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
Langenbeck 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 vacuum 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	Fixed	£ 35,725.00	£ 19.27	2013	Procurement	2	£ 19.66

years							
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		£ 2,978.67	2013	Finance	2	£ 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

*****For fixed costs, the unit cost is fully absorbed and was applied on a per-operation basis

Supplemental table 2: Pilot work - four years clinical outcome MACE data

Variable	CT-EVH (n=70)	OT-EVH (n=70)	p-value
	Number (percentage)		
Repeat angina			
3 months	4 (5.8)	1 (1.4)	0.209
6 months	7 (10.1)	2 (2.9)	0.097
9 months	5 (7.4)	2 (2.9)	0.441
12 months	7 (10.3)	4 (5.9)	0.531
18 months	8 (11.8)	4 (5.9)	0.365
24 months	7 (10.3)	3 (4.5)	0.325
48 months	2 (3.1)	1 (1.5)	0.619
Repeat breathlessness			
3 months	9 (13.0)	12 (17.4)	0.636
6 months	10 (14.5)	13 (19.1)	0.501
9 months	9 (13.2)	7 (10.3)	0.791
12 months	9 (13.2)	13 (19.1)	0.486
18 months	9 (13.2)	16 (23.5)	0.183
24 months	9 (13.2)	9 (13.4)	1.000
48 months	10 (15.4)	8 (12.3)	0.800
Repeat interventions			
3 months	3 (4.3)	1 (1.4)	0.619
6 months	3 (4.3)	3 (4.4)	1.000
9 months	2 (2.9)	6 (8.8)	0.274
12 months	6 (8.8)	5 (7.4)	1.000
18 months	6 (8.8)	1 (1.5)	0.115
24 months	3 (4.4)	3 (4.5)	1.000
48 months	2 (3.1)	1 (1.5)	1.000
Myocardial Infarction/Ischaemia			
3 months	4 (5.8)	0 (0.0)	0.120
6 months	4 (5.8)	1 (1.5)	0.366
9 months	3 (4.4)	1 (1.5)	0.619
12 months	5 (7.4)	2 (2.9)	0.441
18 months	4 (5.9)	3 (4.4)	1.000
24 months	4 (5.9)	1 (1.5)	0.366
48 months	2 (3.1)	1 (1.5)	1.000
Mortality			
3 months	1 (1.4)	1 (1.4)	1.000
6 months	1 (1.4)	2 (2.9)	1.000
9 months	2 (2.9)	2 (2.9)	1.000
12 months	2 (2.9)	2 (2.9)	1.000
18 months	2 (2.9)	2 (2.9)	1.000
24 months	2 (2.9)	3 (4.3)	1.000
48 months	6 (8.8)	4 (5.8)	0.532
Post-operative PTCA	4 (5.7)	1 (1.6)	0.366
Vein graft patency			
No flow limitation	8 (61.5)	5 (100)	0.264
Flow limited	2 (15.4)	0 (0.0)	
Completely blocked	3 (23.1)	0 (0.0)	
ACC/AHA coronary artery score			
Discrete (<10mm) lesion	1 (7.1)	0 (0.0)	0.343
Tubular (10-20mm) lesion	3 (21.4)	0 (0.0)	
Diffuse (>2cm) lesion	10 (71.4)	6 (100.0)	

Findings from our non-randomised pilot study comparing clinical outcomes at 4 years for CT-EVH versus OT-EVH.

Supplemental table 3 – Intraoperative variables recorded for each surgery.

Variable	**Group**			**p-value**
	OT-EVH	**OVH**	**CT-EVH**	
Harvesting time (mins)	19.86 [11.64]	22.26 [17.65]	23.40 [12.48]	**0.031**
Full leg surgery time (mins)	42.93 [20.46]	42.73 [25.43]	53.50 [22.50]	**<0.001**
Total surgery time (mins)	226.77 [56.99]	222.65 [58.34]	228.46 [67.72]	0.806
Bypass time (mins)	93.00 [49.00]	90.00 [43.00]	92.00 [35.75]	0.698
Cross-clamp time (mins)	54.00 [37.00]	58.00 [34.75]	57.00 [23.00]	0.841
Number of vein grafts				
1	26 (26.0%)	26 (26.0%)	13 (13.0%)	0.130
2	54 (54.0%)	51 (51.0%)	57 (57.0%)	
3	20 (20.0%)	22 (22.0%)	30 (30.0%)	
4	0 (0.0%)	1 (1.0%)	0 (0.0%)	
Length of vein obtained (cm – mean±SD)	34.86±12.90	35.60±13.71	39.23±12.09	**0.039**

Longer harvesting times and overall leg surgery time was required for CT-EVH and OVH. The number of vein grafts required was not significantly different between groups.

Supplemental table 4: MACE events composite outcomes up to 48 months.

MACE events **Composite Outcomes**	**Groups**				**p-value**
	CT-EVH	**OT-EVH**	**OVH**	**Total**	
3 months	03/100 (3.0%)	05/100 (5.0%)	04/100 (4.0%)	12/300 (4.0%)	0.77
6 months	05/100 (5.0%)	08/100 (8.0%)	04/100 (4.0%)	17/300 (5.7%)	0.45
12 months	07/100 (7.0%)	11/100 (11.0%)	9/100 (9.0%)	27/300 (9.0%)	0.61
18 months	11/100 (11.0%)	11/100 (11.0%)	10/100 (10.0%)	32/300 (10.7%)	0.97
24 months	11/100 (11.0%)	12/100 (12.0%)	10/99 (10.1%)	33/299 (14.1%)	0.91
36 months	7/60 (11.7%)	12/60 (20.0%)	5/61 (8.2%)	24/181 (13.3%)	0.145
48 months	6/35 (17.1%)	9/36 (25.0%)	2/35 (5.7%)	17/106 (16.0%)	0.08

Events are counted only once, but are included in the cumulative total at each time point (for example, a MACE event at 3 months would also be shown at 6 months). The Pearson chi square test was used and expressed in numbers and percentages. The composite outcomes include repeat angina, re-intervention, mortality, breathlessness, vein graft failure and myocardial infarction/ischaemia.

Supplemental Figure Legends:

Supplemental Figure 1 – This CONSORT flow diagram depicts the planned recruitment and evaluation process for the study.

