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Safety and effectiveness of drug-eluting stents in Chinese patients with coronary artery disease with off- and on-label indications: results from a single-centre registry

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ABSTRACT

Background Off-label use of drug-eluting stents (DES) is more common than on-label use and may be associated with a persistently higher rate of adverse angiographic and clinical outcomes.

Objective To evaluate the safety and effectiveness of unrestricted use of DES in everyday practice in a Chinese population.

Methods Between January 2004 and May 2009, we retrospectively enrolled 1209 consecutive patients who received DES in our single centre. 84.7% of patients were treated with sirolimus-eluting stents (SES) and 15.3% of patients were treated with paclitaxel-eluting stents (PES).

Results 59.0% of patients (n=713) were treated for off-label indications, with a significantly higher proportion of patients with previous coronary artery bypass grafting (CABG) (6.2% vs 0.6%, $p<0.001$). There were no differences in coronary risk factors. During 6–66 months' follow-up, the rate of repeat target vessel revascularisation (TVR) was significantly higher in the off-label group (14.6% vs 9.7%, $p=0.011$). The risk of death and myocardial infarction were not statistically different with off-label from standard use. Multivariate logistic regression showed that the independent predictors of TVR were stent type (SES vs PES, HR=0.567, 95% CI 0.395 to 0.813), previous CABG (HR=2.393, 95% CI 1.440 to 3.977), the treatment of chronic total occlusion (HR=2.786, 95% CI 1.731 to 4.484) and the treatment of left main lesion (HR=1.854, 95% CI 1.022 to 3.363).

Conclusions In our local unselected cohort of Chinese people, off-label use of DES was safe in comparison with on-label use and associated with an excellent procedural success rate, but higher TVR.

INTRODUCTION

Since the first drug-eluting stent (DES) was approved by the Food and Drug Administration (FDA) for use in the USA in 2003,¹ it has become the most commonly used stent type in percutaneous coronary intervention (PCI). However, many uses of DES are not restricted to FDA-labelled recommendations (ie, off-label indications)—for example, they are used in bifurcation lesions, coronary artery bypass grafts, chronic total occlusions and long lesions requiring multiple overlapping stents. Observational studies have suggested an increased risk of complications after DES use in PCI of off-label lesions compared with indicated lesions.^{2–5} During the European Society of

Cardiology meeting in September 2006, follow-up of the RAVEL and BASKET-LATE trials documented an increased risk of very late stent thrombosis with DES in comparison with bare-metal stent usage. Since then, DES efficacy and safety has become a hot topic, for patients and the media, and also for cardiologists and the FDA.

The number of PCIs performed in China has increased dramatically over the years. Published data from the Ministry of Health shows that 332 992 PCI procedures were performed in 2011, with 91.4% patients treated with DES. Complications occurred in only 0.7% of the cases and death in 0.3%. Nowadays, physicians are inclined to use the 'best' available device for the individual patient even though it may not be evidence-based. DES use is at the discretion of the treating cardiologist and off-label use has become common practice. To date, the safety and effectiveness of using DES off-label have not been systematically evaluated within China. This study was undertaken to examine these topics in a retrospective, single-centre registry.

METHODS

Consecutive patients undergoing PCI in our centre from January 2004 to May 2009 were included in this analysis. Data on baseline demographic, clinical and angiographic characteristics and procedural characteristics during the index PCI, as well as the occurrence of death, myocardial infarction (MI) and the need for coronary-artery bypass grafting (CABG) during hospitalisation, were collected. DES use was considered 'off-label' if any of the following characteristics were present: restenotic lesion, bypass lesion (vein or arterial conduit), left main lesion, ostial lesion, bifurcation, or chronic total occlusion of more than 3 months, reference vessel diameter <2.5 or >3.75 mm and lesion length >30 mm. Patients who had multivessel PCI or those in whom PCI was performed for acute MI were not considered off-label.^{3–9}

The prespecified primary end point was a major adverse cardiac event (MACE), defined as a composite of all-cause death, non-fatal MI or target vessel revascularisation (TVR). MI was defined as the occurrence of two or more of the following: chest pain for >20 min, abnormal electrocardiographic changes (ST elevation of ≥ 1 mm in two contiguous leads or ST depression of >-2 mm or new left bundle branch block), or increased cardiac biomarkers (creatinine kinase >3 times the upper

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limits of the reference level or troponin T >0.1 ng/mL). TVR was defined as repeat percutaneous or surgical revascularisation of the treated vessel, prompted by recurrence of angina symptoms or other evidence of ischaemia. Clinical follow-up was performed at 6, 12, 24, 36, 48 and 60 months by telephone or office visit.

