PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The treatment effects of systematic two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: Rationale and design of a prospective, randomized, and multicenter DEFINITION Ⅱ Trial
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VERSION 1 – REVIEW

REVIEWER	Massoud Leesar, MD University of Alabama, Birmingham, USA
REVIEW RETURNED	01-Nov-2017

GENERAL COMMENTS	There is a paucity of data on the treatment of complex bifurcation lesions. The present study is powered to show the impact of this study on target vessel failure in patients randomized to 2-stent technique vs. provisional stenting. The design of the study is well-written. The authors proposed a new classification scheme to better define complex bifurcation lesions. The study is novel and would provide knowledge on optimal treatment of complex bifurcation lesions.

REVIEWER	Yiannis Chatzizisis University of Nebraska Medical Center, Omaha, Nebraska, USA
REVIEW RETURNED	02-Nov-2017

GENERAL COMMENTS	This manuscript is a protocol of a prospective, randomized trial. This trial (DEFINITION II) will compare the efficacy of the two-stents approach to the provisional stenting approach on complex coronary bifurcation lesions. This trial is the sequence of an already published trial (DEFINITION trial) which defined the criteria for a bifurcation lesion to be considered as 'complex' and showed that complex bifurcation lesions had higher rates of 1-year MACE and stent thrombosis compared to 'simple (non-complex)' bifurcation lesions. Overall, DEFINITION II is an interesting trial, but similar to DEFINITION (even though DEFINITION II investigates more directly

	the comparison between the two stenting approaches). The manuscript needs extensive revision from a grammatical and syntactic standpoint. I am concerned regarding including the cardiac death as a primary and not a secondary endpoint. The results are highly anticipated but I am not quite sure that even if the 2 stents approach is proven to be superior the current practice of one stent technique will change as still a 'complex' bifurcation lesion will be treated based on the operator's perception. Specific comments: 1. The paper needs grammatical and syntactical revision. Paragraphs 2, 3 and 4 in the discussion sections need to be re-written. It should be decided whether the tense will be present or past (I opt for present tense since even some patients have been already enrolled, this is a protocol for a non-completed trial). 2. This trial compares provisional stenting (PS) vs 2 stents approach for complex bifurcation lesions. What if a number of PS randomized patients eventually need 2 stents? Wouldn't this change the structure, the 1 to 1 comparison (randomization) and the results of the study? 3. In DEFINITION trial, it has been already investigated and shown that for complex bifurcation lesions provisional stenting has increased in-hospital MI and 1-year cardiac death compared to two stents approach. Also, in the same study, it was shown that the rates of MACE, MI, and TVR at 1-year follow-up were similar between the two approaches. All these adverse incidents are also considered to be endpoints of the DEFINITION II trial. So, many of the new trial's endpoints have been already investigated. How the current trial differs from the previous one? 4. This trial defines as a primary endpoint the 12-month target lesion failure, which comprises cardiac death, target vessel myocardial infarction and target lesion revascularization. Why is the general term cardiac death is considered to be a target lesion failure? Also, as already mentioned, in DEFINITION trial it has been already shown that cardiac death is significantly higher in the provisional stenting approach compared to the 2 stents one. 5. It is not defined if target lesion failure addresses both main and side branches or just the side branch. 6. In the section where the stenting techniques of the side branch are being described, the authors should either describe all of the techniques or none. They only describe DK crush and they just give a reference for Culotte. 7. In the follow-up section the authors mention that angiographies will be performed 13 months after the PCI intervention, but in the whole manuscript they are referring to a '1 year' follow up. 8. Figure 1 needs to have a 'fig 1 etiquette' and it would be even better if the authors could add a timeline to make the figure more compelling.

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1:

Q. There is a paucity of data on the treatment of complex bifurcation lesions. The present study is powered to show the impact of this study on target vessel failure in patients randomized to 2-stent technique vs. provisional stenting. The design of the study is well-written. The authors proposed a new classification scheme to better define complex bifurcation lesions. The study is novel and would provide knowledge on optimal treatment of complex bifurcation lesions.
A. Thank you!

RESPONSE TO REVIEWER 2:

This manuscript is a protocol of a prospective, randomized trial. This trial (DEFINITION II) will compare the efficacy of the two-stents approach to the provisional stenting approach on complex coronary bifurcation lesions. This trial is the sequence of an already published trial (DEFINITION trial) which defined the criteria for a bifurcation lesion to be considered as 'complex' and showed that complex bifurcation lesions had higher rates of 1-year MACE and stent thrombosis compared to 'simple (non-complex)' bifurcation lesions.