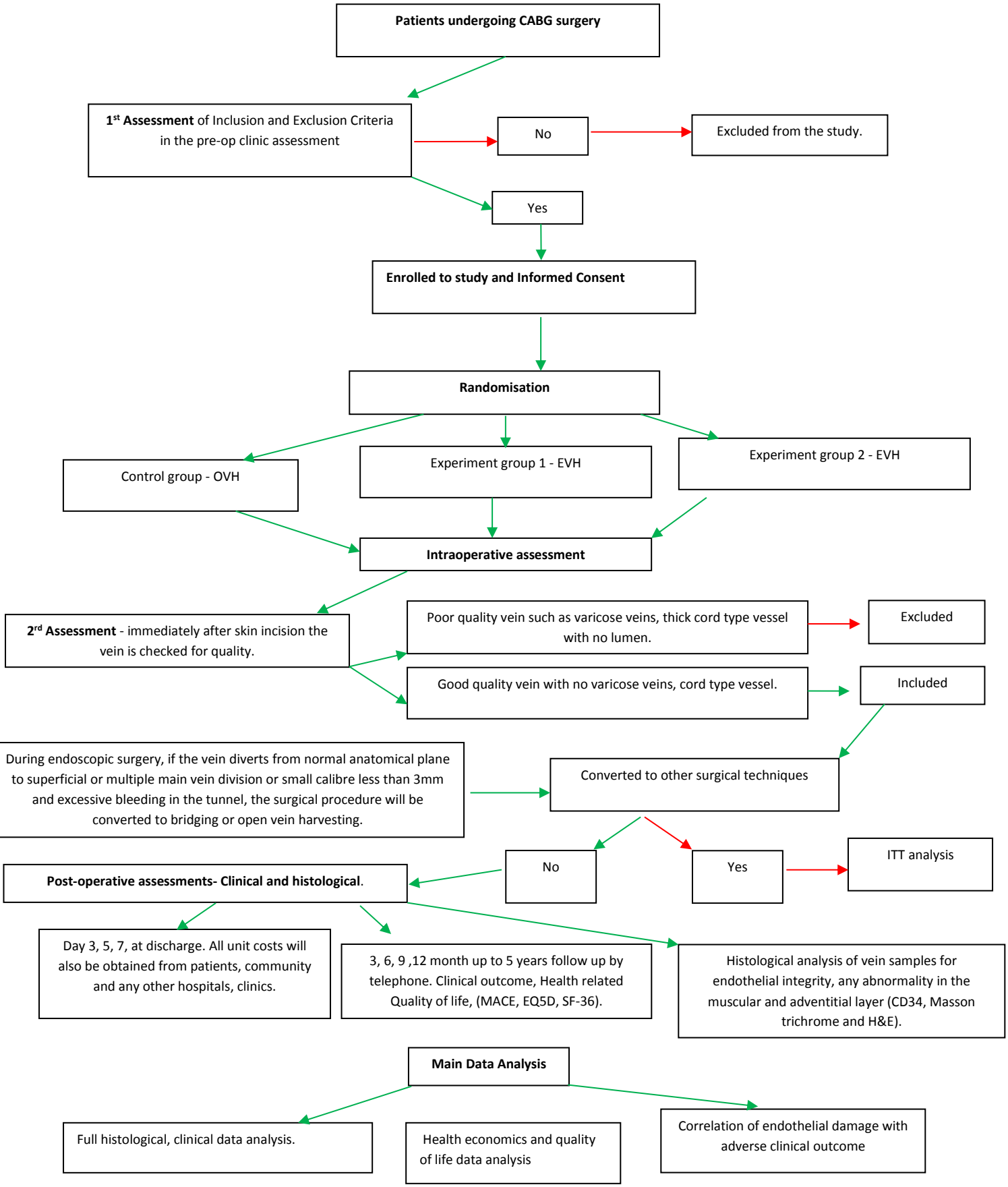
Supplemental Figure 2 – CD34 endothelial staining of long saphenous vein samples demonstrating (a) normal continuous endothelium, (b) mild endothelial disruption, (c) moderate endothelial disruption and (d) severe endothelial disruption. ↑ indicates site disruption.

Supplemental Figure 3 – Picrosirius red staining of long saphenous vein samples demonstrating (a) normal vein structures, (b) mild intimal detachment, (c) detachment within the longitudinal muscle layer and (d) moderate circular hypertrophy. ↑ indicates site of defined injury. *Hypertrophy term in this study indicates acute swelling rather than the chronic process of the muscle.

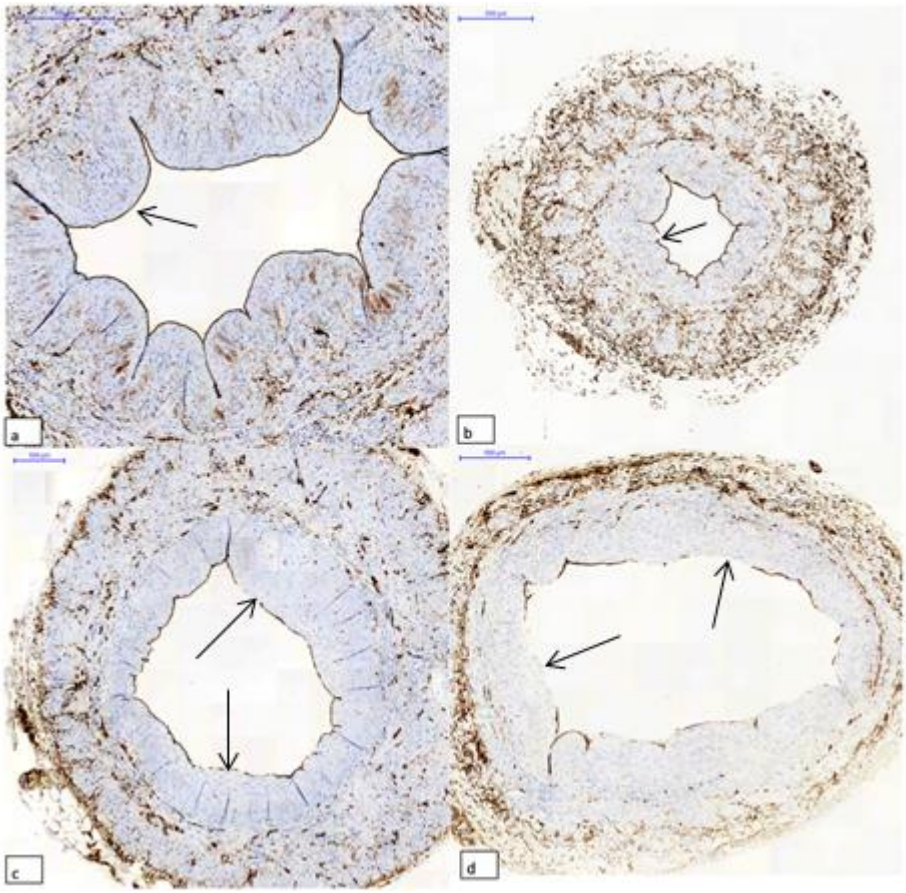
Supplemental Figure 4 – This box plot represents a comparison of the endothelial integrity of veins obtained via closed tunnel CO_2 and open tunnel CO_2 EVH systems. Veins obtained using the open CO_2 method (OT-EVH) exhibited significantly greater endothelial integrity compared to those obtained using the closed tunnel CO_2 technique (CT-EVH).

Supplemental Figure 5 – This figure shows the impact of the vein extraction techniques on health-related quality of life (HRQoL) as measured by the EQ-5D-3L questionnaire with quality weights attached using the UK national tariff. The points displayed are mean estimates for the OVH, CT-EVH and OT-EVH arms with 95% confidence intervals. The point estimate for the baseline HRQoL has been generated using a mapping algorithm to go from the Canadian Cardiovascular Society (CCS) classification of angina to the EQ-5D-3L.

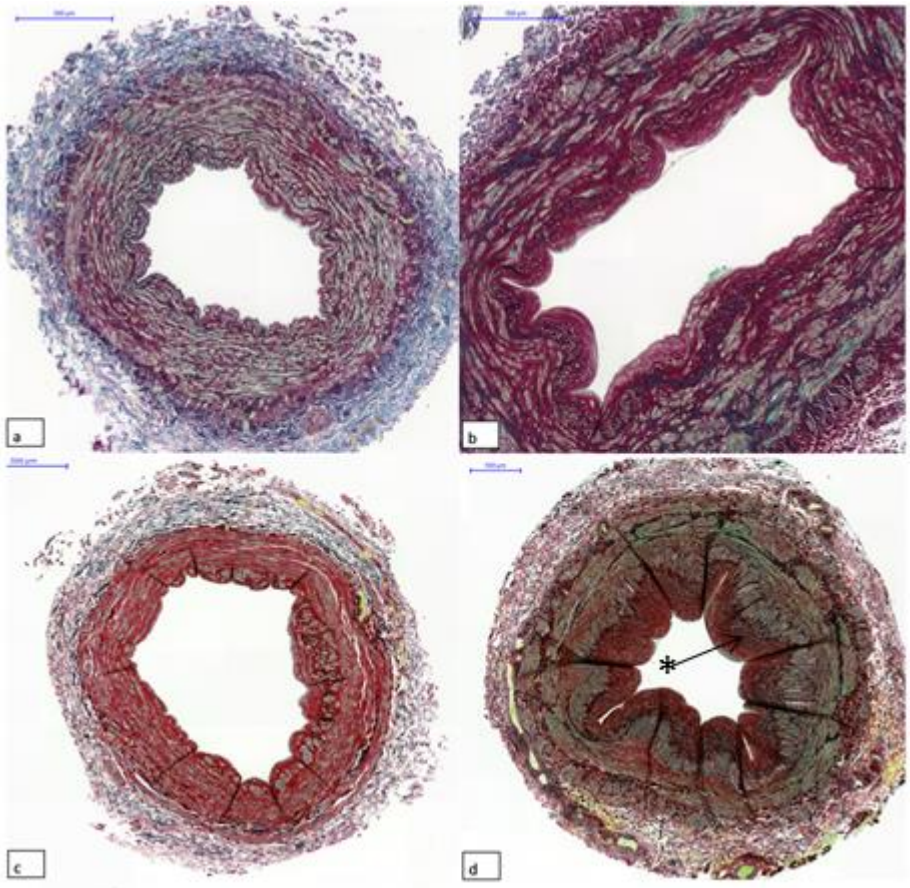
Supplemental figure 1: Consort flow diagram



