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Published in: LANCET

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1998

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 18-03-2019
Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease

Eric Tetteroo, Yolanda van der Graaf, Johanna L Bosch, Andries D van Engelen, Maria G M Hunink, Bert C Eikelboom, Willem P Th M Mali, for the Dutch Iliac Stent Trial Study Group*

Summary

Background Percutaneous transluminal angioplasty (PTA) is a safe, simple, and successful treatment for intermittent claudication caused by iliac-artery occlusive disease. Primary stent placement has been proposed as more effective than PTA. We compared the technical results and clinical outcomes of two treatment strategies—primary placement of a stent across the stenotic segment of the iliac artery, or primary PTA followed by selective stent placement when haemodynamic results were inadequate.

Methods We randomly assigned 279 patients with intermittent claudication, recruited from departments of vascular surgery, either to direct stent placement (group I, n=143) or primary angioplasty (group II, n=136), with subsequent stent placement in case of a residual mean pressure gradient greater than 10 mm Hg across the treated site. The main inclusion criterion was intermittent claudication on the basis of iliac-artery stenosis of more than 50%, proven by angiography. All patients had a clinical assessment before intervention and at 3, 12, and 24 months. Clinical success was defined as improvement of at least one clinical category. Secondary endpoints were technical results, procedural complications, cumulative patency as assessed by duplex ultrasonography, and quality of life.

Findings In group II, selective stent placement was done in 59 (43%) of the 136 patients. The mean follow-up was 9.3 months (range 3–24). Initial haemodynamic success and complication rates were 119 (81%) of 149 limbs and 6 (4%) of 143 limbs (group I) versus 103 (82%) of 126 limbs and 10 (7%) of 136 limbs (group II), respectively. Clinical success rates at 2 years were 29 (78%) of 37 patients and 26 (77%) of 34 patients in groups I and II, respectively (p=0.6); however, 43% and 35% of the patients, respectively, still had symptoms. Quality of life improved significantly after intervention (p<0.05) but we found no difference between the groups during follow-up. 2-year cumulative patency rates were similar at 71% versus 70% (p=0.2), respectively, as were reintervention rates at 7% versus 4%, respectively (95% CI 2%–9%).

Interpretation There were no substantial differences in technical results and clinical outcomes of the two treatment strategies both at short-term and long-term follow-up. Since angioplasty followed by selective stent placement is less expensive than direct placement of a stent, the former seems to be the treatment of choice for lifestyle-limiting intermittent claudication caused by iliac artery occlusive disease.


Introduction

Intermittent claudication caused by atherosclerotic disease of the iliac artery can be a lifestyle-limiting condition. The initial treatment of patients with this disease is physical exercise. Supervised exercise programmes may significantly improve walking distance, but they require a great deal of time and the cost-effectiveness has not been established. Until now, such programmes were not widely available. Percutaneous transluminal angioplasty (PTA) is generally regarded as a safe, simple, and successful alternative for patients with this disease. However, the success of PTA is reduced by residual stenosis and late restenosis. Vascular stents are being increasingly used as an adjunct to iliac-artery PTA. The indications for stent placement, as defined by the US Food and Drug Administration, include suboptimal effect of iliac angioplasty on the basis of either a residual stenosis of more than 30% measured by angiography, a mean pressure gradient of 5 mm Hg or more across the treated site, or extensive intimal dissection. Several investigators in follow-up studies on iliac-artery stenting used the criteria of the US Food and Drug Administration without indicating the specific criteria for secondary stent placement. Angiography is generally regarded as an inadequate test for detection of residual, haemodynamically significant stenosis after PTA, and measurement of the intra-arterial pressure gradient provides a better assessment of the effect of treatment.

