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Selective use of drug-eluting stents in high-risk versus bare metal stents in low-risk patients according to predefined criteria confers similar four-year long-term clinical outcomes

Rajiv Ananthakrishna[1,2]*, DM; Joshua P.Y. Loh[1], MBBS; Domingo Addatu Jr[1,3], MD; Liang Shen[4], PhD; Adrian F. Low[1], MBBS; Chi Hang Lee[1], MBBS; Huay Cheem Tan[1], MBBS

1. National University Heart Centre, Singapore; 2. Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore, India; 3. Chinese General Hospital, Manila, Philippines; 4. Yong Loo Lin School of Medicine, National University of Singapore, Singapore

KEYWORDS

- bare metal stents
- clinical research
- drug-eluting stents

Abstract

Aims: The aim of the study was to evaluate the long-term outcomes following selective implantation of drug-eluting stents (DES) in patients at high risk of restenosis versus bare metal stents (BMS) in low-risk patients, according to predefined criteria.

Methods and results: Patients who underwent elective percutaneous coronary intervention (PCI) between May 2002 and April 2004 were enrolled in this retrospective, single-centre study. All patients received a BMS while undergoing PCI, unless they fulfilled at least two entry criteria that warranted DES usage. The study endpoints were major adverse cardiac events (MACE), comprising death, myocardial infarction, stent thrombosis (ST), and target vessel revascularisation (TVR), at four years between the DES and BMS groups. A total of 1,250 patients were enrolled in the study, among whom 1,095 (88%) received BMS and the rest received DES. At four years, there was no difference in the cumulative incidence of MACE: death (4.5% in DES vs. 5.8% in BMS, p=0.531), myocardial infarction (2.6% in DES vs. 3.1% in BMS, p=0.722), TVR (9.7% in DES vs. 7.9% in BMS, p=0.461), and ST (1.9% in DES vs. 0.8% in BMS, p=0.183). The event-free survival rate at four years was similar in the two groups (87.1% in DES vs. 86.1% in BMS; p=0.741).

Conclusions: In elective PCI, a strategy of selective use of DES in patients at high risk of restenosis based on predefined criteria confers the same favourable long-term clinical outcomes as BMS in low-risk patients.

**Corresponding author: Sri Jayadeva Institute of Cardiovascular Sciences & Research, Jaya Nagar 9th Block, BG Road, Bangalore 560069, India. E-mail: rajiva.ms@gmail.com*

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Abbreviations

BMS	bare metal stent(s)
DES	drug-eluting stent(s)
MACE	major adverse cardiac events
PCI	percutaneous coronary intervention
ST	stent thrombosis
TVR	target vessel revascularisation

Introduction

Percutaneous coronary intervention (PCI) with implantation of stents has become the most commonly performed therapeutic procedure worldwide[1]. In comparison to bare metal stents (BMS), the use of drug-eluting stents (DES) has been shown to be more effective in reducing the rate of restenosis[2]. The overall benefit associated with the use of DES was largely due to a reduction in target lesion revascularisation, without effect on all-cause mortality. In the Norwegian Coronary Stent Trial, there were no significant long-term effects on the rates of death or spontaneous myocardial infarction between patients receiving contemporary DES and those receiving BMS[3]. In large registries such as Ontario and the Swedish database, the benefit with DES, compared to BMS, was most apparent in patients at risk of developing restenosis. These high-risk patients are identified by clinical and angiographic factors such as the presence of diabetes mellitus, small calibre target vessels, diffuse lesions, and the complexity of target lesions[4,5].

The majority of current-generation DES carry a risk of late and very late stent failure due to the persistence of the polymer. The duration of dual antiplatelet therapy is longer with DES, at least in part due to delayed neointimal coverage[6,7]. In addition, DES come at a much higher cost (up to three to four times) compared to BMS, and the rapid growth of their use has raised important concerns about cost from both institutional and societal perspectives[8,9]. It is against this background that we analysed our data retrospectively, comparing DES versus BMS.

Methods

STUDY DESIGN AND POPULATION

This is a retrospective, single-centre study from a tertiary care teaching hospital comparing the selective use of DES in patients at high risk of restenosis versus BMS in low-risk patients according to predefined criteria. In the initial period of coronary stenting, it was the institution's practice to select patients carefully based on predefined criteria and to employ a strategy for the targeted use of DES. We conducted a retrospective analysis of the first 1,250 patients from May 2002 in order to evaluate the long-term clinical outcomes of such a strategy. All patients in the two-year period between May 2002 and April 2004 received a BMS while undergoing elective PCI in our centre, unless they fulfilled at least two entry criteria which warranted DES usage. These criteria included the presence of diabetes mellitus, diffuse lesion as defined by a lesion length of more than 20 millimetres, small vessel (<3.0 mm), proximal lesion, restenosis following PCI, and ostial or bifurcation stenting. Patients who underwent an emergency PCI for acute coronary syndrome and those who received hybrid stenting with BMS and DES were excluded. The study was approved by the National Ethics Committee and the Hospital Research Board.

