End-to-end Versus End-to-side Distal Anastomosis in Femoropopliteal Bypasses; Results of a Randomized Multicenter Trial

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Objective. To compare end-to-side (ETS) and end-to-end (ETE) distal anastomoses for femoropopliteal bypasses.

Design. Prospective, randomized, multicenter trial.

Methods. Patients from 14 centers were randomized to either ETS or ETE distal anastomosis, with stratification according to center and four categories: venous and prosthetic above knee bypass, and venous and prosthetic below knee bypass. Follow-up, with history, physical examination, ankle-brachial pressure index and duplex scan was performed at 3 months, 6 months and every 6 months thereafter until 36 months postoperatively.

Results. A total of 328 femoropopliteal bypass operations were performed in 274 patients. Due to anatomical considerations at the time of surgery, 15 procedures (4.6%) were excluded from further analysis. Patient characteristics, cardiovascular risk factors, Rutherford classification and number of open run-off vessels were similar for both groups. Primary patency was 75 vs 74%, 65 vs 66% and 63 vs 55% for ETE vs ETS after 1, 2 and 3 years, respectively (p = 0.26). During follow up major amputations were necessary in 20 ETE bypasses and in nine ETS bypasses (p = 0.028).

Conclusion. ETE distal anastomosis in femoropopliteal bypasses does not improve patency compared to ETS anastomosis. Major amputations, after failure of the bypass, were required more frequently for ETE distal anastomoses.

Keywords: Femoropopliteal bypass; Anastomosis; Patency; Limb salvage.

Introduction

Most medium and late graft failures in femoropopliteal bypass surgery are attributed to intimal hyperplasia (IH), in particular to IH within the anastomotic region. The development of IH is related to haemodynamic and humoral factors but is incompletely understood. Wall shear stress (WSS) may play a pivotal role in this IH formation. It has been suggested that low and/or oscillating gradients of WSS trigger the formation of IH. This WSS distribution can be modified mechanically by using anastomotic techniques different from the standard end-to-side (ETS) anastomoses, such as end-to-end (ETE) and cuffed anastomoses.

In in vitro studies, ETE anastomoses appear to have a biomechanical advantage over ETS anastomoses with regard to the WSS within the anastomotic region. These experimental models show that ETS anastomoses have three areas at risk for IH formation: the bed (oscillating WSS), the toe (low/reversed WSS) and the heel (low WSS) of the anastomosis. Inlay ETE anastomoses on the other hand evade the problems of bed, toe and heel sites, resulting in only two minor regions with disadvantageous wall shear stress distribution.

The in vitro experiments suggest that ETE anastomoses have a more favourable wall shear stress distribution than ETS anastomoses. Thus, hypothetically, ETE anastomoses may result in less intimal hyperplasia formation and, therefore, in improved patency of femoropopliteal bypasses. However, so far only one retrospective study has been conducted to evaluate the differences in patency and limb salvage between ETE and ETS distal anastomoses for femoropopliteal bypass. This showed a trend (p = 0.09) toward improved...
patency in ETE anastomosed bypasses, with no
difference in the complications. Therefore, we conducted a multicenter, prospective,
randomized trial to clarify the potential benefits of
distal ETE anastomoses over distal ETS anastomoses:
the VASCular ANastomosis (VASCAN) trial.

Methods

Participants

Patients, 18 years or older, with Rutherford I–III/Fon-
taine II–IV, scheduled for prosthetic or venous above
knee or below knee bypass surgery for peripheral
arterial disease were included, and signed informed
consent for the VASCAN-trial. Patients with an acutely
threatened, ischaemic leg, a bypass to an isolated
popliteal segment, a bypass necessitated by trauma, a
life expectancy of less than 3 years or a contra-
indication to the use of anticoagulants were excluded.
Recruitment of patients took place in 14 hospitals
(one academic, six teaching hospitals and seven
community hospitals) between January 1997 and

Surgical procedure

Choice of bypass material (venous or prosthetic) and
site of distal anastomosis was at the discretion of the
surgeon. In all ‘prosthetic’ operations, a 6 mm thin
walled FEP ringed GoreTex PTFE (W.L. Gore, Flagstaff,
Ariz., USA) prosthesis was used.

ETE anastomoses were performed by transecting
and proximally ligating the popliteal artery or super-
ficial femoral artery. Then, the distal end of the artery
was spatulated over a distance of approximately twice
the diameter of the vessel. The two rectangular corners
were cut arcuated. The anastomosis was then com-
pleted by continuous suturing, with prosthetic Gore
CV-6/7 grafts.

