] Thus, we want to explore whether the decision stability of dedicated heart teams organized by the standardized heart team protocol would be associated with better clinical outcomes, which does not influence the main purpose of this study.

VERSION 2 – REVIEW

REVIEWER	Korakoth Towashiraporn Mahidol University, Her Majesty Cardiac Center
REVIEW RETURNED	23-Oct-2022

GENERAL COMMENTS	This revised version of this manuscript has improved in quality. I am satisfied that this manuscript is now appropriate for publication. However, I still have one question regarding the secondary endpoint. As the secondary endpoint of this study is to evaluate the association between decision-making stability and 1-year MACCEs (page 8 line 27). On the other hand, one of the limitations that the author state is that "case discussed are retrospectively selected ..... unable to reveal the true impact and benefits of heart team meetings on real-world decision-making and outcomes in routine clinical practice (page 25 line 25-33). Please explain how the decision-making stability (with the retrospective data) would impact the clinical outcomes.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer #2

Comment 1: This revised version of this manuscript has improved in quality. I am satisfied that this manuscript is now appropriate for publication.

Response: We appreciate the comment.

Comment 2: As the secondary endpoint of this study is to evaluate the association between decision-making stability and 1-year MACCEs (page 8 line 27). On the other hand, one of the limitations that the author state is that "case discussed are retrospectively selected ..... unable to reveal the true impact and benefits of heart team meetings on real-world decision-making and outcomes in routine clinical practice (page 25 line 25-33). Please explain how the decision-making stability (with the retrospective data) would impact the clinical outcomes.

Response: Thanks for the comment. To further explore the association between decision stability and 1-year clinical outcome, we will stratify the agreement and disagreement by the inter-team pairwise comparison, and evaluate whether a patient's treatment adherence to the heart team recommendation with the concordant decision is associated with a better 1-year outcome. As the manuscript mentioned, cases in this study are historic and heart team recommendations do not have a direct impact on the actual treatment, so we only assess the statistical association between decision stability and clinical outcomes for the exploratory purpose, which may not adequately powered but does not influence the main purpose of this study. Prospective design is needed to assess the causal link between heart team decisions and clinical outcomes.

VERSION 3 – REVIEW

REVIEWER	Korakoth Towashiraporn Mahidol University, Her Majesty Cardiac Center
REVIEW RETURNED	14-Nov-2022

GENERAL COMMENTS	The revised version of this manuscript is well-written. I would like to suggest that this manuscript is now ready for publication— congratulation to the authors.