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Health Quality Ontario

Paclitaxel Drug-Eluting Stents in Peripheral Arterial Disease: A Health Technology Assessment

HEALTH QUALITY ONTARIO

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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ABSTRACT

Background

Peripheral arterial disease is a condition in which atherosclerotic plaques partially or completely block blood flow to the legs. Although percutaneous transluminal angioplasty and metallic stenting have high immediate success rates in treating peripheral arterial disease, long-term patency and restenosis rates in long and complex lesions remain unsatisfactory.

Objective

The objective of this analysis was to evaluate the clinical effectiveness, safety, cost-effectiveness and budget impact of Zilver paclitaxel self-expanding drug-eluting stents for the treatment of *de novo* or restenotic lesions in above-the-knee peripheral arterial disease.

Data Sources

Literature searches were performed using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews. For the economic review, a search filter was applied to limit search results to economics-related literature. Data sources for the budget impact analysis included expert opinion, published literature, and Ontario administrative data.

Review Methods

Systematic reviews, meta-analyses, randomized controlled trials, and observational studies were included in the clinical effectiveness review, and full economic evaluations were included in the economic literature review. Studies were included if they examined the effect of Zilver paclitaxel drug-eluting stents in *de novo* or restenotic lesions in above-the-knee arteries. For the budget impact analysis, 3 scenarios were constructed based on different assumptions.

Results

One randomized controlled trial reported a significantly higher patency rate with Zilver paclitaxel drug-eluting stents for lesions ≤ 14 cm than with angioplasty or bare metal stents. One observational study showed no difference in patency rates between Zilver paclitaxel drug-eluting stents and paclitaxel drug-coated balloons. Zilver paclitaxel drug-eluting stents were associated with a significantly higher event-free survival rate than angioplasty, but the event-free survival rate was similar for Zilver paclitaxel drug-eluting stents and paclitaxel drug-coated balloons.

No economic evaluations compared Zilver paclitaxel drug-eluting stents with bare metal stents or angioplasty for peripheral arterial disease. A budget impact analysis showed that the cost savings associated with funding of Zilver paclitaxel drug-eluting stents would be $470,000 to $640,000 per year, assuming that the use of the Zilver paclitaxel drug-eluting stent was associated with a lower risk of subsequent revascularization.

Conclusions

Based on evidence of low to moderate quality, Zilver paclitaxel drug-eluting stents were associated with a higher patency rate than angioplasty or bare metal stents, and with fewer adverse events than angioplasty. The effectiveness and safety of Zilver paclitaxel drug-eluting stents and paclitaxel drug-coated balloons were similar.

PLAIN LANGUAGE SUMMARY

Sometimes blood clots narrow the arteries in the thighs and legs. Treatment includes bypass surgery, or keeping the narrowed blood vessel open using a balloon (called *angioplasty*) or a small metal mesh tube (called a *stent*). Angioplasty and stents are not as invasive as surgery, but they become less effective over time. Paclitaxel is a drug that can stop the arteries from thickening. Stents that release paclitaxel may do a better job of keeping narrowed blood vessels open. This study looked at whether stents that release paclitaxel are safe and effective for treating narrowed arteries above the knee. We found that drug-releasing stents were more effective and had fewer side effects than angioplasty and plain stents. Funding this stent would save money for the Ontario health system if patients needed fewer follow-up surgeries.

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BACKGROUND

Clinical Need and Target Population

Description of Disease/Condition

Peripheral arterial disease is a condition in which atherosclerotic plaques in the arteries partially or completely block blood flow to the legs. Its earliest symptom is intermittent claudication (defined as pain during ambulation). As the disease progresses, patients enter the stage of critical limb ischemia, with symptoms of pain at rest, ischemic ulceration, or gangrene, often requiring endovascular treatment or surgical revascularization. (1) The Trans-Atlantic Inter-Society Consensus (TASC II) guidelines classify femoropopliteal lesions according to four categories based on morphological criteria (TASC A to D) and recommend that TASC A to C lesions be treated with endovascular interventions and TASC D lesions be treated with bypass surgery. (2)

The superficial femoral artery is the blood vessel most commonly treated for PAD, but it presents a challenge for endovascular interventions because it is subjected to significant biomechanical forces, including elongation, compression, and torsion. (3) Although percutaneous transluminal angioplasty (PTA) and metallic stenting have high immediate success rates, long-term patency and restenosis rates in long and complex lesions of the superficial femoral artery remain unsatisfactory. (4) As well, multiple overlapping stents are often required to cover long lesions, and this can potentiate stent fracture. (5) Finally, the potent inflammatory responses following PTA and metallic stenting can lead to proliferation of vascular smooth muscle cells and neointimal hyperplasia (thickening of the inner surface of arterial walls), resulting in restenosis. (6)

Ontario Prevalence

In 2010, 202 million people worldwide were living with PAD, and that prevalence had increased by 23.5% over the preceding decade. (7) It is estimated that approximately 800,000 Canadians are living with PAD, (8) but this could be an underestimate because PAD is frequently unrecognized and underdiagnosed. (9) The prevalence of PAD in Ontario is unknown, but in the fiscal year 2012/2013, the best available data suggest that 418 Ontario patients underwent stenting procedures and 831 patients received non-stenting interventions for PAD of the lower extremities, including both above- and below-the-knee disease.

Technology/Technique

The Zilver paclitaxel drug-eluting peripheral stent is the only DES currently licensed by Health Canada to treat symptomatic lesions in above-the-knee femoropopliteal arteries. It is an endovascular drug/device system that includes a self-expanding nitinol DES and a polymer-free coating of PTX at a dose density of 3 $\mu g/mm^2$ on its outer surface. The stent has a reference vessel diameter of 4 to 9 mm and a total lesion length of up to 140 mm per limb and 280 mm per patient. (11) After deployment of the stent, PTX levels are sustained in the artery wall for approximately 56 days. (12)

Paclitaxel is a hydrophobic and lipophilic drug that binds to cell microtubules in the arterial wall and inhibits proliferation, a cellular response to trauma such as angioplasty and stenting. Local delivery of PTX to the arterial wall where endovascular stents are placed could inhibit intimal hyperplasia and prevent in-stent restenosis. (13, 14) A polymer-free coating avoids inflammatory and thrombotic reactions to polymers. (15)

Ontario Context

Current endovascular treatment options for above-the-knee PAD in Ontario include PTA and bare metal stents. The diffusion rate of Zilver PTX DESs in the province is unknown, but they are being used as an alternative option. There are no billing codes specific to DESs in the Ontario *Schedule of Benefits for Physician Services*. Insertion of DESs is billed as an insured service under existing generic codes for vascular stenting. Associated hospital and device costs are funded via global hospital budgets.

Regulatory Status

The Zilver PTX DES is licensed by Health Canada as a class IV device to treat *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries. There are two licence numbers associated with this device, based on the different French size of the stent. The manufacturer information, licence numbers, and issue dates for the device are presented in Table 1.

Table 1: Manufacturer Information on Zilver PTX DESs Licensed for Use in Canada

Device Name	Manufacturer	Licence Number	Issue Date
Zilver PTX drug-eluting peripheral stent (6FR)	Cook Ireland Ltd.	90774	February 28, 2013
Zilver PTX drug-eluting peripheral stent (7FR)	Cook Inc.	90773	February 28, 2013

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel.

Existing Guidelines

A number of clinical practice guidelines on the management of PAD are available, including the TASC II, (2) the American College of Cardiology Foundation/American Heart Association, (16) the Canadian Cardiovascular Society, (17) and the European Society of Cardiology. (18) While these guidelines include recommendations about endovascular interventions for claudication and critical limb ischemia with femoropopliteal lesions, there are no specific recommendations for the use of DESs.

Research Questions

- What is the clinical effectiveness and safety of Zilver PTX self-expanding DESs compared to 1) other self-expanding DESs, 2) balloon-expanding DESs, 3) bare metal stents, 4) PTA, and 5) drug-coated balloons, in treating *de novo* or restenotic lesions in above-the-knee PAD?
- What is the cost-effectiveness of Zilver PTX DESs in treating *de novo* or restenotic lesions in above-the-knee peripheral arterial disease?
- What is the budget impact of funding Zilver PTX DESs in treating *de novo* or restenotic lesions in above-the-knee peripheral arterial disease from the perspective of the Ontario Ministry of Health and Long-Term Care?

CLINICAL EVIDENCE REVIEW

Objective

The objective of this analysis was to evaluate the clinical effectiveness and safety of Zilver paclitaxel (PTX) self-expanding drug-eluting stents (DESs) for the treatment of *de novo* or restenotic lesions in above-the-knee peripheral arterial disease (PAD).

Methods

Literature Search

Search Strategy

A literature search was performed on November 12, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews, for studies published from January 1, 1946, to November 12, 2014. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists, health technology assessment (HTA) websites, and the Google Scholar Citation Index were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Published between January 1, 1946, and November 12, 2014
- Randomized controlled trials (RCTs), observational studies, systematic reviews, meta-analyses, and HTAs
- Studies that examined Zilver PTX DESs
- Studies on *de novo* or restenotic lesions, including in-stent restenosis, in above-the-knee arteries (i.e., superficial femoral artery and above-the knee segments of the femoropopliteal artery)

Exclusion Criteria

- Non-human studies
- Case reports, case series, editorials, conference abstracts, general reviews
- Studies that examined different arterial anatomy (i.e., below-the-knee arteries [e.g., segments of the infrapopliteal, infrainguinal, or infragenicular artery], the iliac artery, the coronary artery, the renal artery, the intracranial artery, or the carotid artery)

Outcomes of Interest

Primary Outcomes

- Primary patency (effectiveness)
- Event-free survival (safety and effectiveness)

Secondary Outcomes

- Clinical outcomes (i.e., Rutherford classification)
- Functional outcomes (i.e., ankle-brachial index, Walking Impairment Questionnaire)
- Other adverse events (e.g., thrombosis, stent fracture)
- Pain
- Quality of life

Statistical Analysis

Because of the small number of studies included in each comparison and the heterogeneous outcomes reported, the results of the studies were not pooled. Instead, the results were summarized in tables and described in the text.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (19) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: the large magnitude of effect, the dose response gradient, and any residual confounding factors. (19)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Results

The database search yielded 960 citations published between January 1, 1946, and November 12, 2014 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

Twelve studies (2 systematic reviews, 1 HTA, 1 RCT, and 8 observational studies) met the inclusion criteria.

