

External stenting and disease progression in saphenous vein grafts two years after coronary artery bypass grafting: A multicenter randomized trial

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ABSTRACT

Objectives: Little data exist regarding the potential of external stents to mitigate long-term disease progression in saphenous vein grafts. We investigated the effect of external stents on the progression of saphenous vein graft disease.

Methods: A total of 184 patients undergoing isolated coronary artery bypass grafting, using an internal thoracic artery graft and at least 2 additional saphenous vein grafts, were enrolled in 14 European centers. One saphenous vein graft was randomized to an external stent, and 1 nonstented saphenous vein graft served as the control. The primary end point was the saphenous vein graft Fitzgibbon patency scale assessed by angiography, and the secondary end point was saphenous vein graft intimal hyperplasia assessed by intravascular ultrasound in a prespecified subgroup at 2 years.

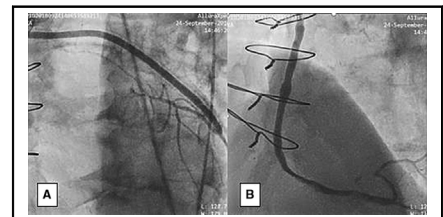
Results: Angiography was completed in 128 patients and intravascular ultrasound in the entire prespecified cohort ($n = 51$) at 2 years. Overall patency rates were similar between stented and nonstented saphenous vein grafts (78.3% vs 82.2%, $P = .43$). However, the Fitzgibbon patency scale was significantly improved in stented versus nonstented saphenous vein grafts, with Fitzgibbon patency scale I, II, and III rates of 66.7% versus 54.9%, 27.8% versus 34.3%, and 5.5% versus 10.8%, respectively (odds ratio, 2.02; $P = .03$). Fitzgibbon patency scale was inversely related to saphenous vein graft minimal lumen diameter, with Fitzgibbon patency scale I, II, and III saphenous vein grafts having an average minimal lumen diameter of 2.62 mm, 1.98 mm, and 1.32 mm, respectively ($P < .05$). Externally stented saphenous vein grafts also showed significant reductions in mean intimal hyperplasia area (22.5%; $P < .001$) and thickness (23.5%; $P < .001$).

Conclusions: Two years after coronary artery bypass grafting, external stenting improves Fitzgibbon patency scales of saphenous vein grafts and significantly reduces intimal hyperplasia area and thickness. Whether this will eventually lead to improved long-term patency is still unknown. (J Thorac Cardiovasc Surg 2021; ■:1-10)

Despite the proposed benefits of multiple arterial grafts, autologous saphenous vein grafts (SVGs) are still the most frequently used (80%) bypass conduits in coronary artery bypass grafting (CABG).¹ SVG failure may be classified into early and late phases. Early SVG failure is largely due to intraoperative technical issues, poor conduit quality or harvesting techniques, or inadequate runoff within the

target vessel and, with the exception of overt technical errors, may not be easily amenable to further intervention.²

In contrast, late SVG failure may be susceptible to intervention because decades of extensive research have provided deep insights into its pathogenesis. Beginning several days after implantation, SVG disease is dominated by intimal hyperplasia whereby smooth muscle cells



Within-patient comparison of an externally stented SVG to the obtuse marginal branch showing Fitzgibbon I patency (A) and an unsupported SVG to the posterior descending artery with Fitzgibbon III patency (B) 2 years after surgical revascularization.

CENTRAL MESSAGE

Two years after CABG, external stenting improves Fitzgibbon patency rates of vein grafts and significantly reduces diffuse intimal hyperplasia.

PERSPECTIVE

Although susceptible to progressive failure, SVGs remain the most frequently used bypass conduits in CABG. Strategies that minimize intimal hyperplasia and SVG structural remodeling postimplantation have the potential to reduce atheroma formation and late SVG failure. Improving SVG longevity should positively affect the clinical outcome of CABG.

See Commentary on page XXX.

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CTA	= computed tomography angiography
EEM	= external elastic media
EVH	= endoscopic vein harvesting
FPS	= Fitzgibbon Patency Scale
ICC	= intraclass correlation coefficient
IVUS	= intravascular ultrasound
MACCE	= major adverse cardiac and cerebrovascular events
MLD	= minimal lumen diameter
SVG	= saphenous vein graft



Scanning this QR code will take you to the table of contents to access supplementary information.

proliferate and migrate to the dysfunctional intima.³ Arterial pressures and high circumferential wall stress, allied to lumen irregularities and abnormal flow patterns, are the main contributors to diffuse intimal hyperplasia that eventually predispose the SVG to thrombosis and accelerated atherosclerosis.^{3,4}

However, until recently, this pathophysiologic understanding has still not translated into particularly effective therapies. To date, only persistent use of statins and beta-blockers has been shown to reduce, at least to some extent, the development of intimal hyperplasia in vein grafts.⁵ Surgical approaches that appear to reduce disease progression in SVG include its harvest with a “no touch” technique⁶

or the use of the SVG as a composite graft from the internal thoracic artery.⁷

Since Parsonnet and colleagues⁸ initially described the concept of external stenting of vein grafts in an animal model in 1963, the potential benefit of the technique has been described extensively in preclinical research.⁹ However, clinical trials with first-generation external stenting technologies provided disappointing results, with early SVG patency of 0% to 28% at 6 to 9 months.^{10,11} Recent trials using current-generation, biomechanically improved external stents have provided more promising results with early SVG patency ranging from 86% to 100%.^{12,13}

From the outset, it is crucial to appreciate that external stenting cannot mitigate many of the causes of early vein graft failure but is instead designed to minimize disease progression in the SVG over the longer term. Indeed, small previous studies of up to 30 patients using intravascular ultrasound (IVUS) and optical coherence tomography produced profound pathophysiologic insights into the biomechanical benefits of external stenting by demonstrating significant reductions in lumen irregularities, intimal hyperplasia, thrombus formation, and oscillatory shear stress in SVG at 1 and 4.5 years after CABG.¹⁴⁻¹⁷

The current trial, Venous External Support Trial III (VEST III), aimed to validate previous observations regarding the effects of external stenting in a larger cohort of patients (n = 184) and to provide additional insights regarding their mechanism of action 2 years after CABG.

