Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial

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Summary

Background **Everolimus-eluting and paclitaxel-eluting stents, compared with bare metal stents, reduced the risk of restenosis in clinical trials with strict inclusion and exclusion criteria. We compared the safety and efficacy of the second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice.**

Methods **We randomly assigned 1800 consecutive patients (aged 18–85 years) undergoing percutaneous coronary intervention at one centre to treatment with everolimus-eluting or paclitaxel-eluting stents. The primary endpoint was a composite of safety and efficacy (all-cause mortality, myocardial infarction, and target vessel revascularisation) within 12 months. Patients were not told which stent they had been allocated. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT01016041.**

Findings **Follow-up was completed in 1797 patients. The primary endpoint occurred in 56 (6%) of 897 patients in the everolimus-eluting stent group versus 82 (9%) of 903 in the paclitaxel-eluting stent group (relative risk 0·69 [95% CI 0·50–0·95], p value for superiority=0·02). The difference was attributable to a lower rate of stent thrombosis (6 [<1%] *vs* 23 [3%], 0·26 [0·11–0–64], p=0·002), myocardial infarction (25 [3%] *vs* 48 [5%], 0·52 [0·33–0·84], p=0·007), and target vessel revascularisation (21 [2%] *vs* 54 [6%], 0·39 [0·24–0·64], p=0·0001). Cardiac death, non-fatal myocardial infarction, or target lesion revascularisation occurred in 44 [5%] patients in the everolimus-eluting stent group versus 74 [8%] patients in the paclitaxel-eluting stent group, p value for superiority was 0·005.**

Interpretation **The everolimus-eluting stent is better than the second generation paclitaxel-eluting stent in unselected patients in terms of safety and efficacy. On the basis of our results, we suggest that paclitaxel-eluting stents should no longer be used in everyday clinical practice.**

Funding **Unrestricted grants from Abbott Vascular and Boston Scientific.**

Lancet 2010; 375: 201–09

Published Online January 8, 2010 DOI:10.1016/S0140-6736(09)62127-9

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Introduction

On the basis of results from randomised trials with strict inclusion and exclusion criteria, first-generation drug-eluting stents, coated with sirolimus or paclitaxel, were approved for clinical use in patients with coronary artery disease.[1–3] Early experience with use of first-generation stents in patients in real-life practice showed that benefit, in terms of the need for reintervention, was most apparent in those with high risk of restenosis.[4] Widespread use of first-generation drug-eluting stents has drawn attention to several unresolved issues that are clinically relevant. First, although the risk is small, stent thrombosis is unpredictable, continues to increase with time, and has serious clinical consequences.[5,6] Second, the deliverability of first-generation drug-eluting stents could be improved. Third, although these stents are more effective than are bare metal stents in patients at high risk of restenosis, the need for reintervention is still a problem in patients with severe coronary disease, as shown in a randomised study in which individuals with complex coronary disease were given percutaneous treatment with the first-generation paclitaxel-eluting stent or coronary artery bypass surgery.[7]

Compared with the currently available first-generation drug-eluting stents, second-generation drug-eluting stents have been designed with the goal of improving safety, efficacy, and device performance. Everolimus, a semisynthetic sirolimus analogue, is released from a thin coating of a biocompatible fluoropolymer on an open cell, thin-strut, cobalt-chromium frame. A significant reduction in serious adverse cardiac events was noted in patients with the everolimus-eluting stent compared with those who had the first-generation paclitaxel-eluting stent.[8] This first-generation stent has been superseded in Europe by the new-generation paclitaxel-eluting stent since September, 2005. Whether such differences persist with a new-generation paclitaxel-eluting stent that consists of the same polymer but has a different stent platform is not known.

We therefore compared the safety and efficacy of the second-generation everolimus-eluting and paclitaxel-eluting stents in unselected patients in real-life practice.

Methods

Study design and patients

Consecutive patients (aged 18–85 years) referred to the Maasstad Ziekenhuis for elective or emergent

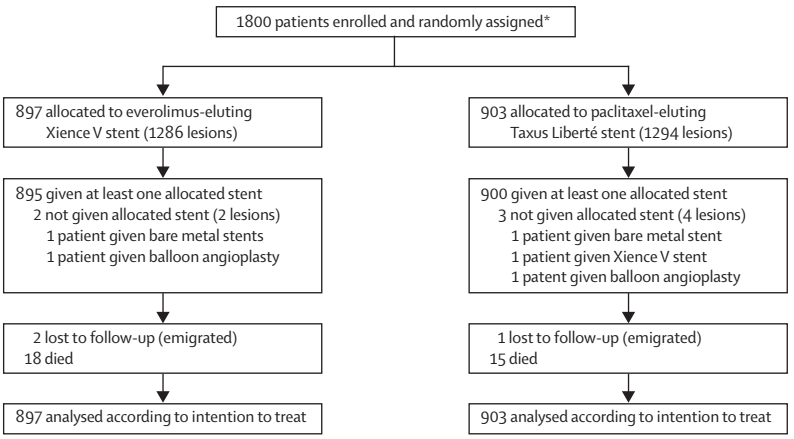

Figure 1: **Trial profile**
*We have no reliable data for patients assessed for eligibility.

