



Endoscopic vein harvest: benefits beyond (a) reasonable doubt?

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“You know [...] that every case is like a puzzle within a puzzle within another puzzle. Some pieces are always missing, and some never would fit no matter what. [...] We call it reasonable doubt.”
—Kenneth Eade

Introduction

Coronary artery bypass grafting (CABG) is one of the commonest and most well-studied surgical procedures performed internationally. Long saphenous vein is used as a conduit in the majority of cases, and this trend is likely to continue (1). Mortality for isolated CABG in straightforward patients is less than 1% in high-volume centres as a result of technical advancements and mandated outcome reporting (2). As mortality rates are so low in many healthcare systems, there has been a drive towards improving a range of other outcome measures including morbidity, health-related quality of life, patient satisfaction and economic outcomes (3).

Endoscopic vein harvest (EVH) emerged in the 1990's as a potential solution to the invasiveness and overall morbidity of open vein harvest (OVH). In traditional methods of OVH, large incisions must be made; however, painful incision, dysmobility, wound complications, prolonged hospital stay, and cosmetically unappealing results may occur. Wound complications are observed in 2–24% of cases and they are associated with increased morbidity and mortality and impose a great economic burden on the health-care system (4). EVH has become the standard of care as evidenced by its 90% adoption in the

USA. There is no question that it is advantageous in terms of wound healing, cosmesis, and pain (5) but, despite the widespread adoption, there are still a few main concerns raised by doubters regarding EVH. Firstly, that the quality of vein (and subsequent endothelial function) is inferior as a result of overstretching and manipulation during harvest. Secondly, that this physical damage results in inferior graft patency and survival. Lastly, that there is no overwhelming advantage in terms of economic value.

Evidence base

The above concerns were driven partly as a result of secondary published analyses of a number of landmark trials. In a secondary analysis of the Project of Ex-vivo Vein Graft Engineering via Transfection IV (PREVENT-IV) trial, it was reported that EVH was associated with a significantly higher rate of angiographically demonstrated vein graft failure at 12 to 18 months (6). A secondary analysis of the ROOBY trial also associated EVH with lower vein graft patency and higher revascularisation rates (7). Small basic science studies demonstrated histological evidence of endothelial dysfunction and damage to the other layers of the vein wall (8).

Proponents of EVH have challenged the validity of the above studies claiming that these non-randomised studies (RCT) were not designed to assess such outcomes, and in any case, they are reports on the outcome of a technique during its relative infancy in terms of commercially available technology and experience of the vein harvesters

(who would have been relative novices at the time of the above studies). In response to the above studies, the U.S. Food and Drug Administration asked for an analysis of the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) to further assess the influence EVH on outcomes. This observational study of 235,394 patients was published by Williams *et al.* in 2012, and in a propensity score analysis, demonstrated at 3 years there was no significant difference in mortality or major adverse cardiovascular events (MACE) (9). This mid-term finding was supported in a subsequent high quality RCT (10) and meta-analysis (5). The International Society for Minimally Invasive Cardiothoracic Surgery in 2017 published a consensus statement giving a Level 1B recommendation for endoscopic conduit harvesting (11). More recent sophisticated basic science studies have demonstrated preserved endothelial function in endoscopically harvested vein (10,12,13). However, the histological findings should be interpreted with caution, as have been examined only the histological features and staining patterns of the vein, which may not reflect the true effects of CO₂ insufflation and thermal damage on the vasomotor function of the saphenous vein graft (12).

The need for more evidence

Given the above, there is a clear need for a high-quality RCT to give further clarity. In the January 2019 edition of *New England Journal of Medicine (NEJM)*, Zenati *et al.* for the REGROUP Trial Investigators published such a study (14). They randomly assigned 1,150 patients (recruited from sixteen Veterans Affairs centres), to OVH or EVH, in an intention to treat study. Only elective or urgent straightforward on-pump CABG's were included, and critically, only experienced vein graft harvesters were allowed to participate (defined as more than 100 endoscopic harvests with a low rate of conversion). Randomisation was performed in a 1:1 ratio using a block randomisation scheme (with a random sequence of block sizes) which ensured a balanced distribution of participants assigned to each harvester and within each medical centre. The groups were well matched in terms of baseline characteristics and coronary complexity (SYNTAX score). The primary outcome (for which the study was powered for) was a composite of major adverse cardiac events (death, non-fatal myocardial infarction and repeat revascularisation). Leg wound complications were also assessed. There were a number of tertiary and post-hoc outcomes assessed

including severity of incisional leg pain, appearance of the leg using a structured tool (ASEPSIS) and health-related quality of life (Veterans RAND-12 and Seattle Angina Questionnaire) assessment at multiple time-points.