For ETS anastomoses, the PTFE or venous bypass
was cut in a similar way as for the ETE-anastomosis.
Then, the artery was opened by a longitudinal incision
of approximately 12–15 mm, the PTFE or venous
bypass was cut curved in such a way that the bypass
could be placed in a 30° angle, and with continuous
suturing, using Gore CV 6/7 for prosthetic bypasses,
the bypass and artery were anastomosed.

Postoperative anticoagulant or antiplatelet therapy
was given, based on the preference of the surgeon.

Objectives

The objective of this trial was to clarify the potential
benefits of distal ETE anastomosed femoropopliteal
bypasses over distal ETS anastomoses. We expected an
improved patency rate in ETE anastomosed bypass
with a similar complication and amputation rate after
failure of the bypass.

Outcomes

The primary outcome of the VASCAN-trial was the
primary patency rate at 36 months postoperatively.
Patency was confirmed by duplex scanning whenever
possible. If a duplex scan was not feasible, patency
was confirmed by a combination of history, physical
examination and ankle brachial pressure index
measurements (ABPI). In case of uncertainty of
patency or marked deterioration of the ABPI, i.e.
decrease of more than 15% angiography was per-
formed. The date of occlusion was defined as the date
on which loss of patency was confirmed by either
duplex scanning or angiography. Patency was noted
on case record forms during follow-up visits. The
follow-up visits were scheduled 3 months after the
surgical procedure, 6 months after surgery and every 6
months thereafter until the follow-up period of 36
months was completed. In case of a symptomatic
occlusion of the bypass between two follow-up visits
an event form was filled out.

Secondary outcomes were the effect of both anasto-
motic techniques on (1) perioperative complications
including early failure of the bypass, re-interventions
and wound complications, and (2) the necessity of
amputation and level of amputation after graft failure.
Amputations were divided in minor and major
amputations. Major amputations were considered
to be below knee, through knee and above knee
amputations. Before surgery as well as in the
perioperative and follow-up period, case record and
event forms were used to record baseline, periopera-
tive and follow-up data, including medical history,
clinical parameters, results of angiography, ABPI,
perioperative complications, interventions, non-recon-
structive and ablative procedures, and patency of the
bypass.

Sample size

Two groups of 160 patients each were needed to prove
a difference of 15% in primary patency rate after 3
years with a power of 90% and an alpha of 0.05.
Randomization

Randomization to either ETE or ETS distal anastomosis was performed by center and patients were stratified into four categories: venous and prosthetic above knee bypass and venous and prosthetic below knee bypass using a computer generated list, made by the participating statistician (W.H.). On the day of surgery participating surgeons were notified by telephone what technique his or her patient was randomized to.

Blinding

For obvious reasons, the surgeon could not be blinded for treatment assignment. The laboratory technicians performing the duplex scan to assess patency were also not blinded, neither were the patient nor the principal investigators (O.S. and M.T.C.H.).

Statistical method

Kaplan–Meier survival curves were constructed to assess patency rate, and limb salvage. A comparison of these curves was made using the log-rank-test. Chi-square analysis was used to compare percentages, while the Mann–Whitney U-test was used to compare outflow scores. Multivariate (Cox) regression was used to compare patency and limb salvage in ETE and ETS groups. Variables with a p-value of <0.1 were entered in the multivariate analysis. A p-value of .05 (two-sided) was considered the limit of significance.

Results

Baseline characteristics

A total of 328 bypass operations were performed in 274 patients. Fifty-four (16%) patients underwent bilateral femoro-popliteal bypass surgery. Baseline characteristics showed no significant differences between the randomized groups as is shown in Table 1. In total 196 (60%) bypass procedures were performed in men. The mean age of the patients at the time of operation was 69 years (range 39–90 years). Medical history of the participants was positive for angina pectoris in 65 (20%), myocardial infarction in 81 (25%), TIA or CVA in 38 (12%), previous vascular interventions in 152 (46%), smoking in 182 (55%), hypertension in 143 (44%), diabetes mellitus in 94 (29%), and hypercholesterolemia in 52 (16%).