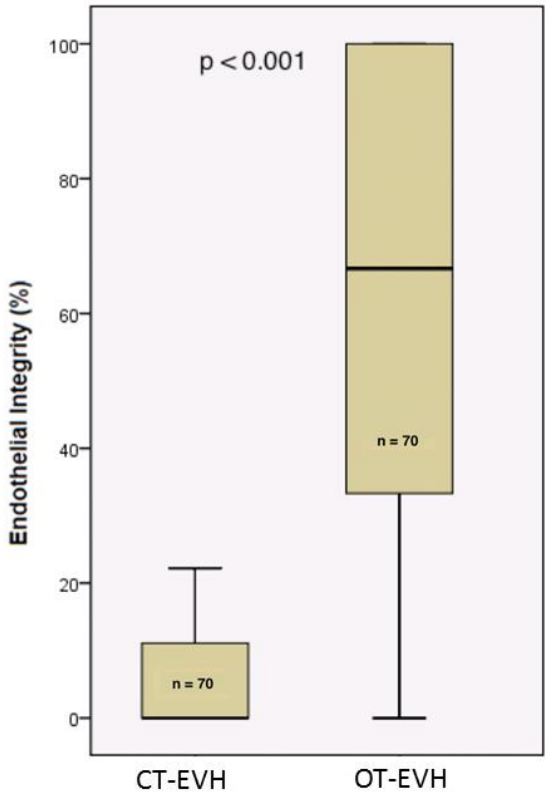
Supplemental figure 2: Endothelial cell staining and detachment.



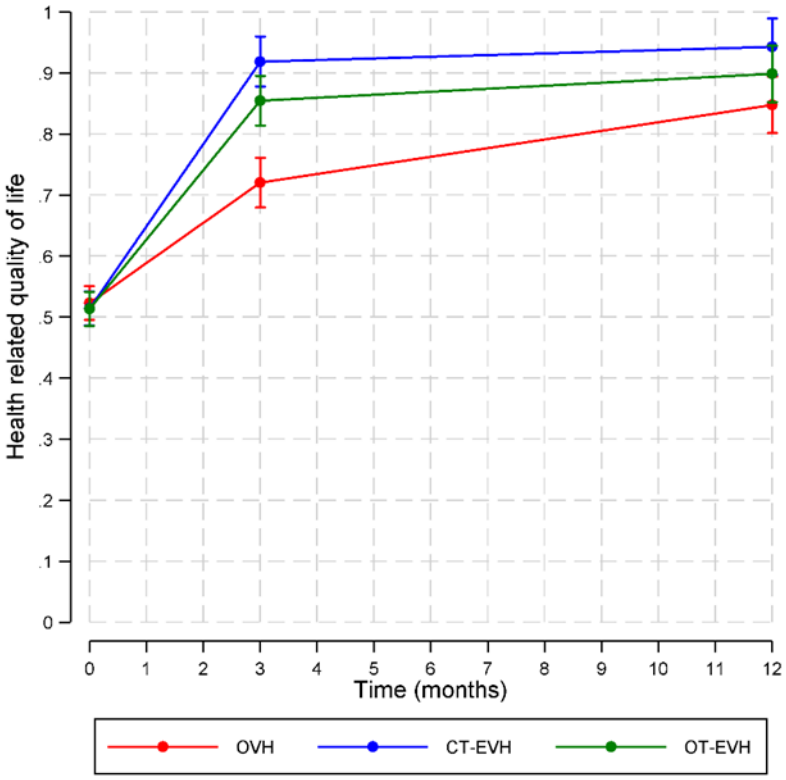
Supplemental figure 3: Picrosirius red staining of the muscle layers.



Supplemental figure 4: Endothelial integrity of the vessel in the pilot study.



Supplemental figure 5: Quality of life changes up to 12 months.



Supplemental methods 1: Protocol

A randomised 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 study protocol.

Authors:

Bhuvaneswari Krishnamoorthy Mphil[1], William R Critchley MSc[2], Julie Morris PhD[3] Ann C Caress PhD[4], James E Fildes PhD[2] , Nizar Yonan MD, FRCS[1].

1. Department of Cardiothoracic Surgery, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK, M23 9LT.
2. The Transplant Centre, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK, M23 9LT.
3. Department of Medical Statistics, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK, M23 9LT.
4. School of Nursing and Midwifery, Faculty of Medical and Human Sciences, University of Manchester, UK, M13 9PL.

Address for correspondence:

Mrs. Bhuvaneswari Krishnamoorthy, BSc (Hons), MPhil, PhD (current NIHR Clinical Research fellow).
Lead Surgical Care Practitioner, Cardiothoracic surgery.
University Hospital of South Manchester NHS Foundation Trust
Manchester, UK, M23 9LT.

bhuvaneswari.bibleraaj@uhsm.nhs.uk
Telephone: 0044 161 291 2078 and fax number : 0044 161 291 5024.

Key words: Coronary artery bypass grafting, cardiac surgery, endoscopic vein harvesting, vein integrity.

Word Count: 4002

Abstract Count: 245

Clinical Trial registration: ISRCTN9148426.

Funded by: NIHR Clinical Doctoral Research Fellowship fund, UK.

Title: A randomised study comparing **V**ein **I**ntegrity and **C**linical **O**utcomes **(VICO)** in open vein harvesting and two types of endoscopic vein harvesting for coronary artery bypass grafting – The VICO study protocol.

Abstract:

Background:

The Vein Integrity and Clinical Outcome (VICO) randomised trial is designed to assess the direct relationship between the histological damage caused during different methods of vein harvesting and clinical outcome post-surgery. Many studies are available in the literature measuring either histological outcome or clinical outcome in relation to different harvesting techniques. However, there remains no definitive randomised data available directly correlating harvesting-induced vein damage with clinical outcome.

Methods and design:

We aimed to randomise 100 patients in each group: Group 1 consists of closed tunnel CO_2 endoscopic vein harvesting (EVH) (CT-EVH) and group 2 consists of open tunnel CO_2 EVH (OT-EVH) with the control group 3 consists of standard open vein harvesting (OVH) which will have a total of 300 patients in this study. All the veins will be harvested by an experienced practitioner for this study. We have planned to analyse the histological level of damage in three different parts of the harvested vein with the post clinical outcome using validated measuring tools. This study will also explore the health economical cost (EQ-5D), quality of life (SF-36) impact on these surgical methods.

Discussion:

We believe that this study will bring a scientific and clinical data which may provide a definite answer of whether the vein damage caused during harvesting is due to operator or procedure or patient dependent. This will also be the ground work for comparing the histological level damage during harvesting will have any effect on long term vein graft patency.

Background:

Coronary artery bypass grafting (CABG) is one of the most frequently performed cardiac surgical procedures. Vein harvesting can be performed using an open (OVH) or endoscopic (EVH) technique. There are two methods of EVH – closed tunnel (CT-EVH) and open-tunnel (OT-EVH), which differ on the basis of CO_2 pressurisation. Importantly, it remains unclear whether there is any difference with regard to vein integrity and clinical outcome between these two methods.

Vein Integrity:

Maintaining the structural integrity of harvested conduits is essential to a successful graft [1-4]. Injury to the endothelium may cause denudation, which promotes platelet aggregation, intimal proliferation and hyperplasia; all of these significantly increase the risk of graft failure [5]. Endoscopic harvesting requires more manipulation and handling of the vein, compared with the traditional non-touch OVH method [6]. The clinical consequences of this are the subject of fierce debate.

