Long Term Outcomes with Selective Drug Eluting Stent Use in ST-Elevation Myocardial Infarction in an Australian Urban Population

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Abstract: *Aim*: To evaluate the safety and effect on long-term outcomes of an approach that selectively uses drug-eluting stent (DES) only in ST elevation myocardial infarction (STEMI) that meet criteria for high risk of in-stent restenosis (ISR).

Methods: Consecutive patients (n=1832) presenting with STEMI to a single large centre between April 2004 and January 2012 were managed according to an algorithm in which those with pre-specified criteria indicating they were at high risk for ISR received DES (46%, n=847), and otherwise received bare metal stents (BMS) (54%, n=985). High risk criteria included: vessel diameter ≤2.5mm (≤3.0mm in diabetic patients); lesion length >18mm; previous ISR; saphenous vein graft lesions; ostial lesions; bifurcation lesions; left main coronary artery lesions; and multi-vessel disease. The two groups were compared for primary composite outcome of major adverse cardiac events (MACE) including death, repeat MI and TVR; and secondary outcomes of target lesion revascularisation (TLR) and stent thrombosis (ST).

Results: Over a median period of 24 months there was no significant difference (DES vs BMS) in MACE (13.6% vs 18.1%, p=0.074), mortality (7.6% vs 10.5%, p=0.327) or definite stent thrombosis (2.6% vs 1.6%, p=0.094). Patients who received DES had a lower rate of clinically driven TLR (1.6% vs 3.9%, p=0.032).

Conclusion: An approach of selectively using DES in STEMI patients at high risk of ISR provides satisfactory long-term outcomes while limiting the number of patients exposed to DES costs.

Keywords: STEMI, drug-eluting stent, bare metal stent, instent restenosis, acute stent thrombosis.

INTRODUCTION

The current standard treatment for ST elevation myocardial infarction (STEMI) is primary percutaneous coronary intervention (PPCI) with stent implantation [1]. The long term benefits and risks of drug-eluting stent (DES) use have been established in the context of coronary artery disease (CAD). Clinical trials have shown that compared with bare metal stents (BMS), DES use reduces the risk of in-stent restenosis (ISR) and the need for target vessel revascularisation (TVR) [2-5]. These findings are consistent in the context of complex lesions [6-8]. However, DES use does not provide a mortality benefit and is associated with an increased incidence of late stent thrombosis (ST) after 1 year [9,10]. The mortality, TVR and ST outcome rates are similar for DES use compared with BMS in PPCI for STEMI [11-13].

Patients receiving DES are also at an increased risk of adverse events resulting from the need for prolonged use of dual anti-platelet medical therapy following stent implantation [1]. In addition, DES use is associated with higher costs and is only cost effective in the setting of patients with high risk of ISR requiring TVR [14].

More selective use of DES would help reduce costs and risks of implantation of DES indiscriminately. We aimed to evaluate an approach implemented at our institution to selectively use DES in patients with STEMI presenting for PPCI who met criteria for high-risk of ISR.

METHODS

Study Design and Patient Population

Outcomes in patients selected for DES use were compared to others who received a BMS using data from a prospective STEMI registry at our hospital. This data was collected by dedicated staff, using a standard case report form, on all prospectively identified STEMI patients presenting to Westmead Hospital, NSW, Australia [15]. All patients provided written informed consent. STEMI patients are defined as persistent chest pain for at least 30 minutes associated with the following criteria on electrocardiogram: ST elevation of ≥ 0.1mV in 2 contiguous limb leads; or ≥ 0.2mV in 2

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contiguous chest leads; or new left bundle branch block. There was no age limit for inclusion in the study.

We utilised data collected between April 2004 and January 2012 for the current analyses. Of the 2160 patients enrolled in that period, we excluded patients treated with balloon angioplasty only (n=286) and those treated with rescue angioplasty following failed thrombolysis (n=42), leaving 1832 patients who were treated with primary angioplasty and stenting.

Follow up was by review of all angiograms, discharge summaries and death registries within the follow-up period. In addition, telephone interviews were conducted at regular intervals: 1 month, 6 months, and then yearly for the duration of the study. Patients lost to follow-up were censored at the time of their last review. Follow-up angiography was not routine and performed for clinically symptomatic patients only.