At a median follow-up of 2.78 years, the primary outcome (a composite of major cardiac events) occurred in 15.5% in the OVH group and 13.9% in the EVH group (P=0.47). In an analysis of recurrent major cardiac events, there was a trend towards more events in the OVH group, and whether this reaches significance in the planned three-year follow-up analysis will be of great interest. Whilst there was no significant difference in leg wound infection between the groups, incisional leg pain, antibiotic use and need for nursing visits for dressings was significantly more common in the OVH group. Surprisingly, these advantages did not translate in to a health-related quality of life benefit. The overall conclusion from this study was that there is no difference between the techniques in terms of major adverse cardiac event. The study confirmed the superiority of EVH only in terms of wound related discomfort while the wound infection rate between the two groups was not statistically significant. Impressively, the time to harvest for the EVH group in the Zenati study was significantly lower than that for the OVH group (57.5±24.4 vs. 61.4±28.7 mins), with a conversion rate of 6.25%. It was interesting to note that the investigators actually assessed 3,394 patients for eligibility to enter this trial, but 1,148 of these did not give consent, which we feel might be an indicator of patients' preference for the EVH technique.

This timely study is unique for a number of reasons. Firstly, it is a high quality, well powered multi-centre RCT which builds on recent studies confirming EVH's non-inferiority. Secondly, in terms of outcomes it is the most sophisticated study to date for the richness of the measures chosen. Lastly, and most importantly, it is the assessment of EVH at a time when it has reached maturity in terms of technology and number of experienced harvesters available. It is astonishing to note that in this study the majority of vein harvesters had over ten years of surgical experience, but this may not be indicative of the real world, where many centres do not have established training programs and have few experienced EVH operators available. Even in the USA, where this study was carried out, 456 eligible patients were not enrolled due to unavailability of an experienced harvester.

Although this study did not assess the grafts' quality angiographically, it doesn't represent a limitation in our view since the coronary assessment in asymptomatic

patients doesn't currently happen in the clinical practice where major cardiac events are identified on clinical basis.

The only caveat of this excellent paper is the absence of some form of economic evaluation that would have helped settle ongoing debate as to whether EVH is cost-effective. Also, whilst the statistical methods employed were sophisticated, we would have liked to see multi-level modelling techniques employed to assess for clustering and to quantify the impact of institution on outcomes.

Clinical significance and conclusion

The RCT by Zenati *et al.* adds to the growing evidence base that EVH is not inferior to OVH in terms of MACE at the mid-term. Also, demonstrated a lower trend in term of incidence of wound infections and in the EVH group, which is one of the cardinal points for adopting this technique. However, incisional leg pain had little or no effect on functioning at 6 weeks after surgery in the majority of the patients of both groups and there was no significant difference in quality of life between the groups as assessed with either the VR-12 survey or the Seattle Angina Questionnaire.

It is our opinion that older studies demonstrating inferior graft quality and patency of EVH were compromised by heterogeneity of surgical technology and study design, but Zenati *et al.* have overcome the most important variable potentially affecting the outcome of the procedure, i.e., the inadequate experience of vein graft harvesters.

Although this study will strengthen existing guidelines which recommend the use of EVH, clearly long-term outcomes (ideally at 5- and 10-year) need to be assessed, and there is still no high-quality evidence for this timepoint. In the emerging era of value-based health-care, detailed economic evaluation will be beneficial and will support the business plans of teams who have not yet set up their EVH programs (15). Also, there is an evolving evidence that open 'no-touch' vein harvest (allowing preservation of perivascular tissue) leads to excellent long-term results (16), and this may challenge further the EVH in the future. Whilst adoption rates for EVH are high in the USA, in many other countries there is a mixed feeling in the absence of obvious advantages beyond reasonable doubts. The causes for this are multifactorial as for any innovation, but importantly the learning curve of the harvesters could represent a significant and yet recognized limiting factor. In fact, this would affect the intraoperative outcome and compromise the long-term patency of the grafts for an

operation that is otherwise characterized by excellent results. However, patients' demand and the growing evidence base suggests clinicians, patient and public involvement bodies, and industry must continue to develop strategies to enhance its adoption.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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