COST-EFFECTIVENESS OF THE SECOND-GENERATION EVEROLIMUS-ELUTING STENT COMPARED TO THE FIRST-GENEREATION PACLITAXEL-ELUTING STENT IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION IN DAILY PRACTICE

Brenda Leeneman; W. Ken Redekop, Dr[1]; Ron T. van Domburg, PhD[2]; Laura T. Burgers MSc[1].

[1] *Institute for Medical Technology Assessment and Institute of Health Policy and Management, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.*

[2] *Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands.*

Abstract

Objectives: To examine the cost-effectiveness of the second-generation everolimus-eluting stent (EES) compared to the first-generation paclitaxel-eluting stent (PES) in patients undergoing percutaneous coronary intervention (PCI) in daily practice.

Methods: The cost-effectiveness analysis was based on data from the TAXUS Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) and XIENCE Stent Evaluated at Rotterdam Cardiology Hospital (X-SEARCH) registries. The primary effectiveness measure was major adverse cardiac events (MACE)-free survival, in which the composite of MACE consisted of death, myocardial infarction (MI), repeat PCI and coronary artery bypass grafting (CABG). The costs were assessed in 2012 Euros (€) and limited to direct medical costs. A bootstrap simulation was used to estimate the uncertainty on the results of MACE-free survival and direct medical costs. An additional analysis was performed to evaluate the impact of patient characteristics on the study results.

Results: At the end of the two year follow-up period, the use of EES was associated with an increased MACE-free survival of 0.076 years and cost savings of €498.34. The probability that EES maintained dominant over PES was confirmed in 76.0% of the bootstrap simulations. The study results were affected by patient characteristics.

Conclusion: EES has proven to be dominant over PES by improving the clinical and economic benefits of PCI in daily practice, even though EES seemed to be worse off based on the patient characteristics.

Introduction

Previous randomized trials have shown that second-generation everolimus-eluting stents (EES) compared with first-generation paclitaxel-eluting stents (PES) resulted in improved safety and efficacy by significantly reducing the rate of myocardial infarction (MI), revascularization and stent thrombosis (Smits et al. 2011, 11-18; Stone et al. 2011, 19-25). However, less is known about the cost-effectiveness of EES compared to PES. Cost-effectiveness analyses are intended to provide information on the costs and effects of medical strategies, which can

be used to inform decision makers regarding wide-scale implementation and reimbursement (Cohen and Reynolds 2008, 2119-2126).

A United States (US) prospective economic substudy alongside the Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System (SPIRIT)-IV trial evaluated the cost-effectiveness of EES compared to PES in patients undergoing percutaneous coronary intervention (PCI) in a real-world setting (i.e. multiple lesions, no angiographic follow-up). The study resulted in cost savings of US$273.00 and 0.0064 quality adjusted life years (QALYs) gained per patient with EES (Amin et al. 2012, 765-770).

Although the cost-effectiveness of EES compared to PES has been assessed in a real-world setting, there is limited information on the cost-effectiveness in daily practice. To examine whether the cost-effectiveness of EES maintains within daily practice, we designed a cost-effectiveness analysis of EES compared to PES in patients undergoing PCI alongside a Dutch prospective cohort study (PCS) of the Erasmus University Medical Center (EMC).

Methods

Patient population

Between March, 2003 and April, 2007, a total of 2943 patients were treated with PES as the default stent for PCI as a part of the TAXUS Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. Between April, 2007 and December, 2009, a total of 2590 patients were treated with EES as the default stent for PCI as a part of the XIENCE Stent Evaluated at Rotterdam Cardiology Hospital (X-SEARCH) registry (Räber et al. 2012, 1110-1121). Both registries have been conducted to evaluate the safety and efficacy of PES and EES in daily practice (Ong et al. 2006, 2996-3003). Patients who have been treated with different types of drug-eluting stents or who did not return a postal questionnaire were excluded from the registries. Consented participation was obtained from all patients (Räber et al. 2012, 1110-1121).

