A study comparing Vein Integrity and Clinical Outcomes (VICO) in open vein harvesting and two types of endoscopic vein harvesting for coronary artery bypass grafting: The VICO Randomised Clinical trial.

Short title:

Vein integrity and outcomes in coronary surgery.

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Abstract:

Background:

Current consensus statements maintain that endoscopic vein harvesting (EVH) should be standard care in coronary artery bypass surgery (CABG) but vein quality and clinical outcomes have been questioned. The Vein Integrity and Clinical Outcome (VICO) trial was designed to assess the impact of different vein harvesting methods on vessel damage and if this contributes to clinical outcomes following CABG.

Methods:

A single centre, randomised clinical trial of patients undergoing CABG with an internal mammary artery, and with one to four vein grafts were recruited. All the veins were harvested by a single experienced practitioner. We randomly allocated n=300 patients into: closed tunnel CO_2 EVH (CT-EVH) (n=100), open tunnel CO_2 EVH (OT-EVH) (n=100) and traditional open vein harvesting (OVH) (n=100) groups. The primary end-point was endothelial integrity and muscular damages of the harvested vein. Secondary end-points included clinical outcomes (major adverse cardiac events, MACE), use of healthcare resources and impact on health status (quality-adjusted life years, QALYs).

Results:

The OVH group demonstrated marginally better endothelial integrity in random samples (85% vs. 88% vs. 93% for CT-EVH, OT-EVH and OVH, $p<0.001$). CT-EVH displayed the lowest longitudinal hypertrophy (1% vs. 13.5% vs. 3%, $p=0.001$). However, no differences in endothelial stretching were observed between groups (37% vs. 37% vs. 31%, $p=0.62$). Secondary clinical outcomes demonstrated no significant differences in composite MACE scores at each time point up to 48 months. The QALY gain per patient was: 0.11 ($p<0.001$) for closed tunnel CO_2 EVH and 0.07 ($p=0.003$) for open tunnel CO_2 EVH compared with open vein harvesting. The likelihood of being cost-effective, at a pre-defined threshold of £20,000 per QALY gained was: 75% for closed tunnel, 19% for open tunnel and 6% for open vein harvesting.

Conclusion:

Our study demonstrates that harvesting techniques do impact upon integrity of different vein layers, albeit with only a small effect. Secondary outcomes suggest that histological findings do not directly contribute to MACE outcomes. Gains in health status were observed and cost-effectiveness was better with CT-EVH. High level experience with endoscopic harvesting performed by a dedicated specialist practitioner gives optimal results which is comparable to open vein harvesting.

Clinical Trial Registration:

ISRCTN: 91485426. URL: https://www.isrctn.com.

Keywords: Coronary artery bypass surgery, open vein harvesting, closed tunnel endoscopic vein harvesting, open tunnel endoscopic vein harvesting, endothelial integrity, clinical outcomes, cost effectiveness.

Clinical perspective:

What is new?

- The VICO trial is the first study to directly evaluate the impact of minimally invasive and open vein harvesting techniques on the collective outcomes of endothelial integrity of the graft, clinical outcomes, health-related quality of life and cost effectiveness.
- The study aimed to determine if vein damage during harvesting contributed to outcomes following surgery. A single centre, sole operator study was selected to minimise the incidence of practitioner skill error as this could markedly impair the validity of any findings between endoscopic vein harvesting methods.

What are the clinical implications?

- This study demonstrates that endoscopic vein harvesting induces minimal damage to vessel integrity yet there is no direct correlation with clinical outcomes in a small sample size.
- In addition, it also highlights that EVH is likely to be cost effective, reduce post-surgery costs and improves patients' health-related quality of life.
- Our data supports the use of endoscopic vein harvesting techniques as a routine care procedure for coronary artery bypass surgery in selected patients.
- Practitioner experience is important in ensuring conduit quality as demonstrated by the difference between our pilot and randomised study data.

Introduction:

Arterial conduits play a vital role in coronary artery bypass grafting (CABG) surgery due to their physical and functional properties. The Internal mammary arteries (IMA) are considered to be a gold standard conduit for bypass surgery due to its high patency rate and its long term survival rate[1]. Only 4% to 12% patients receive bilateral IMA in US and European countries[2]. The long saphenous vein (LSV) still remains the preferred conduit for multiple coronary artery bypass surgery due to its long length, and endoscopic vein harvesting (EVH) has demonstrated reduced postoperative morbidity and improved patient satisfaction [3, 4]. Indeed, EVH is associated with markedly reduced scarring, diminished post-operative pain, greater patient mobility and reduced inflammation[4]. EVH also significantly reduces the likelihood of post-operative wound infections, potentially ameliorating the requirement for antibiotic usage[5]. Two EVH techniques exist: closed tunnel EVH (CT-EVH) and open tunnel EVH (OT-EVH), which differ on the basis of CO_2 pressurisation and instrumentation.

There is major debate regarding vein quality and long term clinical outcomes following EVH, largely due to the findings of a major study[6], which revealed poorer outcomes with EVH. However, this raised questions about the use of different systems (CT-EVH was used for the majority of EVH cases in that study), case selection, operator experience [7] and other comorbidities [8]. Previous studies [9-11] and systematic reviews [12, 13] have highlighted the need for an appropriately designed clinical trial to establish the effect of harvesting on vein integrity, downstream costs and clinical outcomes [14]. This was reinforced by the International Society of Minimally Invasive Cardiac Surgery[3] (ISMICS) and the National Institute for Health and Care Excellence [15, 16] (NICE). There are many studies that have compared EVH and OVH in relation to wound related complications and length of hospital stay, but still there is no study directly comparing three vein harvesting techniques on histological and clinical outcomes.

We designed a prospective single centre 3-armed randomised study comparing vein damage, clinical outcomes between two types of EVH (closed and open tunnel) and traditional open vein harvesting (OVH). A trial-based cost-effectiveness analysis was prospectively integrated within the study design to generate evidence on the cost-effectiveness of the vein harvesting techniques.

Methods:

Study Design:

The study was approved by the NRES Committee and conducted following the principles of the Declaration of Helsinki and Good Clinical Practice. This study was undertaken at the University Hospital of South Manchester NHS Foundation Trust and was overseen by an external steering committee, clinical trial unit, public patient involvement and safety monitoring board. The trial was registered on the IRAS trial registry prior to commencing patient recruitment. We also registered the trial on the International Standard Randomised Controlled Trial Registry (ISCTRN: 91485426) in line with EU regulation 536/2014 (the trial was submitted on 30th April 2014 and EU regulation 536/2014 was released on 27th May 2014. The trial was fully registered on 18th September 2014).

Informed written consented patients were prospectively recruited between November 2011 and May 2015 from the cardiac waiting list (Figure 1). Patients who received single internal mammary artery and individual vein grafts (1-4) by on-pump bypass were included (full study protocol describing recruitment, clinical and health economics data collection, method of histological scoring and standard techniques included in supplemental material). Exclusion criteria included: emergency CABG, superficial LSV (less than ½ cm below the skin) or varicose LSV and/or small or thin legs (<7.5cm diameter at the lower calf), determined via by an ultrasound Sonasite™ scans [4].

Patients were randomised to one of three groups with a 1:1:1 allocation ratio. Computerised simple block randomisation using random block sizes was performed by an independent

statistician. Patient allocation was revealed to the practitioner once the patient was anaesthetised. Data gathering researchers, the statistician, health economist and histologist were completely blinded to the study group assignments.

Surgical techniques:

OVH and EVH were performed as previously described[4, 17]. All veins were harvested by an experienced surgical practitioner (>250 cases for each EVH technique and >2000 open harvesting cases). However, the CABG surgery was performed by seven cardiac surgeons.

Open vein harvesting - Control group:

According to normal practice, a long incision was made from ankle to thigh depending upon the length of vein required for surgery. For the purpose of this study, the patients who required two lengths of vein had conduits harvested from just below the knee (approximately 9cm). Patients who required three lengths of vein had the conduits harvested from 4cm above the medial malleolus bone. The vein side branches were ligated with 4-0 vicyrl ties and titanium clips on both sides[4].

Closed tunnel CO_2 EVH: Intervention group

The Maquet Vasoview Hemopro2® vein harvesting system which involves a pressurised CO_2 tunnel for vein dissection was used. A 2-3cm incision was made just above or below the knee (approximately 9cm) depending upon the length of vein (1 or 2 or 3) required for surgery. The long saphenous vein was exposed and dissected using a West retractor and a Langenbeck retractor. The CO_2 insufflator was set to 3 litres/ min with 0mmHg pressure. Following completion of harvesting, patients received full heparinisation followed by cardio-pulmonary bypass. CT-EVH patients received 5000 units of heparin before EVH to avoid intraluminal clot formation[18]. A 30mm, 0° endoscope with a sharp, clear dissecting cone on the tip was inserted through the skin incision. After 3cm of anterior dissection, the balloon was inflated to seal the incision port. A minimal amount (10ml) of trocar cuff air inflation was

used to reduce the trauma to the vein. The vein was dissected from the surrounding tissues anteriorly and posteriorly until reaching the femoral junction in the groin. The vein side branches were ligated with 4-0 vicyrl ties and titanium clips on both sides[4].

Open tunnel CO_2 EVH: Intervention group

The Sorin ClearGlide® vein harvesting system which involves non-pressurised CO_2 tunnel for vein dissection was used. A 2-3cm incision was made just above or below the knee (approximately 9cm) depending upon the number of vein lengths (1 or 2 or 3) required for surgery. Initially, the long saphenous vein was exposed and dissected using a West retractor and a Langenbeck retractor. A 30mm, 0° telescope with a ClearGlide dissecting retractor was introduced through the skin incision. The CO_2 insufflator was set up at a continuous flow rate of 3 litres per minute and 0mmHg pressure. The vein was dissected from the surrounding tissue anteriorly and posteriorly until reaching the femoral junction in the groin. The vein side branches were ligated with 4-0 vicyrl ties and titanium clips on both sides. The small leg wound was closed in layers and a dressing and pressure bandage was applied[4].

