A Randomized Trial of External Stenting for Saphenous Vein Grafts in Coronary Artery Bypass Grafting

Running title: External Stent for Saphenous Vein Grafts

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Abstract

Background – External stents inhibit saphenous vein graft (SVG) intimal hyperplasia in animal studies. We investigated whether external stenting inhibits SVG diffuse intimal hyperplasia 1 year after coronary artery bypass grafting (CABG).

Methods –30 CABG patients with multi-vessel disease were enrolled. In addition to an internal mammary artery graft each patient received one external stent to a single SVG randomized to either the right or left coronary territories and one or more non-stented SVG served as the control(s). Graft patency was confirmed at the end of surgery in all patients. The primary endpoint was SVG intimal hyperplasia (mean area) assessed by intravascular ultrasound at 1 year. Secondary endpoints were SVG failure, ectasia (>50% initial diameter) and overall uniformity as judged by Fitzgibbon classification.

Results –One-year follow up angiography was completed in 29 patients (96.6%). All internal mammy artery grafts were patent. Overall SVG failure rates did not differ significantly between the 2 groups (30% versus 28.2%, stented versus non-stented SVG, P=0.55). SVG mean intimal hyperplasia area, assessed in 43 SVGs, was significantly reduced in the stented vs. non-stented group (4.37 ±1.40 versus 5.12 ±1.35 mm^{2}, P=0.04). In addition, stented SVGs demonstrated marginally significant improvement in lumen uniformity (P=0.08) and less ectasia (6.7% versus 28.2%, P=0.05). There was some evidence that ligation of side branches with metallic clips increased SVG failure in the stented group.

Conclusions – External stenting has the potential to improve SVG lumen uniformity and reduce diffuse intimal hyperplasia 1 year after CABG.

Introduction

Coronary Artery Bypass Grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease (1). Despite the proposed benefits of multiple arterial grafts (2), autologous saphenous vein grafts (SVGs) are still the most frequently used bypass conduits in CABG. However, progressive SVG failure remains a key limitation to the long-term success of CABG (3). While SVG failure soon after CABG is usually due to technical errors or trauma to the conduit, SVG disease after the first year is typically dominated by intimal hyperplasia which predisposes the SVG to accelerated atherosclerosis (3). Arterial pressure coupled with abnormal flow patterns generated mainly by luminal irregularities are the main contributors to both focal and diffuse intimal hyperplasia that develops in the SVG over time (4-5). In contemporary studies, SVG failure rate has been reported from 10%-30% over the first year while at 10 years only 50% of vein grafts are patent of which half have significant disease (6-8).

Attempts to mitigate intimal hyperplasia and SVG failure have been the focus of intense clinical research. To date, only persistent use of statin therapy and β blockers have been shown to reduce intimal hyperplasia in SVGs (9) while Edifoligide (8) and aspirin + clopidogrel (10), have both failed to do so, respectively, at 12-18 months after CABG. Mechanical external stents for SVGs have shown considerable promise in pre-clinical testing with reduction of proliferative intimal hyperplasia by reducing wall tension, improving lumen uniformity and creating a protective "neo-adventitia" layer rich with micro vasculature (11-13). However, limited clinical data has been published to date with such devices. Murphy et al (14) described 100% occlusion of externally stented SVGs at six months and Schoettler et al (15) reported a 72% occlusion rate at nine months. Recently, Rescigno et al (16) described 66.9% occlusion at 12 months of SVGs supported with nitinol mesh. All of these external stents required gluing and/or suturing to the vein graft during the implantation procedure, maneuvers which may have compromised SVG patency (17).

We present here the first in man use of the VEST (Venous External Stent, Vascular Graft Solutions Ltd, Tel Aviv, Israel), a new cobalt-chromium external stent for SVGs. The VEST has previously shown

promising pre-clinical results in a large animal CABG setting reducing thrombotic occlusion of SVGs as well as significantly reducing the area of intimal hyperplasia (12). Based on the pre-clinical data, a pilot clinical study was designed with a pre specified primary outcome measure of intimal hyperplasia area 12 months post CABG.

