

# Spiral Laminar Flow Prosthetic Bypass Graft: Medium-Term Results From a First-In-Man Structured Registry Study

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**Background:** A number of surgical strategies and graft enhancements have been trialed to improve the performance of prosthetic grafts. Neointimal hyperplasia may, in part, be a normal cellular response to an abnormal (turbulent) flow environment. This first-in-many study assesses the safety and medium-term patency performance of a new graft designed to induce stable laminar flow through the distal anastomosis.

**Method:** Forty patients who required an infrainguinal bypass graft were recruited/registered from a number of centers in Belgium and The Netherlands. Thirty-nine received a Spiral Laminar Flow graft as part of a standard treatment protocol (23 above-the-knee and 16 below-the-knee bypasses). Kaplan–Meier analyses were used to calculate primary and secondary patency rates.

**Results:** The 12-, 24-, and 30-month primary patency rates were 86%, 81%, and 81% for above-the-knee bypasses and 73%, 57%, and 57% for below-the-knee bypasses, respectively. In the case of secondary patency rates, numbers were unchanged for above-the-knee bypasses and were 86%, 64%, and 64%, respectively, for below-the-knee bypasses. There were no amputations in the study population.

**Conclusion:** This first-in-man series shows potential for the idea of spiral flow–enhanced prosthetic grafts. As always, randomized studies are required to explore the role of different enhanced prosthetic grafts.

## INTRODUCTION

A synthetic graft is considered acceptable for infrainguinal bypass only when there is no vein available.

Over the years, a number of techniques have been developed to improve the performance of prosthetic grafts: distal anastomotic adjuncts, vein cuffs and patches, arteriovenous fistula creation, and the exploration of different materials (Dacron and expanded polytetrafluoroethylene [ePTFE]). More

recently, there have been attempts to improve prosthetic graft design with the development of “enhanced” prosthetic grafts, through distal end design (Distaflo, Bard, Covington, GA) and heparin bonding (FlowLine Bipore Heparin, Jotec, Hechingen, Germany; Propaten, Gore, Flagstaff, AZ).

Parallel to this, there has been work done in two related hemodynamic areas, namely, left ventricular form and function based on the helical architecture of the myocardium, and the three-dimensional nature of blood flow within large- and medium-sized vessels.<sup>1–3</sup>

Normal physiological blood flow is laminar (nonturbulent or perturbed), although studies have begun to note additional complexities to the three-dimensional nature of blood flow. In 1991, Stonebridge and Brophy brought together their own work and that of others and postulated that the normal physiological blood flow pattern was spiral laminar flow (rotating or helical laminar

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**Table I.** Published features of spiral laminar flow

Laminar stability
Reduced laterally directed forces
Reduced near-wall turbulence
Suppresses acute thrombus formation with no increase in platelet activation
Enhances oxygen flux to the arterial wall
Reduces luminal surface low-density lipoproteins concentration
Dampens wall stress temporal gradients
Lowers oscillatory shear stress index

flow).<sup>4</sup> There are a number of published potentially beneficial hemorheological properties associated with spiral laminar flow, which could have importance in prosthetic design (Table I).

Many prosthetic grafts fail owing to neointimal hyperplasia at the distal anastomosis, which eventually occludes outflow. One hypothesis tested by stents and grafts, which engender spiral flow, is that the endothelial cells at the distal outflow are sensitive to the flow environment. Neointimal hyperplasia may, in part or in whole, be a normal distal anastomotic, endothelial cell, mechanosensor response to an abnormal flow environment (nonlaminar flow/turbulence/stagnation/oscillatory shear stress). Reducing any flow-mediated drive to neointimal hyperplasia would be anticipated to impact graft patency.

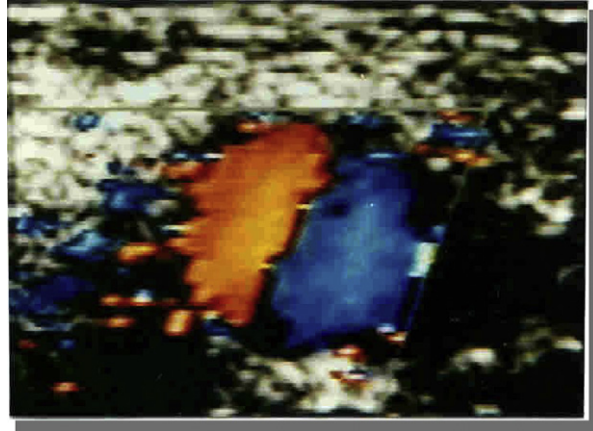
This spiral flow pattern can be readily identified using color flow Doppler by interrogating blood vessels in a true transverse plane at low-velocity settings.<sup>5</sup> This approach produces a characteristic “red/blue” split (Fig. 1) to the transverse color Doppler image.

