Reviewer's report

Title: Transaortic transcatheter aortic valve implantation - rationale and design of the first multicenter, multinational prospective registry (ROUTE)

Version: 1
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Reviewer: Marco Barbanti

Reviewer's report:

In this manuscript, Peter Bramlage and colleagues aims to describe the protocol of the ROUTE registry.

The paper is well written and fluent. I have no major remarks.

Major Compulsory Revisions:
None

Minor Essential Revisions:

Introduction: Authors stated that "The Edwards SAPIEN [...] and can be introduced into the body via transfemoral (TF) or transapical (TA) routes". Actually, authors should mention also the trans-subclavian approach.

Among the inclusion criteria authors listed that patients should have a Log Euroscore I >15% and STS score >10%. These cut-offs are quite unbalanced as the mean value of STS score is generally 1/3 of the Euroscore I. In my view authors should consider to emove the log Euroscore I from the inclusion criteria. (suggested, considering that the Euroscore I has been replaced in clinical practice from the Euroscore v2).

On the paragraph of the exclusion criteria authors should better clarify the concept of "excessive calcification". Do they have any objective criteria to grade the calcium burden?

Regarding the monitoring process, it is not to clear to me why only major bleeding will be monitored? This should be clarified.

In the discussion authors stated that "ROUTE might also allow for the identification of certain patient characteristics that predict procedural success. Indeed, analysis of multivariable adjusted predictors for poor outcome after TAo-TAVI will be useful for determining optimal patient profiles that are suitable for the TAo route."

I'm doubtful regarding the ability of this registry to obtain a meaningful predictors analysis: mortality after transaortic TAVI at 30-day is expected to be no more than 6-10%. This means that with only 12-20 events. I would suggest to remove this sentence from the text.

"TAo-TAVI was initially utilized when conventional approaches were not possible."
It has evolved, however, into a preferred approach in patients not undergoing TF-TAVI. This sentence is not entirely correct. The access route choice is very center-driven. However somebody might argue that in case of unfeasible TF-access, you should prefer first a less invasive approach such as the sublavian one.

I suggest to tone down the conclusions. The ROUTE registry will certainly provide important information regarding the safety and the early efficacy of the Tao approach, but the lack of a control cohort, and the long-term follow-up are important limitations, which prevents this registry to give us more than what I just indicated.

Discretionary Revisions:
None

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests