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The Scandinavian Propaten[®] Trial – 1-Year Patency of PTFE Vascular Prostheses with Heparin-Bonded Luminal Surfaces Compared to Ordinary Pure PTFE Vascular Prostheses – A Randomised Clinical Controlled Multi-centre Trial[☆]

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Abstract Objective: To compare 1-year potencies' of heparin-bonded PTFE [(Hb-PTFE) (Propaten[®])] grafts with those of ordinary polytetrafluoroethylene (PTFE) grafts in a blinded, randomised, clinically controlled, multi-centre study.

Materials and methods: Eleven Scandinavian centres enrolled 569 patients with chronic functional or critical lower limb ischaemia who were scheduled to undergo femoro–femoral bypass or femoro–popliteal bypass. The patients were randomised 1:1 stratified by centre. Patency was assessed by duplex ultrasound scanning. A total of 546 patients (96%) completed the study with adequate follow-up.

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Results: Perioperative bleeding was, on average, 370 ml with PTFE grafts and 399 ml with Heparin-bonded PTFE grafts ($p = 0.32$).

Overall, primary patency after 1 year was 86.4% for Hb-PTFE grafts and 79.9% for PTFE grafts (OR = 0.627, 95% CI: 0.398; 0.989, $p = 0.043$). Secondary patency was 88% in Hb-PTFE grafts and 81% in PTFE grafts (OR = 0.569 (0.353; 0.917, $p = 0.020$)).

Subgroup analyses revealed that significant reduction in risk (50%) was observed when Hb-PTFE was used for femoro–popliteal bypass (OR = 0.515 (0.281; 0.944, $p = 0.030$)), and a significant reduction in risk (50%) was observed with Hb-PTFE in cases with critical ischaemia (OR = 0.490 (0.249; 0.962, $p = 0.036$)).

Conclusion: The Hb-PTFE graft significantly reduced the overall risk of primary graft failure by 37%. Risk reduction was 50% in femoro–popliteal bypass cases and in cases with critical ischaemia.

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Neointimal hyperplasia formation at the anastomoses of bypass surgery is a well-known complication that threatens the patency of the reconstruction. An experimental study from 1988 showed that prolonged heparin injections resulted in reduced neointimal hyperplasia.¹ The benefit of this inhibition was confirmed by clinical trials, including a randomised study of 200 femoro–popliteal bypasses; half of the patients enrolled in the study underwent 3 months of treatment with subcutaneous, low molecular heparin, and the other half received low-dose aspirin and dipyridamole.² After 12 months, the patencies were 87% and 72%, respectively ($p = 0.02$). However, the results were never implemented into clinical practice.

The results urged the execution of experimental studies to create artificial prostheses with heparin bound to the luminal surface. The benefits of heparin were first demonstrated with Dacron. A randomised multi-centre study of 180 femoro–popliteal bypasses randomised patients 1:1 to heparin-bound Dacron grafts or polytetrafluoroethylene (PTFE) grafts; the first-year patency values were 75% and 58%, respectively ($p = 0.037$).³ Despite these findings, there were no significant changes in clinical practice, perhaps due to a preference for PTFE.

Since 2002, PTFE vascular prostheses with heparin-bound luminal surfaces have been commercially available. A small prospective observational study suggested similar effects for long-term subcutaneous heparin application and heparin-bound Dacron prostheses.⁴ However, no Level I evidence of any benefit exists. Consequently, the aim of this study was to compare the primary patency at 1 year of heparin-bound PTFE (Propaten[®]) versus pure PTFE grafts in a robust, randomised, blinded, clinically controlled, multi-centre study.

Materials and Methods

Power calculations

The researchers agreed to conduct the trial with a substantial power of 90% to minimise the risk of failing to detect a relevant difference in patency. Significance level was set at 5%. It seemed realistic and appropriate to expect a difference of 17% in primary patency for femoro–popliteal (fem–pop) bypasses, as reported by Devine and McCollum,³ as well as a corresponding relative risk (RR) of femoro–femoral cross-overs (fem–fem) bypasses using

the results from the Scandinavian FLUX-study as a reference for the crude PTFE graft.⁵ The ratio between fem–fems and fem–pops was expected to be 1:1 based on data from the Danish Vascular Registry (Karbassen). If patients were randomised 1:1, then the 362 participants would be expected to achieve 80% power, and 484 would be expected to achieve 90% power.

Inclusion and exclusion criteria

From 2006 to 2009, patients with intermittent claudication or chronically critical ischaemia evaluated at 11 Scandinavian vascular centres were considered for inclusion in the trial. Inclusion criteria were clinical indication for fem–fem cross-over or fem–pop bypass above or below the knee with an artificial graft, as determined by angiography. Acute patients and patients not likely to attend follow-up, as well as those with heparin allergies, were excluded.

