Health Policy Advisory Committee on Technology

Technology Brief

Drug-eluting stents and balloons for the treatment of peripheral vascular disease

May 2012
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This brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Hospital Principal Committee (HPC). AHMAC supports HealthPACT through funding.

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** TECHNOLOGY BRIEF **

** REGISTER ID **
WP032

** NAME OF TECHNOLOGY **
DRUG-ELUTING STENTS AND BALLOONS

** PURPOSE AND TARGET GROUP **
TO INHIBIT THE PROLIFERATION OF NEOINTIMAL GROWTH OF VASCULAR SMOOTH MUSCLE CELLS AND PREVENT RESTENOSIS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE

** STAGE OF DEVELOPMENT (IN AUSTRALIA) **

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<sup>*</sup>Relevant to drug-eluting stents only, drug-eluting balloons are yet to emerge.

** AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL **

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<td>ARTG number 19333 (21/12/2011): Zilver PTX drug-eluting peripheral stent, Cook Medical Australia Pty Ltd ARTG number 155140 (17/09/2008): CYPHER Select+ Sirolimus, drug-eluting peripheral stent, Johnson &amp; Johnson Medical Pty Ltd</td>
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<td>Drug-eluting balloons</td>
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** INTERNATIONAL UTILISATION **

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Peripheral arterial stenting and angioplasty are used to treat peripheral vascular disease (PVD). These approaches are associated with a high technical success rate in the short-term, but restenosis or reocclusion occurs in a significant percentage of treated segments within six to 12 months due to neointimal growth of vascular smooth muscle cells. Restenosis may impair clinical improvement and lead to symptom recurrence. Drug-eluting stents (DES) and balloons (DEBs), which utilise anti-proliferative drugs, may be a safe and effective way of slowing or preventing restenosis following peripheral stenting and angioplasty.

BACKGROUND

PVD, also known as peripheral arterial disease, refers to the obstruction of large arteries that supply blood to the periphery. The peripheral arteries are narrowed as a result of the accumulation of plaque (atherosclerosis) within the blood vessels, resulting in reduced blood flow. PVD most commonly affects the arteries that supply blood to the legs and feet, specifically the femoropopliteal and infrapopliteal (primarily tibial) arteries. There is a range of modifiable and non-modifiable risk factors for PVD including advanced age, male gender, family history, smoking, diabetes, hypertension, hyperlipidaemia and obesity (Levy 2002).

Most patients with PVD remain asymptomatic for many years and symptoms generally do not present until there is at least 50% narrowing of an artery, making diagnosis difficult. The severity of symptoms is dependent on the degree of stenosis. In the general population, only 10% of people with PVD have classic symptoms of claudication, 40% do not complain of leg pain, while the remaining 50% have a variety of leg symptoms different from classic claudication (Hirsch et al 2001). The Rutherford classification is a commonly used clinical staging system for describing PVD, and has seven stages (0=no symptoms, 1=mild claudication, 2=moderate claudication, 3=severe claudication, 4=ischaeic rest pain, 5= ischaeic ulceration not exceeding the digits of the foot and 6=severe ischaeic ulcers or frank gangrene). In patients with limb-threatening critical ischaemia, as indicated by night pain, rest pain, ischaeic ulcers or gangrene, urgent intervention is required in order to avoid limb loss. In such patients, limb loss occurs at a rate of 80-90% if successful revascularisation is not achieved (Criqui et al 1992).

Non-invasive procedures can be used to diagnose PVD such as the ankle brachial index (ABI), a ratio of the blood pressure readings between the highest ankle pressure and the highest brachial (arm) pressure; this value can provide an indication of the severity of the disease. Other non-invasive diagnostic procedures include Doppler ultrasonography, computed tomography (CT) and magnetic resonance angiography.
However, a definitive diagnosis of PVD can only be made using an invasive catheter-based angiography procedure that shows the roadmap of the arteries and demonstrates the exact location and length of the stenosis or occlusion.

The majority of patients diagnosed with PVD (70%) remain stable or improve in response to lifestyle modifications such as smoking cessation, physical activity and dietary changes, as well as pharmacological interventions including antiplatelet therapies, lipid lowering and glucose control agents, and antihypertensives. However, for patients who do not improve with conservative management, revascularisation procedures can be used to restore peripheral circulation.

