Reviewer's report

Title: Rationale and design of the optimal dual antiplatelet therapy (OPTIDUAL) study, a prospective, 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

Version: 1 Date: 23 December 2012

Reviewer: Jacques Lacroix

Reviewer's report:

Manuscript entitled “Rationale and design of the optimal dual antiplatelet therapy (OPTIDUAL) study, a prospective, 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” by Gérard Helft et al.

Manuscript # 1404364477819806
Submitted to the journal “TRIALS”

SUMMARY. – In this research protocol, Helft and colleagues describe a randomized clinical trial with two arms. The rationale behind this trial is strong: presently, there is good evidence that patients need to take two antiplatelet drugs after implantation of a drug-eluting stent during at least one year, but when such dual medication (aspirin and thienopyridine) must be stopped is unknown. In this trial, all patients with a drug-eluting stent will be treated with dual therapy during one year; then, they will be randomized to keep on with the dual therapy during 3 more years (experimental group) or to stop thienopyridine. The primary outcome measure is a composite outcome that includes any of the following adverse events if it is observed during the study period from 2 to 4 years post-stent implantation: death, myocardial infarction, stroke and major bleeding.

MAJOR COMPULSARY REVISIONS

TITLE
The title of the manuscript is: “Rationale and design of the optimal dual antiplatelet therapy (OPTIDUAL) study, a prospective, 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”. I suggest to change this title to: “Efficacy and safety of 12 versus 48 months of dual antiplatelet therapy (OPTIDUAL) study after implantation of a drug-eluting stent: a multicenter randomized trial”. The latter title is shorter and it deletes some redundancy.

METHODOLOGY

• Patients. – In table 1, it is stated that patients with malignancies or other comorbid conditions with a life expectancy < 2 years will be excluded. How will
be determined that the life expectancy of a given patient is less than 2 years and who will take this decision must be detailed.

- Randomization. – The first sentence of this paragraph is: “Patients with DES for 12 months (± 3) with aspirin and clopidogrel who are event-free (from death, myocardial infarction...”). Actually, this sentence listed inclusion and exclusion criteria; therefore, it must be moved ahead in the section entitled “Inclusion/exclusion criteria”. Moreover, I suggest deleting death from the list because it makes no sense (nobody will consider enrolling dead patients); on the other hand, it makes sense to exclude patients in cerebral death and organ donors.

- Will randomization be blocked by centers?

- What will be time zero in participating patients: when the randomization is done or when the medication is started?

- Intervention and co-interventions. – What will be the doses of the two drugs?

- Aspirin will be used over four years in all patients. What will be the other antiplatelet medication is unclear in my mind: is it thienopyridine or clopidogrel? I do not use and I am not familiar with any of the latter two drugs; I suggest that you describe shortly what they are because other readers will appreciate this information.

- Is there any placebo? If so, how is it prepared and how will it be given?

- If there is no blinding, what measures will be used by the investigators to address any bias related to placebo effect?

- Compliance is not defined.

- How will be checked compliance is not described.

- Cross-overs should be defined.

- End Points and Main Outcome Measures. – The primary outcome measure is a composite outcome that includes death, myocardial infarction, stroke and major bleeding.

- Who choose the different components of this composite outcome measure?

- How will be monitored and who will monitor the components of the primary outcome measure is unclear.

- Major bleeding must be defined.

- When will be stopped the monitoring of patients to detect outcomes: up to 3, 6 or 12 months after the end of the study (after 48 months)?

- Ethics and funding. – I have not found a letter from a Research Ethics Board proving that a Board approved the trial.

- Is there a “Data and Safety Monitoring Board” (DSMB)? Such Board is mandatory in a trial like that.

- I would also like to see the letter from the “Programme Hospitalier en Recherche Clinique” (PHRC) proving that this organism financed the trial.

- Statistical Analysis. – In the last sentence of this section, it is written: “A detailed
statistical analysis plan will be written before the final analysis”. This is inappropriate: a statistical analysis must be planned in details before a trial is started in order to prevent any bias. Thus, this protocol cannot be published if we do not have in our hands more details on the statistical plan. It would help if this statistical plan is written by a statistician.

• An interim analysis is planned; what p-value will be used to stop the study?
• How will be analyzed cross-overs?
• How will be analyzed drop-outs?
• Will there be any per-protocol analysis?

DISCUSSION.
On page 11, 2nd paragraph, 3rd line: “risks of 12 versus 48 months of dual…” rather than “risks of 12 versus 30 months of dual…”.

ETHICS
• Proof of ethics approval: missing.

FUNDING
• Proof of funding: missing.

MINOR ESSENTIAL REVISIONS (not for publication).
Title page.
• Please, add a full address for correspondence, not only an e-mail address.

Abstract (< 350 words).
• Results. – What are the expected results?
• Conclusion: is there any conclusion?

Background.
• Las paragraph, 1st line. – “Very recently, three trials have been published suggesting that a shorter…” rather than “Very recently, three trials have been published with interesting results that suggested that a shorter…”.

Methods.
• Paragraph on randomization, 2nd line: “who are event free (from death, myocardial infarction…” Please, tell us the period when the patient must be event free (during the year after stent implantation?).

List of abbreviations.
• A list of abbreviations and acronyms must be added after the discussion.

Competing interests.
• A statement of conflict of interests is missing.

Authors’ contributions.
• A section on authors’ contributions is missing.

Authors’ information.
• Not mandatory.

Acknowledgements.
• Not mandatory.

Endnotes (if any).
• Not mandatory.

References.
The references must be formatted according to the editorial standards of the journal TRIALS.
• In the body text, references must be reported with plain text and between brackets; thus, they must look like [1-3] rather than 1-3 (superscript).
• In each reference, all authors must be listed, up to 30 authors, before adding “et al”.
• The list of authors must be ended by a colon (:) rather than a period (.) (all references).
• Please, do not use capitalized words in the title unless the capitalized words are defining an acronym (references 3, 14).
• Do not put a period or a semi-coma within or at the end of a journal name (references 8-13, 28).
• The name of the journal must be in italics (all references).
• Full range of pages must be written (references 5-7, 14, 15, 17-24).

DISCRETIONARY REVISIONS.
• Other#KEY WORDS can be added, like “randomized clinical trial”.

REVIEWER
NAME: Jacques Lacroix, professor
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Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the
statistics.

Declaration of competing interests:

I declare that I have no competing interests.