Randomisation

Stratified randomisation by each centre was performed (1:1) by the principal investigator using Epi-Info-6. In connection with the offer of surgery, the patient was informed of the study both verbally and in writing and then asked to participate. Written consent was obtained from each participant. Identification number and date of recruitment were recorded on the enrolment list, and the corresponding numbered envelope was attached to the medical record. The randomisation envelope was opened in the operating room by assisting personnel. The majority of the centres performed this type of randomisation. However, a few centres could not organise this, thereby causing some technical errors (Fig. 1). In all cases, the surgeon was blinded with regard to the group assignment of each patient. However, experienced surgeons were able to distinguish between the two types of grafts due to slightly different blue markings on the two types of PTFE grafts. Follow-up assessments were performed in a double-blinded manner so that information on graft material was not available when clinical follow-up was performed. Throughout the trial, the blinding codes were located at the administration office of Viborg Hospital. These codes were broken by the principal investigator only after 1 complete year of follow-up had been reported by all participating centres, and the primary analyses had been done.

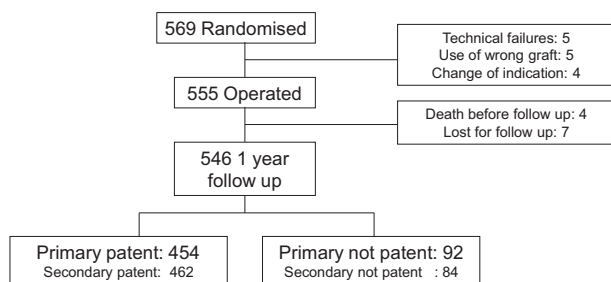


Figure 1 Flow chart.

Baseline variables

Age, gender, diabetic status, weight, height, total cholesterol, S-creatinine, indication for surgery, preoperative and post-operative discharge ankle blood pressure index (ABI), type of intended bypass, anti-platelets and statins given at discharge were recorded as baseline variables.

Participants

A total of 569 patients were randomised. Of these, 555 underwent the planned procedure. Exclusions were primarily due to technical errors, such as a missing envelope or use of the wrong graft. Of those who underwent the scheduled procedure, 11 of the 555 patients operated were lost for follow-up. These were equally divided between the groups. The follow-up time in the control group and the intervention group was 9.75 ± 3.79 versus 10.30 ± 3.35 months, respectively. Consequently, 546 had follow-up data for the assessment of 1-year primary patency, which were equally distributed between crude PTFE ($n = 272$) and heparin-bonded PTFE ($n = 274$). Drop-outs were mainly due to loss of follow-up, although a few deaths occurred before follow-up (Fig. 1).

Follow-up variables

To assess whether the graft was open or closed, we evaluated peripheral pulse and measured systolic ankle/arm blood pressure at each outpatient's follow-up examination up to 12 months postoperatively. Occlusion was suspected when a previously palpated pulse was diminished and/or a significant decrease ($>15\%$) was observed between the ABI value at follow-up versus the ABI value measured in the immediate post-operative period. Confirmation of occlusion was done via duplex scanning of the graft or angiography. The date of occlusion was recorded. At 1 year post-operation, all non-occluded grafts underwent duplex scanning for the valid assessment of patency and for purposes of revealing any 'silent' occlusions.

The type and date of any additional interventions to correct stenoses or reopen the reconstruction were also recorded.

Primary and secondary effect variables

Primary patency was considered as the primary effect variable. The secondary effect variable was secondary patency.

Statistical analysis

To investigate potential failed randomisation, dichotomous and continuous baseline variables were compared between the two study arms by the chi-squared test and Student's *t*-test, respectively.

Primary and secondary first-year patencies were compared between the two groups using logistic regression analysis with and without an adjustment for bypass type and critical ischaemia. These analyses were pre-specified to be by Cox-regression analyses, but were post-hoc changed to logistic regression analysis due to the observation of a substantial number of silent occlusions. Similarly, subgroup analyses were performed for primary patency with regard to the type of bypass and critical ischaemia. These were also performed *post hoc* due to requests from editors and reviewers.

The analyses were performed by the 'intention-to-treat principle' excluding those after randomisation who did not undergo the planned bypass but including early (technical) failures and prosthetic infections.

Ethical aspects

The heparinised graft is approved for commercial use, and there is no clinical suspicion that it increases perioperative bleeding or patient risk. Patients were informed verbally and in writing of the study parameters, and informed consent was obtained from each patient before implantation. The trial was approved by all of the involved Scientific Ethical Committees and data protection authorities in Denmark, Norway and Sweden.

