Zilver PTX Drug-Eluting Peripheral Stents to Treat Peripheral Arterial Disease of the Femoropopliteal Vessels

Summary

✓ The Zilver PTX drug-eluting peripheral stent is a minimally invasive endovascular drug/device combination used to treat the de novo or restenotic, symptomatic lesions of peripheral arterial disease in the (above-the-knee) superficial femoral and popliteal arteries.

✓ There appears to be promising evidence from randomized trials and other studies concerning the sustained safety, effectiveness (anatomic and clinical end points), procedural success and stent integrity to support the use of these stents as initial therapy over their bare metal counterparts, as well as traditional percutaneous transluminal (balloon) angioplasty and, particularly, for less complex lesions.

✓ More evidence may be required to permit reaching a similar conclusion regarding their first-line use with more complex lesions, in-stent restenosis, and patients with diabetes.

✓ The possible cost-effectiveness as initial therapy likely needs to be investigated using Canadian fiscal data, and could depend upon a decreased need to re-intervene for restenosis.

The Technology

Recently designated a notable, emerging health technology,¹ Cook Medical’s (Bloomington, Indiana, US)² Zilver PTX drug-eluting peripheral stent is a minimally invasive endovascular drug/device combination used to treat peripheral arterial disease (PAD) in the (above-the-knee) superficial femoral and popliteal (femoropopliteal) vessels.³⁴ Successfully treating its lesions should improve blood (oxygen) flow, which in the case of femoropopliteal PAD could help slow its progression, and which in general is vital to maintaining the health of the lower limbs.⁵⁻⁸ The tubular stent incorporates a flexible, self-expanding mesh-metal nitinol platform with a polymer-free paclitaxel coating at 3 mcg/mm² dose density on its outer surface; essentially functioning as a drug-eluting mechanical scaffold that holds open a narrowed or blocked artery, the device is deployed percutaneously to treat de novo or restenotic (re-narrowed) symptomatic lesions in femoropopliteal arteries that can have a reference vessel diameter from 4 mm to 9 mm, total lengths up to 140 mm per limb, and a total of 280 mm per patient.⁹⁻¹⁸ Effective in preventing restenosis following coronary artery stenting, paclitaxel is a hydrophobic and highly lipophilic drug whose gradual release alters microtubule formation. This inhibits the vascular smooth muscle cell proliferation and migration primarily in the tunica intima (innermost layer) that is responsible for the thickening of arterial walls following injury (after angioplasty), which in turn prevents vessels from re-narrowing or becoming reoccluded.⁵⁻⁹,¹¹⁻¹⁹,²² With a narrow therapeutic range, at higher concentrations paclitaxel can disrupt the internal elastic lamina (layer), in addition to reducing intimal and medial smooth muscle cells, and collagen content.²³ A polymer-free coating can avert inflammatory and thrombotic reactions.⁹,¹²

A drug, such as paclitaxel, when added to the linear cell design and tight-bending radius of the Zilver PTX stent’s mesh-metal base — whose flexibility and durability allow it to return to its original shape after external pressure is removed — has been thought necessary to help meet the challenge of treating lesions within the long femoropopliteal vessels. Compared to other arteries, these vessels undergo severe and unique conformational changes during limb movement from biomechanical, anatomic, and hemodynamic forces (elongation, foreshortening, flexion, compression, and torsion), and which heighten the risk of adverse events from stenting, especially yet not solely for the longer and more complex lesions commonly seen in clinical settings. Possible outcomes include:

• strong inflammatory responses to stent micro-movements
• fractures from metal fatigue
• fractures from a hinge point produced when stents are overlapped to treat longer lesions
• high rates of recurrent lesion within a year (20.0% to 40.0%).⁹,¹⁵⁻¹⁹,²¹⁻²⁹
PAD refers to any typically chronic and potentially progressive, pathological process causing obstruction to the flow in the arteries, exclusive of the coronary and brain vasculature. These narrowings or complete occlusions usually result from atherosclerosis (the deposition of fatty plaques in the arterial wall). \(5,7,19,30,31\) In the lower extremities, PAD can cause intermittent claudication (leg muscle discomfort on exertion that can be relieved by rest), severely limit mobility, hinder performance of daily tasks at home or work, and diminish quality of life. \(5,7,31-33\) A small proportion of PAD patients progress to critical limb ischemia (pain at rest, ulceration, and gangrene) — a condition which carries a significant risk of amputation if not treated by a revascularization procedure (angioplasty, bypass, etc.). \(34\)

Yet, the presence and severity of PAD’s symptoms can vary across patients, as well as across a lifetime: up to 20.0% of patients exhibit typical symptoms of claudication or critical limb ischemia, up to 50.0% have atypical or no symptoms while walking or exercising, and 2.0% of claudicants may need an amputation. \(35-39\) Many patients are asymptomatic for years, and this changes for some only when an artery has narrowed by 50.0% or more. \(3\) Even so, asymptomatic PAD can bring about impaired lower-extremity functioning, increased mobility loss, and a faster functional decline than in those without PAD. \(40-42\)

In part due to the aging of the world population from 2000 to 2010, the estimated number of global PAD cases increased by 23.5%, from 164 million to 202 million. \(31\) These may be underestimates, though; as the indicator of stenosis in lower limb arteries, the study employed an ankle-brachial pressure index of ≤ 0.90 at rest, and its sensitivity is likely less than 80.0%. \(43\) Other methods (duplex ultrasonography, toe pressures) may more reliably detect PAD’s mild forms. \(44\) About 800,000 Canadians may have PAD. \(1,5,45,46\)

The risk of PAD increases with age. \(8,19,31,37,45,47,48\) Its estimated prevalence in Canadians older than 40 years is 4.0%, and approaches 20.0% in those over the age of 75 years. \(5,46\) Other risk factors include a history of smoking, diabetes, hypertension, and hypercholesterolemia. \(6-8,31,47,49-52\) Among patients with diabetes, for example, the risk of PAD increases two-to-four-fold; symptoms can be severe and extensive, and may be associated with lesions showing a greater degree of calcification or with a greater need for a major amputation due to ischemia (poor blood flow). \(5,8,18,47,52,53\)

PAD is the third-leading cause of atherosclerotic cardiovascular morbidity, after coronary artery disease and stroke. \(30,31,54\) Cardiovascular disease and atherosclerosis in other vascular beds influence its prognosis in patients without diabetes. \(30\) Moreover, especially but not exclusively, PAD’s more advanced forms are associated with an increased risk of ischemic cardiovascular and cerebrovascular events, stroke, coronary heart disease, myocardial infarction, a cardiovascular-related death, and 10-year all-cause mortality. \(34,55-57\) Yet, Canadians are largely unaware of its prevalence, morbidity, and risk of mortality. \(45\)
Current Practice

Globally, it has been estimated that about 25.0% of PAD patients receive some medical attention. Mainstay strategies have included lifestyle risk factor modification and cardiovascular/atherosclerosis risk reduction (smoking cessation, glycemic/diabetes control, treatment of dyslipidemia and hypertension), exercise and rehabilitation programs, pharmacotherapy (to address difficulties associated with claudication, atypical levels of antiplatelets or angiogenic growth factors, and reduced overall functional status and quality of life), and endovascular or surgical revascularization. As many as 70.0% of patients may remain stable or improve in response to the most conservative forms of management (risk modification/reduction, pharmacotherapy for the underlying disorder); but for those who do not, revascularization could be recommended as the initial intervention, with some methods less likely to produce adverse effects. At least 25.0% of Canadian PAD cases may require surgical or other endovascular procedures (angioplasty, stents, etc.). With the increasingly promising clinical and procedural performance of less invasive endovascular strategies, bypass surgery (grafts taken from the patient’s vein or made from synthetic materials), especially for short lesions (< 10 cm), may become a second-line option to be used as initial therapy for complex lesions or upon failure of other endovascular methods. While it can produce durable outcomes, this surgery also brings increased morbidity, prolonged recovery, and an increased risk of mortality. Of the endovascular alternatives, percutaneous transluminal (balloon) angioplasty (PTA) — to stretch and widen a vessel — has been the standard of care.

