Author's response to reviews

Title: The OPTImal DUAL antiplatelet therapy (OPTIDUAL) study: a multicenter randomized trial to assess the efficacy and safety of 12 versus 48 months of dual antiplatelet therapy after implantation of a drug-eluting stent

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Author's response to reviews: see over
Dear Sir,

We thank the reviewers for their comments and enclose our response together with our revised manuscript. We believe the manuscript has been significantly improved as a result and re submit to the journal for consideration.

Thank you

Yours faithfully,

Pr Gérard HELFT

Editorial requests

1. Method sections: We have included this statement: ”All patients will provide written informed consent to participate.” page 6, line 9
2. After the Discussion section, we have added the trial status: “This study is currently recruiting patients.” page 12.
3. We have included a competing interests section at the end of the manuscript page 13
4. We have included an acknowledgment section at the end of the manuscript page 13.
5. We have included an authors’ contributions section at the end of the manuscript page 13.

Reviewer’s report

1. title page 1: as suggested, the title has been changed and is now: The OPTimal DUAL antiplatelet therapy (OPTIDUAL) study: a multicenter randomized trial to assess the efficacy and safety of 12 versus 48 months of dual antiplatelet therapy after implantation of a drug-eluting stent
2. methodology
   - patients: Malignancies and other comorbid conditions with a life expectancy < 2 years are an exclusion criteria screened by the principal investigator of each site (page 7, line 6)
   - randomization: “Patients with DES treated for 12 months ( +/- 3) with aspirin and clopidogrel and who are event-free (from myocardial infarction (MI), stent thrombosis, acute coronary syndrome, stroke, repeat coronary revascularization with a DES in the 9 previous months or with a BMS in the last four weeks, moderate or major bleeding) are eligible for randomization.” This sentence has been moved ahead in the section entitled “Inclusion/exclusion criteria (page 7, line 7)
   - Randomization is stratified by centers (page 7, line 15)
   - Time of randomization that is the time when the studied strategy is beginning (i.e. stopped or sustained dual therapy) will be considered as the time 0 for study endpoints (page 8, line13).
   - Intervention and co-interventions. What will be the doses of the two drugs. This is already in the manuscript page 7, 3rd paragraph: “To minimize bleeding risk, the study will recommend that the aspirin dose should be the lowest acceptable dose, based on the physician’s discretion (75 to 160 mg).”
recommended clopidogrel dosing will be a loading dose between 300 and 600 mg, and a maintenance dose of 75 mg daily to be continued for the duration of the treatment."

- Medications after randomization. We have clarified page 8, 2nd paragraph: Thus, patients randomized in the clopidogrel group will receive dual antiplatelet therapy (clopidogrel plus aspirin) for a total of 4 years (+/- 3 months). The other patients will receive aspirin alone (75 to 160mg daily).
- After randomization: The patients are randomized (1:1) to receive either aspirin alone or a continuation of clopidogrel plus aspirin for an additional 36 months. Also, we have modified: Aspirin and thienopyridines (clopidogrel and prasugrel), page 4, line 15, 4th paragraph.
- Is there any placebo? no, it is a open-label study as specified page 2, line 12
- It is an open-label study, but study end-points are “hard-one”
- Compliance is now defined page 8, line 1: Compliance is checked by a patient’s diary where the daily dose of each drug is reported.
- Cross-overs analysis: patients crossing-over from a strategy to another will be analyzed in function of their group of randomization (page 9, 5th paragraph).
- End-points monitoring: “All end points and events that occur after randomization will be adjudicated by an independent Clinical Events committee, blinded to the assignment strategy. The committee will comprise physicians that are provided with all the data from medical records necessary to perform optimal adjudication.” (page 8, 2nd paragraph)
- Major bleeding have been defined page 9, line 1: Major bleeding events will be classified as a fatal bleeding, intra-cranial bleeding (assessed by MRI, CT, or autopsy), hemorrhagic shock, a need for transfusion of at least 2 units of packed red blood cells, reductions in hemoglobin greater than 3 g/dl, intraocular bleeding that leads to visual loss, or bleeding that requires surgery.
- Monitoring of patients: it is now stated: “Subjects will be contacted at 6, 12, 18, 24, 30, and 36 months after the randomization; i.e., up to 48 months after the DES implantation.”
- Ethics and funding: Letters are now provided.
- a Data and Safety Monitoring Board (DSMB) is in place (page 9, 2nd paragraph)
- the letter from the “Programme Hospitalier en Recherche Clinique” is provided.
- Statistical Analysis: Indeed all statistical details are already in the protocol written by a statistician and the SAP is not requested. We stated more precisely these aspects in the revised version and answer specifically to the following questions.
- An interim analysis is planned; what p-value will be used to stop the study? Peto criterion will be used corresponding to a p value < 0.001 (page 9, 4th paragraph)
- How will be analyzed cross-overs? All patients will be analyzed in ITT (i.e. corresponding to their randomization group as recommended by guidelines), page 9, last paragraph.
- How will be analyzed drop-outs? Drop outs will censorized at the time of last available information (page 9, last line)
- Will there be any per-protocol analysis? No, such an analysis has not been considered useful for this comparison of strategy in real life situation.
3. **Discussion**  
   - We have corrected page12, line 6: “risks of 12 versus 48 months of dual antiplatelet therapy”

4. **Ethics**  
   - proof of ethics are now provided

5. **Funding**  
   - proof of funding now provided

6. **Minor essential revisions**  
   - Title page. The full address for correspondence is added  
   - Background page 5: We have modified in the last paragraph, first line: “three trials have been published suggesting…”  
   - Methods: we have corrected page 7, line : who are event-free since the stent implantation  
   - A list of abbreviations and acronyms has been added

7. **References** have been formatted according to the editorial standards of the journal **TRIALS**

8. “Randomized clinical trial” has been added in Key Words