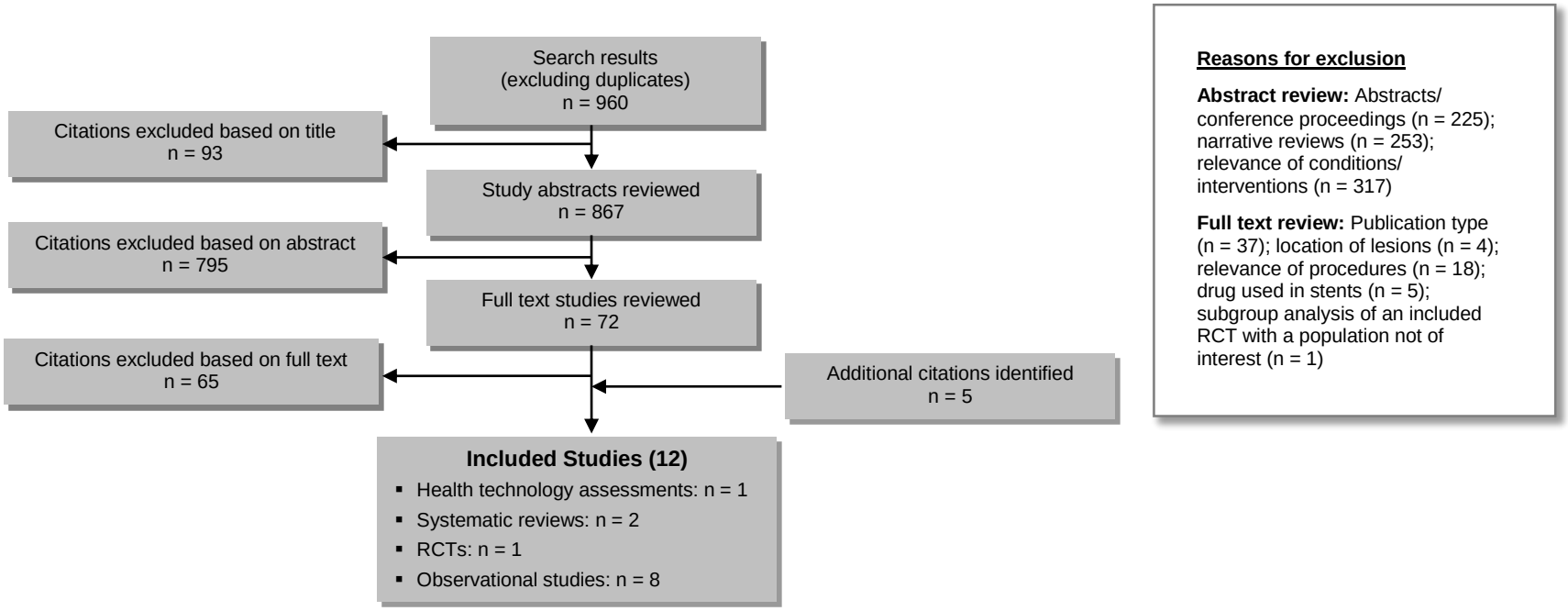

Figure 1: Citation Flow Chart

Abbreviation: RCT, randomized controlled trial.

For each included study, the study design was identified and is summarized below in Table 2, a modified version of a hierarchy of study design by Goodman, 1996. (20)

Table 2: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCTs	
Systematic review of RCTs	3 (including 1 HTA)
Large RCT	1
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	8
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	**12**

Abbreviations: RCT, randomized controlled trial; HTA, health technology assessment.

Of the 12 studies, one (21) reported the follow-up data of both an RCT (22) and an observational study, (23) and three (24-26) were subgroup analyses of an observational study. (23) The literature search did not identify any studies comparing Zilver PTX DESs with other self-expanding DESs or balloon-expanding DESs. None of the included studies reported pain or quality of life as a separate outcome. However, rest pain was embedded in a composite outcome (clinical benefit index) in the RCT. (22)

The search identified two systematic reviews (27, 28) and one HTA conducted by the UK National Institute for Health Research (29) on endovascular treatments of above-the-knee PAD. All three reports evaluated a wide range of interventions, but of all the studies included in these reviews, only the Zilver PTX RCT (22) was relevant to the current review. Since the methodological quality of that RCT was assessed separately in this report, the quality of these three reviews was not assessed.

In November 2014, the Canadian Agency for Drugs and Technologies in Health published a brief report on the Zilver PTX DES for the treatment of PAD of the femoropopliteal vessels in *Issues in Emerging Health Technologies*. (30) It included a peer-reviewed literature search and summarized the results of the Zilver PTX RCT, (22) the Zilver PTX single-arm study, (23) and the 2-year follow-up data. (21) Although the authors stated an intention to exclude conference abstracts, they reported the 3- and 4-year results of the Zilver PTX RCT, which were published only in abstract form. Without formal quality assessments of methodological rigour, the authors concluded that there appeared to be promising effectiveness and safety evidence to support the use of the Zilver PTX DESs to replace bare metal stents or PTA as initial therapy for less complex lesions.

The study by Dake et al (22) was the only RCT that specifically examined the use of Zilver PTX DESs in above-the-knee PAD. This RCT excluded patients with in-stent restenosis and covered lesions up to only 14 cm in length. Eligible patients with *de novo* or restenotic lesions were first randomized to the Zilver PTX DES or to PTA. Patients with acute failure of PTA underwent a second randomization to receive either a Zilver PTX DES or a bare metal stent.

The literature search identified one observational study on the effectiveness of Zilver PTX DESs compared to PTX drug-coated balloons; this study also excluded in-stent restenosis. (31)

There were three noncomparative observational studies on the Zilver PTX DES. The Zilver PTX single-arm study was a large registry of 787 patients; it had broad inclusion criteria that did not exclude enrollment based on lesion length or previous stent placement. (23) Three post-hoc subgroup analyses of the Zilver single-arm study were published in different populations, including diabetes, (24) *de novo* TASC C/D lesions, (25) and in-stent restenosis. (26)

In contrast to the Zilver PTX single-arm study, the other two observational studies were relatively small in sample size (< 70 patients), and their study populations differed from the Zilver PTX registry in that only patients with complex lesions (including those with in-stent restenosis or TASC C/D lesions) were enrolled. (32, 33)

Study authors were contacted for additional information. (22, 32) One author replied and provided specific information on the location of lesions. (32)

Tables 3 and 4 summarize the characteristics of the included studies.

Table 3: Baseline Characteristics of the Included Studies

Author, Year	Study Design	Populations	Sample Size, n	Comparison	Outcomes
Comparison of Zilver PTX DESs With PTA					
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	RCT (primary randomization)	Up to 2 *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery Rutherford classification ≥ 2 Resting ankle-brachial index < 9	DES: 236 PTA: 238	PTA	• Primary patency • Event-free survival • Rutherford classification • Ankle-brachial index • Walking Impairment Questionnaire • Clinical benefit index
Comparison of Zilver PTX DESs With Bare Metal Stents					
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	RCT (secondary randomization)	Up to 2 *de novo* or restenotic lesions of the above-the-knee femoropopliteal artery Rutherford classification ≥ 2 Resting ankle-brachial index < 9	120 (50.4%) with acute PTA failure DES: 61 Bare metal stent: 59	Bare metal stent	• Primary patency • Event-free survival • Rutherford classification • Ankle-brachial index • Walking Impairment Questionnaire • Clinical benefit index
Comparison of Zilver PTX DESs With PTX DCBs					
Zeller et al, 2014 (31)	Retrospective nonrandomized clinical study	*De novo* or restenotic femoropopliteal lesions ≥ 10 cm with > 50% diameter stenosis Rutherford classification ≥ 1	DES: 97 DCB: 131	DCB	• Mortality • Primary patency • Event-free survival • Ankle-brachial index
Noncomparative Observational Studies for Zilver PTX DESs: Primary Studies					
Zilver PTX single-arm study Dake et al, 2011 (23) Dake et al, 2013 (21)	Prospective, open-label, multinational clinical study	*De novo* or restenotic lesions with > 50% diameter stenosis (including ISR) of the above-the-knee femoropopliteal segment Rutherford classification ≥ 2, a reference vessel diameter of 4 to 9 mm, and at least 1 patent runoff vessel No lesion length exclusion	787	NA	• Primary patency • Event-free survival • Rutherford classification • Ankle-brachial index • Walking Impairment Questionnaire

Author, Year	Study Design	Populations	Sample Size, n	Comparison	Outcomes
Fujihara et al, 2014 (32)	Retrospective, nonrandomized clinical study	Complex femoropopliteal artery disease defined by TASC II C/D lesions, ISR, or hemodialysis	60	NA	• Primary patency • Amputation-free survival • Rutherford classification • Ankle-brachial index
Leopardi et al, 2014 (33)	Prospective, nonrandomized clinical study	ISR and symptomatic *de novo* TASC C/D lesions of femoropopliteal segments	69	NA	• Primary patency • Limb salvage
Noncomparative Observational Studies for Zilver PTX DESs: Subgroup Analyses					
Fanelli et al, 2013 (24)	Subgroup analysis of Zilver PTX single-arm study	Diabetes vs. nondiabetes	Diabetes: 285 Nondiabetes: 502	NA	• Primary patency • Event-free survival • Rutherford classification • Ankle-brachial index • Walking Impairment Questionnaire
Bosiers et al, 2013 (25)	Subgroup analysis of Zilver PTX single-arm study	Long *de novo* lesions: > 15 cm (TASC II C/D lesions)	135	NA	• Primary patency • Event-free survival • Rutherford classification • Ankle-brachial index • Walking Impairment Questionnaire
Zeller et al, 2013 (26)	Subgroup analysis of Zilver PTX single-arm study	ISR	108	NA	• Primary patency • Event-free survival • Rutherford classification • Ankle-brachial index • Walking Impairment Questionnaire

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent restenosis; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; NA, not applicable; RCT, randomized controlled trial; TASC, Trans-Atlantic Inter-Society Consensus.

Table 4: Lesion Characteristics of the Included Studies

Author, Year	Number	Mean Length, mm	Location	De novo/ Restenosis	TASC Classification
Comparison of Zilver PTX DESs With PTA					
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	DES: 247 PTA: 251	DES: 66.4 ± 38.9 PTA: 63.1 ± 40.7 Lesion length up to 14 cm	DES: 92.7% SFA, 3.6% SFA/POPA, 3.6% POPA PTA: 92.4% SFA, 2.4% SFA/POPA, 5.2% POPA	*Restenotic lesions* DES: 5.5% PTA: 5.9% ISR excluded	NR
Comparison of Zilver PTX DESs With Bare Metal Stents					
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	DES: 63 Bare metal stent: 62	NR	NR	All restenotic lesions	NR
Comparison of Zilver PTX DESs With PTX DCBs					
Zeller et al, 2014 (31)	DES: 97 DCB: 131	DES: 195.0 ± 64.5 DCB: 194.4 ± 86.3	DES: 52.6% proximal SFA; 17.5% P1[a,b] DCB: 50.4% proximal SFA; 26% P1; 10.7% P2; 7.6% P3[a,b]	*Restenotic lesions* DCB: 51.9% DES: 44.3% ISR excluded	NR
Noncomparative Observational Studies for Zilver PTX DESs: Primary Studies					
Zilver PTX single-arm study Dake et al, 2011 (23) Dake et al, 2013 (21)	900	99.5 ± 82.1	SFA: 96.2% POPA: 4.8%	Restenotic lesions (including ISR): 24.3% ISR: 13.2%	TASC A: 26.2% TASC B: 29.4% TASC C: 25.3% TASC D: 14.0%[b]
Fujihara et al, 2014 (32)	60 patients	188.1 ± 96.1	SFA: 82% Distal SFA to POPA: 18%	ISR: 35.0%	TASC C/D lesions: 61.6% Hemodialysis: 41.6%
Leopardi et al, 2014 (33)	69 patients	130.7	SFA: 85.6% POPA: 8.7% Femoropopliteal bypass: 5.7%	ISR: 52.2%	TASC C/D lesions: 47.8%

Author, Year	Number	Mean Length, mm	Location	De novo/ Restenosis	TASC Classification
Noncomparative Observational Studies for Zilver PTX DESs: Subgroup Analyses					
Fanelli et al, 2013 (24)	Diabetes: 322 Nondiabetes: 578	Diabetes: 97.9 ± 79.6 Nondiabetes: 100.5 ± 83.5	NA	*Restenotic lesions* Diabetes: 25.8% Nondiabetes: 23.5%	*TASC A/B lesions* Diabetes: 61.1% Nondiabetes: 57.2% *TASC C lesions* Diabetes: 30.1% Nondiabetes: 24.8% *TASC D lesions* Diabetes: 8.8% Nondiabetes: 18.0%
Bosiers et al, 2013 (25)	135 patients	226.1 ± 43.6	Distal SFA: 5.2% SFA/popliteal: 3.7% Proximal SFA: 4.4% Proximal SFA/distal SFA: 75.6% Proximal SFA/distal SFA/popliteal: 11.5%[b]	All *de novo* lesions	All TASC C/D lesions
Zeller et al, 2013 (26)	119	133.0 ± 91.7	Proximal SFA: 23.5% Proximal SFA/distal SFA: 29.4% Proximal SFA/distal: SFA/POPA: 6.7% Distal SFA: 32.8% Distal SFA/POPA: 5.9% POPA: 1.7%	All ISR	TASC A lesions: 22.7% TASC B lesions: 28.6% TASC C lesions: 26.9% TASC D lesions: 16.0% Not assessed: 5.9%

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent restenosis; POPA, popliteal artery; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; NR, not reported; RCT, randomized controlled trial; SFA, superficial femoral artery; TASC, Trans-Atlantic Inter-Society Consensus.
[a]P1, P2, P3 refer to the segments of popliteal artery.
[b]Data from the published papers. Total did not add up to 100%.