Data collection

All patients were followed regarding major adverse cardiac events (MACE) by the use of patient-administered postal questionnaires and hospital databases (Räber et al. 2012, 1110-1121). The recorded MACE comprised all-cause mortality (i.e. death), MI, repeat PCI, coronary artery bypass grafting (CABG) and stent thrombosis. Data on vital status was collected by hospital records and municipal civil registries. Medical records, discharge letters and coronary angiography documentation were collected for patients with suspected clinical events, and adjudicated by cardiologists affiliated by the EMC (Räber et al. 2012, 1110-1121). The most recent follow-up status for both patient groups was obtained in December, 2011.

Procedures

The procedure and treatment of both patient groups were performed according to the current standard guidelines [(Hamm et al. 2011, 2999-3054; Steg et al. 2012, 2569-2619)]. EES and PES were available in diameters from 2.25 to 4.0 mm, and in lengths from 8 to 28 mm with EES and 8 to 32 mm with PES. Patients treated with EES were prescribed a loading dose of 300 to 600 mg clopidogrel during or immediately after the procedure, and a daily maintenance dose of 75 mg for a period of 12 months. PES patients received the same loading dose of clopidogrel during or immediately after the procedure, and a daily maintenance dose of 75 mg for at least 6 months. All patients were prescribed lifelong daily aspirin, statins, beta-blockers and ACE inhibitors. The operator decided whether patients should receive glycoprotein IIb/IIIa antagonists for a period of twelve hours during or after the procedure [(Räber et al. 2012, 1110-1121)].

Cost-effectiveness analysis

The analytic perspective of the cost-effectiveness analysis was that of the Dutch health care system. For the analysis, data was derived from the T-SEARCH and X-SEARCH registries of the EMC [(Räber et al. 2012, 1110-1121)]. The time horizon spanned two years, because it was expected that all events and costs occurred within a two year follow-up period as assumed in a previous study on the cost-effectiveness of EES compared to PES [(Amin et al. 2012, 765-770)].

Effects

The primary effectiveness measure used in the analysis was MACE-free survival (i.e. survival without MACE) within a follow-up period of two years. The composite of MACE consisted of death, MI, repeat PCI and CABG. Stent thrombosis was excluded, because a previous study based on the T-SEARCH and X-SEARCH registries has shown that the risk of stent thrombosis was directly translated into the risk of cardiac death or MI [(Räber et al. 2012, 1110-1121)]. The secondary effectiveness measure was the incidence of death, MI, repeat PCI and CABG as single events. The sum of the single events indicated the total amount of events per stent, whereas the composite of MACE indicated the amount of patients with an event. The former was used to estimate the costs related to the occurrence of MACE.

According to the Academic Research Consortium (ARC) death (i.e. all-cause mortality) included cardiac death, vascular death, noncardiovascular death and unexplained sudden death. MI encompassed Q wave MI and non-Q wave MI. Repeat PCI and CABG included target lesion revascularization (TLR) and target vessel revascularization (TVR) [(Cutlip et al. 2007, 2344-2351)].

Costs

All costs were assessed in 2012 Euros (€) and limited to direct medical costs. Procedural costs, including the index procedure and the follow-up procedure, were limited to the price paid for both stents, because resource use for the procedures and length of hospital stay did not differ between both patient groups [(Amin et al. 2012, 765-770)]. Medication costs were limited to clopidogrel, because other medication did not differ between both patient groups as well. Costs related to the occurrence of MI, repeat PCI and CABG were derived from the total amount of events per stent. Costs of death were excluded, because the incidence of death did not differ significantly or clinically between both patient groups (Table 3). Costs of outpatient visits, ongoing medications and productivity were not tracked.

Cost-effectiveness

The primary endpoint of the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER) per MACE-free year. The ICER was obtained by dividing the difference in costs with the difference in MACE-free survival at the end of the two year follow-up period.

Sensitivity analysis

Uncertainty on the differences in costs and effects were quantified through the bootstrapping technique. With this technique, new average costs and effects were estimated by resampling the original sample with replacement until the bootstrap resamples have reached the same size as the original sample [(Cohen and Reynolds 2008, 2119-2126)]. Each bootstrap resample resulted in a recalculated incremental cost, incremental effect and ICER, and this procedure was repeated 500 times. The distribution of the recalculated ICERs was presented in a cost-effectiveness plane.