Procedures and Medical Therapy

Westmead hospital introduced a protocol to use DES in selected patients with STEMI at high risk of ISR in 2004. The criteria used were identified from the literature [16] and included: 1) Target vessel ≤ 2.5mm in diameter in non-diabetic patients and ≤ 3.0mm in diabetic patients; 2) Target vessel lesion length >18mm; 3) Previous instent restenosis; 4) Saphenous vein graft lesions; 5) Ostial lesions; 6) Bifurcation lesions; 7) Left main coronary artery lesions; and 8) multi-vessel disease requiring multiple stents. Patients with STEMI and any one of these criteria had DES used to stent the target lesion. These criteria for stent selection were posted in all the cardiac catheterisation laboratories and communicated to all staff.

All patients were treated with aspirin as well as clopidogrel or prasugrel. During the procedure both heparin and glycoprotein IIb/IIIa inhibitor (abciximab) were used unless contraindicated. Aspirin 100mg daily was prescribed lifelong. Clopidogrel 75mg or Prasugrel 10mg were prescribed for at least 1 month for patients who received BMS. In patients that received DES, dual antiplatelets were prescribed at least 6 months for those who received DES with STEMI prior to 2006 and at least 12 months for patients who presented more recently. Lesion length and diameter were measured independently by a radiographer during angiography. All patients were prescribed statins, ACE-inhibitors and beta-blockers unless contraindicated. From 2009, thrombus aspiration catheters were available and utilised unless contraindicated.

Outcomes

The study endpoint was the incidence of Major Adverse Cardiac Event (MACE), which was a composite endpoint of death, repeat MI and TVR. The secondary endpoints were the rate of target lesion revascularisation (TLR) and stent thrombosis (ST).

The Academic Research Consortium (ARC) definition for TLR was used [17]. TLR included patients who had repeat percutaneous intervention (PCI) or coronary artery bypass graft performed for restenosis at the lesion treated during initial PCI or occurring within 5mm of the site of original stent. Patients who received repeat revascularisation for ST were evaluated separately and not considered in TLR events. TVR included patients who had an unplanned repeat PCI or bypass graft for a restenosis in the same vessel as index PCI.

Repeat MI was defined as a recurrence of symptoms accompanied by either: a rise in serum CK by > 50% over previous measured level after initial peak in the first 7 days post STEMI; or a rise in serum Troponin T to more than twice the upper normal limit after normalisation.

The ARC definitions for ST were used to classify patient outcomes into definite, probable and possible ST [17]. Definite ST required angiographic or pathologic confirmation of partial or total occlusion of peri-stent region with thrombus in addition to at least one of: ischaemic symptoms, ischaemic ECG changes, or elevated cardiac biomarkers. Probable ST included either unexplained death within 30 days or documented myocardial ischaemia in the territory of implanted stent without angiographic evidence at any time following stent implantation. Possible stent thrombosis included unexplained deaths beyond 30 days following the procedure. Patients with stent thrombosis were further subdivided into those with acute, subacute, late or very late thrombosis. Acute ST referred to occurrence of ST within 24 hours of stent implantation; subacute to occurrence between 24 hours and 30 days; late to occurrence between 30 days and 1 year; and very late to ST beyond 1 year. Reperfusion time was defined as time from symptom onset to TIMI III flow.

Statistical Analysis

Continuous variables had a normal distribution and where reported as mean +/- standard deviation using the student t-test or Mann-Whitney test. Categorical

variables were compared using Fischer's exact test and reported as mean +/- standard deviation. A 2-sided p <0.05 was considered statistically significant. Kaplan Meier survival curves were used to depict freedom from events. Independent predictors of MACE and TLR were assessed using Cox regression analysis. Variables used as possible predictors in the multivariate analysis were those that reached a significance of p < 0.15 on univariate analysis. These included comorbidities, artery length, artery diameter and use of drug eluting stent. Statistical analysis was performed with SPSS version 20.0.

Ethics

The study protocol was approved by the Sydney West Human Ethics Committee.

RESULTS

Patient Characteristics

There were at 847 patients at high risk for ISR (46%) who received DES and 985 patients at low risk who received BMS (54%). Patients were followed up for a median period of 24 months (inter-quartile range 6-35months). Baseline characteristics of the 2 groups are shown in Table **1**. Smoking was less prevalent and diabetes was more prevalent in the DES group.

