Does endovascular treatment of infra-inguinal arterial disease with drug-eluting stents offer better results than angioplasty with or without bare metal stents?

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Abstract

A best evidence topic in vascular and endovascular surgery was developed according to a structured protocol. The question addressed was whether treatment of infra-inguinal arterial occlusive disease with drug-eluting stents (DESs) provides improved outcomes compared with bare metal stents (BMSs) or percutaneous balloon angioplasty (PTA) alone. Altogether, 136 papers were found using the reported searches, of which 5 provided the best evidence to answer the question. All papers represent either level 1 or 2 evidence. The authors, journal, date, country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Main outcome measures varied among the studies, and included patency, in-stent restenosis, target lesion revascularization, major adverse events, clinical improvement and limb salvage. Evidence on the comparative efficacy of DESs in femoro-popliteal arterial disease is mainly based on two randomized, controlled trials. Paclitaxel-eluting stents were evaluated in the Zilver PTX trial and demonstrated superior 2-year results to either BMSs or PTA, as indicated/shown by patency (DES vs PTA, 74.8 vs 26.5%, \(P < 0.01\)), clinical benefit (DES vs PTA, \(P < 0.01\)) and event-free survival (DES vs PTA, 86.6 vs 77.9%, \(P = 0.02\)). However, the SIROCCO trial found that the sirolimus-eluting stent did not exhibit statistically significant differences in 2-year in-stent restenosis (22.9 vs 21.1%) and target lesion revascularization (6 vs 13%) compared with the BMS. Treatment of infra-politeal arterial disease with DESs was related with superior outcomes to those of BMSs, as indicated/shown by patency, freedom from target lesion revascularization and freedom from major adverse events. Furthermore, the ACHILLES trial, the only published trial comparing the infra-popliteal DES with PTA, revealed lower angiographic restenosis (22.4 vs 41.9%, \(P = 0.019\)) and greater vessel patency (75 vs 57.1%, \(P = 0.025\)) in the DES group at 1 year. However, data related to clinical parameters in patients with critical limb ischaemia secondary to infrageniculate arterial disease, such as limb salvage and ulcer healing, are insufficient. In conclusion, treatment of infra-inguinal arterial disease with DES is safe and seems to be superior to treatment with PTA alone or BMS. The role of DES in sustained improvement in clinical outcome end-points, such as limb salvage, remains to be elucidated.

Keywords: Drug-eluting stents • Femoro-politeal disease • Infra-politeal disease • Angioplasty • Endovascular

INTRODUCTION

A best evidence topic in vascular and endovascular surgery was developed according to a structured protocol. This protocol has been previously fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients with infra-inguinal arterial occlusive disease amenable to percutaneous intervention with balloon angioplasty/stenting] does [treatment with drug-eluting bare stents (DES)] provide [improved outcomes, as indicated/shown by sustained patency and limb salvage]?
whether such treatment would be in his best interest. As a consultant vascular surgeon, you undertake to review the literature and discuss the case in the multidisciplinary team meeting.

SEARCH STRATEGY

Medline was searched using the PubMed interface from January 2000 to October 2013: [drug-eluting stents (MeSH term)] AND [femoropopliteal] OR [superficial femoral artery] OR [infra-popliteal] OR [tibial arteries (MeSH term)]. Related articles and references were screened for suitable articles.

SEARCH OUTCOME

One hundred and thirty-six papers were found using the reported search. Five of these articles provided best evidence to answer the question [2–6]. These are presented in Tables 1 and 2.

RESULTS

Femoro-popliteal disease

The first randomized, controlled trial (RCT) to investigate outcomes of DESs in atherosclerotic femoro-popliteal disease was the SIROCCO trial [2]. Ninety-three patients with lower limb arterial disease classified as Rutherford category 1–4 and Transatlantic Inter-Society Consensus (TASC) type C were randomized to receive treatment with either a sirolimus-eluting stent or a bare metal stent (BMS) (SMART, Cordis, Johnson & Johnson, Miami Lakes, FL, USA). The in-stent restenosis rate through 2 years, as documented by Duplex Ultrasound, was not significantly different between the DES and BMS groups (23 vs 21%, \(P = 1.00\)). Target lesion revascularization was similar in the two groups.