Standardisation for all three group techniques:

- The vein was harvested with surrounding fat and adventitial layers. The conduit was harvested 2 to 3 mm away from the main long saphenous vein.
- All the branches were cut with at least 1cm length wherever possible.
- The vein was inflated with heparinised arterial blood with 10mmHg inflation pressure using a pressure control syringe.
- The cardioplegia vein perfusion flow pressure through the vein was standardised to 70mmHg for all cases.
- All patients requiring three lengths of vein had the conduits harvested from the ankle to the thigh. For patients who require one or two lengths, was harvested from just below or above the knee.

- The measurement of partial pressure of arterial carbon-dioxide ($Paco_2$), $Etco_2$ and also any changes to the ventilator settings during the vein harvesting procedure was monitored and recorded for this study.

Histological assessment:

2700 vein samples were numerically coded to ensure laboratory blinding. Surgically undistended vein samples (n=900) were obtained proximally at the port of entry and coded H1. Distal vein samples (n=900) obtained after 10mmHg heparinised blood flush to check for leakages were coded H3. Following vein grafting, a random sample was obtained from the remaining conduit, and coded H2 (n=900). Therefore H2 samples underwent all distension and manipulation as required for surgical preparation. As such, these samples provide the best possible representation of the entire vein at different stages following harvesting that could be achieved given the logistics of the operation. These H2 samples were randomly given by the cardiac surgeons who weren't told about the type of vein harvesting procedure to avoid any bias in relation to which segment given for research purposes.

A computerised immunohistochemistry protocol was used to stain CD34 (a validated endothelial marker)[19] of each vein sample from batch 1 (n=900; H1, H2, H3). A validated scoring system was used to grade endothelial integrity[20] (0-100% intact (positive staining), supplemental figure 1). The second batch of 900 vein samples was stained with Picrosirius red muscular and collagen stain (80-picrosirius red; Sigma-Aldrich Ltd, Dorset, UK) to assess structural damage in the muscular layers. We refined/ modified the existing scoring system (full detailed scoring in study Protocol attached as a supplemental file) for simplicity, which was used to grade muscular hypertrophy (the term hypertrophy in this study means acute swelling rather than chronic process of the muscle injury), detachment, muscle migration on a scale of 0-3 (normal, mild, moderate, severe, supplemental figure 2). The final batch of 900 vein samples was stained with Haematoxylin & Eosin (H&E) to assess endothelial stretching and detachment. Endothelial damage was graded on a scale of 0-3 (normal, mild, moderate and severe)[19].

All slides were scanned using a Pannoramic 250™ slide scanning system. All histology images were scored by 5 independent assessors and validated by a consultant histopathologist.

Study outcome measures:

The primary outcome measure was severity of histological damage to the vein conduits. The association between histological damage and pre-defined clinical outcomes was then assessed. Complete demographics, intraoperative details, incidence of wound infection and General Practitioner/district nurse visits were recorded.

The secondary end-points included incidence of Major Adverse Cardiac Events (MACE), use of healthcare resources and impact on health status. MACE was defined as repeat angina, breathlessness, myocardial ischemia/infarction, re-intervention, stroke and death. MACE were determined by telephone interviews, clinic letters, general practitioner and coroner reports at 3 month intervals until 12 months and then at 18, 24, 36 and 48 months. Only symptomatic MACE patients underwent cardiac MRI scans and angiograms were reviewed by an independent cardiologist and a cardiac surgeon.

An NHS and social services perspective was used for the scope of the collection of healthcare resources. All healthcare resources associated with treatment and follow-up care was recorded prospectively. For a full list of healthcare utilisation data collected (supplemental table 1) and unit costs which were sourced from the procurement and finance department at the hospital and national databases where relevant for follow-up care[20, 21]. The vein harvesting procedure was micro-costed, with the fixed cost of the vein harvesting equipment fully absorbed in each arm of the trial. The length of time within theatre required for vein harvesting was recorded and costed.

The impact on each individual's health status was assessed at 3 and 12 months using EQ-5D-3L which has five domains (Mobility, Self-Care, Usual Activities, Pain and Discomfort, Anxiety and Depression) and three levels within each domain ('no problems', 'some

problems', 'severe problems'). Using a published national tariff [22], each completed EQ-5D-3L questionnaire for each patient was converted into an index measure of health-related quality of life (HRQoL) on a scale of 1 equal to full health and 0 equal to death. Health states with a HRQoL less than death were also included. Patients who died had a HRQoL of 0 inputted. QALYs were calculated using the area under the curve method using the trapezoid rule and linear interpolation between the measures of HRQoL at the two time-points. As a one year time horizon was chosen no discounting was applied to the cost or QALY data.

Power calculation:

To generate an accurate power calculation we undertook a non-randomised pilot study comparing the impact of the different vein harvesting techniques on endothelial integrity using 140 patients. Based on this pilot data we calculated that 91 patients in each of the three groups (OVH, CT-EVH and OT-EVH), i.e. 273 in total, would provide 80% power to detect differences in the percentage with zero endothelial integrity of 20% or more (for example 20% vs. 40%) in this study. This calculation was based on a comparison of two groups using a simple chi-square test, with continuity correction at the 5% significance level. A recruitment strategy requiring a total of 300 patients with a 10% drop out rate was used.
Clinical outcomes in our pilot study demonstrated that 19% of closed tunnel CO_2 patients experienced MACE compared to 13% of open tunnel CO_2 patients (ie only a 6% difference in incidence).

Statistical analysis:

All demographics were summarised as frequencies/percentages for categorical variables and means/median with standard deviation/interquartile range as appropriate for continuous variables. Endothelial integrity as determined by CD34 expression was presented as median percentage integrity and other histological outcomes were presented as median scores and analysed using the Kruskal-Wallis test. Composite and individual MACE events were analysed at each time point using the chi-square test. All tests were performed as two-tailed analyses and p-values <0.05 were considered significant.

The chi-squared test was used to compare how patients completed the EQ-5D-3L profile across the arms of the trial with p-values <0.05 considered to be significant. Incremental costs, incremental QALYs and incremental net benefit at a decision-maker's threshold of £20,000 per QALY were calculated using regression analysis controlling for baseline disease severity measured by EQ-5D and the Canadian Cardiovascular Society grading score. For both costs and QALYs, different generalised linear models (GLM) were tested to assess for fit to the data. The appropriate family for the GLMs was assessed using the Park test. The appropriate link for the GLMs was assessed using the Pearson correlation test, the Pregibon link test and the Modified Hosmer & Lemeshow test [23].

For all regression models, a GLM model with an identity link and Gaussian family, equivalent to ordinary least squares, were found to be the best specified and was used for the analysis. Statistical uncertainty was considered by using a non-parametric bootstrap method[24] accommodating for the correlation between costs and QALYs and 1000 bootstrap replicates for each estimate was generated. Probabilities of cost-effectiveness were calculated by measuring the proportion of bootstrap replicates with a positive net-benefit for a given cost-effectiveness threshold. A complete set of data was available for HRQoL and healthcare resource use and so no form of imputation was used.

Pilot work:

A pilot study was designed to determine study sample size for the primary end-point and demonstrated that OT-EVH (n=70) better preserved conduit endothelium compared to CT-EVH (n=70) (median 65.0% vs. 11.4%, p<0.001, supplemental figure 3). However, no significant differences were observed between groups for MACE events including repeat angina (p=0.62), breathlessness (p=0.80), re-intervention (p=1.00), myocardial infarction/ischaemia (p=1.00) or mortality (p=0.44) up to 5 years post-surgery (supplemental table 2).

Results:

Demographics:

398 patients were enrolled but 24.6% (98 patients) were excluded from the study based on predefined exclusion criteria. 98 patients were excluded before the randomisation of the patient allocation numbers, so they were not allocated into any specific trial groups (Figure 1). This method was used to avoid major drop out from the study. Our previous patient recruitment for the clinical trials indicated that patients change their participation in the trial or surgery schedule changes to accommodate emergency and urgent in patient referrals. 301 patients underwent randomisation and there were no clinically relevant differences between groups (table 1). However, one patient in OVH group was excluded after surgery because tissue samples not collected. A higher body mass index, more left main stem and current smokers were observed in the CT-EVH group. Intraoperative variables were recorded, including surgical timings and number of veins required (supplemental table 3).

Primary histological outcomes:

Endothelial integrity: CD34

Endothelial integrity was better preserved in the OVH group in proximal samples compared to endoscopic techniques (median percentage integrity [IQR]: 91.50 [12.50] vs. 91.63 [10.56] vs. 95.75 [6.69] for CT-EVH vs. OT-EVH vs. OVH respectively, $p<0.001$, figure 2). Random samples from the OVH group displayed greatest endothelial integrity compared to the other groups (85.25 [21.13] vs. 87.50 [21.00] vs. 92.71 [13.13] for CT-EVH vs. OT-EVH vs. OVH respectively, $p<0.001$, figure 2). However, no statistical difference was observed in distal samples (92.25 [10.88] vs. 91.75 [13.81] vs. 95.38 [9.25] for CT-EVH vs. OT-EVH vs. OVH respectively, $p=0.07$, figure 2).

Muscular morphology: Picrosirius red and H&E

Endothelial stretching of proximal vein samples was greatest in OT-EVH group (66.0%), followed by CT-EVH (61.0%), with least stretching in OVH (46.0%, p=0.01). No differences in endothelial stretching were observed between groups in distal (53.5% vs. 51.5% vs. 41.0% for OT-EVH, OVH and CT-EVH respectively, p=0.16) or random (37.4% vs. 31.3% vs. 36.7% for OT-EVH, OVH and CT-EVH respectively, p=0.62) samples. The level of endothelial detachment was consistent between groups in proximal (2% vs. 3% vs. 2% for OT-EVH, OVH and CT-EVH, p=0.25), distal (4% vs. 1% vs. 6% for OT-EVH, OVH and CT-EVH, p=0.63) and random (5% vs. 2% vs. 5% for OT-EVH, OVH and CT-EVH, p=0.47) samples.