Statistical analysis was performed using SPSS V.16.0 (SPSS, Chicago, Illinois, USA). Categorical variables are expressed as number (%) and continuous variables as mean±SD with $p<0.05$ considered statistically significant. The χ^2 test was used for comparison of categorical variables and the Student *t* test for comparison of continuous variables between groups. The follow-up cumulative incidence rates of adverse events were estimated according to the Kaplan–Meier method and curves were compared using the log-rank statistic. Separate Cox regression analyses were performed to identify predictors of adverse events, using the clinical, angiographic and procedural variables listed in tables 1 and 2.

RESULTS

Between January 2004 and May 2009, 1209 consecutive patients were retrospectively enrolled in our single centre. The percentage of patients treated with sirolimus-eluting stents (SES) was 84.7% and with paclitaxel-eluting stents (PES), 15.3%. Based on our off-label use definitions, 713 (58.9%) had at least one off-label criterion.

Patients' baseline characteristics are presented in table 1. Those who received stents for off-label indications had a greater likelihood of previous CABG (6.2% vs 0.6%, $p<0.001$) than those receiving stents for on-label indications. There were no differences in cardiac risk factors.

Lesion characteristics are presented in table 1. Off-label DES use was common in lesions whose length was >30 mm (71.7%), bifurcation lesions (26.8%) and ostial lesions (9.4%). There were no significant differences in type of stent ($p=0.055$) and multivessel PCI (45.9% vs 41.3%, $p=0.128$). Although at lesion level, angiographic success was lower for off-label

Table 1 Baseline clinical and angiographic characteristics

	On-label (n=496)	Off-label (n=713)	p Value
Age (years), mean±SD	65.32±10.41	66.0±9.93	0.252
Sex (male)	341 (68.8)	478 (67.0)	0.532
Risk factors			
Diabetes	136 (27.4)	193 (27.1)	0.904
Hypertension	317 (63.9)	474 (66.5)	0.338
Hyperlipidaemia	141 (28.4)	177 (24.8)	0.166
Current smoking	83 (16.7)	118 (16.5)	0.941
History			
Stroke	26 (5.2)	37 (5.2)	0.968
Previous MI	114 (23.0)	177 (24.8)	0.461
Previous PCI	65 (13.1)	117 (16.4)	0.114
Previous CABG	3 (0.6)	44 (6.2)	<0.001
LVEF, mean±SD	41.97±23.69	42.92±23.47	0.657
Target vessel			
LAD	249 (50.2)	356 (49.9)	
LCX	120 (24.2)	111 (15.6)	
RCA	127 (25.6)	178 (25.0)	
LM	0 (0)	45 (6.3)	
SVG	0 (0)	23 (3.2)	
Type of stent			0.055
SES	431 (86.9)	592 (83.0)	
PES	65 (13.1)	121 (17.0)	
Stent length (mm), mean±SD	22.05±5.40	39.77±17.47	<0.001
Multivessel PCI	205 (41.3)	327 (45.9)	0.128
Off-label indications			
Lesion length >30 mm		551 (77.3)	
Bifurcation		191 (26.8)	
Ostial lesion		67 (9.4)	
Total occlusion		67 (9.4)	
Lesion in LM		45 (6.3)	
Reference-vessel diameter			
<2.5 mm		15 (2.1)	
>3.75 mm		59 (8.3)	
Restenotic lesion		32 (4.5)	
Graft lesion		23 (3.2)	
Angiographic success	493 (99.4)	702 (98.5)	0.712

Results are shown as number (%) unless stated otherwise.

CABG, coronary-artery bypass grafting; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main stem; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; RCA, right coronary artery; SES, sirolimus-eluting stent; SVG, saphenous vein graft.