MATERIALS AND METHODS**Patients and Design**

VEST III (NCT02511834) investigated the performance of the CE marked VEST external stent (Vascular Graft Solutions Ltd, Tel Aviv, Israel) over 2 years in a prospective, within-patient, controlled, randomized, multicenter international trial. The study was conducted in accordance

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Clinical Trial Registry Number: NCT02511834. Institutional Review Board Information: UK - REC 15/SC/0311, July 9, 2015, Germany - CIV-15-04-013504, September 8, 2015, Austria - Vienna EC 1330/2015, August 11, 2015, Innsbruck EC AN2016-0036 359/4.11, August 8, 2016, Israel - Rambam 0244-15-RMB, August 12, 2015, Sheba 2357-15-SMC, December 17, 2015.

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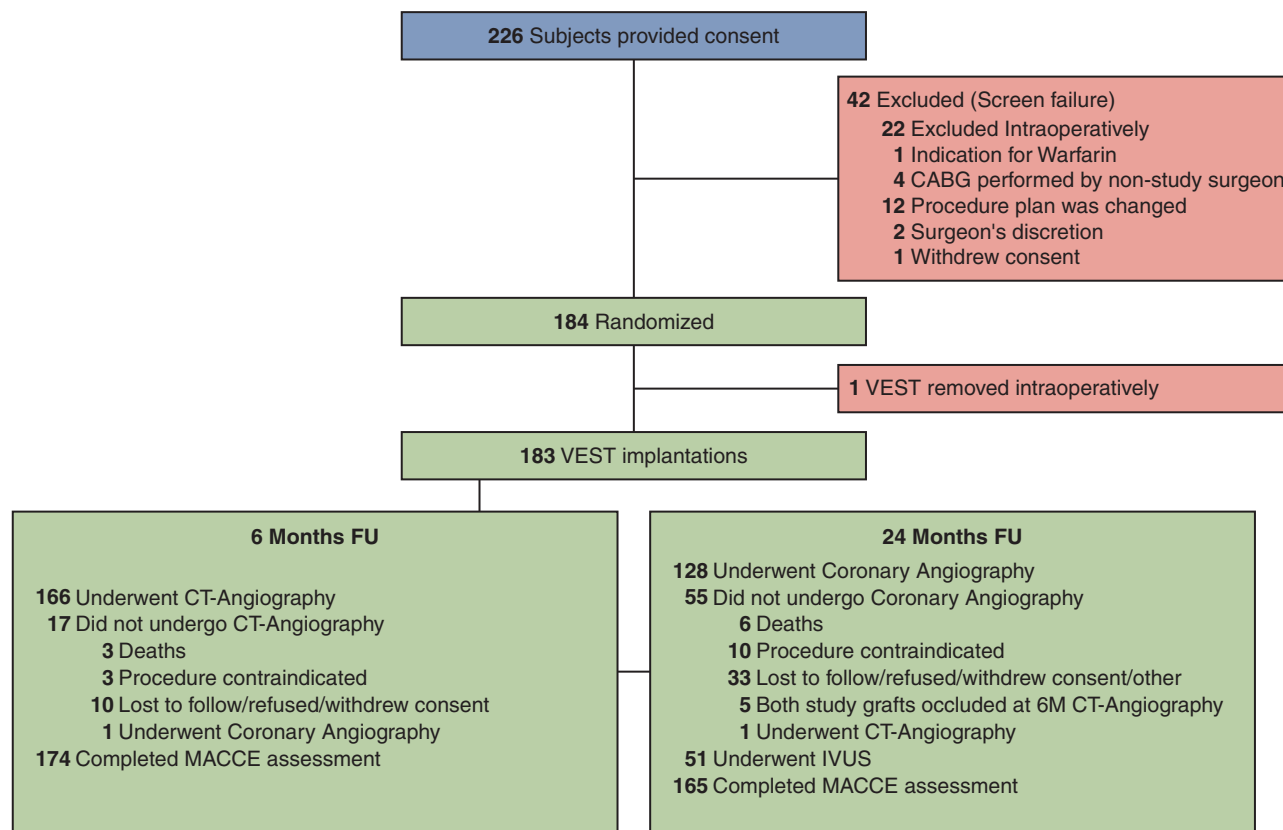


FIGURE 1. CONSORT diagram of study enrollment and follow-up. *IVUS*, Intravascular ultrasound; *MACCE*, major cardiac and cerebrovascular events.

with the principles of the Declaration of Helsinki and all applicable regulations. The protocol was approved by the independent institutional review board or ethics committee responsible for each participating site (UK - REC 15/SC/0311, July 9, 2015, Germany - CIV-15-04-013504, September 8, 2015, Austria - Vienna EC 1330/2015, August 11, 2015, Innsbruck EC AN2016-0036 359/4.11, August 8, 2016, Israel - Rambam 0244-15-RMB, August 12, 2015, Sheba 2357-15-SMC, December 17, 2015), and informed written consent was obtained from all patients.

Patients were eligible if they required an internal thoracic artery graft to the left anterior descending coronary artery in addition to 2 or more aorto-coronary SVGs to the right and left coronary territories. Further inclusion criteria included an adequate distal vascular bed and noncalcified coronary artery target sites 1.5 mm in diameter or greater. After completion of all distal anastomoses, each patient was randomized to receive 1 external stent applied to 1 SVG, and an additional nonstented SVG served as control. In cases in which 3 vein grafts were used, 2 stages of randomization were performed to randomize first the stented graft and then the control SVG.

The primary end point was Fitzgibbon patency scale (FPS) defined by angiography.¹⁸ The secondary end point was intimal hyperplasia area as assessed by IVUS. The primary safety end point evaluated major adverse cardiac and cerebrovascular events (MACCE). The CONSORT diagram is presented in Figure 1. Enrollment was completed on schedule with slightly fewer patients than originally planned (184 vs 200). The trial was completed in May 2019, and the database was locked on October 3, 2019 (Figure 2).

Procedure and Follow-up

Vein grafts were harvested using both open and endoscopic techniques according to the individual site standard of care. Side branches were ligated with ties or sutures. All procedures were performed with cardiopulmonary

bypass. To avoid potential bias, randomization of vein grafts to be treated with external stents or to serve as controls was performed using sealed envelopes only after intraoperative eligibility criteria of target vessel quality was met and subsequent to completion of all distal anastomoses.

The appropriate device model was selected on the basis of SVG length and diameter. The SVG was threaded through the device before performance of the proximal anastomosis and manually expanded over the entire SVG. No further fixation of the device to the vein graft was performed. When available, transit time flow measurements were performed on venous and arterial bypass grafts to identify possible technical shortcomings in the operating room (Video 1). All patients were prescribed statins, beta-blockers, and aspirin as per practice guidelines.

