Long-term outcomes with paclitaxel-eluting stents versus bare metal stents in everyday practice: A Canadian experience

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BACKGROUND: In randomized trials, paclitaxel-eluting stents (PES) are superior to bare metal stents (BMS) in reducing target lesion revascularization (TLR). However, recent reports suggest there may be an increase in late stent thrombosis with long-term follow-up in PES-treated patients. **METHODS:** Prospectively collected data from a regional cardiac referral centre were analyzed to compare PES versus BMS in all consecutive patients undergoing percutaneous coronary intervention from April 2003 to March 2004. Outcomes included combined death, myocardial infarction and clinically driven TLR, as well as stent thrombosis at four years follow-up.

RESULTS: A total of 512 patients were treated with PES and 722 patients with BMS. At four years, there was 92% follow-up in both groups. The composite outcome of death, myocardial infarction and TLR was 13.9% in the PES group compared with 20% in the BMS group ($P=0.01$). This difference was primarily driven by the reduction in TLR in the PES cohort (3.9% versus 8%, $P<0.01$). The rate of definite stent thrombosis was 1.6% in the PES group compared with 0.4% in the BMS group ($P=0.03$).

CONCLUSION: While PES offers an absolute 4.1% reduction in clinically driven TLR at four years, there is an associated increased risk of stent thrombosis. Further long-term studies addressing clinical outcomes including stent thrombosis with PES versus BMS are required to clarify this risk/benefit balance.

Key Words: Coronary artery disease; Drug-eluting stents; Paclitaxel; Percutaneous coronary intervention; Restenosis; Stent thrombosis

Restenosis is a major limitation of percutaneous coronary interventions (PCIs) with bare metal stents (BMS). In a number of randomized clinical trials, paclitaxel-eluting stents (PES) have been shown to be superior to BMS in reducing restenosis rates and target lesion revascularization (TLR) (1-4).

While PES has been shown to be highly effective in preventing restenosis following PCI, concerns have been raised about a possible increased risk of stent thrombosis with drug-eluting stents (DES) (5-8). Four published 'real-world' registries (9-12) have addressed the long-term safety of PES in clinical practice with respect to the end points of target vessel revascularization (TVR), death and myocardial infarction (MI). However, these registries failed to address the issue of stent thrombosis and to assess the more accurate measure of stent restenosis, namely TLR, in everyday clinical practice. Recently published meta-analyses (13,14) of randomized clinical trials (RCTs) with long-term follow-up of PES failed to demonstrate a difference with respect to death and MI. However, these studies highlighted a significant

Les issues à long terme des endoprothèses à élution de paclitaxel par rapport aux endoprothèses à métal nu dans la pratique quotidienne : Une expérience canadienne

HISTORIQUE : Dans des études aléatoires, les endoprothèses à élution de paclitaxel (EÉP) sont supérieures aux endoprothèses à métal nu (EMN) pour réduire la revascularisation de la lésion ciblée (RLC). Cependant, selon de récents rapports, il y aurait peut-être une augmentation des thromboses tardives de l'endoprothèse d'après le suivi à long terme des patients traités par EÉP.

MÉTHODOLOGIE : Les auteurs ont analysé des données prospectives colligées dans un centre de cardiologie régional pour comparer les EÉP aux EMN chez tous les patients consécutifs qui avaient subi une intervention coronaire percutanée entre avril 2003 et mars 2004. Les issues incluaient un composite de décès, d'infarctus du myocarde et de RLC constatées en clinique, ainsi qu'une thrombose de l'endoprothèse au suivi de quatre ans.

RÉSULTATS : Au total, 512 patients ont été traités par EÉP et 722, par EMN. Au bout de quatre ans, on constatait 92 % de suivi dans les deux groupes. L'issue composite de décès, d'infarctus du myocarde et de RLC s'élevait à 13,9 % dans le groupe ayant une EÉP et à 20 % dans celui ayant une EMN ($P=0,01$). Cette différence découlait surtout de la réduction des RLC dans la cohorte d'EÉP (3,9 % par rapport à 8 %, $P<0,01$). Le taux de thrombose bien définie de l'endoprothèse était de 1,6 % dans le groupe ayant une EÉP par rapport à 0,4 % dans celui ayant une EMN ($P=0,03$).