Statistical analysis

The statistical analysis was conducted using IBM SPSS Statistics Version 20. The baseline and procedural characteristics of both patient groups were compared using the Pearson's chi-square test for categorical variables, and by the Student's *t*-test for continuous variables. Categorical variables were presented as counts and percentages, and continuous variables as mean and standard deviation (SD). Event-free survival and the incidence of the single events were estimated according to the Kaplan-Meier method, with event-free survival presented as mean and SD, and the incidence of the single events as counts and percentages. Differences were assessed using the log-rank test. All statistical tests were 2-sided and used an alpha of 0.05, which implied that a p-value<0.05 was statistically significant. The direct medical costs were compared using Microsoft Excel 2010.

Additional analysis

To examine the impact of the patient (i.e. baseline) characteristics on the study results, two additional analyses were performed. The first analysis evaluated the impact of patient characteristics on MACE-free survival, whereas the second analysis evaluated the impact of patient characteristics on the direct medical costs. Both analyses were assessed using a linear regression in IBM SPSS Statistics Version 20.

Results

Patient population

The final patient population consisted of 5354 patients, of whom 2491 were treated with EES and 2863 with PES. A total of 177 patients were excluded, because data on follow-up was lacking. In addition, two PES patients were excluded because of their inexplicable body mass index (BMI).

Baseline and procedural characteristics

The baseline characteristics are summarized in Table 1. The two patient groups were significantly different, with the exception of gender and BMI. Patients treated with EES were more frequently hypertensive, had a more present family history of coronary artery diseases (CAD), smoked more, had more frequently diabetes mellitus and presented frequently more with a cardiogenic shock compared to patients treated with PES. Epidemiological research has demonstrated that hypertension, smoking and diabetes mellitus were associated with a higher risk of MACE [(Khot et al. 2003, 898-904)]. Consequently, patients treated with EES seemed to be worse off based on the baseline characteristics.

The procedural characteristics are presented in Table 2. The frequencies of left main (LM) interventions, left anterior descending (LAD) interventions, right coronary artery (RCA) interventions, arterial bypass graft interventions and clopidogrel at discharge were not significantly different between both patient groups. In addition, number of vessels treated per patient, three vessels treated per patient and average stent diameter were clinically similar among both patient groups. Patients treated with EES were less frequently treated for multivessel treatments, were less frequently treated for bifurcation interventions, were more frequently treated for saphenous vein graft interventions, had a smaller average stent length per patient and had a longer prescription time of clopidogrel compared to patients treated with PES. Clinical research has established multivessel treatment, saphenous vein graft interventions and long stents as risk factors for MACE [(Keeley et al. 2001, 659-665; Mauri et al. 2004, 1340-1346)]. In addition, a longer prescription time of clopidogrel was associated with a reduced risk of MACE [(Eisenstein et al. 2007, 159-168)]. Consequently, patients treated with PES seemed to be worse off based on the procedural characteristics.

Table 1. Baseline characteristics

	EES group	PES group	EES vs. PES (*p*-value)
Total, *n*	2491	2863	
Age, *mean ± SD, years*	64.0 ± 12.1	62.3 ± 11.5	<0.001*
Male sex, *n (%)*	1779 (71.4%)	2098 (73.3%)	0.128
BMI, *mean ± SD, kg/m²*	27.2 ± 4.1	27.0 ± 4.0	0.194*
Hypertension, *n (%)*	1367 (54.9%)	972 (34.0%)	<0.001
Familiy history of CAD, *n (%)*	922 (42.6%)	791 (27.6%)	<0.001
Smoking, *n (%)*	682 (31.5%)	579 (20.2%)	<0.001
Dyslipidemia, *n (%)*	1347 (54.1%)	1249 (43.6%)	<0.001
Diabetes mellitus, *n (%)*	493 (19.8%)	388 (13.6%)	<0.001
Acute coronary syndrome, *n (%)*	1651 (66.3%)	1747 (61.4%)	<0.001
Unstable angina/non-STEMI, *n (%)*	562 (22.6%)	763 (26.7%)	0.001
STEMI, *n (%)*	1089 (43.7%)	988 (34.5%)	<0.001
Cardiogenic shock, *n (%)*	89 (3.6%)	55 (1.9%)	<0.001

EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; BMI, body mass index; CAD, coronary artery disease; STEMI, ST segment elevation myocardial infarction. Comparisons between patient groups were performed with the Student's t-test for continuous variables (*), and with the Pearson's chi-square test for categorical variables.