Table 2 Major adverse cardiac events at follow-up

	On-label (n=496)	Off-label (n=713)	Adjusted HR (95% CI)	p Value
6 Months—death	5 (1.01)	4 (0.56)	0.554 (0.148 to 2.074)	0.374
MI	3 (0.6)	3 (0.42)	0.694 (0.140 to 3.454)	0.654
TVR	7 (1.41)	11 (1.54)	1.095 (0.421 to 2.844)	0.853
MACE	15 (3.02)	18 (2.52)	0.645 (0.322 to 1.291)	0.212
12 Months—death	8 (1.61)	7 (0.98)	0.605 (0.218 to 1.679)	0.329
MI	10 (2.02)	8 (1.12)	0.551 (0.216 to 1.407)	0.207
TVR	15 (3.02)	50 (7.01)	1.858 (1.032 to 3.344)	0.036
MACE	33 (6.65)	65 (9.12)	1.407 (0.910 to 2.176)	0.123
24 Months—death	10 (2.02)	16 (2.24)	1.116 (0.502 to 2.479)	0.788
MI	13 (2.62)	13 (1.82)	0.690 (0.317 to 1.501)	0.347
TVR	26 (5.24)	71 (9.96)	1.999 (1.256 to 3.182)	0.003
MACE	49 (9.88)	100 (14.03)	1.488 (1.035 to 2.139)	0.031
36 Months—death	15 (3.02)	28 (3.93)	1.311 (0.693 to 2.481)	0.404
MI	15 (3.02)	26 (3.65)	1.214 (0.636 to 2.316)	0.556
TVR	35 (7.06)	88 (12.34)	1.855 (1.231 to 2.794)	0.003
MACE	65 (13.1)	142 (19.92)	1.649 (1.199 to 2.269)	0.002
48 Months—death	21 (4.23)	35 (4.91)	1.168 (0.671 to 2.031)	0.583
MI	18 (3.63)	30 (4.21)	1.166 (0.643 to 2.117)	0.612
TVR	44 (8.87)	100 (14.03)	1.583 (1.088 to 2.305)	0.016
MACE	83 (16.73)	165 (23.14)	1.498 (1.118 to 2.008)	0.007
60 Months—death	23 (4.64)	36 (5.05)	1.094 (0.640 to 1.869)	0.744
MI	20 (4.03)	31 (4.35)	1.082 (0.609 to 1.921)	0.788
TVR	48 (9.68)	104 (14.59)	1.594 (1.109 to 2.292)	0.011
MACE	91 (18.35)	171 (23.98)	1.404 (1.056 to 1.867)	0.019

Results are shown as number (%).

MACE, major adverse clinical events; MI, myocardial infarction; TVR, target vessel revascularisation.

(98.5%) use compared with on-label (99.4%), the difference was not statistically significant.

Outcomes at follow-up

Median durations of follow-up were 36 months (range 1–66 months). At the 6-month follow-up, those receiving DES for off-label indications had a lower death rate (0.56% vs 1.01%, $p=0.374$) and MI (0.42% vs 0.6%, $p=0.654$) than patients with on-label indications, but the difference was not statistically significant. There remained no significant difference in death and MI between the groups for 1-year follow-up (table 2). However, a statistically significant early increased risk of TVR was found for off-label use at 1-year follow-up compared with on-label use (7.01% vs 3.02%, $p=0.036$) and it remained so up to the 5-year of follow-up. At the 5th year of follow-up, the incidence of TVR was much higher in the off-label group (14.59% vs 9.68%, $p=0.011$), whereas the incidence of MI (4.35% vs 4.03%, $p=0.788$) and death (5.05% vs 4.64%, $p=0.744$) were similar in off-label and on-label treated patients. As a result of the reductions in repeat intervention for on-label DES use, the composite end point of MACE was significantly less in that group than with off-label use (18.35% vs 23.98%, $p=0.019$) (Figure 1).

The independent predictors of death were age >70 years (HR=4.264, 95% CI 2.540 to 7.160), presence of thrombus (HR=4.716, 95% CI 2.544 to 8.740), previous PCI (HR=2.205, 95% CI 1.235 to 3.934) and ostial lesion treatment (HR=2.416, 95% CI 1.161 to 5.217). The independent predictors of TVR were stent type (SES vs PES, HR=0.567, 95% CI 0.395 to 0.813), previous CABG (HR=2.393, 95% CI 1.440 to 3.977), the treatment of chronic total occlusion (HR=2.786, 95% CI 1.731 to 4.484) and the treatment of left main lesion (HR=1.854, 95% CI 1.022 to 3.363). The independent predictors of MI were age

>70 years (HR=2.167, 95% CI 1.290 to 3.639), hyperlipidaemia (HR=2.188, 95% CI 1.301 to 3.680), previous MI (HR=1.843, 95% CI 1.083 to 3.173) (table 3). After adjustment for lesion classification, baseline clinical and angiographic differences, *there was no significant detrimental impact on MI, death/MI, or TVR during the follow-up with on-label or off-label use of DES.*

Use of clopidogrel and aspirin was more than 85% in both groups at 12 months (table 4). Similarly, at 12 months almost 80% of the study patients were receiving a statin, but the percentages receiving an ACE inhibitor (70%) or a β blocker (60%) were lower.