Peripheral artery stenting involves the implantation of a stent (a wire mesh scaffold) into the artery to keep it open. Stents can be balloon-expandable, which require an angioplasty balloon to expand and set the stent within the artery, or self-expandable. Similarly, peripheral arterial angioplasty, also known as percutaneous transluminal angioplasty, mechanically widens a narrowed or obstructed blood vessel. A balloon catheter (an empty and collapsed balloon on a guide wire), is passed into the narrowed locations and inflated to a fixed size using water pressure. The balloon is then collapsed and withdrawn. While both these approaches are associated with a high technical success rate in the short-term, restenosis or reocclusions occur in a significant percentage of treated segments, with a one-year restenosis rate of up to 60% (Muradin et al 2001). This restenosis, which is due to neointimal growth of vascular smooth muscle cells, may impair clinical improvement and eventually lead to a recurrence of symptoms.

A recent innovation is to employ drug-eluting stents (DES) and balloons (DEBs) in an attempt to reduce restenosis. These drug-eluting devices are coated with anti-proliferative drugs such as paclitaxel and sirolimus, which inhibit the proliferation of neointimal growth of vascular smooth muscle cells. The safety and effectiveness of drug-eluting devices in preventing restenosis following coronary angioplasty has been demonstrated in a number of multicentre randomised clinical trials (Stone et al 2005; Morice et al 2007; Silber et al 2009); however, the evidence-base on their use in the peripheral vascular system is not as extensive.

**Clinical Need and Burden of Disease**

At present, there are no national data available on the number of Australians who have PVD; however, a 2002 study reported that the age-standardised prevalence of PVD among men aged 65–83 years living in the Perth metropolitan area of Western Australia was 16% (Fowler et al 2002). PVD was responsible for 0.7% of the total burden of disease and injury in Australia in 2003 (AIHW 2011). The majority of the PVD burden (69%) was due to years of healthy life lost because of poor health or disability, while the remainder (31%) was due to years of life lost to premature death (Begg et al 2007).
It is unclear what percentage of Australians suffering from PVD experience critical limb ischaemia requiring revascularisation, and would thus be eligible for peripheral stenting and angioplasty using drug-eluting devices. Several stenting (Item numbers 35306 and 35309) and angioplasty procedures (Item numbers 35300 and 35315) for use solely in the peripheral vascular system are currently listed on the Medicare Benefit Schedule (MBS). Based on MBS data, a total of 6,981 claims were made for services covered by the item numbers listed above, between July 2010 and June 2011 (Medicare Australia 2011).

In 2007–08, there were 25,796 hospitalisations in Australia due to PVD, which equated to 0.3% of all hospitalisations and 5% of cardiovascular disease (CVD) hospitalisations (AIHW 2011). During this period, the average length of stay for those hospitalised with PVD for at least one night was 10.8 days, and the average length of stay for a diagnosis of PVD was twice as long as for a diagnosis of coronary heart disease (CHD) (AIHW 2011).

In 2007–08, 5% of hospitalisations with PVD as the principal diagnosis ended in death, and in the 14 years between 1993–94 and 2007–08, PVD deaths comprised 8% of all CVD deaths in hospital (AIHW 2011). In 2001, PVD was the cause of 2,160 deaths, equating to 1.6% of all deaths, and 4.6% of all CVD deaths. Age remained a substantial risk factor with 92% of PVD deaths occurring among those aged 65 years and over (AIHW 2011).

**DIFFUSION**

In Australia there are currently two drug-eluting stents registered on the Australian Register of Therapeutic Goods. The CYPHER SELECT + Sirolimus-eluting infrapopliteal stent (ARTG number 155140, Johnson & Johnson Medical Pty Ltd) is indicated for use in patients suffering from symptomatic critical limb ischaemia or severe claudication caused by lesions at the infrapopliteal level (arteria tibialis anterior, arteria tibialis posterior, arteria fibularis and tibio-fibular trunk). The Zilver PTX drug-eluting peripheral stent (ARTG number 193333, Cook Medical Australia Pty Ltd) is intended for use in the treatment of symptomatic vascular disease of the above-the-knee femoro-popliteal arteries.

There are currently two Medicare Benefits Schedule (MBS) item numbers that may be used to for the insertion of stents for the treatment of peripheral vascular disease. Both of these item numbers were added to the Schedule in 1992 and describe the medical service associated with the insertion of a stent, rather than the stent itself. As the descriptor does not differentiate between the insertion of a bare metal or drug-eluting stent, these item numbers may be used for procedures using either stent.

