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# Clinical Impact of Angiographic Restenosis After Bare-Metal Stent Implantation on Long-Term Outcomes in Patients With Coronary Artery Disease

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***Background:*** In-stent restenosis (ISR) after bare-metal stent (BMS) implantation is thought to be clinically benign, although this notion remains controversial. The long-term clinical outcomes of ISR with BMS have not been established.

***Methods and Results:*** Among 983 consecutive patients (1,227 lesions) implanted with a BMS between 1999 and 2004 at the authors' institution, 746 underwent routine follow-up angiography. Angiographic ISR (ISR group) was evident in 215 patients (28.8%) and 136 of them underwent repeat revascularization. The incidence of major adverse cardiac events (MACE), acute coronary syndrome (ACS), target lesion revascularization and all-cause death were evaluated between patients with and without ISR (non-ISR group). Patients in the ISR group were older and more likely to have diabetes. The median follow-up period was 2,031 days. The rates of MACE and ACS were significantly higher in the ISR group compared with the non-ISR group (33.5% vs. 13.7%, P<0.0001 and 11.2% vs. 7.0%, P<0.05, respectively). Multivariate Cox regression analysis demonstrated that ISR was significantly associated with clinical outcomes (adjusted hazard ratio [HR] for MACE, 2.81; 95% confidence interval [CI]: 2.01–3.94, P<0.01; adjusted HR for ACS, 1.84; 95%CI: 1.08–3.13, P<0.05).

***Conclusions:*** ISR with BMS was significantly associated with long-term adverse clinical outcomes. Risk of future cardiovascular events due to ISR must be carefully considered. (*Circ J* 2011; **75:** 2566–2572)

**Key Words:** Bare-metal stent; Coronary artery disease; Percutaneous coronary intervention; Restenosis

Coronary stenting results in reduced mortality and improved outcomes compared with balloon angioplasty alone.[1,2] In-stent restenosis (ISR), however, began to emerge as a substantial concern among patients implanted with bare-metal stents (BMS).[3,4] The recent introduction of drug-eluting stents (DES) has remarkably reduced the incidence of restenosis compared with BMS.[5–7] Stent thrombosis and late ISR after DES implantation, however, have also emerged as matters of concern and thus BMS implantation is still used in selected cases such as acute coronary syndrome (ACS), high risk for bleeding complication, and comorbid cancer.

Restenosis of BMS has been considered a benign clinical presentation due to the slowly progressive nature of neointimal hyperplasia as a result of smooth muscle cell proliferation.[8–10] Several studies, however, have contradicted this notion[11,12] and long-term clinical outcomes after ISR with BMS have not been established. The aim of the present study was to evaluate the impact of angiographic ISR on long-term clinical outcomes.

## Methods

### Subjects

This single-center, observational historical cohort study included 983 consecutive patients (1,227 lesions) who underwent percutaneous coronary intervention (PCI) with BMS implantation at Juntendo University Hospital between January 1999 and August 2004. Among these 983 patients, 746 (628 men and 118 women) who underwent follow-up angiography at a mean of 181±65 days after the procedure were enrolled in the present study (**Figure 1**). ISR was defined as >50% diameter stenosis at any point along the stent, including 5 mm proximal and distal to the stent edge, at follow-up angiography. The date at follow-up angiography was taken as the start of follow-up. We compared long-term clinical outcomes after follow-up angiog-

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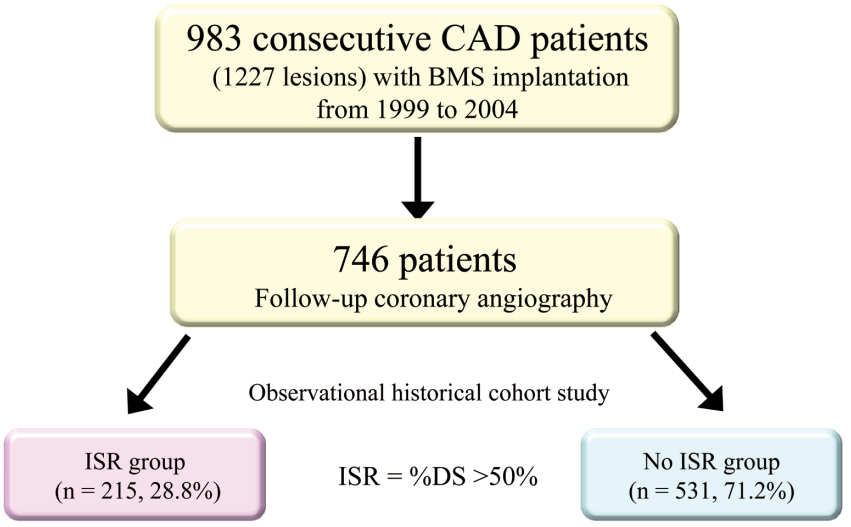


**Figure 1.** Study design. Primary endpoint: major adverse cardiac events after follow-up coronary angiography including all-cause death, acute coronary syndrome and target lesion revascularization. In-stent restenosis (ISR), >50% diameter stenosis (DS) on angiography. CAD, coronary artery disease; BMS, bare-metal stent.