Table 2. Procedural characteristics

	EES group	PES group	EES vs. PES (*p*-value)
Total, *n*	2491	2863	
Multivessel treatment, *n (%)*	300 (12.0%)	564 (19.7%)	<0.001
Vessels treated per patient, *mean ± SD, n*	1.2 ± 0.4	1.2 ± 0.4	<0.001*
1, *n (%)*	2138 (85.8%)	2298 (80.3%)	
2, *n (%)*	340 (13.6%)	551 (19.2%)	
3, *n (%)*	13 (0.5%)	13 (0.5%)	
Target vessel, *n (%)*			
Left main, *n (%)*	100 (4.0%)	113 (3.9%)	0.900
Left anterior descending, *n (%)*	1212 (48.7%)	1447 (50.5%)	0.169
Left circumflex, *n (%)*	600 (24.1%)	786 (27.5%)	0.005
Right coronary artery, *n (%)*	873 (35.0%)	1074 (37.5%)	0.061
Bifurcation, *n (%)*	200 (8.0%)	349 (12.2%)	<0.001
Arterial bypass graft, *n (%)*	1 (0.0%)	1 (0.0%)	0.922
Saphenous vein graft, *n (%)*	71 (2.9%)	19 (0.7%)	<0.001
Stents per patient, *mean ± SD, n*	1.9 ± 1.2	2.2 ± 1.4	<0.001*
Average stent diameter, *mean ± SD , mm*	3.1 ± 0.4	3.0 ± 0.4	<0.001*
Average stent length per patient, *mean ± SD , mm*	34.1 ± 25.5	43.9 ± 30.7	<0.001*
Clopidogrel at discharge, *n (%)*	2415 (98.8%)	2714 (99.2%)	0.127
Prescription duration Clopidogrel, *mean ± SD, months*	12.0 ± 0.2	6.4 ± 2.5	<0.001*

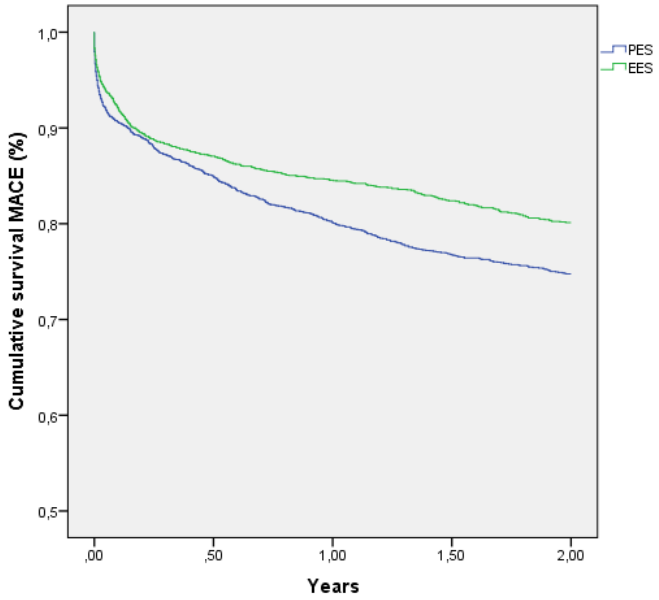
EES, everolimus-eluting stent; PES, paclitaxel-eluting stent. Comparisons between patient groups were performed with the Student's t-test for continuous variables (*), and with the Pearson's chi-square test for categorical variables.

Effects

The result of the primary effectiveness measure of MACE-free survival is shown in Figure 1. At the end of the two year follow-up period, the mean MACE-free survival was significantly longer for EES (1.700±0,013 years; p<0.001) compared to PES (1.624±0.013 years) driven by the significantly increased event-free survival of repeat PCI (1.825 vs. 1.770 years, p<0.001) and to a lesser extent MI (1.969 vs. 1.931 years, p<0.001). The increased event-free survival itself could be explained by the reduced incidence of repeat PCI and MI with

EES (Table 3). The event-free survival of death (1.870 vs. 1.862 years, *p*=0.799) and CABG (1.988 vs. 1.979 years, *p*=0.082) were not significantly different between both patient groups. Survival curves of death, MI, repeat PCI, and CABG are presented in Appendix 2.

