Sequential multidetector computed tomography assessments after venous graft treatment solution in coronary artery bypass grafting

Louis P. Perrault, MD, PhD,[a] Michel Carrier, MD,[a] Pierre Voisine, MD,[b] Peter Skov Olsen, MD,[c] Nicolas Noiseux, MD,[a] Hugues Jeanmart, MD,[d] Filippo Cardemartiri, MD, PhD,[a,e] Dave Veerasingam, MD,[f] Craig Brown, MD,[g] Marie-Claude Guertin, PhD,[h] Vilas Satishchandran, MS,[i] Tracy Goeken, MD,[i] and Maximilian Y. Emmert, MD, PhD[j,k]

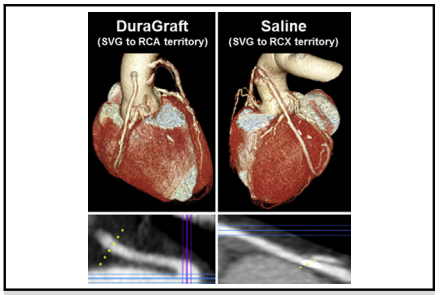
ABSTRACT

Objectives: To assess the effect of DuraGraft (Somahlution Inc, Jupiter, Fla), an intraoperative graft treatment, on saphenous vein grafts in patients undergoing isolated coronary artery bypass grafting.

Methods: Within patients, 2 saphenous vein grafts were randomized to DuraGraft or heparinized saline. Multidetector computed tomography angiography at 1, 3, and 12 months assessed change in wall thickness (primary end point at 3 months), lumen diameter, and maximum narrowing for the whole graft and the proximal 5-cm segment. Safety end points included graft occlusion, death, myocardial infarction, and repeat revascularization.

Results: At 3 months, no significant changes were observed between DuraGraft- and saline-treated grafts (125 each) for wall thickness, lumen diameter, and maximum narrowing. At 12 months, DuraGraft-treated grafts demonstrated smaller mean wall thickness, overall (0.12 ± 0.06 vs 0.20 ± 0.31 mm; $P = .02$) and in the proximal segment (0.11 ± 0.03 vs 0.21 ± 0.33 mm; $P = .01$). Changes in wall thickness were greater in the proximal segment of saline-treated grafts (0.09 ± 0.29 vs 0.00 ± 0.03 mm; $P = .04$). Increase in maximum graft narrowing was larger in the proximal segment in the saline-treated grafts (4.7% ± 12.7% vs 0.2% ± 3.8%; $P = .01$). Nine DuraGraft and 11 saline grafts had occluded or thrombosed. One myocardial infarction was associated with a saline graft occlusion. No deaths or revascularizations were observed.

Conclusions: DuraGraft demonstrated a favorable effect on wall thickness at 12 months, particularly in the proximal segment. Longer-term follow-up in larger studies is needed to evaluate the effect on clinical outcomes. (J Thorac Cardiovasc Surg 2021;161:96-106)



Case example showing smaller wall thickness in DuraGraft-treated SVG (Somahlution Inc, Jupiter, Fla) (0.1 vs 0.5 mm) at 12 months.

CENTRAL MESSAGE

SVGs treated with DuraGraft (Somahlution Inc, Jupiter, Fla) demonstrated favorable results regarding wall thickness and various other SVG characteristics versus SVGs treated with saline in patients undergoing CABG.

PERSPECTIVE

Patency loss of SVGs due to VGD hampers long-term outcomes after CABG. Sufficient intraoperative graft preservation to protect the SVG endothelium can reduce the occurrence of VGD. In this within-patient study, SVGs treated with DuraGraft (Somahlution Inc, Jupiter, Fla), an endothelial damage inhibitor, showed favorable results for wall thickness and other characteristics after CABG, which may improve outcomes.

See Commentaries on pages 107 and 109.

From the [a]Department of Surgery, Montreal Heart Institute, Montréal, Québec, Canada; [b]Institut Universitaire de Cardiologie et de Pneumologie, Québec City, Québec, Canada; [c]Rigshopitalet University of Copenhagen, Copenhagen, Denmark; [d]Hôpital du Sacré-Coeur de Montréal, Montréal, Québec, Canada; [e]SDN IRCCS, Naples, Italy; [f]Galway University Hospital, Galway, Ireland; [g]New Brunswick Heart Centre, Saint John, New Brunswick, Canada; [h]Montreal Health Innovations Coordinating Center, Montreal, Québec, Canada; [i]Somahlution, Jupiter, Fla; [j]Department of Cardiovascular Surgery, Charité Universitätsmedizin Berlin, Berlin, Germany; and [k]Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, Berlin, Germany.

Read at the 99th Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, May 4-7, 2019.

Received for publication May 7, 2019; revisions received Oct 21, 2019; accepted for publication Oct 21, 2019; available ahead of print Nov 9, 2019.

Address for reprints: Louis P. Perrault, MD, PhD, Department of Surgery, Montreal Heart Institute, 5000 Belanger St E, Montréal, Québec, H1T 1C8 Canada (E-mail: louis.perrault@icm-mhi.org).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.10.115

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
MDCT = multidetector computed tomography
SVG = saphenous vein graft
TVD = total vessel diameter
VGD = vein graft disease
VGF = vein graft failure

Scanning this QR code will take you to the article title page to access supplementary information. To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.

Coronary artery bypass grafting (CABG) is the gold standard for multivessel coronary disease.[1,2] However, loss of patency in saphenous vein grafts (SVGs) due to vein graft disease (VGD) and consecutive vein graft failure (VGF) remains a concern after CABG, potentially resulting in long-term complications.[3,4] VGF rates after CABG range from 10% to 25% at 12 months,[5] and can reach 50% at 10 years.[3,6,7] Multiple factors influence long-term SVG patency, including the quality of the target vessel and the anastomosis; bypass run-off; postoperative medical therapy; progression of coronary artery disease; and in particular, the quality of the SVG itself, which strongly depends on harvesting and handling as well as intraoperative storage and preservation.[3,8-10] Besides the need for sophisticated, state-of-the-art atraumatic harvesting techniques and avoidance of excessive handling (including distension), several ex vivo studies have highlighted the importance of sufficient intraoperative graft preservation to reduce the occurrence of VGD and VGF.[11-15] This important aspect was further emphasized in a recent subanalysis of the Project of Ex-Vivo Vein Graft Engineering via Transfection IV trial, which showed that the currently used intraoperative standards (ie, saline-based solutions or autologous whole blood) may not sufficiently preserve the structure and function of SVGs in the period of ischemic storage during CABG.[7]

DuraGraft (Somahlution Inc, Jupiter, Fla) is a 1-time intraoperative graft treatment that inhibits endothelial damage during CABG. In ex vivo studies, DuraGraft (formerly Gala) has proven superior to standard treatments in terms of preserving endothelial function and structural viability.[11,16] In this randomized trial, using a within-patient design and sequential multidetector computed tomography (MDCT) angiographies, the safety and efficacy of DuraGraft versus heparin-dosed saline were assessed at 1, 3, and 12 months post-CABG.

MATERIALS AND METHODS

Trial Design and Trial Population

The trial is registered at www.ClinicalTrials.gov (identifiers: NCT02272582 and NCT02774824) and the study design has been reported previously.[17] Briefly, the trial was a prospective, multicenter, randomized, double-blind, comparative within-patient study that compared the effect of DuraGraft versus heparin-dosed saline in patients undergoing isolated first-time CABG for multivessel coronary artery disease and requiring 2 SVGs (Online Data Supplement). The enrollment criteria are detailed in Appendix E1.