	Everolimus-eluting stent (n=897)	Paclitaxel-eluting stent (n=903)
Age (years; median, IQR)	62·9 (55·4–71·1)	63·6 (55·7–72·9)
Men	619 (69%)	654 (72%)
Diabetes mellitus*	153 (17%)	172 (19%)
Chronic renal failure†	25 (3%)	24 (3%)
Hypertension	417 (46%)	447 (50%)
Hypercholesterolaemia	477 (53%)	451 (50%)
Current smoker	295 (33%)	262 (29%)
Family history of coronary artery disease	399 (44%)	403 (45%)
History of myocardial infarction	136 (15%)	159 (18%)
History of percutaneous coronary intervention	117 (13%)	123 (14%)
History of coronary artery bypass grafting	60 (7%)	53 (6%)
Stable angina pectoris	331 (37%)	349 (39%)
Silent ischaemia	23 (3%)	17 (2%)
Acute coronary syndrome	541 (60%)	534 (59%)
Unstable angina	107 (12%)	105 (12%)
Non-ST-segment elevation myocardial infarction	194 (22%)	217 (24%)
ST-segment elevation myocardial infarction	240 (27%)	212 (23%)
Glycoprotein IIb/IIIa antagonists	288 (32%)	290 (32%)
Multivessel treatment	244 (27%)	239 (26%)
Number of lesions treated per patient (SD)	1·4 (0·7)	1·4 (0·7)
Reference vessel diameter <2·75 mm	458 (51%)	441 (49%)
Lesion length >20 mm	290 (32%)	263 (29%)

Data are number (%), unless otherwise indicated. Percentages have been rounded. *Defined as treatment with diet or drugs for previously diagnosed diabetes. †Defined as serum creatinine greater than 130 μmol/L or patient on dialysis.

Table 1: **Baseline characteristics**

percutaneous coronary intervention, were eligible to participate in the study. There were no limitations about the number of lesions or vessels, location of lesions, or their length. Exclusion criteria were contraindications or expected non-adherence to dual antiplatelet drugs in the 12 months after the procedure; planned major surgery within 30 days; inability or refusal to comply with follow-up procedures; participation in other coronary-device trials; and inability to provide informed consent.

All patients provided written informed consent. The study complied with the Declaration of Helsinki for investigation in human beings, and was approved by the institutional ethics committee of the Maasstad Ziekenhuis, Rotterdam, the Netherlands, and the Dutch Central Committee on Research Involving Human Subjects.

Randomisation and masking

The allocation schedule was based on computer-generated random numbers. The statistician involved in the design of the study generated the randomisation list. Patients were assigned in a one-to-one ratio to a polymer-based, everolimus-eluting stent (Xience V, Abbott Vascular, Santa Clara, CA, USA) or a polymer-based, paclitaxel-eluting stent (Taxus Liberté, Boston Scientific, Natick, MA, USA), using sealed, opaque, sequentially numbered allocation envelopes after passage of the guide wire. The patients knew they had been randomly assigned in a trial of drug-eluting stents, but did not know which stent they had been allocated.

Procedures

Staged procedures were permitted and the same stent type, allocated at initial randomisation, was used. Everolimus-eluting stents were available in diameters of 2·25 mm, 2·50 mm, 3·00 mm, 3·50 mm, and 4·00 mm, and in lengths of 8 mm, 12 mm, 15 mm, 18 mm, 23 mm, and 28 mm. Paclitaxel-eluting stents were available in diameters of 2·25 mm, 2·50 mm, 3·00 mm, 3·50 mm, and 4·00 mm, and in lengths of 8 mm, 12 mm, 16 mm, 20 mm, 24 mm, 28 mm, and 32 mm.

Percutaneous coronary intervention was done according to standard techniques. Crossover to another stent was allowed in the event of an inability to insert the assigned device. Technical details, such as the decision to stent without balloon predilatation, use of adjunctive techniques such as rotational atherectomy, and decision to postdilate the stent, were at the discretion of the operator. Off-line quantitative coronary angiography analysis for the baseline data was done with an automated edge-detection system (CAAS, version 1.1, Pie Medical Imaging, Maastricht, Netherlands). The analyses were done by experienced technicians.

All patients not on dual antiplatelet drugs were given aspirin (300 mg) and clopidogrel (300 mg or 600 mg) before the procedure. The high dose of clopidogrel was given to patients undergoing primary percutaneous intervention for ST-segment elevation myocardial infarction. An initial bolus of unfractionated heparin (70–100 IU/kg) was given to all patients, and additional boluses were given to achieve and maintain an activated clotting time of more than 250 s, which was checked every 30 min. The use of bivaluridin or low-molecular-weight heparin was not allowed. The use of glycoprotein IIb/IIIa antagonists was at the discretion of

the operator. A 12-lead electrocardiograph was done before and after the procedure; before discharge; and at 1 month, 6 months, and 12 months follow-up. Post-procedural measurements of cardiac biomarkers were obtained systematically only in patients in whom procedural complications, such as side-branch closure, residual dissection, or no reflow, occurred or when patients had chest pain or electrocardiographic changes after the procedure. At the time of discharge, all patients were given aspirin (100 mg once a day) for an indefinite period, as well as clopidogrel (75 mg per day) for 12 months.