The indication for surgery was intermittent claudication (Rutherford I) in 188 (55%) of the patients, rest and/or night pain (Rutherford II) in 68 (21%) and tissue loss (Rutherford III) in 72 (23%) patients (Table 2). Angiography showed 141 legs with three open run-off vessels, 102 legs with two, 74 legs with one and 11 legs with no open run-off vessel (Table 2). There was no significant difference between the ETE and the ETS group for either the number of open run-off vessels or the indication for surgery.

Only eight above knee venous bypasses were constructed (three ETE and five ETS), Table 3. The majority of the bypasses were above knee prosthetic bypasses (53%, 84 ETE and 90 ETS) as PTFE was the preferred material for above knee bypasses. Below knee venous bypasses were constructed in 88 (27%) of the procedures (41 ETE and 47 ETS). Below knee prosthetic bypass surgery was required in 58 (18%) of all bypasses (34 ETE and 24 ETS) because no adequate long saphenous vein was available.

Effectiveness of randomization and analysis

In total 162 bypass procedures were assigned to be performed using the ETE technique and 166 the ETS technique (Fig. 1). During three procedures an ETE anastomosis was made instead of an ETS and in three
other procedures an ETS anastomosis was performed instead of an ETE anastomosis. These ‘cross-overs’ were due to technical considerations.

Analysis was performed on an ‘intention to treat’ basis, including all patients. However, in eight patients (five ETE and three ETS) no bypass was constructed due to anatomical considerations during surgery and in seven (five ETE and two ETS) a femoro-crural bypass was constructed. Therefore, patency and limb salvage analysis also was performed after exclusion of these 15 (4.6%) patients.

Three-year survival was 77% with no significant difference between the ETE and ETS group (77 vs 76%, \( p = 0.60 \)). After 3 years 38 ETE and 35 ETS bypasses remained for patency analysis (Fig. 1). In total 67 patients (20%) did not have a duplex scan or ABPI measurement after 36 of follow-up. Twenty-two (33%) of these patients had duplex or ABPI measure between 30 months and 36 months of follow-up. Of 59 patients in the ETE group and 58 of the ETS group calculations on major amputations could be performed (Fig. 2).

### Table 3. Distribution of different types of bypasses and number of patients on anticoagulants or antiplatelet therapy

<table>
<thead>
<tr>
<th>Type of bypass</th>
<th>ETE, ( N = 162 )</th>
<th>ETS, ( N = 166 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above knee venous</td>
<td>3 (2%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Above knee prosthetic</td>
<td>84 (52%)</td>
<td>90 (54%)</td>
</tr>
<tr>
<td>Below knee venous</td>
<td>41 (25%)</td>
<td>47 (28%)</td>
</tr>
<tr>
<td>Below knee prosthetic</td>
<td>34 (21%)</td>
<td>24 (15%)</td>
</tr>
<tr>
<td>Postoperative medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>112 (67%)</td>
<td>116 (72%)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>47 (31%)</td>
<td>41 (26%)</td>
</tr>
</tbody>
</table>

ETE, end-to-end; ETS, end-to-side.

Primary patency did not differ significantly between the ETE and ETS group (Fig. 1). After 3 years primary patency was 63 vs 55% for ETE and ETS anastomosed bypasses, respectively. After correction for cardiovascular risk factors, type of bypass, open run off vessels, and Rutherford classification the difference was still not significant (\( p = 0.268 \)). Also after analysis without the 15 patients in whom no femoropopliteal bypass was constructed, the difference remained non-significant (\( p = 0.439 \)).

Primary patency also was calculated for each type of bypass. The above knee venous bypasses were excluded because of the low number (eight only). Below knee venous bypasses had a better primary patency rate, 75% after 3 years of follow up, than above knee prosthetic bypasses, primary patency 55%. Below knee prosthetic bypasses had the worst outcome, primary patency of 45% after 3 years of follow up.

### Outcome after graft failure

A total of 98 (30%) bypasses occluded, 53 (32%) in the ETS group and 45 (28%) in the ETE group. Occlusion led to 20 (44%) major amputations in the ETE group and nine (17%) major amputations in the ETS group; limb salvage is presented in a Kaplan–Meier curve (Fig. 2). This difference in limb salvage was significant, after adjustment for confounding factors such as diabetes, Rutherford classification, type of bypass, and number of open run-off vessels \( p = 0.027 \). The difference remained significant after exclusion of the 15 patients in whom no femoropopliteal bypass was constructed.