The lesion and stent characteristics of each group are shown in Table **2**. The DES group received longer stents with a smaller diameter, as expected from the DES implant criteria. Symptom onset to reperfusion time was similar in both groups. The DES' used included Promus 39% (Boston Scientific Corporation)

Table 1: Patient Characteristics

Characteristic	DES (n=847)	BMS (n=985)	p-value
Female	21.6%	18.3%	0.088
Age	59.6 +/-12.1	59.7 +/-12.8	0.900
Pre-existing Conditions			
Hypertension	54.3%	52.6%	0.447
Hyperlipidemia	59.2%	54.7%	0.069
Diabetes Mellitus	28.3%	20.0%	<0.001
Smoking	63.0%	71.4%	<0.001
Family history CAD	47.5%	48.5%	0.700
Ischemic Heart Disease	23.9%	21.2%	0.171
CABG	2.9%	2.8%	0.888
Previous stent	11.6%	9.5%	0.141
Previous Stroke/TIA	3.9%	5.6%	0.097

DES= drug eluting stent, BMS= bare metal stent, CAD= coronary artery disease, CABG= coronary artery bypass graft, TIA= transient ischemic attack. Student t-test was used to compare continuous variable and Fischer's exact test was used to compare categorical variables.

Table 2: Lesion and Stent Characteristics

Characteristic	DES (n=847)	BMS (n=985)	p-value
Artery area			
LAD	51.6%	40.1%	<0.001
RCA	33.1%	46.3%	
Cx	13.1%	11.2%	
Other	2.1%	2.3%	
No of diseased vessels			
1 VD	49%	48%	0.605
2 VD	29%	31%	
3 VD	22%	21%	
Stent length (mm)	20.5+/-5.7	18.1+/-4.3	<0.001
Stent diameter (mm)	2.9+/-0.4	3.2+/-0.5	<0.001
Reperfusion time (min)	224 (165-327)	223 (170-325)	0.970

DES= drug eluting stent, BMS= bare metal stent, LAD= left anterior descending, RCA= right coronary artery, Cx= circumflex, VD= vessel disease. Student t-test was used to compare continuous variable and Fischer's exact test was used to compare categorical variables.

and Taxus 61% (Boston Scientific Corporation). The BMS used included: Driver 15% (Medtronic Corporation), Gazelle 5% (Biosensors International), Integrity 6% (Medtronic Corporation), Liberte 12% (Boston Scientific Corporation), Prokinetic 15% (Biotronik SE & Co.), Tsunami 9% (Terumo) and Vision 38% (Abbott Laboratories Group).

Outcomes

The outcomes at the 12 and 24-month follow up are shown in Table **3**. At 24 months, there was no significant difference in MACE (13.6% in DES cohort vs. 18.1% in BMS cohort, p= 0.074). The MACE event-free survival curve is shown in Figure **1**. The mortality rate at 24 months was similar between the two groups (7.6% in DES cohort vs. 10.5% in BMS cohort, p= 0.327) as was the rate of definite stent thrombosis (2.2% in DES cohort vs. 1.6% in BMS cohort, p= 0.094). Patients who received DES had a lower rate of clinically driven target lesion revascularisation (1.8% in DES cohort vs. 4.2% in BMS cohort, p= 0.026) and target vessel revascularization (3.0% in DES cohort vs. 4.8% in BMS cohort, p= 0.036) at 2 years.

The independent predictors of MACE, TLR and ST on Cox multivariate analysis are shown in Table **4**. There was an association between DES use and lower TLR (HR: 0.40; 95% CI: 0.2-0.8, p=0.004) and lower MACE (HR: 0.53; 95% CI 0.4-0.7, p<0.001). Other independent predictors of TLR on multivariate analysis included: diabetes and stent length. Apart from DES, other independent predictors of MACE included: age increase by 10 years, diabetes, previous history of ischemic heart disease, previous history of stroke or transient ischemic accident (TIA), stent diameter increase by 1 mm and stent length increase by 5mm. DES use was not an independent predictor of ST on multivariate analysis (HR: 1.6, 95% CI 0.8-3.0, p=0.180). The independent predictors of ST were age increase by 10 years, history of diabetes and previous history of percutaneous intervention.