An influential New England Journal of Medicine paper by Lopes and colleagues reported that EVH was associated with >75% graft occlusion, repeat vascularisation, myocardial infarction and sudden death [7]. Several centres have closed EVH programmes in response to the Lopes findings. However, subsequent studies demonstrate no major difference between OVH and EVH in mortality and morbidity outcomes [8, 9]. More importantly, a cohort study comparing 8542 patients over four years reported that patients undergoing EVH had a lower mortality than those undergoing OVH (11.3% for EVH versus 13.8% for OVH; $p<0.001$)[8].
Recently, a systematic review with meta-analysis of 27,789 patients concluded that EVH reduced leg wound infections without increasing mid-term risk for vein graft failure and mortality [10]. However, there remains a paucity of high quality studies which have explored the potential risk of endothelial damage in direct relation to clinical outcome.

Wound Complications:

Vein harvesting is traditionally performed as an open procedure, but this is associated with a number of postoperative wound complications, the rates of which range from 5% to 44% [1]. Moreover, several studies have found that EVH significantly lowers wound infection rates - OVH 15-28% vs. EVH 4-6% [10-12]. A recent cost analysis study reported that the cost of

readmissions for wound complications at 30 days was considerably higher in patients who have undergone OVH compared with EVH (£10,905 vs. £5,074) [13, 14].

Other Gaps in Knowledge:

Patient satisfaction and reduced economic burden are key priorities in the modern surgical world. The recent systematic review [10] highlighted the lack of high quality data regarding the cost difference between OVH and EVH. Little is known about patient satisfaction and its comparison with different approaches to vein harvesting. Although studies have compared OVH and EVH, comparisons have either been made against only one form of EVH (open and closed tunnel). No study has yet directly compared all three types of vein harvesting technique, and/or a head to head comparison between the two EVH systems. This is an important omission, since these two forms of EVH may impact vein integrity differently.

Recent evidence in 2015:

A study published in Annals of Surgery by Diepen et al [15] retrospectively analysed data from the PREVENT-IV trial [7], in order to compare the two EVH devices (open tunnel (n=390) and closed tunnel (n=1159)). The authors compared the incidence of vein graft failure (p=0.724) and composite clinical outcome (p=0.221), and concluded that there is no statistical differences between the two EVH surgical techniques. The other clinical studies [16-18] ,meta-analysis[16, 19-21] ,reviews[22-24] ,learning curve[25-27] and histological studies[28, 29] concluded that EVH is favourable but still there is a need of a randomised trial.

However, there is no data available on direct comparison of scientific and clinical with the open vein harvesting control. So, this raises many questions with regard to the effects of EVH, such as practitioner training related problems, immediate vein graft failure due to surgical trauma to the conduit and whether patient risk factors are directly related to the poor outcomes observed in the Prevent IV trial. This clearly highlights the need for a randomised study comparing the scientific and clinical outcome between these three surgical methods.

Need for a trial:

There is a paucity of randomised studies comparing EVH with OVH, and no data available comparing closed tunnel CO_2 with open CO_2 tunnel dissection. The current lack of definitive evidence and the resulting polarisation of opinion regarding vein harvesting technique are resulting in variation in clinical practice. In 2005, the International Society for Minimally Invasive Cardiac Surgery (ISMICS) held a consensus conference which recommended that EVH should now be considered a standard technique for vein harvesting. By contrast, the National Institute for Health and Clinical Excellence (NICE) currently recommends that EVH only be used as part of research or audit programmes, until its clinical effectiveness has

been proven. The need for further high quality research to guide practice in this area has been recognised, including by NICE, which in 2010 recommended that an appropriate comparative assessment of OVH and EVH should be undertaken, which should include clinical outcomes, health economics and patient satisfaction.

Research questions:

1. Is there any difference in conduit integrity following retrieval with the OVH, CT-EVH and OT-EVH techniques?
2. Are there any differences in clinical outcomes (ie mortality, graft failure, myocardial infection) between OVH, CT-EVH and OT-EVH?
3. Is there any association between vein integrity and clinical outcomes?
4. Are there any differences in patient reported outcomes (ie health-related quality of life and satisfaction) between OVH, CT-EVH and OT-EVH?
5. Are there any differences in cost between these techniques?

Primary aims:

1. To assess the integrity of conduits harvested using the OVH, CT-EVH and OT-EVH techniques.
2. To assess whether there is any association between histological changes and clinical outcomes.
3. Comparison of effect of carbon di-oxide on the tissue level on proximal samples will be also collected and analysed. Full biochemistry data will be obtained and will be reported as separate outcomes.
4. Comparison of distended and non-distended vein samples will also be analysed and reported as a separate study outcomes.

Secondary aims:

1. To determine the incidence of adverse clinical outcomes (ie mortality, graft failure, myocardial infection) and compare between the OVH, CT-EVH and OT-EVH groups.
2. To compare patient reported outcomes (ie health-related quality of life and satisfaction) between OVH, CT-EVH and OT-EVH.
3. To perform a health economic cost analysis associated with the three vein harvesting techniques.

Methods:

The study will be conducted as a single centre 3-armed randomised clinical trial based at the cardiothoracic department and transplant research laboratory, University Hospital of South Manchester NHS Foundation Trust, Manchester. The practitioner involved in this study has

carried out more than 250 endoscopic vein harvesting and more than 2000 open vein harvesting surgical procedures.

Recruitment:

Patients will be screened using a two stage assessment process of inclusion and exclusion criteria (supplemental figure 1).

Inclusion criteria:

1. Patients aged over 18 years of age undergoing CABG surgery providing written informed consent will be recruited into this study.
2. All elective and urgent in patients will be included.
3. Patients who need at least one length of long saphenous vein.
4. Patients who are undergoing on-pump CABG surgery.
5. Patients having single LIMA and vein grafts will be included.

Exclusion criteria:

1. Any patient refusing or withdrawing consent will be excluded from the study.
2. Patients undergoing emergency surgery.
3. Contra-indication to a surgical technique, which includes varicosities of the long saphenous vein, small or thin legs (<7.5cm diameter at the lower calf) or superficial LSV (less than ½ cm deep from the skin), determined using ultrasound scans will also be excluded.
4. Enrolled in other clinical trials.
5. Patients undergoing off-pump CABG surgery.

Randomisation:

We aim to randomise 100 patients per group assuming a feasible recruitment of 300 patients from a total of 960 CABG procedures performed at UHSM. EVH is currently performed as a routine procedure in UHSM. All the patients who provide written consent to take part in the study will be recruited and included in the randomisation. The patients will be randomised into three groups using block randomisation which will be provided by an independent statistician. The independent research assistant will conceal the allocation of each patient in a sealed envelope which will be provided to the practitioner on a daily basis in order to determine the group. The concealed envelope will only be opened once the patient has been anaesthetised for surgery.

Methods of recruitment and allocation (supplemental figure 1):

Patients will be allocated to one of the three groups (OVH, CT-EVH and OT-EVH). All the information regarding the procedure, study code and allocation to the treatment will be kept confidential from the research team.

Clinical: All clinical data will be collected by two research team members, as a part of their involvement in this study. Research data collection is part of their normal work. Researchers will be blinded to the procedure allocation, thus reducing any potential bias during data collection.

All the clinical data will be collected prospectively into a relational database. General demographics including age, sex, race, body mass index, hospital admission, pre catheterisation basic information's, history of angina will be collected. Other preoperative risk factors such as hypertension, family history of coronary artery disease, diabetes, peripheral vascular disease, hypercholesterolemia, previous myocardial infarction/ myocardial ischemia, previous percutaneous Transluminal coronary angioplasty (PTCA), Parsonnet score which is a simplified Canadian risk scoring system to estimate the cardiac surgical mortality risk and finally European system for Cardiac Operative Risk Evaluation (Euroscore) will be documented.