Outcomes and data management

The prespecified primary endpoint was a composite of all-cause mortality, non-fatal myocardial infarction, and target vessel revascularisation within 12 months. The secondary endpoints were a composite of major adverse cardiac events (cardiac death, non-fatal myocardial infarction, and clinically justified target lesion revascularisation within 12 months of follow-up), and a composite of all-cause mortality, non-fatal myocardial infarction, and target vessel revascularisation at 3 years and 5 years. All deaths were regarded as cardiac unless an unequivocal non-cardiac cause was established. Periprocedural myocardial infarction, in patients without infarction at baseline, was defined as any elevation in concentrations of creatine kinase to more than double normal value, with elevated values of a confirmatory cardiac biomarker (creatine kinase-MB fraction or troponin). Spontaneous infarction was defined as a typical rise and fall in concentrations of troponin or creatinine kinase-MB with at least one of the following: ischaemic symptoms, development of pathological Q waves, ischaemic electrocardiographic changes, or pathological findings of an acute myocardial infarction.[9] Target lesion revascularisation was defined as revascularisation for a stenosis within the stent or within the 5-mm borders adjacent to the stent. Revascularisation of the target lesion and vessel was regarded as clinically justified if the stenosis of any target lesion or vessel was at least 50% of vessel diameter on the basis of quantitative coronary angiography in the presence of objective evidence of ischaemia on non-invasive or invasive testing or symptoms, or if the stenosis was at least 70% of vessel diameter even in the absence of ischaemic signs or symptoms.

Stent thrombosis was defined according to the definitions provided by the Academic Research Consortium.[10] Adverse events were assessed in the hospital, and at 1 month and 12 months. Data were gathered by study monitors who visited the hospitals in which follow-up was undertaken, reviewed the clinical notes, and collected the protocol-mandated electrocardiographs. Furthermore, medical questionnaires were posted to all patients at 1 month, 6 months, and 12 months to check for adverse events and establish current antiplatelet drugs. Data were stored in our institution. Data processing and adjudication of adverse events were done by an independent contract research organisation and core lab (Cardialysis, Rotterdam, Netherlands). An independent data and safety monitoring board reviewed the data after interim analyses with formal stopping rules.

	Everolimus-eluting stent (1286 lesions)	Paclitaxel-eluting stent (1294 lesions)
Target lesion coronary artery		
Left main	21 (2%)	21 (2%)
Left anterior descending	513 (40%)	485 (37%)
Left circumflex	299 (23%)	333 (26%)
Right	426 (33%)	431 (33%)
Bypass graft	27 (2%)	24 (2%)
ACC-AHA lesion class		
A	81 (6%)	61 (5%)
B1	255 (20%)	278 (21%)
B2	355 (28%)	379 (29%)
C	595 (46%)	576 (45%)
De novo lesions	1252 (97%)	1267 (98%)
Ostial lesion	242 (19%)	243 (19%)
Calcified lesion	422 (33%)	444 (34%)
Bifurcated lesion	223 (17%)	237 (18%)
Thrombus present	310 (24%)	314 (24%)
Chronic total occlusion	39 (3%)	53 (4%)
Preprocedure TIMI flow (grade)		
0	221 (17%)	213 (16%)
1	47 (4%)	56 (4%)
2	85 (7%)	102 (8%)
3	933 (73%)	923 (71%)

Data are number (%). Percentages have been rounded. ACC=American College of Cardiology. AHA=American Heart Association. TIMI=thrombolysis in myocardial infarction.

Table 2: **Baseline lesion characteristics**

	Everolimus-eluting stent (1286 lesions)	Paclitaxel-eluting stent (1294 lesions)	p value
Lesion length (mm)	16·8 (9·5–31·5)	16·0 (9·2–31·0)	0·44
Diameter of reference vessel (mm)	2·56 (2·19–2·95)	2·55 (2·21–3·0)	0·61
Baseline minimum lumen diameter (mm)	0·90 (0·62–1·21)	0·91 (0·66–1·22)	0·66
Baseline stenosis (lumen diameter, %)	64 (53–77)	64 (53–76)	0·98
Postprocedure stenosis (lumen diameter, %)	17 (11–24)	16 (10–24)	0·39
Postprocedure minimum lumen diameter (mm)	2·14 (1·82–2·51)	2·15 (1·80–2·55)	0·88
Acute gain (mm)	1·24 (0·82–1·76)	1·24 (0·81–1·71)	0·71
Number of stents per lesion (mean, SD)	1·7 (0·9)	1·6 (0·9)	0·007
Total stent length per lesion (mm)	28 (18–46)	28 (18–44)	0·85
Direct stenting	432 (34%)	451 (35%)	0·37
Post dilatation	698 (54%)	668 (52%)	0·18

Data are median (IQR) or number (%), unless otherwise indicated. Data for quantitative coronary angiography (QCA) are presented only for lesions with matched views for QCA before and after procedure (1977 lesions).

Table 3: **Quantitative coronary angiography and procedural results**

	Everolimus-eluting stent (n=897)	Paclitaxel-eluting stent (n=903)	Relative risk (95% CI)	p value
Events at 30 days				
All-cause mortality	7 (0·8%)	6 (0·7%)	1·17 (0·40–3·48)	0·77
Cardiac death	7 (0·8%)	6 (0·7%)	1·17 (0·40–3·48)	0·77
Myocardial infarction	15 (2%)	28 (3%)	0·53 (0·29–1·00)	0·05
Q wave	3 (0·3%)	8 (0·9%)	0·38 (0·10–1·42)	0·13
Non-Q wave	12 (1%)	21 (2%)	0·57 (0·28–1·16)	0·12
All-cause mortality or myocardial infarction	21 (2%)	33 (4%)	0·64 (0·37–1·10)	0·10
Cardiac death or myocardial infarction	21 (2%)	33 (4%)	0·64 (0·37–1·10)	0·10
Target vessel revascularisation (clinically justified)	4 (0·4%)	18 (2%)	0·22 (0·08–0·66)	0·003
Percutaneous	1 (0·1%)	16 (2%)	0·06 (0·01–0·47)	0·0003
Surgical	3 (0·3%)	2 (0·2%)	1·51 (0·25–9·02)	0·65
Target vessel revascularisation (any)	5 (0·6%)	19 (2%)	0·26 (0·10–0·71)	0·004
Percutaneous	2 (0·2%)	17 (2%)	0·12 (0·03–0·51)	0·0006
Surgical	3 (0·3%)	2 (0·2%)	1·51 (0·25–9·02)	0·65
Target lesion revascularisation (clinically justified)	3 (0·3%)	16 2%)	0·19 (0·06–0·65)	0·003
Percutaneous	0	14 (2%)	..	0·0002
Surgical	3 (0·3%)	2 (0·2%)	1·51 (0·25–9·02)	0·65
Target lesion revascularisation (any)	4 (0·4%)	17 (2%)	0·24 (0·08–0·70)	0·005
Percutaneous	1 (0·1%)	15 (2%)	0·07 (0·01–0·51)	0·0005
Surgical	3 (0·3%)	2 (0·2%)	1·51 (0·25–9·02)	0·65
Primary endpoint	25 (3%)	35 (4%)	0·72 (0·43–1·19)	0·20
Secondary endpoint	23 (3%)	34 (4%)	0·68 (0·40–1·15)	0·15
Stent thrombosis (definite and probable)	2 (0·2%)	15 (2%)	0·13 (0·03–0·59)	0·002
Acute stent thrombosis (on date of procedure)	1 (0·1%)	1 (0·1%)	1·01 (0·06–16·07)	0·99
Subacute stent thrombosis (1–30 days after procedure)	1 (0·1%)	14 (2%)	0·07 (0·01–0·55)	0·0008
Early stent thrombosis (0–30 days after procedure)	2 (0·2%)	15 (2%)	0·13 (0·03–0·59)	0·002
Definite stent thrombosis	2 (0·2%)	12 (1%)	0·17 (0·04–0·75)	0·008

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Statistical analysis

On the basis of results from the T-SEARCH registry,[4] and SIRTAX[11] and SPIRIT II trials,[12] we assumed an incidence of the primary endpoint of 9% in the everolimus-eluting stent group and 14% in the paclitaxel-eluting stent group. Enrolment of 1800 patients would provide the study with a statistical power of 85% to detect this difference with a two-sided significance level of 0·05, allowing for 3–4% of patients lost to follow-up. All analyses were done according to the intention-to-treat principle. Patients were censored from the Kaplan-Meier plots when they reached any component of the composite endpoint. Categorical variables were assessed with use of χ^2 or Fisher's exact tests, whereas continuous variables were assessed with the Wilcoxon rank-sum test.

The time to the primary endpoint was assessed according to the method of Kaplan-Meier, and the log-rank test was applied to compare the incidence of the endpoint between groups. Relative risks with 95% CIs, were calculated with the log-binomial method.[13] The Kaplan-Meier curves were drawn with the guidelines provided by Pocock and colleagues.[14] All p values were two-sided, and a p value of less than 0·05 was regarded as significant. Analyses were done with SAS (version 8.02).

The trial is registered with ClinicalTrials.gov, number NCT01016041.

Role of the funding source

The sponsors had no involvement in the design, conduct, or analysis of the study. The corresponding author had full access to all the data in the study, and had full responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1800 patients were enrolled between February, 2007, and September, 2008. Five (<1%) were not given the designated stent. Staged procedures were done in 191 (21%) patients in the everolimus-eluting stent group and in 172 (19%) patients in the paclitaxel-eluting stent group (p=0·23). Three were lost to follow-up. The groups had similar baseline clinical (table 1), angiographic (table 2), and procedural characteristics (table 3).

Most patients presented with an acute coronary syndrome (table 1); the subtype of acute coronary syndrome was equally distributed in the two groups; 74% of lesions were complex (type B2 or C; table 2). The