In Canada and elsewhere, bare metal (self-expanding, nitinol) peripheral stents are being increasingly employed. They were developed to avoid PTA’s limitations, which include:
- early elastic recoil
- residual stenosis
- flow-limiting dissections and problematic patency
- difficulty treating more complex (longer, calcified) lesions
- one-year restenosis rates (often ≥ 60.0%) that worsen as lesion complexity increases.

But also, perhaps because of their enhanced conformability and radial strength in holding vessels open, the improved ability of second-generation nitinol stents to foster longer-term patency, prevent restenosis, and avoid the complications linked previously to their use (fracture) makes them a viable initial intervention for some patients. That is, stenting may be more than just a bailout or provisional option in response to suboptimal PTA. In 2010-2011, stenting procedures for PAD in Ontario were estimated at 1.77 per 100,000. However, several studies have revealed limited, sustained benefits associated with the use of bare metal stents, and especially for complex femoropopliteal lesions (19.0% to 37.0% restenosis rates).

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: PubMed, Embase, EuroScan, and The Cochrane Library (2014, Issue 6). Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). No filters were applied to limit the retrieval by study type. Conference abstracts were removed from search results. The search was limited to English language documents published between January 1, 2009 and July 24, 2014. Regular alerts were established to update the search until September 30, 2014.

The Evidence

An industry-sponsored, open-label, randomized trial (Zilver PTX RCT) enrolled 479 patients with symptomatic de novo or restenotic femoropopliteal lesions from 55 sites in the US, Japan, and Germany. The RCT was designed to compare the safety and effectiveness of primary stenting using the Zilver PTX drug-eluting peripheral device (n = 241) first with that of PTA (performed according to a given centre’s practice standard; n = 238), and then with provisional bare metal stenting (Zilver) for patients whose response to PTA was suboptimal (acute failure) (NCT00120406). By randomizing the latter set of patients (n = 120) to provisionally receive either Zilver PTX (n = 61) or bare metal stents (n = 59), the second phase aimed to determine the benefits of paclitaxel. All patients received the same antiplatelet regimen. Anatomic and clinical end points were evaluated. While selection criteria were well-defined, they were narrower than those employed in the complementary, industry-sponsored, single-arm, multi-centre Zilver PTX study...
The latter evaluated the stent’s safety and benefits in a more clinically diverse group of patients: those with symptomatic de novo or restenotic lesions with > 50.0% diameter stenosis, including in-stent stenosis; occlusions present in a third of the patients; and, patients with lesions up to twice the length of those allowed in the RCT.

Primary patency (via duplex ultrasonography) results reveal primary Zilver PTX stents’ statistically significant and sustained comparative advantage over PTA — not to mention when data concerning the use of provisional bare metal stents are combined with the PTA results — and provisional Zilver PTX stents’ superiority over provisional bare metal stents (Table 1).

At 36 and 48 months, the comparative advantage reflected a 42.0% and 41.0% reduction in the restenosis rate, respectively. Of the lesions in the PTA group that were still patent at one year, 13.7% (n = 10/73) had lost patency by two years; 9.3% (n = 17/182) was the corresponding rate in the primary Zilver PTX group (P = 0.37). At 24 months, primary Zilver PTX stenting was likewise superior to PTA for notable subgroups of patients (those with or without diabetes) and lesion complexity (P < 0.01). Also at two years, patients in the single-arm study with the most complex lesions (TASC II C/D) exhibited a 77.6% primary patency rate; and primary patency for patients with in-stent restenosis was 78.8% in this cohort. No significant differences in primary patency at 12 months in the single-arm study distinguished patients with and without diabetes.