The circular muscle layer displayed greatest hypertrophy in proximal samples from the OT-EVH group (65.6%) followed by CT-EVH (45.0%) and OVH (14.3%, p<0.001). A similar pattern was observed in distal (46.3% vs. 24.2% vs. 38.8% for OT-EVH, OVH and CT-EVH, p<0.001) and random (35.4% vs. 14.1% vs. 31.3% for OT-EVH, OVH and CT-EVH, p=0.01) samples. The longitudinal muscle layer displayed greatest hypertrophy in proximal samples from the OT-EVH group (56.2%) compared to OVH (5.1%) and CT-EVH groups (23.0%, p<0.001). Greatest longitudinal hypertrophy was observed in distal samples from the OT-EVH group (26.3%), followed by CT-EVH (8.2%) and OVH (1.0%, p<0.001). Moreover, OT-EVH displayed greatest longitudinal hypertrophy in random samples (13.5%), compared to OVH (3.0%) and CT-EVH (1.0%, p=0.001).

Secondary outcomes – clinical events and cost effectiveness:

Composite and individual MACE scores were analysed in this study to avoid any varying definitions of composite outcomes. Kip et al[15] suggested that authors should focus separately on safety and effectiveness outcomes.

Composite MACE scores:

The incidence of composite MACE events were analysed at each time point up to 48 months. No significant differences were observed between groups at any point (Figure 3a and supplemental table 4). Endothelial integrity did not differ between patients with or without MACE at 24 months (with n=299) in proximal samples (median percentage integrity [IQR]: 93.58 [11.42] vs. 92.33 [7.54] for MACE-free and MACE-affected respectively, p=0.48), distal samples (93.08 [11.81] vs. 96.25 [11.50], p=0.26) or random samples (88.75 [18.56] vs. 87.25 [23.92], p=0.64).

A statistically significant body mass index (BMI), left main stem and current smokers were observed in CT-EVH group. A Cox proportional hazard model was considered. After adjusting for these variables, it does not appear to be a statistically significant relationship between the groups and time to first MACE event (p=0.61) (table 2). However, these results should be interpreted cautiously due to small number of MACE events occurred in this study.

Individual MACE events:

The secondary outcomes demonstrated that no significant difference in MACE events was observed between groups, other than slightly higher mortality at 3 and 6 months (p=0.05 and p=0.03 respectively), in the OT-EVH group (Figure 3b) although these deaths were not MACE related mortalities. Atrial fibrillation occurred in 9 patients and vein graft blockage was noted in 6 patients, although incidence was not influenced by group (p=0.69 and p=0.42 respectively, table 3). No statistically significant difference in MACE outcomes at each time

point up to 48 months was observed between operating surgeons (p=0.76, p=0.78, p=0.26, p=0.23 and p=0.21 respectively).

Cost effectiveness analyses:

Vein harvesting costs for both the endoscopic approaches were more expensive than the use of traditional OVH. The use of CT-EVH increased costs by £1180 (p<0.001) whilst OT-EVH increased costs by £981 (p<0.001) per patient over OVH. This increase in cost was due to one-off payments for the visual equipment needed to conduct the endoscopic extraction as well as an increase in variables costs required for each operation, such as the need for additional disposable tubing and camera drapes. However, both endoscopic approaches led to lower downstream costs associated with follow-up care.

There was a reduction in post-operation costs for GP visits, district nurse visits and hospital stays (p<0.001). There was also a reduction in the cost for postoperative antibiotics usage, other medications, as well as the cost associated with 'wound infection packages' which includes readmission to the hospital, re-theatre costs for additional procedures and vac therapy. Consequently, for follow-up care, CT-EVH led to a mean reduction in downstream costs of £814 (p=0.002) per person versus OVH whilst OT-EVH led to a mean reduction of £598 (p=0.03). Overall, when combining the vein harvesting cost and the downstream costs, both EVH methods led to net cost increases over OVH, by £274 (p=0.34) for CT-EVH and £436 (p=0.16) for OT-EVH per patient although neither were statistically significant.

Both endoscopic approaches led to a marked improvement in health-related quality of life compared to the use of OVH. Figure 4a and Figure 4b shows how patients completed the EQ-5D-3L at 3 and 12-months respectively. At 3-months, in the domains for Mobility, Self-Care, Usual Activities and Pain and Discomfort, patients were more likely to report having some problems in the OVH arm compared to the endoscopic arms (p<0.001). At 12-months, patients were still more likely to report as having some problems for the domains Self-Care (p=0.02), Usual Activities (p=0.01) and Pain and Discomfort (p=0.004) but there was no

significant effect for Mobility (p=0.051). For the domain Anxiety and Depression there was no difference between the arms at either 3-months (p=0.30) or 12-months (p=0.32).

Supplemental figure 4 illustrates the impact on the EQ-5D-3L index after the EQ-5D-3L profiles have been weighted by the UK national tariff. The biggest difference in HRQoL occurs at 3-months where patients in both endoscopic arms have higher HRQoL compared to OVH (p<0.001). At 12-months there is an improvement in HRQoL across all arms and some narrowing between the harvesting methods. At 12-months both endoscopic approaches have higher mean values than OVH which is statistically significant for CT-EVH versus OVH (p=0.004) although insignificant for OT-EVH (p=0.128). After calculating the area under the curves, there was an increase in QALYs of 0.11 per patient (p=0.001) for the CT-EVH arm versus OVH whilst OT-EVH had an increase in QALYs of 0.07 per patient (p<0.003) versus OVH.

When considering the costs and health benefits together to assess cost-effectiveness, CT-EVH had an incremental net-benefit per patient of £1927 versus OVH and a 75% likelihood of being cost-effective. This probability for cost-effectiveness is based on a decision-maker being willing to spend an additional £20,000 for every additional QALY generated, called the cost-effectiveness threshold. OT-EVH had an incremental net-benefit per patient of £950 versus OVH and a 19% likelihood of being cost-effective at a threshold of £20,000 per QALY. OVH had a low likelihood (6%) of being cost-effective (figure 5a & b)

Safety and clinical relevance:

At 24 months, composite MACE events were observed in 33 patients; (OVH (10/100), CT-EVH (11/100) and OT-EVH (12/100)). 289 patients survived, with non-cardiovascular associated mortality in 11 patients due to ischemic bowel, pneumonia, liver failure and cancer. No mortality associated with cardiovascular events was observed. MACE repeat angina events (table 3) were observed in 16 patients during the study period. Follow-up MRI and angiogram evaluation in symptomatic patients concluded that angina was caused by

native artery disease progression (4/16), vein graft insertional site stenosis (4/16), vein graft blocked (2/16), previous patent stent blocked (4/16) and left internal mammary artery insertional site stenosis (5/16). The vein conduits could not be grafted at the time of operation due to calcified/small coronaries in 3/16 patients. Multiple causes were observed in 5 patients.

Discussion:

This is the first study with direct head to head comparison of two EVH techniques with traditional OVH in relation to histological vein integrity and clinical outcomes. EVH has a number of important benefits, and is associated with markedly improved post-operative patient satisfaction due to significantly less scarring, contributing to reduced pain and improved patient mobility compared to OVH. The smaller scar is also less likely to become infected, therefore necessitating less post-operative follow-up care. If graft patency can be maintained with EVH, then this would be a preferred option to OVH in suitable patients.

We report there was some vein injury in EVH compared to OVH (with loss of endothelial integrity, increased endothelial stretching, and muscle hypertrophy most severe in OT-EVH compared to CT-EVH and OVH). This study was powered for primary outcome using our pilot work results to see percentage of patients with zero endothelial injury but we have not observed any conduits with zero endothelial integrity any of the groups. Severe stretching and muscle migration has been associated with graft occlusion[25, 26], yet only a small proportion of vein samples had severe intimal stretching in the OT-EVH group, and our sub-analysis could not detect an association with MACE events.

In 2009, a major non-randomised study concluded that EVH had higher rates of vein graft failure and mortality within 12-18 months post-surgery[6]. However, secondary outcomes from our randomised study demonstrate no statistically significant difference in composite or individual MACE scores with EVH, albeit with a low sample size precluding firm conclusions from being made. Furthermore, MACE scores did not correlate with vessel injury. This corroborates findings from previous studies describing positive clinical outcomes[3, 12, 14] with both EVH and OVH and provides insight into the risk factors for MACE.

Repeat angina and re-intervention in patients in this study were mainly due to grafting technique and technical error[27, 28], poor target artery quality[11], progression of native coronary artery diseases[8] and previous stent blockage post CABG surgery. Whilst the importance of

grafting technique is highlighted by our findings, we did not observe significant intra-operator effects on MACE outcomes.

According to the ISMICS consensus statement [3], studies comparing OVH versus EVH have focused only on the cost of wound complications[29], readmissions and hospital stay[30] but no analysis of incremental cost-effectiveness has been conducted. Our study highlights that both EVH techniques led to modest net increases in cost versus OVH during surgery. However, both EVH techniques substantially reduced post-surgery costs and improved patients' health-related quality of life leading to relatively large gains in QALYs when compared with other technologies[31]. The use of CT-EVH was associated with lower costs and better outcomes when compared with OT-EVH. Therefore CT-EVH may represent the optimal cost-effective technique for vein harvesting.

Limitations:

This study was designed to utilise a single experienced practitioner from one centre to determine the impact of harvesting techniques. Different operators will inevitably introduce variability in surgical skills which could confound a true comparison. The practitioner had experience of >2000 OVH cases but only 250 EVH cases and this may have implications on surgical timings, quality of the OVH vein conduit and post-operative complications, which need to be taken into consideration when interpreting the data. Also, not all study participants underwent routine angiogram or cardiac MRI scans due to ethical, financial restrictions within the NHS and risks involved due to patients' age. The current study is underpowered to detect small differences in clinical outcomes as >1000 patients would be required in each arm, which would not be possible for a single centre study. However, this study was designed with graft histology as the primary outcome as this has been understudied to date and is an important area. For these purposes, a single centre, single practitioner model was most appropriate. The principal reason for using a sole operator for this study is to minimise the incidence of practitioner skill error. Also, we performed

comparisons of MACE incidence at multiple time points, which could increase the likelihood of type 1 error and obtaining statistically significant results by chance. However, we did not detect statistical differences in individual MACE events at any time point, and so type 1 error did not alter our conclusions.