All intraoperative data including number of coronary vessel grafted, number of grafted planned, types of conduits harvested, surgical timings, details of member of staff done the surgery and cardioplegia details will be recorded. In hospital mortality, community mortality outcomes will be collected from validated registry and post-mortem reports from coroner's court. Long-term Major Adverse Cardiac Events (MACE) outcomes were measured for this study at different time points (3, 6, 9, 12, 24, 36, 48 months) post-surgery. The MACE is defined as post CABG recurrent angina, MI, target vessel revascularisation, coronary artery/vein graft stenting, stroke and death [30].

Repeat angina is classified using Canadian Cardiovascular society grading system (CCS) which is a validated scoring system for standardisation of angina grade ranging from I-IV. The class I specifies angina with sustained, strenuous exertion, class II characterises slight limitation with angina upon vigorous action, class III represents moderate limitation with symptoms during everyday activity and class IV indicates severe limitation and inability to perform any activity with angina even at rest[31]. Breathlessness will be assessed using the New York Heart Association (NYHA) scoring system ranged from I-IV [32]. Class I indicates

no limitation of physical activity, class II represents a mild shortness of breath and slight limitation of physical activity, class III indicates marked limitation of physical activity and class IV indicates severe limitation, with the inability to carry out any physical activities. Magnetic Cardiac Resonance Imaging (MRI), repeat angiogram and echocardiogram (ECHO) results will be obtained via the UHSM cardiology database. The American College of Cardiology (ACC) and American Heart Association coronary lesion scoring system will be used to identify the quality of coronary vessels in pre and post-operative angiographic pictures. This system is based on parameters such as length of the lesion, eccentricity, angulation, calcification, side branch involvement and severity of stenosis. The lesions are classified as Type A (discrete, 2cm)[30, 33]. All the patients will be followed up by the telephone interview from day of surgery, 3, 6, 9, 12, 24, 36, 48 months using a validated MACE questionnaire. In addition, the symptomatic and non-symptomatic patients' notes will be obtained from the outpatient clinics, other community hospitals, GP surgery, cardiology database; district nurses files, consultant's secretaries' online notes.

Histological: The samples will be collected by the principal investigator after the procedure and stored with relevant study code at -80°C in a secure laboratory. A total of 2700 vein samples will be obtained from n=900 from each groups and all samples will be numeric coded to blind the histologist. Proximal undistended sample will be coded as H1, Distal minimally distended (10mmHg) with heparinised blood will be coded as H3 and finally following vein grafting surgery, a random sample (undergone all surgical distension) will be obtained from remaining of the conduit which will be coded as H2. We will be using endothelial stain (CD34), Picrosirius red muscular and collagen stain (80-pr; Sigma-Aldrich ltd, Dorset, UK) and finally basic Haematoxylin & Esoin will be used to assess endothelial stretching and detachment.

Each slide will be allocated a random number before any assessors assigned a score. The slides will be imaged using Pannoramic 250™ slide scanner at The University of Manchester. This machine has a special high-NA Carl Zeiss™ optic lens to achieve maximum resolution of up to 0.16 µm per pixel image. Samples will be scored by five blinded, independent and fully trained assessors by using Pannoramic Viewer™ software for efficient image viewing, annotation and archiving purposes. All the scores will be verified by a UHSM Consultant Histopathologist. None of these assessors will be involved at any stage of this research project. The slides will be assessed for endothelial integrity (inter assessor variability will be >15%). A validated scoring system [34] will be adopted and modified using the following criteria: 0 (no endothelium), 1 (islands of endothelium), 2 (loosely netted endothelium), 3 (partially confluent endothelium) and 4 (completely confluent endothelium).

For Picrosirius red scoring, obtained from The University of Manchester histology lab will be used on following criteria (detailed in supplemental table 5):

Supplemental table 5: Picrosirius red scoring system

Area of damage	**scores**	**Detailed scores**
Circular and longitudinal muscle hypertrophy	On a scale of 0 – 3.	0 – normal. 1 – mild. 2 – moderate. 3 – severe.
Medial muscle detachment	0 % to 100%	0% - no detachment. <10% 11 – 25% 26 – 50% 51 – 75% 76 – 100% - complete detachment.
Circular and longitudinal muscle migration (internally and externally)	On a scale of 0 – 3.	0 – normal. 1 – mild. 2 – moderate. 3 – severe.

For H& E scoring, obtained from The University of Manchester histology lab will be used on following criteria (detailed in supplemental table 6):

Supplemental table 6: H&E scoring system

Area of damage	**scores**	**Detailed scores**
Endothelial damage	Normal endothelial layer	Grade 0.
	Stretched layer	1.1- mild. 1.2-moderate. 1.3-severe.
	Detached layer	2.1-mild. 2.2-moderate. 2.3-severe.
	Partial endothelial loss	Grade 3
	Complete loss of endothelial layer	Grade 4.

Health economics:

To evaluate the health economics perspective, complete cost data, EQ- 5D-3L and SF36 will be collected at baseline, 3 months, 12 months and 5 years interval period. We will be calculating full surgical, medical costs based on resource utilisation and clinical events during the surgical procedure, hospitalisation and prospective postoperative follow up. We will be counting number of surgical items used in both groups, sutures, disposable kits, medications, wound infection costs, antibiotics usage in hospital and community, any adverse events, length of hospital stay, readmission costs, re intervention costs (angiogram, ECG, Chest x-ray, MRI scan, CT heart scan, stenting the coronary arteries), theatre cots, surgeon and allied health professionals costs, cardiologists, GP, district nurse costs as well as any applied cost weights in UK pounds to calculate costs of the surgical procedure. All community costs post-surgical procedure will be obtained from GP surgery, cardiology department, outpatient department from other neighbouring hospitals.

The EQ-5D-3L will also be collected for this study, which is a generic instrument involving of two sections: a 5-dimension single summary health status index and a self-rated visual analogue scale which ranges from 0 (best imaginable health state) to 100 (worst health state) [35]. The cost-effectiveness analysis will be carried out by the total costs assessed against the effects in terms of quality adjusted life in years (QALY) based on the EQ-5D-3L. In addition, the estimated incremental cost per QALY from the hospital service will be compared with the willingness to pay threshold of £20,000 to £30,000 per extra QALY which is currently used by the National Institute of Health and Care Excellence (NICE)[36] . The total costs will be derived by intervention plus or minus any subsequent differences in the NHS costs.

Blinding of tissue samples:

1. All the samples will be coded in the operating theatre prior to being sent to the laboratory. The codes will be kept confidential by the principal investigator.
2. Once the samples have been processed and stained for immunohistochemistry, they will be labelled from 1-300 to avoid any additional bias during scoring of the slides.
3. All the slides will be digitally scanned and the images will be scored by 5 independent assessors. The consultant histopathologist will also score the slides rather than the images.

Sample size, power calculation:

Primary outcome: endothelial integrity:

In the non-randomised pilot study, less than 20% of open tunnel CO_2 and greater than 50% of closed tunnel CO_2 patients had zero endothelial integrity.
With just 100 patients per group (assuming a feasible recruitment of 300 patients over 40 months), the study would have 80% power to detect differences in the percentage of patients with zero endothelial integrity of 15% or more, eg 20% vs 35%.

Secondary outcome: composite end point MACE at 12 months:

In the non-randomised pilot study, 19% of closed tunnel CO_2 patients had MACE compared to 13% of open tunnel CO_2 patients (ie only a 6% difference in incidence). We calculated that 91 patients in each of the three group (OVH, OT_EVH< CT_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%). 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.
(MACE defined as having one of the following outcomes: death, repeat angina, re-intervention, MI/ischaemia, AF or graft blockage).

Data Analysis:

The percentage of patients with zero endothelial integrity will be compared between the two randomised groups using firstly a simple chi-square test, followed by logistic regression analysis to incorporate any potential confounding factors. The percentage of patients with MACE in each group will be assessed using similar statistical methodology. Thus, no allowance is made for testing differences between the three groups in pairs, using three pair-wise comparisons.

Methods for minimising potential study bias:

1. This study is single centred, owing to the nature of the research. We aim to determine the causation of any underlying histological vein damage. Observations from our pilot study and previous endoscopic procedures demonstrate histological

vein damage can be caused by practitioner inexperience when performing endoscopic surgery.