Computed tomography angiography (CTA) was performed 6 months after CABG to detect early SVG occlusions. Two years after CABG, patients with at least 1 patent study graft based on CTA findings underwent contrast coronary angiography. In addition, a preplanned subgroup of patients in which both study grafts were patent based on the 6-month CTA underwent IVUS assessment for intimal hyperplasia. These patients were examined on an all-comer basis in centers that possessed the technical capability to perform the procedure according to the protocol until the predetermined number of studies had been carried out. Because angiography and IVUS were performed in the same session, there was no potential for selection bias on the basis of the angiographic FPS.

Angiography and Intravascular Ultrasound

All angiograms and IVUS images were analyzed by an independent Intravascular Imaging Core Laboratory at the Mount Sinai Hospital (New York, NY) by 2 independent observers. Coronary angiograms were acquired in at least 4 vertical planes. Initial assessment was performed to determine graft patency. The FPS classification of intimal irregularity

VEST III Trial design, endpoints and main findings 2 years following coronary artery bypass grafting

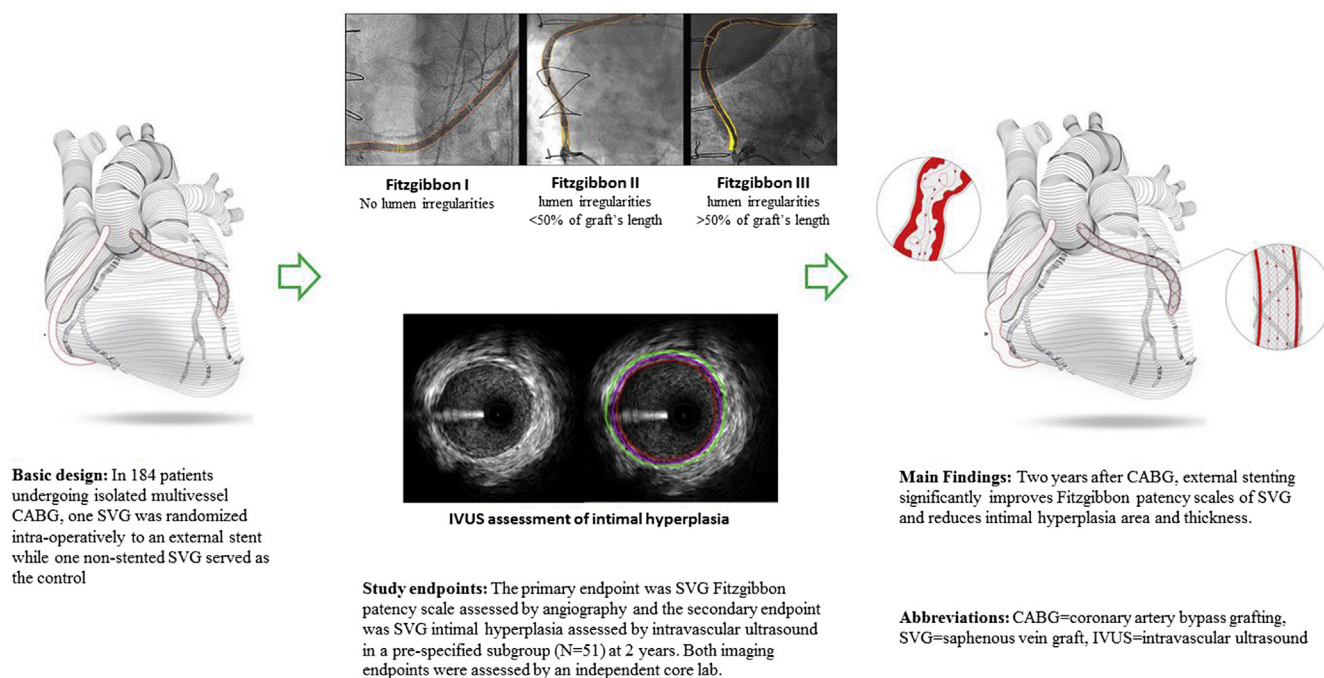
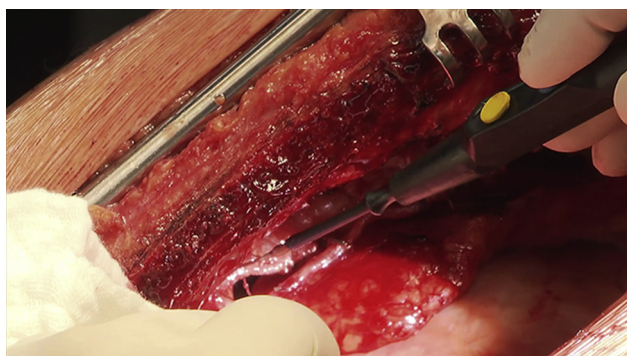


FIGURE 2. Left: Basic design of the study. Center: Primary and secondary end points. Right: Main findings.

(which should not be confused with the flow-based ABO Fitzgibbon classification) was assessed for all patent study grafts by 4-plane angiography.¹⁸ All patent study SVGs were graded from the worst appearance in 4-plane views (Figure 3) as perfectly patent SVG: smooth graft outline with no intimal irregularities; intimal irregularities of less than 50% of estimated intimal surface; and intimal irregularities of greater than 50% of estimated intimal surface.

Quantitative coronary angiography analysis was performed using QAngio XA software (Medis, Leiden, The Netherlands) for each patent SVG. Minimal, maximal, and mean diameters were measured for each SVG and averaged for every 5-mm segment using an angiographic plane and frame showing the worst appearance. Ectasia was defined as a segmental dilation more than 50% compared with the normal adjacent segments.

IVUS imaging of the entire lengths of both study grafts, stented and nonstented, was performed on a preplanned subgroup of 51 patients at 6



VIDEO 1. The rationale for external vein graft stenting is explained, and the implantation technique for the VEST is demonstrated under actual operating room conditions. Video available at: [https://www.jtcvs.org/article/S0022-5223\(21\)00723-6/fulltext](https://www.jtcvs.org/article/S0022-5223(21)00723-6/fulltext).

study sites that possessed the required expertise and equipment. Imaging was acquired using a motorized pullback 40 to 45 MHz IVUS catheter. The IVUS catheter was advanced beyond the distal anastomosis and then pulled back using a motorized system at a rate of 0.5 mm/s to the aorto-ostial junction and repeated several times for each graft. IVUS image analyses were performed by experienced analysts blinded to angiographic analysis using QIvus software (Medis), according to published consensus document definitions.¹⁹ Quantitative IVUS measurements included measurements of the external elastic media (EEM) area and lumen cross-sectional areas, EEM, and lumen diameters at 10-mm intervals along the graft from the distal to proximal anastomosis (Figure 4). Manual tracings were performed on frames with the intimal hyperplasia layer clearly visualized and without image artifacts. The intimal hyperplasia area 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 2.