Endovascular stent placement is reported to improve the immediate angiographic and haemodynamic results of iliac balloon angioplasty in cases of residual stenosis caused by elastic recoil or intimal dissection. No conclusive evidence exists, however, that stent placement is better in the long term when used as an adjunct to failed angioplasty. A search of research published between 1984 and 1996 (in English) revealed no reports of randomised clinical trials of the long-term results of peripheral-artery stenting. The value of stent placement as the primary treatment of iliac atherosclerotic lesions compared with its use as an adjunct to suboptimal angioplasty has not been established either. However, a potential advantage of stent placement as primary therapy is that it provides better initial angiographic and haemodynamic results with less chance of elastic recoil, and an improved sealing of intimal flaps. But the efficacy of the stents is widely recognised as limited in the long term owing to the narrowing of the luminal diameter of the devices caused by intimal...
proliferations,14 and there may be risks associated with the presence of a foreign body. In addition, since the stents are expensive devices and the long-term results are unknown, a selective approach to stent use seems warranted.

To assess the role of stent placement in the treatment of iliac-artery occlusive disease, we carried out a prospective, randomised, multicentre trial to compare two treatment strategies. Patients either received stent placement as the primary method of treatment for their disease (group I) or initially underwent PTA followed by placement of a stent when PTA provided suboptimal results (group II).

Patients and methods

Study population
Patients were recruited from the departments of vascular surgery in six study centres from November, 1993, to March, 1997. The centres included two university hospitals and four large regional hospitals, selected on the basis of experience with peripheral-vascular intervention techniques, including endovascular stent placement. The study protocol was approved by the local institutional review boards. All patients gave informed, written consent. Inclusion criteria for patients were intermittent claudication consisting of pain localised in the buttock, upper leg, or calf; reduced pulsation of the femoral artery and reduced ankle-brachial index (ABI); reduction, evident by angiography, in arterial diameter greater than 50%; and stenosis of 10 cm or less in length in the common or external iliac artery or occlusion of 5 cm or less that allowed passage with a guide wire. Exclusion criteria were stenosis of more than 10 cm in length; arterial occlusion of more than 5 cm in length, or of 5 cm or less not allowing the passage of a guide wire; stenosis involving the distal aorta; severe comorbidity (eg, severe cardiac or cerebrovascular abnormality, malignant disease); and non-medical factors such as inability to understand Dutch, or expected poor compliance. Patients with recurrent symptoms after vascular surgery of the iliac artery or PTA more than 12 months before were not included. In patients with multiple unilateral or bilateral iliac stenoses, all lesions were assigned to the same treatment regimen. Multiple stenosis localised in one arterial segment (ie, common iliac artery or external iliac artery) were classified as a single lesion.

Randomisation
Patients were randomly assigned to either primary stent placement (group I) or primary PTA with selective stent placement (group II). For each hospital, a separate computer-generated randomisation table was produced to limit imbalance between treatment assignments to four. This table was kept at the trial office and was not available to the treating physicians. The treatment assignment was revealed in the angiography suite by a trial co-worker after the diagnostic arterial angiography was done, and before intervention was started. In the event of an occlusion, randomisation was postponed until mechanical passage of the occluded segment by a guide wire proved possible. We decided that to conceal the assigned treatment from patients or physicians was not feasible.

Treatment protocols
For diagnosis of the extent and severity of stenosis, all patients considered for intervention underwent intra-arterial digital subtraction angiography of the aorto-iliac tract in two projections. In all patients, mean intra-arterial pressures were acquired before intervention. The pressure-gradient measurements were obtained by simultaneous recording of the pressure proximal and distal to the lesion. If the lesion was of questionable haemodynamic significance (translesional gradient <10 mm Hg), additional measurement with intra-arterial vasoconstriction (by the use of 25 mg papaverine, 40 mg tolazoline, or 100 µg glyceryl trinitrate) was obtained for definitive quantification.

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Results

Conclusion
Clinical examination was carried out in all patients before intervention, and at 3, 12, and 24 months; assessment included physical examination, treadmill exercise with measurement of ABI, and colour duplex ultrasonography. Recurrent stenosis
Discrete variables were expressed as counts and percentages; 3 years.