Figure 1. Primary effectiveness measure of MACE-free survival



The findings of the secondary effectiveness measure on the incidence of death, MI, repeat PCI, and CABG are summarized in Table 3. EES has proven to be superior compared to PES regarding first MI, first repeat PCI and second repeat PCI by reducing the incidence of the events. The incidence of death, second MI, third repeat PCI and first CABG were not significantly different between both patient groups.

Table 3. Incidence of MACE

	EES (*n* = 2491)	**PES (*n* = 2863)**	**EES vs PES (*p*-value)**
Death, *n (%)*	214 (8.59%)	247 (8.63%)	0.766
First MI, *n (%)*	51 (2.05%)	123 (4.30%)	<0.001
Second MI, *n (%)*	2 (0.08%)	6 (0.21%)	0.198
First repeat PCI, *n (%)*	255 (10.24%)	406 (14.18%)	<0.001
Second repeat PCI, *n (%)*	26 (1.04%)	90 (3.14%)	<0.001
Third repeat PCI, *n (%)*	2 (0.08%)	8 (0.28%)	0.081
First CABG, *n (%)*	22 (0.88%)	39 (1.36%)	0.082

EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting. Comparisons between patient groups were performed according to the Kaplan-Meier method by using the log-rank test.

Costs

The direct medical costs are shown in Table 4. Costs from years other than 2012 were adjusted for inflation using the medical care component of the Consumer Price Index (CPI)

(Statistics Netherlands July, 4 2013). Medication costs were based on 2013 and not adjusted for inflation, because the CPI for 2013 was not available yet. To estimate the incremental procedural costs, the acquisition costs per stent were multiplied by the average number of EES or PES received per patient. The acquisition costs were assumed to be equal, and set at €1,000.00 per stent based on the acquisition costs paid by the EMC for EES in 2007 (Boogaers HJ). Consequently, the mean procedural costs were €1.908.07 with EES and €2,190.71 with PES, resulting in cost savings of €282.64. The incremental medication costs were estimated by multiplying the consumer reimbursement price (CRP) of the Health Care Insurance Board (CVZ) by the risk of receiving clopidogrel (Health Care Insurance Board Juni, 21 2013). The mean CRP was calculated due to multiple manufacturers. In addition, the prescription dose was taken from the pharmacotherapeutic compass of the CVZ (Health Care Insurance Board July, 1 2013). The mean CRP of clopidogrel was €0.60 per 75 mg/day, resulting in medication costs of €219.15 per patient for EES and €109.58 per patient for PES. Consequently, the mean medication costs of clopidogrel were €212.46 with EES and €103.87 with PES, resulting in increased costs of €108.59. To estimate the incremental costs related to the occurrence of MI, repeat PCI or CABG, the treatment costs per event were multiplied by the risk of the events. The treatment costs per MI and repeat PCI were taken from a national study on treatment costs of acute MI (AMI) in the Netherlands for 2012 (Soekhlal et al. 2013, 230-235). The mean treatment costs for ST segment elevation myocardial infarction (STEMI) AMI patients receiving PCI were €5,700.00, whereas the mean treatment costs for non-STEMI AMI patients receiving PCI were €6,060.00. In addition, the risk of STEMI AMI patients receiving PCI was 81.79% compared to the risk (i.e. 18.21%) of non-STEMI AMI patients receiving PCI. Consequently, the weighted mean treatment cost for MI was €5,765.54. Consequently, the mean costs of MI were €122.67 with EES and €259.78 with PES, resulting in cost savings of €137.11. The treatment costs per repeat PCI were €2,611.00 driven by the costs of the exercise therapy, chest X-ray, electrocardiography (ECG), catheterization, PCI procedure and coronary stent. Length of hospital stay was not tracked for both patient groups. A total of 146 repeat PCIs were excluded, because these were already included in the estimation of the incremental costs of MI. Consequently, the mean costs per repeat PCI were €237.94 with EES and €377.56 with PES, resulting in cost savings of €139.62. The treatment costs per CABG were taken from the tariff applications of the Dutch Healthcare Authority (NZa) (Dutch Healthcare Authority July, 2013). The treatment costs per CABG were €9,927.08 driven by hospital costs and specialist fees. Consequently, the mean costs per CABG were €87.67 with EES and €135.23 with PES, resulting in cost savings of €47.55.

