Author's response to reviews

Title: Detection of silent myocardial ischemia in asymptomatic diabetic patients: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening

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Author's response to reviews:

Dear Editors,

Thank you for having submitted our article to the referees. Please find hereunder the answers to the referees remarks, and the revised text.

Reviewer 1 (JJ Altman)
- Follow-up
  in fact, as stated in the last sentence of the "Endpoints" section, all the endpoints were adjudicated centrally and blinded to study group.
- Endpoints
  The endpoints were specified by the protocol and cannot be changed. The main endpoint included total mortality instead of cardiovascular mortality for two reasons. Firstly, DYNAMIT was a strategy trial, not an explicative trial, and we adopted the patient - or public health - point of view; secondly, with the kind of follow-up that we adopted, mainly based on patient contact, it is usually very difficult to obtain sufficient documentation to make an unambiguous classification of the cause of death.
  Heart failure was included in the main endpoint because it constitutes a frequent complication of myocardial ischemia, especially in patients with diabetes. As it has been done in many recent trials in hypertension, only heart failure leading to hospitalization or intervention of emergency services was considered as an endpoint, which makes the diagnosis easier. All cases were documented by the hospital in which the patient was admitted. Thes events were of course adjudicated by the event committee.
- Statistics
We agree that it was optimistic to expect the inclusion of 3000 patients in DYNAMIT while guidelines recommended systematic screening of the patients corresponding to the study selection criteria. The 22% event rate was calculated from that observed in a similar patient population included in the DIABHYCAR trial and followed-up for 4.5 years.

- patient characteristics

In the presence of an unpredictable randomization (which is the case in DYNAMIT), it is considered of no use to run statistical tests comparing the characteristics of patients at baseline. Due to multiplicity, indeed, there is a high risk that such comparisons lead to some spurious differences at a p<0.05 level.

Diabetes management was not an objective of the study, and was left at the discretion of the investigators and primary care physicians in this strategy trial. This explains why very few details were given on diabetes itself.

- Outcomes

The authors consider that their interpretation of the results was prudent, and took into account the confidence interval in an explicit manner. Although "trend" was used regarding the result on stroke, it was stressed in the discussion that this trend was likely to be a chance finding.

- Meta-analysis

The authors disagree strongly with the reviewer in this regard. The meta-analysis was used to get a more precise estimation of the confidence interval of the difference, not to compensate for any disappointment. Given the very high similarity of DYNAMIT and DIAD, a meta-analysis was warranted. Grouping results of underpowered studies is perfectly in the scope of meta-analysis.

- Conclusion

Although underpowered due to its premature termination, the DYNAMIT study should be, and can be interpreted, although in a prudent manner, as any inconclusive study.

Regarding DIAD, we considered that our statement is only factual. We have made repeatedly, but without success, a proposal to the DIAD investigators for a joined publication of DYNAMIT and DIAD results after they published their own results.

As regards the "weak points" and any possibility of a better study design, firstly the open nature of the trial was mandatory. Secondly, the insufficient power was independent of the study design. Even if we had anticipated that the patient risk would be smaller than expected based on DIABHYCAR results, this would have resulted in an increase in the study sample size.

Reviewer 2 (S Kelsey)

1 All the occurrences of "diabetic patient" have been replaced by "patient with diabetes"

2 Silent ischemia refered to as "doubtful" in the original text correspond to "small defects" at SPECT (see: SPECT myocardial perfusion imaging: guidelines for
interpretation and reporting. J Nucl Cardio 1999;6: G67-84), and may be termed "uncertain". These small defects are often considered as not definitely abnormal, and were grouped in DYNAMIT with definitely abnormal results due to the small number of patients. The same was done in the DIAD report. The is now explained in the article.

3-8: changes were done according to reviewer's remarks.
9: "intervention" and "control" have been changed for "screening" and "usual care"