Patients and Methods

Study design and population

The VEST trial, conducted from October 2011 to September 2013, was a prospective, multi-center, randomized and self-controlled. The study was approved by a UK Research Ethics Committee and all subjects gave informed consent. Patients were eligible if they were scheduled for on-pump multi-vessel CABG including a left internal mammary artery (LIMA) to the left anterior descending (LAD) coronary artery and SVGs to right and circumflex territories. Eligibility required a target vessel diameter $\geq$1.5mm with a coronary stenosis >75% and with an adequate distal vascular bed, as assessed by preoperative angiography. Each patient received one external stent device to a single SVG, randomly assigned intra-operatively, to either the right or the circumflex coronary territories. One or more SVG remained non-stented and served as the control group. The primary safety end point was the composite occurrence at 6 weeks post-surgery of all-cause mortality, stroke, myocardial infarction, and coronary revascularization. The primary effectiveness endpoint compared intimal hyperplasia area as assessed by intra vascular ultrasound (IVUS) at 12 months, between stented and non-stented SVG groups.

Procedure and follow up

All SVGs were harvested in an open technique and surgery was performed with use of cardiopulmonary bypass. Randomization to either stent deployment to the circumflex or stent deployment to the right coronary artery took place intra-operatively, by the opening of a sealed envelope, only after all distal anastomoses were performed. An adequate device size was selected from twelve available models based on the graft's diameter and length. The device was threaded over the randomized SVG, the proximal

anastomoses were subsequently performed, and finally the device, which combines radial elasticity and axial plasticity, was expanded along the entire vein graft length and simultaneously reduced its diameter to mildly constrict the SVG. Once shaped to its final configuration, taking into consideration the specific SVG anatomy, the device maintains its position and there is no need for further fixation. Although uncalled by the protocol or the instructions for use, in 9 cases, the study device was fixated to the proximal and/or distal anastomoses using sutures. Procedural steps are depicted in Figure 1. Transit Time Flow Measurement (TTFM) was applied to all grafts. Contrast angiography of all grafts and IVUS of SVG to the right and the circumflex territories were attempted at the 12 months visit as described in Figure 2. All patients were prescribed statins and aspirin for 12 months post operatively.

Quantitative angiography analysis

Contrast angiography was attempted for all grafts and quantitative coronary angiography (QCA; QAngio® XA, Medis, The Netherlands) was performed for all patent vein grafts. Analysis was performed by an independent observer. Mean diameters were measured for all patent SVG and averaged for every 10 mm segment, as previously described (18) using an angiographic frame showing the worst appearance (7). Vein graft failure was defined as >50% stenosis (6-7) and ectasia was defined as segmental dilatation that exceeded the diameter of normal adjacent segments by 50% (19). Blood flow and velocity were assessed using the TIMI frame count (20). Graft uniformity was graded by an independent observer using the Fitzgibbon classification; I – uniform graft, II - non-uniformity that involves <50% graft length, III - non-uniformity that involves >50% graft length (7).

Intravascular ultrasound

A 40 MHz IVUS catheter (Boston Scientific, Hemel Hempstead, UK) was advanced beyond the distal anastomosis of all patent vein grafts and then pulled back using a motorized pull-back device at a rate of 1.0 mm/s through to and including the proximal anastomosis in a series of up to 3 pullbacks per graft. Images were analyzed using QIVUS® software (Medis, The Netherlands) and the lumen and the external elastic membrane (EEM) were identified and marked by an independent observer according to American

College of Cardiology guidelines (21).To assess the extent of diffuse intimal hyperplasia, measurements of each vessel's EEM, and lumen cross-sectional area were made approximately every 10mm along the graft from the distal to the proximal anastomosis. The area of Intimal and medial hyperplasia was calculated as the EEM area minus the lumen area. The average intimal-medial thickness was calculated by subtracting the average lumen diameter from the average EEM diameter and dividing by two. The effect of external stenting was further analyzed to evaluate the influence of side branches ligation method (metallic clips/sutures) on the primary endpoint.