Effectiveness of Zilver PTX DESs in Above-the-Knee Peripheral Arterial Disease

Primary Patency

Table 5 presents findings for the outcome of primary patency. The included studies used different thresholds to define primary patency, making comparison across studies more difficult.

Table 5: Primary Patency

Author, Year	Primary Patency, %		
	6 Months	12 Months	24 Months
Comparison of Zilver PTX DESs With PTA			
Zilver PTX RCT[a] Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	DES: 83.1 ± 2.4 PTA: 32.8 ± 3.0 (*P* < 0.001)	DES: 74.8 ± 2.9 PTA: 26.5 ± 3.1 (*P* < 0.01)
Comparison of Zilver PTX DESs With Bare Metal Stents			
Zilver PTX RCT[a] Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	DES: 89.9 ± 3.9 Bare metal stent: 73.0 ± 5.8 (*P* = 0.01)	DES: 83.4 ± 4.8 Bare metal stent: 64.1 ± 6.3 (*P* < 0.01)
Comparison of Zilver PTX DESs With PTX DCBs			
Zeller et al, 2014 (31)[b]	NR	DES: 69.6 DCB: 76.1 (NS)	NR
Noncomparative Observational Studies for Zilver PTX DESs: Primary Studies			
Zilver PTX single-arm study[c] Dake et al, 2011 (23) Dake et al, 2013 (21)	96.4[d] 97.2[e]	83.0[d] 86.2[e]	NR
Fujihara et al, 2014 (32)[f]	69.9	50.2	NR
Leopardi et al, 2014 (33)[g]	88.4	85.5	NR
Noncomparative Observational Studies for Zilver PTX DESs: Subgroup Analyses			
Fanelli et al, 2013 (24)[h]	NR	Diabetes: 86.6 Nondiabetes: 85.4 (NS)	NR
Bosiers et al, 2013 (25)[h]	NR	77.6	NR
Zeller et al, 2013 (26)[h]	95.7	78.8	NR

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; NR, not reported; NS, not significant; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; RCT, randomized controlled trial.

[a]Primary patency was defined as a peak systolic velocity ratio of < 2.0 from duplex ultrasound or < 50% diameter stenosis from angiography.

[b]Zeller et al, 2014 (31) reported binary restenosis rates. The primary patency rate was calculated as a 100% binary restenosis rate. Primary patency was defined as < 50% diameter stenosis assessed by duplex ultrasound using a peak systolic velocity ratio of < 2.4 as the threshold.

[c]Primary patency was defined as < 50% diameter stenosis and no target lesion revascularization as assessed by angiography or duplex ultrasound.

[d]Based on the duplex criterion of a peak systolic velocity ratio < 2.0.

[e]Based on the duplex criterion of a peak systolic velocity ratio < 2.5.

[f]Primary patency was defined as freedom from restenosis at 12 months as verified by duplex ultrasound with a peak systolic velocity ratio of ≤ 2.5 with no reintervention.

[g]No description of the threshold by which primary patency was defined.

[h]Primary patency was defined as < 50% diameter stenosis assessed by angiography or duplex ultrasound, based on the duplex criterion of a peak systolic velocity ratio < 2.5.

Comparison of Zilver PTX DESs With PTA
The Zilver PTX RCT reported a statistically higher patency rate for DESs than for PTA at 12-month and 24-month follow-up, but only a select subgroup of patients randomized to PTA was followed up at 24 months, increasing the risk of bias. (21, 22)

Comparison of Zilver PTX DESs With Bare Metal Stents
In the secondary randomization for patients with acute failure of PTA in the Zilver PTX RCT, the patency rate was significantly higher in the DES group than in the bare metal stent group at 12-month and 24-month follow-up. (21, 22)

Comparison of Zilver PTX DESs With PTX Drug-Coated Balloons
In an observational study, Zeller et al (31) found no significant difference in primary patency between the DES and drug-coated balloon groups in 12-month follow-up.

Noncomparative Observational Studies on Zilver PTX DESs: Primary Studies
The Zilver PTX single-arm study reported high primary patency rates at 12 months, based on duplex criteria of peak systolic velocity ratio < 2.0 and < 2.5. (23) Leopardi et al (33) reported a similarly high primary patency rate at 12 months, but Fujihara et al (32) reported a much lower 12-month rate.

Noncomparative Observational Studies on Zilver PTX DESs: Subgroup Analyses
Three subgroup analyses were published from the data of the Zilver PTX single-arm study. (23) Fanelli et al (24) reported no significant difference in 12-month primary patency rate by diabetes status. About three-quarters of patients with *de novo* TASC C/D lesions (25) and in-stent restenosis showed primary patency at 12 months. (26)

Clinical Benefit Index
The Zilver PTX RCT (22) reported clinical benefit index, a composite outcome that included freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss after initial study treatment.

Comparison of Zilver PTX DESs With PTA
In the primary randomization of the Zilver PTX RCT, the clinical benefit index at 12 months was significantly higher in the DES group (88.3%) than in the PTA group (75.8%) ($P < 0.001$). This significant difference was sustained at 24 months (81.8% for DES versus 71.3% for PTA) ($P < 0.01$). (21, 22)

Comparison of Zilver PTX DESs With Bare Metal Stents
In the secondary randomization of the Zilver PTX RCT, the clinical benefit index was significantly higher in the DES group than in the bare metal stent group at both 12 and 24 months (90.5% versus 72.3% at 12 months [$P = 0.009$] and 83.9% versus 68.4% at 24 months [$P = 0.05$]). (21, 22)

Ankle-Brachial Index

Table 6 presents findings for the outcome of ankle-brachial index, an objective measure of lower-limb hemodynamic status. (34)

Table 6: Ankle-Brachial Index

Author, Year	Ankle-Brachial Index		
	6 Months	12 Months	24 Months
Comparison of Zilver PTX DESs With PTA			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	DES: 0.91 ± 0.23 vs. 0.67 ± 0.20 at baseline ($P < 0.001$) PTA: 0.89 ± 0.20 vs. 0.68 ± 0.20 at baseline ($P < 0.001$)	NR
Comparison of Zilver PTX DESs With Bare Metal Stents			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	NR	NR
Comparison of Zilver PTX DESs With PTX DCBs			
Zeller et al, 2014 (31)	DES: 0.81 ± 0.23 vs. 0.53 ± 0.29 at baseline (SS, *P* value not reported) DCB: 0.78 ± 0.27 vs. 0.50 ± 0.29 at baseline (SS, *P* value not reported) NS between groups	DES: 0.85 ± 0.27 vs. 0.53 ± 0.29 at baseline (SS, *P* value not reported) DCB: 0.75 ± 0.28 vs. 0.50 ± 0.29 at baseline (SS, *P* value not reported) NS between groups	NR
Noncomparative Observational Studies for Zilver PTX DESs: Primary Studies			
Zilver PTX single-arm study Dake et al, 2011 (23) Dake et al, 2013 (21)	0.9 ± 0.2 vs. 0.6 ± 0.3 at baseline ($P < 0.001$)	0.9 ± 0.2 vs. 0.6 ± 0.3 at baseline ($P < 0.001$)	Improved from baseline ($P < 0.001$)
Fujihara et al, 2014 (32)	0.79 ± 0.3 vs. 0.56 ± 0.3 at baseline ($P < 0.001$)	0.76 ± 0.3 vs. 0.56 ± 0.3 at baseline ($P < 0.001$)	NR
Leopardi et al, 2014 (33)	NR	NR	NR
Noncomparative Observational Studies for Zilver PTX DESs: Subgroup Analyses			
Fanelli et al, 2013 (24)	NR	Improved significantly from baseline	NR
Bosiers et al, 2013 (25)	0.89 ± 0.27 vs. 0.59 ± 0.17 at baseline	0.87 ± 0.21 vs. 0.59 ± 0.17 at baseline	NR
Zeller et al, 2013 (26)	0.87 ± 0.25 vs. 0.60 ± 0.28 at baseline ($P < 0.001$)	0.87 ± 0.28 vs. 0.60 ± 0.28 at baseline ($P < 0.001$)	0.84 ± 0.22 vs. 0.60 ± 0.28 at baseline ($P < 0.001$)

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; NR, not reported; NS, not significant; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; RCT, randomized controlled trial; SS, statistically significant.

Comparison of Zilver PTX DESs With PTA
In the Zilver PTX RCT, ankle-brachial index improved from baseline to 12-month follow-up in both DES and PTA groups, but the difference between groups was not statistically significant. (22)

Comparison of Zilver PTX DESs With Bare Metal Stents
Ankle-brachial index was not reported in the secondary randomization of the Zilver PTX RCT, which compared Zilver PTX DESs with bare metal stents. (22)

Comparison of Zilver PTX DES With PTX Drug-Coated Balloon
In the Zeller et al observational study, (31) ankle-brachial index was not significantly different between the DES and drug-coated balloon groups at 6-month and 12-month follow-up, but there was a significant increase from baseline to follow-up in both groups.

Noncomparative Observational Studies on Zilver PTX DESs: Primary Studies
In the Zilver PTX single-arm study, ankle-brachial index was significantly improved at 6 months, 12 months, and 24 months. (21, 23) Fujihara et al (32) also reported a significant improvement in ankle-brachial index at 6 and 12 months. Leopardi et al (33) did not report ankle-brachial index as an outcome.

Noncomparative Observational Studies on Zilver PTX DESs: Subgroup Analyses
Ankle-brachial index was improved from baseline to 12 months in all three subgroup analyses (diabetes status, *de novo* TASC C/D lesions, and in-stent restenosis). (24-26)

Rutherford Classification
Table 7 presents findings for the outcome of Rutherford classification, which describes the severity of PAD. It includes a clinical description of symptoms and objective criteria involving a treadmill exercise and measurement of ankle and toe pressure. The scores range from 0 to 6 and correspond to asymptomatic, mild claudication, moderate claudication, severe claudication, ischemic rest pain, minor tissue loss, and major tissue loss, respectively. (35) An improvement in Rutherford classification represents a decrease in the severity of PAD.

Table 7: Rutherford Classification

Author, Year	Rutherford Classification		
	6 Months	12 Months	24 Months
Comparison of Zilver PTX DESs With PTA			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	*DES (vs. baseline)* Class 0: 44.7% vs. 0% Class 1: 20.9% vs. 0.9% Class 2: 23.3% vs. 52.5% Class 3: 9.2% vs. 37.7% Class 4: 1.9% vs. 5.9% Class 5: 0% vs. 3% Class 6: 0% vs. 0% (P < 0.001) *PTA (vs. baseline)* Class 0: 45.4% vs. 0% Class 1: 21.7% vs. 0.8% Class 2: 20.3% vs. 46.2% Class 3: 10.1% vs. 44.5% Class 4: 1% vs. 4.7% Class 5: 1.5% vs. 3.4% Class 6: 0% vs. 0.4% (P < 0.001) NS between groups	NR
Comparison of Zilver PTX DESs With Bare Metal Stents			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	NR	NR
Comparison of Zilver PTX DESs With PTX DCBs			
Zeller et al, 2014 (31)	NR	NS between groups	NR
Noncomparative Observational Studies for Zilver PTX DESs: Primary Studies			
Zilver PTX single-arm study Dake et al, 2011 (23) Dake et al, 2013 (21)	Median score 0 vs. 3 at baseline (P < 0.001)	Median score 0 vs. 3 at baseline (P < 0.001)	Significantly improved from baseline (P < 0.001)
Fujihara et al, 2014 (32)	1.6 ± 1.2 vs. 3.3 ± 0.9 at baseline (P < 0.001)	1.9 ± 1.6 vs. 3.3 ± 0.9 at baseline (P < 0.001)	NR
Leopardi et al, 2014 (33)	NR	NR	NR
Noncomparative Observational Studies for Zilver PTX DESs: Subgroup Analyses			
Fanelli et al, 2013 (24)	*Diabetes (vs. baseline)* Class 0/1: 70.7% vs. 0.7% Class 2/3: 25.6% vs. 85.5% Class 4/5/6: 3.7% vs. 13.8% *Nondiabetes (vs. baseline)* Class 0/1: 80.0% vs. 0.2% Class 2/3: 18.0% vs. 90.4% Class 4/5/6: 2.0% vs. 9.4% Statistical significance NR	*Diabetes (vs. baseline)* Class 0/1: 62.9% vs. 0.7% Class 2/3: 32.1% vs. 85.5% Class 4/5/6: 5.1% vs. 13.8% *Nondiabetes (vs. baseline)* Class 0/1: 77.2% vs. 0.2% Class 2/3: 20.8% vs. 90.4% Class 4/5/6: 2.0% vs. 9.4% Statistical significance NR	NR
Bosiers et al, 2013 (25)	NR	NR	NR
Zeller et al, 2013 (26)	Median score 0 vs. 3 at baseline	Median score 0 vs. 3 at baseline	Median score 1 vs. 3 at baseline

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; NR, not reported; NS, not significant; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; RCT, randomized controlled trial.

Comparison of Zilver PTX DESs With PTA
In the Zilver PTX RCT, Rutherford classification was significantly improved from baseline to 12 months in both the DES and PTA groups, but the difference between groups was not statistically significant. (22)

Comparison of Zilver PTX DESs With Bare Metal Stents
Rutherford classification was not reported in the secondary randomization of the Zilver PTX RCT. (22)

Comparison of Zilver PTX DESs With PTX Drug-Coated Balloons
Zeller et al (31) reported no significant difference in Rutherford classification between the DES and drug-coated balloon groups at 12-month follow-up.

Noncomparative Observational Studies on Zilver PTX DESs: Primary Studies
In the Zilver PTX single-arm study, Rutherford classification was significantly improved from baseline to 12- and 24-month follow-up. (21, 23) Fujihara et al (32) reported similar improvement at 12 months. Leopardi et al (33) did not report Rutherford classification as an outcome.

Noncomparative Observational Studies on Zilver PTX DESs: Subgroup Analyses
In a subgroup analysis of the Zilver PTX single-arm study, there was an improvement in Rutherford classification from baseline to 12 months in both the diabetes and nondiabetes groups, but statistical significance was not reported. (24) Similarly, the median score of Rutherford classification for patients with in-stent restenosis had improved at 12-month follow-up. (26) Bosiers et al (25) did not report Rutherford classification as an outcome in their subgroup analysis of patients with *de novo* TASC C/D lesions.

Walking Impairment Questionnaire
Table 8 presents findings for the outcome of the Walking Impairment Questionnaire, a measure of patient-perceived walking capacity, including walking distance, walking speed, and climbing. (36)

Table 8: Walking Impairment Questionnaire

Author, Year	Walking Impairment Questionnaire, Score		
	6 Months	12 Months	24 Months
Comparison of Zilver PTX DESs With PTA			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	*DES (vs. baseline)* Walking distance: 57.8 ± 37.9% vs. 25.0 ± 27.6% ($P < 0.001$) Walking speed: 55.7 ± 37.1% vs. 27.5 ± 27.1% ($P < 0.001$) Climbing: 55.6 ± 37.3% vs. 35.9 ± 32.2% ($P < 0.001$) *PTA (vs. baseline)* Walking distance: 57.7 ± 36.9% vs. 26.3 ± 28.6% ($P < 0.001$) Walking speed: 58.2 ± 35.7% vs. 29.7 ± 30.3% ($P < 0.001$) Climbing: 61.5 ± 34.0%	NR

Author, Year	Walking Impairment Questionnaire, Score		
	6 Months	12 Months	24 Months
		vs. 38.7 ± 32.5% (P < 0.001) NS between groups	
Comparison of Zilver PTX DESs With Bare Metal Stents			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	NR	NR
Comparison of Zilver PTX DESs With PTX DCBs			
Zeller et al, 2014 (31)	NR	NR	NR
Noncomparative Observational Studies for Zilver PTX DESs: Primary Studies			
Zilver PTX single-arm study Dake et al, 2011 (23) Dake et al, 2013 (21)	Walking distance: 71 ± 32% vs. 31 ± 26% at baseline (P < 0.001) Walking speed: 67 ± 31% vs. 35 ± 28% at baseline (P < 0.001)	Walking distance: 71 ± 32% vs. 31 ± 26% at baseline (P < 0.001) Walking speed: 66 ± 31% vs. 35 ± 28% at baseline (P < 0.001)	Significantly improved from baseline (P < 0.001)
Fujihara et al, 2014 (32)	NR	NR	NR
Leopardi et al, 2014 (33)	NR	NR	NR
Noncomparative Observational Studies for Zilver PTX DESs: Subgroup Analyses			
Fanelli et al, 2013 (24)	NR	Improved significantly from baseline in both diabetes and nondiabetes groups	NR
Bosiers et al, 2013 (25)	Walking distance: 76.2 ± 32.1% vs. 28.4 ± 25.7% at baseline Walking speed: 68.3 ± 32.1% vs. 29.5 ± 27.8% at baseline Climbing: 76.7 ± 31.4% vs. 42.7 ± 31.6% at baseline	Walking distance: 71.1 ± 32.8% vs. 28.4 ± 25.7% at baseline Walking speed: 63.9 ± 31.7% vs. 29.5 ± 27.8% at baseline Climbing: 72.9 ± 30.7% vs. 42.7 ± 31.6% at baseline	NR
Zeller et al, 2013 (26)	Walking distance: 66 ± 34% vs. 27 ± 26% at baseline (P < 0.001) Walking speed: 62 ± 30% vs. 33 ± 28% at baseline (P < 0.001) Climbing: 66 ± 33% vs. 377 ± 29% at baseline (P < 0.001)	Walking distance: 68 ± 33% vs. 27 ± 26% at baseline (P < 0.001) Walking speed: 58 ± 32% vs. 33 ± 28% at baseline (P < 0.001) Climbing: 65 ± 31% vs. 37 ± 29% at baseline (P < 0.001)	Walking distance: 63 ± 37% vs. 27 ± 26% at baseline (P < 0.001) Walking speed: 63 ± 32% vs. 33 ± 28% at baseline (P < 0.001) Climbing: 67 ± 34% vs. 37 ± 29% at baseline (P < 0.001)

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; NR, not reported; NS, not significant; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; RCT, randomized controlled trial.

Comparison of Zilver PTX DESs with PTA
In the Zilver PTX RCT, walking distance, walking speed, and climbing were all significantly improved from baseline to 12-month follow-up in both the DES and PTA groups, but there was no significant difference between groups. (22)

Comparison of Zilver PTX DESs with Bare Metal Stents
Walking Impairment Questionnaire results were not reported in the secondary randomization of the Zilver PTX RCT. (22)

Comparison of Zilver PTX DESs with PTX Drug-Coated Balloons
Zeller et al (31) did not report the Walking Impairment Questionnaire as an outcome.

Noncomparative Observational Studies on Zilver PTX DESs: Primary Studies
The Zilver PTX single-arm study reported a significant improvement in both walking distance and walking speed from baseline to 12-month follow-up. (23) The studies by Fujihara et al (32) and Leopardi et al (33) did not report the Walking Impairment Questionnaire as an outcome.

Noncomparative Observational Studies on Zilver PTX DESs: Subgroup Analyses
Fanelli et al (24) reported a significant improvement in walking distance, walking speed, and climbing sustained for 12 months in both diabetes and nondiabetes patients, although nondiabetes patients had significantly higher scores than diabetes patients in all three components of the Walking Impairment Questionnaire. Patients with *de novo* TASC C/D lesions or with in-stent restenosis also had improved walking capacity after Zilver PTX DES implantation. (25, 26)

Safety and Adverse Events Associated With Zilver PTX DES

Table 9 presents the findings for event-free survival, defined as freedom from major adverse events, including procedure- or device-related death; amputation; clinically driven target lesion revascularization (TLR); target limb ischemia requiring surgical intervention or surgical repair of target vessel; and worsening of the Rutherford classification by two classes or to class 5 or 6.

Table 9: Event-Free Survival

Author, Year	Event-Free Survival,[a] %		
	6 Months	12 Months	24 Months
Comparison of Zilver PTX DESs With PTA			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	DES: 90.4 ± 1.9 PTA: 82.6 ± 2.5 (*P* = 0.004)	DES: 86.6 ± 2.3 PTA: 77.9 ± 2.8 (*P* = 0.02)
Comparison of Zilver PTX DESs With Bare Metal Stents			
Zilver PTX RCT Dake et al, 2011 (22) Dake et al, 2013 (21)	NR	NR	NR
Comparison of Zilver PTX DES With DCB			
Zeller et al, 2014 (31)	NR	DES: 78.0% DCB: 80.7% (NS)	NR
Noncomparative Observational Studies for Zilver PTX DESs: Primary Studies			
Zilver PTX single-arm study Dake et al, 2011 (23) Dake et al, 2013 (21)	97.4	89.0	79.3
Fujihara et al, 2014 (32)	NR	NR	NR
Leopardi et al, 2014 (33)	NR	NR	NR
Noncomparative Observational Studies for Zilver PTX DESs: Subgroup Analyses			
Fanelli et al, 2013 (24)	NR	Diabetes: 90.0 Nondiabetes: 88.5	NR
Bosiers et al, 2013 (25)	NR	84.7	NR
Zeller et al, 2013 (26)	96.2	81.0	60.8

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; NR, not reported; NS, not significant; RCT, randomized controlled trial.

[a]Event-free survival was defined as freedom from major adverse events (procedure- or device-related death; amputation; clinically driven target lesion revascularization; target limb ischemia requiring surgical intervention or surgical repair of target vessel; and worsening of the Rutherford classification by two classes or to class 5 or 6).

Two observational studies reported amputation-free survival rate or limb salvage rate. (32, 33) Since these outcomes were only a component of the event-free survival composite outcome, these results are described in text separately. Several included studies also presented freedom from TLR as a separate outcome, even though it was grouped in the composite outcome; the results are described separately in the text.

Comparison of Zilver PTX DESs With PTA

No patients died during the procedure in the Zilver PTX RCT. The event-free survival rate was significantly higher in the DES group than in the PTA group at both 12 months and 24 months. The freedom from TLR rate was also significantly higher in the DES group than in the PTA group (90.5% vs. 82.5%) at 12 months. The 12-month stent fracture rate for DESs was 0.9%. (22)

Comparison of Zilver PTX DESs With Bare Metal Stents

The authors did not report event-free survival for the secondary randomization of the Zilver PTX RCT. The 12-month stent fracture rates for both DESs and bare metal stents were 0.9%. (22)

Comparison of Zilver PTX DES With PTX Drug-Coated Balloons

Zeller et al (31) reported no procedure-related deaths in either group. The 12-month event-free survival rate was similar between the two groups. The freedom from TLR rate was not significantly different between the two groups at 12 months (DES 81.0% vs. drug-coated balloon 84.4%).

