Original Article

Medium to Long-Term Clinical Outcomes with Everolimus-Eluting Stents in Real-Life Percutaneous Coronary Intervention

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Abstract

   Introduction: **Everolimus eluting stents (EES) have demonstrated excellent re-stenosis and thrombosis rates in a number of randomised controlled trials. This study reported the real world experience in a single tertiary centre with EES in predominantly acute coronary syndrome (ACS) patients and compared the outcomes in small and large vessels. We measured the medium to long-term major adverse cardiovascular events (MACE) defined as all-cause mortality, myocardial infarction (MI) and target vessel revascularisation (TVR) and stent thrombosis.** Materials and Methods: **All consecutive patients underwent percutaneous coronary intervention (PCI) with EES (PROMUS™, Boston Scientific, Natick USA; XIENCE V™, Abbott Vascular, Santa Clara USA) between March 2007 and September 2009 recorded in our coronary intervention registry were included in this study. All patients were advised to stay on dual antiplatelet therapy with Aspirin 100 mg/day and Clopidogrel 75 mg/day. All patients had at least 6 months of clopidogrel, government funded and a further 6 months required self funding.** Results: **Four hundred and six consecutive patients received EES during the study period; 403 were included in this study and 3 were lost to follow-up. Indications for PCI were stable angina in 11% of the patients, unstable angina in 38%, non-ST elevation myocardial infarction in 43%, and ST-elevation myocardial infarction in 8%. Procedural success was achieved in 99.5% of the cases. During a median follow-up of 23 months, 3% of the patients had an MI, 3% underwent TVR, 5% all-cause mortality and 2 (0.5%) cases of definite or probable stent thrombosis. The Kaplan Meier 2-year survival and MACE free survival were 95% and 89% respectively. A subgroup analysis comparing MACE in patients who were treated with a single small (≤2.75 mm; n = 91) or large (≥3 mm; n = 118). EES did not show significant difference during the 2-year follow-up (12% vs 9%; *P* = 0.34).** Conclusion: **Everolimus eluting stent appears to be safe in a real world setting with satisfactory median-term outcomes which include low rates of TVR and other adverse events. EES appear to be equally effective in both small and large vessels.**

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   Key words: Acute coronary syndrome, Drug eluting stents, Ischaemic heart disease

Introduction

   Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has demonstrated improved clinical outcomes compared with bare-metal stents (BMS) in many randomised controlled trials and observational registries.[1,2] The improved outcome is mainly limited to reduced clinical and angiographic restenosis without significant reduction in cardiovascular mortality or myocardial infarction. The second generation DES everolimus-eluting stents (EES) in many recent large-scale trials have demonstrated superior clinical outcomes and safety when compared with paclitaxel-eluting stents.[3-5] In this study, we investigate the real world outcomes of EES in a single, high volume tertiary centre and compare the results of EES in small and large vessels. We measured the medium to long-term major adverse cardiovascular events (MACE) defined as all-cause mortality, myocardial infarction (MI) and target vessel revascularisation (TVR) and stent thrombosis.

Materials and Methods

Patient Population

   All consecutive patients who underwent PCI with EES (PROMUS™, Boston Scientific, Natick USA or XIENCE V™, Abbott Vascular, Santa Clara USA) between March

2007 and September 2009 at Waikato Hospital, New Zealand, a high volume tertiary referral centre for PCI in the central North Island of New Zealand, were included in this retrospective analysis. During the study period, a total of 1839 PCI procedures were performed. Those patients who received EES with different drug-eluting stents and/or bare-metal stents were not included in the registry (78%). The selection of available drug-eluting stents on shelf is subjected to the discretion of individual operators and all local operators would commit to the same type of stents during the routine PCI, unless technical issues are encountered.