The trial was carried out at seven investigational sites in Canada, Ireland, and Denmark.[17] The first patient was enrolled in September 2014 and the last patient in December 2016. In addition to the 119 patients enrolled during this period, a further 6 patients underwent the same protocol plus a histological evaluation of the vein grafts, and their clinical data are included in this analysis. Follow-up with MDCT imaging (with an approximate dose of 24 millisieverts) was performed at 1 month (4-6 weeks) and 3 months; following approval of an extension protocol (April 2015), MDCT imaging was also performed at 12 months. Approval was obtained from the ethics committees at each site. All patients provided written informed consent before enrollment and were reconsented for the extension of follow-up. Distribution of patients across study sites is summarized in the Table E1.

Preservation Solution

DuraGraft is a 1-time intraoperative treatment to protect against damage to the structure and function of the vascular endothelium. It is formulated into an ionically and pH-balanced physiological salt solution containing glutathione, L-ascorbic acid, and L-arginine, and other components that protect the conduit from the damaging effects of ischemia (during storage) and reperfusion injury during CABG.[17] Grafts randomized to the standard of care were treated with a heparinized saline solution as routinely used at participating centers.

Randomization Schedule

Two SVGs from each patient were randomized to treatment with DuraGraft or saline using a balanced allocation scheme stratified for target region A (circumflex or diagonal or other) and target region B (right coronary system or diagonal or other), and proximal versus distal segments of the harvested SVG. The surgeon and other operating room staff were blinded to the solutions used for the SVGs.

Vein Harvesting and CABG Procedures

Preoperative clinical evaluation of SVG quality and size was performed using ultrasound, as needed. SVGs were harvested by either open or endoscopic techniques, and avoiding overdistension, excessive handling or distortion, to minimize damage to the endothelium. After harvest, each SVG segment was divided into a proximal and a distal segment, which were randomly assigned to the 2 different target regions. Each segment was carefully flushed with, and stored in, the assigned treatment solution for a minimum of 15 minutes. Use of on-pump or off-pump techniques was at the discretion of the surgeon. Flow measurements were performed using a hand-held flow meter after reperfusion and before chest closure.

Image Acquisition

The detailed protocol was adapted from Lau and colleagues[18] and has been reported previously.[17] In brief, MDCT angiography was done using a 64-slice (or better) scanner. Metoprolol 50 to 100 mg was administered

with a targeted heart rate below 60 beats per minute. A noncontrast electrocardiogram-synchronized computed tomography scan was performed. Contrast material synchronization was done using test bolus or bolus-tracking techniques. Nonionic iodinated contrast material was used for vascular enhancement in the angiographic phase. A contrast-enhanced scan was carried out using intravenous contrast according to locally optimized protocols. All images were taken during a single breath-hold. To ensure consistency between patients, scans were reconstructed using a soft convolution kernel from a data acquisition window centered at 70% of the RR interval. When available, iterative reconstruction algorithms were applied to improve image quality and to reduce background image noise.[17]

Image Analysis

A centralized core laboratory uploaded the anonymized Digital Imaging and Communications in Medicine files onto a software platform for evaluation (SyngoVia; Siemens Medical Solutions, Forchheim, Germany). Each SVG was evaluated using a semiautomated vessel-tracking algorithm to stretch the SVG along a straight line from the ostium to the distal anastomosis allowing measurements at 10-mm spatial intervals and comparability of the same SVG at different time points. The parameters measured were total vessel diameter (TVD) and lumen diameter. Measurements of the TVD and lumen diameter were measured on postcontrast scans. Lumen diameter and TVD were assessed every 10 mm from the ostium, with these segmental measurements averaged for each graft for the analysis. Wall thickness was calculated with the formula:

$$\frac{(\text{TVD} - \text{lumen diameter})}{2}$$

Narrowing was calculated at each location of the graft by subtracting the lumen diameter from the TVD and dividing the result by the TVD. The maximum value of all narrowings measured within each graft was multiplied by 100 for conversion into percentage of TVD. When noncontrast computed tomography did not grant sufficient image quality for evaluation, TVD was obtained on postcontrast scans. All MDCT images were evaluated by a single radiologist (FC), who was blinded to the storage solution used.

Study End Points

The primary short-term efficacy end point was the change in wall thickness between 1 and 3 months. The primary long-term efficacy end point was the change in maximum narrowing between 1 and 12 months. Other efficacy end points were the MDCT angiography measurements at 3 and 12 months and the changes over time between measurements at 1 and 3 months, and between 1 and 12 months, for wall thickness, lumen diameter, maximum narrowing, and vessel diameter obtained for the whole graft. In addition, a post hoc analysis on the proximal 5 cm of the graft was performed. The safety outcomes were the incidence of vein graft thrombosis and occlusion, major adverse cardiac events (ie, death, myocardial infarction, or repeat revascularization), increased angina, arrhythmias, shortness of breath, and significant stenosis based on Fitzgibbon class B and O. Safety end points were adjudicated by an independent, blinded review committee to determine whether the events could be attributed to a graft-level event.

Statistical Analysis

For the primary short-term end point of change in mean wall thickness between 1 and 3 months, assuming an effect size of at least 0.30 ([difference between DuraGraft and saline in change in mean wall thickness]/standard deviation of the change), 90 patients with 2 grafts each treated with DuraGraft or saline would yield 80% power using a 2-sided type I error of 0.05.[17] To account for any nonmeasurable grafts or dropouts during the trial period, at least 100 patients had to be enrolled to meet the targeted evaluable cohort of at least 90 patients (180 SVGs).

Continuous variables are presented as mean ± standard deviation and median (first quartile, third quartile). Categorical variables are presented as counts and percentages. For wall thickness and maximum stenosis at each time point, as well as for the changes over time, the 2 groups (DuraGraft and saline) were compared using Wilcoxon signed rank tests because of the nonnormal distribution. For lumen and vessel diameter, linear mixed models, including terms for group, target region, time and group × time interaction, were used. The incidence of safety end points is presented using counts and proportions, and also using number of events per patient follow-up year to account for the patients that discontinued participation after 3 months. Proportions of patients with events were compared between groups using McNemar tests. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and were based on the intention-to-treat population.

MDCT data for grafts that were not analyzable because of a total occlusion were imputed. For maximum stenosis and lumen diameter, the imputed values were, respectively, the maximum stenosis and the minimum lumen diameter of the subjects with nonoccluded grafts in the same treatment arm at that visit. For TVD and wall thickness, the imputed values were derived from the imputed values of stenosis and lumen diameter in the same treatment arm at that visit. If no MDCT was performed at a follow-up visit, missing follow-up data were imputed using the last observation carried forward (Online Data Supplement).

RESULTS

Patient Characteristics and Preoperative Status

Of 224 patients screened for eligibility, 125 (mean age, 66.2 ± 6.8 years) were randomized and underwent CABG. Patients presented with typical cardiovascular risk profiles, including diabetes (32.8%), hypertension (86.4%), and dyslipidemia (90.4%) (Table 1). Forty-six patients (36.8%) had a history of myocardial infarction and small proportions had cerebrovascular (8.8%) or peripheral vascular (6.4%) disease. The majority of patients underwent elective CABG surgery (n = 85; 68.0%). Most patients had 3-vessel disease (n = 104; 83.2%); left main disease (≥50%) was present in 36.8% of patients. Mean left ventricular ejection fraction was 56.4% ± 6.0%. Mean Society of Thoracic Surgeons score for mortality was 0.9 ± 0.6 and mean European System for Cardiac Operative Risk Evaluation II score was 1.1 ± 0.6.