2. To reduce bias caused by different operators carrying out different techniques, one experienced practitioner, who has carried out more than 250 endoscopic vein harvesting and more than 2000 open vein harvesting will be harvesting all the veins for this study. Importantly, EVH has been associated with a long learning curve, which varies from 30[11] to 100 [37] cases. The use of a single experienced practitioner will allow us to control for this.
3. The principal reason for using a sole operator for this study is to minimise the incidence of practitioner skill error. Varied practitioner skill would markedly impair the validity of any findings between endoscopic vein harvesting methods. In addition, evidence provided by our recent pilot study suggests experienced practitioners optimise vein quality through improved hand eye coordination.
4. Computerised randomisation will be provided by an independent statistician. The concealed envelope will be kept by an independent person to reduce study bias.
5. The manual immunohistological staining method has the potential for slight bias. The histological protocol is well developed and has been used in many endothelial studies. However, experience developed during our pilot work has allowed the team to improve the protocol by staining slides in batches of 12. Nevertheless, the potential exists for batch staining variation. Therefore, we will utilise automated, computerised immunohistological staining at the UHSM histology department. This system can perform staining with 120 slides, which reduces human error and bias.

Surgical intervention is as follows:

Open vein harvesting - Control group:

In normal practice, a long incision will be made from ankle to thigh depending upon the length of vein required for surgery. For the purpose of this study, if the patient requires two lengths of vein, it will be harvested from just below the knee (approximately 9cm). If the patient requires three lengths of vein, it will be harvested from 4cm above the medial malleolus bone. The vein side branches will be ligated with 4-0 vicryl ties and titanium clips on both sides. The leg wound will be closed in layers and a dressing and pressure bandage will be applied [38].

Closed tunnel CO_2 - Group 1:

- We will be using a Maquet Vasoview Hemopro2® vein harvesting system which involves a pressurised CO_2 tunnel for vein dissection. A 2-3cm incision will be made just above or below the knee (approximately 9cm) depending upon the length of vein (1 or 2) required for surgery. The long saphenous vein will be exposed and dissected using a West retractor and a Langenbeck retractor. A 30mm, 0° endoscope with a sharp, clear dissecting cone on the tip will be inserted through the skin incision. After 3cm of anterior dissection, the balloon will be inflated to seal the incision port. The vein will be dissected from the surrounding tissues anteriorly and posteriorly until reaching the femoral junction in the groin. The vein side branches will be ligated with 4-0 vicryl ties and titanium clips on both sides. The small leg wound will be closed in layers and a dressing and pressure bandage will be applied [38].

Standardisation:

- The CO_2 tunnel pressure will be set to 10 - 12mmHg and a flow rate of 3 litres per minute will be applied for all cases. A minimal amount (10ml) of trocar cuff air inflation will be used to reduce the trauma to the vein.

- The vein branches will be cut from the insertion port towards the thigh or ankle to minimise the trauma to vein branches. The major stress on the base of the branch during harvesting causes intimal injury which leads to platelet adherence, release of mitogenic proteins, smooth muscle cell proliferation and intimal hyperplasia[39, 40].

Heparin:

- All the patients in this EVH group will be administered intravenous heparin just 5 minutes before sealing the skin insertion port, which reduces the intraluminal clot strand formation inside the vein during CO2 insufflation [40].
- Our pilot study demonstrated that patients who received anticoagulant therapy until the day of surgery experienced increased bleeding in the tunnel. As a result, only 2500 units of intravenous heparin will be administered for these patients.
- 5000 units of intravenous heparin will be administered for all other patients in this group.

Endoscopic vein harvesting method 2:

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

Standardisation for all three group techniques:

1. The vein will be harvested with fat and adventitial layers. The conduit will be harvested 2 to 3 mm away from the main vein.
2. All the branches will be cut with at least 1cm length wherever possible.
3. The vein will be inflated with heparinised arterial blood with minimal inflation pressure.
4. The cardioplegia vein perfusion pressure will be standardised to 70mmHg for all cases.
5. All patients requiring three lengths of vein will have the conduits harvested from the ankle to the thigh. For patients who require one or two lengths, these will be harvested from just below or above the thigh.
6. 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 will be monitored and recorded for this study.
7. All the endoscopic vein harvesting patients will have a leg drain on the wound [41] which will be opened 10 minutes after the protamine sulphate is given. However, in the open vein harvesting group, only patients who received antiplatelet medication until the day of surgery will have the leg wound drain inserted.

Study outcome and Measurements:

The primary outcome of this study will be whether histological changes occurring in the long saphenous vein correlate with clinical outcome post-surgery on CABG patients.

Laboratory based assessment of the endothelium in collected samples:

Endothelial integrity will be determined using standard streptavidin/peroxidase techniques. Briefly, samples will be dehydrated using xlyene/alcohol before embedding in paraffin and sectioning to 4um using a microstat. Sections will be placed on poly-l-lysine coated histology slides, rehydrated, and endogenous peroxidase activity inhibited using hydrogen peroxide. Sections will then be incubated with endothelial specific antibodies, including CD31 and CD34, which will be localised and visualised on a section of vessel. CD31 or PECAM-1 is a 130 kDa member of the immunoglobulin superfamily required for cell-to-cell adhesion. CD31 is expressed constitutively on the surface of adult endothelial cells. CD34 is a single-chain transmembrane protein of approximately 116 kDa, which is also expressed on vascular endothelial cells. A validation of endothelial staining will be carried out to choose the correct marker for this study. Following antibody incubation, samples will be washed and incubated with a secondary antibody conjugated with biotin. This induces a colorimetric reaction. Following this, samples will be counter-stained using haematoxylin and eosin, and endothelial integrity will be visualised using microscopy.

In addition to endothelial marker (CD31 or CD34), Picrosirius Red muscular stain will be used to assess the circular and longitudinal muscle morphology and Haematoxylin and Eosin will be used for basic vein structural assessments. All samples will be initially assessed by the Principal Histopathologist at UHSM, and then graded by five independent assessors using a previously reported scale system (0-100%) which will be grouped into four categories, where 0 represents no endothelium and 4 represents continuous endothelial layer [34]. A validated scoring system will be used to grade muscular damages in the vein muscle layers on a scale of 0-3 (normal, mild, moderate and severe). Haematoxylin and Eosin staining, endothelial damage will be assessed on a scale of 0-3 (normal, mild, moderate and severe).

Extra details on collection of clinical data:

General demographic baseline data including pre-operative risk factors will be collected. Intra-operative data includes pre-surgical coronary vessel analysis, number of grafts, type of conduits and cardioplegia choice. In-hospital mortality and community mortality will be

obtained from validated registry data and post-mortem reports. A validated disinfect wound scoring system will be used within the first 30 days to evaluate incidence of wound infection. A modified Likert scale will be utilised to determine patient satisfaction. The major clinical outcome will be assessed in terms of Major Cardiac Adverse Event (MACE) incidence, collected at 3 month intervals within the first year, and then at 2,3 and 5 years. Health related quality of life will be assessed every three months, 12 months and 5 years via telephone interview using the SF-36 and EQ-5D questionnaires. Use of telephone follow-up, rather than post, provides enhanced data quality/completeness and minimises respondent burden, taking account of patient age (many will be elderly) and the question volume. Our pilot work and also supporting literature [42] suggests that the use of postal (and email) questionnaires for follow-up, yields low response rates.

Planned Statistical analyses:

We have planned to utilise an intent-to-treat analysis for this study. Simple descriptive summary statistics (percentages, means, medians, range and standard deviation) will be calculated. The distribution of data will be assessed by analysing skewness, kurtosis and histogram plots.

Histological and clinical outcome analysis:

The percentage of patients with zero endothelial integrity will be compared between the three randomised groups using median percentage integrity and will be analysed using Kruskal-Wallis test. All demographics will be presented as frequencies/percentages for categorical variables and means/medians with standard deviation/interquartile range for categorical variables. Any other histological outcomes will be displayed as median scores and will be analysed using simple chi-square test. All tests will be performed as two-tailed analyses and p-values <0.05 will be considered as significant.