Statistical analysis

To evaluate the effect of VEST on continuous parameters (plaque area and thickness), a linear mixed model with subject random effect and presence of VEST as a fixed factor was used. To evaluate the effect of VEST on categorical parameters, a generalized mixed model (for binomial and multinomial distributions) with subject random effect and presence of VEST as a fixed factor was used. A mixed model with random subject effect was used also to compare baseline characteristics between stented and non-stented SVGs. Significance was set at 5%. Continuous data are presented as mean ± standard deviation (SD).

Results

Patients, procedure, and follow up

35 patients were enrolled and 30 were randomized into the VEST trial between October 2011 and September 2012. Demographic characteristics for the randomized patients are shown in Table 1. During surgery, four patients were deemed ineligible due either to inadequate vein quality or target coronary artery calcification and one patient was not randomized for administrative reasons. Thirty grafts, 1 per patient, were successfully stented with the study device and compared with 39 non-stented SVGs. Baseline grafting parameters were well balanced between the two study groups with no significant difference as showed in Table 2. All 30 patients were seen at 6 weeks with no complications, as defined in the primary safety endpoint. 29 randomized patients completed 12 months follow up, including angiography. One patient died 11 months post-operatively. This death occurred eight months after repeat revascularization by PCI to two non-stented SVGs territories.

Angiography, QCA, and IVUS

One-year follow up angiography and IVUS were completed in 29 patients (96.6%). IVUS data was available for analysis for a total of 43 SVG (20/30 stented (66.6%) and 23/30 (76.6%) non-stented SVG). IVUS was not performed in occluded SVG (n=12), or in diseased SVG in which canulation for the IVUS was not considered safe (n=3), and/or SVG that were not bypassed to the right or circumflex territory as indicated in the protocol (n=9). In one patient, IVUS data of both the stented and non-stented SVG could not be analyzed due to incompatibility of the IVUS software that was used. All patent SVGs (n= 53, 76.8%) were analyzed by QCA including 21/30 stented (70%) and 32/39 non-stented SVGs (82%). In one patient, QCA analysis of all SVGs was based on angiography that was performed 3 months post CABG as part of revascularization treatment as described above. 30/30 LIMA grafts were patent but were not analyzed as part of the study.

The primary outcome measure (Table 3), SVG mean intimal-medial area, differed significantly between the stented and non-stented groups (4.37 ±1.40 mm^2 versus 5.12 ±1.35 mm^2, p=0.04). External stenting

also led to reduction in intimal thickness with marginal significance (0.37 ±0.1 versus 0.42 ±0.1 mm, stented versus non-stented SVG, p=0.06). Comparing stented and non-stented SVGs, ligating SVGs side branches with sutures rather than metallic clips was associated with a marginally significant reduction in both plaque area (27.4% ,p=0.05) and plaque thickness (23.8% , p=0.04) unlike ligation with metallic clips which resulted in a non-significant reduction in both plaque area (4.6%, p=0.33) and thickness (2.4% p=0.60) . As shown in Table 4 there was no significant difference in overall SVG failure rates at 12 months between the two groups (30% stented versus 28.2% non-stented SVG, P=0.55). However, the stented versus non-stented SVG failure rates were significantly lower in the circumflex territory (17.6% versus 27.5%; p=0.02) and significantly higher in the right territory (46.2% versus 13.4%; p=0.01). Mean lumen diameter, overall blood flow and blood velocities were similar in both the stented and non-stented groups. However with regards to lumen regularity, using the Fitzgibbon classification, a higher proportion of stented SVGs were in Fitzgibbon Class I (62% vs 39%; p=0.08) and with a lower incidence of SVG ectasia (6.7% vs 28.2%; p=0.05). Ligation of side branches with sutures rather than metallic clips resulted also in more uniform SVG lumen in the stented group. When sutures were used, 88% of the stented SVGs showed perfectly uniform lumen (Fitzgibbon I) compared to 41% in the non-stented group (p=0.04).