DISCUSSION

In this report, we presented long-term clinical outcomes after the use of DES in an all-comers registry. DES in this population was found to be safe with no increase in all-cause death and non-fatal MI in our off-label indication cohort compared with the on-label group. The high rate of MACE seen in the off-label group was due to a significant difference in TVR at a medium of 3 years of follow-up, which reflected the complex nature of the 'off-label' population.

Our study confirms the findings reported by Beohar *et al*⁸ and Win *et al*⁵—that off-label use of DES is common. In our study, 59% of patients had their stent usage classified as off-label. In the study by Beohar *et al*, 47% of patients received a DES for either an off-label or an untested indication and in the study by Win *et al*, 55% of patients had at least one off-label characteristic. Furthermore, the 1-year TVR rates in the off-label group (7.01%) in our study are similar to those reported by Beohar *et al* (7.6%) and Win *et al* (6.3%).

Evidence from randomised trials and registries exists showing the benefit of DES in many off-label indications, which supports

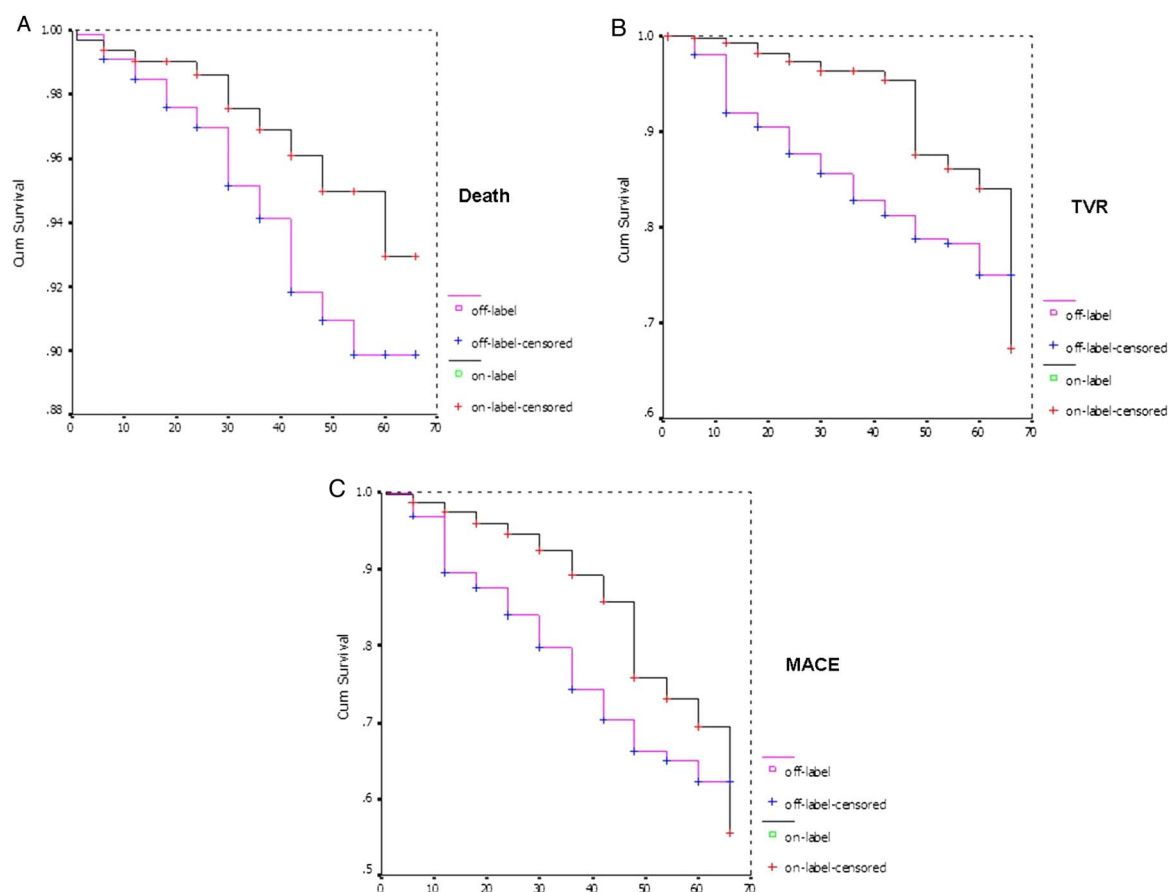


Figure 1 Kaplan–Meier curves for outcome according to label indication. MACE, major adverse cardiac events.

