Journal of Cardiology 62 (2013) 151–157

Contents lists available at SciVerse ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Long-term outcomes following off-label use of sirolimus-eluting stent

Jun-ichi Kotani (MD, PhD)[a,*,1], Yuji Ikari (MD, FJCC)[b,1], Eishou Kyo (MD)[c,1], Masato Nakamura (MD, FJCC)[d,1], Hiroyoshi Yokoi (MD)[e,1]

[a] Cardiovascular Division, National Cerebral and Cardiovascular Center, Suita, Japan
[b] Tokai University, Isehara, Japan
[c] Kusatsu Heart Center, Kusatsu, Japan
[d] Toho University Ohashi Medical Center, Tokyo, Japan
[e] Kokura Memorial Hospital, Kitakyusyu, Japan

ARTICLE INFO

Article history:
Received 12 December 2012
Received in revised form 7 March 2013
Accepted 27 March 2013
Available online 14 May 2013

Keywords:
Follow-up studies
Stents
Coronary disease

ABSTRACT

Objective: To clarify the impact of off-label use of drug-eluting stent (DES) on 5-year outcomes.
Background: Studies on the outcomes of on- vs off-label use of DES have been limited by the duration of observation.
Methods: We analyzed 1937 patients from a multicenter registry that includes 95% of patients with 5-year follow-up data. We defined 10 variables as off-label indications according to the manufacturer's instructions for use, and 1665 of 1937 patients (86.0%) met the criteria for at least 1 off-label indication.
Results: At 5 years, there were no differences in the rates of death, myocardial infarction (MI), and stent thrombosis between off-label and on-label use. The frequency of major adverse cardiac events (MACE), target lesion revascularization (TLR), non-TL but target vessel revascularization (TVR), and target vessel failure were higher in the off-label only during the first year. Among the off-label, having 2 indications was associated with TVR hazard ratio (HR) 1.62; 95% confidence interval (95%CI), 1.09–2.36 and TLR (HR, 1.90; 95%CI, 1.30–2.85). Moreover, having ≥3 off-label indications increased the risk of MACE (HR, 1.70; 95%CI, 1.23–2.40) compared with on-label use. Thrombosis rates increased with the number of off-label indications; it was 0.32% with 1, 0.69% with 2, and 3.54% with ≥3 off-label indications ($p < 0.001$). This trend was also seen with other outcomes, except for non-TL TVR. Patients with ≥3 off-label indications had a remarkably different clinical course.
Conclusion: Off-label use did not increase rates of death and MI as compared with on-label use, but the number of off-label indications influenced outcomes at 5 years.

Introduction

The long-term safety and efficacy of drug-eluting stents (DES) remain important topics under debate, especially with the increased incidence of late and very late stent thromboses directly associated with life-threatening clinical outcomes such as death and myocardial infarction (MI) [1–4]. On the other hand, discrepancies in results from pivotal clinical trials and large-scale registries also affected the direction for clinicians in practice [4–7]. Such differences might be attributable to differences in patient selection. Early clinical trials included only patients who met inclusion criteria approved by the US Food and Drug Administration (FDA), i.e. on-label indications. However, in actual clinical practice DES are routinely used for off-label indications. Off-label DES use, which the FDA has cautioned against, can be associated with an excessive late risk of death and MI [8]. However, studies investigating outcomes based on on- vs off-label indications in the real world have been of short duration.

Given this context, the purpose of this study is to clarify (1) the impact of off-label use on long-term clinical outcomes compared with on-label (standard) use and (2) the impact of individual off-label parameters and the number of off-label indications on the outcome after sirolimus-eluting stent (SES) implantation during the 5 years of observation.

Methods

Population and data collection

This analysis used data from the Cypher™ stent Japan Post-Marketing Surveillance (J-PMS) database. J-PMS is a registry for prospective post-marketing surveillance lasting 5 years following

* Corresponding author at: 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.
E-mail address: Shamallv8@aol.com (J. Kotani).
[1] On behalf of the J-PMS investigators.

0914-5087/$ – see front matter © 2013 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2013.03.007

the index procedure. It was mandated by the Japanese government as one of the conditions for regulatory approval. The details of this program have been described previously [9,10]. Briefly, the registry enrolled the consecutive 2050 cases of SES implantation from September 2004 through September 2005 at 50 institutions across Japan. The decision to perform stent implantation was left to the discretion of each cardiologist participating in the registry. Angiographic follow-up is mandated at 8 months, and clinical follow-up was scheduled annually up to 5 years. Angiographic data on 1063 of 2459 lesions were analyzed by an independent core laboratory (Cardiocore, Tokyo, Japan) and the remaining angiograms were analyzed by on-site quantitative coronary angiography (QCA). The institutional review board at each participating center approved the study.

Definition of off-label

The manufacturer's directions for use of the Cypher™ stent (Cordis, Miami, FL, USA) state that it is indicated for "improving the coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions of length ≤30 mm in native coronary arteries with a reference vessel diameter of ≥2.5 and ≤3.5 mm" [11]. The following 10 conditions were defined as off-label indications by DES manufacturer's instructions for use: acute myocardial infarction (acute MI), bifurcation lesions (type B/C of the American College of Cardiology/American Heart Association classification), ostial disease (<5 mm from orifice), left main coronary artery, reference diameter less than 2.5 mm, reference diameter greater than 3.5 mm, lesions greater than 30 mm in length, restenotic lesions including in-stent restenosis, bypass graft, and chronic total occlusion.