Patient Preparation and Procedure

All patients received 300 mg aspirin and 300 mg clopidogrel loading prior to the procedure and were advised dual antiplatelet therapy (100 mg aspirin and 75 mg clopidogrel) for at least 12 months. Clopidogrel was government funded for 6 months and patients were required to self fund for a further 6 months. At the start of interventional procedure, all patients were given intra-arterial or intravenous heparin at 70 units per kilogram unless continuous intravenous heparin was given, e.g. in cases of post-thrombolysis patients. Activated coagulation time (ACT) measurement, balloon pre-dilatation and concomitant glycoprotein IIb/IIIa inhibitor use were subjected to the operator's discretion. The lesion characteristics were recorded by individual operators according to the ACC/AHA classifications.[6]

Quantitative Coronary Angiography

Quantitative coronary angiography (QCA) for all patients was reviewed using GE CA1000TM Workstation System (GE Healthcare Bio-Sciences, Uppsala, Sweden) by a single experienced observer. Calibration was performed using the catheter in the same plane as the vessel in 2 orthogonal views.

Small and Large Vessel Analysis

A subgroup analysis of patients who received a single large ($\geq$ 3mm) or small ($\leq$2.75mm) stent was conducted, specifically to examine the performance of EES in small and large vessels.

Clinical Outcomes

Clinical outcome assessment was conducted by searching the New Zealand national health-events registry, hospital records or through telephone follow-up. The primary end point was cumulative major adverse cardiac events (MACE) which included, all-cause mortality, myocardial infarction (MI), target vessel revascularisation (TVR) and definite stent

thrombosis (ST) as per ARC definition. Individual endpoints included in MACE were reported as secondary endpoints.

Statistical Analysis

Statistical analysis was performed with PASW Statistics 18 (SPSS Institute, Chicago, IL). All analysis was based on intention-to-treat. The continuous variables are presented as mean plus/minus standard deviation (SD) and are compared with t-test. Survival and MACE-free survival were derived by Kaplan-Meier methods. Binary variables were summarised as counts and percentage and were compared with Fisher Exact Test as appropriate.

Results

A total of 406 consecutive patients were treated with either Promus or Xience V EES during the period. Four hundred and three patients were included in the analysis; 3 patients were lost in the follow-up due to geographical migration. Four patients (1%) had staged PCI with EES. Baseline demographics and indications for PCI are summarised in Table 1. The mean age is 64 $\pm$ 12 years old (Range, 39 to 82), 70% were male. Diabetes mellitus (type I or II) was present in 25% of the study population. The majority of patients (81%) presented with acute coronary syndrome.

The procedure related results are summarised in Table 2. Femoral access (77%) was used in the majority of the procedure compared to radial approach (23%). Thirty-two percent of patients received concomitant glycoprotein IIb/IIIa inhibitor. Overall, 568 lesions were treated in 510 vessels with 690 stents deployed; an average of 1.7 stents per patient. Successful stent deployment was achieved in 99.5% of the cases. The majority, 77%, of lesions treated were complex (B2 or C). The mean reference vessel diameter was 2.6 $\pm$ 0.5 mm with a mean final stent length of 23.2 $\pm$ 8.2 mm.

During a median follow-up of 23 months (1st and 3rd

Table 1. Baseline Demographic Data of Patients

Baseline Demographics	Patients, n = 403
Mean age, years	64 $\pm$ 12
Male, n (%)	286 (70%)
Major cardiac risk factors	
Diabetes Mellitus, n (%)	102 (25%)
Hypertension, n (%)	287 (71%)
Dyslipidaemia, n (%)	361 (90%)
Smoker or ex-smoker, n(%)	227 (56%)
Indications for PCI	
Unstable angina	172 (43%)
NSTEMI	154 (38%)
STEMI	32 (8%)
Stable Angina	45 (11%)