Results

As mentioned, 546 patients had sufficient follow-up data. Among these patients, the mean age was 65.6 ± 5.8 years; 53% were male; 54% were current smokers; 15% had diabetes; mean ABI was 0.43 ± 0.19 ; 36% had critical ischaemia and 54% had a fem–fem cross-over bypass. No significant differences between groups were noted for any of these baseline variables (Table 1). No differences were noted in operation time, preoperative bleeding or primary admission time.

Primary patency

In all, 454 grafts were primarily patent during the first year (Fig. 1). Of the 274 implanted crude PTFE grafts, 219 (79.9%) were primarily patent after 1 year, as compared to 235 out of 272 (86.6%) implanted heparin-bonded PTFE grafts (odds ratio (OR) = 0.627, 95% CI: 0.398; 0.989, $p = 0.043$, Fig. 2). The 37% lower risk in patients with heparin-bonded PTFE grafts remained unchanged after adjustment for the type of bypass, but significance was lost (adjusted OR = 0.629; 95% CI: 0.393; 1.001, $p = 0.051$). Fem–pop bypasses were significantly associated with a threefold higher risk of losing primary patency (adjusted OR: 2.994; 95% CI: 1.860; 4.1819, $p < 0.001$), and critical ischaemia was associated with more than twice the risk of losing primary patency (adjusted OR = 2.260; 95% CI: 1.416; 3.607).

Table 1 Baseline characteristics classified according to type of graft.

	Graft		P-value	Total
	PTFE	Heparin-bonded PTFE		
Dichotomous variables				
Male	148 (54.0%)	140 (51.5%)	0.552	288 (52.7%)
Smokers	147 (54.2%)	144 (53.3%)	0.832	291 (53.8%)
Diabetes Mellitus	39 (14.6%)	39 (15.0%)	0.398	68 (14.8%)
Critical ischaemia	98 (36.5%)	100 (36.0%)	0.910	198 (36.3%)
Fem–fem bypass	148 (51.2%)	160 (56.7%)	0.372	308 (54.1%)
No statins at discharge	43 (15.0%)	31 (11.0%)	0.179	74 (13.0%)
No anti-platelets at discharge	4 (1.39%)	12 (4.25%)	0.089	16 (1.75%)
Continuous variables				
Age	65.7 (5.78)	65.4 (5.97)	0.961	65.6 (5.84)
Body mass index	25.2 (4.79)	25.3 (4.79)	0.707	25.2 (0.21)
P-total cholesterol	4.50 (1.05)	4.44 (1.03)	0.558	4.46 (1.04)
S-creatinine	89.4 (48.7)	86.4 (43.5)	0.554	87.9 (46.2)
Preoperative ankle blood pressure index	0.43 (0.17)	0.44 (0.19)	0.571	0.43 (0.19)

Secondary patency

In all, 462 (84.4%) grafts were secondarily patent after the first year. Of the 274 implanted crude PTFE grafts, 222 (81%) remained secondarily patent, whereas 240 out of 272 (88%) implanted heparin-bonded PTFE grafts remained secondarily patent (RR = 0.60; 95% CI: 0.39; 0.93, $p = 0.024$). The significant 40% reduction in risk for heparin-bonded PTFE grafts remained unchanged after adjustment for type of bypass and critical ischaemia (adjusted OR = 0.565; 95% CI: 0.346; 0.923, $p = 0.023$). Fem–pop bypasses and critical ischaemia were both

associated with over a twofold higher risk of losing secondary patency (adjusted OR = 2.650; 95% CI: 1.625; 4.322, $p < 0.001$; adjusted OR: 2.506 95% CI: 1.545; 4.066, $p < 0.001$, respectively).

Subgroup analyses

In all, 275 of 307 (89.6%) fem–fem cross-over bypasses were primarily patent throughout the first year; of the 147 implanted crude PTFE grafts, 131 (89.1%) remained primarily patent as compared to 144 out of 160 (90.0%)