To assess the intervariability of quantitative coronary angiography and IVUS measurements, 30 angiograms and 40 IVUS cross-sectional images were randomly selected from the study database and analyzed by the 2 independent observers that evaluated the primary and secondary end points. To evaluate the intraobserver variability, 1 of the observers repeated the same analyses 1 month later. Intraobserver and interobserver agreement for quantitative measurements were assessed by intraclass correlation coefficient (ICC) based on the random-effects analysis of variance model. Cohen's kappa was used for categorical variables. The agreement on Fitzgibbon grading was excellent ($k = 0.92$). Likewise, interobserver reproducibility was high for IVUS intimal hyperplasia area (ICC = 0.94; 95% confidence interval, 0.86-0.97) and thickness (ICC = 0.96; 95% confidence interval, 0.90-0.98).

Statistical Analysis

Sample size was determined using the following assumptions previously reported in the literature: Fitzgibbon I patency scale (perfect patency)

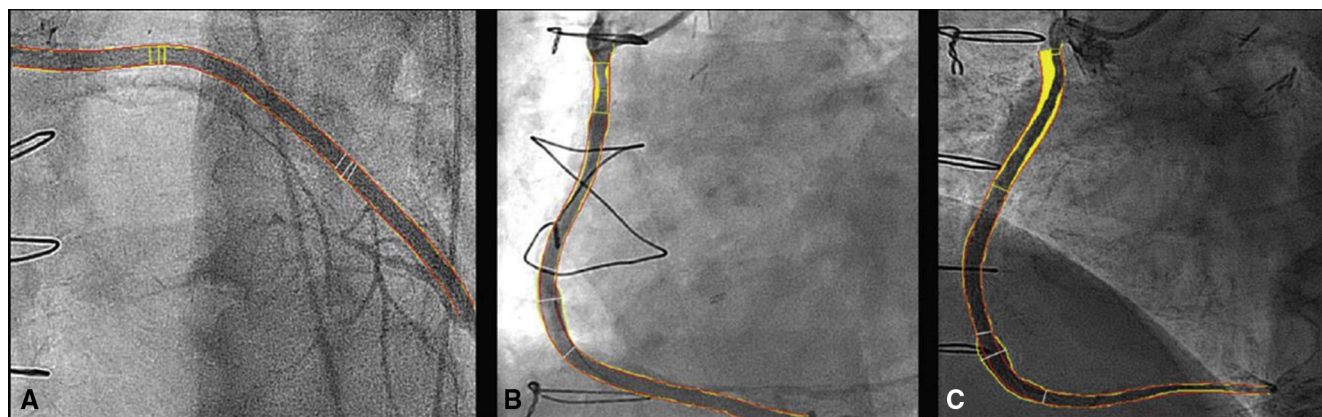


FIGURE 3. The angiographic appearance of the Fitzgibbon classification: A, Fitzgibbon I patency (perfect patency) with no lumen irregularities. B, Fitzgibbon II patency with lumen irregularities that involve less than 50% of SVG length. C, Fitzgibbon III patency with lumen irregularities that involve more than 50% of SVG length. SVG, Saphenous vein graft.

rate in the control group at 2 years is 50%.^{16,20} Treatment effect of the VEST external stent is 25%.¹⁶

In addition, it was assumed that the intersubject correlation between intimal area measured in supported and unsupported grafts is 0.50. Assuming a dropout rate of approximately 20%, it was planned to recruit 200 patients between October 2015 and January 2017 that would provide 90% power to demonstrate superiority in the FPS. Analysis was performed by an independent statistician according to statistical analysis plan (TechnoSTAT, Raanana, Israel). This plan later underwent minor revision to harmonize it with the specifications of the Cardiothoracic Surgical Trials Network PIVOTAL Trial (NCT 03209609) and to extend analysis of FPS I scores to include FPS II and III scores. The revised statistical analysis plan, which was completed before database lock and data analysis, is included in [Appendix E1](#).

To compare the full spectrum of SVG disease progression (FPS I/II/III), primary analysis of Fitzgibbon classification was performed using an ordinal multinomial regression with patient random effect. Analysis of occlusion was carried out using logistic regression with patient random effect for comparison between the 2 graft groups. Instances of occlusion at 6 months, for which there was no 24-month follow-up, were included as occlusion at 24 months. Odds ratios for each of these end points were calculated directly from their respective regression results.

The IVUS analysis set consisted of all patients with intimal hyperplasia measurements at 2 years for at least 1 study graft or missing IVUS data due to SVG stenosis or occlusion that had developed between 6 to 24 months. Intimal hyperplasia and lumen diameter were analyzed using a mixed linear model with repeated measurements per subject for stented and non-stented grafts. Values of intimal hyperplasia and lumen diameter at 24 months that were missing due to SVG stenosis or occlusion were imputed as worst-case values, that is, 80th percentile of the group for intimal hyperplasia and 20th percentile of the group for lumen diameter. Any values missing because of nonclinical reasons were not imputed. Estimate of MACCE and its component rates was performed using 95% exact binomial confidence intervals. All statistical analyses were carried out using SAS software version 9.4 (SAS Institute Inc, Cary, NC). A detailed description of the statistical methodology is available in [Appendix E1](#).

RESULTS

Patients, Procedure, and Follow-up

Of the 226 patients who gave informed consent, 42 did not satisfy the screening criteria and 184 were enrolled and randomized. An external stent was implanted in 183 patients; 1 device was removed intraoperatively because of

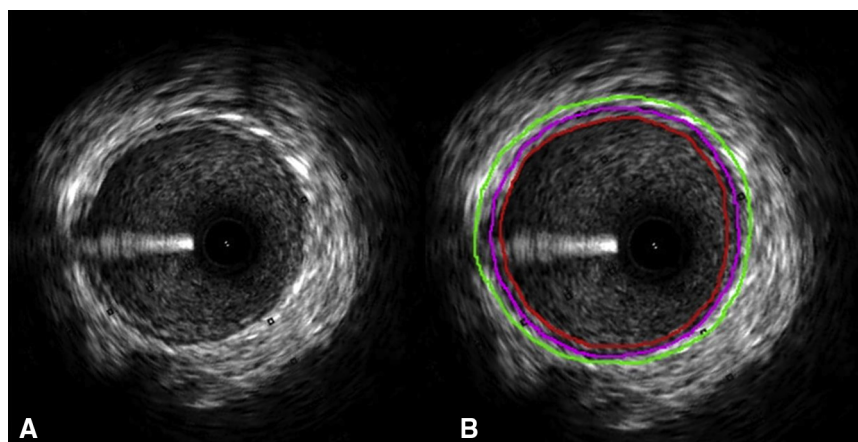


FIGURE 4. Intravascular analysis of an externally stented SVG segment 2 years after surgery without (A) and with (B) highlighting of the lumen (red), external elastic membrane (purple), and external stent (green).