Table 2. Procedure, Lesions and Quantitative Coronary Angiography Data

Access	
Femoral, n (%)	311 (77%)
Radial, n (%)	92 (23%)
Procedural Success, n (%)	401 (99.5%)
Vessel Treated, n	690
Left main, n (%)	27 (4%)
Left anterior descending, n (%)	327 (47%)
Left circumflex, n (%)	162 (24%)
Right coronary artery, n (%)	166 (24%)
Others (ramus intermediate, grafts), n (%)	8 (1%)
Lesion number	568
Lesion types	
A	16 (2.8%)
B1	116 (20.4%)
B2	196 (34.5%)
C	240 (42.3%)
Quantitative coronary angiography	
Reference vessel diameter, mm	2.6 ± 0.5
Lesion length, mm	19.3 ± 10.8
Minimum luminal diameter (MLD), mm	0.91 ± 0.56
Lesion stenosis, %	66 ± 19
Stent diameter, mm	2.7 ± 0.6
Individual stent length, mm	18.2 ± 9.2
Total stent length, mm	23.2 ± 8.2
MLD after PCI, mm	2.6 ± 0.6
Residual stenosis, %	8.7 ± 12.3

Table 3. A Summary of Cumulative Clinical Outcomes

Median follow-up, months	23
Total cumulative MACE, n (%)	45 (11%)
All-cause mortality	19 (5%)
Cardiac, including sudden death	12 (3%)
Sudden cardiac death	3 (1%)
Non-cardiac	7 (2%)
Myocardial infarction	13 (3%)
Target vessel revascularisation	12 (3%)
Definite stent thrombosis	1 (<0.5%)
Probable stent thrombosis	1 (<0.5%)
Possible stent thrombosis	4 (1%)
Overall stent thrombosis	6 (1.4%)

Table 4. A Summary of Cardiac Mortality Cases

No.	Age/ Gender	Indication of PCI	Days post indexed procedure	Comments, cause of death
1.	46F	Community cardiac arrest	0	No stent thrombosis
2.	56F	Primary angioplasty	365	Heart failure
3.	79M	Angina	770	Heart failure
4.	50M	Unstable angina	86	Possible stent thrombosis
5.	58M	Primary angioplasty, cardiogenic shock	0	No stent thrombosis
6.	51M	NSTEMI	2	Probable stent thrombosis
7.	88F	Unstable angina	103	Heart failure due to severe aortic stenosis
8.	76M	NSTEMI	127	Possible stent thrombosis
9.	79F	NSTEMI	121	Possible stent thrombosis
10.	78M	Unstable angina	403	Heart failure with multiple co-morbidities
11.	78M	Unstable angina	155	Possible stent thrombosis
12.	60M	Angina	217	Cardiac arrest during surgical operation from bleeding complications

quartiles, 19 and 28 months respectively), 3% of the patients had an MI, 3% underwent TVR, 5% died and 1 (<0.5%) case of definite stent thrombosis was reported. There was 1 case (0.2%) of EES in-stent restenosis treated with another EES. Of the 5% mortality, 2% were non-cardiac causes. The cumulative MACE was 11% (Table 3). A summary of cardiac mortality is also presented in Table 4. Of note, there was one case of probable stent thrombosis and 4 cases of possible stent thrombosis, thus, giving an overall of 1.5% (6 cases) of stent thrombosis rate. The Kaplan Meier 2-year survival and MACE free survival were 95% and 89% respectively (Fig. 1).

Forty-five percent of the EES used (≤2.75 mm) were in smaller vessels. We analysed the clinical outcomes in large and small vessels treated with EES. Of a total of 403 patients, 209 patients had a single stent inserted and were divided into 2 cohorts; (1) ≤2.75mm or (2) ≥3.0 mm. The patient demographic data and baseline characteristics are