**Statistical analysis**

We calculated that a sample size of 180 patients in each group of

Definition of success and endpoints

We defined clinical and haemodynamic success according to the
criteria proposed by the Society of Vascular Surgery and the
International Society for Cardiovascular Surgery:* clinical success
was defined as improvement of at least one clinical category
compared with the pretreatment assessment; haemodynamic
success as improvement of the ABI by 0-10 or more and no no
more than 0-15 deterioration from the first postprocedural
measurement obtained at 3 months. The iliac artery was deemed
patent if a peak-systolic-velocity ratio of less than 2·5 was found at
duplex ultrasonography.17–19

We defined the primary endpoint of the study as no
improvement or a worsening of the clinical category compared
with the preprocedural clinical assessment. If we found a
discrepancy between clinical symptoms and objective criteria of
the treadmill-exercise test (ie, ABI, walking distance), we gave
clinical values within the treatment groups with the Wilcoxon
matched-pairs signed rank-sum test. The Mann-Whitney U test
was used to calculate the significance of differences between
cumulative-frequency distribution curves of the two groups.

2-year arterial patency rates based on duplex ultrasound were
calculated by life-table analysis. We compared cumulative
patencies in both trial groups using the Wilcoxon Gehan test,
and defined significance as a two-tailed p value of less than 0·05.
Calculations were done with SPSS/PC statistical software (version
6-0).

**Results**

**Patient enrolment**

During the accrual period, 365 potentially eligible patients
were identified and screened for participation. Patients
were deemed potentially eligible when instead of
diagnostic arterial angiography, colour duplex indicated
significant iliac-artery stenosis. Of these 365, 27 (8%) patients refused participation, and 59 (17%) were
excluded owing to specific protocol restrictions (21 had
stenoses extending into the distal aorta detected by
angiography; in 20 angiography could not confirm
the extent of disease as assessed by the screening colour
duplex ultrasonography; eight had stenosis >10 cm or
occlusion >5 cm; in seven the lesion could not be crossed with
a guide wire; and three had extensive, diffuse athroesclerotic changes of the vessels for which PTA or
stenting under the protocol would have been insufficient).
The baseline characteristics of the remaining 279 randomised patients were similar in the two treatment
groups (table I). The groups were also similar with regard
to the characteristics by angiography of the lesions (table
2).

Outcome of procedures

Group I included 143 patients randomly assigned primary
stenent placement, and 187 lesions were treated in this group
with a total of 208 stents. One patient experienced severe
vascular spasm during an attempted stent placement,
which made angiographic or haemodynamic identification
of the stenosis impossible, and no stent was placed. Five
patients had a history of vascular surgery of the same
arterial segment, of whom two had undergone
endarterectomy and three had had iliac-femoral bypass.
Of the latter three, one patient had developed a stenosis at
the anastomosis site. The results of intra-arterial pressure
measurements are given in table 3. The mean pressure
gradient across the treated segments decreased from 16
mm Hg before treatment to post-treatment values of 3 mm
Hg at rest (95% CI for the decrease 12–15), and to 6 mm
Hg during vasodilation.

Group II included 136 patients randomly assigned to

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lesions</td>
<td>146</td>
<td>134</td>
</tr>
<tr>
<td>Mean (SD) value</td>
<td>15 (11)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Pressure gradient (mm Hg) before procedure</td>
<td>146</td>
<td>134</td>
</tr>
<tr>
<td>After procedure, at rest</td>
<td>156</td>
<td>150</td>
</tr>
<tr>
<td>After procedure, after vasodilation</td>
<td>151</td>
<td>138</td>
</tr>
<tr>
<td>Peak systolic velocity ratio*</td>
<td>4·8 (3·4)</td>
<td>4·9 (3·1)</td>
</tr>
<tr>
<td>Before procedure</td>
<td>109</td>
<td>94</td>
</tr>
<tr>
<td>After procedure</td>
<td>152</td>
<td>132</td>
</tr>
<tr>
<td>Mean (SD) value</td>
<td>1·2 (0·8)</td>
<td>1·2 (0·5)</td>
</tr>
</tbody>
</table>

*As measured by colour duplex ultrasonography.