CONCLUSION : Même si l'EÉP offre une réduction absolue de 4,1 % des RLC constatées en clinique au bout de quatre ans, on observe un risque connexe accru de thrombose de l'endoprothèse. D'autres études à long terme portant sur les issues cliniques s'imposent pour tirer au clair cet équilibre risques-avantages, y compris la thrombose d'une EÉP par rapport à une EMN.

increase in late stent thrombosis in patients treated with PES. The randomized trials have generally excluded important subsets of patients treated in routine practice, such as those with multivessel disease, bifurcation lesions, small-diameter vessels, long lesions, vein graft stenoses and acute coronary syndromes. Thus, more data addressing the safety and effectiveness of PES compared with BMS in complex, unselected patients treated outside of randomized trials, are urgently required.

The purpose of the present study was to report on the long-term clinical outcomes of patients undergoing PCI with PES versus BMS as well as the rates of stent thrombosis in both groups, at a tertiary cardiac referral centre in Canada.

METHODS

Patient population

All patients undergoing revascularization with PCI at Hamilton Health Sciences (Hamilton, Ontario) are entered into a database

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registry that includes prospectively collected demographic, clinical, procedural, angiographic and in-hospital outcomes details including death, recurrent nonfatal MI, TLR and stent thrombosis.

A retrospective comparison of PES versus BMS was conducted in all consecutive patients at the institution with at least one stent successfully deployed in de novo lesions over a 12-month period. Patients undergoing primary or rescue PCI, those presenting with cardiogenic shock, and patients with a dual population of stents (ie, combination of BMS and PES) or presenting with restenosis were excluded from the analyses. All patients provided informed consent to be followed up after their procedure for study purposes. The protocol was approved by the institution's research ethics board.

Patients undergoing PCI at the institution during the first six months of the study only had access to BMS. However, during the last six months of the study period, PES (TAXUS Express, Boston Scientific Corporation, USA) became available for use with relatively unrestricted access. PES were to be preferentially used in lesions known to be at higher risk of restenosis (eg, bifurcating positions, longer lesions and smaller-diameter vessels), but ultimately, the decision was left to the interventional cardiologist at the time of PCI. During the latter half of the study period, the majority of patients underwent PCI with PES.

Intervention

All procedures were performed according to standardized techniques. The use of periprocedural antithrombotic agents at the time of PCI was at the discretion of the interventional cardiologist. Angiographic success was defined as a residual stenosis of less than 20% in the presence of Thrombolysis In Myocardial Infarction (TIMI) 3 flow. Recommended postprocedural medications included lifelong acetylsalicylic acid (ASA) and clopidogrel 75 mg/day for one year, with a minimum recommended duration of six months in the PES cohort and one month in the BMS cohort. A loading dose of at least 300 mg (alternatively 600 mg) of clopidogrel was administered before PCI if the patient was not already on clopidogrel.

Definitions and follow-up

The primary outcome was defined as the composite of death, recurrent nonfatal MI and TLR at four years. In-hospital MI was defined as recurrent chest pain with ischemic electrocardiogram (ECG) changes (mainly ST elevation) and/or elevation of total creatine kinase to twice the upper limit of normal and a positive troponin T as per local standards. A diagnosis of recurrent nonfatal MI postdischarge required the presence of two of the following: ischemic symptoms, creatine kinase elevation twice the upper limit of normal with a positive troponin, or diagnostic Q waves on subsequent ECGs. TLR was defined as clinically motivated repeat PCI or coronary artery bypass graft to treat luminal restenosis of greater than 50% within the stent or within the immediate 5 mm of vessel adjacent to the stent.

The secondary outcomes included the individual events of death, MI, TLR and stent thrombosis at four years. Stent thrombosis was defined as angiographic evidence of thrombus in or within 5 mm of the stented segment in conjunction with one of the following: acute rest ischemic symptoms, new ischemic ECG changes, and/or a typical rise and fall of cardiac biomarkers as per the Academic Research Consortium for definite stent thrombosis (15). The timing of stent thrombosis was defined as follows: acute stent thrombosis (24 h or less poststent insertion), subacute stent thrombosis (more than 24 h to 30 days postinsertion), late stent thrombosis (more than 30 days to one year postinsertion) and very late stent thrombosis (more than one year postinsertion) (15).