From the “paclitaxel effect” analyses, the comparative advantages at 12, 36, and 48 months reflect a more than 60.0%, 53.0%, and 41.0% reduction in the restenosis rate, respectively. Of the lesions in the provisional bare metal stent and provisional Zilver PTX groups that were still patent at one year, 12.2% (n = 5/41) and 7.4% (n = 4/54) had lost patency by 24 months, respectively (P = 0.49). At 12 months, the likelihood of patency did not distinguish the primary Zilver PTX and provisional Zilver PTX stent groups (log rank P = 0.11). Covariate analysis of early RCT data found that patients who received the Zilver PTX stent and adhered to dual-antiplatelet therapy at one month — but not at three months — exhibited a higher patency rate than those on single-antiplatelet therapy.

<table>
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<th>Table 1: Analyses of Primary Patency Data (Zilver PTX RCT)</th>
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<td><strong>Comparison</strong></td>
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<td>Primary Analysis: Primary Zilver PTX stent vs —</td>
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<td>• PTA</td>
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<td>Secondary Analysis: Primary Zilver PTX stent vs optimal PTA</td>
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<td>“Paclitaxel Effect”: Provisional Zilver PTX stent vs provisional BMS</td>
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</table>

BMS = bare metal stents; NR = not reported in identified disseminations (published and unpublished); PTA = percutaneous transluminal (balloon) angioplasty; RCT = randomized controlled trial; vs = versus.

aLog rank P < 0.001.
bLog rank P < 0.01.
cLog rank P = 0.01.
dLog rank P = 0.02.
eLog rank P = 0.04.

Results from analyses of data concerning a possible “clinical benefit” (freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss) establish primary Zilver PTX stents’ statistically significant and sustained comparative advantage over PTA, as well as provisional Zilver PTX stents’ superiority over provisional bare metal stents (Table 2).
In both the primary Zilver PTX and PTA groups within the RCT, the Rutherford classification, ankle-brachial pressure index (ankle:wrist ratio) at rest, and the Walking Impairment Questionnaire scores at 12 months, although patients within the latter subgroup obtained a significantly better walking score than those within the former one. Only longer lesion length, less favourable Rutherford classification, and lack of hypertension — but not diabetes status — negatively influenced patency. Zilver PTX RCT results at two years were similar in the Japanese and non-Japanese cohorts, yet positive outcomes, such as patency, were even more likely in Japanese patients treated with primary Zilver PTX stents than in their counterparts. An independent quality appraisal has raised the possibility that there may have been some bias characterizing this otherwise well-conceived and complex RCT, and which, if confirmed, might temper some of the confidence in its results. It was unclear as to how the trialists concealed patients’ allocation to treatment arms or achieved blinding of outcome assessments; alone, each of these limitations in methodology can undermine even the gold standards of random sequence generation. Also, participants and personnel were not blinded, all risk factors may not have been checked for possible baseline differences, and there may have been incomplete outcomes data. Five-year results will initially be presented at the November VIVA —Vascular Interventional Advances — 2014 meeting in Las Vegas.

Results from completed and ongoing, and prospective, post-marketing studies of varying sizes —with some data shared recently at conferences — support the 12-month effectiveness of the Zilver PTX stents regarding primary patency; their variable rates might be explained by differences in the complexity of lesions, including in-stent restenosis or other patient qualities: 84.8% (n = 907);77 71.0% (n = 89);80 67.0% (n = 75);81 57.0% (n = 65);82 86.1% (n = 45);83 85.5% (n = 69). Data from smaller prospective studies, as well as from efforts that collated data retrospectively, appear to confirm the stent’s value. Other prospective trials have recently been completed or continue to recruit or enroll patients (James Gardner, Cook Medical, Bloomington (IN): personal communication, 2014 Aug.):