DISCUSSION

This study demonstrates that the described strategy is both effective and safe, with low rates of TLR and ST in the overall cohort. There was a small increase in TLR and TVR rates in the BMS group, despite that

Table 3: Kaplan-Meier Estimated Probability of Outcome by 1 Year and 2 Years

Outcome	By 1 year	By 2 years	p-value
MACE			0.074
DES	10.4+/-1.1%	13.6+/-1.3%	
BMS	14.5+/-1.2%	18.1+/-1.4%	
Overall	12.6+/-0.8%	16.1+/-1.0%	
Mortality (all cause)			0.327
DES	6.9+/-0.9%	7.6+/- 1.0%	
BMS	8.3+/-1.1%	10.5+/-1.1%	
Overall	7.6+/-0.7%	9.1+/-0.7%	
Repeat MI			0.530
DES	0.7+/-0.5%	1.9+/-0.6%	
BMS	1.6+/-0.5%	2.5+/-0.6%	
Overall	1.2+/-0.8%	2.2+/-0.4%	
TVR			0.036
DES	1.3+/-0.5%	3.0+/-0.7%	
BMS	3.3+/-0.7%	4.8+/-0.8%	
Overall	2.4+/-0.4%	4.0+/-0.6%	
TLR			0.032
DES	0.8+/-0.4%	1.6+/-0.5%	
BMS	2.7+/-0.6%	3.9+/-0.8%	
Overall	1.8+/-0.4%	2.9+/-0.5%	
ST			0.094
DES	1.7+/-0.5%	2.6+/-0.6%	
BMS	1.2+/-0.4%	1.6+/-0.5%	
Overall	1.4+/-0.3%	2.1+/-0.4%	

DES= drug eluting stent, BMS= bare metal stent, MACE= major adverse cardiac events, MI= myocardial infarction, TVR= target vessel revascularisation, TLR= target lesion revascularisation, ST= stent thrombosis.

Table 4: Multivariate Cox Regression Analysis

	Hazard Ratio	Confidence Interval	p-value
MACE			
Age	1.2	1.1-1.3	0.002
Diabetes	1.5	1.2-2.0	0.001
Previous IHD	1.5	1.1-1.9	0.004
Previous stroke/TIA	1.6	1.0-2.6	0.029
DES	0.6	0.4-0.7	<0.001
Stent diameter (per 1mm)	0.6	0.4-0.7	<0.001
Stent length (per 5mm)	1.2	1.1-1.3	0.016
TLR			
DES	0.4	0.2-0.8	0.004
Diabetes	2.1	1.2-3.8	0.015
Stent length (per 5mm)	1.4	1.1-1.9	0.021
ST			
Age	0.7	0.5-0.9	0.008
Diabetes	2.3	1.2-4.4	0.013
Previous PTCA	2.7	1.2-5.9	0.014
DES	1.6	0.8-3.0	0.180

DES= drug eluting stent, BMS= bare metal stent, TIA= transient ischemic attack, IHD= ischemic heart disease, PTCA= percutaneous coronary intervention, MACE= major adverse cardiac events, TLR= target lesion revascularisation, ST= stent thrombosis.

group considered to be at lower risk for ISR. However, this was not associated with increased mortality and this approach resulted in a low incidence of ST in the overall group.

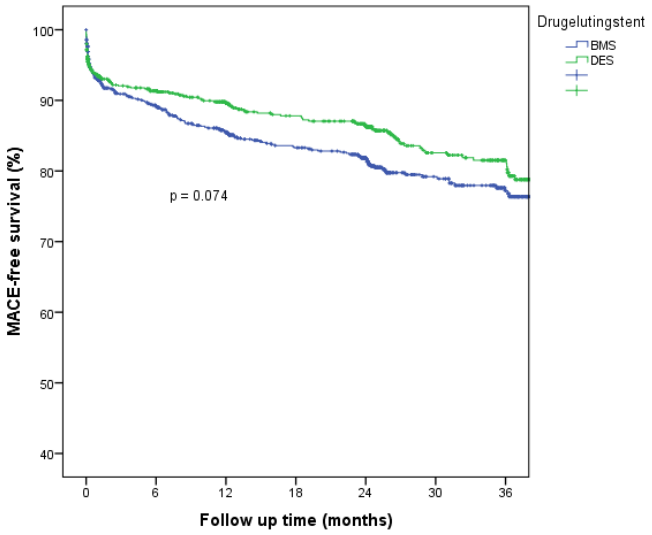

Figure 1: Event-free survival curve for major adverse cardiac events (MACE).