Comment

The key finding in the current study is that a mechanical external stent has the potential to reduce the process of diffuse intimal hyperplasia in SVGs one-year after CABG. External stenting of SVG resulted in a statistically significant reduction of this area by around 15% (p=0.04). Several studies have previously reported comparable plaque areas in SVG 12 months after implantation (9, 22) and to date only statins and β blockers have been shown to reduce the process (10).

A particular strength of the trial was the paired study design. In effect each patient acted as their own control, thereby eliminating many of the potential factors that could affect SVG disease progression. Accordingly, the stented and non-stented groups were well balanced with respect to baseline anatomical and physiological parameters that might contribute to the development of intimal hyperplasia including

the diameter of the native coronary artery and the severity of the proximal coronary artery stenosis. This was also evidenced by the similarity of measured graft flows in both the stented and non-stented SVGs during surgery and at one-year angiography. As shown in Table 3, the ability of the external stent to mitigate intimal hyperplasia was affected by whether metallic clips or sutures were used to ligate SVG side branches. When sutures were used, the stented SVGs showed greater reduction in both plaque area and thickness (27%, p=0.05 and 24%, p=0.04 respectively) compared to a minor, non-significant effect that was observed when metallic clips were used (4.6%, p=0.33 and 2.4%, p=0.60 respectively). This could be explained by the fact that the use of metallic clips compromised the optimal alignment between the stent and the SVG and resulted in more lumen irregularities (as reflected by the Fitzgibbon classification in Table 5) and flow disturbances which accelerated the development of intimal hyperplasia. Early vein graft failure, defined by occlusion or stenosis >50%, was not reduced by the VEST. In contrast to non-stented SVGs the failure rate of stented SVGs was significantly lower than in the left territory but significantly higher in the right territory. In the right territory, a higher failure rate of stented SVGs was observed when either metallic clips, rather than sutures, were used to ligate side branches of SVGs (62% versus 20% respectively) or when the stent was sutured and fixated to the proximal and/or distal anastomoses (75% versus 33.3% respectively). The use of metal clips to ligate SVG side branches does not usually deform the vessel wall. However, it appears that when constrained within the stent, metallic clips may locally deform the vessel causing stenosis and interruptions to flow that may trigger the conduit's occlusion. This is especially true in grafts to the right territory where there is a more acute angulation of the graft around the acute margin of the heart and an example of this is shown in Figure 3. Unlike SVGs to the left territory, SVGs to the right territory "wrap" the heart as part of their path from the aorta to the distal anastomosis in the inferior wall. As a result, more tension can be applied on the anastomoses sites when the heart inflates and recovers its original dimensions with physiological blood pressures. For this reason, like previously reported by Schoettler et al, fixation of the external stent to the anastomosis may have led to high tension at the anastomosis site and SVG failure (15).

Together with the small sample size, a notable limitation of this study was the lack of very early patency data to enable more precise timing of vein graft occlusion. In addition, the long term effect of external stent on vein graft pathophysiology couldn't be determined due to the short follow up period. However, the preliminary findings from this first in human study demonstrate that external stent has the potential to mitigate intimal hyperplasia progression in SVGs implanted during CABG. If maintained over the longer–term, this has a potential to change the natural history of vein graft failure and to improve the outcomes of surgical revascularization. Large clinical studies with long term follow up are required to determine if external stenting of vein grafts is associated with a continuing reduction in the progression of intimal hyperplasia and any associated potential clinical benefits.

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David Taggart – Consultant to Vascular Graft Solutions, stock options ownership.

Yanai Ben Gal – Co inventor of VEST, consultant to Vascular Graft Solutions, stock options ownership and royalties.