	Everolimus-eluting stent (n=897)	Paclitaxel-eluting stent (n=903)	Relative risk (95% CI)	p value
(Continued from previous page)				
Events at 12 months				
All-cause mortality	18 (2%)	15 (2%)	1·21 (0·61–2·38)	0·58
Cardiac death	11 (1%)	10 (1%)	1·11 (0·47–2·59)	0·81
Myocardial infarction	25 (3%)	48 (5%)	0·52 (0·33–0·84)	0·007
Q wave	3 (0·3%)	11 (1%)	0·27 (0·08–0·98)	0·03
Non-Q wave	22 (2%)	39 (4%)	0·57 (0·34–0·95)	0·03
All-cause mortality or myocardial infarction	42 (5%)	62 (7%)	0·68 (0·47–1·00)*	0·05*
Cardiac death or myocardial infarction	35 (4%)	57 (6%)	0·62 (0·41–0·93)	0·02
Target vessel revascularisation (clinically justified)	19 (2%)	51 (6%)	0·38 (0·22–0·63)	0·0001
Percutaneous	13 (1%)	38 (4%)	0·34 (0·18–0·64)	0·0004
Surgical	6 (0·7%)	13 (1%)	0·46 (0·18–1·22)	0·11
Target vessel revascularisation (any)	21 (2%)	54 (6%)	0·39 (0·24–0·64)	0·0001
Percutaneous	15 (2%)	41 (5%)	0·37 (0·21–0·66)	0·0005
Surgical	6 (0·7%)	13 (1%)	0·46 (0·18–1·22)	0·11
Target lesion revascularisation (clinically justified)	15 (2%)	43 (5%)	0·35 (0·20–0·63)	0·0002
Percutaneous	9 (1%)	31 (3%)	0·29 (0·14–0·61)	0·0005
Surgical	6 (0·7%)	12 (1%)	0·50 (0·19–1·34)	0·16
Target lesion revascularisation (any)	18 (2%)	48 (5%)	0·38 (0·22–0·64)	0·0002
Percutaneous	12 (1%)	36 (4%)	0·34 (0·18–0·64)	0·0005
Surgical	6 (0·7%)	12 (1%)	0·50 (0·19–1·34)	0·16
Primary endpoint	56 (6%)	82 (9%)	0·69 (0·50–0·95)	0·02
Secondary endpoint	44 (5%)	74 (8%)	0·60 (0·42–0·86)	0·005
Stent thrombosis (definite and probable)	6 (0·7%)	23 (3%)	0·26 (0·11–0·64)	0·002
Late stent thrombosis (30 days to 1 year after procedure)	4 (0·4%)	8 (0·9%)	0·50 (0·25–1·67)	0·25
Definite stent thrombosis	4 (0·4%)	18 (2%)	0·22 (0·08–0·66)	0·003

Data are number (%). Percentages have been rounded. *The 1·00 upper limit of 95% CI was 0·998, and p value was 0·047.

Table 4: **Clinical events during follow-up**

median total stent length per lesion, compared with previous studies, and the number of stents per lesion were high; the number of stents was slightly, but significantly, higher in the everolimus-eluting stent group because of a shorter available maximum stent length (table 3). Postprocedural cardiac biomarkers were assessed in 364 (41%) patients in the everolimus-eluting stent group and in 338 (37%) in the paclitaxel-eluting stent group (p=0·17).

Table 4 shows the major adverse cardiac events during follow-up. The primary endpoint occurred in fewer patients in the everolimus-eluting stent group than in the paclitaxel-eluting stent group (table 4; figure 2A). The difference resulted from a lower rate of myocardial infarction and of target vessel revascularisation at 12 months in patients with everolimus-eluting stents, whereas all-cause mortality did not differ between the groups (figure 2B–D). Periprocedural myocardial infarction occurred in 15 (2%) patients in the everolimus-eluting stent group and 19 (2%) patients in the paclitaxel-eluting stent group (p=0·49). The lower rate of non-fatal myocardial infarction during 12 months in patients given everolimus-eluting stents reflects a significant difference in early stent thrombosis (table 4; figure 3A). The rate of definite and probable stent thrombosis for up to 1 year remained significantly lower in the everolimus-eluting stent group compared with the paclitaxel-eluting stent group (table 4). There were more late-stent thromboses in the paclitaxel-eluting stent group than in the everolimus-eluting stent group at 1 year but the difference was not significant (figure 3B).

The rate of target vessel revascularisation was significantly lower in patients who had everolimus-eluting stents. This difference between the groups was already apparent at 30 days, and remained significant at 1 year (figure 2D; table 4).

The main secondary endpoint occurred in fewer patients in the everolimus-eluting stent group than in the paclitaxel-eluting stent group (table 4).

We did an exploratory stratified analysis of the primary endpoint that was not prespecified in the protocol (figure 4). The outcome of the primary endpoint was consistent across all but two subgroups—ie, patients with diabetes (n=325) and those with long lesions (n=553). CIs were wide and the results of a test of interaction were not significant.