- **35306** TRANSLUMINAL STENT INSERTION including associated balloon dilatation for 1 peripheral artery or vein of 1 limb, percutaneous or by open exposure, excluding associated radiological
services or preparation, and excluding aftercare. **Fee:** $598.55 **Benefit:**
75% = $448.95 85% = $524.85
- **35309** TRANSLUMINAL STENT INSERTION including associated balloon dilatation for visceral arteries or veins, or more than 1 peripheral artery or vein of 1 limb, percutaneous or by open exposure, excluding associated radiological services or preparation, and excluding aftercare. **Fee:** $748.15 **Benefit:** 75% = $561.15 85% = $674.45

An appropriate MBS item number is a prerequisite for a device to be listed on the Australian Government’s Prostheses List. On the basis of the above MBS item numbers, Cook Medical Australia Pty Ltd successfully applied for listing of the Zilver PTX in February 2012 (Prostheses List number WC289). Although the Zilver PTX has not undergone a formal health technology assessment, listing on the Prostheses List enables the Zilver PTX to be used by patients with private hospital insurance, with a minimum private health insurance benefit payable of $2,400. The CYPHER SELECT + Sirolimus-eluting infrapopliteal stent is not listed on the Prostheses List.

Drug-eluting stents are currently being used to treat PVD in a several European countries, including the United Kingdom, as well as in Australia. There are a number of ongoing clinical trials assessing the use of DES for PVD being conducted in Europe (NCT01094678, NCT00471289, NCT00510393, NCT01348425, NCT00664963 and NCT00640770). Some ongoing international trials have included study centres in the United States (US) and Japan (NCT00120406), as well as Australia (NCT01442636), in addition to the European centres. The Australian trial is being conducted at the Prince of Wales Private Hospital in New South Wales, but is not yet recruiting patients.

There are currently no DEBs for use in the peripheral vascular system listed on the ARTG. Importantly, as angioplasty balloons are not considered implantable devices, they are not funded by private health insurers and do not appear on the Prosthesis List. Similarly, in the US, no DEBs have been approved by the Food and Drug Administration (FDA) for use in the peripheral vascular system. However, in early 2010, Medrad Interventional/Possis asked the FDA to allow an investigational device exemption (IDE) trial for its Cotavance paclitaxel-eluting balloon, the first DEB to be brought before the FDA. It is unclear whether the FDA approved this IDE trial, which to date has not been registered.

Currently, DEBs are used as a treatment tool for PVD in a number of European countries, with published trials conducted in Germany and five ongoing clinical trials being conducted in Europe: three in Germany (NCT01175850, NCT01007578 and NCT00640770), and one each in Belgium (NCT01366482) and Austria (NCT01247402).
COMPARATORS

For patients suffering from PVD whose symptoms do not improve with lifestyle modifications and pharmacological therapy, a variety of procedures can be used to restore peripheral circulation. These include peripheral arterial angioplasty using standard, uncoated balloons, angioplasty combined with brachytherapy, peripheral arterial stenting using standard, uncoated stents, atherectomy, endarterectomy, and bypass surgery. Factors considered when deciding which patients will benefit from a particular procedure include the location of the lesion, patient-related risks and comorbidities, procedure-related risks, and contraindications to thrombolysis.

Angioplasty combined with brachytherapy delivers radiation to peripheral arteries through local catheters to reduce restenosis following peripheral arterial angioplasty.

Atherectomy devices cut and remove atherosclerotic plaque from a vessel wall or grind the atheroma into small particles. Elastic recoil is reduced after this procedure, due to the fact that the lumen is widened without stretching the arterial wall.

During an endarterectomy procedure, an incision is made in the leg to remove the plaque contained in the inner lining of the diseased artery and restore blood flow. The effectiveness of this method is dependent upon the location and extent of the arterial blockage.

Bypass surgery creates a detour around a narrowed or blocked section of an artery in the leg. A vein from another part of the body or an artificial blood vessel is inserted above and below the blocked area, creating a new path for blood flow. It is particularly effective for extensive artery blockages. However, in patients with chronic limb ischaemia, surgical bypass grafting is often not an option due to the lack of outflow vessels or the availability of suitable venous graft material.

SAFETY AND EFFECTIVENESS ISSUES

Three randomised multicentre trials which assessed the safety and efficacy of drug-eluting devices for the treatment of PVD were eligible for inclusion in this technology brief. Two trials examined the use of DES (Duda et al 2002, Duda et al 2006, Dake et al 2011a), while the other examined the use of DEBs (Tepe et al 2008). In addition, a large case series describing the use of DES was included for assessment (Dake et al 2011b).