Eyal Orion – Co inventor of VEST, CEO of Vascular Graft Solution, Stock ownership

References

1. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013 Feb 23;381(9867):629-38

2. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularization on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet. 2001;358:870–875

3. Motwani JG and Topol EJ. Aortocoronary Saphenous Vein Graft Disease : Pathogenesis, Predisposition, and prevention. *Circulation* 1998;97;916-931

4. Owens CD, Ho KJ and Conte MS. Lower extremity vein graft failure: a translational approach. *Vascular Medicine* 2008; 13: 63–74

5. Chiu JJ and Chien S. Effects of Disturbed Flow on Vascular Endothelium: Pathophysiological Basis and Clinical Perspectives. *Physiol Rev* 91: 327–387, 2011.

6. 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. *J Thorac Cardiovasc Surg*. 2005;129: 496–503.

7. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper D, Burton JR. Coronary bypass graft fate and patient outcome: Angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol* 1996;28:616–626.

8. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB Jr, Lorenz TJ, Goyal A, Gibson M, Mack MJ, Gennevois D, Califf RM, Kouchoukos NT; PREVENT IV Investigators. Efficacy and Safety of Edifoligide, an E2F Transcription Factor Decoy, for Prevention of Vein Graft Failure Following Coronary Artery Bypass Graft Surgery. *JAMA*. 2005;294:2446-2454

9. Une D, Kulik A, Voisine P, Le May M, Ruel M. Correlates of saphenous vein graft hyperplasia and occlusion 1 year after coronary artery bypass grafting: analysis from the CASCADE randomized trial. Circulation. 2013 Sep 10;128:(S213-S218)

10. Kulik A, Le May MR, Voisine P, Tardif JC, Delarochelliere R, Naidoo S, Wells GA, Mesana TG, Ruel M. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) Trial. *Circulation*. 2010;122:2680–2687.

11. Angelini GD, Lloyd C, Bush R, Johnson J, Newby AC. An external, oversized, porous polyester stent reduces vein graft neointima formation, cholesterol concentration, and vascular cell adhesion molecule 1 expression in cholesterolfed pigs. *J Thorac Cardiovasc Surg* 2002; 124: 950–956.

12. Ben-Gal Y, Taggart DP, Williams MR, Orion E, Uretzky G, Shofti R, Banai S, Yosef L, Bolotin G. Expandable external stent device to improve Saphenous Vein Graft Patency after CABG. *J Cardiothorac Surg*. 2013 May 6;8(1):122

13. Jeremy JY, Gadsdon P, Shukla N, Vijayan V, Wyatt M, Newby AC, Angelini GD. On the biology of saphenous vein grafts fitted with external synthetic sheaths and stents. *Biomaterials* 2007; 28: 895–908.

14. Murphy GJ, Newby AC, Jeremy JY, Baumbach A, Angelini GD. A randomized trial of an external Dacron sheath for the prevention of vein graft disease: The Extent study. *J Thorac Cardiovasc Surg*. 2007;134:504–505.

15. Schoettler J, Jussli-Melchers J, Grothusen C, Stracke L, Schoeneich F, Stohn, Hoffmann G, Cremer J. Highly flexible nitinol mesh to encase aortocoronary saphenous vein grafts: first clinical experiences and angiographic results nine months postoperatively. *Interact CardioVasc Thorac Surg* 2011;13:396-400

16. Rescigno G, Aratari C, Matteucci SM, Parisi R, Gironi G, Schicchi N, D'Alfonso A, Cola V, Torracca L . Saphenous Vein Graft Wrapping by Nitinol Mesh: A Word of Caution. Thorac Cardiovasc Surg. 2014 Oct 31. [Epub ahead of print]

17. Song Wan, Ahmed A. Arifi , Michael C.W. Chan, Johnson H.Y. Yip, Calvin S.H. Ng , Louis T.C. Chow , Anthony P.C. Yim , Jamie Y. Jeremy. Differential, time-dependent effects of perivenous application of fibrin glue on medial thickening in porcine saphenous vein grafts. European Journal of Cardio-thoracic Surgery 29 (2006) 742—747.