Table 3: Outcome of procedures
primary PTA, and 169 lesions were treated with PTA in this group. Angioplasty was followed by selective stent placement in 59 (43%; 65 lesions; 77 stents) of these patients because a haemodynamically significant residual pressure gradient across the angioplasty site was found. In nine (7%) patients in this group, treatment was not in accordance with the study protocol. Three of the nine patients were inappropriately treated with stent placement in the first months of the study after angioplasty-induced dissections, without substantial translesional pressure gradients; the other six were denied selective stent placement owing either to complications related to
angioplasty (four) or to absence of residual stenosis visible by angiography after PTA in the presence of a haemodynamically significant gradient (two). Two patients had a history of vascular surgery of the same arterial segment; one had undergone endarterectomy and was treated with stent placement, the other had had an iliaceo-femoral bypass with a patent anastomosis and was treated with PTA alone. In group II, the mean pressure gradient across the treated segments decreased from 17 mm Hg before treatment to post-treatment values of 3 mm Hg at rest (95% CI for the decrease 12–15) and to 6 mm Hg during vasodilation (table 3).

We found no significant differences between groups I and II in the mean pressure gradient after intervention (95% CI for the difference between means –1 to 1 mm Hg) or the percentage of post-treatment gradients exceeding 10 mm Hg at rest (five [3%] in both groups) or during vasodilation (24 [16%] in group I vs 16 [12%] in group II; 95% CI for difference in proportions –4% to 12%). Detailed information on the intra-arterial pressure measurements has been given elsewhere.20

Complications occurred in six (4%) patients in group I and in ten (7%) in group II (95% CI for difference –2% to 9%). Complications included haematoma at the puncture site, arterial-wall perforation, acute occlusion of the treated arterial segment, embolism, and vasovagal collapse. Surgical intervention was necessary in two patients in group II. Stent occlusion as indicated by arterial thrombosis did not occur.

Clinical and haemodynamic results

At 3 months after intervention, clinical data were obtained in 265 (95%) of the 279 randomised patients and treadmill exercise testing was done in 257 patients (figure 1). At 12 months, follow-up clinical data were obtained in 171 (93%) of 183 patients eligible for follow-up and 24 months, we obtained clinical data in 81 (91%) of 89 patients eligible for follow-up and treadmill exercise testing was done in 66 patients. Missing data were distributed equally across the groups. We found no difference between the two groups in the rate of repeated intervention at the treated site; repeated intervention occurred in ten (7%) patients in group I, and in six (4%) patients in group II (95% CI for difference –3% to 8%). Vascular interventions at levels distal to the iliac arteries (ie, femoropopliteal arteries) were also distributed equally in both groups during the follow-up period. The mean follow-up for all patients was 9·3 months (range 3–24).

We found no significant differences between the treatment groups in post-treatment improvement of at least one clinical category (p=0·6 at 24 months; figure 2). Clinical success rates at 3, 12, and 24 months’ follow-up are given in table 4. From figure 2 can be derived that 43% (16/37 patients) in group I and 35% (12/34 patients) in group II still had symptoms and signs of intermittent claudication after 2 years.

The treatment groups showed similar haemodynamic success (table 4 and figure 2; p values at 3, 12, and 24 months were 0·7, 0·4, and 0·9, respectively). For the patients in each treatment group, the results of both clinical and haemodynamic assessments were significantly improved at 3 months’ follow-up (p<0·05), and we found no deterioration during follow-up at 12 and 24 months.

Figure 3: Cumulative distribution curves of a particular ABI exercise or better at baseline and 24 months’ follow-up.
Colour duplex sonography
The mean peak-systolic-velocity ratio decreased substantially after the intervention in both groups (table 3). Cumulative primary-patency rates on the basis of duplex examination are shown in figure 4. At 2-years’ follow-up, patency rates were similar for groups I and II (71·3% vs 69·9%). Overall comparison of the cumulative patencies in the two treatment groups showed no difference (p=0.2).