Procedure Data and Graft-specific Characteristics

Procedural data are summarized in Table 2 and graft-specific characteristics in Table 3. SVG harvesting was performed using an open approach in 91 patients (72.8%); the remaining 34 patients (27.2%) underwent endoscopic vein harvesting. A total of 203 SVGs were harvested (95 from the thigh and 108 from the lower leg), from which 125 grafts that were long enough to be divided into a proximal part and a distal part, were selected for the study. The remaining SVGs were used for other bypasses. Mean exposure times in the 2 treatment solutions were similar (36.0 ± 24.3 minutes for DuraGraft, 36.6 ± 21.3 minutes for saline). Segments in both groups were similar in regard to their size, quality, target region

TABLE 1. Patient baseline characteristics (N = 125)

Characteristic	Result
Age (y)	66.2 ± 6.8
Age range (y)	48-78
Men	114 (91.2)
Body mass index	28.6 ± 4.6
Former or current smoker	87 (69.6)
Family history of coronary artery disease*	65 (61.3)
Diabetes mellitus	41 (32.8)
Dyslipidemia	113 (90.4)
Hypertension	108 (86.4)
Previous myocardial infarction	46 (36.8)
Cerebrovascular disease	11 (8.8)
Peripheral vascular disease	8 (6.4)
Respiratory disease	11 (8.8)
Society of Thoracic Surgeons score parameter	
Mortality	0.9 ± 0.6
Permanent stroke	0.8 ± 0.3
Renal failure	1.7 ± 1.2
Prolonged ventilation >24 h	7.6 ± 4.7
Deep sternal wound infection	0.2 ± 0.1
Complications	10.7 ± 4.8
Reoperation	4.1 ± 1.2
European System for Cardiac Operative Risk Evaluation II score	1.1 ± 0.6
Procedure status: Elective	85 (68.0)
Left main stenosis ≥50%	46 (36.8)
No. of diseased vessels	
2	7 (5.6)
3	104 (83.2)
4	14 (11.2)
Left ventricular ejection fraction (%)	56.4 ± 6.0

Values are presented as mean ± standard deviation or n (%). *Data available for 106 patients.

(A or B), and distal target vessel grafted. Approximately 10% of SVG segments showed signs of irregularities and varicosities. The target vessel size for all distal vessels was approximately 2 mm (1.9 ± 0.6 mm for DuraGraft and 1.8 ± 0.6 mm for saline).

TABLE 2. Operative characteristics and surgical data (N = 125)

Characteristic	Result
Surgery duration (min)	195 ± 51
Use of cardiopulmonary bypass	118 (94.4)
On-pump with cardioplegia*	117 (98.3)
Hybrid on-pump with beating heart*	1 (0.8)
Cardiopulmonary bypass duration* (min)	80 ± 28
Crossclamp time† (min)	52 ± 25

Values are presented as mean ± standard deviation or n (%). *n = 118. †n = 117.

TABLE 3. Intraoperative DuraGraft (Somahlution, Jupiter, Fla) and saline graft characteristics

Characteristic	DuraGraft (n = 125)	Saline (n = 125)	*P* value
Target region			.5312*
A	66 (52.8)	59 (47.2)	
B	59 (47.2)	66 (52.8)	
Graft length† (cm)	17.1 ± 4.7	17.2 ± 4.9	.7991‡
Graft segment†			.9270*
Proximal	61 (50.0)	62 (50.8)	
Distal	61 (50.0)	60 (49.2)	
Grafting areas			.9983§
Circumflex	17 (13.6)	11 (8.8)	
Diagonal	14 (11.2)	21 (16.8)	
Ramus intermedius	7 (5.6)	4 (3.2)	
Left posterolateral	0	1 (0.8)	
Obtuse marginal	40 (32.0)	34 (27.2)	
Posterior descending	2 (1.6)	6 (4.8)	
Posterior interventricular	19 (15.2)	18 (14.4)	
Right coronary system	24 (19.2)	27 (21.6)	
Right posterolateral	2 (1.6)	3 (2.4)	
Vein external diameter (mm)	4.3 ± 1.3	4.4 ± 1.3	.4382‡
Thin vein-wall thickness‖	28 (22.6)	23/124 (18.5)	.2253*
Poor vein quality	4 (3.2)	4 (3.2)	1.000*
Varicosities	12 (9.6)	11 (8.8)	.7815*
Vein irregularities	12 (9.6)	14 (11.2)	.5637*
Target coronary artery size (mm)	1.9 ± 0.6	1.8 ± 0.6	.8988‡
Solution exposure time (min)	36.0 ± 24.3	36.6 ± 21.3	.7552‡
Suboptimal flow signal frequency	13 (10.4)	8 (6.4)	.1655*
Flow frequency¶ (mL/min)	47.7 ± 30.9	49.7 ± 32.1	.7527‡

Values are presented as mean ± standard deviation or n (%). *McNemar test. †n = 122. ‡Paired *t*-test. §Bowker test. ‖n = 124. ¶n = 26.

Performance Outcomes

The numbers of patients analyzed at each time point are detailed in Figure 1.

Whole graft analysis. There was no difference between the DuraGraft group and the saline group in terms of change in wall thickness between 1 and 3 months (Table 4). Similarly, there was no difference in the change in wall thickness between 1 and 12 months. At 1 and 3 months, there were no differences in wall thickness between treatment groups. However, at 12 months, DuraGraft-treated SVGs had a significantly smaller mean wall thickness versus their saline-treated counterparts ($P = .02$). No significant differences in lumen diameter or maximum narrowing were observed between groups at 1, 3, or 12 months, nor in the changes over time. At 3 and

