Original article

The Japanese experience with sirolimus-eluting stent implantation in the infarct-related artery: Five years of observation from the J-PMS study

Taichi Adachi (MD) a,1, Jun-ichi Kotani (MD) a,1, Yuji Ikari (MD, FJCC) b,1, Eisho Kyo (MD) c,1, Masato Nakamura (MD, FJCC) d,1, Hiroyoshi Yokoi (MD) e,1

a National Cerebral and Cardiovascular Center, Suita, Japan
b Tokai University, Isehara, Japan
c Kasatsu Heart Center, Kasatsu, Japan
d Toho University Ohashi Medical Center, Tokyo, Japan
e Rokura Memorial Hospital, Kitakyusyu, Japan

A B S T R A C T

Background: Long-term outcome and safety concerns regarding drug-eluting stents (DES) for acute myocardial infarction (AMI) treatment is still debated.

Methods and results: We analyzed data from 1937 patients with complete 5-year follow-up (94.5%) from a multicenter registry of sirolimus-eluting stents (J-PMS). The patients were divided into 2 groups: AMI (n = 133) and non-AMI (n = 1804) by clinical presentation of index procedure, and compared the outcomes. At 5-year follow-up, there were no significant differences in major adverse cardiac events (MACE), death, MI, or stent thrombosis between the groups. However, target vessel related events (TVF; revascularization, cardiac death, MI, thrombosis) were higher in the non-AMI group (p = 0.03). In the early phase (0–6 months), MACE and death/MI were higher in the AMI group (6.0% vs. 3.0%; p = 0.02 and 6.8% vs. 2.1%; p < 0.001). However, in the late phase (6–60 months), there was a difference in TVF between the 2 groups, with a steady increase in the non-AMI group (p = 0.03). Over 60% of patients with AMIs were started on dual antiplatelet therapy after stent implantation or on the same day. However, dual anti-platelet therapy duration was similar (867 ± 18 days in the AMI and 727 ± 57 days in the non-AMI group, p = 0.5). Frequency of bleeding was similar.

Conclusion: Five-year observation of AMI treatment using drug-eluting stent compared with non-AMI has no clinical disadvantage.

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Introduction

Although most worldwide registry and meta-analysis data support the effectiveness of drug-eluting stent (DES) implantation for the treatment of acute myocardial infarction (AMI) [1–3], some conflicting results have been reported [4]. Pathological investigations claim that there are risks with DES for AMI during percutaneous coronary intervention (PCI) [5–7], but do not address the long-term safety of DES. In addition, the Japanese experience with AMI treatment using DES has not been well assessed [8]. Given this context, we investigated whether DES implantation for AMI should be discriminated from routine PCI using DES from 5 years of experience.

Methods

Patient selection

The Cypher™ Stent Japan Post-Marketing Surveillance Registry (J-PMS) is a post-marketing surveillance program mandated by the Japanese government as one of the conditions for regulatory approval. The study outline has been previously described [9,10]. Briefly, 2050 consecutive patients who underwent sirolimus-eluting stent (SES) implantation between September 2004 and September 2005 at 50 institutions representative of the clinical environment across Japan were enrolled. The indications for SES implantation were left to the discretion of each participating cardiologist. In this study, we analyzed 1937 patients with complete 5-year follow-up data (94.5% of the cohort). The patients analyzed were divided into 2 groups according to AMI status based on the clinical presentation during the index procedure. The AMI group (n = 133) included patients who received emergent acute infarct angioplasty (n = 84, 63.2%). The non-AMI group (n = 1804) included
272 (15.1%) patients with on-label lesions. AMI was defined according to the criteria of each participating institution. The method used to measure the left ventricle ejection fraction (LVEF) depended on each institution. Any method of the following was available for records: echocardiography, left ventriculography, and radioisotope imaging. In this study, we clarified the long-term clinical outcomes, including dual anti-platelet therapy (DAPT) duration after SES implantation, in the AMI and non-AMI groups. In addition, we included a specific analysis of long-term events associated with the infarct-related artery (IRA).