The 2-year follow-up outcomes of the Zilver PTX RCT, an industry-sponsored study evaluating paclitaxel-eluting stents (Zilver PTX, Cook Medical, Bloomington, IN, USA) in femoro-popliteal lesions, were recently published [3]. Patients with femoro-popliteal

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Table 1: Best evidence papers for femoro-popliteal revascularization

<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
<th>Patient groups</th>
<th>Main outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duda et al. (2006), J Endovasc Ther, Germany [2]</td>
<td>Sirolimus-eluting stent compared with BMS for treatment of femoro-popliteal arterial disease</td>
<td>In-stent restenosis</td>
<td>2-year in-stent restenosis: DES group: 23% BMS group: 21% ((P = 1.00))</td>
<td>Industry-sponsored trial</td>
</tr>
<tr>
<td>RCT (level 2)</td>
<td>DES group: 47 patients BMS group: 46 patients</td>
<td></td>
<td></td>
<td>DES treatment for femoro-popliteal arterial disease is safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target lesion revascularization</td>
<td>2-year target lesion revascularization: DES group 6% BMS group 13% (not significant)</td>
<td>Similar outcomes between DES and BMS treatment</td>
</tr>
<tr>
<td>Dake et al. (2013), J Am Coll Cardiol, USA [3]</td>
<td>Paclitaxel-eluting stent compared with PTA or BMS for treatment of femoro-popliteal arterial disease</td>
<td>Event-free survival</td>
<td>2-year event-free survival(^a): DES group 87% PTA group 78% (log-rank (P = 0.02))</td>
<td>Industry-sponsored trial</td>
</tr>
<tr>
<td>RCT (level 2)</td>
<td>DES group: 236 patients PTA group: 238 patients</td>
<td>Primary patency</td>
<td>2-year primary patency: DES group 75% PTA group 27% (log-rank (P &lt; 0.01))</td>
<td>DES treatment for femoro-popliteal arterial disease is safe</td>
</tr>
<tr>
<td></td>
<td>Failed PTA</td>
<td></td>
<td>2-year primary patency: Provisional DES group 83% Provisional BMS group 64% (log-rank (P &lt; 0.01))</td>
<td>DES treatment provides clinical outcomes superior to PTA or BMS</td>
</tr>
<tr>
<td></td>
<td>Provisional DES: 61 patients Provisional BMS: 59 patients</td>
<td>Clinical benefit</td>
<td>2-year clinical benefit(^b) higher in DES than PTA (log-rank (P &lt; 0.01))</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{DES: drug-eluting stent; PTA: percutaneous balloon angioplasty; BMS: bare metal stent; RCT: randomized, controlled trial.}\)

\(^a\)Freedom from major adverse events, such as death, amputation, target lesion revascularization and limb ischaemia requiring surgical intervention.

\(^b\)Freedom from persistent or worsening claudication, rest pain, ulcer or tissue loss.
Infra-popliteal disease

A systematic review investigated the endovascular treatment of infra-popliteal arterial occlusive disease with DES [4]. Four RCTs and two observational studies comparing treatments with DES (287 patients) and BMS (257 patients) entered meta-analysis models. At 1 year, patients who received treatment with DESs had significantly higher primary patency, freedom from target lesion revascularization and clinical improvement than those treated with BMSs; however, limb salvage was not different between the groups.

Rastan et al. have published the long-term results of treatment with sirolimus-eluting stents when compared with treatment with BMSs for infra-popliteal arterial disease [5]. One hundred and sixty-one patients with peripheral arterial disease, classified as Rutherford category 3–5, were randomly assigned to receive DESs (82 patients) or BMSs (79 patients). The mean follow-up period for the DES and BMS group was 1005 ± 139 and 1027 ± 123 days, respectively. The event-free survival rate, defined as freedom from target lesion revascularization, major and minor index-limb amputation, myocardial infarction and death, was significantly higher in the DES group (log-rank P = 0.02). Limb salvage was similar in the two groups (99 vs 95%, P = 0.17), and clinically driven target-vessel revascularization occurred in 9% of the DES and 20% of the BMS patients (P = 0.06).