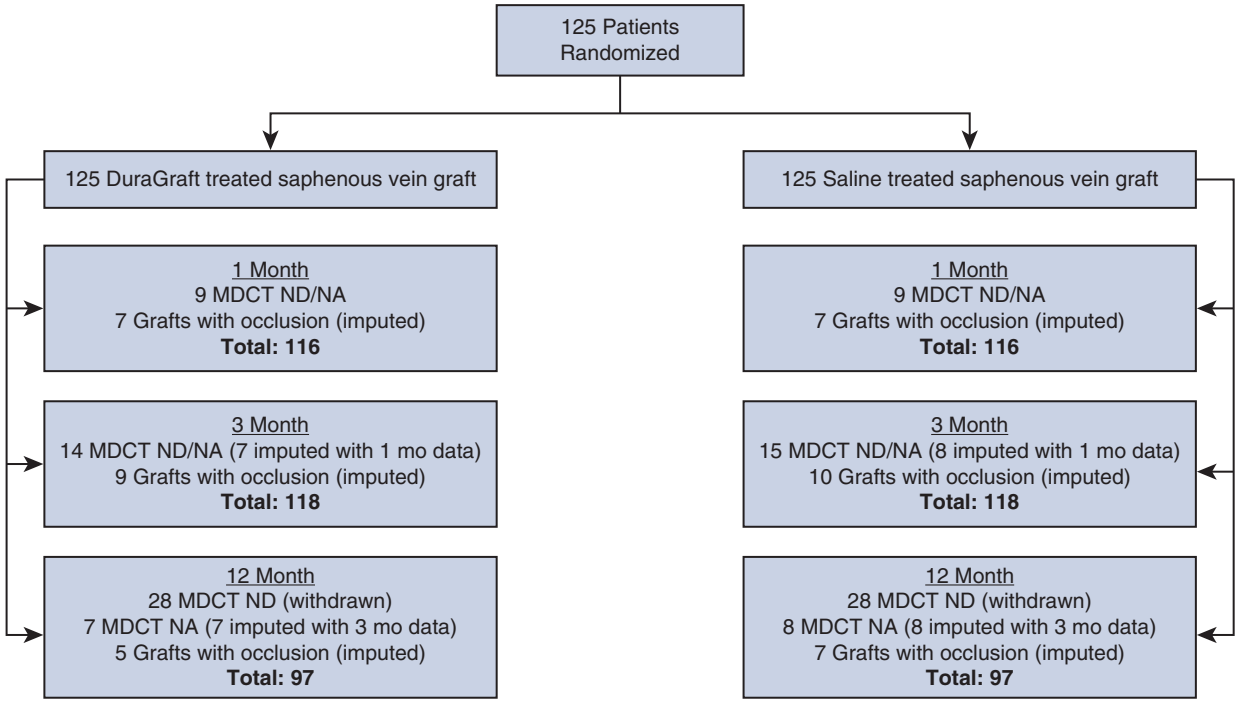


FIGURE 1. Study flow chart (CONSORT diagram). A total of 125 patients were randomized, with 125 grafts treated with DuraGraft versus 125 grafts treated with saline. Grafts were assessed using serial multidetector computed tomography (*MDCT*) at 1 month (n = 116), 3 months (n = 118), and 12 months (n = 97), respectively. Data for grafts that were not able to be analyzed because of a total occlusion were imputed using data from nonoccluded grafts. Missing follow-up data were imputed using the last observation carried forward. Number of occlusions represent the imputed number of occlusions identified at respective time point. *mo*, Month; *ND*, not done; *NA*, not analyzable.

12 months, TVD was significantly lower in the DuraGraft group (Table 4), but no significant differences were observed for the changes from 1 to 3 or 1 to 12 months.

Proximal graft segment analysis. The wall thicknesses in proximal segments of grafts were significantly lower for the DuraGraft- versus saline-treated grafts at 12 months ($P = .01$) (Table 5). The increase in mean wall thickness from 1 to 12 months was also significantly smaller in the DuraGraft group ($P = .04$). The lumen diameter did not differ between the 2 groups at any follow-up time, nor were the changes over time different. The maximum narrowing was not different at 1, 3, or 12 months between the DuraGraft- and saline-treated grafts. The change in maximum narrowing was significantly smaller for the DuraGraft-treated group between 1 and 12 months ($P = .01$). Vessel diameters in the proximal segments were smaller in the DuraGraft group at 3 and 12 months.

Safety Outcomes

The total follow-up was 110.3 patient years. The incidence of events and the number of events per patient-year are detailed in Table 6. In total, 20 SVGs (9 DuraGraft [7.2%] and 11 saline [8.8%]) were thrombosed or occluded during the follow-up period. The majority (n = 19) of the thromboses or occlusions were observed at the 3-month MDCT. There was 1 major adverse cardiac event: a myocardial infarction that was attributed to an occlusion >3 months after surgery in a saline-treated graft (0.8%). There were no deaths or repeat revascularizations. A significant stenosis (Fitzgibbon class B or O) was observed in 2 (1.6%) DuraGraft and 3 (2.4%) saline treated grafts. No statistically significant differences were observed in safety outcomes.

DISCUSSION

In this randomized within-patient trial, the effect of DuraGraft, an endothelial damage inhibitor for intraoperative treatment of SVGs, was evaluated on the SVG by MDCT at 3 different time points after isolated CABG. Favorable changes in morphologic characteristics associated with VGD were observed in the DuraGraft group (Figure 2 and Video 1).

Firstly, DuraGraft-treated SVGs showed a significantly smaller wall thickness at 12 months. Secondly, a trend for a larger increase in maximum graft narrowing from 1 to 12 months in the saline group was observed ($P = .08$). Thirdly, we further performed a post hoc analysis on proximal segments of SVGs, which are prone to VGD due to flow turbulence and increased wall stress near the proximal anastomosis.[19] In proximal segments, as in whole

TABLE 4. Outcomes of multidetector computed tomography (MDCT) analysis in the DuraGraft (Somahlution, Jupiter, Fla) and saline whole grafts at 1, 3, and 12 mo

Outcome	DuraGraft (n = 125)	Saline (n = 125)	*P* value
Mean wall thickness (mm)			
1 mo*	0.11 ± 0.04	0.11 ± 0.03	.23†
	0.10 (0.10, 0.10)	0.10 (0.10, 0.10)	
3 mo‡	0.12 ± 0.09	0.21 ± 0.37	.29†
	0.10 (0.10, 0.10)	0.10 (0.10, 0.10)	
12 mo§	0.12 ± 0.06	0.20 ± 0.31	.02†
	0.10 (0.10, 0.10)	0.10 (0.10, 0.10)	
Change from 1 to 3 mo*	0.01 ± 0.05	0.10 ± 0.34	.98†
	0.00 (−0.00, 0.00)	0.00 (−0.00, 0.01)	
Change from 1 to 12 mo‖	0.01 ± 0.03	0.08 ± 0.27	.35†
	0.00 (−0.00, 0.01)	0.00 (−0.00, 0.01)	
Mean lumen diameter (mm)			
1 mo*	3.38 ± 1.00	3.50 ± 0.98	.25†
	3.26 (2.79, 3.93)	3.47 (2.89, 4.10)	
3 mo‡	3.10 ± 0.92	3.17 ± 0.83	.45†
	3.07 (2.51, 3.59)	3.12 (2.59, 3.76)	
12 mo§	3.08 ± 0.81	3.15 ± 0.82	.48†
	2.96 (2.56, 3.56)	3.11 (2.52, 3.68)	
Change from 1 to 3 mo*	−0.28 ± 0.46	−0.32 ± 0.47	.42†
	−0.20 (−0.56, 0.07)	−0.19 (−0.61, 0.00)	
Change from 1 to 12 mo‖	−0.34 ± 0.57	−0.36 ± 0.61	.80†
	−0.29 (−0.75, 0.14)	−0.20 (−0.66, 0.10)	
Maximum graft narrowing (%)			
1 mo*	9.2 ± 5.0	8.8 ± 4.2	.35†
	8.0 (6.7, 9.5)	7.4 (6.1, 9.8)	
3 mo‡	11.0 ± 7.8	13.8 ± 16.4	.60†
	8.3 (6.9, 10.5)	8.3 (6.9, 10.0)	
12 mo§	9.5 ± 5.4	13.6 ± 15.4	.20†
	8.0 (6.7, 10.0)	8.2 (6.7, 10.3)	
Change from 1 to 3 mo*	1.8 ± 5.5	5.1 ± 13.5	.30†
	0.3 (−0.7, 3.6)	0.8 (−0.4, 2.6)	
Change from 1 to 12 mo‖	0.6 ± 3.9	4.5 ± 12.3	.08†
	0.0 (−1.2, 1.8)	0.6 (−1.0, 3.3)	
Total vessel diameter (mm)			
1 mo*	3.60 ± 0.96	3.71 ± 0.95	.29¶
	3.45 (2.99, 4.13)	3.67 (3.06, 4.33)	
3 mo‡	3.34 ± 0.86	3.59 ± 0.77	<.01¶
	3.27 (2.71, 3.78)	3.56 (3.04, 4.18)	
12 mo§	3.31 ± 0.78	3.54 ± 0.78	.02¶
	3.17 (2.76, 3.80)	3.46 (3.08, 4.15)	
Change from 1 to 3 mo*	−0.25 ± 0.48	−0.11 ± 0.87	.10¶
	−0.21 (−0.56, 0.08)	−0.19 (−0.53, 0.01)	
Change from 1 to 12 mo‖	−0.32 ± 0.58	−0.21 ± 0.87	.22¶
	−0.28 (−0.75, 0.15)	−0.19 (−0.67, 0.12)	