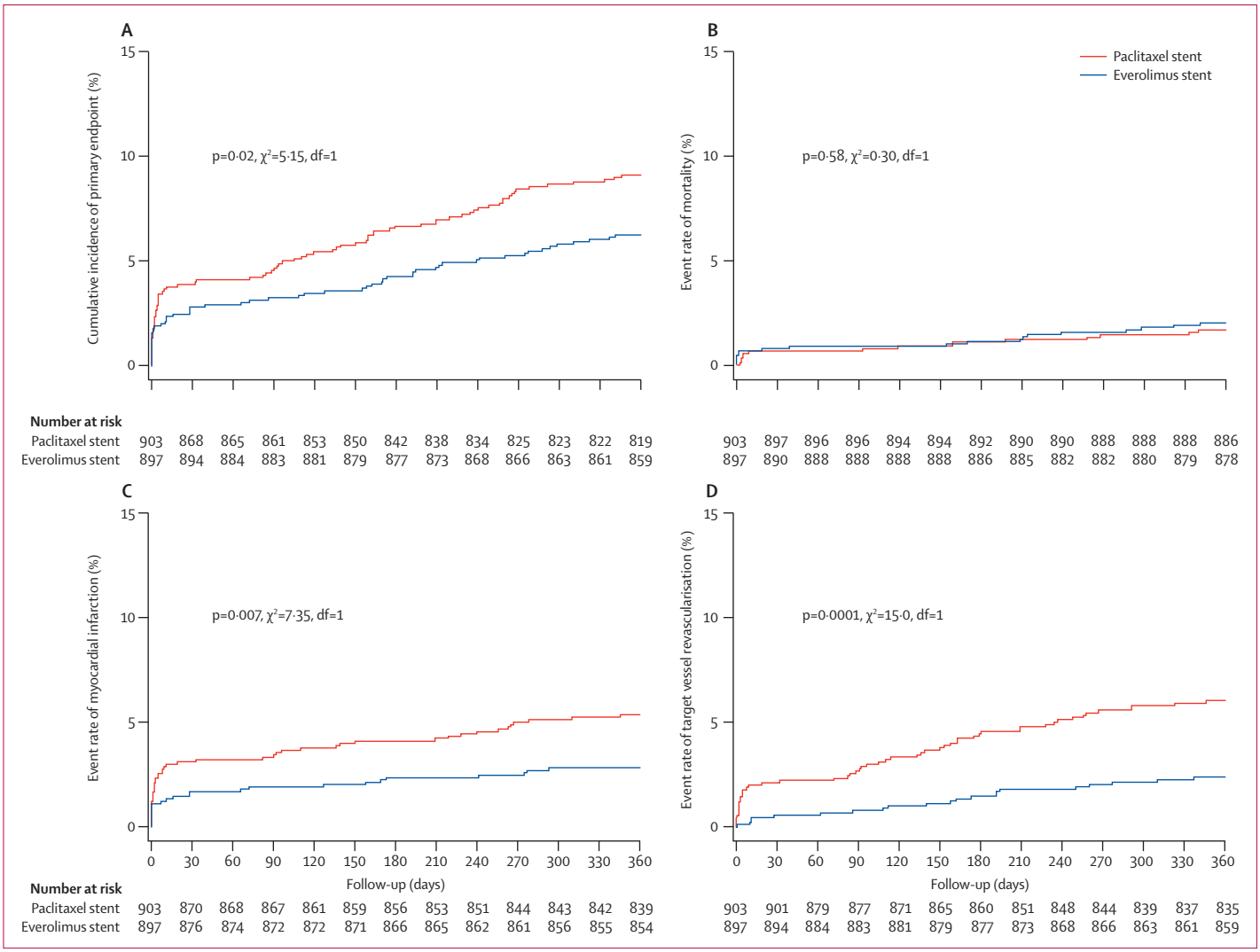

Figure 2: **Kaplan-Meier cumulative events curves at 12 months for primary endpoint (A), mortality (B), myocardial infarction (C), and target vessel revascularisation (D)**

Compliance with aspirin and clopidogrel was 809 (91%) in the everolimus-eluting stent group versus 829 (92%) in the paclitaxel-eluting stent group at 1 month; 805 (91%) and 815 (91%), respectively, at 6 months; and 611 (70%) in the everolimus-eluting stent group and 625 (70%) in the paclitaxel-eluting stent group at 1 year.

Discussion

The use of second-generation everolimus-eluting stents, compared with paclitaxel-eluting stents, was associated with a significant reduction in the risk of major adverse cardiac events at 1 year. This difference was a result of reduction in the rate of myocardial infarction, a safety component of the primary endpoint, and reduction in repeat revascularisation of the target vessel.

Rates of all-cause or cardiac mortality did not differ between the two groups; however the rate of myocardial infarction was significantly reduced in the everolimus-eluting stent group. This reduction was already apparent at 1 month. The significantly lower rate of myocardial infarction at 30 days with the everolimus stent was attributable to a significantly lower rate of early stent thrombosis because there was no significant difference between the groups in the rate of periprocedural myocardial infarction.

Use of the paclitaxel-eluting stent was associated with a higher rate of early stent thrombosis in the unselected population we studied than that reported in previous randomised trials in selected patient populations.[8,12] A large proportion of the unselected patients enrolled had high-risk clinical or angiographic characteristics. Since the proportion of patients with such high-risk characteristics did not differ significantly between groups, differences between the devices—stent design, polymer coating, or the drug used—are the most

plausible explanations for the high rate of stent thrombosis with the paclitaxel stent. By contrast, the rate of stent thrombosis with the everolimus-eluting stent in our study was similar to that reported in the randomised trials of selected populations that led to marketing approval.[8,12]

The significant difference in stent thrombosis at 12 months between the two groups was mainly attributable to early stent thrombosis. Because the groups did not differ in terms of baseline characteristics, preprocedural and postprocedural antiplatelet and antithrombotic drugs, or procedural technique, we believe that the noted difference in early stent thrombosis rates relate to differences between the two devices that become apparent in an unselected population. An open-cell, thin-strut stent frame mounted on a semicompliant balloon might result in better apposition and less side-branch compromise than would a closed-cell, thick-strut device on a non-compliant balloon. The thinner layer of polymer on the everolimus-eluting stent might also play a part. Preclinical data have shown that the everolimus-eluting stent has more rapid and more extensive re-endothelialisation than has the second-generation paclitaxel-eluting stent.[15] Numerically more stent thromboses were noted in the paclitaxel-eluting stent group than in the everolimus-eluting stent group between 1–12 months. The absolute numbers were small and the differences were not significant. However, definitive conclusions about late stent thrombosis must await the prespecified analyses at 3 years and 5 years because results from several studies have shown a predictable, continued, risk of stent thrombosis with time, particularly with paclitaxel-eluting stents.[6]