Conclusion:

Our study demonstrated that endoscopic vein harvesting does cause minimal damage to the layers of the vein. However, the small sample size in this study makes it difficult to conclude what impact this injury has on clinical outcomes with large sample size. Endoscopic vein harvesting also provides better health-related quality of life, QALYs and is more cost-effective than open vein harvesting post CABG surgery. Therefore endoscopic vein harvesting can be utilised for vein harvesting safely with appropriate patient selection, equipment and better structured training in future practitioners. This study provides a base for future multicentre studies and also clarifies that histological damage is minimal when practitioners are experienced.

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Conflict of Interest:

There was no conflict of interest.

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Contributors:

All authors meet the ICMJE criteria for authorship. BK, NY: full study concept, design, data collection, study integrity, manuscript writing and final approval. JM: Statistical data analysis, manuscript drafting, final approval. JE, WC: concept, histology data analysis, manuscript writing and final approval. RVV, AC: concept, drafting and revising the article. AT, KP: health economics data analysis and HE input manuscript writing and final approval.

Data sharing statement: The authors have collected the clinical data from the participants. The independent steering and data monitoring committee, clinical trial unit were involved throughout the study period and also raw data will be available from the correspondence author anytime for quality check if needed.

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Figure Legends:

Figure 1: Consort diagram demonstrates the detailed enrolment, treatment and follow up of the VICO trial patients.

Figure 2: This figure illustrates the median percentage endothelial integrity on proximal (H1), random (H2) and distal (H3) vein samples between CT-EVH, OT-EVH and OVH groups.

igure 3: This Kaplan-Meier figure illustrates the time to MACE events (a) and cumulative survival (b) at different time points until 48 months. There does not appear to be a statistically significant difference between the groups in their MACE event times (log-rank test p=0.56) nor their mortality and survival.

Figure 4: This figure shows how patients completed the EQ-5D-3L (% selecting level) for each arm of the trial at 3-months (a) and 12 months (b).

Figure 5: A) Cost-effectiveness plane showing incremental costs and QALYs of CT-EVH and OT-EVH versus OVH. Bootstrap replicates (n=2000) show the uncertainty with the larger points showing the point estimates. A cost-effectiveness threshold of £20,000 per QALY is presented. For a technology in the North-East quadrant, a cost-effective technology is one where the point estimate and a high proportion of bootstrap replicates falls below (South-East) the threshold line. B) Cost-effectiveness acceptability curve for OVH, CT-EVH and OT-EVH which is plotted by calculating the proportion of bootstrap replicates falling below the cost-effectiveness threshold line as the threshold is varied. The typical threshold used by NICE is taken to be between £20,000-£30,000 per QALY.

Table 1: Demographic data including pre-operative co-morbidities, risk factors and cardiac history.

Demographic variables		**Group**			**p-value**
		OT-EVH (n=100)	**OVH (n=100)**	**CT-EVH (n=100)**	
Age (years)		66.92±10.08	65.96±9.34	64.06±10.20	0.12
Sex (M/F)		82/18 (82.0%/18.0%)	79/21 (79.0%/21.0%)	79/21 (79.0%/21.0%)	0.83
Body Mass Index (BMI)		27.77 [6.41]	27.93 [5.45]	28.78 [6.54]	**0.04**
Surgery:	*Elective*	46 (46.0%)	49 (49.0%)	41 (41.0%)	0.52
	Urgent	54 (54.0%)	51 (51.0%)	59 (59.0%)	
Diabetes:	*Diet controlled*	8 (8.0%)	6 (6.0%)	4 (4.0%)	0.49
	Tablet controlled	21 (21.0%)	27 (27.0%)	22 (22.0%)	0.56
	Insulin controlled	8 (8.0%)	11 (11.0%)	4 (4.0%)	0.18
CCS* score	*I*	17 (17.0%)	17 (17.0%)	12 (12.0%)	0.69
	II	25 (25.0%)	29 (29.0%)	33 (33.0%)	
	III	45 (45.0%)	45 (45.0%)	46 (46.0%)	
	IV	13 (13.0%)	9 (9.0%)	9 (9.0%)	
New York Heart Association:	*I*	27 (27.0%)	32 (32.0%)	40 (40.0%)	0.05
	II	45 (45.0%)	35 (35.0%)	26 (26.0%)	
	III	26 (26.0%)	25 (25.0%)	29 (29.0%)	
	IV	2 (2.0%)	8 (8.0%)	5 (5.0%)	
STEMI*		18 (18.0%)	19 (19.0%)	29 (29.0%)	0.12
NSTEMI*		42 (42.0%)	48 (48.0%)	44 (44.0%)	0.69
Previous PTCA*		16 (16.0%)	12 (12.0%)	20 (20.0%)	0.30
Previous MI		52 (52.0%)	43 (43.0%)	54 (54.0%)	0.25
Multivessel disease		82 (82.0%)	81 (81.0%)	86 (86.0%)	0.61
Left main stem		25 (25.0%)	25 (25.0%)	40 (40.0%)	**0.03**
Hypertension		87 (87.0%)	83 (83.0%)	88 (88.0%)	0.56
Smoking:	*Never smoked*	32 (32.0%)	33 (33.0%)	23 (23.0%)	**0.03**
	Previous smoker	52 (52.0%)	54 (54.0%)	47 (47.0%)	
	Current smoker	16 (16.0%)	13 (13.0%)	30 (30.0%)	
Hypercholesterolemia		96 (96.0%)	90 (90.0%)	92 (92.0%)	0.25
Peripheral vascular disease		19 (19.0%)	20 (20.0%)	21 (21.0%)	0.94
Left Ventricular ejection fraction					0.88
	>50%	74 (74.0%)	74 (74.0%)	72 (72.0%)	
	30-50%	21 (21.0%)	18 (18.0%)	22 (22.0%)	
	<30%	5 (5.0%)	8 (8.0%)	6 (6.0%)	

Categorical variables are expressed as number (%) and assessed by the χ^2 test. Continuous variables are expressed as either mean±standard deviation (parametric data) or median [interquartile range] (non-parametric data) and analysed by ANOVA or Independent samples Kruskal-Wallis test respectively. * STEMI- ST elevated myocardial infarction, NSTEMI – Non ST

elevated myocardial infarction, PTCA – Percutaneous coronary angioplasty and CCS score – Canadian Cardiovascular Society score.

Table 2: Cox PH model for MACE events.

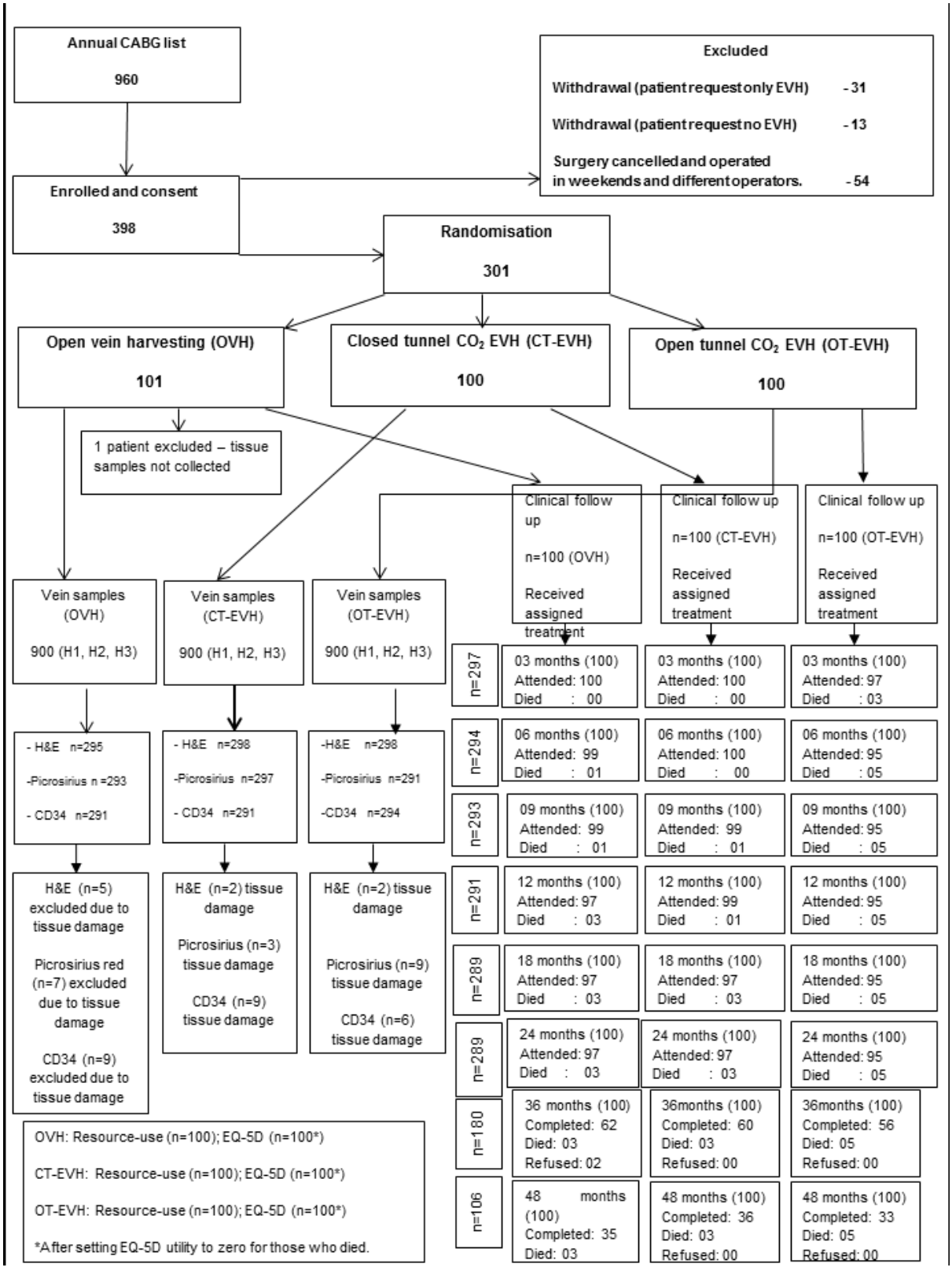
Unadjusted Cox PH model for MACE events		
Variable: **Groups**	**Hazards ratio (95% CI)**	**p-value**
CT-EVH OT-EVH OVH	1 (-) 1.30 (0.62-2.70) 0.86 (0.39-1.93)	0.56
Adjusted Cox PH model for MACE events		
Variable: **Groups**	**Hazards ratio (95% CI)**	**p-value**
CT-EVH OT-EVH OVH	1 (-) 1.24 (0.58-2.66) 0.85 (0.37-1.95)	0.61
BMI (per unit increase)	0.96 (0.89-1.04)	0.30
Left main stem No Yes	 1 (-) 2.00 (1.05-3.80)	0.034
Smoking Never smoked Previous smoker Current smoker	 1 (-) 1.29 (0.61-2.72) 1.19 (0.46-3.03)	0.80
New York Heart Association I II or more	 1 (-) 4.91 (1.74-13.86)	0.003

