Author’s response to reviews

Title: Expandable External Support Device to Improve Saphenous Vein Graft Patency after CABG.

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Author’s response to reviews: see over
Authors answers to the comments made by the reviewer:

(Reviewer comments are in bold italic letters):

“The method elected for angiographic graft evaluation, namely arbitrarily measuring at seven equal distances along the graft may skip the points of maximal and minimal diameters, the magnitude of the difference between which may be more relevant to the prognosis of the graft [1]. The proximal segment of the supported graft of sheep 2196 in Figure 5c at 12 weeks could be an example of irregularity which can potentially be overlooked, resulting in lower coefficient of variance.”

The decision to perform an arbitrary partition of all graft segments to seven equal segments and measure the lumen at these partition points was made in order to circumvent claims of non objectivity. We used the same method also for the histopathologic evaluation, slicing each graft to 5 (or seven when long enough) equal segments. This method enabled us to assess, in a truthful and objective manner, the overall uniformity and regularity of the graft. To measure a graft only in the point of extremis (widest and narrowest angiographic image of the lumen) may result in a situation where a regular and uniform graft with one or two points of lumen diameter alterations, would be interpreted as a “non regular”
vessel, while a diffusely rough and irregular graft but with only slight alterations in the lumen diameter ("chain-saw" like lumen) would have been interpreted as a regular uniform graft. Implementing the suggested technique by the reviewer would probably have resulted in an even higher variance between supported and non supported grafts, in favor of the device group, but, we assume, in a more “subjective” and skewed manner.

“The statement regarding the number of sheep undergoing immediate post-operative control angiography (end of first paragraph in the Results section) should be corrected. Nine of the ten animals surviving to the end of follow-up had complete information”

We thank the reviewer for his comment. The statement in the text was changed to (page 6 line 7 in the results section) “All sheep underwent immediate post-operative angiographic evaluation in an attempt to demonstrate patency and integrity of supported and control grafts. “

“In discussing the limitations of the study the authors correctly pointed out that the follow-up period of 12 weeks could be too short. The follow-up period of 180 days in the baboon model of aorto-coronary bypass grafting reported recently [1] may be more appropriate to demonstrate the protection afforded by the external support device”

We agree to the statement made by the reviewer. In the currently performed clinical trial evaluating the Fluent external support device: “Venus External Support Trial – VEST” conducted by Prof. David P. Taggart as principal investigator, all patients undergo a follow-up angiography with intra-vascular ultrasound and Optical Coherence Tomography (OCT), one year after the procedure. In addition a statement regarding the relative short term follow up appear in the limitation paragraph of the discussion (Page 9 line 11) “Several years of follow up may be needed to fully demonstrate the exact impact of external support on vein graft occlusive disease”.

“Some questions arise, or remain open. What is the potential advantage of the alloy used in this device over the already CE-approved external support mesh made of nitinol?”

We believe that there are several advantages for the technology of the braided cobalt-chromium-nickel-molybdenum-iron alloy expandable support device which we evaluated over the nitinol mesh:

- No need for mounting device
- No need for utilization of bio-glue or other adhesive material for integration of the device and the vein graft
- No need to incorporate proximal and distal anastomotic stitches through the mesh to avoid fragmentation of the device (as advocated by the investigator who developed the nitinol mesh).
- Kink resistance abilities (obvious in the external expandable device and still unclear for the nitinol mesh)
- Irreversibility of the process while utilizing the nitinol mesh glued over the saphenous vein, while with the external expandable device you can simply shorten it or cut it out from the vein using Potts scissors.
- The Fluent expandable external support device just received CE approval (please see the attached Expandable external support device CE-notification number 3900633CE01)

**Were any breakages detected in the device at the end of follow-up?**

There were no device breakages detected. This fact was added to the text of the manuscript (page 7 line 6 in the result section) “In the externally supported group the graft’s adventitia was incorporated into the device’s pores, fixated also by a thin layer of lucent connective tissue (figure 3) with no change of the device position over the graft and without any detected breakage or disintegration points of the device”

**Previous experiments with nitinol mesh demonstrated effective suppression of intimal hyperplasia only when aggressive downsizing of vein diameter, to better match the target vessel caliber was accomplished [reference 11 in the manuscript]. Is it also necessary with this new device? And why did such an approach result in the poor results obtained in a small group of patients included in a randomized trial reported a little more than a year ago**

We assume that slight downsizing the vein graft diameter closer to the diameter of the target coronary vessel may provide some beneficial effect while attempting to improve patency performance of vein grafts in CABG procedures. The said reduction of the venous to arterial diameter mismatch may be related to suppression of intimal hyperplasia (1), acceleration of flow (Hagen-Poiseuill’s law) and, to a certain extent, augmentation of shear stresses inside the graft (2). This may also be related to the symmetry imposed on the vessel wall, enforcing laminar flow inside the graft and reduction of the wall tension (Laplace’s law) of the vessel.

Further investigation is needed, to determine the adequate level of constriction, since, as mentioned by the reviewer, poor results were reported with aggressive downsizing of vein grafts used for CABG procedures utilizing nitinol mesh external support (3).

In this study we provided grafts with only gentle external constriction and followed the same approach for human patients in our currently conducted clinical trial (VEST trial). We refrain from any conclusion
or determination of the appropriate extent of graft downsizing on the basis of still developing and inconclusive results by competing technologies.