Data collection and outcomes

The post-marketing surveillance databases were developed by the Japanese branch of Johnson & Johnson (Warren, NJ, USA). Follow-up data were collected at 3, 8, and 12 months, and annually thereafter up to 5 years. An independent safety and efficacy evaluation committee adjudicated all reported and suspected events. The study was designed to focus on IRA failure, which corresponds to target vessel failure (TVF) in the non-AMI group. TVF was defined as cardiac death, recurrent MI, target vessel revascularization (TVR), and thrombosis associated with the IRA. Death was classified as all-cause or non-cardiac death. TVR was defined as a combination of target lesion revascularization (TLR) and revascularization remote from target lesion in the IRA territory (non-TL TVR). A major adverse cardiac event (MACE) was defined as a composite of all-cause death, MI, any TLR, and thrombosis. In this study, lesions meeting the Academic Research Consortium criteria for definite and probable stent thrombosis were considered stent thrombosis [11]. Bleeding definition was according to BARC (Bleeding Academic Research Consortium) definition: Type 2, 3, and 5 were included for this study [12].

Statistical analysis

Continuous variables are expressed as means ± standard deviation (SD) and categorical data are presented as frequencies. For comparisons between groups, the chi-square test, Fisher’s exact test, or the Wilcoxon rank-sum test was used as appropriate. Time-to-event data were analyzed by Kaplan–Meier estimates, and values are expressed as means ± standard error of the mean (SEM). Survival analysis was performed using a log-rank test or Cox proportional hazards regression modeling with a step-wise selection process. Landmark analysis was performed to assess events occurring in different time periods. The landmark point was set at 6 months from the index procedure to avoid life-threatening conditions inherent to AMI. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patient and lesion characteristics

Patient characteristics of the 2 groups are shown in Table 1. A higher proportion of patients in the AMI group had LVEF < 30% (p = 0.019) and multi-vessel disease (p = 0.02), but there was a higher proportion of patients with a history of MI or previous revascularization in the non-AMI group (p < 0.001). Hypertension (p = 0.04) and dyslipidemia (p = 0.008) were more frequently seen in the non-AMI group, but there was a higher percentage of current smokers in the AMI group (p < 0.001). Lesion characteristics are presented in Table 2. The number of de novo lesions and occluded vessels was higher in the AMI group (p < 0.001), but there were no significant differences in parameters

| Table 1 Patient characteristics. | AMI (n = 133) | Non-AMI (n = 1804) | P-Value
|---------------------------------|--------------|------------------|------
| Mean age, years                | 66.9 ± 11.7 (133) | 67.2 ± 9.7 (1804) | 0.86
| Age > 75 years                 | 40 (30.1) | 431 (23.9) | 0.12
| Male sex                       | 106 (78.7) | 1358 (75.3) | 0.30
| LVEF < 30%                     | 9 (8.1) | 52 (3.4) | 0.02
| BMI, kg/m²                     | 24.2 ± 3.8 (132) | 24.0 ± 3.2 (1799) | 0.97
| Previous MI                    | 25 (18.8) | 720 (39.9) | <0.001
| Previous PCI                   | 28 (21.1) | 1065 (59.0) | <0.001
| Previous CABG                  | 1 (0.8) | 158 (8.8) | <0.001
| Diabetes                       | 47 (35.3) | 795 (44.1) | 0.06
| Insulin treated diabetes       | 9 (6.8) | 189 (10.5) | 0.23
| Dialysis                       | 3 (2.3) | 97 (5.4) | 0.15
| Hypertension                   | 82 (61.7) | 1273 (70.6) | 0.04
| Dyslipidemia                   | 61 (45.9) | 1043 (57.8) | 0.01
| Peripheral vascular disease    | 6 (4.5) | 119 (6.6) | 0.46
| Cerebrovascular disease        | 10 (7.5) | 138 (7.6) | 0.95
| Family history of CAD          | 12 (9.0) | 119 (6.5) | 0.28
| Current smoker                 | 49 (36.8) | 316 (17.5) | <0.001
| Multi-vessel disease           | 68 (51.1) | 729 (40.4) | 0.02