Using this methodology, arteries, grafts, and graft outflows can be interrogated for the presence of spiral laminar flow. This has allowed the development of a straight conduit internally engineered to produce outflow conditions identical to those seen in normal healthy vessels—the Spiral Laminar Flow graft (Dundee, United Kingdom).

We report the results of a prospective first-in-man study with medium-term (30 months) results in patients receiving a Spiral Laminar Flow graft.

## METHODS

A multicenter structured registry study was set up in The Netherlands and Belgium, and all relevant ethics approvals were obtained. A list of the 10 centers that took part and the surgeons who were involved in the study is given in the Acknowledgments section.



**Fig. 1.** Characteristic spiral flow pattern in healthy arteries.

## Study Population

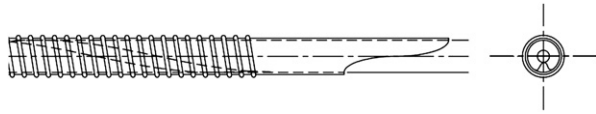
Forty patients presenting with peripheral arterial disease leading to rest pain or lifestyle-inhibiting/severe claudication requiring an above-the-knee or a below-the-knee bypass graft were recruited. As this was a first-in-man registry study, to be able to assess graft performance, the study was limited to a patient group requiring only a unilateral bypass graft to optimize patient survival and add a degree of group homogeneity. Nonconsecutive selection and enrollment was conducted by the treating physician and took place between February 2006 and November 2007. As this was a structured registry study, there is no information available concerning the numbers treated outside the study population by enrolling physicians. All patients received the Spiral Laminar Flow graft in an open phase I study.

## Inclusion Criteria

- Aged between 40 and 75 years.
- Subject to require above-the-knee or below-the-knee outflow unilateral infrainguinal bypass graft for peripheral arterial disease of superficial femoral artery.
- Use of a perioperative/postoperative antiplatelet agent (aspirin [75–100 mg/d] or clopidogrel [75 mg/d]) for >7 days before surgery in line with local protocols. (Alternative anticoagulant/antiplatelet treatments could be applied instead, dependent on center-specific routine.).
- Subject must provide written informed consent.

## Exclusion Criteria

- Known hypersensitivity to graft constituents.
- Sensitivity, allergy, or contraindication to antithrombotics and antiplatelet medication.



**Fig. 2.** Drawing of spiral flow graft.

- Severe comorbid condition, such that the patient is not expected to survive 24 months.
- Significantly disordered hepatic function (transaminase [alanine transaminase, aspartate aminotransferase, gamma-glytaryl transpeptidase]  $>2 \times$  upper limit of range index; alkaline phosphatase  $3 \times$  upper limit of range index) or significant renal impairment (creatinine  $>180$  mmol/L).
- A recognized form of thrombophilia, a history of deep vein thrombosis, and/or early pregnancy loss.
- Presence of a significant medical condition that, in the opinion of the clinician responsible for their care, is a contraindication to enrollment into the study.
- Vascular operative reconstruction in the same leg.
- Poorly controlled diabetes mellitus (haemoglobin A1C  $>7.5\%$ ).

### Anticoagulation and Antiplatelet Therapy

All patients entering the study were started on aspirin (75–100 mg/d) or clopidogrel (75 mg/d) at least 7 days before surgery and continued thereafter as background therapy.

Unfractionated heparin was administered during surgery, and low-dose unfractionated heparin or low-molecular-weight heparin was used after surgery for DVT prophylaxis.

The graft available for use in the trial was a 6-mm standard-wall externally reinforced ePTFE with an engineered spiral inducer segment in the distal 9 cm (Fig. 2). The distal spiral segment engenders a stable rotating laminar profile to flow within the distal graft. This is then delivered to the distal anastomosis and circulation, minimizing any blood flow turbulence.

The operation was performed in accordance with local preference, with no special requirement, save securing (but not completing) the distal anastomosis first to allow the correct length of the graft required to be measured from the distal anastomosis rather than the proximal. This allows the graft to be cut to length proximally, rather than distally, to preserve the distal flow-inducing segment. No adjuvant surgical technique was used. A completion angiography was performed in all cases. All patients were seen to have had one or more minimally diseased outflow tibial vessels.