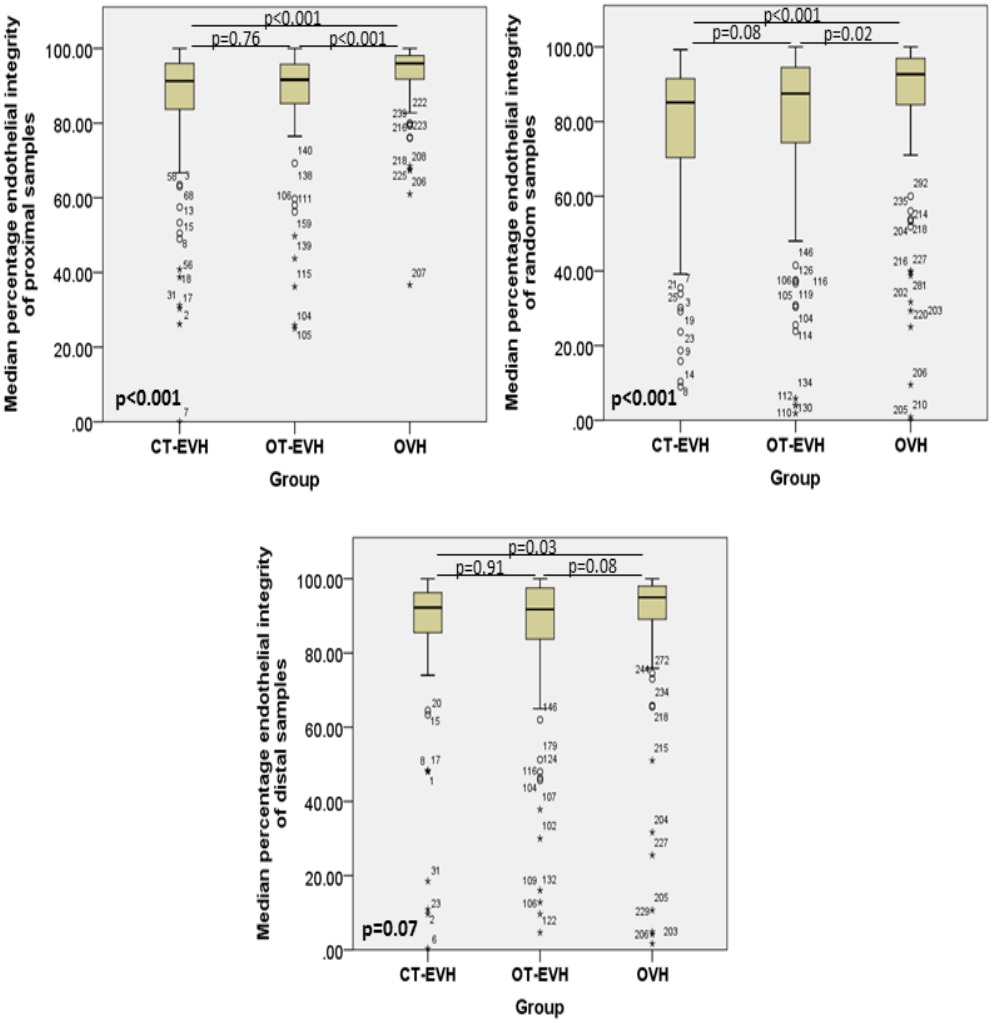
After adjusting for BMI, left main stem, smoking status and New York Heart Association grade – the variables that appear to be unbalanced between the randomisation groups – there does not appear to be a statistically significant relationship between group and time to first MACE event (p=0.61). The regression parameters and hazard ratios appear similar for the group variable in the unadjusted and the adjusted Cox PH analysis, suggesting the possible imbalances in the 4 other variables between the randomisation groups do not impact its relationship with time to first MACE event. These results should be interpreted cautiously due to the number of MACE events (totalling 33) and the number of parameters estimated in the adjusted Cox PH model, which was seven.

Table 3: The incidence of post-operative complications and investigations

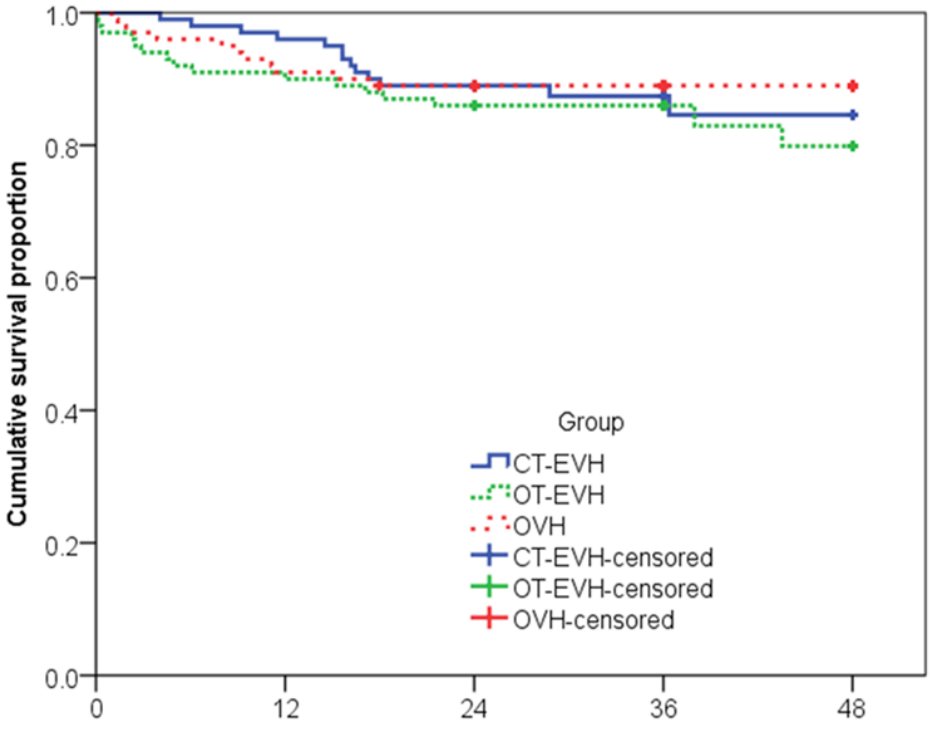
Variable	**CT-EVH**	**OT-EVH**	**OVH**	**p-value**
Chest wound numbness	57 (57.0%)	39 (40.2%)	52 (52.0%)	**0.05**
Chest wound tenderness	49 (49.0%)	34 (35.1%)	42 (42.4%)	0.14
Leg wound numbness	3 (3.0%)	10 (10.3%)	52 (52.5%)	**<0.001**
Leg wound tenderness	3 (3.0%)	7 (7.2%)	36 (36.4%)	**<0.001**
Arrhythmias	2 (2.0%)	3 (3.0%)	2 (2.1%)	0.87
Atrial fibrillation	2 (2.0%)	3 (3.0%)	4 (4.1%)	0.69
Ventricular fibrillation/tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	---
Pacemaker fitted	2 (2.0%)	2 (2.0%)	1 (1.0%)	0.83
MRI performed	2 (2.0%)	6 (6.0%)	3 (3.1%)	0.30
Angiography performed	2 (2.0%)	5 (5.2%)	5 (5.2%)	0.43
Total MACE	4 (4.0%)	6 (6.0%)	6 (6.0%)	0.77
Cause of MACE events.				
Vein not used due to small native coronary artery	2*	1	0	---
Native artery disease	1	1*	2	
Previous stent blocked	2*	1	1	
LIMA blocked	1*	2*	2	
Vein graft insertional stenosis	0	2*	2	
Vein graft blockage	0	2*	0	

Post-operative complications and investigations carried out for the participants post CABG surgery during the follow up period are listed from the day of surgery until 48 months. In addition to the incidences, the detailed causes of MACE events have been listed. ***** represents that the same patient had multiple MACE causes.