AMI, acute myocardial infarction; 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. Values are means ± SD (n) or n (%) 

| Table 2 Lesion characteristics. | AMI (n = 133) | Non-AMI (n = 1804) | P-Value
|---------------------------------|--------------|------------------|------
| Number of lesions               | 147 | 2168 | 0.41
| Target vessel                   | 40 (27.2) | 666 (30.7) | 0.41
| RCA                             | 73 (49.7) | 943 (43.5) | 0.15
| LAD                             | 27 (18.4) | 476 (22.0) | 0.35
| LMT                             | 7 (4.8) | 83 (3.8) | 0.51
| ACC/AHA type B2/C               | 123 (86.8) | 1743 (80.6) | 0.08
| Prior PCI                       | 144 (98.0) | 1681 (77.5) | <0.001
| In-stent restenosis             | 2 (1.4) | 340 (15.7) | <0.001
| Concentric                      | 66 (46.8) | 959 (45.5) | 0.80
| Mod./sv. calcification          | 21 (14.3) | 375 (17.3) | 0.43
| Bifurcation                     | 57 (38.8) | 715 (33.0) | 0.15
| Ostial location                 | 22 (15.0) | 377 (17.4) | 0.50
| Total occlusion                 | 47 (32.0) | 207 (9.5) | <0.001

QCA data

| Lesion length, mm               | 17.4 ± 10.4 | 17.4 ± 10.2 | 0.85
| Ref. diameter, mm               | 2.53 ± 0.58 | 2.57 ± 0.60 | 0.94
| MLD                             | 0.49 ± 0.49 | 0.77 ± 0.48 | <0.001
| Post, mm                       | 2.29 ± 0.68 | 2.25 ± 0.66 | 0.42
| % DS                           | 80.7 ± 18.3 | 70.6 ± 16.6 | <0.001
| Post, %                        | 19.2 ± 13.2 | 19.0 ± 13.8 | 0.86

Procedural data

| Direct stenting                 | 37 (25.2) | 472 (21.8) | 0.35
| Rotablator usage                | 0 (0.0) | 91 (4.2) | 0.004
| IVUS usage                      | 107 (72.8) | 1582 (73.0) | 0.96
| Maximum pressure, atm           | 16.0 ± 3.7 (197) | 16.0 ± 3.5 (2899) | 0.67
| Stent diameter, mm              | 3.05 ± 0.36 (197) | 2.99 ± 0.36 (2900) | 0.03
| Total stent length, mm          | 29.5 ± 14.1 (147) | 28.7 ± 14.9 (2168) | 0.25
| Number of stents per patient    | 1.48 ± 0.74 (133) | 1.60 ± 0.82 (1804) | 0.10
| Number of stents per lesion     | 1.34 ± 0.59 (147) | 1.34 ± 0.60 (2168) | 0.97
| Post-dilatation                 | 75 (51.0) | 1002 (46.2) | 0.27

AMI, acute myocardial infarction; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; LMT, left main trunk; ACC/AHA, American College of Cardiology/American Heart Association; Mod./Sv., moderate or severe; QCA, quantitative coronary angiography; MLD, minimal luminal diameter; % DS, percent diameter stenosis; IVUS, intravascular ultrasound. Values are means ± SD n (%)
related to target vessel distribution, lesion complexity, frequency of type B2/C lesions, calcification, bifurcation, and ostial location between the 2 groups. Pre-procedural quantitative coronary angiography parameters of the AMI group revealed a smaller minimal lumen diameter and more severe stenosis (p < 0.001), but reference vessel diameter and lesion length were similar in the 2 groups.

Five-year clinical outcomes

Clinical outcomes at 5 years are listed in Table 3. At the 5-year follow-up, there were no statistically significant differences in MACE, death, MI, and frequency of stent thrombosis between the AMI and non-AMI groups. Only one patient in the AMI group presented with a very late stent thrombosis (0.8%). The accumulated number of TVF was significantly higher in the non-AMI group (p = 0.032). To assess the impact of DES on local conditions, i.e. vulnerable plaque, necrotic core, and thrombus, we compared patients who received emergent intervention for AMI to patients with on-label lesions in the non-AMI group as a sub-analysis. However, there were no remarkable differences in the 5-year clinical results between these lesion subsets (Fig. 1).