The percentage of the MACE total score in each group at the end of follow-up will be assessed using similar statistical methodology as for endothelial integrity.

Baseline and finalisation follow-up SF-36 and EQ-5D scores will be summarised and compared between the three groups using analyses of covariance. Repeated 3-monthly scores will be assessed using longitudinal regression modelling.

Data will be analysed using SPSS v20. Statistical significance will be taken as $p \leq 0.05$.

Frequency of data analyses:

Data will be analysed every quarter of the data collection timeframe, with mid-term analyses to ensure no serious adverse events accrue for the participants.

Health economic analysis:

The primary aim of the economic analysis is to compare the cost and clinical outcome of the three vein harvesting approaches. Unit cost data will be attached to the resource use data and collected during surgery, along with in-patient admission, 3 months and 12 months to 5 year follow up. Descriptive statistics will be used to summarise the mean costs and their variations. The mean cost per patient, and total cost for each approach will be calculated then analysed alongside the data on health status. It will be collected using the EQ-5D, to help understand the relative costs and outcomes of the three vein harvesting approaches. Appropriate statistical methods will be used to compare the cost and health status data, taking into account the skewed nature of the data (for example, boot strapping methods used to analyse cost data).

Limitation of this study:

This study does not have post-surgery angiographic evidence for all patients. However, the patients who are symptomatic will undergo cardiac MRI scans, angiograms and any other relevant investigations which will be addressed in this study.

Discussion:

Vein harvesting techniques can potentially cause structural damage to the vessel wall leading to graft failure as shown in angiographic and ultra-structural studies revealing mural thinning and endothelial cell damage [43, 44]. Some vein studies concentrating on the biological effects of endothelial layer impairment demonstrated that myointimal proliferation affects short and long term graft performance [43, 45, 46].

Impairment of the endothelial layer in OVH samples was demonstrated during pre or post-surgical preparation while distending [47, 48] or stretching the vein[6, 49, 50]. Manderson et al [51] suggest that histological studies of the vein harvested using different minimally invasive techniques should be performed periodically on different timings to assess endothelial integrity, since endothelial denudation leads to intimal and medial layer repair with neointimal thickening.

Meticulous preservation of the layers of the saphenous vein during harvesting is an important factor in determining graft patency rate [52]. There continues to be concern that excessive manipulation of the vein via EVH may cause trauma to the vessel leading to early graft failure and stenosis [1, 53-56]. We believe that the use of CO_2 during EVH can affect the endothelium of the LSV. It is crucial to delineate the effects of CO_2 pressure on vessel integrity and clinical outcome following CABG. This trial will provide insight into the effects of pressurised CO_2 on the vessel, and will be compared to both non-pressured CO_2 EVH and OVH.

We believe that this trial will provide important clinical data that is currently lacking in the literature, and can provide an answer to the concerns, controversies around the vein harvesting techniques for Coronary artery bypass surgery.

References:

[1] DeLaria GA, Hunter JA, Goldin MD, Serry C, Javid H, Najafi H. Leg wound complications associated with coronary revascularization. The Journal of thoracic and cardiovascular surgery 1981;81:403-407.

[2] Thatte HS, Khuri SF. The coronary artery bypass conduit: I. Intraoperative endothelial injury and its implication on graft patency. The Annals of thoracic surgery 2001;72:S2245-2252; discussion S2267-2270.

[3] LoGerfo FW, Quist WC, Cantelmo NL, Haudenschild CC. Integrity of vein grafts as a function of initial intimal and medial preservation. Circulation 1983;68:II117-124.

[4] Rousou LJ, Taylor KB, Lu XG, Healey N, Crittenden MD, Khuri SF, Thatte HS. Saphenous vein conduits harvested by endoscopic technique exhibit structural and functional damage. The Annals of thoracic surgery 2009;87:62-70.

[5] Mills NL, Everson CT. Vein graft failure. Current opinion in cardiology 1995;10:562-568.

[6] Bonchek LI. Prevention of endothelial damage during preparation of saphenous veins for bypass grafting. The Journal of thoracic and cardiovascular surgery 1980;79:911-915.

[7] Lopes RD, Hafley GE, Allen KB, Ferguson TB, Peterson ED, Harrington RA, Mehta RH, Gibson CM, Mack MJ, Kouchoukos NT, Califf RM, Alexander JH. Endoscopic versus open vein-graft harvesting in coronary-artery bypass surgery. The New England journal of medicine 2009;361:235-244.

[8] Dacey LJ, Braxton JH, Kramer RS, Schmoker JD, Charlesworth DC, Helm RE, Frumiento C, Sardella GL, Clough RA, Jones SR. Long-term outcomes of endoscopic vein harvesting after coronary artery bypass grafting. Circulation 2011;123:147-153.

[9] Yun KL, Wu Y, Aharonian V, Mansukhani P, Pfeffer TA, Sintek CF, Kochamba GS, Grunkemeier G, Khonsari S. Randomized trial of endoscopic versus open vein harvest for coronary artery bypass grafting: six-month patency rates. The Journal of thoracic and cardiovascular surgery 2005;129:496-503.

[10] Deppe A-C, Liakopoulos OJ, Choi Y-H, Slottosch I, Kuhn EW, Scherner M, Stange S, Wahlers T. Endoscopic vein harvesting for coronary artery bypass grafting: a systematic review with meta-analysis of 27,789 patients. Journal of Surgical Research 2013;180:114-124.

[11] Desai P, Kiani S, Thiruvanthan N, Henkin S, Kurian D, Ziu P, Brown A, Patel N, Poston R. Impact of the learning curve for endoscopic vein harvest on conduit quality and early graft patency. The Annals of thoracic surgery 2011;91:1385-1392.

[12] Kiani S, Poston R. Is endoscopic harvesting bad for saphenous vein graft patency in coronary surgery? Current opinion in cardiology 2011;26:518-522.

[13] Athanasiou T, Aziz O, Skapinakis P, Perunovic B, Hart J, Crossman MC, Gorgoulis V, Glenville B, Casula R. Leg wound infection after coronary artery bypass grafting: a meta-analysis comparing minimally invasive versus conventional vein harvesting. The Annals of thoracic surgery 2003;76:2141-2146.

[14] Carpino PA, Khabbaz KR, Bojar RM, Rastegar H, Warner KG, Murphy RE, Payne DD. Clinical benefits of endoscopic vein harvesting in patients with risk factors for saphenectomy wound infections undergoing coronary artery bypass grafting. The Journal of thoracic and cardiovascular surgery 2000;119:69-75.

[15] Sean van Diepen M, Brennan JM, Hafley GE, Reyes EM, Allen KB, Ferguson TB, Peterson ED, Williams JB, Gibson CM, Mack MJ. Endoscopic Harvesting Device Type and Outcomes in Patients Undergoing Coronary Artery Bypass Surgery. 2013.

[16] Hess CN, Lopes RD, Gibson CM, Hager R, Wojdyla DM, Englum BR, Mack MJ, Califf RM, Kouchoukos NT, Peterson ED, Alexander JH. Saphenous vein graft failure after coronary artery bypass surgery: insights from PREVENT IV. Circulation 2014;130:1445-1451.