Noncomparative Observational Studies on Zilver PTX DESs: Primary Studies

In the Zilver PTX single-arm study, the event-free survival rate was very high at 6 months, but declined over time. The freedom from TLR rate (97.9% at 6 months, 90.5% at 12 months, and 80.5% at 24 months) was similar to the event-free survival rate, since TLR was the major adverse event reported. There were no PTX-related adverse events, but four procedure-related deaths (0.5%)—due to pulmonary embolism, cardiac ischemia, myocardial infarction, and renal failure—occurred within 30 days. The 6-month and 12-month stent fracture rates were 1.2% and 1.5%, respectively. (23)

Fujihara et al (32) reported an amputation-free rate of 91.5% at 6 months and 83.2% at 12 months. Four patients (7%) required major amputation. The freedom from TLR rate was 91.4% at 6 months and 68.6% at 12 months. Two cases of acute thrombosis were reported. Nine patients (15%) died from myocardial infarction (n = 1), infection (n = 4), heart failure (n = 3), and sudden death (n = 1). The authors did not specify whether these deaths were procedure-related.

Leopardi et al (33) reported no procedure- or device-related deaths or adverse events related to the PTX coating. Two patients had immediate intra-stent thrombosis. The 6-month and 12-month limb salvage rate was 100%.

Noncomparative Observational Studies on Zilver PTX DESs: Subgroup Analyses

Fanelli et al (24) reported no significant differences in 12-month event-free survival rates between diabetes (90.0%) and nondiabetes (88.5%) patients. The freedom from TLR rate was similar to the event-free survival rate (90.6% for diabetes patients vs. 88.9% for nondiabetes patients). Four procedure-related deaths were reported: within 30 days of DES implantation, three patients with diabetes died (cardiac ischemia, myocardial infarction, and renal failure) and one patient without diabetes died (pulmonary embolism).

In a subgroup of patients with *de novo* TASC C/D lesions, the 12-month event-free survival rate and freedom from TLR rate were 84.7% and 85.4%, respectively. There were two procedure-related deaths. Nine patients (6.9%) had acute thrombosis. The 12-month stent fracture rate was 2.1%. (25)

In a subgroup of patients with in-stent restenosis, the event-free survival rate was very high at 6 months and declined over time. The freedom from TLR rate was the same as the event-free survival rate. No procedure-related deaths were reported. The 12-month stent fracture rate was 1.2%. (26)

Limitations

- A single RCT comparing the Zilver PTX DES with PTA and bare metal stent was identified.
- The largest study published on the Zilver PTX DES was a noncomparative observational study.
- Lesion length or previous stent placement varied among studies, limiting generalizability.

Conclusions

Based on evidence of low quality, Zilver PTX DESs were associated with a higher patency rate than PTA and bare metal stents, and with fewer adverse events than PTA. The effectiveness and safety of Zilver PTX DESs and PTX drug-coated balloons appear to be similar (Table 10).

Table 10: Summary of Evidence on Zilver PTX DESs for Above-the-Knee PAD

Comparator	Population	Outcome	Result	GRADE
PTA (1 RCT, primary randomization)	*De novo* or restenotic lesions (excluding ISR) Lesion length up to 14 cm	12-month primary patency	Significantly higher for DES vs. PTA	Low
		24-month primary patency		Very low
		Clinical benefit index	Significantly higher for DES vs. PTA	Low
		Ankle-brachial index	No significant difference between DES and PTA	Moderate
		Rutherford classification		
		Walking Impairment Questionnaire		
		Event-free survival	Significantly higher for DES vs. PTA	Low
Bare metal stent (1 RCT, secondary randomization)	Restenotic lesions (excluding ISR) Lesion length up to 14 cm	12-month primary patency	Significantly higher for DES vs. bare metal stent	Low
		Clinical benefit index		
Drug-coated balloon	*De novo* or restenotic lesions (excluding ISR)	12-month primary patency	No significant difference between DES and drug-coated balloon	Very low
		Ankle-brachial index		Low
		Event-free survival		Very low
Noncomparative: primary studies	*De novo* or restenotic lesions (including ISR)	12-month primary patency	Noncomparative results	Very low
		Ankle-brachial index	Improved significantly after DES implantation	Low
		Rutherford classification		Very low
		Walking Impairment Questionnaire		
		Event-free survival	Noncomparative results	
Noncomparative: subgroup analyses	• Diabetes/ nondiabetes • *De novo* TASC C/D lesions • ISR	12-month primary patency	Noncomparative results	Very low
		Ankle-brachial index	Improved significantly after DES implantation	
		Rutherford classification		
		Walking Impairment Questionnaire		
		Event-free survival	Noncomparative results	

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; ISR, in-stent restenosis; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; RCT, randomized controlled trial; TASC, Trans-Atlantic Inter-Society Consensus.

REVIEW OF THE ECONOMIC LITERATURE

Objective

The objective of this analysis was to review the literature on the cost-effectiveness of Zilver PTX DESs compared with bare metal stents and PTA for the treatment of *de novo* and restenotic lesions in above-the-knee PAD.

Methods

Sources

We performed an economic literature search on May 20, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and the Cochrane Library database—including the NHS Economic Evaluation Database (NHS EED)—for studies published from January 1, 2000, to May 20, 2015. We also extracted economic evaluation reports developed by HTA agencies by searching the websites of organizations such as the Canadian Agency for Drugs and Technologies in Health, the Institute of Health Economics, the Institut national d'excellence en sante et en services, the McGill University Health Centre Health Technology Assessment Unit and the Cost-Effectiveness Analysis Registry (available at; https://research.tufts-nemc.org/cear4/). Finally, we reviewed the reference lists of the included economic literature for any additional relevant studies not identified through the systematic search.

Search Strategy

We based our search terms on those used in the clinical evidence review of this report, applying economic filters to the search results. Study eligibility criteria for the literature search are listed below. Appendix 1 provides details of the search strategies.

Inclusion Criteria

- English-language full-text publications
- Studies published up to May 20, 2015
- Studies in patients with PAD requiring surgical intervention
- Studies reporting on Zilver PTX DES

Exclusion Criteria

- Abstracts, commentary, editorials, conference proceedings

Outcomes of Interest

- Full economic evaluations: cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses

Literature Screening

A single reviewer reviewed titles and abstracts. For those studies meeting the eligibility criteria, we obtained full-text articles.

Applicability Assessment and Methodological Appraisal of the Economic Evidence

We determined the usefulness of each identified study for decision-making by applying a modified methodology checklist for economic evaluations developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The original checklist is used by NICE to inform development of clinical guidelines. (37) Examples of the modified methodology checklist can be found in Appendix 3. We modified the wording of the questions to remove references to guidelines and to make it Ontario-specific. This checklist is separated into two sections. In the first section, the applicability of the study to the research question is assessed. If the study is deemed directly applicable or partially applicable to the research question, the quality of the study is assessed in the second half of the checklist. From the assessment of the methodological quality, the study is assessed as having minor limitations, potentially serious limitations, or very serious limitations. A summary of the number of studies judged to be directly applicable, partially applicable, or not applicable to the research question is presented. For the studies deemed directly or partially applicable, the number with minor limitations, potentially serious limitations, or very serious limitations is presented.

Limitations

The economic literature review was conducted by a single reviewer; the results could not be independently evaluated by another reviewer.

Results

Literature Search

The database search yielded 329 citations published between January 1, 2000, and May 20, 2015 (with duplicates removed). We excluded articles based on information in the title and abstract. No potentially relevant articles were found for further assessment. Figure 2 presents the flow diagram for a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) analysis.

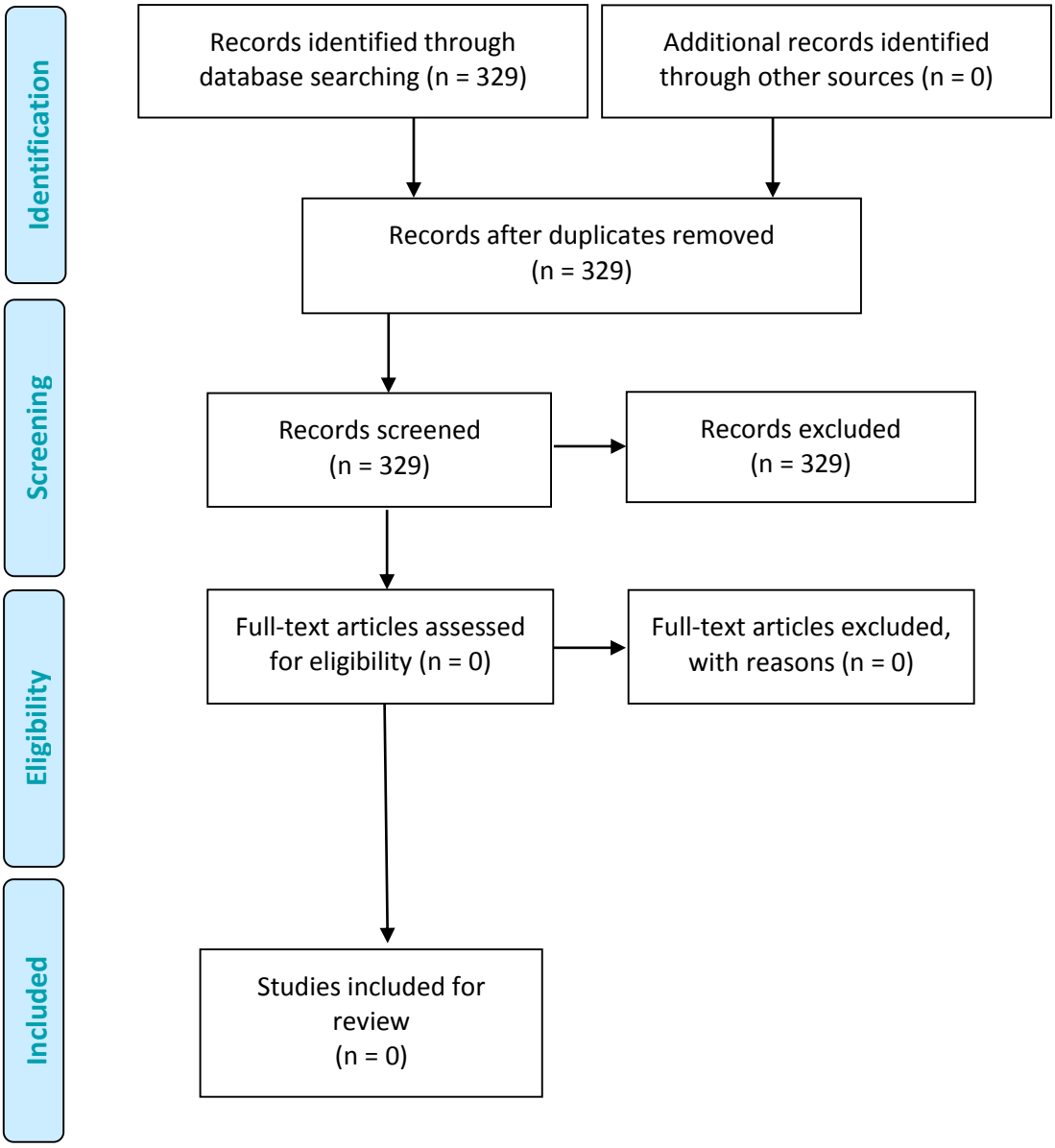

Figure 2: PRISMA Flow Diagram

Source: Adapted from Moher et al. (38)

Critical Review

All citations were excluded at the initial screening; we did not conduct a critical review.

Discussion and Conclusions

The results of the economic literature review confirmed the absence of economic evaluations comparing Zilver PTX DESs to bare metal stents or PTA for PAD. This may be because the Zilver PTX DES for above-the-knee PAD has only recently entered the market. The clinical evidence review identified only a single RCT (22) and one long-term single-arm trial. (21) With additional data and experience with the technology, economic evaluations of Zilver PTX DESs for PAD may be published in the future.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to determine the estimated cost burden of Zilver PTX DESs over the next 5 years. All costs are reported in 2015 Canadian dollars.