As opposed to comparison of DES and BMS, the ACHILLES trial compared outcomes of balloon angioplasty with those of sirolimus-eluting stents compared with BMS for infra-popliteal arterial disease [5]. One hundred and sixty-one patients with peripheral arterial disease, classified as Rutherford category 3–5, were randomly assigned to receive DESs (287 patients) and BMS (257 patients) entered meta-analysis models. At 1 year, patients who received treatment with DESs had significantly higher primary patency, freedom from target lesion revascularization and clinical improvement than those treated with BMSs; however, limb salvage was not different between the groups.

Table 2: Best evidence papers for infra-popliteal revascularization

<table>
<thead>
<tr>
<th>Author, date, journal and country (level of evidence)</th>
<th>Patient groups</th>
<th>Main outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniou et al. (2013), J Endovasc Ther, UK [4]</td>
<td>4 RCTs and 2 observational studies comparing outcomes of DES in infra-popliteal arterial disease</td>
<td>Superior outcomes of DES compared with BMS treatment:</td>
<td>Superior short-term (1 year) outcomes of DES to BMS for infra-popliteal arterial disease</td>
<td></td>
</tr>
<tr>
<td>Meta-analysis of RCTs and observational studies (level 1)</td>
<td>DES group: 287 patients BMS group: 257 patients</td>
<td>Primary patency, Freedom from target lesion revascularization</td>
<td>P &lt; 0.01</td>
<td>Long-term outcomes unknown</td>
</tr>
<tr>
<td>Rastan et al. (2012), J Am Coll Cardiol, Germany [5]</td>
<td>Sirolimus-eluting stent compared with BMS for treatment of infra-popliteal arterial disease</td>
<td>Event-free survival*, Limb salvage</td>
<td>Superior in DES, log-rank P = 0.02 DES, 99% vs BMS, 95% (P = 0.17) DES, 9% vs BMS, 20% (P = 0.06)</td>
<td>Improved long-term outcomes of DES when compared with BMS for treatment of infra-popliteal arterial disease</td>
</tr>
<tr>
<td>RCT (level 2)</td>
<td>Long-term follow-up</td>
<td>Clinical improvement, Limb salvage, Target-vessel revascularization</td>
<td>P = 0.036</td>
<td>Industry-sponsored trial</td>
</tr>
<tr>
<td>Schneiert et al. (2012), J Am Coll Cardiol, Germany [6]</td>
<td>Sirolimus-eluting stent compared with PTA for treatment of infra-popliteal arterial disease</td>
<td>Angiographic restenosis, Vessel patency, Clinically driven target lesion revascularization, Index-limb amputation</td>
<td>DES, 22% vs PTA, 42% (P = 0.019) DES, 75% vs PTA, 57% (P = 0.025) DES, 10% vs PTA, 17% (P = 0.257) DES, 14% vs PTA, 20% (P = 0.037)</td>
<td>DES may be an alternative to PTA in infra-popliteal arterial disease</td>
</tr>
<tr>
<td>RCT (level 2)</td>
<td>DES group: 99 patients PTA group: 101 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DES: drug-eluting stent; PTA: percutaneous balloon angioplasty; BMS: bare metal stent; RCT: randomized, controlled trial.

*Freedom from target lesion revascularization, major and minor index-limb amputation, myocardial infarction and death.
eluting stents (CYpher SELECT, Cordis, Johnson & Johnson, Bridgewater, NJ, USA) in patients with infra-popliteal arterial occlusive disease [6]. Patients with lower limb arterial disease, Rutherford category 3–5, were randomized to DES treatment (99 patients) or PTA (101 patients). The angiographic restenosis rate at 1 year was lower in the DES than the PTA group (P = 0.019). Furthermore, vessel patency was significantly higher in the DES than the PTA group (P = 0.025). No significant differences in clinically driven target lesion revascularization (P = 0.257) and index-limb amputation (P = 0.307) between DES and PTA patients were found.