summarised in Table 5. There is a trend of older patients and higher prevalence of a history of smoking in the larger stent group. No difference in lesion complexity was evident. Furthermore, there were no differences in the lengths of
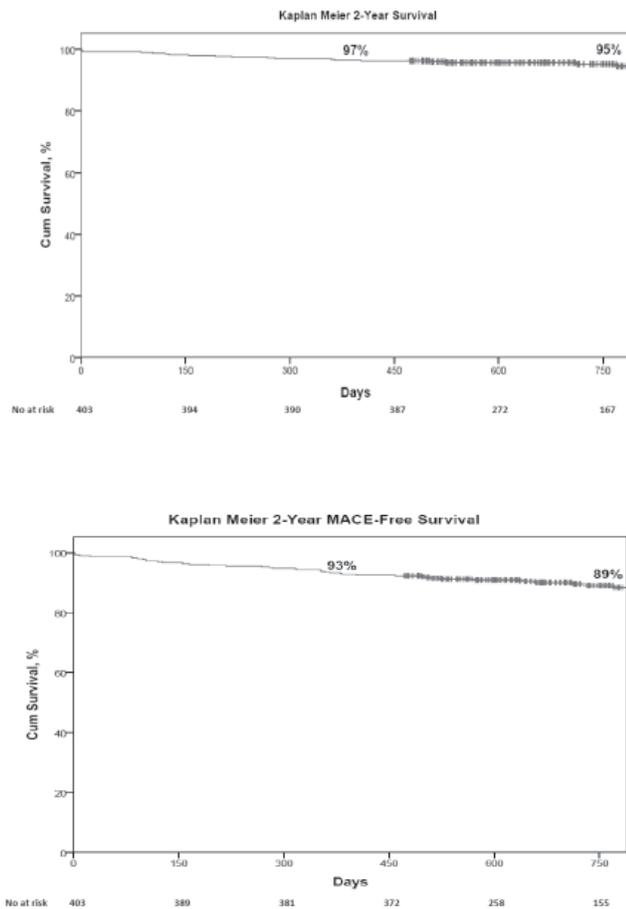
Fig. 1. Kaplan-Meier 2-Year survival and MACE-free survival curves.

Table 5. Demographic and QCA Data in Small (≤2.75 mm) and Large (≥3.0 mm) Vessels Treated with a Single Everolimus-eluting Stent (EES)

	Cohort 1 (≤2.75 mm EES) n = 91	Cohort 2 (≥3.00 mm EES) n = 118	P value
Age	62 ± 11yrs	65 ± 10yrs	0.04
Male	59%	70%	0.11
Cardiac risks			
Hypertension	61 (67%)	83 (70%)	0.61
Diabetes	24 (26%)	33 (30%)	0.80
Dyslipidaemia	82 (90%)	105 (89%)	0.95
Smoker/Ex-smoker	47 (52%)	75 (64%)	0.09
Lesion types			
A	1 (1%)	2 (2%)	1.00
B1	26 (29%)	29 (24%)	0.53
B2	32 (35%)	52 (44%)	0.20
C	32 (35%)	35 (30%)	0.46
Quantitative coronary angiography			
Baseline reference vessel diameter, mm	2.36 ± 0.49	2.90 ± 0.47	<0.01
Lesion length, mm	16 ± 6	16 ± 6	0.85
Minimum luminal diameter (MLD), mm	0.70 + 0.48	0.98 ± 0.58	<0.01
Lesion stenosis, %	70 ± 20	66 ± 19	0.19
Residual stenosis, %	10 ± 14	8 ± 12	0.20
Stent characteristic			
Stent diameter, mm	2.53 ± 0.19	3.15 ± 0.25	<0.01
Stent length, mm	19 ± 6	20 ± 6	0.11

stent implanted. As expected, the ≤2.75 mm EES cohort had significantly smaller average reference vessel diameters, minimum luminal diameters and stent diameters.

Table 6 illustrates the outcome data for both cohorts. MACE and independent outcomes were not significantly different during the follow-up with low TVR and ST reported in both cohorts (MACE for Cohort 1 vs Cohort 2; 12% vs 9%; P = 0.34).