Dake et al (2011a) described the use of the Zilver PTX drug-eluting stent, a self-expanding nitinol stent coated with 3µg/mm² paclitaxel, in patients with femoropopliteal peripheral artery disease who had up to two de novo or restenotic lesions (one per limb). Patients were randomised to receive either the DES (n=236) or percutaneous transluminal angioplasty (PTA) (n=238) (level II intervention evidence). The baseline characteristics of both patient groups were similar. Patients
were followed up for 12-months, with clinical evaluations conducted at 6- and 12-months including duplex ultrasound evaluation of patency.

A total of 359 drug-eluting stents were inserted (mean 1.5, range 1-4 stents per patient) with a 95 per cent procedural success rate. In the PTA group, 120 patients (50.4%) experienced acute PTA failure. These patients underwent further randomisation to receive either a bare-metal stent (n=59, 93 stents implanted to treat 62 lesions) or DES (n=61, 94 stents implanted to treat 63 lesions). There were no procedure- or device-related deaths reported in either group. In addition, there was no significant difference between the number of deaths due to all causes in the DES group (n=9) and the PTA group (n=4). The 12-month event free survival rate was, however, significantly higher in the DES group compared to the PTA group (90.4% vs 82.6%, \( p=0.004 \)). The most common reported adverse event was clinically driven target lesion revascularisation, which occurred more often in PTA patients (17.5%) than in DES patients (9.5%, \( p=0.01 \)) (Dake et al 2011a).

Reported 12-month patency rates\(^1\) were significantly higher in the DES group (83.1%) compared to the PTA group (32.8%, \( p=<0.001 \)), with acute failure counting as a loss of patency. Patency rates remained superior in the DES group even when the 120 acute failure PTA patients were removed from analysis and only optimal PTA patients were considered (83.1% vs 65.3%, \( p=0.001 \)). In the patient group who experienced acute PTA failure who then underwent further randomisation, patients with drug-eluting stents inserted had higher rates of patency at 12-months (89.9%) compared to those inserted with bare metal stents (73%, \( p=0.01 \)). These early results appear to show promise for the treatment of patients with peripheral vascular disease compared to conventional PTA and bare metal stents, however long-term follow-up data would be of interest (Dake et al 2011a).

Dake et al (2011b) conducted a large case series (n=787) on patients with PVD after the completion of the above RCT (level IV intervention evidence). The majority of patients were male (n=578) with hypertension (80%), hypercholesterolaemia (58%) and a history of smoking (80%). A total of 900 lesions were identified with an average length of 99.5 ± 82.1 mm (range 3-400). Patients were followed up at 1, 6 and 12-months with patency assessed using angiography or duplex ultrasound. At 12-months, 740 (94%) patients were available for follow-up.

A mean number of 1.9 Zilver PTX stents per lesion and 2.2 stents per patient were inserted, with 197 (25%) patients receiving two stents, 126 (16%) receiving three and 134 (17%) receiving four. Procedural success was achieved in 878 (97.6%) of lesions. Four deaths (0.5%) occurred within 30-days of the procedure and were therefore considered to be procedure-related: pulmonary embolism, cardiac ischaemia, myocardial infarction and renal failure due to excess use of contrast. Clinically driven

\(^1\) Restenosis rates are the complement of patency rates i.e. a patency rate of 83.1% results in a restenosis rate of 16.9%
target lesion revascularisation occurred in 70 patients (9.5%) and five patients (0.7%) experienced a worsening of their Rutherford Classification\(^2\) to class 5. Other adverse events included three (0.4%) patients with a haematoma that required intervention at the access site, 25 (3.2%) patients with cardiac ischaemia requiring intervention, stroke (n=3), myocardial infarction (n=3), renal failure requiring dialysis (n=2), pulmonary embolism (n=2), pulmonary oedema (n=2) and a reaction to contrast (n=4). A total of 22 (1.54%) stent fractures were reported at 12-month follow-up, the majority of which (n=14) were multiple strut fractures resulting in the displacement of segments of the stent (Dake et al 2011b).

At 12-months the event-free survival rate was 89 per cent with a primary patency rate of 86.2 per cent (restenosis = 13.8%). The ankle-brachial index, the Rutherford Classification and the walking distance/speed scores improved significantly from baseline measures to 12-month follow-up (Dake et al 2011b).