TABLE 1. Demographics and baseline data

Characteristic	Mean (\pm SD) or n (%)
Sample size	N = 183
Age (y)	66.6 \pm 7.9
Male	154 (84.2%)
Body mass index (kg/m ²)	28.6 \pm 4.4
Smoking status	
Current	48 (26.2%)
Ex-smoker (>6 mo)	70 (38.3%)
Never	50 (27.3%)
Unknown	15 (8.2%)
Diabetes	
IDDM	25 (13.7%)
NIDDM	29 (15.8%)
No history	129 (70.5%)
Hypertension	168 (91.8%)
Hyperlipidemia	164 (89.6%)
Documented hypercoagulable state	2 (1.1%)
Diffuse peripheral vascular disease	26 (14.2%)
Prior cardiovascular surgery	6 (3.3%)
Prior stroke (nondebilitating)	3 (1.6%)
Indication for Warfarin	1 (0.5%)
Chronic obstructive pulmonary disease	23 (12.6%)
Unknown	1 (0.5%)
Prior myocardial infarction	58 (31.7%)
Unknown	2 (1.1%)
Prior PCI	48 (26.2%)
New York Heart Association Class	
I	28 (15.3%)
II	91 (49.7%)
III	55 (30.1%)
IV	4 (2.2%)
Unknown	5 (2.7%)
Canadian Cardiovascular Society Class	
I	18 (9.8%)
II	77 (42.1%)
III	54 (29.5%)
IV	14 (7.7%)
Unknown	20 (10.9%)
LVEF (%)	
<35	5 (2.7%)
35-55	78 (42.6%)
>55	89 (48.6%)
Unknown	11 (6%)
Creatinine (μ mol/L)	88.6 \pm 21.1
Preoperative logistic euroSCORE (%)	2.5 \pm 2.6
Unknown euroSCORE (%)	20 (11%)

Baseline characteristics of the entire study population are shown. *SD*, Standard deviation; *IDDM*, insulin-dependent diabetes mellitus; *NIDDM*, noninsulin-dependent diabetes mellitus; *PCI*, percutaneous coronary intervention; *euroSCORE*, European System for Cardiac Operative Risk Evaluation.

TABLE 2. Procedure and perioperative data

Characteristic (n = 183)	Mean (\pm SD) or n (%)
Surgery scheduling	
Elective	159 (86.9%)
Urgent	24 (13.1%)
Emergency	0
Surgery duration (min)	237.4 \pm 51.4
Pump duration (min)	97.7 \pm 26.8
Clamp duration (min)	60.4 \pm 21.1
SVG harvesting technique	
Direct vision (open)	118 (64.5%)
Endoscopic	57 (31.1%)
Bridge	5 (2.7%)
Other	3 (1.6%)
Vein origin	
Above the knee	36 (19.7%)
Below the knee	28 (15.3%)
Both above and below the knee	119 (65%)
Vein varicosity	
None	146 (79.8%)
Mild	33 (18%)
Moderate	4 (2.2%)
Severe	0
Total No. of grafts (SVGs + arteries)	597 (100%)
Study SVGs (VEST and control)	366 (61.3%)
Additional/other SVGs	32 (5.4%)
ITA-LAD	182 (30.5%)
Second arterial graft	17 (2.8%)
No. of grafts per patient	
3	138 (75.4%)
4	42 (23%)
5	3 (1.6%)
Postoperative hospitalization duration (d)	9.34 \pm 5.18

Data on scheduling priority, intraoperative bypass and clamp times, operative technique, graft placement, and time of stay for the entire study population are shown. *SD*, Standard deviation; *SVG*, saphenous vein graft; *VEST*, venous external stent; *ITA*, internal thoracic artery; *LAD*, left anterior descending.

technical failure. Demographic and baseline characteristics are presented in Table 1.

A comparable grafting pattern was observed in both the stented and nonstented groups. Within the left coronary territory, there was a similar distribution of stented and nonstented SVGs to the obtuse marginal (60 vs 61), diagonal (14 vs 10), circumflex (11 vs 11), and intermediate (9 vs 7) coronary arteries, respectively. The right coronary territory was bypassed with 89 stented versus 94 nonstented SVGs. Transit time flow measurements and pulsatility index were assessed in 129 patients, and 2 grafts were revised (1 stented and 1 not stented) in 1 patient before chest closure (Table 2).

As shown in Table 3, baseline native coronary parameters that may contribute to SVG patency and the development of intimal hyperplasia did not differ between the stented and nonstented groups. A total of 166 patients (90.7%)

TABLE 3. Baseline grafting parameters of study grafts

Characteristic	VEST mean (95% CL)	Control mean (95% CL)	P value
Host coronary artery diameter (mm)	1.76 (1.71-1.80) (n = 182)	1.75 (1.70-1.79) (n = 183)	.693
Graft length (cm)	15.59 (15.16-16.02) (n = 183)	15.70 (15.27-16.13) (n = 180)	.723
Systolic pressure at TTFM (mm Hg)	101.57 (98.65-104.49) (n = 121)	101.19 (98.26-104.11) (n = 120)	.586
Final TTFM flow (mL/min)	52.09 (46.68-57.49) (n = 129)	54.44 (49.03-59.84) (n = 129)	.447
Final TTFM pulsatility index	2.28 (1.82-2.73) (n = 119)	2.54 (2.08-2.99) (n = 119)	.073
Coronary target vessels N (%)			
Circumflex	11 (6.0)	11 (6.0)	1.000
Obtuse marginal	60 (32.8)	61 (33.3)	.912
Diagonal	14 (7.7)	10 (5.5)	.401
Intermediate	9 (4.9)	7 (3.8)	.611
RCA	31 (16.9)	29 (15.8)	.778
PDA	58 (31.7)	65 (35.5)	.440

Baseline graft and target vessel data compared between externally stented and control saphenous venous grafts. VEST, Venous external stent; CL, confidence level; TTFM, transit time flow measurement; RCA, right coronary artery; PDA, posterior descending artery.

underwent CTA 6 months post-CABG. Two years after the index procedure, 128 patients (80% of eligible patients) were assessed by contrast angiography and 51 patients (96 SVG) underwent IVUS imaging of the study grafts.