CLINICAL BOTTOM LINE

Evidence on the efficacy of DES in femoro-popliteal arterial disease is mainly based on two RCTs [2, 3]. Paclitaxel-eluting stents seem to be associated with superior medium-term outcomes to those of either PTA or BMSs, as indicated/shown by primary patency, clinical benefit and freedom from major adverse events. Inconclusive evidence regarding the sirolimus-eluting stent exists, with a single RCT having found similar in-stent restenosis and target lesion revascularization in patients treated with DES or BMS [3].

More solid evidence with regard to the efficacy of the DES in infra-popliteal arterial disease has been identified. DESs have demonstrated improved patency and freedom from target lesion revascularization compared with BMSs or PTA; however, the effect on clinical outcome parameters, such as limb salvage and wound healing, remains unidentified.

Conflict of interest: none declared.

REFERENCES


eComment. Drug-eluting stents versus angioplasty with or without bare metal stents in infra-inguinal arterial disease

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I read with great interest the position paper by Antoniou and colleagues [1] reviewing the data on endovascular treatment of infrainguinal arterial disease comparing drug-eluting stents (DES) versus percutaneous transluminal angioplasty (PTA) with or without adjunctive bare metal stents (BMS). Over a 14-year period from January 2000 to October 2013, their literature search of specific query terms yielded 136 papers of which 5 provided the best evidence to answer the question posed. Related articles and references were also screened for suitable articles. As necessary, the data is separated into femoral-popliteal disease and infra-popliteal disease.

The two major randomized controlled trials usually referenced for femoral-popliteal disease include the SIROCCO trial (with sirolimus as the active drug) and the Zilver-PTX trial (using paclitaxel). Although the former failed to demonstrate a statistically significant difference between DES using sirolimus and BMS [2], the latter showed a primary patency of 75% in patients with the Zilver PTX (Cook Medical, Bloomington IN, USA) as compared to 27% with PTA, and a provisional 2-year primary patency of 83% with DES compared to 64% with BMS which was statistically significant concluding that DES treatment with the Zilver PTX provided superior outcomes with regard to the outcomes of event-free survival and primary patency compared to PTA or BMS [3].

In the infra-popliteal segment, data has demonstrated that at 1 year, patients with DES had a significantly higher primary patency, freedom from target lesion revascularization and clinical improvement than those with BMS, however, the ultimate outcome of limb salvage was not different between these groups. The three multicentre randomized controlled trials included in a recent qualitative analysis and quantitative data synthesis are the YUKON-BTX (using sirolimus), DESTINY (using everolimus), and ACHILLES (using sirolimus) trials [4,5]. These trials had several differences among them, namely the inclusion of only patients with critical limb ischaemia in the DESTINY trial as compared to both claudicants and patients with critical limb ischaemia in YUKON-BTX and ACHILLES; furthermore, ACHILLES included a greater proportion of patients with tibial chronic total occlusions compared with the other two. The pooled estimates have shown that primary DES placement for focal infra-popliteal lesions significantly improved primary patency, increased overall event-free survival and decreased the need for repeat procedures [4,5]. The ultimate outcome of patient survival and limb salvage, however, demonstrated no significant differences. It should also be noted that these trials were not powered for these outcome measures.

Translating these data for both femoral-popliteal and infra-popliteal lesions into the clinical environment must be exercised with caution. Although Antoniou and colleagues present a case with a TASC II B lesion, the above trials evaluate short segment focal lesions that are not the majority of patients seen in everyday practice; more commonly seen patients usually involve complex, multiple and sequential lesions.

Although multiple and tandem stenoses or occlusions may be treated percutaneously, Katsanos and colleagues in their meta-analysis of infra-popliteal DES should be reminded on their foresight that “in the absence of randomized data about longer infra-popliteal lesions, it may be frivolous and unwise to extrapolate the reported results [of their meta-analysis] to the setting of long tibial obstructions that require multiple DES placement with still unproven clinical- and cost-effectiveness” [5]. The option and durability of primary open infra-inguinal bypass must be considered in the treatment algorithm of multi-segmental lower extremity arterial disease. And in an era of increasing health care economics, cost-containment, and clinical outcomes, quality-of-life metrics and cost-utility parameters must be critically evaluated.

Conflict of interest: none declared.

References