Annual CABG list
960
Excluded
Withdrawal (patient request only EVH) - 31
Withdrawal (patient request no EVH) - 13
Surgery cancelled and operated in weekends and different operators. - 54
Enrolled and consent
398
Randomisation
301
Open vein harvesting (OVH)
101
Closed tunnel CO_2 EVH (CT-EVH)
100
Open tunnel CO_2 EVH (OT-EVH)
100
1 patient excluded – tissue samples not collected
Clinical follow up
n=100 (OVH)
Received assigned treatment
Clinical follow up
n=100 (CT-EVH)
Received assigned treatment
Clinical follow up
n=100 (OT-EVH)
Received assigned treatment
Vein samples (OVH)
900 (H1, H2, H3)
Vein samples (CT-EVH)
900 (H1, H2, H3)
Vein samples (OT-EVH)
900 (H1, H2, H3)
- H&E n=295
-Picrosirius n =293
- CD34 n=291
- H&E n=298
-Picrosirius n=297
- CD34 n=291
-H&E n=298
-Picrosirius n=291
-CD34 n=294
H&E (n=5) excluded due to tissue damage
Picrosirius red (n=7) excluded due to tissue damage
CD34 (n=9) excluded due to tissue damage
H&E (n=2) tissue damage
Picrosirius (n=3) tissue damage
CD34 (n=9) tissue damage
H&E (n=2) tissue damage
Picrosirius (n=9) tissue damage
CD34 (n=6) tissue damage
n=297
03 months (100) Attended: 100 Died : 00
03 months (100) Attended: 100 Died : 00
03 months (100) Attended: 97 Died : 03
n=294
06 months (100) Attended: 99 Died : 01
06 months (100) Attended: 100 Died : 00
06 months (100) Attended: 95 Died : 05
n=293
09 months (100) Attended: 99 Died : 01
09 months (100) Attended: 99 Died : 01
09 months (100) Attended: 95 Died : 05
n=291
12 months (100) Attended: 97 Died : 03
12 months (100) Attended: 99 Died : 01
12 months (100) Attended: 95 Died : 05
n=289
18 months (100) Attended: 97 Died : 03
18 months (100) Attended: 97 Died : 03
18 months (100) Attended: 95 Died : 05
n=289
24 months (100) Attended: 97 Died : 03
24 months (100) Attended: 97 Died : 03
24 months (100) Attended: 95 Died : 05
n=180
36 months (100) Completed: 62 Died: 03 Refused: 02
36months (100) Completed: 60 Died: 03 Refused: 00
36months (100) Completed: 56 Died: 05 Refused: 00
n=106
48 months (100) Completed: 35 Died: 03
48 months (100) Completed: 36 Died: 03 Refused: 00
48 months (100) Completed: 33 Died: 05 Refused: 00
OVH: Resource-use (n=100); EQ-5D (n=100*)
CT-EVH: Resource-use (n=100); EQ-5D (n=100*)
OT-EVH: Resource-use (n=100); EQ-5D (n=100*)
*After setting EQ-5D utility to zero for those who died.

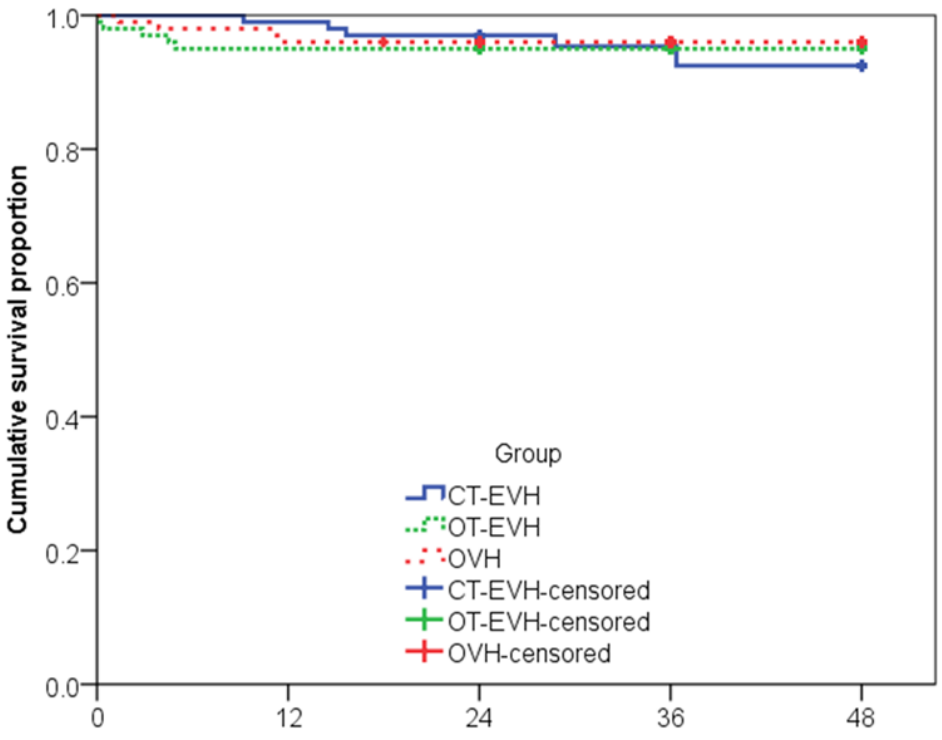

Median percentage endothelial integrity of proximal samples
p<0.001
p=0.76
p<0.001
p<0.001
CT-EVH
OT-EVH
OVH
Group
Median percentage endothelial integrity of random samples
p<0.001
p=0.08
p=0.02
p<0.001
CT-EVH
OT-EVH
OVH
Group
Median percentage endothelial integrity of distal samples
p=0.03
p=0.91
p=0.08
p=0.07
CT-EVH
OT-EVH
OVH
Group

A)



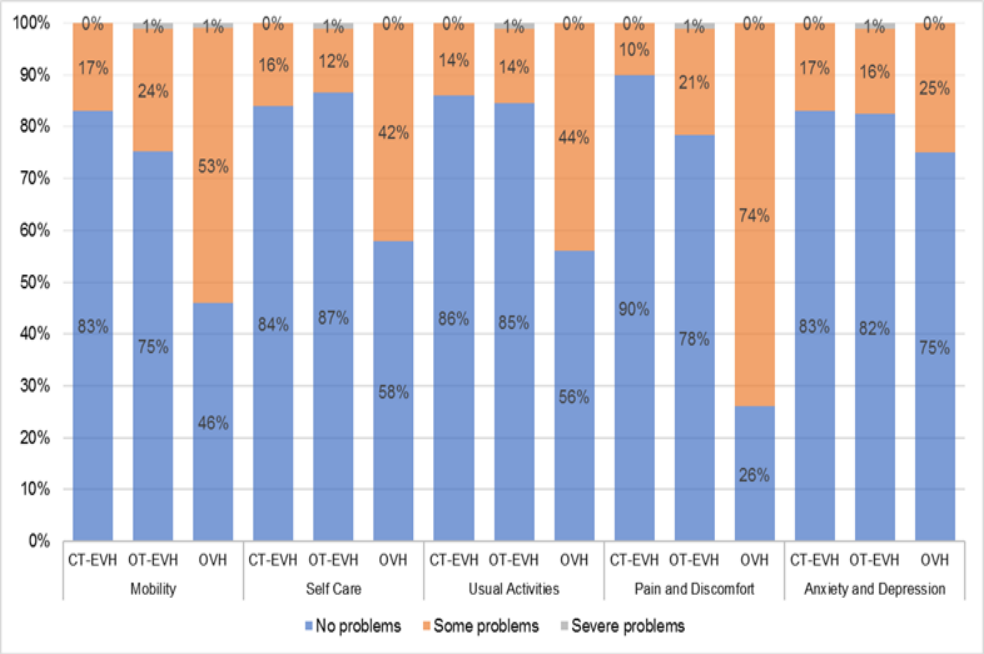
Numbers at risk					
CT-EVH	100	96	88	55	30
OT-EVH	100	90	85	48	26
OVH	100	91	88	55	33

B)

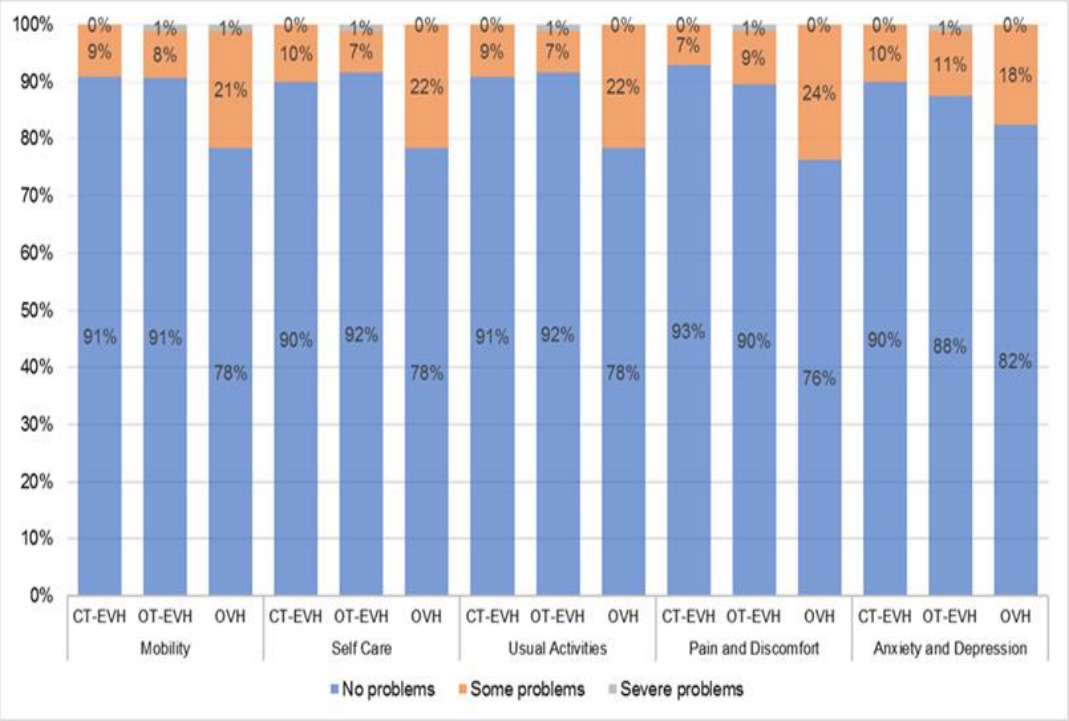


Numbers at risk					
CT-EVH	100	99	97	58	32
OT-EVH	100	95	95	54	31
OVH	100	96	95	59	35

A)


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0% 17% 83%
1% 24% 75%
1% 53% 46%
0% 16% 84%
1% 12% 87%
0% 42% 58%
0% 14% 86%
1% 14% 85%
0% 44% 56%
0% 10% 90%
1% 21% 78%
0% 74% 26%
0% 17% 83%
1% 16% 82%
0% 25% 75%
CT-EVH OT-EVH OVH
Mobility
CT-EVH OT-EVH OVH
Self Care
CT-EVH OT-EVH OVH
Usual Activities
CT-EVH OT-EVH OVH
Pain and Discomfort
CT-EVH OT-EVH OVH
Anxiety and Depression
No problems
Some problems
Severe problems