**What is the relevance of findings from this and other experimental animal models, using healthy veins, when applied to elderly patients with age-dependent venous degeneration including wall thickening, focal areas of fibrosis and even varicosities?**

Like any other developing technology and most preclinical studies, we believe that one can deduce on the relevance of a new technology for different patient population diseases (and even disease type and patterns) on the basis of incremental data collected over studies and years and on the basis of clinical judgment, rationale and logic. A statement on the relevance of the model described in the study appear in the limitation paragraph (page 9 lines 9-25 and specifically in lines 22-26 “... this study’s animal (sheep) model or the abrupt occlusion (ligation) that was inflicted on native coronary targets may not accurately reflect a human heart with chronic atherosclerotic disease. Still, among recent studies on venous external support, to our knowledge only in the current study was an actual CABG model actually used”

In the currently conducted VEST clinical trial, evaluating the expandable external support device on humans, we have enrolled patients with typical base line characteristics that match the vast population of people with coronary artery disease in need of myocardial revascularization. We hope that this study, as well as studies that will follow, will help us to better understand the exact role of vein graft external support in patients undergoing CABG.


Author response to reviewer 2

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Authors answers to the comments made by the reviewer :

(Reviewer comments are in bold italic letters):

“The study findings are certainly intriguing and with enormous potentials for subsequent clinical application and expectations. The results are well presented, with clear iconography and data. The study methods however has some weakness which must be underlined and commented by the authors. First of all, the majority of the device-related animals had the device applied to the grafts anastomosed to the LAD in contrast to the control group which had more device on the obtuse margin coronary arteries. Therefore, comparing the supported grafts to the ones without the device may account for a substantial impact due to the different territory revascularized, which is notoriously linked to different flow conditions and, hence, to potential interference with postoperative tissue reaction based on different pressure and flow characteristics. The authors should address this limitation and explain how they would overcome such a discrepancy in data interpretation.”

There were 14 animals enrolled in the study, of which only ten survived the full follow up period of 3 months. The plan to alternate between the supported vessel in each case (LAD and LCX territory) was
implemented in all the fourteen animals but in one sheep, in which we could not find any vessel in the LCX territory, and implanted the device in a very lateral and large diagonal branch. This sheep expired during the periprocedural period, hence, was not included in the final analysis. So initially, we had 8 supported grafts to LAD territory and 6 to the LCX territory. Finally, among the ten surviving sheep, there were six with an external support to the LAD territory and four to the LCX territory, and this difference was merely the result of the periprocedural mortality of two sheep who received a supported graft to the LAD territory and two sheep who received a supported graft to the LCX territory. Indeed, this difference may have theoretically contributed to the different outcome between supported and non-supported grafts due to possible dissimilarity in flow characteristics between LAD and OM territories.

Following the reviewer’s comment, we have now addressed this limitation in the manuscript (discussion section, limitations paragraph, page 9 lines 15-19) “..In addition, the majority of the surviving animals that entered the angiographic and histopathologic evaluation had the device applied to the grafts anastomosed to the LAD (six out of ten sheep), hence a potential difference may have theoretically contributed to the different outcome between supported and non supported grafts due to possible dissimilarity in flow characteristics between different coronary territories”.

“Secondly, any study involving vein grafts should consider the damage induced during harvesting. Were the unutilized grafts assessed to evaluate the post-harvesting conditions and elucidate whether structural integrity was present in all implanted grafts? The Reviewer is aware that such an assessment would have been applied to segments not implanted, but preimplant integrity is usually always neglected although might have a remarkable impact of postoperative patency and structural outcome of venous conduits”

Indeed, we have not evaluated unutilized vein segments for post harvesting trauma and structural integrity, but did so for all utilized graft segments during the post-sacrifice pathologic evaluation, and found no difference between grafts when examined for trauma, inflammation or thrombosis (as depicted in table 1 in the manuscript). It is worth mentioning that the surgeons who harvested vein segments were blinded to which segment will receive an external support and which will be utilized as a control graft. Another comment is that unutilized segments (taken most often from vein edges) do not always represent trauma or injury in the utilized more central segments of the vein.

“.. the lack of description of the findings in the vessel layers, mainly about cellular or tissue changes, apart from thickness, in order to elucidate whether more new vessels, or the extent of immunoreaction was induced by such an external device. Do the authors possess any data in this respect (like macrophages, or other type of blood cells)? Finally, I would like to congratulate the authors for such a nice piece of work and for the important findings which, I hope, will be soon applied in clinical trial”
In this study we did not perform an immunohistochemistry evaluation that would have enabled us to differentiate and quantitate (also partially due to high specificity but low sensitivity of such a test) changes in specific cell populations in the vessel wall of supported versus non supported grafts. Possessing this type of information would indeed be beneficial and would have added an additional value to the analysis. Of note is that in the histopathologic evaluation performed immediately after sacrificing the animals, we found no difference between groups in terms of level of inflammatory cell infiltration as depicted in the text (page 7 line 2) “In gross pathology and histopathologic evaluation, all grafts and anastomotic sites appeared normal with no apparent difference between grafts in terms of inflammatory cell infiltration and intimal laceration (injury)”. It also appear in table 1 of the manuscript.