Overall, DEFINITION II is an interesting trial, but similar to DEFINITION (even though DEFINITION II investigates more directly the comparison between the two stenting approaches). The manuscript needs extensive revision from a grammatical and syntactic standpoint. I am concerned regarding including the cardiac death as a primary and not a secondary endpoint. The results are highly anticipated but I am not quite sure that even if the 2 stents approach is proven to be superior the current practice of one stent technique will change as still a 'complex' bifurcation lesion will be treated based on the operator's perception.
Thank you very much. The detailed answers for comments are listed as follows.

Specific comments:
Q1. The paper needs grammatical and syntactical revision. Paragraphs 2, 3 and 4 in the discussion sections need to be re-written. It should be decided whether the tense will be present or past (I opt for present tense since even some patients have been already enrolled, this is a protocol for a non-completed trial).
A1. Thanks! Our revised manuscript has been further polished by American Journal Experts (AJE, a well-known organization for language editing).

Q2. This trial compares provisional stenting (PS) vs 2 stents approach for complex bifurcation lesions. What if a number of PS randomized patients eventually need 2 stents? Wouldn't this change the structure, the 1 to 1 comparison (randomization) and the results of the study?
A2. Thank you for the comments. As we have stated in Statistical Analysis in Methods on Page 8, the comparison of primary endpoint and individual component of secondary endpoints would be performed by "Intention-to-treatment (ITT)" principle. Crossover from 1-stent to 2-stent in Provisional group would have had no any impact on the final analysis.

Q3. In DEFINITION trial, it has been already investigated and shown that for complex bifurcation lesions provisional stenting has increased in-hospital MI and 1-year cardiac death compared to two stents approach. Also, in the same study, it was shown that the rates of MACE, MI, and TVR at 1-year follow-up were similar between the two approaches. All these adverse incidents are also considered to be endpoints of the DEFINITION II trial. So, many of the new trial's endpoints have been already investigated. How the current trial differs from the previous one?
A3. Thanks. DEFINITION was a two-center, registry study, from which the bias could not be completely excluded. Another point is that two-stent techniques were not defined before initialization of registry. Finally, complex bifurcation lesions served as a subgroup analysis in DEFINITION study,

an already known under-power to elucidate the real difference among stenting techniques. These are key reasons why DEFENITION-II study was designed with only complex bifurcation lesions being studied.

Q4. This trial defines as a primary endpoint the 12-month target lesion failure, which comprises cardiac death, target vessel myocardial infarction and target lesion revascularization. Why is the general term cardiac death is considered to be a target lesion failure? Also, as already mentioned, in DEFINITION trial it has been already shown that cardiac death is significantly higher in the provisional stenting approach compared to the 2 stents one.
Q4. Thank you for comment. The term of target lesion failure comprises cardiac death, target vessel myocardial infarction and clinically driven target lesion revascularization, an endpoint universally accepted by most top-level studies.
Again, the difference in cardiac death between provisional and systematic stenting approaches in DEFENITION study (as a registry trial) have to be confirmed by a RCT. Similarly, TLF was not the primary endpoint and criteria of MIs in DEFENITION study were different to those used in this new DEFENITION-II study.

Q5. It is not defined if target lesion failure addresses both main and side branches or just the side branch.
A5. Thank you! Target lesion failure addresses both main and side branches, which has been added in the definition of endpoints in the supplemental material. However, the differentiation from MV to SB in the setting of sudden cardiac death is impossible, and usually restenotic lesions involve both the MV and SB. TLR is defined as clinically-driven revascularization, which will unmask the effect of visual-stenotic reflex.

Q6. In the section where the stenting techniques of the side branch are being described, the authors should either describe all of the techniques or none. They only describe DK crush and they just give a reference for Culotte.
A6. Thanks for your reminder. We have added the description of Culotte in Method part on page 6.

Q7. In the follow-up section the authors mention that angiographies will be performed 13 months after the PCI intervention, but in the whole manuscript they are referring to a ‘1 year’ follow up.
A7. We appreciate your comments very much! Clinical follow-up is performed by office visit or telephone contact at 12months (Primary endpoint, Figure 1). Follow-up coronary angiography is scheduled at 13 months following the index procedure in all patients (after ascertainment of the primary clinical endpoint), unless it is performed earlier for clinical indications.

Q8. Figure 1 needs to have a ‘fig 1 etiquette’ and it would be even better if the authors could add a timeline to make the figure more compelling.
A8. Thank you. Figure 1 has been revised following your suggestion, and Figure Legend is added in the manuscript on page 17.

VERSION 2 – REVIEW

REVIEWER	Yiannis Chatzizisis University of Nebraska Medical Center, USA
REVIEW RETURNED	13-Dec-2017

GENERAL COMMENTS	In the revised version of the manuscript the authors adequately covered my comments.