- industry-sponsored, open label, single-group studies in the US (n = 200: NCT01901289);85 and China (n = 175: NCT02171962);86
- industry-supported RCTs in Europe (ZILVERPASS: Zilver PTX stents versus bypass surgery of complex lesions (n = 220: NCT01952457);97
- REAL PTX: Zilver PTX stents versus paclitaxel-eluting balloons (n = 150: NCT01728441);98
- three, independent RCTs: bare metal stents versus Zilver PTX stents in intermediate lesions in France (BATTLE, n = 186: NCT02004951);99 Finnish patients with long lesions given Zilver PTX stents or bypass surgery (FINNPTX, n = 400: NCT01450722);100 and Danish patients receiving PTA plus Zilver PTX stents plus risk modification plus medical therapy, or risk modification plus medical therapy (PESETA, n = 84: NCT02033135).101

<table>
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<th>Table 2: Analyses of Clinical Benefit (Zilver PTX RCT)</th>
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<td>Comparison</td>
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<td>Primary Zilver PTX stent vs PTA</td>
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<td>Provisional Zilver PTX stent vs provisional BMS (“paclitaxel effect”)</td>
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</table>

BMS = bare metal stents; NR = not reported in identified disseminations (published and unpublished); RCT = randomized controlled trial; vs = versus.

<sup>a</sup>Log rank P < 0.01.
<sup>b</sup>Log rank P < 0.01.
<sup>c</sup>Log rank P = 0.009.
<sup>d</sup>Log rank P = 0.05.
### Adverse Effects

Event-free survival results (EFS: freedom from adjudicated major adverse events of death, amputation, clinically driven target lesion revascularization [TLR], target limb ischemia requiring bypass surgery or surgical repair of the target vessel, and freedom from worsening of the Rutherford classification by two classes or to class 5 or 6) exhibit primary Zilver PTX stents’ statistically significant and sustained superiority over PTA (Table 3).

#### Table 3: Analyses of Adverse Effects (Zilver PTX RCT)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>At 12 Months</th>
<th>At 24 Months</th>
<th>At 36 Months</th>
<th>At 48 Months</th>
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<tr>
<td>EFS: Primary Zilver PTX stent vs PTA</td>
<td>90.4% vs 82.6%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>86.6% vs 77.9%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Freedom from TLR: Primary Zilver PTX stent vs —</td>
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<tr>
<td>• PTA</td>
<td>90.5% vs 82.5%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>86.6% vs NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>• Optimal PTA or provisional BMS</td>
<td>NR</td>
<td>NR</td>
<td>83.7% vs 70.2%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>83.2% vs 69.4%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

BMS = bare metal stents; EFS = event-free survival; NR = not reported in identified disseminations (published and unpublished); RCT = randomized controlled trial; TLR = target lesion revascularization; vs = versus.

<sup>a</sup>Log rank, *P* = 0.004.

<sup>b</sup>Log rank, *P* = 0.02.

<sup>c</sup>Log rank, *P* = 0.01.

<sup>d</sup>Log rank, *P* < 0.01.

The single-arm study’s two-year and one-year EFS rates were 79.3% and 89.0%, respectively, for Zilver PTX stents; at 24 months, the rate for patients with the most complex lesions was 84.7%. At 12 months, patients with and without diabetes did not differ significantly in EFS.

At each of 12 and 24 months, the most common adverse event within the RCT and single-arm study — including for patients either with or without diabetes — was clinically driven TLR (re-intervention required for worsening symptoms and greater than 50% diameter stenosis); decisions to re-intervene were made by an unblinded physician. Two-year results for this outcome were reported as having extended primary Zilver PTX stents’ statistically significant comparative advantage over PTA, although one 24-month datum and the related *P*-value were not provided. Results at 36 and 48 months demonstrated the sustained superiority of Zilver PTX stents over a control group of patients who received either optimal PTA or provisional bare metal stents. At both follow-ups, this amounted to a 45.0% reduction in the need to re-intervene; overall, these observations suggest the durability of the treatment. Moreover, cases of restenosis at 36 months appeared to be more focal and less complex; as these less complicated lesions typically afford greater flow rates to the lower extremities, simpler and less costly re-interventions could be indicated.