Table 4. Direct medical costs

	Unit costs (€)	EES (*n* =2491)	EES (€)	PES (*n* =2863)	PES (€)	Incremental costs EES vs. PES
Procedure						
Study stent						
EES	€ 1,000.00	1,91	€ 1,908.07			
PES	€ 1,000.00			2,19	€ 2,190.71	– € 282.64
Total procedure costs			€ 1,908.07		€ 2,190.71	– € 282.64
Medication						
Clopidogrel						
EES (12 months)	€ 219.15	0,97	€ 212.46			
PES (6 months)	€ 109.58			0,95	€ 103.87	€ 108.59
Total medication costs			€ 212.46		€ 103.87	€ 108.59
Follow-up						
Death	€ 0.00	0,09	€ 0.00	0,09	€ 0.00	€ 0.00
MI	€ 5,765.54	0,02	€ 122.67	0,05	€ 259.78	– € 137.11
Repeat PCI	€ 2611.00	0,09	€ 237.94	0.14	€ 377.56	– € 139.62
CABG	€ 9,927.08	0,01	€ 87.67	0,01	€ 135.23	– € 47.55
Total follow-up costs			€ 448.28		€ 772.57	– € 324,29
Total direct medical costs			€ 2,568.81		€ 3,067.15	– € 498.34

EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting. Clopidogrel, death, MI, repeat PCI and CABG were presented as risks, and EES and PES were presented as mean stents per patient in column three and five.

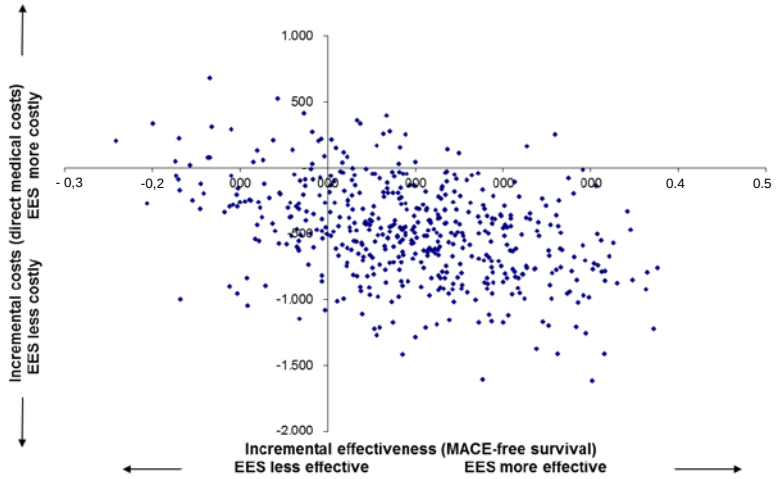
Cost-effectiveness

At the end of the two year follow-up period, EES has proven to be dominant over PES with an increased MACE-free survival of 0.076 years and cost savings of €498.34. Hence, the estimation of the ICER per MACE-free year is unnecessary.

Sensitivity analysis

The cost-effectiveness plane is presented in Figure 2. Each point in the cost-effectiveness plane represents one bootstrap simulation. The bootstrap simulation demonstrated that EES was dominant (i.e. less costly, more effective) over PES in 76.0% of the simulations. EES was dominated (i.e. more costly, less effective) by PES in 4.4% of the simulations. In addition, EES was more costly but more effective in 3.8% of the simulations, and less costly but less effective in 15.8% of the simulations. However, the acceptability of the ICER per MACE-free survival within the North East (NE) and South West (SW) quadrants depend on the willingness-to-pay (WTP) per MACE-free year gained. For example, if the WTP to gain a MACE-free year was zero, only the ICERs below the x-axis would have been acceptable.