**Table II.** Patient demographics

Age	70.3 (38–83) years
Sex (M:F)	3:1
Side (right/left)	23/16
Recorded diabetes (yes/no)	8/31
Smoking (current/past/never/not recorded)	16/4/18/1
Fontaine stage	
2a	5
2b	26
3	7
4	1
Previous vascular surgery	19
Above-the-knee/below-the-knee	23/16

### Follow-Up

Patients' follow-up was asked for at 6 weeks and at 3, 6, 9, 12, 18, 24, and finally 30 months. Follow-up assessment included clinical assessment and color Doppler assessment.

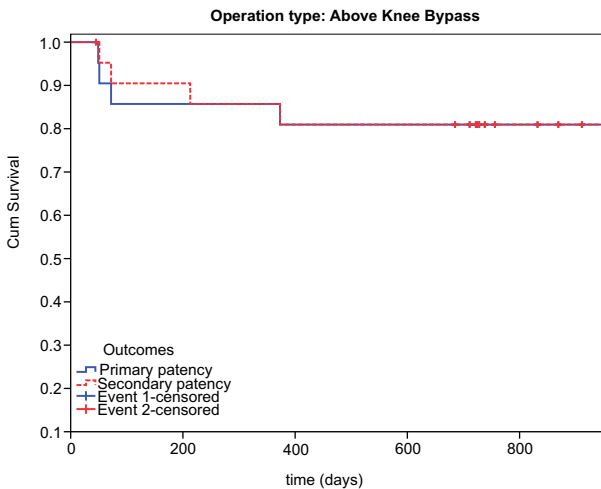
To assess whether the graft actually produced and maintained spiral laminar flow within the distal anastomosis and artery after implantation, 10 randomly selected patients agreed to an additional examination by a specialist technician with particular training and experience, brought across to the study sites from Scotland at 3 and 6 months. There were seven above-the-knee and three below-the-knee grafts.

### Statistical Plan

The number recruited was planned to be in line with the recommendations received for medical device safety assessment and to allow for sufficient numbers to allow informative analysis at 24+ months in the above-the-knee and below-the-knee groups, based on a standard prosthetic graft patency rate (40% at 2 years) and dropouts. Patency was calculated using Kaplan–Meier analysis (using SPSS software [IBM, New York, NY]). As this was an observation study, no statistical comparison was carried out.

### RESULTS

Table II shows patient demographics, indications for treatment, and distribution of graft type for the 39 patients available for follow-up. There were two withdrawals (a graft dehiscence after trauma [at 14 days], and a graft infection [at 45 days]); both cases required graft excision. There was one death due to cancer. There was one patient on whom no data were received, except for initial demographics and an intention to treat. There were three early



Remaining cases		12 months	18 months	24 months	30 months
	Primary Patency	18	17	12	8
Secondary Patency	18	17	12	8	

Fig. 3. Above-the-knee bypass—primary and secondary patency.

occlusions in the above-the-knee group; all from the same center (49 days, 51 days, and 72 days). None of these underwent either thrombolysis or re-exploration, so no information is available as to the underlying cause. Two of the cases in the below-the-knee group underwent thrombolysis on occlusion (247 days and 276 days); the former occluded due to an iliac stenosis and the latter due to a distal outflow artery stenosis, not identified by preoperative angiography.

The characteristic appearance of spiral laminar flow was observed through the distal anastomoses and beyond into the distal outflow arteries in all of the 10 grafts subjected to special postoperative color Doppler examinations.

The Kaplan–Meier charts for above-the-knee bypasses (primary and secondary patency) are shown in Figure 3 and for below-the-knee bypasses (primary and secondary patency) are shown in Figure 4.

The patency rates are shown in Table III. The 12-, 24-, and 30-month primary patency rates were 86%, 81%, and 81% for above-the-knee bypasses and 73%, 57%, and 57% for below-the-knee bypasses, respectively. In the case of secondary patency rates, numbers were the same for above-the-knee and were 86%, 64%, and 64%, respectively, for below-the-knee bypasses.

There were no amputations in the study population.



Remaining cases		12 months	18 months	24 months	30 months
	Primary Patency	10	10	7	1
Secondary Patency	11	11	8	2	

Fig. 4. Below-the-knee bypass—primary and secondary patency.