By contrast, the proportion of patients free from TLR with Zilver PTX placement in the single-arm study was 80.5% at 24 months (12 months: 90.5% for all patients; 60.8% for those with in-stent restenosis); the rate for those with the most complex lesions was 85.4%. At 12 months, there was no evidence suggesting a difference between patients with and without diabetes. As with the picture of benefits, safety profiles in the Zilver PTX RCT were similar in the Japanese and non-Japanese cohorts, yet freedom from various adverse effects was even more likely in Japanese patients treated with primary Zilver PTX stents than in their counterparts. Covariate analysis of early RCT data found that only smoking affected the likelihood of TLR.

No device-related deaths were observed over two years in both Zilver PTX studies. All-cause death (malignancy, pulmonary disease, congestive heart failure) was higher in the primary Zilver PTX group (7.6% [n = 18]) than in the PTA arm (3.4% [n = 8]); a significant difference was not found at 12 months (*P* = 0.17). The all-cause death rate in the single-arm study was 5.2% (n = 41), which did not differ significantly from either of the RCT’s primary Zilver PTX or PTA groups (*P* = 0.12). In both Zilver PTX studies, amputation (< 1%) and worsening Rutherford classification (< 2%) were rare at both one and two years. No reports of hypersensitivity reactions or adverse effects due to the paclitaxel coating or nitinol base were made over two years in either study.
Assessed by radiograph at 12 months, no periprocedural stent fractures were identified; the fracture rate for any Zilver stent was 0.9% (4/457), and no fracture produced a major adverse event. At 12 months, patients in the single-arm study exhibited a 1.5% fracture rate.

Two-year post-marketing data support the safety profile of Zilver PTX stents. A Japanese registry found that, of those receiving the device, 91.4% did not require reintervention. The thrombosis/occlusion rate was low (3.2%) and was more similar to what was found at one year in the Zilver PTX RCT’s bare metal stent group (3.6%) than in this trial’s paclitaxel-coated stent group (1.9%) or in the single-arm study (2.7%). Other one-year data revealed a freedom from TLR rate of 85.0% in two efforts (n = 89; n = 75), and 63.0% for mostly complex lesions; the EFS rate was 86.1% in a study of long lesions (n = 45).

In April 2013, Cook Medical initiated a global recall of its stent based on a small number of complaints that its delivery system had separated at the tip of the inner catheter. To avoid causing any possible harm, the company instructed customers to stop use, quarantine, and return all affected products (all sizes, diameters, and lot numbers prior to April 16, 2013). After an exhaustive quality assessment and audit of the affected components, the issue was resolved and the manufacturer began redistributing the product in August 2013.

Administration and Cost

Input from the manufacturer indicated that, as a number of factors will likely affect the price of the Zilver PTX stent for any given Canadian hospital, it prefers not to quote a single price (James Gardner, Cook Medical, Bloomington (IN): personal communication, 2014 Aug.). Still, it anticipates that the price will fall between that of bare metal stents and covered stents. Reimbursement for a Zilver PTX stent in 2011 in France was €1,000, which reflected a 19.0% premium over the value of a bare metal stent.

Employing hospital episode data, as well as early input from the Zilver PTX RCT, two-year data from its complementary single-arm study, and the wider literature concerning bare metal stents, a French budget impact model was developed. It looked at the impact on reimbursement of the introduction of the Zilver PTX stent, and the possible, progressive transition to its use over five years from bare metal stents. After estimating that a re-intervention procedure to treat in-stent restenosis (i.e., TLR) can cost between €3,225 and €8,072 per patient, it was concluded that adoption of the Zilver PTX stent could lead to a cost savings from one year onward, and would be sustained for five years for the French public health care payer. As a result, compared to bare metal stents, and despite a higher initial cost, fewer required therapeutic re-interventions (and hospitalizations) due to restenosis following primary Zilver PTX implantation would result in a net savings. A cumulative, five-year budget reduction of €6,807,202 was estimated on the basis of a projected patient population of 83,316; of those patients, 26.0% (n = 21,361) would be receiving the Zilver PTX device. Long-term data from the Zilver PTX studies, and with a special emphasis on evidence from patients with more complex lesions, are likely required to confirm that this benefit applies to real-world clinical settings.