Outcome parameters

An independent safety and efficacy evaluation committee adjudicated all reported and suspected major adverse cardiac events (MACE) defined as death, MI, and target lesion revascularization (TLR) by percutaneous coronary intervention (PCI) or coronary-arterial bypass grafting (CABG). Deaths were classified as cardiac or non-cardiac, and death of any unidentified cause or in which a cardiac cause could not be excluded was classified as cardiac in this study. MI was classified as Q wave or non-Q wave, and was defined as a rise in creatine kinase enzyme concentrations above twice the upper limit normal. Re-interventions inside the implanted stent or within 5 mm proximal or distal to the stent were classified as TLR. The definition of TLR had been registered according to the SIRIUS criteria. That is, TLR is defined as any "clinically-driven" repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel. Clinically-driven revascularizations are those in which the patient has a positive functional study, ischemic electrocardiographic (ECG) changes at rest in a distribution consistent with the target vessel, or ischemic symptoms, and an in-lesion diameter stenosis ≥50% by QCA. Revascularization of a target lesion with an in-lesion diameter stenosis ≥70% (by QCA) in the absence of the above-mentioned ischemic signs or symptoms is also considered clinically driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization is adjudicated using the presence or absence of ischemic signs and symptoms. Repeated PCI to the same vessel with the exception of TLR was counted as non-TL target vessel revascularization (TVR). Target vessel failure (TVF) was defined as all target vessel-related events, which included cardiac death, MI, thrombosis, and TVR. Definite and probable stent thromboses according to the Academic Research Consortium (ARC) classification were considered stent thrombosis [12].

Statistical analysis

Continuous variables are expressed as means ± standard deviation and categorical data are presented as frequencies. For comparisons between groups, Fisher's exact test or an ANOVA test was used as appropriate. Time-to-event data are presented as Kaplan–Meier estimates. Both TLR and MACE rates during the follow-up period were analyzed by the Kaplan–Meier method. A log-rank test was used for survival comparisons. Multivariable Cox proportional hazards regression model was used by stepwise selection process ($p < 0.1$). Variables for 5-year outcomes were selected from patient background and lesion characteristics; age ≧ 75 years old, male, body mass index ≥ 25, previous MI, previous PCI, previous CABG, hypertension, dyslipidemia, dialysis, peripheral vascular disease, cardiovascular disease, family history of coronary artery disease, diabetes, current smoking, and multi-vessel disease. And acute MI, bifurcation, ostial, left main trunk, reference vessel diameter < 2.5 mm, reference vessel diameter > 3.5 mm, length > 30 mm, restenosis, bypass graft, and total occlusion were used for predicting risk factors for TVF. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed with the use of SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patient and lesion characteristics

Initially, the registry planned to enroll 2053 patients, but 3 patients with off-label use were not included due to stent delivery failure. There were 1937 patients with complete 5-year follow-up data available, of whom 272 had on-label indications (standard use). The remaining 1665 patients (86.0%) met the criteria for at least 1 off-label indication. Patients with off-label indications were more likely to have had a previous MI, previous PCI, multi-vessel disease, and a lower body mass index (Table 1). Lesion characteristics are listed in Table 2. Because label indications were mainly

Table 1
Baseline patient characteristics.

	Off-label (n = 1665)	On-label (n = 272)	P value
Mean age, years	67.1 ± 9.9	67.9 ± 9.6	0.32
Age ≥ 75 years	407 (24.4)	64 (23.5)	0.82
Male sex	1254 (75.3)	210 (77.2)	0.54
LVEF < 30%	55 (3.9)	6 (2.6)	0.45
BMI, kg/m^2	24.0 ± 3.3	24.3 ± 3.1	0.043
Acute MI	84 (5.1)	0 (0.0)	–
Recent/old MI	274 (16.5)	33 (12.4)	0.07
Stable/silent ischemia	1092 (65.6)	181 (66.5)	0.78
Unstable angina	206 (12.4)	57 (21.0)	<0.001
Other	9 (0.5)	1 (0.5)	1.00
Previous MI	664 (39.9)	81 (29.8)	0.002
Previous PCI	965 (58.0)	128 (47.1)	0.001
Previous CABG	141 (8.5)	18 (6.6)	0.34
Diabetes	733 (44.0)	109 (40.1)	0.24
Requiring insulin	177 (10.6)	21 (7.7)	0.16
Dialysis	91 (5.5)	9 (3.3)	0.18
Hypertension	1155 (69.4)	200 (73.5)	0.18
Dyslipidemia	944 (56.7)	160 (58.8)	0.55
Peripheral vascular disease	111 (6.7)	14 (5.1)	0.42
Cerebrovascular disease	131 (7.9)	17 (6.3)	0.39
Family history of CAD	113 (6.8)	18 (6.6)	0.92
Current smoker	311 (18.7)	54 (19.9)	0.68
Multi-vessel disease	702 (42.2)	95 (34.9)	0.028
DAPT administration at 5 year follow-up	593 (36.5)	85 (31.3)	0.10

LVEF, left ventricular ejection fraction; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual anti-platelet therapy.