[17] Mizumoto M, Uchida T, Gomi S, Hamasaki A, Kuroda Y, Yamashita A, Hayashi J, Takahashi A, Watanabe D, Sadahiro M. [Endoscopic Long Saphenous Vein Harvest from Femoralsite to Below

the Knee through a Single Small Incision for Minimally Invasive Coronary Artery Bypass Grafting]. Kyobu geka The Japanese journal of thoracic surgery 2015;68:35-40.
[18] Yoshimoto K, Oba J, Sugimoto S, Okuyama A, Miyatake T, Aoki H. [Endoscopic saphenous vein harvesting with non-disposable device]. Kyobu geka The Japanese journal of thoracic surgery 2014;67:121-124.
[19] Sastry P, Rivinius R, Harvey R, Parker RA, Rahm AK, Thomas D, Nair S, Large SR. The influence of endoscopic vein harvesting on outcomes after coronary bypass grafting: a meta-analysis of 267,525 patients. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2013;44:980-989.
[20] Deppe AC, Liakopoulos OJ, Choi YH, Slottosch I, Kuhn EW, Scherner M, Stange S, Wahlers T. Endoscopic vein harvesting for coronary artery bypass grafting: a systematic review with meta-analysis of 27,789 patients. The Journal of surgical research 2013;180:114-124.
[21] Markar SR, Kutty R, Edmonds L, Sadat U, Nair S. A meta-analysis of minimally invasive versus traditional open vein harvest technique for coronary artery bypass graft surgery. Interact Cardiovasc Thorac Surg 2010;10:266-270.
[22] Bisleri G, Muneretto C. Endoscopic saphenous vein and radial harvest: state-of-the-art. Current opinion in cardiology 2015.
[23] Raja SG, Sarang Z. Endoscopic vein harvesting: technique, outcomes, concerns & controversies. Journal of thoracic disease 2013;5 Suppl 6:S630-637.
[24] Bisleri G, Moggi A, Muneretto C. Endoscopic vessel harvesting: good or bad? Current opinion in cardiology 2013;28:666-670.
[25] Arora KS, Khan N, Abboudi H, Khan MS, Dasgupta P, Ahmed K. Learning curves for cardiothoracic and vascular surgical procedures--a systematic review. Postgraduate medicine 2015;127:202-214.
[26] Krishnamoorthy B, Critchley WR, Bhinda P, Crockett J, John A, Bridgewater BJ, Waterworth PD, Fildes J, Yonan N. Does the introduction of a comprehensive structured training programme for endoscopic vein harvesting improve conduit quality? A multicentre pilot study. Interact Cardiovasc Thorac Surg 2015;20:186-193.
[27] Kim do Y, Song H, Kim HW, Jo GH, Kang J. Early Outcomes of Endoscopic Vein Harvesting during the Initial Learning Period. The Korean journal of thoracic and cardiovascular surgery 2015;48:174-179.
[28] Hashmi SF, Krishnamoorthy B, Critchley WR, Walker P, Bishop PW, Venkateswaran RV, Fildes JE, Yonan N. Histological and immunohistochemical evaluation of human saphenous vein harvested by endoscopic and open conventional methods. Interact Cardiovasc Thorac Surg 2015;20:178-185.
[29] Nezafati MH, Nezafati P, Amoueian S, Attaranzadeh A, Rahimi HR. Immunohistochemistry comparing endoscopic vein harvesting vs. open vein harvesting on saphenous vein endothelium. Journal of cardiothoracic surgery 2014;9:101.
[30] Krishnamoorthy B. Clinical and molecular effect of endoscopic vein harvesting. 2014.
[31] Campeau L. Letter: Grading of angina pectoris. Circulation 1976;54:522-523.
[32] Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, Mayet J, Francis DP. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart 2007;93:476-482.
[33] Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2005;1:219-227.
[34] Fischlein T, Schutz A, Uhlig A, Frey R, Krupa W, Babic R, Thiery J, Reichart B. Integrity and viability of homograft valves. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 1994;8:425-430.

[35] EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health policy 1990;16:199-208.
[36] Excellence. NIfHaC. Guide to the methods of technology appraisal secondary guide to the methods of technology appraisal., 2013.
[37] Cadwallader RA, Walsh SR, Cooper DG, Tang TY, Sadat U, Boyle JR. Great saphenous vein harvesting: a systematic review and meta-analysis of open versus endoscopic techniques. Vascular and endovascular surgery 2009;43:561-566.
[38] Krishnamoorthy B, Critchley WR, Glover AT, Nair J, Jones MT, Waterworth PD, Fildes JE, Yonan N. A randomized study comparing three groups of vein harvesting methods for coronary artery bypass grafting: endoscopic harvest versus standard bridging and open techniques. Interact Cardiovasc Thorac Surg 2012;15:224-228.
[39] Davis Z, Jacobs HK, Zhang M, Thomas C, Castellanos Y. Endoscopic vein harvest for coronary artery bypass grafting: technique and outcomes. The Journal of thoracic and cardiovascular surgery 1998;116:228-235.
[40] Brown EN, Kon ZN, Tran R, Burris NS, Gu J, Laird P, Brazio PS, Kallam S, Schwartz K, Bechtel L. Strategies to reduce intraluminal clot formation in endoscopically harvested saphenous veins. The Journal of thoracic and cardiovascular surgery 2007;134:1259-1265.
[41] Krishnamoorthy B, Al-Fagih OS, Madi MI, Najam O, Waterworth PD, Fildes JE, Yonan N. Closed suction drainage improves clinical outcome in patients undergoing endoscopic vein harvesting for coronary artery bypass grafting. The Annals of thoracic surgery 2012;93:1201-1205.
[42] Curtis EA, Redmond RA. Survey postal questionnaire: optimising response and dealing with non-response: Non-response is a major concern for users of surveys as it threatens the validity of the findings and consequently any conclusions drawn, and trend studies indicate that participation in surveys is declining. This paper by Elizabeth Curtis and Richard Redmond aims to raise awareness about non-response in survey research and to suggest strategies researchers can use for increasing response rates. Nurse researcher 2009;16:76-88.
[43] Kennedy J, Tedgui A. Normal and pathological aspects of mass transport across the vascular wall. Vascular 1995;3:611-615.
[44] Catinella FP, Cunningham JN, Jr., Srungaram RK, Baumann FG, Nathan IM, Glassman EA, Knopp EA, Spencer FC. The factors influencing early patency of coronary artery bypass vein grafts: correlation of angiographic and ultrastructural findings. The Journal of thoracic and cardiovascular surgery 1982;83:686-700.
[45] Dhein S, Reiss N, Gerwin R, Borowski A, Korb H, Klaus W, de Vivie ER. Endothelial function and contractility of human vena saphena magna prepared for aortocoronary bypass grafting. The Thoracic and cardiovascular surgeon 1991;39:66-69.
[46] Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373-376.
[47] Angelini GD, Christie MI, Bryan AJ, Lewis MJ. Surgical preparation impairs release of endothelium-derived relaxing factor from human saphenous vein. The Annals of thoracic surgery 1989;48:417-420.
[48] Gundry SR, Jones M, Ishihara T, Ferrans VJ. Intraoperative trauma to human saphenous veins: scanning electron microscopic comparison of preparation techniques. The Annals of thoracic surgery 1980;30:40-47.
[49] Hasse J, Graedel E, Hofer H, Guggenheim R, Amsler B, Mihatsch MJ. Morphologic studies in saphenous vein grafts for aorto-coronary bypass surgery. Part II: Influence of a pressure-limited graft dilation. The Thoracic and cardiovascular surgeon 1981;29:38-40.
[50] Bush HL, Jr., Jakubowski JA, Curl GR, Deykin D, Nabseth DC. The natural history of endothelial structure and function in arterialized vein grafts. Journal of vascular surgery 1986;3:204-215.
[51] Manderson JA, Campbell GR. Venous response to endothelial denudation. Pathology 1986;18:77-87.

[52] Alrawi SJ, Raju R, Alshkaki G, Acinapura AJ, Cunningham JN, Jr. Saphenous vein endothelial cell viability: a comparative study of endoscopic and open saphenectomy for coronary artery bypass grafting. JSLS : Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons 2001;5:37-45.

[53] Cable DG, Dearani JA. Endoscopic saphenous vein harvesting: minimally invasive video-assisted saphenectomy. The Annals of thoracic surgery 1997;64:1183-1185.

[54] Slaughter MS, Gerchar DC, Pappas PS. Modified minimally invasive technique for greater saphenous vein harvesting. The Annals of thoracic surgery 1998;65:571-572.

[55] Tevaearai HT, Mueller XM, von Segesser LK. Minimally invasive harvest of the saphenous vein for coronary artery bypass grafting. The Annals of thoracic surgery 1997;63:S119-121.

[56] Wipke-Tevis DD, Stotts NA, Skov P, Carrieri-Kohlman V. Frequency, manifestations, and correlates of impaired healing of saphenous vein harvest incisions. Heart & lung : the journal of critical care 1996;25:108-116.