the findings of this study. Our data indicate that PCI of off-label lesions is not associated with worse late outcomes for death and MI compared with PCI of on-label lesions. Although off-label

use involved more complex anatomy, including multi-lesion stenting, a high degree of angiographic success occurred in patients receiving DES for off-label (98.5%) and on-label (99.4%) indications. This indicates widespread proficiency and stent performance in treating a variety of lesions and clinical subtypes. Since the patient population of this study was gathered between 2006 and 2009, improvements in stent design and technical refinement in performing PCI might also have contributed to the results. Another possible explanation for our findings may relate to the augmentation of ancillary medical treatment—almost 85% of the study patients were compliant with at least 1 year dual antiplatelet therapy (DAPT). The impact of prolonged DAPT is an important consideration for the safety of DES. Previous data have indicated that premature discontinuation of antiplatelet therapy after use of DES contributes to stent thrombosis.¹⁰ Moreover, prolonged DAPT with aspirin and clopidogrel has been associated with a reduced risk of death or MI after use of DES.¹¹

Table 3 Independent clinical predictors of clinical outcomes

Predictors	HR	95% CI	p Value
Death			
Age >70	4.264	2.540 to 7.160	<0.001
Previous PCI	2.205	1.235 to 3.934	0.007
Thrombotic lesion	4.716	2.544 to 8.740	<0.001
Ostial lesion	2.416	1.161 to 5.217	0.019
TVR			
Stent type (SES vs PES)	0.567	0.395 to 0.813	0.002
Previous CABG	2.393	1.440 to 3.977	0.001
Chronic total occlusion	2.786	1.731 to 4.484	<0.001
Left main lesion	1.854	1.022 to 3.363	0.042
MI			
Age >70	2.167	1.290 to 3.639	0.003
Hyperlipidaemia	2.188	1.301 to 3.680	0.003
Previous MI	1.843	1.083 to 3.173	0.024
MACE			
Age >70	1.646	1.272 to 2.127	<0.001
Previous CABG	1.989	1.297 to 3.049	0.002
Chronic total occlusion	2.265	1.491 to 3.440	<0.001
Hyperlipidaemia	1.383	1.062 to 1.802	0.016
Left main lesion	1.738	1.044 to 2.895	0.034

CABG, coronary-artery bypass grafting; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; TVR, target vessel revascularisation.

Table 4 Medication at 1-year follow-up

	On-label (n=496)	Off-label use (n=713)	p Value
Aspirin	442 (89.1)	634 (88.9)	0.916
Clopidogrel	424 (85.5)	607 (85.1)	0.866
Statin	416 (83.9)	585 (82.0)	0.409
β Blocker	300 (60.5)	415 (58.2)	0.428
ACE inhibitor	353 (71.2)	493 (69.1)	0.450

Results are shown as number (%).

Significantly more MACE occurred in the off-label group than in the on-label group. This finding was expected since off-label indications usually represent more complex lesions and are probably associated with more severe degree of coronary atherosclerosis and with higher cardiovascular risks. Our study shows that the overall poorer outcome with off-label than with on-label use is related to TVR during long-term follow-up. In addition, we found that the increased hazard of TVR is associated with PES usage, but not with SES. Recent large trials of first-generation SES and PES such as REALITY,¹² SORT OUT II,¹³ SIRTAX LATE¹⁴ and PROSIT¹⁵ failed to show a significant difference in target lesion revascularisation (TLR)/TVR during long-term follow-up. Kufner *et al*¹⁶ reported a meta-analysis in diabetic patients, based on six randomised trials including 1183 patients. They found that SES were associated with a significant reduction in the risk of TLR (HR=0.65 (0.47–0.91), *p*=0.01). For our study, this difference in outcome between PES and SES could be related to the differences in drug release kinetics, differential recovery of the cell cycle of quiescent smooth muscle cells and differences in vascular healing in response to the two different drugs or polymers used in the respective stent designs.^{17–20}

Our study has some limitations. First, it is based on an observational registry and is a single-centre retrospective study; such a study design has inherent limitations. Second, the number of patients who received PES in our study was relatively small, compared with those receiving SES. Hence, while the observed difference in the results between the two stent choices might be real, we cannot exclude the possibility that this finding occurred by chance alone, or is due to selection bias for a particular DES as stent choice was not randomised. Lastly, we used all-cause mortality rather than cardiac mortality as an end point. Perhaps the latter might be a more relevant measurement of differences between the two groups of study subjects.

CONCLUSIONS

The main findings of our study were that DES were associated with an excellent procedural success rate and were safe and efficacious in a large cohort of relatively non-selected Chinese patients with coronary artery disease. In addition, there was no significant difference in outcome between the on-label group and the off-label group.

Contributors X-MH: conception and design, drafting the article. W-ZH: analysis and interpretation of data. X-BQ and HC: acquisition of data. W-YF: final approval of the version published.

Competing interests None.

Patient consent Obtained.

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