Discussion

This registry data provides the expected clinical outcomes in day to day PCI practice with PROMUS™ and XIENCE V™ second generation DES. The observed 97% one-year survival and 93% MACE-free survival are consistent with the available evidence from trials and registry data.[3,4,7-11]

Large randomised-controlled trials from the SPIRIT series, which use the same stent, have consistently demonstrated low major cardiovascular adverse events

Table 6. Clinical Outcomes in Small (≤ 2.75 mm) and Large (≥3.0 mm) Vessels Treated with a Single Everolimus-eluting Stent (EES)

	Cohort 1 (≤2.75 mm EES) n = 91	Cohort2 (≥3.00 mm EES) n = 118	P value
Median Follow-up	25 months	23 months	
All-cause mortality	5 (6%)	6 (5%)	1.00
Cardiac	3 (4%)	4 (3%)	
Non-cardiac	2 (2%)	2 (2%)	
MI	2 (2%)	1 (1%)	0.58
TVR	3 (3%)	3 (3%)	1.00
ST	1 (1%)	0 (0%)	0.44
MACE	11 (12%)	10 (9%)	0.34

with EES.[3,7-9] In the SPIRIT V trial, which included 2700 patients with multiple de novo lesions, the one-year cardiac death, myocardial infarction, target lesion revascularisation and definite or probable stent thrombosis rates were 1.1%, 3.5%, 1.8% and 0.66%, respectively. This data represent approximately 7% of one-year MACE and our reported 93% MACE-free survival at one-year in a complex real world setting is remarkably similar. However, the SPIRIT trials excluded high-risk patients with acute or recent myocardial infarctions. The COMPARE trial is an "all comers" design and excluded only those patients who were unable to comply with dual antiplatelet therapy or study procedure and more closely matches our patient cohort.[4] In the EES arm of 897 patients, the one-year MACE is reported at 5%. A more recent follow-up study with the COMPARE study provided a 2-year MACE of 9% in the EES arm comparable to our 11% projected 2-year MACE rate.

Stent thrombosis rate has been noted to be consistently low (<1%) across the SPIRIT and COMPARE trials. In our series, only 1 case of definite stent thrombosis, which occurred within 24 hours while on dual antiplatelet therapy, was noted. Five other patients with cardiac deaths may have had this attributed to stent thrombosis (1 probable and 4 possible). However, these were not confirmed. Of note, due to limited access to clopidogrel for prolonged periods in New Zealand, most of the patients received dual antiplatelet therapy for 6 months only during the study.

A number of trials have proven the benefits of DES against BMS especially in the treatment of small vessels (reference vessel diameter <3 mm).[12-15] Recently, Stone et al[3] have reported the net clinical benefits of second generation EES over Paclitaxel eluting stent. Nevertheless, it is well established that small vessel calibre is a significant risk factor for procedural failure or restenosis with both BMS and DES.[14,16] Of note, although the average reference lumen diameter for both SPIRIT V and COMPARE are similar to ours at 2.75 mm (SPIRIT V), 2.63 mm (COMPARE) and 2.6 mm (our data), no comparison has been made of the outcomes in small diameter vs large diameter vessels in the two other study groups. Thus far, there are no published comparisons of the performance of EES stents in small vessels vs large vessels. Such data, if any, would have focused on the comparison between SES and PES in small vessels.[17]

In our study, both the ≤2.75 mm and ≥3 mm cohorts were well matched for all other risk factors predicting procedural failure and restenosis apart from the vessel and stent diameter. In addition, QCA confirmed correspondingly matching vessel reference diameters and stent diameters, ruling out operator undersizing or oversizing stents. Despite this, we found no significant difference in residual stenosis or outcome for both cohorts after nearly 2 years of follow-up. This suggests that the newer generation of EES is equally effective in small as well as larger calibre vessels. This result may go some way to explain the negative result of the PICCOLETTO trial of DEB vs DES, if DES are equally effective in both small and large vessels, even in a DES that has been shown to be slightly less effective than current second generation DES.[3,18] Nevertheless, we must accept that this is a small registry analysis with a high risk of type II error; the number is not powered enough to detect the true difference between groups. Further information is required from a large randomised control trial.

Limitations

This is a retrospective single centre registry review with a small patient sample size. We also acknowledge that the study probably is not powered to detect the MACE differences between the stent groups.

Conclusion

Despite the limitations, our registry results demonstrate EES appears to be safe in the real world day-to-day practice setting with satisfactory medium to long-term outcomes and low rates of major adverse cardiac events in simple and complicated lesions involving large or small vessels.

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