The aim of the Sirolimus Coated Cordis Self-expandable Stent (SIROCCO) trial was to evaluate the use of DES for the treatment of occluded superficial femoral arteries. This trial was conducted in two stages, an initial study with a follow-up period of six months (Duda et al 2002), and a later study of an expanded cohort of patients, followed-up prospectively for two years (Duda et al 2006). Patients were included in the study if they were at least 30 years of age, with symptomatic PVD classified as Rutherford stage 1 (mild claudication) to 4 (rest pain). Other inclusion criteria were obstructive (≥70%) de novo or restenotic lesions that ranged in length from 7 to 20 cm, or occlusions that ranged in length from 4 to 20 cm, in the superficial femoral artery. Exclusion criteria included poor aortoiliac or common femoral inflow, uraemia, aneurysmal target vessels, previously stented lesions, tandem lesions, ischaemic tissue loss, hepatic insufficiency, pregnancy, end-stage renal failure requiring dialysis, immunosuppressant therapy, and allergies to aspirin, heparin, sirolimus, nitinol, anti-coagulants, anti-platelet therapy or contrast media.

Study participants were recruited from a total of six centres, and randomised to treatment with sirolimus-eluting nitinol self-expandable stents or the nitinol self-expandable stents without the sirolimus coating (bare stent). Angiography was performed prior to, and after, stent placement, and at six months follow-up, while Rutherford classification, ABI assessment and duplex ultrasonography of the target lesion were performed post-procedure and at 1, 6, 9, 18 and 24 months follow-up. Analysis of angiographic data and duplex ultrasound examinations were performed by an independent core laboratory.

A total of 93 patients were enrolled in this study. Forty seven patients were randomly assigned to treatment with DES and 46 patients were treated with bare stents. The two

\(^2\) The Rutherford Classification is a clinical staging system used to describe PVD: Stage 0 = asymptomatic, Stage 1 = mild claudication, Stage 2 = moderate claudication, Stage 3 = severe claudication, Stage 4 = rest pain, Stage 5 = ischaemic ulceration not exceeding ulcer of the digits of the foot, Stage 6 = severe ischemic ulcers or frank gangrene.
treatment groups were well matched for baseline demographics and cardiovascular risk factors, with the exception of lesion calcification, with more patients experiencing severe calcification in the DES group (57%) compared with the bare stent control group (35%) (p=0.03).

In the SIROCCO trial, two patients in the DES group developed localised erythema a few days after stent implantation, and were treated with antibiotics for suspected cellulitis (Duda et al 2002). The erythema resolved without further therapy in both patients. The authors reported that the possibility that these events may have been related to the drug elution could not be ruled out; however, the occurrence of adverse events due to the systemic effects sirolimus was unlikely (Duda et al 2002).

Stent fractures (≥1 broken strut) were detected in nine patients (36%) in the DES group and eight patients (20%) in the control group (p=0.245), within the 18-month follow-up period (Duda et al 2006). An additional patient with a stent fracture was identified at the 24-month radiographic examination; however, the authors did not report which treatment this patient received. All of the patients that experienced stent fractures were asymptomatic, with the exception of one patient who was hospitalised for prophylactic placement of a covered stent-graft due to vessel ulceration at the site of a strut fracture (Duda et al 2006). At 24 months follow-up, no amputations had been performed as a complication of the stent procedure in either treatment group. A total of seven patients (15%) in the DES group died within the 24-month follow-up period, compared with two patients (4%) in the control group. In the DES group, death was due to stroke, lung emboli and cancer in one patient each, and cardiac disease and natural causes in two patients each. In the control group, death was due to complications of coronary bypass surgery in one patient, and progressive cardiac failure in the other.

Duda et al (2006) reported that technical success, defined as successful access and deployment of the device with recanalisation, was achieved in 100 per cent of procedures, while procedural success, defined as successful implantation without a SAE, was achieved in 95.7 per cent of procedures in both treatment groups. Table 1 presents the key clinical and angiographic outcomes reported by Duda et al (2006).

In both treatment groups, an immediate improvement in symptoms of claudication, as indicated by the Rutherford classification, was reported following stent implantation, and this was sustained over the 24-month follow-up period (data not shown). Similarly, the ABI improved in both groups following the stent procedure, and this improvement was maintained up to 24 months follow-up; however, no significant differences between the groups were observed at 24 months (p=0.127). Target-lesion revascularisation (TLR) was performed at a higher rate in control group patients compared with DES group patients during the 24-month follow-up period; however, no statistical analyses were provided for this outcome.
There was no difference in-stent restenosis rate, as measured by duplex ultrasound, between the two groups at 24-months follow-up ($p=1.00$), however there was a degree of variation in both groups as indicated by the wide confidence intervals. The cumulative in-stent restenosis rates were 4.7, 9.0, 15.6 and 21.9 per cent, respectively, at 6, 9, 18 and 24 months, and did not differ significantly between the two groups. The rate of total occlusion appeared higher in the control group; however, no statistical analyses were provided for this outcome.