Angiography and Intravascular Ultrasound

SVG patency at 2 years was not significantly different between the stented and nonstented groups (78.3% vs 82.2%, respectively, $P = .432$). In both the stented and nonstented groups, SVG occlusion rates were similar in the left (23.6% stented vs 20% nonstented) and right (19.7% stented vs 15.7% nonstented) coronary territories. Intraoperative flow rates and pulsatility index did not differ between the subsequently early (6 months) occluded (49.7 ± 32.1 mL/

min, 2.4 ± 0.7 , respectively, $N = 24$) and patent SVG (53.8 ± 30.9 mL/min, 2.4 ± 2.7 , respectively, $N = 207$).

As shown in Table 4, the primary end point analysis demonstrated that patent grafts, as graded by the Fitzgibbon scale, were significantly less likely to have intimal irregularities in stented versus nonstented grafts (odds ratio, 2.02; $P = .03$). Likewise, there was less SVG ectasia in stented versus nonstented grafts (4.8% vs 11.3%, respectively, $P = .078$). The Fitzgibbon scale was inversely related to SVG minimal lumen diameter (MLD) with Fitzgibbon I, II, and III SVG having an average MLD of 2.62 mm, 1.98 mm, and 1.32 mm, respectively ($P < .05$).

As shown in Table 5, intimal hyperplasia area and thickness were both significantly reduced in the stented

TABLE 4. Angiographic findings 2 years after coronary artery bypass grafting

	VEST N = 138% (n)	Control N = 135% (n)	P value
Vein graft occlusion	21.7% (30)	17.8% (24)	.4315 (OR, 1.278)
Vein graft patency	78.3% (108)	82.2% (111)	
Fitzgibbon I	66.7% (72)	54.9% (61)	.031 (OR, 2.02)
Fitzgibbon II	27.8% (30)	34.3% (38)	
Fitzgibbon III	5.5% (6)	10.8% (12)	
Correlation analysis of QCA MLD vs Fitzgibbon (I, II, III)			
Fitzgibbon classification	MLD (mm)		P value
I	2.62 (2.41, 2.82)		
II	1.98 (1.66, 2.31)		
III	1.31 (0.69, 1.92)		
I vs II	-0.63 (-1.00, -0.27)		.001
I vs III	-1.31 (-1.95, -0.67)		<.001
II vs III	-0.68 (-0.00, -1.36)		.051

The upper portion compares 2-years angiographic data on graft occlusion rates and FPS (I-III) between externally stented saphenous venous grafts and controls. The lower portion shows the relevance of the Fitzgibbon scale with regard to graft degeneration due to its close correlation with minimal lumen diameter. Between-group comparison of vein graft patency at 2 years was performed using logistic regression with random subject effects. Between-group comparison of Fitzgibbon classifications was performed using ordinal multinomial regression with random subject effects. Correlation analysis comparing minimal lumen diameter between each pair of Fitzgibbon classifications was performed using a mixed model with random subject effects. VEST, Venous external stent; OR, odds ratio; QCA, quantitative coronary angiography; MLD, minimal lumen diameter.

TABLE 5. Intravascular ultrasound–based measurements 2 years after coronary artery bypass grafting

	VEST N = 50 Mean (95% CL)	Control N = 46 Mean (95% CL)	% Difference	P value
IH area [mm ²]	3.07 (2.70, 3.44)	3.96 (3.58, 4.34)	–22.5%	<.001
IH thickness [mm]	0.26 (0.23, 0.29)	0.34 (0.31, 0.37)	–23.5%	<.001
IVUS average lumen diameter [mm]	3.51 (3.32, 3.69)	3.34 (3.14, 3.53)	5%	.106
IVUS findings for Fitzgibbon grade I SVGs only				
	N = 39	N = 25	% Difference	P value
IH area [mm ²]	2.75 (2.40, 3.09)	3.86 (3.42, 4.29)	–28.7%	<.001
IH thickness [mm]	0.23 (0.20, 0.25)	0.31 (0.28, 0.34)	–25.8%	<.001
IVUS average lumen diameter [mm]	3.57 (3.36, 3.77)	3.66 (3.40, 3.91)	–2.5%	.577
Correlation between IH thickness and minimal lumen diameter and lumen area			Coefficient	P value
IH thickness vs IVUS minimal lumen diameter			–0.28	.01
IH thickness vs IVUS lumen area			–0.24	.02
IH thickness vs QCA minimal lumen diameter			–0.27	.02

The upper portion shows the differences in intimal thickness, intimal area, and average lumen diameter between all SVGs the VEST and control groups at 2 years as measured by IVUS. The central portion shows this comparison exclusively for Fitzgibbon grade I grafts. The lower portion shows the correlation between intimal thickness and the minimal lumen diameter and area as measured by IVUS, as well as the correlation between intimal thickness and minimal lumen diameter as measured by qualitative coronary angiography. Between-group comparison of IVUS findings was performed using a mixed model with random subject effects. Correlation coefficients and *P* values were calculated using Pearson correlation. CL, Confidence level; IH, intimal hyperplasia; IVUS, intravascular ultrasound; SVG, saphenous vein graft; QCA, quantitative coronary angiography; CABG, coronary artery bypass grafting.

compared with the nonstented grafts (–22.5% and –23.5%, respectively, *P* < .001). When analyzing only Fitzgibbon I SVG, differences in intimal hyperplasia area and thickness between stented and nonstented groups remained highly significant (–28.7% and –25.8%, respectively, *P* < .001). A significant correlation among intimal hyperplasia thickness, MLD, and lumen area was also observed.

For all groups of randomized and additional vein grafts (*n* = 294), patency at 2 years was significantly better when veins were harvested by use of an open (*n* = 193) compared with an endoscopic (*n* = 101) surgical technique (88.6% vs 65.3%, *P* < .001). The effect of harvesting technique on SVG patency was observed in both the stented (87.8% open vs 60.4% endoscopic) and nonstented groups (88.8% open vs 69.6% endoscopic).

SVG patency at 6 months was not significantly different between the stented and nonstented groups (86.7% vs 90.9%, respectively, *P* = .22). In both study groups, patency rates at 6 months were higher when veins were harvested with an open technique (91.1% stented and 94.6% nonstented, *P* = .31) compared with an endoscopic surgical technique (77.4% stented and 83.3% nonstented, *P* = .44).