Event accumulation and landmark analysis at 6 months

Event frequency curves for MACE, death/MI, TLR, and TVF are shown in Fig. 2. In the early phase (0–6 months), the frequency of MACE and all-cause death/MI was higher in the AMI group (6.0% vs. 3.0%; p = 0.02 and 6.8% vs. 2.1%; p < 0.001). However, in the late phase (6–60 months) difference was observed only in the TVF event rate between the 2 groups; the number of events associated with the target vessel in the non-AMI group steadily increased as compared to the IRA of AMI group (p = 0.03). There was no difference in the frequency of angiography during the late phase between the two groups (83.4% [11/13] in AMI and 87.2% [15/18] in non-AMI, p = 0.229).

DAPT and bleeding

Details on the introduction and continuation of DAPT during the 5 years of the study are shown in Fig. 3. In this study, over 60% of patients with AMIs were started on DAPT after stent implantation or on the same day. Conversely, over 60% of the non-AMI group started DAPT at least 3 days before DES implantation (p < 0.001). However, there were no differences in rates of DAPT continuation, based on the frequency of drop-out ratio, throughout the 5-year period. Mean DAPT duration between the 2 groups was similar (867 ± 18 days in the AMI group and 727 ± 57 days in the non-AMI group, p = 0.5). Bleeding was observed in 59 of 1937 patients (3.0%) at 5 years. Of these, 5 patients were in the AMI group (8.5%, p = 0.6).

Discussion

Safety issues regarding DES use during acute infarct angioplasty involved concerns over stenting ruptured or thrombotic segments of vulnerable vessels and the uncertain risk of future bleeding and tolerance of DAPT. The current study does not show a marked increase in worse outcomes in AMI patients who received DES compared to non-AMI controls over a 5-year observation period. Both DAPT continuation duration and frequency of bleeding were similar in the 2 groups. Several meta-analyses and randomized trials with head-to-head comparisons between DES and bare-metal stents (BMSs) for AMI have already been reported in the early DES era [1–3,13]. These reports similarly showed no significant differences in hard endpoints such as death, recurrent MI, or stent thrombosis, but the rate of repeat revascularization, re-stenosis, or re-occlusion have been significantly lower in patients receiving DES. These studies have clarified device-specific differences in the treatment of AMI. However, AMI treatment using BMS also carries the potential of event occurrence. Conversely, comparison of the clinical presentation (i.e. stable angina, AMI) among all patients treated by DES can better predict disease- or lesion-specific outcomes. In the

**Table 3**

<table>
<thead>
<tr>
<th>Clinical outcomes at 5 years.</th>
<th>AMI (n = 133)</th>
<th>Non-AMI (n = 1804)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>32 (24.1)</td>
<td>417 (23.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Death</td>
<td>21 (15.8)</td>
<td>238 (13.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>5 (3.8)</td>
<td>89 (4.9)</td>
<td>0.68</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>16 (12.0)</td>
<td>149 (8.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>MI</td>
<td>5 (3.8)</td>
<td>60 (3.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>2 (1.5)</td>
<td>24 (1.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>1 (0.8)</td>
<td>2 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>TLR</td>
<td>7 (5.3)</td>
<td>178 (9.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>TVR</td>
<td>15 (11.3)</td>
<td>291 (16.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Non-target lesion TVR</td>
<td>10 (7.5)</td>
<td>171 (9.5)</td>
<td>0.54</td>
</tr>
<tr>
<td>TVF</td>
<td>17 (12.8)</td>
<td>371 (20.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Definite/probable stent thrombosis</td>
<td>1 (0.8)</td>
<td>24 (1.3)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; MACE, major adverse cardiac event; MI, myocardial infarction; CABG, coronary artery bypass graft; TLR, target lesion revascularization; TVR, target vessel revascularization; TVF, target vessel failure. Values are n (%).

