PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quantitative coronary angiography versus intravascular ultrasound guidance for drug-eluting stent implantation (GUIDE-DES): study protocol for a randomised controlled non-inferiority trial
AUTHORS	Lee, Pil Hyung; Hong, Soon Jun; Kim, Hyun-Sook; Yoon, Young won; Lee, Jong-Young; Oh, Seung-Jin; Kang, Soo-Jin; Kim, Young-Hak; Park, Seong-Wook; Lee, Seung-Whan; Lee, Cheol Whan

VERSION 1 – REVIEW

REVIEWER	Sato , A Tsukuba Daigaku Igaku Bumon, Cardiology
REVIEW RETURNED	15-Jun-2021

GENERAL COMMENTS	The authors aimed to assess whether choosing the appropriate DES size by a novel on-site QCA-based algorithm and routine incorporation of high-pressure post-dilation with an IVUS may attenuate the disadvantage of the traditional angiography-guided PCI. The author's manuscripts are actual and clinically relevant design protocol. However, several issues should be considered to assess the results in this paper. My comments are related to the following points: 1) Many previous papers have been reported in the past comparing IVUS- and angio-guided PCI. What are the differences and highlights compared to many studies reported in the past? 2) The authors mentioned that "Multiple balloon dilations within the stent should be performed until adequate stent expansion is achieved, preferably assessed by stent boost subtract imaging." Please discuss if use of stent boost subtract imaging affects the results of this study. 3) How do you evaluate the side branches?

REVIEWER	van Royen, Niels Radboudumc, Cardiology
REVIEW RETURNED	18-Jun-2021

GENERAL COMMENTS	This is an important study that is well designed. Only a few remarks: The inclusion criterium "Typical chest pain or objective evidence of myocardial ischaemia"' suggests that only patients with CCS and not with ACS are included. However, in the text it is stated that both CCS and ACS can be included. I think it is better to do the

	study either in CCS or in ACS because the endpoints that will accumulate are different in number and also in importance. For CCS it would for example be important to include also angina class, since imperfect stent result could translate in persistence of angina. An alternative is a prespecified subanalysis but this would probably lead to a lack of power for the two different entities. In the angio-guided group no post-PCI QCA is performed, could this not further improve the outcome of this strategy? The stent optimization criteria for IVUS are not entirely clear with regard to the proximal vessel reference. How is this handled? Also, what is meant with complete vessel apposition. Is there a maximum number of non-apposed struts? Distance to vessel wall? Is it mandatory to perform post-PCI IVUS or is this left to the discretion of the operator. Please specify in the protocol. Please use 4th instead of 3rd Universal Definiton of MI

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1

The authors aimed to assess whether choosing the appropriate DES size by a novel on-site QCA-based algorithm and routine incorporation of high-pressure post-dilation with an IVUS may attenuate the disadvantage of the traditional angiography-guided PCI.
The author's manuscripts are actual and clinically relevant design protocol. However, several issues should be considered to assess the results in this paper.

RESPONSE: Thank you for your in-depth review of our protocol paper. We have accepted all the comments you provided and were reflected in the final manuscript. Please consider that our study compares QCA-guided PCI vs. IVUS guided PCI, and thus, IVUS is not used in the QCA-guided PCI group.

1. Many previous papers have been reported in the past comparing IVUS- and angio-guided PCI. What are the differences and highlights compared to many studies reported in the past?

RESPONSE: Traditional angiography-based PCI is inherent to 2-step variability that significantly affects the operators' size selection of stent or balloon, frequently associated with underestimating vessel size and suboptimal stent results. The first step variability is made during visual estimation of the coronary artery diameter with the angiogram. The second step variability is made during size selection based on this visually assessed vessel diameter (It is well known that there is a significant discrepancy between the diameter evaluated by angiography and IVUS). All previous trials comparing IVUS- vs. angio-guided PCI penalized the angio-guided group in that they did not provide any guidance for the angiography-guided PCI, and the PCI process was left to the operator's visual estimation and experience. Our study can be clearly distinguished from previous studies in that the investigational group (designated as QCA-guided group) in our study uses a standardized QCA-based PCI protocol. We have incorporated on-site QCA to overcome the first step variability and developed a size selection algorithm based on the QCA measurement that closely corresponds to the IVUS measurement to overcome the second step variability. This standardized angiography-based PCI procedure will contribute to select an appropriately sized stent or balloon and reduce intra- or interindividual variability during PCI. We believe our study results may significantly impact many

catheterisation laboratories where IVUS is not available. We already have explained this aspect in the manuscript but additionally modified some parts to highlight it.