A second economic study looked at the budget impact over 24 months of both drug-eluting and non-drug-eluting angioplasty balloons and stents for femoropopliteal lesions in the United States and Germany. They concluded that drug-eluting procedures (when taken together) had a lower projected budget impact, drug-eluting stents had a notably lower projected impact than did their bare metal counterparts, and drug-eluting balloons exhibited a lower projected impact than did drug-eluting stents. However, the Zilver PTX device was not the only drug-eluting stent entered into the model. The application of a less rigorous modelling strategy to early Zilver PTX data exclude a third cost analysis from consideration here.

While the economic ramifications of the use of Zilver PTX stents for Canadian hospitals and provincial funding authorities have not been formally studied, when compared with bare metal stents, their somewhat higher anticipated purchase price in Canada could be offset by reduced spending on re-interventions; this expectation should hold despite the fact that the systems and practices by which health care is financed within the countries whose data informed the aforementioned economic studies (completed activity-based funding) differ from those in Canada (primarily global budget funding) (James Gardner, Cook Medical, Bloomington (IN): personal communication, 2014 Aug.).
Concurrent Developments

Arguably foremost among the recent developments are two sets of endovascular interventions that were designed to achieve revascularization and prevent restenosis: self-expanding nitinol stents that elute other drugs to reduce cell proliferation (everolimus, sirolimus), and drug-eluting balloons (paclitaxel) that are intended to do the same.

Of note, at present it is unknown how paclitaxel-eluting balloons and Zilver PTX stents fared head-to-head in the recently completed REAL PTX RCT. Also intended to limit in-stent restenosis are polytetrafluoroethylene-covered, self-expanding nitinol stents; a recent Bayesian network meta-analysis has suggested that, while covered stents may exhibit better procedural success, paclitaxel-eluting stents and balloons may show superior long-term patency. But within current Canadian or other practice documents, no drug-eluting technology is yet considered an example of reliable provisional/bailout or initial care, let alone a standard of such care. Other developments include:

- drug-eluting, as well as non-drug-eluting, bioresorbable vascular scaffolds, which were designed to avoid leaving residual material that can promote inflammation or the risk of fracture seen with metal stents.
- stent grafts (a tube composed of fabric, supported by a mesh-metal stent)
- various forms of (excisional, rotational, laser) atherectomy that remove atherosclerotic plaque from a vessel or grind it into small particles.

Rate of Technology Diffusion

There appear to be no legal, ethical, political, or social-value barriers to the adoption of the practice of Zilver PTX implantation. If, at the very least, when compared with bare metal stents, its greater effectiveness and cost-effectiveness continue to be affirmed via post-marketing studies, its rate of diffusion could largely depend upon it being made available (and reimbursed) for use in Canadian jurisdictions. This would require decision-makers’ knowledge of the growing evidence-based case in favour of their use, as well as practitioners’ willingness to employ them.

Implementation Issues

There are no technical or logistical barriers to their implementation, as their implantation and maintenance require the same procedures that are currently used for bare metal stents. Notable training or implementation/infrastructure costs are unlikely.

In conclusion, there appears to be promising evidence of the sustained safety, effectiveness (anatomic and clinical end points), procedural success, and stent integrity — particularly yet not exclusively from the complex, and in all probability, methodologically sound Zilver PTX RCT — of Zilver PTX stents to support its use as initial therapy over bare metal stents, as well as PTA whose balloons are not drug-eluting, and particularly for less complex femoropopliteal arterial lesions. More evidence may be required to permit reaching a similar conclusion regarding their front-line use with more complex lesions, in-stent restenosis, and patients with diabetes. Their possible cost-effectiveness as initial therapy likely needs to be investigated using Canadian fiscal data, and could depend upon a decreased need to re-intervene to deal with restenosis. A formal health technology assessment may be indicated in the next 12 to 18 months.

References


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