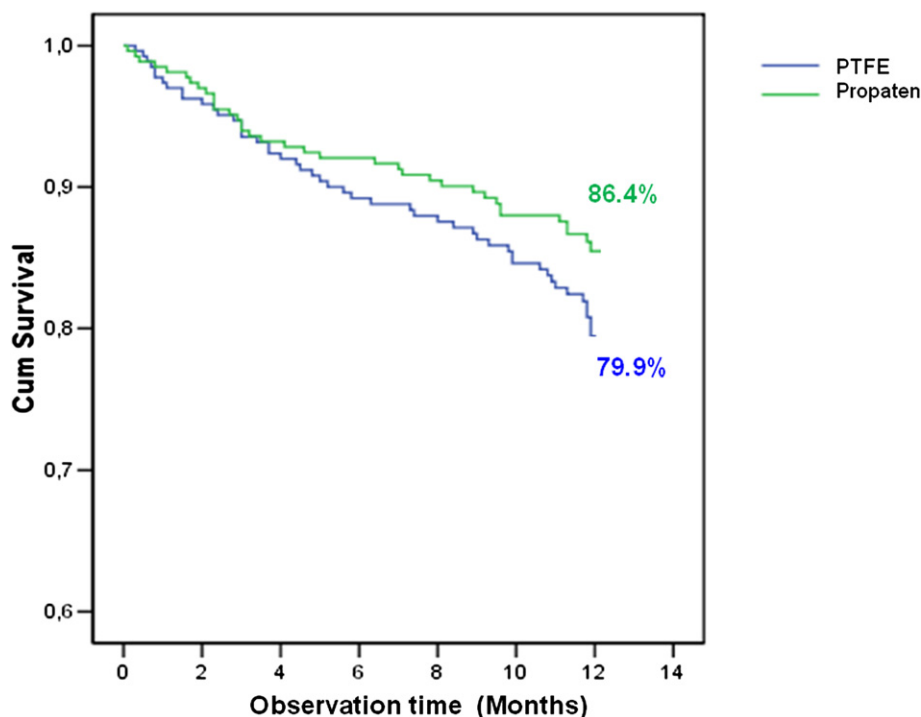


Figure 2 One-year primary patency of Heparin-bonded PTFE and crude PTFE grafts incl. silent occlusions discovered after one year.

implanted heparin-bonded PTFE grafts (OR = 0.910; 95% CI: 0.437; 1.896, $p = 0.800$).

In all, 173 of 232 (74.6%) fem–pop bypasses were primarily patent throughout the first year; of the 107 implanted heparin-bonded PTFE grafts, 86 (80.4%) remained primarily patent as compared to 87 out of 125 (69.6%) implanted crude PTFE grafts (OR = 0.515; 95% CI: 0.281; 0.944, $p = 0.030$).

In all, 151 of 198 (76.3%) bypasses implanted for chronically critical ischaemia were primarily patent after the first year; of the 100 implanted crude PTFE grafts, 70 (70%) remained primarily patent as compared to 81 out of 98 (82.7%) implanted heparin-bonded PTFE grafts (OR = 0.490; 95% CI: 0.249; 0.962, $p = 0.036$). This difference remained significant after adjustment for type of bypass (OR = 0.47; 95% CI: 0.26; 0.86).

The subgroup results are further described with details in Table 2.

Discussion

In this relatively large, randomised, clinically controlled trial, heparin-bonded PTFE grafts significantly decreased the relative risk of losing primary and secondary patency by 36% and 40%, respectively. The benefit was most marked in cases reconstructed for critical ischaemia and in fem–pop bypasses, in which the risk of losing primary patency was halved. The aim of this trial was to test whether there are any differences in the patencies of the two types of grafts, not which graft to choose in a specific clinical situation. The randomised design secures, by principle, equal distribution of the heterogeneous populations between the two arms. However, retrospectively, it was debatable that we did not stratify the randomisation concerning these very different populations. Supplemental analyses adjusting for these variations were performed without changing the results, indicating that randomisation was successful. However, there was loss of significance concerning overall primary patency, which must be interpreted as a consequence of the power for such analysis. In addition, the results of subgroup analyses are given due to clinical relevance; again

with the knowledge that power is lost and therefore increasing the risk of Type II errors. However, due to the controversial indication for bypass surgery in patients with intermittent claudication, we did this subgroup analysis in order to make the results generalisable to centres only doing bypass surgery for critical ischaemia. In addition, the subgroup analyses concerning type of bypass were performed due to a substantial expected interest. However, it must be emphasised that the trial was not powered for this, and the results must be interpreted with caution.

In spite of being a sufficiently powered, multi-centre randomised trial and thus providing the highest level of evidence, potential bias ought to be identified and discussed as in any other study.

Selection bias may have weakened the external validity and generalisability of the results. Unfortunately, the structured information on who accepted the study offer and who did not was not obtained. However, by extracting data from the Danish vascular registry concerning fem–fem cross-overs and fem–pops, we calculated that the proportion of patients recruited was about 60%. The Danish Centres provided information for 85% of the cases. Consequently, no severe selection bias is suspected.

