Author's response to reviews

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

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**Author's response to reviews:** see over
Dear Dr. Shipley,

Thank you for reviewing our manuscript and for the positive assessment made. We have revised the article now considering all the comments raised by the reviewers and detailed these in the attached point-by-point response. We look forward to having our manuscript published in BMC Cardiovascular Disorders.

Yours sincerely, Peter Bramlage, MD
Point-by-point response: Transaortic transcatheter aortic valve implantation - rationale and design of the first multicenter multinational prospective registry (ROUTE)

Reviewer 1: Stefan Stortecky

The present manuscript provides detailed information on the rationale and the design of the multinational, multicenter ROUTE registry, investigating clinical outcomes after transaortic transcatheter aortic valve interventions (TAo). The ROUTE registry and its protocol is original and will provide important information on the safety and efficacy of the transaortic access route with the Edwards Sapien bioprosthesis. The manuscript is well written and the methodology is described in detail. I still have the following remaining comments:

Comment 1.1: Throughout the manuscript, the authors describe the use of the Edwards Sapien THV prosthesis for the treatment of TAo patients. As the Edwards Sapien THV refers to the first generation Edwards Sapien device, the authors might wish to provide detailed information on the device itself – are the operators also allowed to use the Sapien XT or the Sapien 3 prosthesis within this registry?

Response 1.1: You are right and this may have been misleading. The operators are allowed to use SAPIEN XT or SAPIEN 3 within the ROUTE registry. To clarify this, we changed the first sentence of “Patients selection” accordingly:

Patients can be included in ROUTE if they display symptomatic severe calcific AS and are scheduled to receive TAo-TAVI using an Edwards SAPIEN THV (SAPIEN XT or SAPIEN 3) and the Ascendra+ Delivery System irrespective of the feasibility of other access routes.

Comment 1.2: It might be of interest to add the European centers with the local PI as supplemental information.

Response 1.2: We changed the section “Investigators” and added the name of the institutions participating.

Comment 1.3: As indicated in the methods section, the investigators decided to choose a follow-up period from day 23 to day 37 after TAVI for the 30-day follow-up assessment. Follow-up assessment for the peri-procedural endpoint at 30 days should not be assessed prior to 30 days, but can have an assessment range until 45 days after the procedure.
Response 1.3: We agree with your comment in principle. This has been a decision of the steering committee however and cannot be reverted. When presenting the results we will be able to check how many of the patients actually had an assessment prior to 30 days.

Comment 1.4: Please indicated, whether events and event severity are self-reported or will undergo independent event adjudication according to the updated VARC endpoint definitions. As the authors are also interested in investigating all other VARC endpoints as secondary endpoint, independent event adjudication could increase the scientific value of this registry.

Response 1.4: We agree that independent event adjudication would increase the scientific value of ROUTE. However, per protocol no independent event adjudication will be done. To increase data verification of all serious adverse events will be performed. In addition, at least 20% of centres will be monitored in person.

Reviewer 2: Marco Barbanti

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

Comment 2.1: 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.

Response 2.1: Thanks, we have changed the introduction accordingly.

Comment 2.2: 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 remove the log Euroscore I from the inclusion criteria. (suggested, considering that the Euroscore I has been replaced in clinical practice from the Euroscore v2).

Response 2.2: This cut-offs of the STS and the Euroscore I are according to the instruction of use of the Edwards SAPIEN XT and SAPIEN 3. Thus, we have inserted the addition “according to the IFU of the Edwards SAPIEN THV”. But you are right, the Euroscore I is replaced in clinical practice by the Euroscore 2.
Comment 2.3: 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?

Response 2.3: The exclusion criteria were chosen according to the IFU of the Edwards SAPIEN THV. All patients enrolled in this registry underwent echocardiography or CT scan, on-table aortography and digital palpation to evaluate the suitability of the aorta for cannulation. However, there were no objective criteria for the grade of calcification of the aorta.

Comment 2.4: Regarding the monitoring process, it is not to clear to me why only major bleeding will be monitored? This should be clarified

Response 2.4: Data verification will be performed for all serious adverse events (death, stroke, major bleeding, etc.). Adverse events which are not serious will be assessed in the eCRF and monitored in 20% of the sites. If any questions remain in the eCRF, queries are written or the center is contacted by e-mail or phone to clarify the AE.

Comment 2.5: 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 T Ao-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.

Response 2.5: We agree that a larger sample size would be valuable. We want to mention however that, if only mortality is considered for prediction of procedural outcome, you are right. However, poor outcome of patients after Tao-TAVI implies mortality as well as the incidence of stroke, major bleeding, NYHA class III or IV, etc. ROUTE might allow the identification of patient characteristics predicting poor outcome after Tao-TAVI.
Comment 2.6: “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 subclavian one.

Response 2.6: We agree and have therefore changed the sentence accordingly: In some sites it has evolved, however, into a preferred approach in patients not undergoing TF-TAVI.

Comment 2.7: 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.

Response 2.7: We think, ROUTE as a registry has limitations compared to randomized clinical trials as well as long-term follow-up after Tao-TAVI as mentioned in the section “Potential limitations of ROUTE”. However, we think ROUTE is an important step for TAo-TAVI for the early outcome after intervention. Therefore, we have changed the conclusion as follows: The results of this registry will provide essential information on procedural success rates and early mortality in a large cohort of patients undergoing TAo-TAVI. Therefore, completion of ROUTE represents an important step in assessing the early clinical efficacy and safety of TAO-TAVI in patients with severe calcific AS.

Editor

Comment E1: Please could you structure your abstract according to the guidelines provided at this page: http://www.biomedcentral.com/info/ifora/abstracts

Response E1: We have adapted the structure of the abstract according to the guidelines of biomedcentral. However, we changed the section “Results” to “Design of ROUTE”.

Comment E2: Please revise your manuscript to confirm that ethical approval has been obtained from centres participating in the registry.

Response E2: We changed the sentence accordingly: Ethical approval has been obtained at the ethics committee responsible for each site prior to patient enrollment.
Comment E3: Please also ensure that all participating centres are listed in your manuscript (this information may be included in an additional file.

Response E3: We changed the section “Investigators” to “Investigators and participating centres” and added the name of the institutions.

Comment E4: Please remove your additional files (ethics approval) from your article.

Response E4: We will do it. Thanks.

Comment E5: Please include a 'Competing interests' section between the Conclusions and Authors’ contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'.

Response E5: We have declaring competing interests.

Comment E6: Please include an 'Authors' contributions' section before the Acknowledgements and Reference list.

Response E6: We have added the following section accordingly: **Authors’ Contributions:** Peter Bramlage (PB), Mauro Romano, Nikolaos Bonaros, Ricardo Cocchieri, and Vinayak Bapat were involved in the conception and design of the registry. PB has drafted the manuscript and all other authors have been revising the article for important intellectual content. All authors have finally approved the version to be published.