Values are presented as mean ± standard deviation or median (first quartile, third quartile). *n = 116. †Wilcoxon signed rank test. ‡n = 118. §n = 97. ‖n = 96. ¶Linear mixed model.

grafts, DuraGraft-treated veins showed a significantly smaller wall thickness at 12 months. Additionally, the increase in wall thickness and maximum graft narrowing from 1 to 12 months was significantly smaller in the DuraGraft group. These findings are promising and may be clinically relevant because a 12-month follow-up period constitutes an early time point in the process of the onset and progression of VGD, which usually spans several years.[3]

VGD and subsequent failure remain a significant problem in patients undergoing CABG because SVGs are still used extensively in surgical revascularization.[3,4] To

TABLE 5. Outcomes of multidetector computed tomography (MDCT) analysis in proximal segments (5 cm) of DuraGraft (Somahlution, Jupiter, Fla) and saline grafts at 1, 3, and 12 months

MDCT outcome	DuraGraft (n = 125)	Saline (n = 125)	*P* value
Mean wall thickness (mm)			
1 mo*	0.11 ± 0.05 0.10 (0.09, 0.10)	0.11 ± 0.03 0.10 (0.10, 0.10)	.23†
3 mo‡	0.12 ± 0.07 0.10 (0.10, 0.10)	0.22 ± 0.39 0.10 (0.10, 0.10)	.33†
12 mo§	0.11 ± 0.03 0.10 (0.10, 0.10)	0.21 ± 0.33 0.10 (0.10, 0.10)	.01†
Change from 1 to 3 mo*	0.01 ± 0.04 0.00 (−0.00, 0.01)	0.12 ± 0.37 0.00 (−0.00, 0.01)	.97†
Change from 1 to 12 mo‖	0.00 ± 0.03 (n = 95) 0.00 (−0.00, 0.01)	0.09 ± 0.29 (n = 96) 0.00 (−0.00, 0.01)	.04†
Mean lumen diameter (mm)			
1 mo	3.43 ± 1.00 (n = 115) 3.42 (2.78, 3.98)	3.56 ± 1.03 (n = 116) 3.51 (2.93, 4.22)	.34†
3 mo	3.18 ± 0.98 (n = 118) 3.10 (2.60, 3.76)	3.21 ± 0.86 (n = 118) 3.12 (2.60, 3.82)	.75†
12 mo	3.11 ± 0.84 (n = 97) 2.98 (2.46, 3.74)	3.18 ± 0.89 (n = 97) 3.08 (2.56, 3.68)	.49†
Change from 1 to 3 mo	−0.28 ± 0.56 (n = 115) −0.20 (−0.60, 0.00)	−0.35 ± 0.52 (n = 116) −0.19 (−0.62, 0.00)	.22†
Change from 1 to 12 mo	−0.37 ± 0.65 (n = 95) −0.24 (−0.76, 0.10)	−0.38 ± 0.67 (n = 96) −0.21 (−0.76, 0.14)	.97†
Maximum graft narrowing (%)			
1 mo	7.9 ± 5.1 (n = 115) 6.7 (5.4, 8.0)	7.3 ± 3.9 (n = 116) 6.3 (5.0, 7.4)	.27*
3 mo	9.5 ± 7.8 (n = 118) 7.0 (5.6, 8.7)	12.3 ± 16.9 (n = 118) 6.7 (5.4, 8.0)	.64*
12 mo	7.8 ± 3.6 (n = 97) 7.1 (5.7, 8.3)	12.5 ± 15.7 (n = 97) 6.9 (5.7, 9.1)	.27*
Change from 1 to 3 mo	1.8 ± 5.4 (n = 115) 0.4 (−0.3, 1.7)	5.1 ± 14.0 (n = 116) 0.4 (−1.4, 1.3)	.46*
Change from 1 to 12 mo	0.2 ± 3.8 (n = 95) 0.3 (−0.4, 1.5)	4.7 ± 12.7 (n = 96) 0.4 (−0.4, 2.3)	.01*
Total vessel diameter (mm)			
1 mo*	3.65 ± 0.96 3.60 (2.98, 4.14)	3.77 ± 1.00 3.71 (3.12, 4.43)	.37¶
3 mo†	3.41 ± 0.92 3.34 (2.78, 3.94)	3.65 ± 0.82 3.58 (3.02, 4.38)	.02¶
12 mo§	3.33 ± 0.84 3.18 (2.66, 3.94)	3.60 ± 0.87 3.50 (3.06, 4.28)	.01¶
Change from 1 to 3 mo*	−0.25 ± 0.55 −0.13 (−0.58, 0.04)	−0.12 ± 0.96 −0.18 (−0.62, 0.00)	.20¶
Change from 1 to 12 mo‖	−0.37 ± 0.65 −0.22 (−0.76, 0.12)	−0.19 ± 0.92 −0.23 (−0.72, 0.17)	.07¶

Values are presented as mean ± standard deviation or median (first quartile, third quartile). *MDCT*, Multidetector computed tomography. *n = 15 (DuraGraft) and n = 16 (saline). †Wilcoxon signed rank test. ‡n = 18. §n = 97. ‖n = 95 (DuraGraft) and n = 96 (saline). ¶Linear mixed model.

date, only the long-term use of statins and beta-blockers has been shown to efficiently reduce the occurrence of intimal hyperplasia. Hence, alternative therapeutic strategies against VGD (and VGF) are critically needed to reduce VGF and associated long-term clinical complications. Apart from handling trauma, which may occur during harvest and preparation, graft storage in saline, in particular before anastomosis, has been shown to be deleterious to the graft endothelium, a key determinant for the development of VGD and VGF.[4,7,11,17]

The overall event incidence was low and there was no evidence of safety concerns. The majority of the SVG

TABLE 6. Adjudicated safety outcomes after graft treatment by either DuraGraft (Somahlution, Jupiter, Fla) or saline after a follow-up duration of 110.3 patient-years

Outcome	DuraGraft (n = 125)	Saline (n = 125)	*P* value*
Major adverse cardiac events†	0	1 (0.8) [0.009]	.32
Composite end point‡	11 (8.8) [0.100]	14 (11.2) [0.127]	.51
Death	0	0	–
Myocardial infarction	0	1 (0.8) [0.009]	.32
Repeat revascularization	0	0	–
Increased angina	0	1 (0.8) [0.009]	.32
Increased arrhythmia	0	0	–
Increased shortness of breath	0	0	–
Vein graft thrombosis/ occlusion	9 (7.2) [0.082]	11 (8.8) [0.100]	.62
Fitzgibbon class B and O	2 (1.6) [0.018]	3 (2.4) [0.027]	.65

Values are n (%) [number of events per patient-year]. **P* values are for the comparison of proportions between groups. †Death, myocardial infarction, or repeat revascularization. ‡Composite of all adverse events.

thromboses and occlusions occurred within 3 months and were most likely attributable to technical failure, poor coronary target, or limited outflow. The incidences of graft occlusion for both arms (DuraGraft, 7.2% and saline, 8.8%) were substantially lower than the established incidence of approximately 15%,[3] potentially due to more stringent inclusion criteria including favorable coronary anatomy (patients with diffuse disease and native coronary <1.5 mm were excluded).[6]