Figure 2. Cost-effectiveness plane



Additional analysis

According to the linear regression on the impact of patient characteristics, MACE-free survival was positively affected by dyslipidemia, smoking, family history of CAD and type of stent (the predictor of MACE-free survival), and negatively affected by cardiogenic shock and STEMI indication. However, after the exclusion of the non affecting patient characteristics, the incremental MACE-free survival maintained nearly equal (i.e. 0.063 years) to 0.076 years. The direct medical costs were negatively affected by STEMI indication, type of stent (the predictor of direct medical costs), non-STEMI indication and smoking. Consequently, after the exclusion of the non affecting patient characteristics, the cost savings decreased to €360.98.

Discussion

In this study, we determined the cost-effectiveness of EES compared to PES in patients undergoing PCI in daily practice alongside a Dutch PCS of the EMC. The results of the two year follow-up period demonstrated the dominance of EES with an increased MACE-free survival of 0.076 years and cost savings of €498.34. The study results were driven by the increased event-free survival of repeat PCI and MI, which subsequently could be explained by the reduced incidence of first MI, first repeat PCI and second repeat PCI. The reduced incidence of first MI, first repeat PCI and second repeat PCI themselves could be declared by the decreased number of multivessel treatments with EES, because multivessel treatments are associated with a higher risk of MACE (Keeley et al. 2001, 659-665). In addition, the reduced incidence of first MI could even be explained by the longer prescription time of clopidogrel with EES, or by the reduced rate of stent thrombosis which has been shown in a previous study based on the T-SEARCH and X-SEARCH registries (Eisenstein et al. 2007, 159-168; Räber et al. 2012,

1110-1121). The reduced incidence of repeat PCI could even be declared by the smaller average stent length implanted per patient with EES, because long stents are associated with a higher risk of restenosis (Mauri et al. 2004, 1340-1346). The dominance of EES was confirmed in 76.0% of the bootstrap simulations. In addition, the regression analysis confirmed the dominance of EES as well, even though the cost savings have decreased.

Comparison with other studies

As mentioned in the introduction, the US prospective economic substudy alongside the SPIRIT-IV trial has shown that at the end of a two year follow-up period the use of EES was associated with cost savings of US$273.00 (health care system perspective) and 0.0064 QALYs gained per patient (Amin et al. 2012, 765-770). In comparison with the present study, both cost-effectiveness analyses included a two year follow-up period and a national health care system perspective. However, the US substudy was performed alongside a randomized trial, whereas the present study was performed alongside a cohort study. In addition, the primary effectiveness measure of the US substudy was QALYs, whereas the primary effectiveness measure of the present study was MACE-free survival. Though, both cost-effectiveness analyses demonstrated the clinical and economic benefits of EES compared to PES. Therefore, the results of the present study have confirmed that the dominance of EES over PES in a real-world setting maintained in daily practice.

Policy implications

Since the study has been performed within daily practice, the results can be generalized to a broader population. Therefore, the clinical and economic benefits of EES could possibly be used to inform decision makers regarding wide-scale implementation and reimbursement of EES, in which the increased MACE-free survival will benefit the patients and the cost savings the policymakers. However, several important considerations need to be made before the results can be used for policymaking. To begin with, the question arises whether MACE-free survival can be used as effectiveness measure to inform decision makers regarding resource allocation, because MACE-free survival does not incorporate the impact of MACE on patients. Based on the US substudy, it is expected that the present results on MACE-free survival will somewhat decrease when using QALYs (result US substudy: 0.0064 QALYs) instead of MACE-free survival (result present study: 0.076 years) as effectiveness measure (Amin et al. 2012, 765-770). Therefore, to improve the possibility of decision making based on MACE, it is important to incorporate both quantity and quality of life (i.e. QALYs). For example, the estimation of quality of life can be used to examine the impact of revascularization (i.e. repeat PCI or CABG) without the occurrence of MI as presented in both registries. In addition, the use of QALYs is preferred by health authorities due to the possibility of