Table 1: Clinical and angiographic outcomes at 24 months (Duda et al 2006)

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<th>Control group</th>
<th>DES Group</th>
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<td>ABI 0.84 ± 0.2 (n=37)</td>
<td>0.90 ± 0.17 (n=35)</td>
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<td>95% CI</td>
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<tr>
<td>Total occlusion, n/N (%)</td>
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Plus – minus values are mean ± SD; ABI: Ankle-brachial index; DES: Drug-eluting stent; TLR: Target-lesion revascularisation

Tepe et al (2008) investigated the effect of paclitaxel on restenosis after angioplasty of stenotic or occluded superficial femoral or popliteal arteries. Included patients were between 18 and 95 years of age and had symptomatic PVD (Rutherford stages 1 to 5). All patients had one or more obstructive lesions (either new lesions or restenosis) impacting at least 70 per cent of vessel diameter and at least 2 cm in length, in the superficial femoral artery, the popliteal artery, or both. If more than one lesion required intervention, only one was treated as the study lesion. Patients were excluded if they had poor inflow, an absence of a patent crural artery, an acute onset of symptoms, a life expectancy of less than one year, contraindications to required medication, or if they were pregnant.

There were three study groups, including those receiving: (a) standard balloon catheters coated with paclitaxel (DEBs), (b) uncoated balloons with paclitaxel dissolved in the contrast medium, and (c) uncoated balloons without paclitaxel (controls). Patients and investigators were not informed of the treatment assignment; however, the distinctive appearance of the DEBs could have been recognised by the investigators who also undertook some of the post-study assessments. Patients were evaluated at baseline, at 24 to 72 hours after the intervention, and six months after the intervention. All 6-month angiograms were assessed in a blinded fashion by an independent angiographic core laboratory. Additional assessments at 1 and 2 years were planned if differences between the groups were observed at six months, and these were in fact carried out.

A total of 154 patients were enrolled in the study between June 2004 and June 2005. Forty-eight patients were randomly assigned to treatment with DEBs, 52 to uncoated balloons with paclitaxel in the contrast medium, and 54 to the uncoated balloon.
control group. In this brief, the outcomes for second group (drug in contrast medium) will not be reported. At baseline, there were no statistically significant differences between the treatment groups.

Tepe et al (2008) reported that during or soon after the intervention, there were six (12%) adverse events in the control group, and four (8%) in the DEB group. In the control group, reported adverse events included one peripheral embolism (2%), one case of minor bleeding (2%), two cases of acute thrombosis up to two days after the intervention (4%), one case of increased blood pressure (2%) and one pseudoaneurysm of the left groin (2%). In the DEB group, reported adverse events included one peripheral embolism (2%), one case of minor bleeding (2%), one case of acute thrombosis up to two days after the intervention (2%), and one case of a swelling of the left forefoot (2%). During the intervention, there were two (4%) serious adverse events (SAEs) in the control group, and three (6%) in the DEB group. In the control group, reported SAEs included one case of left ventricular failure (2%), and one case of a peripheral artery occlusion (2%). In the DEB group, reported adverse events included one toe amputation (2%), one abrupt total occlusion (2%), and one cerebellar infarction (2%).

During the period from two weeks after the intervention until follow-up angiography at six months, 28 (52%) patients in the control group and 22 (46%) patients in the DEB group, experienced at least one SAE ($p >0.05$); the majority of these events were related to progression of atherosclerosis or underlying disease. In the DEB group, none of these SAEs were judged by the investigators to be related to the study medication. By six months follow-up, two (4%) patients in the DEB group and one (2%) patient in the control group had died. In addition, two (4%) patients in the DEB group had undergone major amputation (above the foot or higher). Importantly, both amputations were performed in elderly, obese patients who had Type 1 diabetes, and who entered the study with advanced disease. The authors reported that no haematologic or biochemical results suggested systemic effects of paclitaxel.

Tepe et al (2008) reported that procedural success, defined as completion of the procedure with less than 30 per cent residual stenosis of the target lesion, was achieved in 151 of 154 patients (98%) across all three treatment groups. In the three remaining patients, a residual restenosis of 30 to 40 per cent of the reference diameter was achieved. Table 2 presents the key clinical and angiographic outcomes reported by Tepe et al (2008).