The long-term effect of DuraGraft on clinical events has been reported in a large, retrospective study, including 1036 patients treated with DuraGraft and 1400 patients treated with saline.[20] The mean follow-up periods were 8.5 ± 4.2 years for the DuraGraft group and 9.9 ± 5.6 years for the saline group. At 3 years, DuraGraft was associated with a lower occurrence of nonfatal myocardial infarctions (hazard ratio, 0.55; 95% confidence interval, 0.41-0.74; $P < .0001$) and repeat revascularizations (hazard ratio, 0.65; 95% confidence interval, 0.44-0.97; $P = .037$). The authors concluded that the results suggest, taking into account the design limitations, that intraoperative treatment with DuraGraft may reduce VGF-related complications post-CABG.[20]

In general, wall thickness is considered a relevant variable for the assessment of intimal hyperplasia and the risk of related clinical complications, including cardiac events or death. However, to what extent the amount of wall thickness and, importantly, its changes (ie, wall thickening) represents a reliable surrogate marker for patency, and importantly, graft-related clinical complications (ie, myocardial infarction or recurrent angina) remains is unclear. To assess that, long-term, imaging-controlled trials in large cohorts are required.

In fact, wall thickness also strongly depends on the imaging technique and method of analysis used. In this trial, we used MDCT angiography, which is established as an accurate tool to detect morphologic changes (eg, wall thickening and stenosis) in SVGs.[21] In particular, 64-slice MDCT (or better) has been shown to be effective for the assessment of wall thickness and patency rates as early as 1 and 12 months after CABG.[22] Therefore, in this trial, 64-slice (or better) MDCT angiography was exclusively used for the consecutive assessment of graft parameters. The effectiveness of the protocol (adapted from the Lau and colleagues protocol[18]) was further confirmed by the fact that more than 95% of the recorded segments could be evaluated.

We also assessed for other relevant remodeling parameters (ie, lumen diameter and narrowing and TVD), which did not show significant differences at 12 months. However, when compared with wall thickness (as a measure for intimal hyperplasia), it is important to recognize that changes in such parameters often occur later (ie, beyond 12 months) in the process of VGD and VGF, highlighting the importance of long-term studies when assessing SVG remodeling.

A major strength of this trial is the within-patient study design, which eliminated patient-specific confounding variables. The 2 treatment groups were well balanced in regard to SVG characteristics and anatomic and anastomosis-specific parameters, such as grafting territory, target coronary size, and distal run-off, indicating the effectiveness of the randomization scheme used. Postgrafting profiles were comparable, with a good quality anastomosis for most patients in both groups. Operators and the MDCT assessor were blinded to the assigned treatment of the graft. In addition, this is the first trial to report systematic imaging data on graft behavior from 3 consecutive assessments, from 1, 3, and 12 months post-CABG.

Several other approaches to reduce intimal hyperplasia and subsequent VGD and VGF have been or are currently under clinical evaluation. Edifoligide (an oligonucleotide decoy that binds to and inhibits E2F transcription factors to prevent neointimal hyperplasia and VGF) was investigated in the Project of Ex-vivo Vein Graft Engineering via Transfection IV trial,[6] but failed to show a benefit at 12-month angiographic follow-up. Based on the concept to mitigate negative graft remodeling in SVGs during arterialization, external stenting of SVGs has been repeatedly suggested to reduce the occurrence of VGD and subsequent failure. However, previous clinical results were mixed, and even reported increased SVG failure rates.[23-25] On the contrary, Taggart and colleagues,[26] using a new cobalt-chromium venous external stent, recently

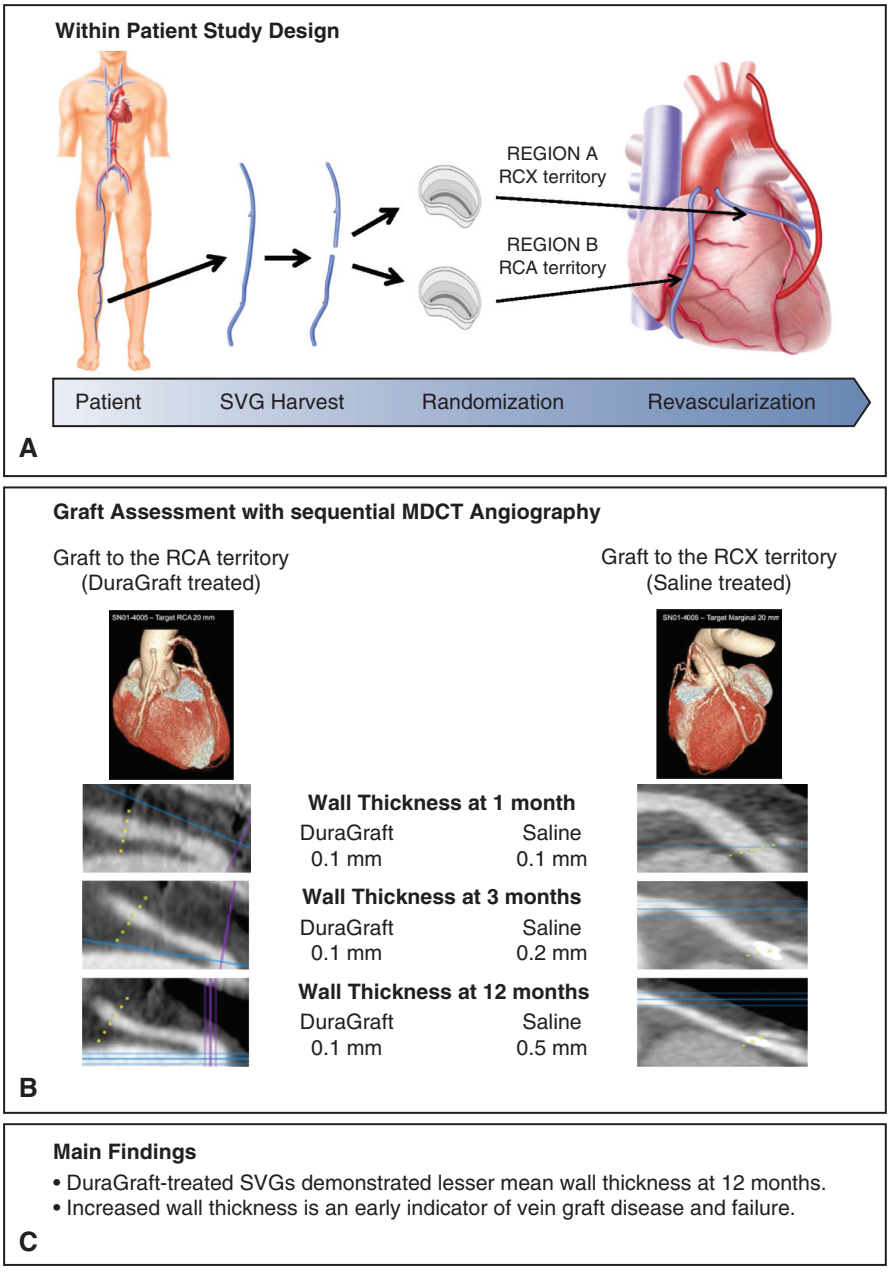
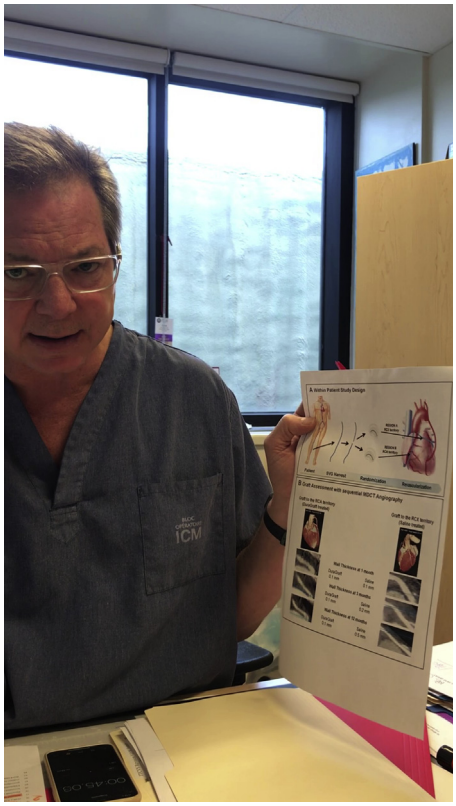