As with safety, a significant difference in efficacy was also noted with the everolimus-eluting stent. Both target vessel and target lesion revascularisation were significantly reduced in the everolimus-eluting stent group compared with the paclitaxel-eluting stent group. This difference was already evident at 30 days and continued to increase up to 1 year, with similar relative risk ratios at 30 days and at 12 months, consistent with a continued treatment effect. Up to 30 days, the difference in revascularisation between groups was related to the lower rate of stent thrombosis in the everolimus-eluting stent group than in the paclitaxel-eluting stent group. At 12 months, the difference suggested a significantly lower rate of clinically justified reinterventions for restenosis and lower rate of stent thrombosis in the everolimus-eluting stent group.

The lower rate of reintervention might relate to the more potent reduction in neointimal hyperplasia with the everolimus-eluting stent than with the paclitaxel-eluting stent.

The rate of major adverse cardiac events with the everolimus-eluting stent in our trial is similar to the rates reported in registries that also enrolled unselected populations—namely, the X-Search study[16] and the Spirit V registry (E Grube, Helios Heart Centre, personal communication).

Since the test for interaction was not significant, the post-hoc exploratory subgroup analyses we did do not allow us to infer whether the superiority of the everolimus-eluting stent differs between subgroups. However, in a similar analysis done in the SPIRIT IV trial (G Stone, New York-Presbyterian Hospital, Columbia University Medical Center, personal communication), the superiority of everolimus-eluting compared with paclitaxel-eluting stents was less apparent in patients with diabetes. This finding can only be regarded as exploratory. Patients with diabetes undergoing percutaneous coronary intervention have

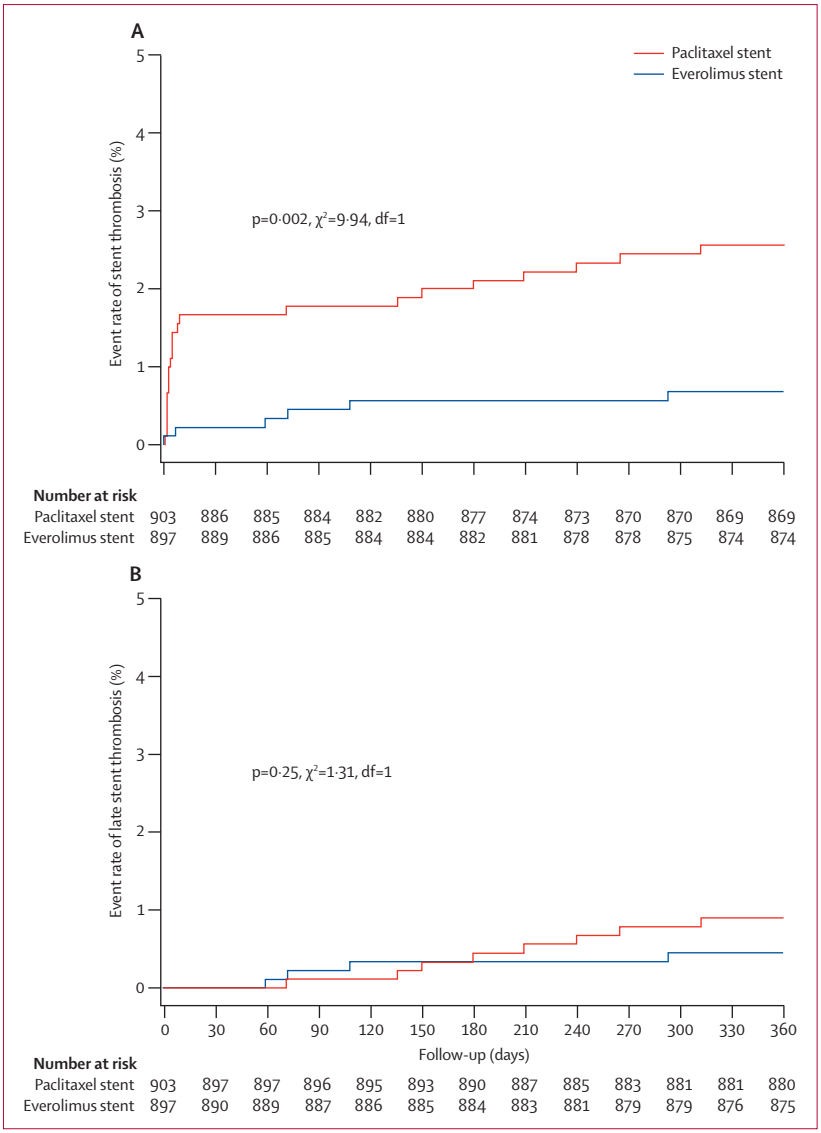

Figure 3: **Kaplan-Meier event curves at 12 months for stent thrombosis (A) and late stent thrombosis (B)**