In-hospital outcomes were verified by review of hospital charts. One- and four-year outcomes were verified by telephone contact. When patients had repeat hospitalizations for chest pain or cardiac catheterization, details of the admission were obtained for verification of outcomes. At four years, all patients included in the study were cross-referenced with the medical records database and the PCI database to ensure that no repeat admissions or interventions were missed.

TABLE 1

Baseline clinical characteristics of patients treated with paclitaxel-eluting stents (PES) and those treated with bare metal stents (BMS)

	PES (n=512)	BMS (n=722)	P
Age, years, mean $\pm$ SD	63 $\pm$ 12	65 $\pm$ 12	0.4
Female sex, %	29	31	0.5
Diabetes, %	27	26	0.6
Insulin treated	9	9	0.9
Hypertension, %	68	70	0.5
Present cigarette smoking, %	22	22	0.9
Dyslipidemia, %	76	81	0.05
Previous MI, %	58	68	0.001
Previous PTCA, %	15	12	0.1
Previous CABG, %	13	12	0.6
Multivessel disease, %	53	49	0.2
Clinical presentation, %			
Stable angina	40	30	<0.001
Unstable angina/NSTEMI	60	70	<0.001

CABG Coronary artery bypass grafting; MI Myocardial infarction; NSTEMI Non-ST elevation myocardial infarction; PTCA Percutaneous angioplasty

Statistical analysis

The data from a locked database were analyzed using SAS version 8.2 (SAS Institute Inc, USA). Descriptive statistics were provided for baseline demographics and procedural characteristics. Logistic regression models were developed using SAS Proc Logistic (SAS Institute Inc). Univariate logistic models were examined for each baseline explanatory variable.

Multivariable logistic regression models were developed to describe the relationship between the composite outcome and a set of baseline explanatory variables using a forward selection method. This method started with an empty model, in which variables were entered into the model if the P-value for the variables was less than the prespecified alpha level of 0.05. The process was then repeated until none of the remaining variables met the specified alpha level for entry. A final multivariable model included all variables with $P < 0.05$. The Kaplan-Meier method was used to estimate the time to first event (death, MI and TLR).

A logistic analysis using the propensity score approach to estimate the exposure to PES and BMS as a function of prespecified covariates and to further estimate the impact of the exposure on the combined outcome by introducing the propensity score as a covariate was undertaken.

RESULTS

A total of 1234 patients (512 PES and 722 BMS) underwent PCI for de novo lesions between April 2003 and March 2004. All patients met the inclusion criteria for the study and were eligible for analysis.

Table 1 shows the baseline characteristics of the study patients. The mean age was 64.1 years and 26.3% had diabetes. Overall, 56.3% of patients underwent PCI for acute coronary syndromes. A significantly higher proportion of patients in the BMS cohort had a history of dyslipidemia and previous MI. There was a trend toward more multivessel disease and previous revascularization procedures (both PCI and coronary artery bypass graft) in the PES group. There were no significant differences with respect to other baseline characteristics.

The key angiographic and procedural characteristics appear in Table 2. The periprocedural use of glycoprotein IIb/IIIa inhibitors and the proportion of patients receiving stents for lesions in the left anterior descending artery were similar in both groups. However, significantly more patients in the PES group received stents that were 2.5 mm or less in diameter, 20 mm or greater in length, and in bifurcation positions.