FIGURE 2. Study design and main findings. A, Using a within-patient study design, from each patient the saphenous vein was harvested and divided into 2 segments before these were randomized to treatment with DuraGraft (Somahlution, Jupiter, Fla) or saline stratified for anastomosis to target region A (right circumflex [*RCX*] or diagonal or other) or target region B (right coronary [*RCA*] system or diagonal or other) and use of the proximal or the distal segments of the harvested graft. B, After coronary artery bypass graft, sequential multidetector computed tomography (*MDCT*) angiography imaging was performed at 4 to 6 weeks, 3 months, and 12 months, respectively. Representative imagery from a patient showing an DuraGraft-treated saphenous vein graft [*SVG*] to the RCA territory (*left panel*) and a SVG to the RCX territory treated with saline (*right panel*). Wall thickness is calculated from graft filled with contrast (shown) to determine lumen diameter and images without contrast (not shown) to determine vessel diameter. There was an unchanged mean wall thickness in the DuraGraft-treated graft; the mean wall thickness in the saline treated graft increased over time. C, Main study findings showed that DuraGraft-treated SVGs had a lesser mean wall thickness at 12 months compared to saline-treated grafts.

presented favorable data on the concept of external stenting that showed a significant reduction in intimal hyperplasia at 1 year by intravascular ultrasonography. However, large-scale and longer-term studies are needed to validate these findings and it is important to recognize that such techniques add further complexity to the CABG procedure.



VIDEO 1. Summary of the study by the principal investigator Dr Louis P. Perrault. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32503-6/fulltext.

Study Limitations

This was a small study, and larger cohorts and longer-term evaluations are needed to validate our findings, particularly in regard to patency and clinical outcomes. This will be also crucial to determine whether and to what degree wall thickness assessments qualify as a reliable surrogate parameter to determine clinically relevant VGD.

Larger studies are also needed to account for the nonnormal distribution requiring the use of nonparametric statistical tests and the larger-than-expected standard deviation, particularly for the saline group. Next, it is important to mention that variability across centers may have contributed to some extent to the overall variability in the study. Although an ad hoc exploratory center-specific subgroup analyses did not reveal a site-specific effect (difference) at 4 to 6 weeks or 3 months, it showed a significant difference between centers at 12 months. It appears that the significant difference observed for wall thickness favoring DuraGraft at 12 months was mainly driven by patients from 1 center (site 1), which enrolled by far most of the study patients, contributing 42% of all patients (n = 52) to the entire study cohort. Although this observation is indeed interesting, its (clinical) relevance remains unclear and needs to be addressed in future studies, especially when considering the overall small study size and set up (n = 125 patients at 7 sites), the within-patient study design and because CABG was carried out in a standardized fashion (ie, surgical technique and grafting strategy) in all centers. Despite the high precision of MDCT angiography, the results can vary depending on the imaging modality used. The 12-month data still represent a relatively early time point in the pathophysiology of VGD and VGF.[3] Twenty-eight patients (22.4%) declined to undergo 12-month imaging. Next, because the first MDCT angiography was performed at 1 month (baseline, per protocol), the early postoperative period was not evaluated in this study. Finally, it is important to recognize that vein graft remodeling is influenced by multiple factors which can be either related to the patient's characteristics (ie, diabetes control or hypercholesterolemia), medication (ie, antiplatelet therapy or lipid-lowering drugs), graft and anastomosis characteristics (eg, quality, size, and diameter of target vessel), or surgical technique (ie, open vs endoscopic harvest). Therefore, additional studies are needed to assess the influence of such factors on vein graft remodeling.

CONCLUSIONS

In this randomized, within-patient trial with serial MDCT angiography imaging at 3 time points following CABG surgery, DuraGraft treatment demonstrated a good safety profile and a favorable effect on wall thickness and maximum narrowing in SVGs. Changes were particularly pronounced in proximal segments of grafts. Longer-term evaluation with a larger population is needed to assess the true clinical influence. Taken together, these data suggest that DuraGraft may reduce clinical event rates associated with VGD, and this warrants further investigation in large clinical studies with longer follow-up. This study further adds valuable insights into our understanding of graft behavior after CABG.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Monday_May6/206E/206E/S82%20-%20Rapid%20fire%20abstracts%20V/S82_7_webcast_023129738.mp4.

Conflict of Interest Statement

This trial was funded by Somahlution Inc, Jupiter, Fla. Drs Emmert and Perrault are consultants to and

V. Satishchandran and T. Goeken are an employees at Somalution Inc. All other authors have nothing to disclose with regard to commercial support.

The authors thank the patients and investigators who participated in the study.