DATA COLLECTION AND STUDY OUTCOMES

Baseline demographics, clinical characteristics, and procedural data were collected retrospectively from our institution's cardiac database. These patients had clinical follow-up for four years and outcomes were analysed. The study endpoints were the major adverse cardiac events (MACE) of death, myocardial infarction, stent thrombosis (ST), and target vessel revascularisation (TVR) at four years between the BMS and DES groups. ST was classified according to the Academic Research Consortium criteria. The clinical endpoints were reviewed and adjudicated by members of the study team.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS, Version 18 (SPSS Inc., Chicago, IL, USA). Patients' demographic and clinical data were summarised descriptively. Categorical and quantitative data are presented as frequency (percentage) and mean±standard deviation, respectively. The categorical variables were compared between those receiving BMS and DES using either the chi-square test or Fisher's exact test where applicable, while numerical variables were compared using either the two-sample t-test or the Mann-Whitney U test. The occurrence of the clinical outcomes such as death, myocardial infarction, TVR, and ST were compared using either the chi-square test or Fisher's exact test between the two groups. Multivariate analysis was performed with logistic regression models for the prediction of MACE. The known predictive factors such as diabetes mellitus, diffuse disease, ostial lesion, bifurcation lesion, American Heart Association type C lesion, location of lesion in the left main or left anterior descending artery, and stent diameter less than 3 mm were included in the multivariate model. This selection was based on the well-described association of these variables with MACE. All statistical tests were performed at a 5% level of significance and with 95% confidence intervals.

Results

Between May 2002 and April 2004, a total of 1,250 patients were enrolled in the study, among whom 1,095 (88%) received BMS and the rest received first-generation DES, which included the CYPHER® (Cordis, Cardinal Health, Milpitas, CA, USA) sirolimus-eluting stent and TAXUS® (Boston Scientific, Marlborough, MA, USA) paclitaxel-eluting stent. The baseline demographic and risk factor profiles are shown in **Table 1**. The mean age was 57 years in both groups and three fourths of the patients were male. There was no difference in the prevalence of hypertension, hyperlipidaemia, and family history of premature coronary artery disease between the two groups. Patients who received DES were more likely to be diabetic when compared to those in the BMS group (44.5% in the DES group vs. 36.3% in the BMS group, p=0.049).

The lesion and stent characteristics of the study population are shown in **Table 2** and **Table 3**. Patients who received DES

Table 1. Baseline demographic data.

		BMS	DES	*p*-value
Number of patients		1,095	155	
Age (years)		57.4±11.0	57.4±10.2	0.932
Males		835 (76.3%)	117 (75.5%)	0.813
Diabetes		397 (36.3%)	69 (44.5%)	0.049
Hypertension		670 (61.2%)	93 (60.0%)	0.777
Hyperlipidaemia		775 (70.8%)	113 (72.9%)	0.585
Family history of premature CAD		27 (2.5%)	4 (2.6%)	0.931
Smoker	Current	374 (34.2%)	34 (21.9%)	0.009
	Ex	219 (20.0%)	35 (22.6%)	
	Non	502 (45.8%)	86 (55.5%)	

BMS: bare metal stents; CAD: coronary artery disease; DES: drug-eluting stents

Table 2. Lesion characteristics.

	BMS (n=1,095)	DES (n=155)	*p*-value
Diffuse	243 (22.2%)	62 (40.1%)	<0.001
AHA type C	246 (22.5%)	66 (42.7%)	<0.001
Ostial	42 (3.9%)	10 (6.4%)	0.063
Eccentric	763 (69.7%)	114 (73.8%)	0.173
Calcification	105 (9.6%)	18 (11.6%)	0.297
Angulation	128 (11.7%)	20 (13.1%)	0.507
Bifurcation	188 (17.2%)	29 (18.4%)	0.655
Left main and LAD lesion	488 (44.6%)	90 (58.1%)	<0.001
Mean diameter stenosis pre-PCI (%)	84.6±10.9	82.9±10.0	0.02
Mean diameter stenosis post-PCI (%)	9.62±7.96	8.98±5.96	0.213
Multivessel PCI	194 (17.8%)	35 (22.6%)	0.154

AHA: American Heart Association; BMS: bare metal stents; DES: drug-eluting stents; LAD: left anterior descending artery; PCI: percutaneous coronary intervention

Table 3. Stent characteristics.