TABLE 2
Angiographic and procedural characteristics

	PES (n=512)	BMS (n=722)	P
Stented coronary vessel*, %			0.33
Left main	1	1	
Left anterior descending	37	35	
Circumflex	27	25	
Right coronary	31	33	
Bypass graft	0.03	5	
Lesion type†, %			0.02
A	2	3	
B1	21	26	
B2	56	48	
C	21	23	
Periprocedural GP IIb/IIIa inhibitors, %	31	31	0.9
Bifurcation stenting‡, %	15	12	0.02
Implanted stents/patient, n, mean ± SD	1.4±0.7	1.4±0.7	0.09
Stent diameter ≤2.5 mm‡, %	27	11	<0.001
Stent length ≥20 mm‡, %	43	27	<0.001
Post-PCI TIMI grade 3 flow§, %	99	97	0.1

*n=604 for paclitaxel-eluting stent (PES) group, n=832 for bare metal stent (BMS) group; †n=714 for PES, n=971 for BMS; ‡n=701 for PES, n=1036 for BMS; §n=714 for PES, n=939 for BMS. GP Glycoprotein; PCI Percutaneous coronary intervention; TIMI Thrombolysis In Myocardial Infarction

TABLE 3
Medications at discharge

	PES (n=512)	BMS (n=722)	P
Acetylsalicylic acid, %	99	100	0.008
Clopidogrel, %	100	100	0.4
Oral anticoagulation, %	3	4	0.6
ACE inhibitor, %	78	79	0.8
Beta-blocker, %	80	81	0.5
Statin, %	95	95	0.6

ACE Angiotensin-converting enzyme; BMS Bare metal stent; PES Paclitaxel-eluting stent

Medical therapy at discharge included prescriptions for ASA 81 mg/day (encouraged to continue lifelong) and clopidogrel 75 mg/day, for a minimum of six months in the PES group and a minimum of one month in the BMS group. ASA, clopidogrel and statin use exceeded 90% in both groups (Table 3).

There were no in-hospital deaths or repeat interventional procedures in either group. The in-hospital MI rate was 0.8% in the PES group and 1.4% in the BMS group (P=0.32).

There was 100% follow-up at one year in both groups. The results of the one-year follow-up are reported elsewhere (16). There was 92% follow-up at four years in both groups (7.8% in DES and 8.9% in BMS were lost to follow-up at four years; P=0.5). Cumulative four-year clinical outcomes are presented in Figure 1. There was a significant reduction in the primary outcome of combined death, MI and TLR at four years with PES compared with BMS. The unadjusted composite event rate was 13.9% in the PES group versus 20% in the BMS group (P=0.014). Figure 2 is a Kaplan-Meier curve outlining the four-year survival free of death, MI and TLR.

There were no significant differences in death or MI between the two groups at four years. However, treatment with PES was associated with a significant reduction in clinically driven TLR compared with BMS. At four years, the rate of clinically driven TLR was 3.9% in the PES group compared with 8% in the BMS group (P<0.003).

The rate of definite stent thrombosis was 1.6% in the PES group compared with 0.4% in the BMS group (P=0.03). There was one acute

Figure 1) Clinical outcomes at one year. BMS Bare metal stent; MI Myocardial infarction; PES Paclitaxel-eluting stent; TLR Target lesion revascularization

Figure 2) Kaplan-Meier curve outlining the four-year survival free of death, myocardial infarction and target lesion revascularization. BMS Bare metal stent; PES Paclitaxel-eluting stent

stent thrombosis and two subacute stent thromboses in the BMS cohort, with no late stent thrombosis. The PES group had three subacute, two late and three very late stent thromboses.

Multivariate analyses were performed to identify independent predictors of the primary outcome of death, MI and TLR at four years (Table 4). Significant variables entered into the model included location of stent insertion (proximal left anterior descending artery), age, multivessel stenting, diabetes and clinical presentation (unstable angina/non-ST elevation MI versus stable angina). In logistic analysis, using the propensity score approach to estimate the exposure to PES and BMS, and further estimate the impact of the exposure on the outcome, treatment with PES was again associated with significantly reduced risk (OR 0.69, 95% CI 0.49 to 0.95; P=0.014).