P2. Abstract
A novel, standardized, QCA-based PCI protocol for the QCA-guided group will be provided to all participating operators, while the PCI optimisation criteria will be predefined for both strategies.

P17. Discussion
Thus, an overlooked unmet need regarding PCI is to find a way to improve outcomes of DES in a typical circumstance when IVUS is not available. An important step forward would be developing a method to overcome the drawback of conventional angiography-guided PCI. Our study has incorporated QCA into clinical context and developed a novel size selection algorithm based on the QCA measurement, which standardizes the angiography-based PCI procedure to select an appropriately sized stent or balloon without significant intra- or interindividual variability.

2. The authors mentioned that “Multiple balloon dilations within the stent should be performed until adequate stent expansion is achieved, preferably assessed by stent boost subtract imaging.” Please discuss if use of stent boost subtract imaging affects the results of this study.

RESPONSE: The purpose of encouraging the use of stent boost subtract imaging is 1) to reliably detect an under-expanded portion of the stent and 2) to accurately locate the high-pressure balloon at stent edges and lower the risk of edge dissection. Incorporating the stent boost imaging will likely aid stent optimization during the QCA-guided PCI. The methodology and purpose of this technique have been presented in Figure 2, Supplemental Figure 3, and the Discussion section (P19, line 9-14). Thank you for this comment.

3. How do you evaluate the side branches?

RESPONSE: We appreciate this comment. Our trial does not exclude any native coronary vessels or lesions except for those in which impaired delivery of IVUS is expected. Our novel PCI protocol used for QCA-guided PCI is readily applicable to main epicardial arteries and side branches in the same way and can also be used for the 2-stent technique. We made this clear in the manuscript.

P10. Methods and analysis, Study procedure
This QCA-based PCI algorithm is applicable to main epicardial arteries and side branches and can also be used for the 2-stent technique. The ideal final result would be a harmonious appearance between the reference segment and the stent without dissection and minimal residual stenosis (<10%) on angiography.25

REVIEWER #2
1. This is an important study that is well designed. Only a few remarks:
The inclusion criterium “Typical chest pain or objective evidence of myocardial ischaemia”’ suggests that only patients with CCS and not with ACS are included. However, in the text it is stated that both CCS and ACS can be included. I think it is better to do the study either in CCS or in ACS because the endpoints that will accumulate are different in number and also in importance. For CCS it would for example be important to include also angina class, since imperfect stent result could translate in persistence of angina. An alternative is a prespecified subanalysis but this would probably lead to a lack of power for the two different entities.

RESPONSE: We sincerely thank you for acknowledging the value of our work and for your valuable comments. We agree that the wording “Typical chest pain or objective evidence of myocardial ischaemia” in the inclusion criteria may somehow imply that only CCS but not ACS can be included in the trial. However, the wording “objective evidence of myocardial ischaemia” also contains a broad CAD population (both CCS and ACS) considering that ECG change, the rise of cardiac biomarkers, findings of echo or stress test can all fall into this criterion. Please understand that it would be inappropriate to reword the phrase because the official protocol has already been distributed.
We agree that it would be ideal to separate the CCS and ACS population into two independent trials because of the reasons you mentioned. However, considering the difficulty of conducting such independent trials and the need for our PCI methodology to be tested in both clinical scenarios, we have decided to include various PCI-indicated patients in this trial. Please consider that numerous PCI trials evaluating DESs or drugs have done it similarly. Angina symptoms can be dependent not only on the immediate DES result but also on remnant coronary disease, anti-anginal medications, or so; thus, we have decided not to include CCS class as a secondary endpoint.