Information bias concerning patency was present to some degree because several occlusions were first diagnosed at the mandatory one-year ultrasound-based follow-up appointment. This independent, and thus non-funded trial, did not have the resources for regular duplex surveillance every 3 months. The lack of regular duplex surveillance caused a potentially substantial information bias, as the magnitude of the silent occlusions discovered at the mandatory 1-year duplex scanning was surprisingly high. The use of survival analysis obviously causes a bias towards the null-hypothesis. Consequently, the Kaplan–Meier Curve (Fig. 2) and survival analyses include this bias. As a consequence, the first year risk estimation was used with and without adjustment for critical ischaemia and type of bypass. This seems acceptable due to the very high proportion of patients having sufficient 1-year follow-up data.

Nevertheless, this information bias challenges the reported benefit of Propaten®.

Table 2 Subgroup analyses concerning the type of bypass in general and further subgrouped according to present chronic critical lower limb ischaemia or intermittent claudication.

		Primary patent	N	Primary patency	Odds ratio	P-value
Fem–fem cross over bypasses						
All	Crude PTFE	131	147	89 (84–93)%	0.910 (0.437; 1.896)	0.800
	Propaten	144	160	90 (84–94)%		
Claudicants	Crude PTFE	85	88	97 (91–99)%	2.312 (0.595; 8.997)	0.215
	Propaten	98	106	92 (86–96)%		
Critical ischaemia	Crude PTFE	46	59	78 (66–87)%	0.615 (0.233; 1.625)	0.327
	Propaten	46	54	85 (73–93)%		
Fem–pop bypasses						
All	Crude PTFE	87	126	69 (61–77)%	0.515 (0.281; 0.944)	0.030
	Propaten	91	112	81 (73–88)%		
Claudicants	Crude PTFE	64	86	74 (64–83)%	0.623 (0.283; 1.373)	0.238
	Propaten	56	68	82 (72–90)%		
Critical ischaemia	Crude PTFE	23	40	58 (42–72)%	0.348 (0.133; 0.912)	0.032
	Propaten	35	44	80 (66–90)%		

Although randomisation was performed in order to avoid known and unknown confounders, any randomised trial poses the risk of being confounded by unsuccessful randomisation. In this trial, there was no indication that the randomisation had failed to distribute confounders equally across the two arms (Table 1). However, looking back, the lack of stratified randomisation concerning type of bypass must be admitted to be suboptimal. Consequently, logistic regression analyses were performed univariately and adjusted for the type of bypass. This adjustment did not change the significance of results, and thus, confounding due to this weakness seems to be absent.

This trial is the first randomised trial testing the end-bonding of heparin to the luminal PTFE surface in the Propaten® graft. Whether the results can be generalised to other heparin-bonded PTFE grafts may be questionable, as the manufacturers claim it to be more bioactive than other heparin-bonded PTFE grafts due to the end-bonding of heparin, while other techniques also causes side-bonding of heparin, which could impair the bioactive part of heparin, but published data confirming this is not available. Another heparin-bonded PTFE graft, the Jotec® graft, has been tested in a large multi-centre randomised trial in Germany, but the study failed to show overall significance and has not yet been published.⁶ Nonetheless, the PTFE graft was significantly associated with better patencies concerning fem–pops above the knee. Taking these two trials into consideration, the authors strongly suggest that heparin-bonding improves the patency of PTFE grafts.

The present trial enrolled nearly 100 cases more than initially required by power calculations. Nonetheless, the overall results were not very robust. In addition, the long-term benefit of the Propaten graft may or may not depend upon the permanent presence of heparin on the grafts. In a canine model,⁷ heparin activity was unchanged after 3 months, but in a sheep model, the bioreactivity of heparin was similar in crude PTFE and Propaten grafts after 6 months.⁸ Consequently, the present 1 year results may be the best that are achievable with this graft, and it is a major limitation of the study, that follow-up does not extend longer. The heparin in the Dacron-bonded grafts disappears after 3 months, but the benefit reported by Devine and McCollum sustained for at least 5 years.³ Only time can tell us whether this is also the case for Propaten grafts. As such, a longer follow-up is needed and is currently planned for early 2011.

Acknowledgements

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annual meeting of the authors, which showed to be crucial for the success of the trial design, execution, analysis and reporting.

Disclosures

The project was performed, analysed and reported independently by the authors without influence from the company Gore and its representatives. However, Gore indirectly supported the enrolment by selling heparin-bonded PTFE grafts for the same price as crude PTFE grafts. In addition, Gore supported an annual meeting in Copenhagen for the authors. Finally, most of the researchers have participated in conferences sponsored by Gore, namely, the Veith and Charing Cross symposiums.

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Conflict of Interest

None.

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