B)


100%
90%
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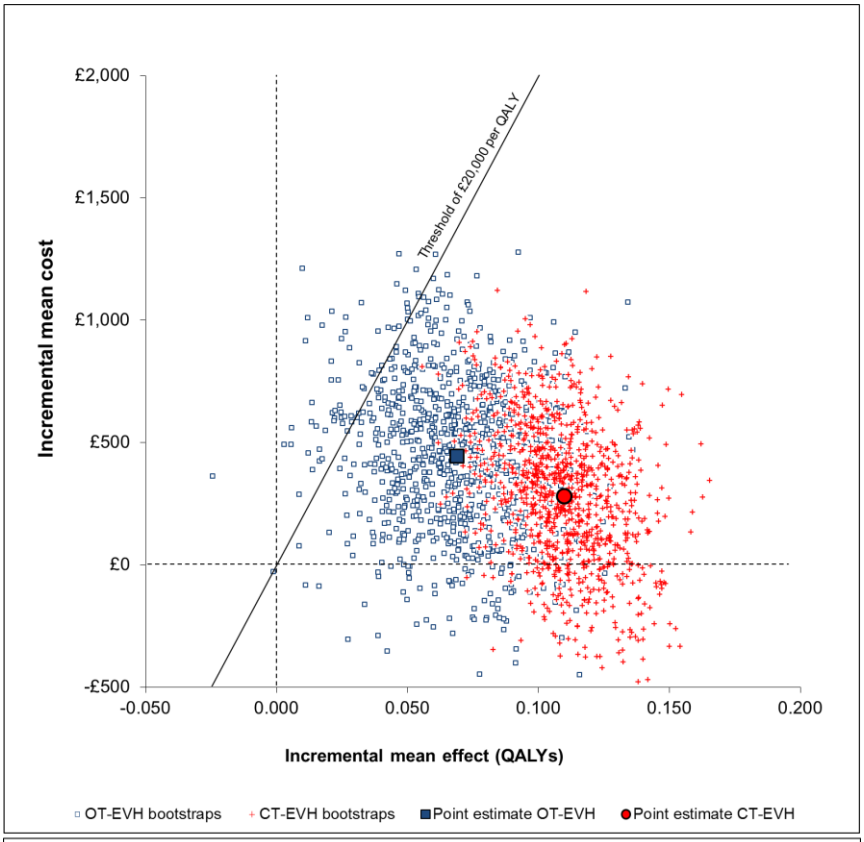
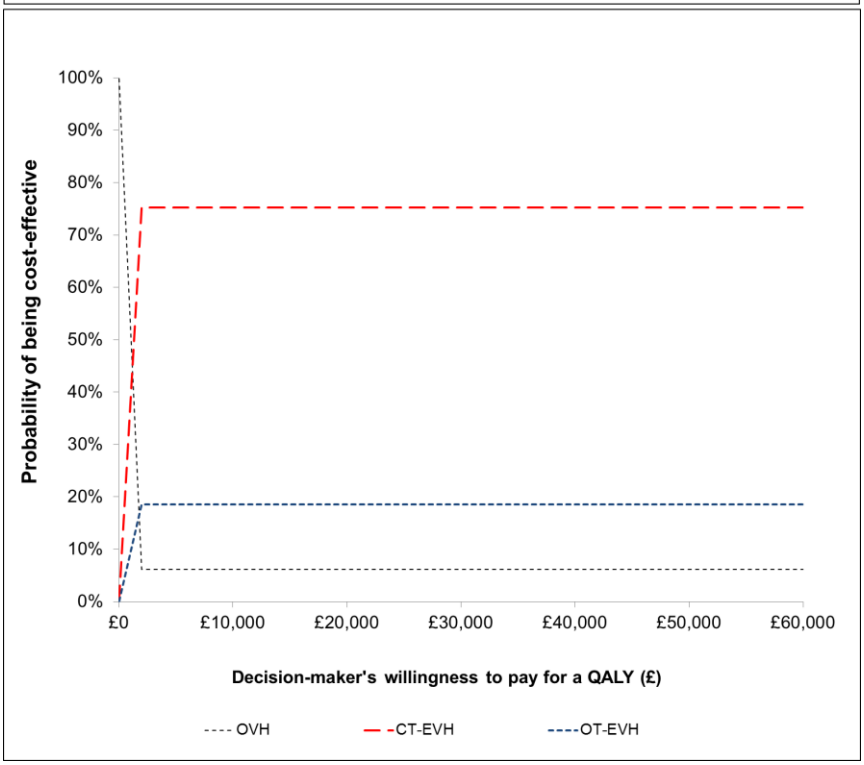
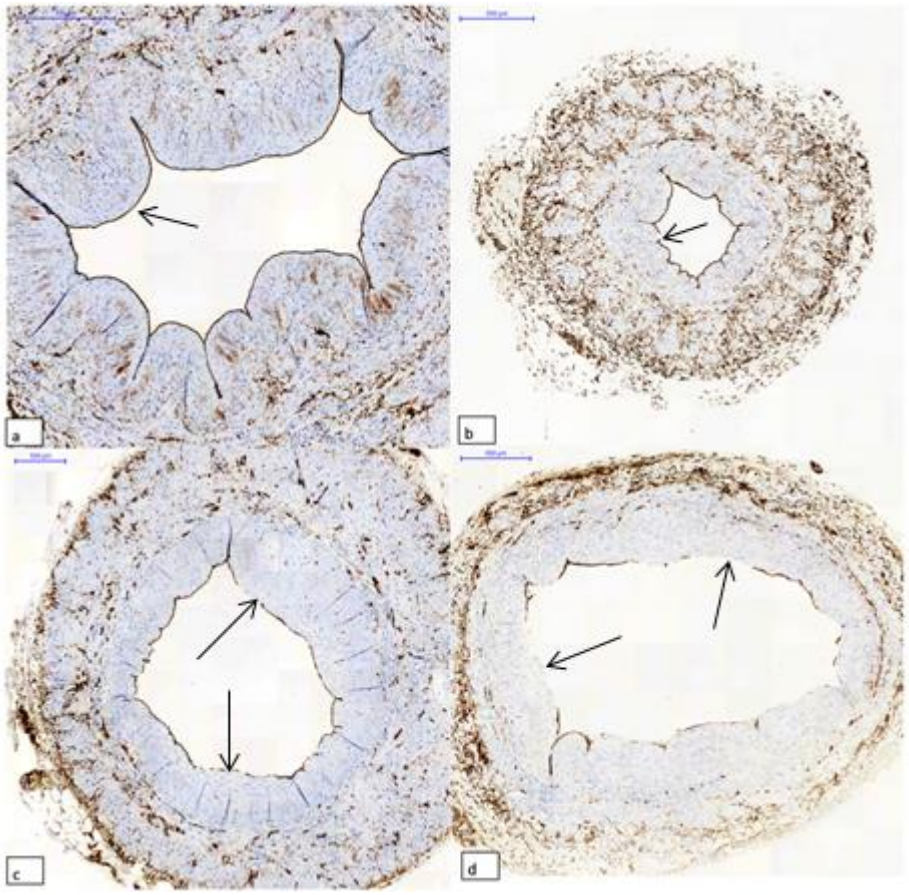
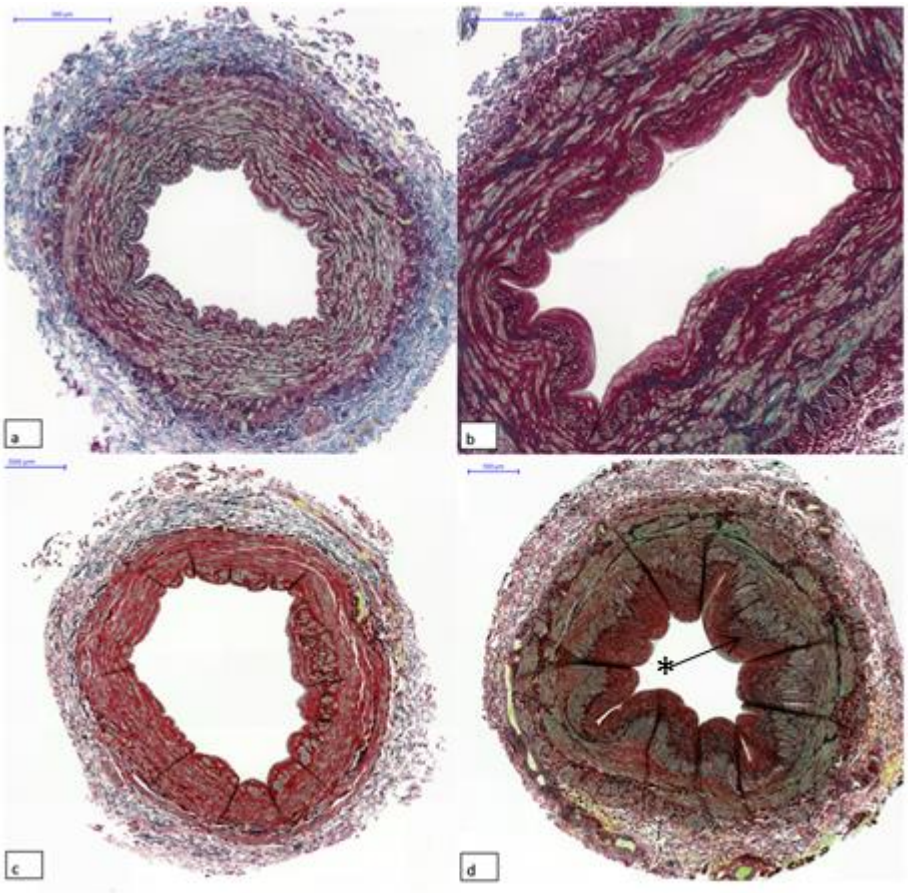
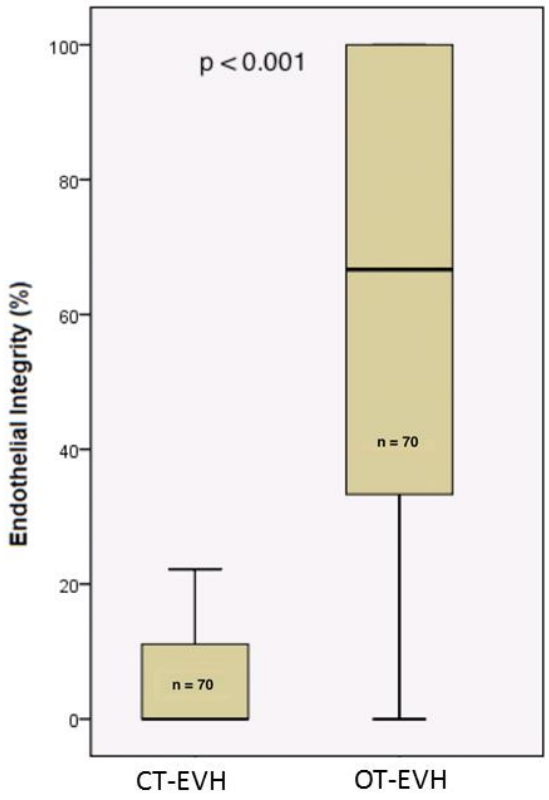
1% 8% 91%
1% 21% 78%
0% 10% 90%
1% 7% 92%
0% 22% 78%
0% 9% 91%
1% 7% 92%
0% 22% 78%
0% 7% 93%
1% 9% 90%
0% 24% 76%
0% 10% 90%
1% 11% 88%
0% 18% 82%
CT-EVH OT-EVH OVH
Mobility
Self Care
Usual Activities
Pain and Discomfort
Anxiety and Depression
No problems
Some problems
Severe problems