18. Webb CM, Ghatei MA, McNeill JG, Collins P. 17beta-estradiol decreases endothelin-1 levels in the coronary circulation of postmenopausal women with coronary artery disease. *Circulation.* 2000;102:1617-1622.

19. Swaye PS, Fisher LD, Litwin P, Vignola PA, Judkins MP, Kemp HG, Mudd JG, Gosselin AJ. Aneurysmal coronary artery disease. *Circulation* 1983;67:134–138.

20. Gibson CM, Cannon CP, Daley WL, Dodge JT, Alexander B, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. The TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation*. 1996;93:879–888.

21. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2001;37:1478–1492.

22. Hozumi T, J Yoshikawa, K Yoshida, T Akasaka, T Takagi, Y Honda, H Okura. Use of intravascular ultrasound for in vivo assessment of changes in intimal thickness of angiographically normal saphenous vein grafts one year after aortocoronary bypass surgery. *Heart* 1996;76:317-320

Table 1. Patient demographics

Characteristic (n=30)	Mean (±SD) or n (%)
Age (years)	65.3±8.1
Male	90%
Height (cm)	173±7.2
Weight (kg)	84.7±9.6
Smoking status:	
Current	3 (10%)
Ex-smoker	22 (73.3%)
Never	5 (16.7%)
Diabetes:	
IDDM	5 (17%)
NIDDM	6 (20%)
No history	19 (63%)
Hypertension:	20 (66.7%)
Hyperlipidaemia	29 (96.7%)
Prior stroke (non-debilitating)	1 (3.3%)
COPD	1 (3.3%)
NYHA class:	
I	11 (36.7%)
II	13 (43.3%)
III	4 (13.3%)
IV	2 (6.7%)
LVEF (%)	56.4±9.8
Creatinine (umol/L)	85±18.9
Pre-op Logistic EuroSCORE (%)	1.58±1.29

Table 2. Baseline characteristics of SVG groups

Variable	Mean (±SD)		P value
	Stented (n=30)	Non-stented (n=30)	
Host coronary artery stenosis (%)	86.9±12.7	86.6±10	0.63
Host coronary artery diameter (mm)	1.8±0.2	1.9±0.3	0.14
Graft length (cm)	15.4±2.5	15±2.4	0.45
Systolic pressure at TTFM (mmHg)	109.1±15.2	109.7±15.9	0.57
Final TTFM flow (ml/min)	67±27.8	66.2±33.4	0.89
Final TTFM pulsatility index	2.2±1.1	2.2±1.0	1.0

Data are expressed as mean ± SD

Table 3. IVUS data

Mean (±SD)

Variable All SVGs	Stented (n=21)	Non-stented (n=23)	Percent difference	P value
Plaque area (mm^2)	4.37 ±1.40	5.12 ±1.35	-14.6%	0.04
Plaque thickness (mm)	0.37 ±0.10	0.42 ±0.10	-11.9%	0.06
Average lumen diameter (mm)	3.36 ±0.57	3.42 ±0.53	-1.0%	0.60

Effect of Side Branches (SB) ligation method on intimal hyperplasia

	Stented	Non-stented	Percent difference	P value
Plaque area (mm^2)				
SB ligated with metal clips	5.01 ±1.23 (n=11)	5.25 ±1.42 (n=13)	-4.6%	0.33
SB ligated with sutures	3.59 ±1.22 (n=9)	4.95 ±1.32 (n=10)	-27.4%	0.05
Plaque thickness (mm)				
SB ligated with metal clips	0.41 ±0.10 (n=11)	0.42 ±0.10 (n=13)	-2.4%	0.60
SB ligated with sutures	0.32 ±0.09 (n=9)	0.42 ±0.10 (n=10)	-23.8%	0.04

