Author's response to reviews

Title: Silent Cerebral Infarct After Cardiac Catheterization as Detected by Diffusion Weighted Magnetic Resonance Imaging: A Randomized Comparison of Radial and Femoral arterial approaches.

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Silent Cerebral Infarct After Cardiac Catheterization as Detected by Diffusion Weighted Magnetic Resonance Imaging: A Randomized Comparison of Radial and Femoral arterial approaches.

To Reviewer # 1:
We appreciate these comments which we have taken into account in the revised manuscript.

Major:
1) As suggested by reviewer 1 we have added a reference for the cumulative effect of ischemic brain injury on cognitive impairment but we acknowledge that such demonstration does not exist for invasive procedures like cardiac catheterization. Reference 11 in the revised manuscript page 4.
2) We agree that cognitive impairment after surgery is just an observation and that clear connection between emboli and cognitive impairment remains a hypothesis. This subtle difference has been introduced in the new version rephrasing the sentence in the introduction (“might be related replacing is related”).
3) DW - MRI is very sensitive (90%) for detecting cerebral infarction early when other imaging techniques like CT are not able to detect any abnormalities. The use of this new imaging modality allows diagnosis of unsuspected silent brain infarctions in different clinical settings like cardiac catheterization and therefore given the rate of silent brain infarctions of up to 15-22% in some centers can be used as a surrogate endpoint for risk of stroke assessment given the fact that symptomatic stroke is far less frequent (0.2 to 0.4%). The use of DW-MRI as a surrogate marker is now clearly written in the introduction, page 4.
4) 4 centers are currently involved in SCIPION trial (2 centers in France, 1 center in Austria and 1 in Italy corresponding to 3 Academic centers and 1 private center). Page 6, Method section.
5) Symptomatic stroke is included in the endpoint because all positive DW-MRI will be counted - silent and symptomatic. We completely agree that it is important that rates of both symptomatic and silent stroke are reported. This issue is now clearly written in the primary endpoint.
6) Cognitive assessment and alternative forms of assessment to minimize learning effect, as well as recommendations on how to conduct such assessments, will be preformed. The statistical plan is now described in the revised version.

Minor
Grammatical errors have been revised in the present version.

To reviewer # 2
We appreciate comments and interest in our manuscript.

Major: None

Minor:
1) 4 centers currently engaged see response to reviewer 1.
2) The TCD doppler group will be restricted to two centers (availability of the TCD in the Cath lab).
3) We agree that the different terms used to describe cerebral lesions could be confusing and we have modified that in the study objectives.
4) Non-silent strokes will be taken into account as well as silent ones and individual rates will be reported, as requested by reviewer #1.
5) Complete neurologic assessment will be ensured by neurologist before and after catheterization.
6) We agree that long term follow-up is important and that T2 MRI could be proposed for patients with new DW-MRI lesions to ensure that those correspond to permanent ones.