comparing various health conditions [Cohen and Reynolds 2008, 2119-2126]. Second, the regression analysis has shown that various patient characteristics affect MACE-free survival and direct medical costs. Therefore, the study results were not only affected by the quality of both stents, but even by the baseline and procedural characteristics. Hence, it is questionable whether it was justified to draw conclusions about the clinical and economic benefits of EES based on uncorrected data, even though the dominance of EES over PES maintained. Finally, the question arises whether the dominance of EES over PES will maintain in the future and consequently can be used for decision making regarding resource allocation, because data on long-term survival and costs is not available yet. Besides, it is questionable whether the acquisition costs of EES and PES are actually equal as assumed in the study. If EES becomes more expensive than PES, the results of the present study might be underrated. For example, the US substudy has shown that the ICER for EES compared to PES remained <US$50,000/QALY gained as long as the incremental acquisition costs were <US$400/stent [Amin et al. 2012, 765-770].

Study limitations

The study results should be interpreted in the light of several limitations. To begin with, the time horizon used in the analysis spanned two years, while it was recommended to include a lifetime perspective to cover all relevant cost and consequences [Cohen et al. 2001, 3039-3045]. However, in this study it was assumed that all events and costs occurred within a two year follow-up period [Amin et al. 2012, 765-770]. Second, when the time horizon exceeds one year, discounting is required according to the current Dutch guidelines [Rutten-van, Groot, and Al 2010]. Nevertheless, discounting was not applied in this study, because it was expected that discounting would not affect the results due to the limited follow-up period. Third, the focus on direct medical costs does not reflect a societal perspective in which all potential costs should be incorporated. As a result, it might be less possible to inform decision makers regarding wide-scale implementation and reimbursement of EES [Cohen and Reynolds 2008, 2119-2126]. Fourth, the internal validity of the study is limited due to incomparable patient groups. However, EES resulted in increased MACE-free survival and cost savings, even though EES seemed to be worse off based on the patient characteristics. In addition, after the correction of the patient characteristics, EES remained dominant over PES. Finally, EES was only compared with PES, while it was recommended to compare with all possible comparators (i.e. bare-metal stents and sirolimus-eluting stents).

Recommendations

Several recommendations for future research can be made based on the discussed limitations. First, a lifetime time horizon should be applied to examine whether the

assumption on the two year follow-up period was justified, and whether the clinical and economic benefits of EES will maintain in the future. Therefore, modelling should be included to extrapolate the observed study results beyond the two year follow-up period (Drummond, Sculpher, and Torrance 2005). Second, discounting should be applied to examine whether discounting would have affected the study results. According to the current Dutch guidelines, all future costs should be discounted by 4% and effects by 1.5% (Rutten-van, Groot, and Al 2010). Third, other costs than direct medical costs should be incorporated to determine whether the cost savings associated with EES will maintain. The other costs are indirect medical costs (f.e. costs related to life years gained), direct non-medical costs (f.e. out-of-pocket expenses) and indirect non-medical costs (f.e. productivity costs) (Drummond, Sculpher, and Torrance 2005). Fourth, to improve the comparability of both patients groups and consequently the possibility to draw conclusions about the clinical and economic benefits of EES, corrected patient characteristics should be used. Finally, PCI procedures implemented over the years should be compared to examine whether the exclusion of procedural costs and costs related to the length of hospital stay was justified.

Conclusion

At the end of the two year follow-up period, EES has proven to be dominant over PES by improving the clinical and economic benefits of PCI in daily practice. Hence, EES has the potential to save costs without affecting patients' health negatively.

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Appendix 1. Abbreviations and acronyms

CABG	Coronary artery bypass grafting
CPI	Consumer price index
CRP	Consumer reimbursement price
CVZ	Health Care Insurance Board
EES	Everolimus-eluting stent(s)
EMC	Erasmus University Medical Center
ICER	Incremental cost-effectiveness ratio
MACE	Major adverse cardiac events
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PES	Paclitaxel-eluting stent(s)
QALY	Quality adjusted life year
STEMI	ST segment elevation myocardial infarction
T-SEARCH	TAXUS Stent Evaluated at Rotterdam Cardiology Hospital
X-SEARCH	XIENCE Stent Evaluated at Rotterdam Cardiology Hospital

Appendix 2. Survival curves MACE