Major Adverse Cardiac and Cerebrovascular Events

The overall composite MACCE rate at 2 years was 12% (22 of 183). The all-cause mortality, stroke, and myocardial infarction rates at 2 years were 2.7% (5 of 183), 3.3% (6 of 183), and 2.7% (5 of 183), respectively. Ischemia-driven revascularization was performed in 6% (11 of 183) of patients. Reinterventions were more frequently driven by

ischemia in the nonstented territory, 3.8% (7 of 183), than in the stented territory, 2.2% (4 of 183).

DISCUSSION

As explained previously, external stenting for SVG is not primarily designed to mitigate early SVG failure but instead to prevent disease progression over the longer term. With respect to its primary and secondary end points, the current VEST III trial reveals that 2 years after CABG, external stenting mitigates SVG disease progression by significantly improving SVG Fitzgibbon patency and reducing diffuse intimal hyperplasia. Another novel observation is that both angiographic and IVUS findings were significantly correlated with changes in SVG MLD.

Our study has a number of methodological strengths: With 184 patients, VEST III is, by far, the largest randomized clinical trial to evaluate the potential benefit of external stenting on SVG disease progression. The study design included the use of individual patients to act as their own control to eliminate patient-related factors that could potentially influence SVG disease. The successful avoidance of selection bias could influence the balance of baseline grafting parameters by postponing randomization of vein grafts to the external stent until completion of all distal anastomoses. The use of several imaging modalities at different time points provides deeper insights into SVG disease mechanisms, enabling accurate mapping of the different failure modes of SVGs over time.

The importance of trying to mitigate progression of vein graft disease development is underpinned by the landmark publication of Fitzgibbon and colleagues,¹⁸ demonstrating that SVGs undergo progressive remodeling, resulting in

lumen irregularities and eventual SVG occlusion. At 5, 10, and 15 years, occlusion rates were 25%, 40%, and 50%, respectively; of the remaining nonoccluded SVGs and perfect patency (Fitzgibbon I) rates were 52%, 23%, and 19%, respectively. In addition, 5 and 15 years after CABG, 42% and 44% of the Fitzgibbon II and III SVGs, respectively, developed high profile lesions with more than 50% lumen stenosis.¹⁸

The prognostic value of FPS was demonstrated in the longitudinal studies by Fitzgibbon and colleagues,²¹ which found a direct correlation between FPS and late SVG occlusion. Some 28% of SVGs with FPS II or III 1 year post-CABG were occluded at 5 years compared with only 10% of those with FPS I ($P < .0005$). This correlation between lumen irregularities and SVG occlusion was also demonstrated over a longer follow-up period with 39% of irregular SVGs at 5 years occluded 10 years after CABG compared with only 20% of the perfectly patent SVGs ($P < .001$).²⁰ In addition, there was a significant difference in late occlusion rates between FPS II and III, with the latter showing an approximately 3 times higher occlusion rate.^{20,21}

Imaging-derived correlates of restenosis propensity, such as MLD and late lumen loss, are powerful efficacy end points that provide additional trend data in patients who have not (yet) developed a major clinical adverse event.²² Indeed, similar angiographic measurements have been used to assess other potentially therapeutic treatments such as lipid-lowering agents, as in the POST-CABG TRIAL.²² Similar to the MLD differences according to the Fitzgibbon classification groups observed in our study, in the POST-CABG TRIAL, clinically significant reduction in MLD was predefined as a reduction of more than 0.6 mm in MLD compared with baseline. At 5 to 16 years after CABG, MLD deterioration was found to be significantly lower with the aggressive use of lipid-lowering agents, but this reduction also correlated well with an improved SVG patency rate.^{22,23}

In the current trial, the ability of the external stent to significantly reduce diffuse intimal hyperplasia over the entire length of 96 SVG compares well with the findings in the CASCADE trial in which a combination of clopidogrel and aspirin resulted in a insignificant decrease of 7% in intimal hyperplasia in a more limited examination of the proximal segment of 91 SVGs.²⁴ The within-patient control design in VEST III and the fact that all patients in the trial received statins and aspirin strongly suggest that the beneficial effects of external stenting with regard to the mitigation of intimal hyperplasia and the promotion of lumen uniformity were adjunctive to any effect of the medical therapy. In addition, a novel finding in our study was that uniform (Fitzgibbon I) grafts in the nonstented group still showed significantly more intimal hyperplasia than the stented uniform grafts.

The majority of SVG occlusions (68.4%) occurred during the first 6 months. These early failures are usually due to technical errors, SVG trauma during harvesting, poor-quality conduit, or poor coronary runoff rather than the development of intimal hyperplasia.^{2,3} In the current study, the use of an endoscopic vein harvesting (EVH) technique in some of the study centers seemed to contribute to early vein graft failure. Although EVH was used in only 31.1% of the cases overall, it was associated with 63.3% and 58.3% of the total SVG occlusions in the stented and nonstented groups, respectively. Although EVH may be associated with higher SVG failure rates,²⁵ recent data also suggest that the quality of the conduit is highly dependent on the experience of the harvester.²⁶ In our trial, EVH experience was not mandated, and differences were observed in EVH experience and SVG patency between centers that used this technique.

Study Limitations

In contrast to routine clinical follow-up, maintaining patient enthusiasm for and acceptance of repeat angiography is a well-recognized difficulty in prospective trials as previously documented in the ROOBY trial (overall retention rate of 62% at 1 year), PREVENT IV (overall retention rate of 73% at 18 months), and CASCADE trial (overall retention rate of 79% at 1 year).^{22,27,28} Taking into account the longer duration of follow-up of our study and that most of the patients had also undergone CT angiography at 6 months, VEST III compares favorably to previous studies as at 2 years, with 70% of the overall cohort and 80% of eligible patients undergoing protocol-driven angiography.

The VEST III sample size remains relatively small ($n = 184$), and the currently reported duration of follow-up is limited. Furthermore, although the within-patient randomization design is essential to eliminate other patient-related factors that can affect vein graft disease, it cannot currently address the question whether the observed reduction in vein graft disease progression with external stenting will ultimately lead to improved patency and consequently anticipated clinical benefits.

CONCLUSIONS

Two years after CABG, external stenting of saphenous grafts leads to improved Fitzgibbon patency and significantly reduces SVG disease progression by reducing both the volume and the thickness of intimal hyperplasia. Whether this stabilization of the SVG wall with an external stent will ultimately lead to a reduction in vein graft failure and improved clinical benefits to the patient is not yet known and mandates longer-term follow-up.