**Fig. 1.** Relationship between clinical outcome and target lesion condition after drug-eluting stent implantation. emAMI, acute infarct angioplasty; MACE, major adverse cardiac event; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; TVF, target vessel failure. CI indicates confidence of interval.
current registry, we eliminated early events attributable to AMI itself through landmark analysis, and clarified the differences in long-term outcomes among patients with DES implantation according to AMI status. Similar approaches have been used in previous large-scale DES registries [14,15]. Based on another large-scale Japanese registry, the J-Cypher study presented a similar incidence of death and MI between patients with and without acute coronary syndrome after 2 years of follow-up [14]. The e-Cypher registry included 1883 patients with MI, but DES has not been shown as a predictor of both MACE and stent thrombosis [15].

Pathologically and clinically based lesion-specific studies of the relationship between pre-stenting lesion conditions and the type of device used are more likely to warn against DES implantation in the IRA or culprit lesion. Such studies have focused on the healing process and neothrombosis after DES vs. BMS implantation and the occurrence rates of thrombotic events [4,6,16]. Nakazawa et al. compared cases of DES implanted within 30 days of AMI with stable angina on pathological parameters, and found that vessel healing after DES implantation for AMI was substantially delayed when compared with stable angina, emphasizing the importance of underlying plaque morphology in the arterial response to DES [5,7]. Kang and colleagues reported that the number of neothrombotic optical coherence tomography findings was greater in patients with an unstable clinical presentation during the index procedure [16]. An angiography-oriented clinical study showed a correlation between angiographic lesion features and the late clinical events in patients with DES implantation to treat ST-segment elevation MI [17]. The study reported that large thrombus burden was an independent predictor of mortality and MACE, and large thrombus at presentation was also an independent predictor of stent thrombosis. These interesting insights were enough to send a cautionary message to clinicians. However, the long-term outcomes of DES implantation in the IRA remain unclear, because the observation period of available studies was not long enough to assess safety concerns. In the current study, although a higher frequency of death/MI within 6 months was seen in the AMI vs. the non-AMI group, a difference throughout the 5-year observation period was not observed. Instead, after the 6-month landmark point, all events

Fig. 2. Cumulative incidence of the events in the AMI and non-AMI groups during 5 years of observation: 6-month landmark analysis. AMI, acute myocardial infarction; MACE, major adverse cardiac event; all cause death/MI, composite of all cause death and myocardial infarction; TLR, target lesion revascularization; TVF, target vessel failure.

Fig. 3. Use of dual anti-platelet therapy (DAPT) in the AMI and non-AMI groups during 5 years of observation. AMI, acute myocardial infarction.
associated with the IRA, i.e. TVFs, were significantly increased in the non-AMI group, in contrast to previous knowledge and hypotheses [18,19]. There are several speculations. First, no further intensive care would be performed on the IRA. Only vessels supplying viable muscle received detailed follow-up and/or treatment. Second, AMI patients might have received more secondary preventative care than patients with chronic ischemic heart disease. Reports on statin therapy for IRA (i.e. target vessel of AMI) have shown dramatic plaque regression compared to chronic coronary artery disease [20,21]. Third, it might be due merely to the difference in the backgrounds, such as frequency of in-stent restenosis and stent diameter.

There were several limitations in this study. There were relatively small numbers of patients in the AMI group. Details on the admission status, such as the presence of shock and infarct size, were not available. However, the main purpose of this study was to investigate long-term outcomes and the investigation was focused on safety concerns of patients with AMI when compared to non-AMI patients who do not have a life-threatening presentation. Moreover, we employed landmark analysis to avoid issues related to the clinical condition at admission. The study was designed with consecutive patient enrollment, but the registered population included only patients who received at least one DES. Therefore, the enrolled AMI population might be affected by selection bias. Because long-term medication data other than DAPT had been considered to be unimportant for post-marketing study of DES, these data lacked. The current study only investigated first-generation stents, but this SES has already been replaced by subsequent generations, on which there is little long-term safety data. In contrast, the long-term follow-up rate in this study provides valuable information, especially for current clinical practice in Japan.

Conclusion

Five-year observation of AMI treatment using DES compared with non-AMI has no clinical disadvantage, i.e. increase in death/MI, bleeding, revascularization, or discontinuation of DAPT.

References