Objective

The objective of this study was to determine the budget impact of funding Zilver PTX DESs for the treatment of *de novo* or restenotic lesions in above-the-knee PAD.

Methods

Scenarios

We developed 3 scenarios to understand the potential variability in budget impact as a result of different assumptions. In the base-case scenario, inputs originated from published literature, administrative data, and expert opinion. We considered inputs provided by expert opinion to be relatively optimistic compared to those used in the budget impact analyses of other jurisdictions (i.e., the percentage of patients eligible for the new technology and the rate of adoption in the first few years), potentially leading to bias in favour of the Zilver PTX DES. For this reason, we calculated a more conservative scenario that relied on administrative data and published literature, including an adoption rate reported in a French budget impact analysis. (39) Then, we developed a worst-case scenario assuming that Zilver PTX DESs provided no improvement in revascularization rates compared to bare metal stents. This third scenario provided the budget impact that would occur if the results observed in clinical trials did not translate to real life in Ontario.

Target Population

To determine the number of individuals in Ontario with PAD in 2015 who would require stenting and non-stenting interventions for the superficial femoral artery, we used administrative data from the Institute for Clinical Evaluative Sciences for 2005 to 2012. (31) The specific procedure codes used to identify hospitalization volumes are presented in Table 11.

Table 11: Canadian Classification of Intervention Codes Used to Identify the Target Population

Intervention	Intervention Code
Stenting for PAD of the lower extremities using percutaneous transluminal approach and balloon dilator with endovascular stent insertion	1.KG.50.GQ-OA
Non-stenting intervention for PAD of the lower extremities using one of the following: percutaneous transluminal approach and balloon dilator; percutaneous transluminal approach with laser and balloon dilator; percutaneous transluminal approach and dilating device	1.KG.50.GQ-BD and/or 1.KG.50.GQ-BF and/or 1.KG.50.GQ-BP

Abbreviation: PAD, peripheral arterial disease.
Source: Canadian Institute for Health Information. (40)

We estimated the number of individuals who would require stenting and non-stenting interventions in future years using linear extrapolation. The total estimated numbers of stenting and non-stenting interventions in Ontario between 2015 and 2019 are presented in Table 12.

Table 12: Estimated Volumes of Stenting and Non-stenting Interventions

Intervention	2015	2016	2017	2018	2019
Stenting for PAD of the lower extremities using percutaneous transluminal approach and balloon dilator with endovascular stent insertion	474	509	545	580	616
Non-stenting intervention for PAD of the lower extremities using one of the following: percutaneous transluminal approach and balloon dilator; percutaneous transluminal approach with laser and balloon dilator; percutaneous transluminal approach and dilating device	807	871	935	998	1,062
Total	**1,281**	**1,380**	**1,480**	**1,578**	**1,678**

Abbreviation: PAD, peripheral arterial disease.

For the base-case scenario, we estimated the number of individuals who would qualify for the Zilver PTX DES to be approximately 50% of the total cohort above (personal communication, Dr. K.T. Tan, May 2015). For the conservative scenario, we limited the number of individuals qualified to receive the new technology to 48% of those who were qualified to receive a bare metal stent (about 18% of the total cohort above). (39) For the worst-case scenario, we assumed the number of individuals qualified to receive a Zilver PTX DES to be the same as for the base-case scenario, since it represented a plausible upper limit. The number of qualified individuals for each scenario is outlined in Table 13.

Table 13: Estimated Number of Individuals Qualified to Receive Zilver PTX DES

Scenario	2015	2016	2017	2018	2019
Base case	640	690	739[a]	789	839
Conservative	228	244	262	278	296
Worst case	640	690	739	789	839

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel
[a]Numbers may slightly higher or lower due to rounding.

Resources and Costs

Cost of Procedure

The additional cost of Zilver PTX DESs compared to bare metal stents in Ontario has not been reported in the literature. As was noted in a Canadian Agency for Drugs and Technologies in Health review, this is because a number of factors may affect the hospital acquisition cost of this technology. (30)

In the only published budget impact analysis of Zilver PTX DESs, the additional premium of this stent in France was €160 ($265 CAD). We used this cost in the base-case and conservative scenarios. With a mean cost of $16,317 for a hospital visit in which bare metal stenting for lower-extremity PAD was the main procedure, the additional cost of $265 for a Zilver PTX DES would increase the cost to $16,582. In the worst-case scenario, we used the cost premium of all DESs from a United States budget impact analysis ($700 USD/$856 CAD). This represented the upper boundary of the cost for Zilver PTX DESs; the manufacturer has noted that the cost of its technology will fall between the cost of bare metal stents and that of other DESs. (30)

To determine the cost of a bare metal stent procedure, we obtained the mean resource intensity weight for all non-stenting interventions for PAD of the lower extremities using a percutaneous transluminal approach and balloon dilator alone, a laser and balloon dilator, or another dilator, from administrative data for the most recent year requested (2012). (31) We multiplied the mean resource intensity weight by the mean cost per weighted case reported in Ontario to produce a mean cost per intervention. (41)

We used the same methodology to calculate the mean cost of a bypass that terminated in a lower-limb artery using autograft or a synthetic graft. We determined a cost premium of €700 ($1,147 CAD) for a drug-coated balloon dilator compared to a non-drug-coated balloon from a German budget impact analysis. (42)

In the current analysis, we assumed that the cost of procedures would be the same whether the procedure was primary or for revascularization due to restenosis. We converted costs from other jurisdictions to Canadian dollars using purchasing power parity as reported by the Organisation for Economic Co-operation and Development. (43) We inflated costs using the Bank of Canada inflation calculator. (44) All unit cost inputs are shown in Table 14.

Table 14: Unit Costs

Variable	Cost	Source
Hospital cost of bare metal stent procedure	$16,317	2011/12 acute care cost per equivalent weighted case ($5,675) multiplied by a mean RIW of 2.875 obtained from administrative data (41)
Hospital cost of PTA	$15,987	2011/12 acute care cost per equivalent weighted case ($5,675) multiplied by a mean RIW of 2.817 obtained from administrative data (41)
Hospital cost of bypass terminating in lower limb artery using autograft	$16,208	2011/12 acute care cost per equivalent weighted case ($5,675) multiplied by a mean RIW of 2.856 obtained from administrative data (41)
Hospital cost of bypass terminating in lower limb artery using synthetic material	$13,393	2011/12 acute care cost per equivalent weighted case ($5,675) multiplied by a mean RIW of 2.36 obtained from administrative data (41)
Physician fees, non-stenting	$272	Angiography by catheterization—insertion of catheter (J021) and angiography by catheterization—selective catheterization (J022) (45)
Physician fees, stenting	$463	Angiography by catheterization—insertion of catheter (J021), angiography by catheterization—selective catheterization (J022), and angiograph with vascular stenting (J058) (45)

Abbreviation: PTA, percutaneous transluminal angioplasty; RIW, resource intensity weight.

Physician Fees

The cost of physician time to conduct each procedure was based on the Ontario *Schedule of Benefits for Physician Services*. (45) For PTA, physicians would bill for angiography by catheterization. For stenting procedures, physicians would bill angiography by catheterization plus angiograph with vascular stenting (personal communication, Dr. K.T. Tan, May 2015). Costs included primary physician and anesthetist time. All unit cost inputs are shown in Table 14.

Revascularization Rates

We based revascularization rates for Zilver PTX DESs, bare metal stents and PTA on studies identified in a targeted literature review (Table 15). We based 1- and 2-year Zilver PTX DES revascularization rates on a 2-year single-arm trial reported by Dake and colleagues. (21) We based 3- to 5-year Zilver PTX DES rates on extrapolations by DeCock et al (39) and 1- to 5-year revascularization rates for bare metal stent on the same study. (39) We extracted 1- to 5-year revascularization rates for PTA from a publication by Pietzsch et al. (46)

Table 15: Cumulative Revascularization Rates

Intervention	1 Year	2 Years	3 Years	4 Years	5 Years
Zilver PTX DES	11%	20%	26%	32%	38%
Bare metal stent	16%	22%	28%	34%	40%
PTA	19%	40%	46%	52%	58%

Abbreviations: DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel.

Distribution of Revascularization Interventions

In the base-case and worst-case scenarios, we based the distribution of revascularization intervention options on expert opinion (Table 16). For the conservative scenario, we based this distribution of interventions on the literature (Table 17).

Table 16: Distribution of Revascularization Interventions, Base-Case and Worst-Case Scenarios

Revascularization Intervention	Primary Intervention		
	Zilver PTX DES	Bare Metal Stent	PTA
Zilver PTX DES	50%	0%	30%
Bare metal stent	0%	50%	0%
PTA	0%	0%	0%
Drug-coated balloon	50%	50%	40%
Surgical bypass with autograft	0%	0%	15%
Surgical bypass with synthetic graft	0%	0%	15%

Abbreviations: DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel

Table 17: Distribution of Revascularization Interventions, Conservative Scenario

Revascularization Intervention	Primary Intervention		
	Zilver PTX DES	Bare Metal Stent	PTA
Zilver PTX DES	8%	8%	50%
Bare metal stent	24%	24%	19%
PTA	28%	28%	0%
Drug coated balloon	28%	28%	19%
Surgical bypass with autograft	9%	9%	9%
Surgical bypass with synthetic graft	3%	3%	3%

Abbreviations: DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel

Technology Adoption Rates

For the base-case and worst-case scenarios, we estimated that Zilver PTX DESs would infuse into the Ontario health care system at a rate of 100% (personal communication, Dr. K.T. Tan, May 2015). In other words, we estimated that all eligible patients would receive a Zilver PTX DES instead of a bare metal stent in the first year this technology was funded. In the conservative scenario, we used an adoption rate of 15% in the first year, followed by increases of 5% each year afterward (i.e., 20% in second year, 25% in third year), as reported in a French budget impact analysis. (39)

Analysis

We determined the budget impact of Zilver PTX DESs by calculating the total cost of treating individuals with this technology less the cost of treating the same cohort with bare metal stents. The total cost for each year included the cost of treating both incident and prevalent patients.

Results

Table 18 presents the number of new cases of PAD each year for 5 years, for all 3 scenarios.

Table 18: Estimated Number of Individuals Receiving Zilver PTX DES

Scenario	2015	2016	2017	2018	2019
Base case	640	690	739	789	839
Conservative	34	49	65	83	104
Worst case	640	690	739	789	839

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel

Tables 19 to 21 show the incremental cost or cost savings as a result of funding Zilver PTX DESs for PAD.

Table 19: Incremental Cost Savings With the Implementation of Zilver PTX DES—Base-Case Scenario

Total Costs ($100,000)	2015	2016	2017	2018	2019
Zilver PTX DES	$124.8	$144.3	$161.4	$179.0	$197.2
Bare metal stent/PTA	$129.5	$150.0	$167.4	$185.2	$203.6
Incremental cost	–$4.7	–$5.7	–$6.0	–$6.2	–$6.4

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel

Table 20: Incremental Cost Savings With the Implementation of Zilver PTX DES—Conservative Scenario

Total Costs ($100,000)	2015	2016	2017	2018	2019
Zilver PTX DES	$6.6	$10.0	$13.8	$18.1	$22.9
Bare metal stent/PTA	$6.8	$10.1	$14.0	$18.3	$23.1
Incremental cost	–$0.2	–$0.1	–$0.2	–$0.2	–$0.2

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel

Table 21: Incremental Cost Impact With the Implementation of Zilver PTX DES—Worst-Case Scenario

Total Costs ($100,000)	2015	2016	2017	2018	2019
Zilver PTX DES	$135.0	$169.9	$213.4	$266.0	$328.3
Bare metal stent/PTA	$128.9	$162.7	$204.9	$256.0	$316.6
Incremental cost	$6.1	$7.2	$8.5	$10.0	$11.7

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel

Limitations

Several limitations in our analysis may affect the interpretation of the results. First, the actual cost of Zilver PTX DESs in Ontario has not been reported; the input used in this analysis was based on costs reported for the French health care system. Second, this analysis included adoption rates that were based on expert opinion in the base-case and worst-case scenarios or on a French budget impact analysis in the conservative scenario; these rates are only an estimate and may not actually unfold if Zilver PTX DESs are funded in Ontario. Third, we based the number of eligible PAD patients in Ontario during the 5-year period on projections of current numbers; future rates may be higher or lower than the projected numbers. Fourth, we based long-term revascularization rates beyond 2 years on expert opinion from a French budget impact analysis; they may not represent actual rates of revascularization. As well, revascularization rates were based on more than one literature source and cohort characteristics in the various studies were different. Finally, mortality rates were not incorporated into the analysis; changes to any of these factors will change the results of this budget impact analysis. The results should be interpreted with caution.