DISCUSSION

PES have been shown to be highly effective in reducing restenosis in randomized trials. Their safety and effectiveness in everyday practice requires ongoing evaluation given the concern of increased stent thrombosis compared with BMS. Most RCTs have generally enrolled noncomplex patients referred for elective interventions. The purpose of our study was to determine the safety and effectiveness of PES compared with BMS in patients treated in routine practice. To our knowledge, this is the only Canadian registry to report four-year clinical

TABLE 4
Variables included in the propensity score analysis of the combined end point of death, myocardial infarction and target lesion revascularization

	OR	95% CI	P
Paclitaxel-eluting stent	0.69	0.49–0.95	0.03
Proximal LAD stenting	2.24	1.49–3.36	<0.01
Age	1.03	1.01–1.04	<0.01
Multivessel disease	1.84	1.34–2.53	<0.01
Diabetes	1.8	1.29–2.49	<0.01
Clinical presentation (unstable angina/ NSTEMI versus stable angina)	1.6	1.11–2.19	0.01

LAD Left anterior descending artery; NSTEMI Non-ST elevation myocardial infarction

follow-up, including death, MI, TLR and stent thrombosis, in PES- and BMS-treated patients.

In the current study, PES were used in significantly more patients with bifurcation lesions, small-diameter vessels and longer lesions compared with BMS. Despite being used in lesions associated with a higher risk of restenosis, treatment with PES resulted in a significant reduction in the primary outcome of the composite of death, MI and TLR at four years compared with BMS. This reduction in the composite outcome was largely driven by the reduction in TLR, consistent with the results of reported RCTs. There was a trend toward a reduction in death (7.2% versus 9.7%) in the PES group; however, this was not statistically significant ($P=0.13$). While the results from recent meta-analyses failed to demonstrate a reduction in mortality alone with DES versus BMS, three 'real-world' registries suggest a reduction in mortality with DES versus BMS in long-term follow-up (10,12-14,17). To further dilute the true benefit of DES, a recently published multicentre registry suggested an increased risk of death or repeat revascularization after the first year of follow-up in patients treated with DES (11). Whether DES offers a mortality benefit over BMS has yet to be established. The potential reduction in death with DES can possibly be explained by the following. First, selection bias may account for the reduction in mortality, because only observational trials suggested this benefit. Meta-analyses, which ideally eliminate selection bias, failed to demonstrate a reduction in mortality with DES (13,14). Second, perhaps the increased TLR in BMS-treated patients is not as benign as initially believed and may translate into increased mortality. Finally, perhaps the prolonged use of dual antiplatelet therapy offers a protective effect with respect to mortality in patients treated with DES.

The rate of TLR in the present study was lower than that reported in the literature (13,14). Our rate of TLR may have been lower for several reasons. First, our rate of TLR was clinically driven rather than protocol-driven follow-up angiography. Second, all patients were on excellent medical therapy with the use of antiplatelet agents, and statin and angiotensin-converting enzyme inhibitor therapy exceeding rates reported in various registries (18-20). While the reported rate of TLR in both groups was lower in the present study, the absolute reduction in clinically driven TLR with PES versus BMS was similar to the absolute reduction in TVR published from other registry data (10,12).

The reduction in TLR with PES was accomplished with an associated significant increase in the rate of stent thrombosis at four years. However, the cumulative rate of stent thrombosis in the present study was less than that reported for PES in a recent registry and meta-analyses (13,14,21). For example, in the collaborative network meta-analysis of 22 trials with PES (13), the cumulative incidence of stent thrombosis at four years was more than 2%. A registry (21) of both sirolimus-eluting stents and PES with four-year follow-up, demonstrated a cumulative rate of definite stent thrombosis as high as 3.3%. Larger randomized trials and registries with longer-term follow-up are

required to clarify the incidence and risk factors of stent thrombosis with DES.

Unfortunately, accurate medication profiles of each patient were not available at the four-year follow-up. The durations of ASA and clopidogrel therapy, and concomitant proton-pump inhibitor use were not identified. However, the three very late stent thromboses in the PES group likely occurred on ASA monotherapy, given that clopidogrel was prescribed for a maximum of six to 12 months post-PES insertion as per the current guideline recommendations for 2003 to 2004.