### DISCUSSION

Taking into account patency and graft infection risk, the current gold standard graft material for infrainguinal arterial bypass is a single-segment greater saphenous vein (Project of Ex vivo Vein graft Engineering via Transfection [PREVENT III]).<sup>6</sup>

The inferiority of prosthetic bypasses to greater saphenous vein<sup>7–9</sup> has prompted attempts to enhance manufactured bypasses. There are currently two leading strategies to enhance graft patency and reduce the risk of limb loss. These are anticoagulation and flow modification. Coagulation modulation can be attempted either systemically<sup>10</sup> or by graft-based technologies. Systemic intervention has recently been explored by the Clopidogrel and Acetyl Salicylic Acid in Bypass Surgery for Peripheral ARterial Disease (CASPAR) study.<sup>11</sup> This placebo-controlled randomized trial showed improved graft patency outcomes for prosthetic infrainguinal bypasses with a combination of the antiplatelet agents clopidogrel and aspirin.

A more recent method of enhancing prosthetic graft performance is the use of heparin bonding. Studies with the Propaten graft (WL Gore, Flagstaff, AZ), with a covalently bonded end point linkage of heparin within the graft, showed heparin activity for 12 weeks,<sup>12</sup> and have shown reduced thrombogenicity.<sup>13</sup>

A recent retrospective nonrandomized study comparing a series of vein grafts versus heparin-

**Table III.** Graft percentage patency

Site of distal anastomosis and criteria and patency	Percentage patency rates (standard error)			
	12 mo	18 mo	24 mo	30 mo
Above-the-knee				
Primary patency	86 (7.6)	81 (8.6)	81 (8.6)	81 (8.6)
Secondary patency	86 (7.6)	81 (8.6)	81 (8.6)	81 (8.6)
Below-the-knee				
Primary patency	73 (11.7)	73 (11.7)	57 (13.4)	57 (13.4)
Secondary patency	86 (9.1)	79 (10.8)	64 (13.0)	64 (13.0)

bonded ePTFE reported 2-year patency rates of 83% for both above-the-knee and below-the-knee prosthetic grafts. These were compared with 80% and 72%, respectively, for saphenous vein grafts.<sup>14</sup> More recently, heparin-bonded below-the-knee grafts have been reported as showing 81% primary patency rate at 1 year.<sup>15</sup>

Counterbalancing this are the results of a 1-year randomized trial comparing the performance of Gore Propaten with Gore-Tex Stretch vascular grafts published by WL Gore on their Web site. At the end of follow-up, both grafts showed a primary patency rate of 67.2%, with limb salvage rates of 96.3% and 94.9% for the Propaten and the Stretch graft, respectively.<sup>16</sup> The benefits of heparin-bonded grafts in higher-flow bypasses is also questioned by the report of a retrospective series comparing standard-wall ePTFE and heparin-bonded ePTFE as brachiocephalic arteriovenous grafts, presented at the Society for Clinical Vascular Surgery (Scottsdale, AZ, 2010). In this study, there was no significant difference between the two ePTFE grafts, with 1-year patency rates of 78.8% and 65.5% for standard-wall and heparin-bonded ePTFE grafts, respectively.<sup>15</sup>

The role of fluid mechanics on the site and severity of arterial wall pathology is well accepted.<sup>17–20</sup> This has led to the development of physical changes to the construction of bypass grafts and operations (cuffs, patches, arteriovenous fistulae). The vein cuff (Miller cuff) fashioned at the distal anastomosis, onto which the prosthetic graft is then in turn anastomosed, is perhaps the most widely trialled.<sup>21,22</sup> The Joint Vascular Research Group Miller cuff study showed a cumulative 2-year patency rate for above-the-knee bypass grafts with and without a cuff of 72% and 70%, respectively, and below-the-knee bypass with a Miller cuff was 52%, compared with 29% for noncuffed bypasses.