References

1. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541-619.
2. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354-471.
3. de Vries MR, Simons KH, Jukema JW, Braun J, Quax PH. Vein graft failure: from pathophysiology to clinical outcomes. *Nat Rev Cardiol*. 2016;13:451-70.
4. Caliskan E, de Souza DR, Boning A, Liakopoulos OJ, Choi YH, Pepper J, et al. Saphenous vein grafts in contemporary coronary artery bypass graft surgery. *Nat Rev Cardiol*. August 27, 2019 [Epub ahead of print].
5. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, et al. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA*. 2011;305:167-74.
6. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB Jr, Lorenz TJ, et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA*. 2005;294:2446-54.
7. Harskamp RE, Alexander JH, Schulte PJ, Brophy CM, Mack MJ, Peterson ED, et al. Vein graft preservation solutions, patency, and outcomes after coronary artery bypass graft surgery: follow-up from the PREVENT IV randomized clinical trial. *JAMA Surg*. 2014;149:798-805.
8. Samano N, Geijer H, Liden M, Fremes S, Bodin L, Souza D. The no-touch saphenous vein for coronary artery bypass grafting maintains a patency, after 16 years, comparable to the left internal thoracic artery: a randomized trial. *J Thorac Cardiovasc Surg*. 2015;150:880-8.
9. Souza DS, Johansson B, Bojo L, Karlsson R, Geijer H, Filbey D, et al. Harvesting the saphenous vein with surrounding tissue for CABG provides long-term graft patency comparable to the left internal thoracic artery: results of a randomized longitudinal trial. *J Thorac Cardiovasc Surg*. 2006;132:373-8.
10. Woodward LC, Antoniades C, Taggart DP. Intraoperative vein graft preservation: what is the solution? *Ann Thorac Surg*. 2016;102:1736-46.
11. Thatte HS, Biswas KS, Najjar SF, Birjiniuk V, Crittenden MD, Michel T, et al. Multi-photon microscopic evaluation of saphenous vein endothelium and its preservation with a new solution, GALA. *Ann Thorac Surg*. 2003;75:1145-52.
12. Tsakok M, Montgomery-Taylor S, Tsakok T. Storage of saphenous vein grafts prior to coronary artery bypass grafting: is autologous whole blood more effective than saline in preserving graft function? *Interact Cardiovasc Thorac Surg*. 2012;15:720-5.
13. Weiss DR, Juchem G, Kemkes BM, Gansera B, Nees S. Extensive deendothelialization and thrombogenicity in routinely prepared vein grafts for coronary bypass operations: facts and remedy. *Int J Clin Exp Med*. 2009;2:95-113.
14. Wilbring M, Tugtekin SM, Zatschler B, Ebner A, Reichenspurner H, Matschke K, et al. Even short-time storage in physiological saline solution impairs endothelial vascular function of saphenous vein grafts. *Eur J Cardiothorac Surg*. 2011;40:811-5.
15. Wise ES, Hocking KM, Eagle S, Absi T, Komalavilas P, Cheung-Flynn J, et al. Preservation solution impacts physiologic function and cellular viability of human saphenous vein graft. *Surgery*. 2015;158:537-46.
16. Thatte HS, Khuri SF. The coronary artery bypass conduit: I. Intraoperative endothelial injury and its implication on graft patency. *Ann Thorac Surg*. 2001;72:S2245-52.
17. Ben Ali W, Voisine P, Olsen PS, Jeanmart H, Noiseux N, Goeken T, et al. DuraGraft vascular conduit preservation solution in patients undergoing coronary artery bypass grafting: rationale and design of a within-patient randomised multicentre trial. *Open Heart*. 2018;5:e000780.
18. Lau GT, Ridley LJ, Bannon PG, Wong LA, Trieu J, Brieger DB, et al. Lumen loss in the first year in saphenous vein grafts is predominantly a result of negative remodeling of the whole vessel rather than a result of changes in wall thickness. *Circulation*. 2006;114:I435-40.
19. Berkowitz HD, Fox AD, Deaton DH. Reversed vein graft stenosis: early diagnosis and management. *J Vasc Surg*. 1992;15:130-41.
20. Haime M, McLean RR, Kurgansky KE, Emmert MY, Kosik N, Nelson C, et al. Relationship between intra-operative vein graft treatment with DuraGraft(R) or saline and clinical outcomes after coronary artery bypass grafting. *Expert Rev Cardiovasc Ther*. 2018;16:963-70.
21. Ropers D, Ulzheimer S, Wenkel E, Baum U, Giesler T, Derlien H, et al. Investigation of aortocoronary artery bypass grafts by multislice spiral computed tomography with electrocardiographic-gated image reconstruction. *Am J Cardiol*. 2001;88:792-5.
22. Gao C, Ren C, Li D, Li L. Clopidogrel and aspirin versus clopidogrel alone on graft patency after coronary artery bypass grafting. *Ann Thorac Surg*. 2009;88:59-62.
23. Inderbitzin DT, Bremerich J, Matt P, Grapow MT, Eckstein FS, Reuthebuch O. One-year patency control and risk analysis of eSVS(R)-mesh-supported coronary saphenous vein grafts. *J Cardiothorac Surg*. 2015;10:108.
24. Rescigno G, Aratari C, Matteucci SM, Parisi R, Gironi G, Schicchi N, et al. Saphenous vein graft wrapping by nitinol mesh: a word of caution. *Thorac Cardiovasc Surg*. 2015;63:292-7.
25. Schoettler J, Jussli-Melchers J, Grothusen C, Stracke L, Schoeneich F, Stohn S, et al. 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.
26. Taggart DP, Ben Gal Y, Lees B, Patel N, Webb C, Rehman SM, et al. A - randomized trial of external stenting for saphenous vein grafts in coronary artery bypass grafting. *Ann Thorac Surg*. 2015;99:2039-45.

Key Words: saphenous vein graft, vein graft disease, computed tomography, coronary artery bypass grafting, patency, endothelial damage inhibitor

APPENDIX E1. STUDY ELIGIBILITY CRITERIA

Inclusion Criteria

Patients will be eligible for inclusion in the study if they meet ALL of the following criteria:

1. Patient is to undergo primary, multivessel CABG with at least 2 SVGs.
2. Patient is aged >18 years and <75 years.
3. Patient has no contraindications to cardiopulmonary bypass.
4. Patient is willing and able to provide consent and shows commitment to participate in a follow-up evaluation, including a clinical visit between 1 month and 3 months post-CABG.
5. If female, patient is surgically sterile or postmenopausal.
6. Patient has not had previous CABG surgery.
7. Patient is hemodynamically stable.

Exclusion Criteria

Patients will be excluded from the study if ANY of the following conditions are present:

1. In situ internal mammary artery graft(s) only (no SVG or free arterial grafts).
2. Prior CABG or planned concomitant valve surgery or aortic aneurysm repair.
3. Pregnant or lactating woman.
4. Left ventricular ejection fraction <40%.
5. Known to be human immunodeficiency virus positive, is receiving antiretroviral drugs, or is immunosuppressed.
6. Patient has an acute infection at screening.
7. Active chronic bacterial, parasitic or viral infection within 3 months before CABG surgery.
8. Malignancy diagnosed within the previous 5 years (except successfully resected basal cell cancer).
9. Unable to provide consent or undergoing emergency cardiac surgery for an immediately life-threatening condition.
10. Participating in a device study or received active drug product in an investigational drug study within 3 months before screening.
11. Patient has a history of transient ischemic attack or stroke within the 12 weeks before the CABG procedure.
12. Significant renal impairment (glomerular filtration rate <50 mL/min).
13. Patient has liver impairment as demonstrated by hepatic transaminases (aspartate transaminase and/or alanine transaminase) >2.5 × upper limit of normal or conjugated bilirubin >1.5 × upper limit of normal.
14. Any condition or disease detected before study start that would render the patient unsuitable for the study, place the patient at undue risk, or interfere with the ability of the patient to complete the study in the opinion of the investigator (eg, drug dependence or mental illness).
15. Uncontrolled diabetes mellitus (glycated hemoglobin >10%).
16. Confirmed significant allergic reactions against any drug or multiple allergies (nonactive hay fever is acceptable).
17. Uninterrupted use of systemic steroids or immunosuppressive agents.
18. Platelet count <100,000/mm^3, hematocrit >62% (hemoglobin >18 g/dL) or <30% (hemoglobin <10 g/L).
19. Varicose veins or veins <2 mm diameter.
20. Target coronary artery <1.5 mm in internal diameter.
21. Diffuse coronary disease.
22. Severe uncontrolled systemic hypertension (ie, systolic pressure >160 mm Hg).
23. Prior severe reaction to contrast dye.

TABLE E1. Participating study centers and distribution of patients across study sites

Study center	Patients enrolled (%)
Montreal Heart Institute, Montréal, Québec, Canada (01)	52 (41.6)
Institut Universitaire de Cardiologie et de Pneumologie, Québec City, Québec, Canada (02)	29 (23.2)
Hôpital du Sacré-Coeur de Montréal, Montréal, Québec, Canada (03)	6 (4.8)
Centre hospitalier de l'Université de Montréal, Montréal, Québec, Canada (04)	8 (6.4)
New Brunswick Heart Centre, Saint John, New Brunswick, Canada (05)	3 (2.4)
Rigshopitalet University of Copenhagen, Copenhagen, Denmark (07)	22 (17.6)
Galway University Hospital, Galway, Ireland (08)	5 (4.0)
Total No. of patients enrolled	125 (100.0)