Clinical assessment at six months was performed for 146 of the original 154 patients (95%). In both treatment groups, the degree of claudication, as indicated by the Rutherford classification, improved from severe at baseline (DEB: 3.4 ± 0.8; Control: 3.1 ± 0.8) to mild 72 hours after stent implantation (DEB: 1.1 ± 1.2; Control: 1.2 ± 1.5), and this improvement was sustained at six months follow-up (DEB: 1.2 ± 1.7; Control: 1.6 ± 1.6). However, the change in Rutherford stage between 72 hours and
six months follow-up was not significantly different between the two groups ($p=0.48$). Similarly, the change in ABI between 72 hours and six months follow-up was not significantly different between the two groups ($p=0.37$). The rate of TLR was significantly lower in the DEB group compared with the control group at 6, 12 and 24 months ($p<0.001$ for all).

### Table 2: Clinical and angiographic outcomes (Tepe et al 2008)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (N=54)</th>
<th>DEB Group (N=48)</th>
<th>% Difference between Control and DEB (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Rutherford stage from 72h to 6 mo</td>
<td>0.3 ± 1.8</td>
<td>0.1 ± 1.7</td>
<td>0.22 (-0.55 to 0.99)</td>
<td>0.48</td>
</tr>
<tr>
<td>Change in ABI from 72h to 6 mo</td>
<td>-0.1 ± 0.2</td>
<td>-0.1 ± 0.3</td>
<td>-0.03 (-0.16 to 0.09)</td>
<td>0.37</td>
</tr>
<tr>
<td>TLR at 6 mo, n (%)</td>
<td>20 (37)</td>
<td>2 (4)</td>
<td>33 (19 to 47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLR at 12 mo, n (%)</td>
<td>26 (48)</td>
<td>5 (10)</td>
<td>38 (22 to 54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLR at 24 mo, n (%)</td>
<td>28 (52)</td>
<td>7 (15)</td>
<td>37 (21 to 54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late lumen loss (mm)</td>
<td>1.7 ± 1.8</td>
<td>0.4 ± 1.2</td>
<td>1.3 (0.65 to 1.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiographic restenosis n/N (%)</td>
<td>21/48 (44)</td>
<td>7/41 (17)</td>
<td>27 (9 to 45)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total occlusion n/N (%)</td>
<td>4/48 (8)</td>
<td>1/41 (2)</td>
<td>6 (-3 to 15)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Plus–minus values are mean ± SD; ABI: Ankle-brachial index; DEB: Drug-eluting balloon; TLR: Target-lesion revascularisation.

Angiography was completed at six months in 128 of the original 154 study patients (83%). The primary efficacy end-point of mean late lumen loss was significantly lower in the DEB group compared with the control group ($p<0.001$). Similarly, the angiographic restenosis rate was significantly lower in the DEB group ($p=0.01$); however, the rate of total occlusion was not significantly different between groups ($p=0.37$).

**COST IMPACT**

A recent study examined the economic implications of treating atherothrombotic disease (including PVD) in Australia, from a government perspective (Ademi et al 2010). Subjects were eligible if they were aged ≥45 years and had either established atherothrombotic disease (coronary artery disease, cerebrovascular disease, or PVD) or ≥3 CVD risk factors. Established PVD was defined as either a history of intermittent claudication with a previous related intervention (e.g. angioplasty, stenting, atherectomy, peripheral artery bypass graft surgery, or other vascular intervention, including amputation), or current intermittent claudication with an ABI of <0.9. This study reported that the management of atherothrombotic disease in Australia was costly during the period studied, particularly among those with PVD. Specifically, for participants suffering from PVD only, the annual pharmaceutical,
ambulatory care and hospital costs per person were $1177, $798 and $14,727, respectively. The hospital costs for participants suffering from PVD were higher than those for other atherothrombotic diseases due to their high rates of vascular intervention.

No cost-effectiveness studies were identified for the use of drug-eluting devices in PVD treatment. Similarly, the cost of individual DEBs currently in use in clinical practice in other countries could not be obtained. The cost of the CYPHER SELECT + Sirolimus-eluting infrapopliteal stent in Australia, provided by the Sponsor (Johnson & Johnson Medical Pty Ltd), is $3,450.