Data are expressed as mean±SD

Table 4. Angiography and QCA data: Occlusion and Disease

Variable	Vein grafts % (n)		
	Stented **(n=30)**	**Non-stented** **(n=39)**	**P value**
All territories:			
SVG disease (50-99% stenosis)	0 (0)	10.3 (4)	
SVG occlusion	30 (9)	17.9 (7)	
Total SVG failure (>50% stenosis)	30 (9)	28.2 (11)	0.55
Left territory:	**(n=17)**	**(n=24)**	
SVG disease (50-99% stenosis)	0 (0)	12.5 (3)	
SVG occlusion	17.6 (3)	25 (6)	
Total SVG failure (>50% stenosis)	17.6 (3)	27.5 (9)	0.02
Right territory:	**(n=13)**	**(n=15)**	
SVG disease (50-99% stenosis)	0 (0)	6.7 (1)	
SVG occlusion	46.2 (6)	6.7 (1)	
Total SVG failure (>50% stenosis)	46.2 (6)	13.4 (2)	0.01
Lumen uniformity	**(n=21)**	**(n=31)**	
All SVGs			
Fitzgibbon I classification (%)	61.9	38.7	
Fitzgibbon II+III classification (%)	38.1	61.3	0.08
Side branches ligated with metal clips	**(n=12)**	**(n=19)**	
Fitzgibbon I classification (%)	41.6	36.8	
Fitzgibbon II+III classification (%)	58.4	63.2	0.48
Side branches ligated with sutures	**(n=9)**	**(n=12)**	
Fitzgibbon I classification (%)	88.8	41.6	
Fitzgibbon II+III classification (%)	11.2	58.4	0.04
	(n=21)	**(n=31)**	
SVG Ectasia (%)	6.7	28.2	0.05
Blood flow and velocity	**(n=21)**	**(n=29)**	
Blood flow in SVG (ml/s)	94.7 ± 49.5	94.3 ± 46.6	0.97
Blood velocity in SVG (cm/s)	15.8 ± 6.5	15.5 ± 7.2	0.90

Figure Legends:

Figure 1: VEST implantation procedure. (A) Threading on SVG; (B) Suturing SVG proximal

anastomosis; (C) Expanding VEST on the entire SVG length

Figure 2: Contrast angiography at 12 months of Non-stented SVGs to the right (A, B) and left (C,D)

territories and stented SVGs to the right (E,F) and left (G,H) territories

Figure 3: Stented SVG to the right coronary artery. Metal clips (white arrows) were used to ligate the

SVG side branches (A). Contrast angiography demonstrates SVG displacement (red arrow) and stenosis

at the SVG acute angulation (yellow arrow) where metal clips are present (B).

Abbreviations

CABG – Coronary artery bypass grafting

COPD – Chronic obstructive pulmonary disease

EEM – External elastic media

FIH – First in Human

IDDM – Insulin dependent diabetes mellitus

IVUS – Intravascular ultrasound

LAD – Left anterior descending

LIMA – Left internal mammary artery

LVEF – Left ventricular ejection fraction

NIDDM – Non insulin dependent diabetes mellitus

NYHA – New York Heart Association

OM – Obtuse marginal

PCI – percutaneous coronary intervention

QCA- Quantitative coronary angiography

RCA – Right coronary artery

SD – Standard deviation

SVG/s – Saphenous vein graft/s

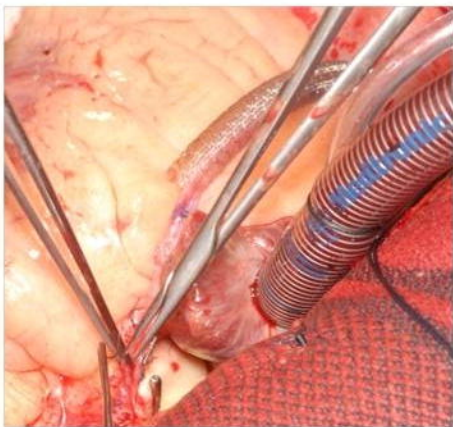TIMI - Thrombolysis in myocardial infarction

TTFM - Transit time flow measurement

VEST – Venous external stent trial and the name of the investigational device.

A

B

C