Technical failure, i.e. occlusion of the bypass within 1 month after surgery, led to four amputations in the ETS group and six in the ETE group. Therefore, five amputations in the ETS group and 14 amputations in the ETE group were not attributed to technical failure (\( p = 0.028 \)).

Of the 29 major amputations 12 were performed in patients with diabetes mellitus, six in below knee venous, 10 in below knee prosthetic, and 13 in the above knee prosthetic bypasses. Eight patients who eventually underwent amputations had disabling claudication as indication for surgery, 10 had night and/or rest pain, and 11 had already tissue loss at time of surgery. Two patients with amputations had no patent run-off vessels at time of surgery, eight had one open run-off vessel, 12 had two and seven patients had three open run-off vessels at time of surgery. Together with type of distal anastomosis, the number of open...
run off vessels was the only independent risk factor for major amputations ($p = 0.03$).

**In hospital outcome**

Median hospital stay was 12 days for both groups (range 2–209 for the ETS and 0–229 for the ETE group). During hospitalization 12 (7%) bypasses in the ETE group and 11 (7%) in the ETS group occluded. Twelve (7%) of the bypasses in the ETE group required reintervention versus 19 (11%) in the ETS group. Eventually seven (4%) major amputations (below knee and higher) were performed in the ETE group versus four (3%) in the ETS group. Thirteen (5%) patients (six ETE and seven ETS) died in hospital, of which nine (3%) deaths were within 30 days after surgery.

**Discussion**

The VASCAN trial did not show that ETE distal anastomoses improved patency after 3 years of follow up. Limb salvage was superior in the ETS anastomosed bypasses.

Our results for patency are comparable to other reported multicenter trials. The superiority of autologous vein over prosthetic grafts and above knee over below knee bypasses is well known. Also the limb salvage rate was similar as to that in previous reports.11–22

The reasons underlying the worse limb salvage for ETE distal anastomoses is not clear. Since, the difference in limb salvage was caused principally by an excess in amputations in the first 12 months for distal ETE anastomosed bypasses, it is possible that collateral vessels play an important role. The use of ETE anastomoses implies the exclusion of collateral vessels, which have been developed prior to and during the total occlusion of (parts) of the femoropopliteal arterial segment. Consequently, in case of graft failure the limb distal to the bypass is at high risk of acute ischemia and subsequent complications. In distal ETS anastomosed bypasses, the collateral vessel system remains patent up to 12 months postoperatively (unpublished data). In the event of bypass occlusion in the first year after surgery the collateral vessels might protect against acute ischemia and the subsequent need for amputation. After the first year, the collateral vessels appear not to be functional. This may explain the difference in limb salvage in the first postoperative year and the almost equal rate of amputations in later years.

In the only comparative clinical study of the differences between ETE and ETS anastomoses published so far there was no difference in limb salvage.10 However, that was a retrospective study. The influence of preference and experience of the surgeon and consequently the judgement of the intraoperative anatomical situation could have been an important confounder. In our prospective randomized trial these biases were avoided.

This trial was established to clarify the potential benefit of ETE anastomoses over ETS anastomoses in femoropopliteal bypasses based on theoretical and experimental data suggesting better hemodynamic properties and consequently less chance on intimal hyperplasia in ETE anastomosed bypasses. However, the in vivo measurement of intimal hyperplasia by repeated angiography, IVUS or histology, is technically difficult and time consuming. Since we did not obtain quantitative data on intimal hyperplasia formation we used patenty as a surrogate marker of intimal hyperplasia, particularly in the period between 1 month and 1 year after surgery. Therefore, we do not have hard evidence that intimal hyperplasia formation is similar in ETE and ETS anastomoses in femoropopliteal bypasses but we feel justified, based on our data, to proposing this conclusion.

Unfortunately, a substantial number of patients in both groups were lost to follow up for patency calculations, while limb salvage figures were almost complete. This was because some patients did not attend their scheduled follow up visit and further information was obtained from the general practitioner. He or she could give accurate information on amputations and hospitalizations but not on patency. As in both the ETE and the ETS group a similar proportion of patients were lost to follow up, it is
unlikely that differences in patency, would have been altered by more complete follow up.

Conclusion

Despite the theoretical advantages of ETE over ETS configuration for distal bypass anastomoses, the VASCAN trial showed that there is no clinical advantage. On the contrary, due to better limb salvage in distal ETS anastomosed grafts the ETE technique for distal anastomosis in femoropopliteal bypass surgery should be used with reservation, using the ETS technique and unless this is not feasible.

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