It is still unclear whether the costs associated with using drug-eluting devices would offset the additional costs associated with performing procedures to treat restenosis following standard peripheral stenting and angioplasty procedures. Importantly, DEBs are designed for single-inflation only, and some calcified, long, or locally dissected lesions may require multiple inflations and multiple DEBs, thus increasing the cost of the procedure (Chan and Cheng 2011).

**ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

There were no issues identified from the retrieved material.

**OTHER ISSUES**

The two studies conducted by Dake et al (2011a and 2011b) were sponsored by Cook Medical.

The SIROCCO trial (Duda et al 2002, Duda et al 2006) was sponsored by Cordis Corporation (the manufacturer of the stents used in the study). One author was a paid consultant for Cordis, two authors were employees of Cordis, and three authors received research grants from Cordis, or parent company Johnson & Johnson. All other authors received financial support to conduct the study.

The trial by Tepe et al (2008) was sponsored by Bavaria Medizintechnologie (the manufacturer of the balloon catheters used in the study) and Schering, Germany; however, it was stated that the sponsor had no involvement in the design of the trial, collection and analysis of the data, or writing of the report. Other conflicts of interest reported in the study were:

- Two authors reported serving as consultants to and receiving grant support from Schering, Germany.
- One author reported serving as a consultant to Abbott and receiving grant support from Abbott, BSP, Cordis, Cook Medical, Eli Lilly, and Sanofi-Aventis.
- Two authors reported being co-inventors on a patent application for various methods of inhibiting restenosis (including the techniques used in the current trial), which was submitted by Charité University Hospital in Berlin.
• One author reported receiving consulting fees from OptiMed and Pathway Medical Technologies; lecture fees from Cardax Pharmaceuticals, Invatec/Krauth, Bard, and Straub Medical; and grant support from Krauth Medical.

• One author reported receiving consulting fees from Cordis Johnson & Johnson and Sanofi Synthelabo and lecture fees from EV3, Boston Scientific, and Cordis Johnson & Johnson.

**SUMMARY OF FINDINGS**

The use of DES did not appear to confer any specific advantages over the use of bare stents for the treatment of PVD, based on the results from one randomised, multicentre trial included in this brief. Improvements in clinical outcomes, including symptoms of claudication and ABI were seen in both groups; however, no significant differences between the treatment groups were reported at two years follow-up. Similarly, angiographic outcomes including in-stent restenosis and rate of total occlusion did not differ significantly between the two groups. The use of DES appears to be safe, and no adverse events were directly attributed to the systemic effects of sirolimus.

However, the later study by Dake et al (2011a) indicates that drug-eluting stents do appear to confer an advantage when compared to percutaneous transluminal angioplasty alone and bare metal stents, with improved clinical outcomes including significantly higher rates of patency at 12-month follow-up.

Consideration should be given to the increased cost of drug-eluting stents in comparison with bare metal stents. Currently the only DES for insertion into the peripheral vasculature listed on the Prostheses List has a minimum benefit of $2,400 compared to a listed bare metal stent, the Maris Plus Peripheral Self-Expanding Stent System, which has a minimum benefit of $1,800.

The results from one randomised, multicentre trial included in this brief showed that the use of DEBs for the treatment of PVD significantly improved some outcomes up to two years after treatment when compared with the use of uncoated balloons. Significant reductions in late lumen loss, rate of restenosis and rate of target-lesion revascularisation were observed. However, rates of total occlusion, and reductions in Rutherford stage and ABI did not differ significantly between groups. The use of DEBs appears to be safe. No adverse events were attributed to the use of paclitaxel and no haematological or biochemical results suggested systemic effects of the drug.

**HealthPACT Assessment**

The Zilver PTX stent is listed on the Australian Government Department of Health and Ageing Private Health Insurance Prosthesis List, which indicates that there is no barrier to using these stents in the private sector. Therefore HealthPACT has
recommended that information on this technology be noted and that no further research by HealthPACT is warranted at this point in time.

**NUMBER OF STUDIES INCLUDED**

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
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<tr>
<td>Total number of studies</td>
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</tr>
<tr>
<td>Total number of Level II intervention evidence studies</td>
<td>3</td>
</tr>
<tr>
<td>Total number of Level IV intervention evidence studies</td>
<td>1</td>
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</tbody>
</table>

**REFERENCES**


**SEARCH CRITERIA TO BE USED**

(Drug-eluting balloon* (text) OR Drug-eluting stents (MeSH) AND (Peripheral vascular diseases (MeSH) OR Peripheral arterial disease (MeSH)))