Despite reduction in the incidence of ISR, there are many clinical situations where it is preferable to avoid DES use. Dual anti-platelet therapy (DAPT) is recommended for at least 12 months post stent insertion for ACS to prevent stent thrombosis and [18]. However, many patients have a contraindication for prolonged DAPT including patients at risk of bleeding or those scheduled for surgery [1]. Patients with BMS can have a minimum of 4 weeks of DAPT whereas those with DES require a minimum of 12 months, and hence BMS use may be preferred in patients with bleeding risks [1]. Patients with DES are also at higher risk of late acute stent thrombosis, which can be life-threatening [1]. These risks versus potential risks of higher rates of less life-threatening restenosis need to be weighed up.

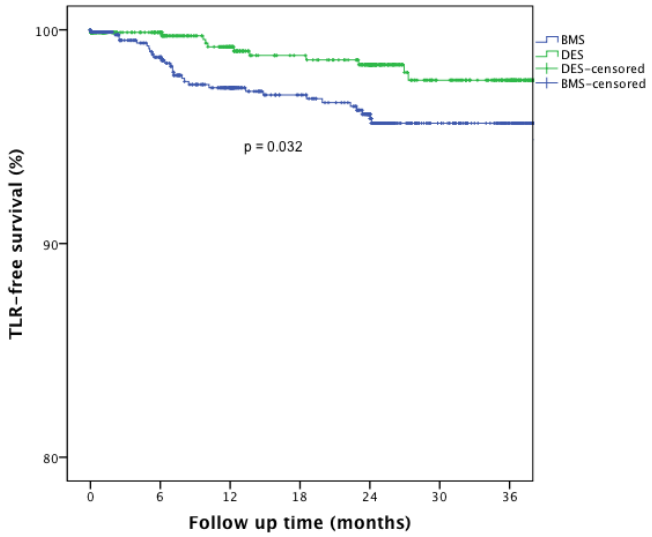

Figure 2: Event-free survival curve for target lesion revascularisation (TLR).

Another limitation of DES use is increased cost. DES are considerably more expensive than BMS

(greater than1500 USD more) and there are also additional costs to patients and the health system associated with prolonged DAPT [19]. Despite cost, use of DES is considered more cost-effective in populations that are at high risk of restenosis and more likely to benefit from them [16]. These include non-elective patients who have had previous coronary artery bypass grafting and those who have diabetes, narrow vessels or long lesions [14, 20].

The approach described here reduced the number of STEMI patients receiving DES to 46%. We identified that patients who received BMS in our study and had diabetes had a 2.4 times higher rate of TLR. If we had more liberal criteria for DES in all diabetic patients, this would have increased our DES implantation rate, but reduced TLR. The potential cost-benefits of these could be assessed in future studies.

There is few data that assess long-term outcomes of approaches to selectively use DES in 'real world' STEMI patients. One small study of 126 patients presenting with STEMI that were selectively given DES if they had long lesions (>20mm), small vessels (<2.5mm) or were diabetic patients found low rates of MACE, re-infarction, TVR and ST at 34 months indicating the strategy appeared to be safe [21]. Recently, a large prospective trial evaluated the short-term outcomes of a selection strategy for DES with criteria identical to our study [22]. They followed 2115 patients who underwent PCI and reported low rates of overall adverse outcomes at one year. Our study has demonstrated that this strategy of selectively using DES in STEMI patients remains safe and effective with long-term follow up.

The randomised control trials comparing outcomes of DES with BMS use in STEMI include TYPHOON, PASSION, SESAMI, DEDICATION and EXAMINATION [8, 23-27]. These studies used DES non-selectively, independent of the risk of restenosis in individual patients. At one-year follow-up, the PASSION trial reported rates of TLR in 7.8% in BMS arm and 5.3% in DES arm. The DEDICATION trial included more complex patient and lesion subsets and reported TLR rates at 8-months of 5.1% in DES arm and 13.1% in BMS arm. In our study, overall we achieved a satisfactory TLR rate of 1.8% at one year. Our overall rate at 2 years of 2.9% was also comparable with the rates reported in the EXAMINATION trial, 2.9% in DES arm and 5.6% in BMS arm.