Quality-of-life analysis
Quality-of-life assessment was completed in 255 (91%) of all 279 patients. All eight health dimensions of the RAND-36 survey were significantly improved in patients after intervention (p<0·05); physical functioning, pain, and role-functioning limited by physical difficulties were improved most. After the first follow-up, quality-of-life scores did not change further over time. The improvements in quality-of-life measures were similar in both treatment groups, and we found no significant differences.

Discussion
We found no significant differences in technical results or clinical outcomes of the two treatment strategies. Our investigation showed, moreover, that both at 3-month follow-up and during the 2-year follow-up the results remained the same irrespective of whether the intervention consisted of primary placement of a stent across the arterial stenosis or primary angioplasty followed by selective stent placement in case of a failed balloon procedure. Immediately after intervention the haemodynamically significant pressure gradients across the vascular segments resolved with both treatments, resulting in substantial improvement of the peak-systolic-velocity ratios. During the 2-year follow-up the results remained similar with substantial improvements in quality of life for both groups. Although the clinical success ratios (defined as improvement of at least one clinical category) were equally high for groups I and II (78% and 77%, respectively), a large proportion of patients still had symptoms after 2 years (43% and 35%, respectively). Although in the vast majority of these patients good results were obtained at the time of the intervention (ie, the vascular patency at the iliac stenosis was restored and remained patent at duplex sonography during follow-up), the disappointingly high number of patients with residual symptoms probably reflects the diffuse nature of atherosclerosis, which affects all vessels and not just the area of the treated stenosis. Nevertheless, since we did not find significant differences in the number of immediate complications or in the rate of reinterventions between the treatment methods, primary angioplasty followed by selective stent placement seems to be the strategy of choice for treatment of lifestyle-limiting intermittent claudication—particularly since the strategy also seems the most cost-effective, requiring only a fraction of the stents needed in a strategy of primary stent placement (65 [38%] of 169 in our study).

A review of several non-randomised studies on the clinical benefits of percutaneous treatment for iliac-artery occlusive disease showed substantial variation in reported success rates. Immediately after intervention, success rates ranged from 97% to 100% after stent placement and from 91% to 97% after PTA, at 1 year from 80% to 95% and 73% to 91%, and at 2 years from 71% to 91% and 65% to 89%, respectively.13,19-21 A 1997 meta-analysis that compared the results of eight non-randomised stent-placement studies and six PTA studies showed that stenting reduced the risk of long-term failure by 39% compared with PTA.22 Study selection ensured that a comparison was made with contemporary controls, and the investigators adjusted the data for differences in case-mix and reporting methods across studies. Nevertheless, the results should be interpreted with caution because long-term success was not uniformly defined in the analysed studies, and patients were not randomly assigned to one treatment versus the other. In general, non-randomised studies tend to overestimate the effect of new treatments, which may, at least in part, explain the differences in results after PTA and stent placement.23 Whereas the meta-analysis compared stent placement, either primary or selectively, with PTA, our study was designed to assess the difference between primary stent placement and primary PTA followed by stent placement in selected cases. We know of only one randomised comparison of stent placement versus PTA for peripheral-vascular occlusive disease, by Richter and colleagues from Germany. Although this study has not yet been published in full, its findings are widely quoted and provide reasons to conclude that the outcomes with stent placement are more durable than those with angioplasty alone, since cumulative clinical success at 5 years was 70% in the PTA group and 93% in the stent group.24 However, no specific information is given on the definition of clinical success. In the light of our present knowledge, we might have decided on a different study design to compare direct stent placement with angioplasty alone.

All these findings taken together suggest that angioplasty followed by stent placement for failures may be preferred. Whether the gain in quality of life after selective stent placement compared with angioplasty alone justifies the additional cost, however, has yet to be established.

The criteria we used for carrying out selective stent placement were different from those recommended by the US Food and Drug Administration. In particular, we chose a mean pressure gradient of more than 10 mm Hg across the PTA site13,18-21 as indication for stent placement after PTA, rather than the 5 mm Hg proposed by the Administration. Use of our more lenient criterion for definition of a haemodynamic success after PTA represents a more conservative approach to selective stent placement, which we believed would avoid unnecessary stent placements in a substantial number of patients.