P6. Methods and analysis, Study population and randomisation
We will not impose restrictions regarding the clinical diagnosis (chronic or acute coronary syndrome) or location, length, or numbers of lesions to validate the QCA-based PCI algorithm in various PCI-indicated patients.

2. In the angio-guided group no post-PCI QCA is performed, could this not further improve the outcome of this strategy?

RESPONSE: We do not think that performing post-PCI QCA would affect the outcome in the QCA-guided PCI group. To overcome the well-known discrepancy between the diameter evaluated by angiography and IVUS, we adjusted (oversized) the pre-PCI QCA measurements to closely correspond to the IVUS measurements to guide PCI. Because we did not target post-PCI QCA parameters as a surrogate for stent optimization, we cannot provide any positive guidance on using on-site post-PCI QCA measurements for the study endpoint.

3. The stent optimization criteria for IVUS are not entirely clear with regard to the proximal vessel reference. How is this handled?

RESPONSE: We appreciate this comment. The second and third IVUS stent optimization criteria apply equally to both the proximal and distal vessel reference. In other words, there should be complete stent apposition, adequate stent expansion, and no significant edge dissection at the proximal vessel reference. We have slightly modified the terms to make this clearer. Please consider that the IVUS criteria for stent optimization adopted in our trial have been used and validated in prior landmark studies.

P11. Methods and analysis, Study procedure
The IVUS criteria for stent optimisation in this trial are as follows: 1) in-stent minimal lumen cross-sectional area > distal reference segment’s lumen cross-sectional area; 2) complete stent apposition; and 3) no significant proximal or distal edge dissection (media dissection, dissection angle ≥ 60o, or dissection length > 2 mm).3,26,27

4. Also, what is meant with complete vessel apposition. Is there a maximum number of non-apposed struts? Distance to vessel wall?

RESPONSE: Thank you for this comment. Unlike OCT which provides high axial resolution images and has an explicit criterion for strut malapposition (distance between a strut and vessel wall of ≤200μm), it is difficult to propose a specific image-based criterion for relatively low-resolution IVUS (accordingly, a clear IVUS definition of stent malapposition lacks from literature and consensus). In this case, a complete vessel apposition should mean that there should be no definite stent struts floating in the vessel lumen and are not apposed to the vessel wall by visual assessment. By experience, it is not difficult to assess a definite malapposition by IVUS, and we also think that trying to quantitatively measure the distance between the strut and vessel wall in the cath lab during PCI would be impractical.

5. Is it mandatory to perform post-PCI IVUS or is this left to the discretion of the operator. Please specify in the protocol.

RESPONSE: We appreciate this comment. Although IVUS can be used at any step of PCI, it is mandatory to perform post-stenting IVUS to assess stent optimization, which is critically important for the study endpoint. This recommendation is clearly written in the official protocol. We have included a sentence in the manuscript to make this clear.

P11. Methods and analysis, Study procedure
It is mandatory to perform IVUS after PCI to assess stent optimisation. The IVUS criteria for stent optimisation in this trial are as follows: 1) in-stent minimal lumen cross-sectional area > distal reference segment's lumen cross-sectional area; 2) complete stent apposition; and 3) no significant proximal or distal edge dissection (media dissection, dissection angle ≥ 60o, or dissection length > 2 mm).3,26,27 If the IVUS-defined optimal criteria are not met, additional procedures are needed.

6. Please use 4th instead of 3rd Universal Definiton of MI

RESPONSE: We appreciate this comment. Our study protocol was developed in 2016, and the first patient was enrolled in Feb 2017. We have used the third UDMI because the third UDMI was available at the time of study initiation, and the fourth UDMI was released in 2018. We would like to maintain to use the third UDMI because the official protocol including it was approved by the local IRB has already been distributed. However, please understand that it would not affect the study endpoint because the definition of spontaneous MI is identical between the third and fourth UDMI.

VERSION 2 – REVIEW

REVIEWER	Sato , A Tsukuba Daigaku Igaku Bumon, Cardiology
REVIEW RETURNED	27-Sep-2021

GENERAL COMMENTS	There are no comments for your revision. Thank you for the change and the explanations.