	BMS	DES	*p*-value
Mean number of stents per patient	1.1±0.4	1.2±0.5	<0.001
Mean number of stents per lesion	1.1±0.5	1.3±0.6	<0.001
Mean stent diameter (mm)	3.2±1.0	2.8±0.3	<0.001
Mean stent length (mm)	18.7±6.6	21.8±6.6	<0.001

BMS: bare metal stents; DES: drug-eluting stents

had a higher prevalence of diffuse lesions and American Heart Association type C lesions. Patients with a lesion in the left main and left anterior descending artery were more likely to receive a DES. There was no difference in the incidence of multivessel PCI between the two groups (22.6% in the DES group vs. 17.8% in the BMS group, p=0.154). There were more stents implanted per patient and per lesion in the DES group compared with the BMS group (1.2±0.5 and 1.3±0.6 in the DES group vs. 1.1±0.4 and 1.1±0.5 in the BMS group, p<0.001). The DES used were significantly longer in length and smaller in diameter than the BMS (21.8±6.6 mm and 2.8±0.3 mm in the DES group vs. 18.7±6.6 mm and 3.2±1.0 mm in the BMS group, p<0.001).

The incidence of MACE at four years was similar between the two groups **(Table 4)**. Cumulative death rates at four years were 5.8% in the BMS group and 4.5% in the DES group (p=0.531). Cumulative rates of myocardial infarction at four years were 3.1% in the BMS group and 2.6% in the DES group (p=0.722). The cumulative TVR rates at four years were 7.9% in the BMS group and 9.7% in the DES group (p=0.461). The event-free rates at four years between the two groups were similar (86.1% in the BMS group and 87.1% in the DES group, p=0.741). There was no significant difference between the two groups even after adjusting for significant covariates **(Table 5)**. Diabetes mellitus was a significant predictor of death and TVR, while the presence of diffuse disease was a predictor of death and myocardial infarction.

Table 4. Major adverse cardiac events at four years.

MACE	BMS n=1,095	DES n=155	*p*-value
Death	64 (5.8%)	7 (4.5%)	0.531
MI	34 (3.1%)	4 (2.6%)	0.722
TVR	87 (7.9%)	15 (9.7%)	0.461
Stent thrombosis	9 (0.8%)	3 (1.9%)	0.183
Event-free rate (%)	86.1	87.1	0.741

BMS: bare metal stents; DES: drug-eluting stents; MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularisation

There was no difference in the ST rate at four years (0.8% in the BMS group and 1.9% in the DES group, p=0.183). On further analysis of this subgroup of patients, nine patients in the BMS group and three patients in the DES group developed ST. In the BMS group, five were classified as definite ST and four were classified as probable ST. In the DES group, all three patients had definite ST. For patients with definite ST, three in the BMS group were classified as early (0 to 30 days) and two as late (30 days to one year). In the DES group, two were classified as early and one as late. There were no cases of very late ST in this study **(Table 6)**.

Discussion

This is a retrospective, single-centre study comparing the strategy of the selective use of DES based on high-risk characteristics that increase the likelihood of developing in-stent restenosis versus BMS in patients undergoing elective PCI. Based on predefined criteria, we did not find a significant difference between DES and BMS in the rates of death, myocardial infarction, TVR, or ST during four years of follow-up. The event-free rates at four years were similar between the two groups.

Since their introduction, DES have substantially changed the practice of interventional cardiology. Various studies have consistently demonstrated a significant reduction in restenosis with the use of DES when compared with BMS[10]. Although DES are used in the majority of PCI cases, there is debate as to whether the devices are too often being used inappropriately[11]. In addition, it

Table 5. Multivariate analysis for the occurrence of major adverse cardiac events of death, myocardial infarction, target vessel revascularisation and stent thrombosis.

	Death		MI		TVR		ST	
	Adjusted OR [95% CI]	*p*-value	Adjusted OR [95% CI]	*p*-value	Adjusted OR [95% CI]	*p*-value	Adjusted OR [95% CI]	*p*-value
DES vs. BMS	0.588 (0.254-1.363)	0.216	0.537 (0.178-1.622)	0.27	1.211 (0.658-2.229)	0.539	1.752 (0.43-7.136)	0.434
Diabetes mellitus	2.088 (1.276-3.415)	0.003*	1.45 (0.751-2.8)	0.268	2.091 (1.379-3.17)	0.001*	1.036 (0.323-3.326)	0.952
Diffuse disease	2.476 (1.367-4.483)	0.003*	2.347 (1.075-5.123)	0.032*	1.286 (0.747-2.215)	0.364	2.065 (0.502-8.501)	0.315
Ostial lesion	1.768 (0.603-5.184)	0.299	0.731 (0.097-5.537)	0.762	0.494 (0.117-2.094)	0.339	–	–
Bifurcation lesion	0.925 (0.477-1.791)	0.817	0.827 (0.333-2.054)	0.683	0.862 (0.479-1.55)	0.619	0.33 (0.042-2.615)	0.294
Stent diameter <3 mm	1.152 (0.658-2.018)	0.621	1.972 (0.983-3.956)	0.056	0.784 (0.472-1.303)	0.349	2.901 (0.875-9.623)	0.082
AHA type C lesion	0.835 (0.437-1.595)	0.585	1.111 (0.49-2.517)	0.801	1.115 (0.642-1.936)	0.699	0.552 (0.114-2.679)	0.461
Left main and LAD lesion	1.158 (0.7-1.915)	0.568	1.077 (0.55-2.109)	0.829	1.006 (0.656-1.541)	0.979	1.521 (0.468-4.945)	0.486