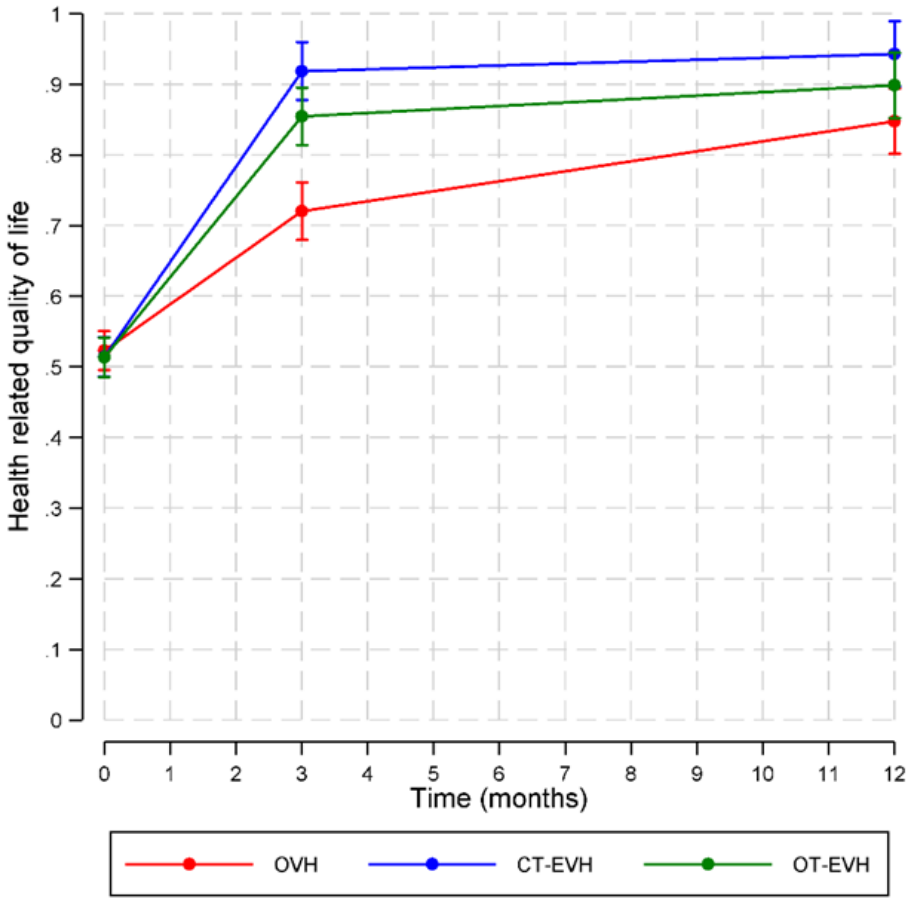

£2,000
£1,500
£1,000
£500
£0
-£500
Incremental mean cost
Threshold of £20,000 per QALY
-0.050
0.000
0.050
0.100
0.150
0.200
Incremental mean effect (QALYs)
OT-EVH bootstraps
CT-EVH bootstraps
Point estimate OT-EVH
Point estimate CT-EVH


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability of being cost-effective
£0
£10,000
£20,000
£30,000
£40,000
£50,000
£60,000
Decision-maker's willingness to pay for a QALY (£)
OVH
CT-EVH
OT-EVH


a
b
c
d


a
b
c
d


p < 0.001
Endothelial Integrity (%)
100
80
60
40
20
0
n = 70
n = 70
CT-EVH
OT-EVH


Health related quality of life
1
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Time (months)
OVH
CT-EVH
OT-EVH

Supplemental material:

Supplemental table 1: Resource use and unit costs in the analysis

Resource-use item	Cost type	Fixed cost total	Unit cost*	Source Year	Source	Years need inflating	Unit cost
Vein Extraction							
West retractor (one off payment)	Fixed	£ 78.80	£ 2.75	2014	Finance department	1	£ 2.78
Sterilisation 1	Variable		£ 2.00	2014	Finance	1	£ 2.02
Langebeck retractor small(one off payment)	Fixed	£ 46.52	£ 3.32	2014	Finance	1	£ 3.36
Sterilisation 2	Variable		£ 2.00	2014	Finance	1	£ 2.02
Vein harvesting set (cut down)one off payment	Fixed	£ 293.70	£ 6.59	2014	Finance	1	£ 6.66
Sterilisation 3	Variable		£ 12.00	2014	Finance	1	£ 12.13
Disposables (in theatres and ward, community)			-				
Leg vaccum drain size 10	Variable		£ 7.52	2013	Procurement	2	£ 7.67
Dressings large each	Variable		£ 1.15	2013	Procurement	2	£ 1.17
Dressings small each	Variable		£ 0.66	2013	Procurement	2	£ 0.67
Bandages 6" each	Variable		£ 0.84	2013	Procurement	2	£ 0.86
Sutures							
2/0vicryl each	Variable		£ 3.45	2013	Procurement	2	£ 3.52
3/0monocryl	Variable		£ 3.50	2013	Procurement	2	£ 3.57
Vicryl ties4/0 each	Variable		£ 4.22	2013	Procurement	2	£ 4.31
Drain stitch each	Variable		£ 1.57	2013	Procurement	2	£ 1.60
Swabs(5 pieces per pack)	Variable		£ 1.12	2013	Procurement	2	£ 1.14

Red ligaclips pack 4	Variable		£ 27.60	2013	Procurement	2	£ 28.16
Blue ligaclips pack 4	Variable		£ 29.20	2013	Procurement	2	£ 29.79
Theatre time	Variable		£ 15.12	2013	Procurement	2	£ 15.43
Total leg operation surgery timings							
EVH- disposable kit	Variable		£ 550.00	2013	Procurement	2	£ 561.10
Camera drapes	Variable		£ 190.58	2013	Procurement	2	£ 194.43
Lens cleaner	Variable		£ 79.59	2013	Procurement	2	£ 81.20
CO2 tubing	Variable		£ 173.13	2013	Procurement	2	£ 176.63
Light lead one off payment	Fixed	£ 295.00	£ 0.06	2013	Procurement	2	£ 0.06
Telescope one off payment	Fixed	£ 2,571.00	£ 0.47	2013	Procurement	2	£ 0.48
Hemoprobe cable one off payment	Fixed	£ 220.00	£ 0.04	2013	Procurement	2	£ 0.04
TV, camera monitor stack machine one off payment for 10 years	Fixed	£ 35,725.00	£ 19.27	2013	Procurement	2	£ 19.66
Power supply Haemoprobe one off payment	Fixed	£ 4,025.00	£ 2.17	2013	Procurement	2	£ 2.22
Follow-up care							
ECG per visit	Variable		£ 62.00	2013	Finance	2	£ 63.25
ECHO per visit	Variable		£ 111.00	2013	Finance	2	£ 113.24
Cardiac MRI scan per visit	Variable		£ 534.00	2013	Finance	2	£ 544.78
Angiogram visit urgent	Variable		£ 3,213.87	2013	Finance	2	£ 3,278.75
Angiogram day case	Variable		£ 1,367.36	2013	Finance	2	£ 1,394.96
PTCA elective	Variable		£ 3,045.28	2013	Finance	2	£ 3,106.76
PTCA day case	Variable		£	2013	Finance	2	£

			2,978.67				3,038.80
GP visit	Variable		£ 53.00	2015	PSSRU	0	£ 53.00
District nurse home visits	Variable		£ 24.00	2015	PSSRU	0	£ 24.00
Antibiotic	Variable		£ 7.20	2015	Pharmacy	0	£ 7.20
Cardiology follow-up	Variable		£ 97.78	2013	Finance	2	£ 99.75
Cardiac surgeon follow-up	Variable		£ 189.69	2013	Finance	2	£ 193.52
Pacemaker stay and cost of the device etc)	Variable		£ 1,495.00	2013	Finance	2	£ 1,525.18
wound infection full package(includes readmission, itu, ward, retheatre procedure, vac therapy)	Variable		£ 7,250.00	2013	Finance	2	£ 7,396.36
Hospital stay	Variable		£ 250.00	2013	Finance	2	£ 255.05
Medications	Variable		£ 1,000.00	2015	Pharmacy	0	£ 1,000.00
Surgical intervention	Variable		£ 6,000.00	2015	Finance	0	£ 6,000.00