Interpretation of our results is limited in several ways. First, most of our patients (94%) were treated for intermittent claudication and, in the majority of them (92%), the disorder was caused by an iliac-artery stenosis. Our results cannot therefore be extended to patients with critical ischaemia or occlusion. A selective stent-placement strategy in patients with occlusions would probably result in a high proportion of stent placements. In the 12 occlusions in our study treated with initial PTA, ten (83%) required stent placement. Total occlusions, therefore, may not be appropriate for a selective approach. Ten patients could not be treated in accordance with the study protocol; these protocol violations reflect clinical practice in the type of study we have done. To avoid a biased patient selection associated with exclusion of these cases, we adhered to the intention-to-treat principle during data analysis.
We had also expected a higher patency in the primary-stent group than in the primary-angioplasty group, but we found that the two treatments were equally effective. To prove with confidence that two treatment strategies have similar effects, a substantial number of patients are required. At 3 months the patency rate, based on peak-systolic-velocity measurements, was 95% in both trial groups. The number of the treated segments was high enough to state with 95% confidence and power 80% that the difference in 3-month patency rates was 6.5% at most. At 1 year the patency rate in both groups was 90%, and the number of treated segments was sufficiently high to state that the difference was 12% at most.

Although 67% of the patients were followed up for at least 1 year, the mean follow-up of our study was only 9.3 months. Studies that investigated PTA have shown that the failure rate is higher in the first year after treatment.23,24 Thus, a difference in failure rates between the treatment groups could probably not be shown beyond 1 year. Long-term follow-up data on patients with vascular stents are still scarce. With longer follow-up (2–5 years) late complications of stent placement may be recorded.

Although our results showed no difference in patency or complication rates, functional status, or quality of life, a small difference might have gone undetected. In particular, the incidence of complications is reported as significantly higher in PTA procedures compared with endovascular stent placement.25 In our study, surgical intervention was necessary in two patients in the primary angioplasty group; such intervention may be a potential drawback of this strategy.

Since we could not use a control group in our trial, the improvement in quality of life after intervention may be explained by a placebo effect rather than by the intervention itself. However, improvement of other clinical and haemodynamic values does not suggest a placebo effect.

**Participating centres in Dutch Iliac Stent Trial Study**

St Antonius Hospital, Nieuwegein (T. C. Overtoom, J. C. de Valois, F. L. Moll, H. D. W. M. van de Pavoorde); Slingeland Hospital, Doetinchem (J. H. Spithoven, G. J. M. van Iersel, J. Seegers); University Hospital, Utrecht (P. J. van Schak, P. A. Boek); University Hospital Rotterdam Dijkzigt (H. Peterman, H. van Urk); Twente Hospital, Almelo (J. J. Kouwenberg, P. B. Tuyman, J. van der Heuvel, J. G. van Baal); Catharina Hospital, Eindhoven (G. H. M. Landman, A. V. Tielbörger, J. Buith); University of Groningen (E. E. van Wijk); and University of Virginia, USA (E. E. de Lange).

**Contributors**

Willem P. Th. M. Mali and Yolanda van der Graaf were the principal investigators; they designed the study, advised on data analysis, and applied for grants. Eric Tetteroo coordinated the project, and collected, checked, and analysed the data. Johanna L. Bosch and Maria G. M. Hunink were responsible for design, data collection, and analysis of quality-of-life and cost-effectiveness studies. Andries D. van Engelen participated in trial coordination, data management, and analysis. Bert C. Eikelboom advised on design of the trial and data analysis. All authors contributed to the writing of the paper.

**Acknowledgments**

This study was supported by grant (OG-93/001) from the Commission of Investigative Medicine of the Dutch National Health Insurance Council and a Pioneer award from the Netherlands Organisation for Scientific Research.

**References**