*Statistically significant. AHA: American Heart Association; BMS: bare metal stents; DES: drug-eluting stents; LAD: left anterior descending artery; MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularisation

Table 6. Stent thrombosis rates at four years.

Stent thrombosis	BMS – 9 out of 1,095 patients	DES – 3 out of 155 patients
Definite	5	3
Early	3	2
Late	2	1
Probable	4	0

BMS: bare metal stents; DES: drug-eluting stents

has been demonstrated that unrestricted use of DES is less cost-effective and unlikely to reflect effective utilisation of available healthcare resources[9,12]. Hence, the use of DES could be restricted to patients in certain high-risk groups.

In the Ontario registry, the benefit of DES in reducing the need for TVR was limited to those patients with two or three risk factors for restenosis (presence of diabetes mellitus, vessel diameter of <3 mm, and lesions of ≥20 mm in length), but not among low-risk patients[4]. Similarly, in the Swedish Coronary Angiography and Angioplasty Registry, the benefit of DES compared with BMS was most apparent when any one of these high-risk features was present[5]. In our institution, it was a routine clinical practice to risk-stratify patients into the likelihood of developing restenosis following PCI. Any patient fulfilling two or more of the predefined risk factors was considered for a DES. In our study, the patients in the two groups were well matched in their baseline demographics, except for a higher prevalence of diabetes mellitus in the DES group, reflecting our predefined clinical criteria. Patients who received DES also had a higher prevalence of diffuse lesions and American Heart Association type C lesions. The DES implanted were significantly narrower in diameter and longer in length than the BMS, which suggests that the DES were being placed in more diffuse lesions in smaller calibre vessels. This reflects the criteria of reserving DES for complex coronary lesions. The BASKET-PROVE study found no significant difference among patients requiring stenting of large coronary arteries in the DES and BMS groups regarding the rates of death or myocardial infarction at two years[13]. Similar findings were observed in the Norwegian Coronary Stent Trial at six-year follow-up, comparing contemporary DES with BMS[3]. In our study, a strategy of the selective use of DES reserved for high-risk patients for restenosis based on predefined criteria conferred the same favourable long-term clinical outcomes as BMS for low-risk patients. Thus, an identification of established predictors of restenosis is important during PCI and should guide the choice of stent selection. Interestingly, our data did not suggest a higher incidence of TVR in the BMS group, nor were there higher rates of ST in the DES group as observed in some analyses[14-17].

Our study suggests that a DES is not required for all patients undergoing elective PCI. In fact, BMS should continue to have a place in this era of PCI, with reasonable safety and efficacy. This is one of the few studies to address the use of DES compared with BMS in South-East Asia, with long-term clinical outcomes. This may be especially important in the Asian context, in which selective utilisation of stents based on predefined criteria may prove to be safe, efficacious, and lead to significant cost savings.

Study limitations

This is a retrospective study with inherent limitations. The sample size for this retrospective study was not adequately powered. This is one of the major limitations of the study. Our findings are based on a single-centre experience and may not be applicable to other institutions with different study populations. The study population consisted of only stable patients who underwent elective PCI. The study compared BMS with the first-generation DES, and not the current generation of stents, which may have influenced the outcome. Stent designs have been refined, resulting in a significant improvement in clinical outcomes. We did not perform an analysis of cost-effectiveness comparing DES versus BMS. As it was a non-randomised study, there may still have been unmeasured confounding factors that contributed to our findings. It was not possible to ascertain retrospectively the compliance and duration of dual antiplatelet therapy in each individual patient.

Conclusions

In the setting of elective PCI, our strategy of the selective use of DES reserved only for patients at high risk of restenosis based on

predefined criteria confers the same favourable long-term clinical outcomes as BMS for low-risk patients. Such a strategy may prove to be cost-effective in most healthcare systems.

Impact on daily practice

DES are effective in reducing restenosis when compared to BMS. Limited data are available on long-term outcomes following selective implantation of DES in patients at high risk of restenosis versus BMS in low-risk patients. In this retrospective study, the selective use of DES reserved only for patients at high risk of restenosis based on predefined criteria conferred the same favourable long-term clinical outcomes as BMS for low-risk patients. This strategy may lead to significant cost savings and provide a platform for evaluation of the current generation of DES against BMS.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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