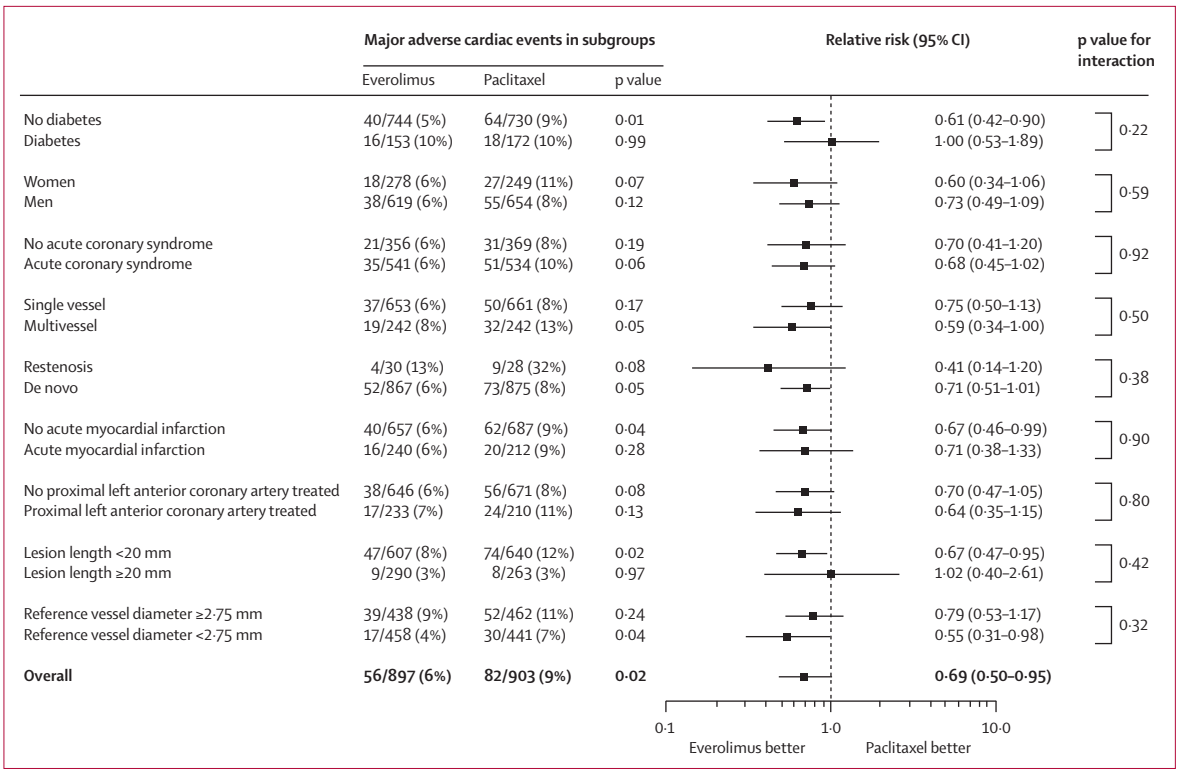

Figure 4: **Subgroup analysis**
Data are n/N (%). Percentages have been rounded.

poorer outcomes overall than do those without diabetes even when treated with drug-eluting stents. However, results from previous studies have consistently suggested that stents eluting limus derivatives might offer an advantage over paclitaxel-eluting stents in patients with diabetes.[17,18]

Enrolment of unselected patients and the entirely clinical follow-up were the strengths of our study. Furthermore, we studied the second-generation paclitaxel-eluting stent whereas the first-generation paclitaxel-eluting stent was used in previous comparisons.[19]

There are some limitations to our investigation. The trial was done in one, high-volume, tertiary centre in which implantation of drug-eluting stents was the default strategy for coronary intervention, and therefore the results might not be applicable in other settings. Consistent with usual clinical practice in our institution, systematic sampling of cardiac biomarkers was not done for all patients, and is unlikely to have affected the outcome because the proportion of patients who had biomarkers measured did not differ significantly between groups. In the Spirit III trial,[8] more postprocedure infarctions were noted in the paclitaxel-eluting stent group than in the everolimus-eluting stent group, whereas no significant difference was noted in the rate of periprocedural infarctions between groups in our study.

Our conclusions about safety and efficacy are consistent with the outcome of previous studies of selected patient cohorts in which everolimus-eluting and paclitaxel-eluting stents were compared[8,12] and with the results of an all-comer registry in which the everolimus-eluting stent was compared with the first-generation paclitaxel-eluting stent.[16]

In conclusion, we have shown that the everolimus-eluting Xience V stent is better than the second-generation paclitaxel-eluting Taxus Liberté stent in treatment of patients in real-life practice in terms of safety and efficacy. On the basis of our results, we suggest that paclitaxel-eluting stents should no longer be used in everyday clinical practice.

Contributors

EK wrote the first draft of the report, and was responsible for the study at Maasstad Ziekenhuis. EM participated in drafting and revising the report. JW was responsible for data entry. PCS designed the study, and wrote the protocol. EK, KSJ, EM, CVM, and PCS participated in data gathering. KSJ, EM, and DG did the data analysis. DG and PCS interpreted the data. KSJ, JW, CVM, DG, and PCS participated in writing the report.

Conflicts of interest

EM has received honoraria or expenses from Abbot Vascular, Medtronic, Cordis, and Boston Scientific; and has been on speakers' bureaus for Medtronic. The other authors declare that they have no conflicts of interest.

Acknowledgments

The Research Foundation received unrestricted research grants from Abbott Vascular and Boston Scientific. We gratefully acknowledge the help of the research nurses, technicians, and medical staff in Maasstad Ziekenhuis and referring hospitals whose cooperation made this study possible.

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