The current study results are comparable with those presented in the recently published Ontario database addressing the long-term clinical outcomes of death, MI and TVR (10). The Ontario study, however, included both PES and sirolimus-eluting stents, and the follow-up was two years for MI and TVR, and three years for death (10). The Ontario study reported a significant reduction in TVR (10.7% versus 7.4%, $P<0.001$) and death (7.8% versus 5.5%, $P<0.001$) in the DES cohort, with no increase in MI (5.2% versus 5.7%, $P=0.95$). The Ontario study did not address the end point of stent thrombosis in long-term follow-up. While stent thrombosis was not directly assessed in the Ontario study, there were no increased clinical events in the DES group.

Weighing the benefit of reduced TLR (absolute risk reduction of 4.1%) versus the risk of increased stent thrombosis (absolute increase of 1.1%) with PES-treated patients is of utmost importance. When deciding between BMS and PES for a patient undergoing PCI, the interventional cardiologist must consider multiple factors. First, patient factors including the presence of diabetes, bleeding risks, medical conditions warranting concomitant anticoagulant therapy (atrial fibrillation, mechanical cardiac valves, etc), compliance and affordability of continued antiplatelet therapy (clopidogrel and ASA) need to be addressed. Second, procedural factors, including size of the vessel, stent length, previous restenosis and location of the lesion, need to be considered. Further evidence from large-scale registries and RCTs with long-term clinical outcomes, including stent thrombosis, are required to help clarify which patients will derive the most benefit and least risk from PES compared with BMS. Finally, given the substantial increased upfront cost of PES over BMS, the risk and cost of prolonged dual antiplatelet therapy required with PES, the small absolute reduction in clinically driven TLR, and the increased risk of stent thrombosis, a 'real-world' economic analysis addressing the cost-benefit of PES versus BMS should be carefully executed.

Limitations

Although the present study showed a significant reduction in TLR from implantation of PES versus BMS in routine daily practice, it had some important limitations. First, the use of PES versus BMS was not randomized and as such, there were some differences in the baseline characteristics of the patients. However, in multivariate analysis, none of these factors appeared to be predictive of the composite outcome.

Second, the present study involved retrospective analyses of prospectively collected observational data. While retrospective analyses can introduce bias, this design enabled real-world evaluation of PES versus BMS in contrast to the ideal patients and setting of a randomized clinical trial.

Third, the final stent choice was left to the discretion of the interventional cardiologist, which could have introduced bias. As shown in Table 2, PES appeared to be used in significantly more patients with higher-risk lesions (small-diameter vessels, long lesions, bifurcation positions). These features might partially account for the increased frequency of stent thrombosis in the PES group.

Fourth, complete follow-up at four years was not possible in each group. Thus, the possibility of missed events in one or both groups at four years must be considered. However, our institution is the regional PCI centre. Thus, it is unlikely that we missed a significant number of TLRs or cardiac readmissions. The family physicians of all missing patients were also contacted to ensure that no significant events (death or re-intervention) were missed at four years.

Fifth, the two study groups were not evaluated concurrently; thus, there may have been varying management strategies considering temporal trends in medicine. However, both groups were evaluated within one year, limiting the discrepancies in medical therapies between the two groups. Time period analysis comparing the first six months of the study period (95% BMS) versus the latter six months (76% PES), demonstrated no significant differences between these groups compared with the baseline characteristics of BMS and PES groups (16). While the loading dose of clopidogrel (600 mg versus 300 mg) may have varied in the latter six months, this would not have affected the outcomes over the four years of follow-up. This change of dose would also likely not impact the rates of late and very late stent thrombosis.

Finally, the duration of combined antiplatelet therapy likely differed between the two groups. As per local practice patterns during the study period, patients in the BMS group were treated with dual antiplatelet therapy for a minimum of one month, while those in the PES group were treated for a minimum of six months. However, whenever possible, all patients were encouraged to remain on dual antiplatelet

therapy for one year. Long-term follow-up regarding the duration of antiplatelet use postindex PCI was not possible.

CONCLUSION

While PES offers a 4% absolute risk reduction in clinically driven TLR at four years, there is an associated significant increased risk of stent thrombosis. There were no differences in MI or death between the two groups. Further studies addressing clinical outcomes, including stent thrombosis involving long-term follow-up of PES compared with BMS, are required to clarify the risk/benefit balance and ideal patient population.

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