The MACE (target-vessel-related death, recurrent MI or TVR) rates at one-year in the TYPHOON trial were 7.3% in DES arm and 14.3% in BMS arm. Although our MACE outcome included all deaths rather than only those attributable to the target vessel, our overall rate of MACE were comparable at 12.6% at one year. The STRATEGY trial used a composite outcome MACE, which included the same outcomes as MACE in this study: death, AMI or TVR [28]. The rates of MACE in the STRATEGY trial at two-year follow up were 24.2% in the sirolimus-eluting stent (SES) group and 38.6% in the BMS group. These were higher than overall MACE in our study, which was 16.1%

DES use in PCI reduces the incidence of stent restenosis and need for revascularisation compared with BMS [3, 4, 7]. The absolute risk reduction is higher in patients with lesions at high risk of restenosis [29]. The rate of adverse outcomes including death and repeat MI are not significantly increased with use of DES [9]. However, the rates of very late stent thrombosis were higher in patients who received first generation DES [10]. Patients with acute MI have been excluded from the initial studies and DES use in these patients has been considered off-label. There has been concern about the risk of stent thrombosis in STEMI patients due to the pro-thrombotic condition [30-32]. However, similar long-term outcomes were found in meta-analyses comparing DES and BMS use in acute myocardial infarction [13, 23, 24, 28, 33-35]. The ST rates in the DEDICATION trial were not significantly different in DES and BMS arms at 2.0 and 2.6% at 8-months follow-up [26]. The ST rate in our cohort, which also included complex subsets, was lower (1.4%) even out to one year of follow up.

There has been a discrepancy in outcomes between clinical trial populations and registries of real-world patients [21]. The latter studies tend to include more complex patients and lesions, which were excluded in many of the RCTs. Hence; it is more appropriate to compare our outcomes with those in these real-world studies. The Massachusetts Registry reported 2-year mortality rates of 8.5% and 11.6% and the STENT Registry reported 2-year TVR rates of 8.0% and 11.3% in DES and BMS cohorts respectively [29, 36]. One registry of non-selective DES use in a Korean PCI centre, which included 684 patients, reported similar rates of adverse outcomes at two-year follow-up except for higher rates of TVR and TLR in the BMS group of 22.8% and 17.9% [35]. Our overall 2-year mortality rate of 9.1%, TLR rate of 2.9% and TVR rate of 4.0% were comparatively low.

STUDY LIMITATIONS

The main limitation of this study is that the strategy of selective use was not evaluated in a randomised controlled trial setting. However, it does present a real world evaluation of an approach in which selection criteria were applied prospectively to select type use of DES vs BMS, thus limiting bias. The selection criteria were objective measures of lesion characteristics of the lesions and patient characteristics. There were a range of both BMS and DES used in our study and recent research has indicated that there are variations in outcomes with different types of stents [37]. The DAPT use in our study was shorter than 12 months as recommended in the current guidelines [38]. However, despite this the long-term risk of ST was low. Adjusting the outcomes for duration of DAPT use and compliance, had this data been available, would have provided more precise results. Finally we did not evaluate other measures of safety in particular major and minor bleeding.

A recent pooled meta-analysis has shown that DES use is more effective and safe in women and should be considered the standard of care[39]. The gender differences in selective use of DES in STEMI were not assessed in our study as the study design pre-dated this meta-analysis. Finally, the cost-effectiveness of this protocol is yet to be assessed.

SUMMARY

We have demonstrated that this strategy of limiting DES to STEMI patients at high risk of ISR is safe and effective with long-term follow up. This strategy could reduce health care costs by limiting the more expensive DES use and by limiting the duration of DAPT. There is also the possibility that this strategy might reduce the risk of late ST.

ABBREVIATIONS

STEMI = ST elevation myocardial infarction

DES = drug eluting stent

CAD = coronary artery disease

BMS = bare metal stent

TVR = target vessel revascularisation

ST = stent thrombosis

TLR = target lesion revascularisation

ARC = academic research consortium

PCI = percutaneous coronary intervention

HR = hazard ratio

MI = myocardial infaction

MACE = major adverse cardiac events

DAPT = dual anti-platelet therapy

SES = sirolimus eluting stent

EES = everolimus eluting stent

ZES = zotarolimus eluting stent

TIA = transient ischaemic attack

ISR = instent restenosis

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