Discussion and Conclusions

From the perspective of the Ontario Ministry of Health and Long-Term Care, the funding of Zilver PTX DESs for above-the-knee PAD may result in a budget savings of between $470,000 to 640,000 per year. However, budget savings may be as low as $10,000 to $20,000 per year depending on parameter estimates. In the worst-case scenario, if Zilver PTX DESs offered no improvement in revascularization rates compared to bare metal stents, the cost impact per year would be between $600,000 and $1.2 million.

LIST OF ABBREVIATIONS

DES	Drug-eluting stent
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
PAD	Peripheral arterial disease
PTA	Percutaneous transluminal angioplasty
PTX	Paclitaxel
RCT	Randomized controlled trial
TASC	Trans-Atlantic Inter-Society Consensus
TLR	Target lesion revascularization

APPENDICES

Appendix 1: Literature Search Strategies for the Clinical Evidence Review

Clinical Evidence Review

Search date: November 12, 2014
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Embase, All EBM Databases (see below)
Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2014>, EBM Reviews - ACP Journal Club <1991 to October 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <October 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2014>, Embase <1980 to 2014 Week 45>, Ovid MEDLINE(R) <1946 to October Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 11, 2014>

Search Strategy

#	Searches	Results
1	Popliteal Artery/ or Femoral Artery/	57790
2	Peripheral Arterial Disease/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Peripheral Vascular Diseases/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Atherosclerosis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	37270
3	Peripheral Occlusive Artery Disease/ use emez	23915
4	((peripheral adj3 (disease* or arter* or vascular or angiopath*)) or ((vessel* or arter*) adj3 (femoral or popliteal or femoropopliteal or femoro-popliteal or infrainguinal)) or (above adj2 knee*) or (below adj2 pelvis)).ti,ab.	144999
5	or/1-4	210561
6	exp Stents/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	58577
7	Stent/ use emez or Drug Eluting Stent/ use emez	81596
8	Paclitaxel/	90832
9	((stent* adj5 (eluting or coated or drug)) or DES or PES).ti,ab.	95451
10	(paclitaxel or "abi 007" or abi007 or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc125973 or nsc-125973 or onxol or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan or zilver).mp.	106884
11	or/6-10	306341
12	5 and 11	8918
13	(Meta Analysis or Controlled Clinical Trial or Randomized Controlled Trial).pt.	967884
14	Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Meta-Analysis as Topic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	78012
15	Meta Analysis/ use emez or "Meta Analysis (Topic)"/ use emez or Biomedical Technology Assessment/ use emez	109612

16	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab.	395990
17	(meta analy* or metaanaly* or health technolog* assess*).mp.	276839
18	exp Randomized Controlled Trial/ or exp controlled clinical trial/	972789
19	exp Random Allocation/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Double-Blind Method/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Controlled Clinical Trials as Topic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Placebos/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	457936
20	exp randomization/ use emez or double blind procedure/ use emez or exp "controlled clinical trial (topic)"/ use emez or Random sample/ use emez or Placebo/ use emez	425608
21	(random* or RCT or RCTs or placebo* or sham* or (control* adj2 (trial* or study or studies))).ti,ab.	2670317
22	or/13-21	3720989
23	12 and 22	1509
24	limit 23 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained]	1392
25	remove duplicates from 24	971

Review of the Economic Literature

MEDLINE Search

Databases: Ovid MEDLINE(R) 1946 to May Week 2 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 19, 2015
Limits: English language, Humans
Filters: Economic Evaluation Filter: NHS EED MEDLINE, best sensitivity validated filter from Glanville2009

Search Strategy

#	Searches	Results
1	Popliteal Artery/ or Femoral Artery/ or Peripheral Arterial Disease/ or Peripheral Vascular Diseases/ or Atherosclerosis/ or ((peripheral adj3 (disease* or arter* or vascular or angiopath*)) or ((vessel* or arter*) adj3 (femoral or popliteal or femoropopliteal or femoro-popliteal or infrainguinal)) or (above adj2 knee*) or (below adj2 pelvis)).ti,ab.	104306
2	exp Stents/ or Paclitaxel/ or ((stent* adj5 (eluting or coated or drug)) or DES or PES).ti,ab. or (paclitaxel or "abi 007" or abi007 or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc125973 or nsc-125973 or onxol or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan or zilver).mp.	104747
3	1 and 2	3606
4	economics/ or exp "costs and cost analysis"/ or economics, dental/ or exp "economics, hospital"/ or economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj1 money) or budget$).ti,ab.	634201
5	(((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure)).ti,ab.	21412
6	(letter or editorial or historical article).pt.	1556407
7	Animals/ not (Animals/ and Humans/)	3943670
8	4 not (5 or 6 or 7)	564502
9	3 and 8	130
10	limit 9 to english language	117
11	remove duplicates from 10	114

Embase Search

Database: Embase Classic+Embase 1947 to 2015 Week 20
Limits: English language , Humans
Filters: Economic Evaluation Filter: NHS EED EMBASE, best sensitivity validated filter from Glanville2009
Search Strategy

#	Searches	Results
1	Popliteal Artery/ or Femoral Artery/ or Peripheral Occlusive Artery Disease/ or ((peripheral adj3 (disease* or arter* or vascular or angiopath*)) or ((vessel* or arter*) adj3 (femoral or popliteal or femoropopliteal or femoro-popliteal or infrainguinal)) or (above adj2 knee*) or (below adj2 pelvis)).ti,ab.	120310
2	Stent/ or Drug Eluting Stent/ or Paclitaxel/ or ((stent* adj5 (eluting or coated or drug)) or DES or PES).ti,ab. or (paclitaxel or "abi 007" or abi007 or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc125973 or nsc-125973 or onxol or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan or zilver).mp.	206629
3	(health-economics/ or exp economic-evaluation/ or exp health-care-cost/ or exp pharmacoeconomics/ or (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj2 money) or budget$).ti,ab.) not ((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab.	991420
4	1 and 2 and 3	282
5	limit 4 to english language	266

Cochrane Library Search

Databases

Cochrane Database of Systematic Reviews: Issue 5 of 12, May 2015
Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015
Cochrane Central Register of Controlled Trials: Issue 4 of 12, April 2015
Health Technology Assessment Database: Issue 2 of 4, April 2015
NHS Economic Evaluation Database: Issue 2 of 4, April 2015

Search Strategy

ID	Search	Hits
#1	MeSH descriptor: [Popliteal Artery] this term only	297
#2	MeSH descriptor: [Femoral Artery] this term only	811
#3	MeSH descriptor: [Peripheral Arterial Disease] this term only	206
#4	MeSH descriptor: [Peripheral Vascular Diseases] this term only	578
#5	MeSH descriptor: [Atherosclerosis] this term only	536
#6	(peripheral adj3 (disease* or arter* or vascular or angiopath*)) or ((vessel* or arter*) adj3 (femoral or popliteal or femoropopliteal or femoro-popliteal or infrainguinal)) or (above adj2 knee*) or (below adj2 pelvis):ti,ab,kw (Word variations have been searched)	0
#7	#1 or #2 or #3 or #4 or #5 or #6	2070
#8	MeSH descriptor: [Stents] explode all trees	3715
#9	MeSH descriptor: [Paclitaxel] this term only	1535
#10	(stent* adj5 (eluting or coated or drug)) or DES or PES:ti,ab,kw (Word variations have been searched)	2052
#11	paclitaxel or "abi 007" or abi007 or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc125973 or nsc-125973 or onxol or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan or zilver (Word variations have been searched)	4096
#12	#8 or #9 or #10 or #11	8901
#13	#7 and #12	170
#14	MeSH descriptor: [Economics] this term only	60
#15	MeSH descriptor: [Costs and Cost Analysis] explode all trees	23816
#16	MeSH descriptor: [Economics, Dental] this term only	3
#17	MeSH descriptor: [Economics, Hospital] explode all trees	1680
#18	MeSH descriptor: [Economics, Medical] this term only	38
#19	MeSH descriptor: [Economics, Nursing] this term only	17
#20	MeSH descriptor: [Economics, Pharmaceutical] this term only	237
#21	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*) or (expenditure* not energy) or (value near/1 money) or budget*:ti,ab,kw (Word variations have been searched)	49185
#22	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	49274
#23	((energy or oxygen) near cost) or (metabolic near cost) or ((energy or oxygen) near expenditure):ti,ab,kw (Word variations have been searched)	2515
#24	#22 not #23	48742
#25	letter or editorial or historical article:pt (Word variations have been searched)	6797
#26	#24 not #25	48634
#27	MeSH descriptor: [Animals] explode all trees	6952
#28	MeSH descriptor: [Humans] explode all trees	1232
#29	#27 not (#27 and #28)	5720
#30	#26 not #29	48452
#31	#13 and #30	25

Appendix 2: Evidence Quality Assessment

Primary Studies

Table A1: GRADE Evidence Profile for Comparison of Zilver PTX DESs With PTA

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12-Month Primary Patency							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations[b]	Serious limitations (–1)[c]	No serious limitations	Undetected[d]	None	⊕⊕ Low
24-Month Primary Patency							
1 (RCT)	Very serious limitations (–2)[a,e]	No serious limitations[b]	Serious limitations (–1)[c]	No serious limitations	Undetected[d]	None	⊕ Very low
Clinical Benefit Index							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations[b]	Serious limitations (–1)[f]	No serious limitations	Undetected[d]	None	⊕⊕ Low
Ankle-Brachial Index							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations[b]	No serious limitations	No serious limitations	Undetected[d]	None	⊕⊕⊕ Moderate
Rutherford Classification							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations[b]	No serious limitations	No serious limitations	Undetected[d]	None	⊕⊕⊕ Moderate
Walking Impairment Questionnaire							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations[b]	No serious limitations	No serious limitations	Undetected[d]	None	⊕⊕⊕ Moderate
Event-Free Survival							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations[b]	Serious limitations (–1)[g]	No serious limitations	Undetected[d]	None	⊕⊕ Low

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; PTA, percutaneous transluminal angioplasty PTX, paclitaxel; RCT, randomized controlled trial.

[a]Lack of blinding of participants and personnel. Uncertain on the role of funding sources on the conduct of the RCT.

[b]Consistency unknown because this was a single study.

[c]A surrogate to predict clinically important outcomes (e.g., amputation).

[d]A single study funded by the manufacturer of the device.

[e]The 24-month primary patency rate was based on a subgroup of patients selected for follow-up.

[f]The clinical benefit index was not a validated outcome measure.

[g]A composite outcome with a mix of safety (e.g., target lesion revascularization) and clinical measures (e.g., worsening of Rutherford classification).

Table A2: Risk of Bias Among Randomized Controlled Trials Comparing Zilver PTX DESs With PTA

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Dake et al, 2011 (22) (Zilver PTX RCT)	No limitations	Limitations[a]	No limitations	No limitations	Limitations[b]

Abbreviations: DES, drug eluting stent; PTX, paclitaxel; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial.
[a]Lack of blinding of participants and personnel. The rate of PTA acute failure was much higher than expected. Without blinding, there was a risk of bias toward reporting that PTA has failed to proceed to stenting as PTA was not the control group of choice.
[b]No statement in the paper indicating the involvement or lack of involvement from the funding sources in the conduct of the RCT.