The Distaflow graft (Bard) mimicked the concept of a dilated distal graft segment by adding a preformed cuff to the distal end of an ePTFE graft. The

underlying principle of its action was reported as the establishment of a stable vortex in line with the axis of the graft.<sup>23</sup> A nonrandomized study comparing precuffed and vein cuffed bypasses to a mixture of distal anastomosis sites reported 1-year patency rates of 39% versus 49%.<sup>24</sup> A further randomized trial comparing a precuffed graft with a vein cuffed graft showed no difference in 2-year patency, 49% versus 44%, and limb salvage, 65% versus 62%, rates.<sup>25</sup>

Work spanning 2 decades in cardiac and peripheral vascular flow has indicated that there is a spiral/rotational/helical nature to flow within the heart and in the large- to medium-sized arteries.<sup>26–30</sup> Stonebridge and Brophy, when describing spiral laminar flow, hypothesized that this flow pattern could exert a beneficial effect on the mechanisms of endothelial damage/repair.<sup>3</sup> A study by Caro et al. supported this hypothesis and demonstrated that spiral flow may lead to relative uniformity of wall shear and inhibition of flow stagnation, separation, and instability.<sup>31</sup> Spiral flow has been shown to promote laminar stability, with the preservation of laminar flow through stenoses markedly reducing turbulent kinetic energy. Spiral flow also reduces poststenotic laterally directed forces impacting on the vessel wall.<sup>32,33</sup>

There is also a relationship between flow and thrombosis. The initiating step is the interaction of platelets with the thrombogenic surfaces of the grafts. Sauvage et al. proposed that thrombus can be prevented from forming on the wall of the graft by the action of shear forces, if the blood flow in the graft is higher than the “thrombotic threshold velocity.”<sup>34</sup> Spiral flow has also been shown to increase the blood velocity near the vessel wall and wall shear rate. This was speculated by the authors to potentially reduce acute thrombus formation and intimal hyperplasia, thereby potentially improving graft patency.<sup>35</sup>

A recent study also showed that spiral flow generated less adhesion of platelets. The authors concluded that intentionally inducing spiral flow

in arterial grafts had no adverse effect on platelet activation and may indeed be a nonpharmacologic solution to improve the patency of the grafts by suppressing acute thrombus formation.<sup>36</sup>

In our preclinical studies, it was observed that all the standard grafts tested did not maintain laminar flow, and all produced turbulent outflow conditions. Neointimal hyperplasia may, in part, be a normal cellular response to an abnormal (turbulent) flow environment. Mechanisms to promote or stabilize laminar flow and reduce the likelihood of turbulent flow may therefore be advantageous. The graft design incorporates a spiral flow inducer in the distal segment of the grafts. If nonlaminar flow is a driver for neointimal hyperplasia, then it would be anticipated that the potentially protective effect of spiral flow induction should be present for more than the immediate postimplantation period. A small number of patients (10 [25%]) in the series were also examined for persistent presence of spiral flow. All grafts engendered spiral laminar flow, and this effect was also demonstrated at a follow-up examination.

This first study of a graft replicating spiral laminar flow shows primary patency rate at 30 months of 81% and 57.3% for above-the-knee and below-the-knee bypasses, respectively. The above-the-knee bypass appears to compare well with reported results. In the above-the-knee group, there were three early failures from one center and only one further failure past the 6-month mark. The graft's performance places it on a par with, or better than, some of the recently published results for other enhanced grafts.

This current study does show the usual difference in performance between above-the-knee and below-the-knee distal anastomosis grafts, with a 30-month patency rate of 81% versus 57%. The below-the-knee result compares well with other reported series, except for the most recent heparin-bonded graft results.<sup>14</sup> The lack of any amputations in the series suggests a different mode of prosthetic graft failure that may not be predominantly distal anastomotic neointimal hyperplasia.

It is possible to speculate that there will be a bigger flow-inducing advantage in the presence of greater flow rates. This would be expected in above-the-knee bypasses and in arteriovenous grafts for dialysis, circumstances where the role of heparin-bonded grafts appears to be in doubt. Conversely, lower flow rates within some more distal grafts may not generate the necessary rotational velocities to stabilize flow. This suggests that the flow inducer design may need to be tailored differently for low-flow/more distal environments.

Current evidence appears to support the idea that some "enhanced" prosthetic grafts are an improvement on plain grafts. Some centers are therefore being more stringent with regard to vein grafts,<sup>24</sup> switching to enhanced grafts where there are significant concerns about vein quality, as mapped out in the PREVENT III trial.<sup>6</sup>

This first-in-man registry study shows potential for the idea of spiral flow—enhanced prosthetic grafts. However, this is a multicenter nonrandomized nonconsecutive study and may be subject to selection bias. Graft development continues to evolve. Ultimately, prosthetic graft design may combine both flow and pharmacologic enhancements. As always, randomized studies are required to explore the role of different enhanced prosthetic grafts.

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