Conflict of Interest Statement

D.P.T. has received research funding and speaking and traveling fees from Vascular Graft Solutions, and has share

options with Vascular Graft Solutions. M.N.B. has received speaking fees from Vascular Graft Solutions for reporting the Blackpool experience with VEST. L.L. reports grants from Vascular Graft Solutions during the conduct of the study. M.B. received financial support from Vascular Graft Solutions for the hospital research and development department in connection with the study. S.S. reports grants, personal fees, and other support from Vascular Graft Solutions. I.F. has received proctoring fees from Vascular Graft Solutions. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: CABG, external bypass stent, Fitzgibbon patency, intimal hyperplasia, long-term patency, venous grafts

APPENDIX E1: STATISTICAL MODEL SPECIFICATIONS

Details on the 3 statistical methodologies used in the study:

1. Ordinal multinomial regression that was used for the ordinal Fitzgibbon score
2. Logistic regression that was used for all binary variables (Success/Failure)
3. Linear (mixed model) regression that was used for all continuous variables (IH parameters).

Ordinal Multinomial Regression (Primary Analysis)

The primary end point was analyzed using proportional odds ordinal multinomial regression, with random intercept (defined per subject). In this model, we estimated the following probabilities:

1. Probability of having Fitzgibbon 1 versus Fitzgibbon 2 and 3
2. Probability of having Fitzgibbon 1 and 2 versus Fitzgibbon 3

For each probability, a separate model was fit, where the intercepts are different, but the group coefficient is the same. In other words, this model assumes that though the overall odds of any event can differ, the effect of the graft group (VEST/control) on the odds of an event occurring in every subsequent category is the same for every category.

The model is:

$$\text{logit}(\text{Prob.Fitz 1 vs Fitz 2\&3}) = (\beta_{01} + \delta) + \beta_1 I\{\text{Group} = \text{VEST}\} + \varepsilon$$

$$\text{logit}(\text{Prob.Fitz 1\&2 vs Fitz 3}) = (\beta_{02} + \delta) + \beta_1 I\{\text{Group} = \text{VEST}\} + \varepsilon$$

In this logistic regression, intercepts represent the rate of Fitzgibbon 1 and Fitzgibbon 1 and 2 in the control group (after anti-logit transformation), whereas the group coefficient represents the odds ratio.

For convenience, we provide the full output.

Covariance parameter	Estimate	Standard error
δ^2	1.3672	0.8783

Effect	Estimate	Standard error	t DF	Pr > t	95% CIs
β_{01}	0.2135	0.2413	123 0.88	0.3780	
β_{02}	2.6437	0.4056	123 6.52	<0.0001	
β_1 (VEST)	0.7018	0.3209	93 2.19	0.0312	(0.0728-1.3308)

The odds ratio, is then, given by

$$\text{odds ratio} = \exp(0.7018) = 2.017, 95\% \text{ CI } (1.07-3.82).$$

Logistic Regression (Vein Graft Occlusion/Patency)

Analysis of binary variables was done using logistic regression with random by-subject intercept.

$$\text{logit}(P) = (\beta_{01} + \delta) + \beta_1 I\{\text{Group} = \text{VEST}\} + \varepsilon$$

In this logistic regression, intercept represents the rate of successes in the control group (after anti-logit transformation), whereas the group coefficient represents the odds ratio. Both quantities are reported in Table 4. The only element that was not reported in Table 4 (which is typically not reported) is the variance between by-subjects intercepts.

For convenience we provide the full output.

Covariance parameter	Estimate	Standard error
δ^2	0.8246	0.4410

Effect	Estimate	Standard error	t DF	Pr > t	95% CIs
β_{01}	-1.5655	0.2421	138 -6.47	<.0001	
β_1 (VEST)	0.2453	0.3109	133 0.79	0.4315	(-0.36, 0.85)

The odds ratio, is then, given by

$$\text{odds ratio} = \exp(0.2453) = 1.28, 95\% \text{ CI } (0.69-2.36).$$

Linear (Mixed Model) Regression (IH Area, Thickness, Average Lumen Diameter)

Analysis of continuous variables was done using mixed linear regression with random by-subject intercept.

$$\text{IHParameter} = (\beta_{01} + \delta) + \beta_1 I\{\text{Group} = \text{VEST}\} + \varepsilon$$

Where δ is the standard deviation between the subjects' intercepts and ε is the residual standard deviation.

In this linear regression, intercept represents the average value of the examined parameter in the control group, whereas the group coefficient represents the difference between the groups. Table 4 reports only the differences (group coefficients). Table 5 reports both coefficients.

For convenience, we provide the full output.

Dependent variable	Covariance parameter	Estimate	Standard error
IH area	δ^2	0.8256	0.2706
	ε^2	0.8624	0.1806
IH thickness	δ^2	0.004720	0.001680
	ε^2	0.005837	0.001226
Average lumen diameter	δ^2	0.1743	0.06888
	ε^2	0.2551	0.05421
IH area Fitzgibbon I only	δ^2	0.7034	0.2705
	ε^2	0.4982	0.1629
IH thickness Fitzgibbon I only	δ^2	0.002407	0.001629
	ε^2	0.003933	0.001362
Average lumen diameter Fitzgibbon I only	δ^2	0.1818	0.08083
	ε^2	0.2202	0.06424

Dependent variable	Effect	Estimate	Standard error	95% CI	DF	t value	P value
IH area	β_{01}	3.9627	0.1893		50	20.93	<.0001
	β_1 (VEST)	-0.8962	0.1927	(-1.2844, -0.5079)	44	-4.65	<.0001
IH thickness	β_{01}	0.3389	0.01500		50	22.59	<.0001
	β_1 (VEST)	-0.08102	0.01583	(-0.1129, -0.0491)	44	-5.12	<.0001
Average lumen diameter	β_{01}	3.3350	0.09584		50	34.80	<.0001
	β_1 (VEST)	0.1723	0.1045	(-0.0383, 0.3830)	44	1.65	.1063
IH area Fitzgibbon I only	β_{01}	3.7981	0.2037		42	18.64	<.0001
	β_1 (VEST)	-0.9879	0.2008	(-1.4067, -0.5692)	20	-4.92	<.0001
IH thickness Fitzgibbon I only	β_{01}	0.3084	0.01547		42	19.94	<.0001
	β_1 (VEST)	-0.07590	0.01718	(-0.1117, -0.04008)	20	-4.42	.0003
Average lumen diameter Fitzgibbon I only	β_{01}	3.6093	0.1216		42	29.69	<.0001
	β_1 (VEST)	-0.04893	0.1302	(-0.3205, 0.2227)	20	-0.38	.7111

CI, Confidence interval; DF, degrees of freedom; IH, intimal hyperplasia; VEST, venous external stent.