Table A3: GRADE Evidence Profile for Comparison of Zilver PTX DESs With Bare Metal Stents

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12-Month Primary Patency							
1 (RCT)	Serious limitations (–1)[a,b]	No serious limitations[c]	Serious limitations (–1)[d,e]	No serious limitations	Undetected[f]	None	⊕⊕ Low
Clinical Benefit Index							
1 (RCT)	Serious limitations (–1)[a,b]	No serious limitations[c]	Serious limitations (–1)[d,g]	No serious limitations	Undetected[g]	None	⊕⊕ Low

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; PTA, percutaneous transluminal angioplasty; PTX, paclitaxel; RCT, randomized controlled trial.
[a]Lack of blinding of participants and personnel. Uncertain on the role of funding sources on the conduct of the RCT.
[b]Unclear whether the baseline characteristics between groups were balanced.
[c]Consistency unknown because this was a single study.
[d]The Zilver PTX RCT was designed to include both *de novo* and restenotic lesions. The comparison between Zilver PTX DESs and bare metal stents was a secondary randomization based on acute failure of PTA, so the population was restricted to a subgroup with restenotic lesions.
[e]A surrogate to predict clinically important outcomes, e.g., amputation.
[f]A single study funded by the manufacturer of the device.
[g]The clinical benefit index was not a validated outcome measure.

Table A4: Risk of Bias Among Randomized Controlled Trials Comparing Zilver PTX DESs With Bare Metal Stents

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Dake et al, 2011 (22) (Zilver PTX RCT)	No limitations	Limitations[a]	No limitations	No limitations	Limitations[b,c]

Abbreviations: DES, drug eluting stent; PTX, paclitaxel; RCT, randomized controlled trial.
[a]Lack of blinding of participants and personnel.
[b]No statement in the paper indicating the involvement or lack of involvement from the funding sources in the conduct of the RCT.
[c]No information on the baseline characteristics of patients for the secondary randomization.

Table A5: GRADE Evidence Profile for Comparison of Zilver PTX DESs With PTX Drug-Coated Balloons

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12-Month Primary Patency							
1 (observational study)	No serious limitations	No serious limitations[a]	Serious limitations (–1)[b]	No serious limitations	Undetected	None	⊕ Very low
Ankle-Brachial Index							
1 (observational study)	No serious limitations	No serious limitations[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Event-Free Survival							
1 (observational study)	No serious limitations	No serious limitations[a]	Serious limitations (–1)[c]	No serious limitations	Undetected	None	⊕ Very low

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; PTX, paclitaxel.
[a]Consistency unknown because this was a single study.
[b]A surrogate to predict clinically important outcomes, e.g., amputation.
[c]A composite outcome with a mix of safety (e.g., target lesion revascularization) and clinical measures (e.g., worsening of Rutherford classification).

Table A6: Risk of Bias Among Observational Studies Comparing Zilver PTX DESs With PTX Drug-Coated Balloons

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Zeller et al, 2014 (31)	No limitations	No limitations	No limitations	No limitations[a]	No limitations

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel.
[a]This was a retrospective study with the inherent limitations of retrospective design. However, Zeller et al (31) attempted to control for confounding using propensity score stratification of major covariates.

Table A7: GRADE Evidence Profile for Noncomparative Observational Studies of Zilver PTX DESs

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12-Month Primary Patency							
3 (observational studies)	No serious limitations	Serious limitations (–1)[a]	Serious limitations (–1)[b]	No serious limitations	Undetected	None	⊕ Very low
Ankle-Brachial Index							
2 (observational studies)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Rutherford Classification							
2 (observational studies)	Serious limitations (–1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Walking Impairment Questionnaire							
1 (observational study)	Serious limitations (–1)[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Event-Free Survival							
1 (observational study)	No serious limitations	No serious limitations	Serious limitations (–1)[e]	No serious limitations	Undetected	None	⊕ Very low

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; PTX, paclitaxel.
[a]The primary patency rate reported by Dake et al (23) was substantially higher than that reported by Fujihara et al (32).
[b]A surrogate to predict clinically important outcomes (e.g., amputation).
[c]Lack of blinding of patients. The outcome of the Walking Impairment Questionnaire was patient-perceived.
[d]Lack of blinding of research personnel. The outcome of Rutherford classification required subjective assessment.
[e]A composite outcome with a mix of safety (e.g., target lesion revascularization) and clinical measures (e.g., worsening of Rutherford classification).

Table A8: Risk of Bias Among Noncomparative Observational Studies of Zilver PTX DESs

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Dake et al, 2011 (23)	No limitations	No limitations	Limitations[a]	No limitations	No limitations
Fujihara et al, 2014 (32)	No limitations	No limitations	No limitations	No limitations	Limitations[b]
Leopardi et al, 2014 (33)	No limitations	No limitations	No limitations	No limitations	No limitations

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel.
[a]Angiography and duplex ultrasound results were self-reported by sites without a core laboratory to standardize data.
[b]No description of the number of patients lost to follow-up.

Subgroup Analyses

Table A9: GRADE Evidence Profile for Noncomparative Observational Studies of Zilver PTX DESs in Patients With Diabetes

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12-Month Primary Patency							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	Serious limitations (–1)[b]	No serious limitations	Undetected	None	⊕ Very low
Ankle-Brachial Index							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Rutherford Classification							
1 (observational study)	Serious limitations (–1)[a,d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Walking Impairment Questionnaire							
1 (observational study)	Serious limitations (–1)[a,d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Event-Free Survival							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	Serious limitations (–1)[e]	No serious limitations	Undetected	None	⊕ Very low

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; PTX, paclitaxel.
[a]A methodological limitation related to the single study being a subgroup analysis not specified a priori.
[b]A surrogate to predict clinically important outcomes (e.g., amputation).
[c]Lack of blinding of research personnel. The outcome of Rutherford classification required subjective assessment.
[d]Lack of blinding of patients. The outcome of the Walking Impairment Questionnaire was patient-perceived.
[e]A composite outcome with a mix of safety (e.g., target lesion revascularization) and clinical measures (e.g., worsening of Rutherford classification).

Table A10: Risk of Bias Among Noncomparative Observational Studies of Zilver PTX DESs in Patients With Diabetes

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Fanelli et al, 2014 (24)	Limitations[a]	No limitations	No limitations	No limitations	No limitations

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel.
[a]No description of how diabetes status was ascertained.

Table A11: GRADE Evidence Profile for Noncomparative Observational Studies of Zilver PTX DESs in Patients With Complex Lesions

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12-Month Primary Patency							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	Serious limitations (–1)[b]	No serious limitations	Undetected	None	⊕ Very low
Ankle-Brachial Index							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Walking Impairment Questionnaire							
1 (observational study)	Serious limitations (–1)[a,c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Event-Free Survival							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	Serious limitations (–1)[d]	No serious limitations	Undetected	None	⊕ Very low

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; PTX, paclitaxel.
[a]A methodological limitation related to the single study being a subgroup analysis not specified a priori.
[b]A surrogate to predict clinically important outcomes (e.g., amputation).
[c]Lack of blinding of patients. The outcome of the Walking Impairment Questionnaire was patient-perceived.
[d]A composite outcome with a mix of safety (e.g., target lesion revascularization) and clinical measures (e.g., worsening of Rutherford classification).

Table A12: Risk of Bias Among Noncomparative Observational Studies of Zilver PTX DESs in Patients With Complex Lesions

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Bosiers et al, 2013 (25)	No limitations	No limitations	No limitations	No limitations	No limitations

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel.

Table A13: GRADE Evidence Profile for Noncomparative Observational Studies of Zilver PTX DESs in Patients With In-Stent Restenosis

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
12-Month Primary Patency							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	Serious limitations (–1)[b]	No serious limitations	Undetected	None	⊕ Very low
Ankle-Brachial Index							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Rutherford Classification							
1 (observational study)	Serious limitations (–1)[a,c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Walking Impairment Questionnaire							
1 (observational study)	Serious limitations (–1)[a,d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very low
Event-Free Survival							
1 (observational study)	Serious limitations (–1)[a]	No serious limitations	Serious limitations (–1)[e]	No serious limitations	Undetected	None	⊕ Very low

Abbreviations: DES, drug-eluting stent; GRADE, Grading of Recommendations Assessment, Development, Evaluation; PTX, paclitaxel.
[a]A methodological limitation related to the single study being a subgroup analysis not specified *a priori*.
[b]A surrogate to predict clinically important outcomes (e.g., amputation).
[c]Lack of blinding of research personnel. The outcome of Rutherford classification required subjective assessment.
[d]Lack of blinding of patients. The outcome of the Walking Impairment Questionnaire was patient-perceived.
[e]A composite outcome with a mix of safety (e.g., target lesion revascularization) and clinical measures (e.g., worsening of Rutherford classification).

Table A14: Risk of Bias Among Noncomparative Observational Studies of Zilver PTX DESs in Patients With In-Stent Restenosis

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Zeller et al, 2013 (26)	No limitations	No limitations	No limitations	No limitations	No limitations

Abbreviations: DES, drug-eluting stent; PTX, paclitaxel.

Appendix 3: Modified Methodological Checklist for Economic Evaluations

Question topic:		
Study reference:		
Checklist completed by:		
APPLICABILITY (relevance to question under review)		
Item	**Yes/Partly/ No/Unclear/NA**	**Comments**
Is the study population appropriate to the question?		
Are the interventions appropriate to the question?		
Are all relevant interventions compared?		
What country was this study conducted in?		
Is the healthcare system in which the study was conducted sufficiently similar to Ontario with respect to this question/topic? Explain the ways in which they differ.		
Are estimates of relative treatment effect the same as those included in the EBA?		
Are costs measured from a healthcare payer perspective?		
Are non-direct health effects on individuals excluded?		
Are both costs and health effects discounted at an annual rate of 5%?		
Do the estimates of resource use differ from that which would be expected in an Ontario context?		
Is the value of health expressed in terms of QALYs?		
Are changes in health related quality of life (HRQL) obtained directly from patients and/or carers?		
Has the valuation of changes in HRQL (utilities) obtained from a representative sample of the general public?		
Overall Judgement (Directly applicable/partially applicable/not applicable): Not applicable If a study is considered not applicable, there is no need to assess its quality.		

QUALITY (the level of methodological quality)
Use this checklist if the overall judgement of the applicability of the study is directly or partially applicable.

Item	Yes/Partly/ No/Unclear/NA	Comments
Does the model structure adequately reflect the nature of the health condition under evaluation?		
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? (e.g., if the rate of mortality differs between interventions, does the model take a lifetime horizon?)		
Are all important and relevant health outcomes included?		
Are the estimates of relative treatment effects obtained from best available sources?		
Do the estimates of relative treatment effect match the estimates contained in the EBA?		
Are all important and relevant (direct) costs included in the analysis?		
Are the estimates of resource use obtained from best available sources?		
Are the unit costs of resources obtained from best available resources?		
Is an appropriate incremental analysis presented or can it be calculated from the reported data?		
Are all important and uncertain parameters subjected to appropriate sensitivity analysis?		
Is there a potential conflict of interest?		

Overall assessment (minor limitations/potentially serious limitations/very serious limitations):

Other comments:

Reference: National Institute for Health and Care Excellence. The guidelines manual: appendices B-I, Appendix G: Methodology checklist: economic evaluations [Internet]. United Kingdom: National Institute for Health and Care Excellence; 2012 [cited 2014 Oct 6]. Available from: http://publications.nice.org.uk/the-guidelines-manual-appendices-bi-pmg6b/appendix-g-methodology-checklist-economic-evaluations.

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

About the Ontario Health Technology Advisory Committee (OHTAC)

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