**Table 1. Baseline Characteristics**

| | ISR (n=215) | No ISR (n=531) | P value |
|---|---|---|---|
| Age (years) | 64.7±9.5 | 63.1±10.1 | <0.05 |
| Male, n (%) | 183 (85.1) | 445 (83.8) | 0.66 |
| Diabetes, n (%) | 96 (44.7) | 175 (33.0) | <0.01 |
| Hypertension, n (%) | 144 (67.0) | 321 (60.5) | 0.10 |
| Dyslipidemia, n (%) | 143 (67.1) | 348 (65.8) | 0.73 |
| Current smoker, n (%) | 59 (27.4) | 140 (26.4) | 0.76 |
| Family history, n (%) | 62 (28.8) | 148 (28.0) | 0.81 |
| Multivessel disease, n (%) | 97 (45.1) | 265 (49.9) | 0.26 |
| Prior MI, n (%) | 50 (23.3) | 95 (17.9) | 0.09 |
| Prior CABG, n (%) | 24 (11.2) | 60 (11.3) | 0.95 |
| Prior PCI, n (%) | 48 (22.3) | 87 (16.4) | 0.06 |
| BMI ($kg/m^2$) | 23.9±3.0 | 24.3±3.3 | 0.16 |
| SBP (mmHg) | 132.1±22.6 | 130.7±21.1 | 0.74 |
| DBP (mmHg) | 70.5±11.8 | 72.2±26.0 | 0.33 |
| TC (mg/dl) | 187.9±32.6 | 188.5±36.5 | 0.81 |
| LDL-C (mg/dl) | 118.6±30.2 | 117.6±32.1 | 0.67 |
| HDL-C (mg/dl) | 43.2±11.8 | 44.6±15.3 | 0.21 |
| TG (mg/dl) | 130.2±64.3 | 131.6±73.3 | 0.81 |
| FBG (mg/dl) | 128.0±52.0 | 122.8±47.1 | 0.22 |
| $HbA_{1c}$, % | 6.14±1.48 | 5.85±1.26 | <0.01 |
| eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) | 69.1±20.9 | 70.8±23.2 | 0.35 |
| CKD, n (%) | 59 (27.4) | 148 (27.9) | 0.91 |
| HD, n (%) | 6 (2.8) | 12 (2.3) | 0.67 |
| Clinical presentation, n (%) | | | 0.70 |
| AMI | 51 (23.7) | 137 (25.8) | |
| UAP | 43 (20.0) | 94 (17.7) | |
| SAP | 121 (56.3) | 299 (56.4) | |

ISR, in-stent restenosis; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride; FBG, fasting blood glucose; $HbA_{1c}$, hemoglobin $A_{1c}$; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; HD, hemodialysis; AMI, acute myocardial infarction; UAP, unstable angina pectoris; SAP, stable angina pectoris.

**Table 2. Medication and Angiographic Profile**

| | ISR (n=215) | No ISR (n=531) | P value |
|---|---|---|---|
| Insulin, n (%) | 35 (16.4) | 37 (7.0) | <0.01 |
| OHA, n (%) | 68 (31.6) | 129 (24.3) | <0.05 |
| Aspirin, n (%) | 213 (99.1) | 497 (93.6) | <0.01 |
| Ticlopidine, n (%) | 171 (79.5) | 428 (80.6) | 0.74 |
| ACEI/ARB, n (%) | 119 (55.3) | 269 (50.7) | 0.25 |
| $\beta$-blocker, n (%) | 97 (45.1) | 235 (44.3) | 0.83 |
| Statin, n (%) | 89 (41.4) | 258 (48.6) | 0.07 |
| Target lesion, n (%) | | | 0.30 |
| LMT | 2 (0.9) | 6 (1.1) | |
| LAD | 111 (51.6) | 227 (42.7) | |
| LCX | 35 (16.3) | 102 (19.2) | |
| RCA | 58 (27.0) | 172 (32.4) | |
| SVG | 9 (4.2) | 24 (4.5) | |
| LVEF (%) | 63.1±12.4 | 63.3±13.5 | 0.89 |
| Reference lumen diameter (mm) | 3.01±0.44 | 3.18±0.47 | <0.01 |
| MLD after procedure | 2.73±0.53 | 2.91±0.49 | <0.01 |
| No. stents | 1.1±0.4 | 1.1±0.3 | 0.27 |
| Mean stent size (mm) | 3.11±0.33 | 3.28±0.39 | <0.01 |
| Total stent length (mm) | 21.4±5.9 | 21.9±6.0 | 0.07 |
| Pattern of ISR | | | |
| Focal | 116 (54.0) | | |
| Diffuse | 90 (41.9) | | |
| Occlusion | 9 (4.2) | | |
| Treatment of ISR | | | |
| Medical | 79 (36.7) | | |
| POBA | 26 (12.1) | | |
| POBA (cutting balloon) | 84 (39.1) | | |
| BMS re-implantation | 22 (10.2) | | |
| DES | 4 (1.9) | | |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LMT, left main trunk; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SVG, saphenous vein graft. LVEF, left ventricular ejection fraction; MLD, minimum lumen diameter; POBA, plain old balloon angioplasty; BMS, bare-metal stent; DES, drug-eluting stent; Other abbreviation see in Table 1.

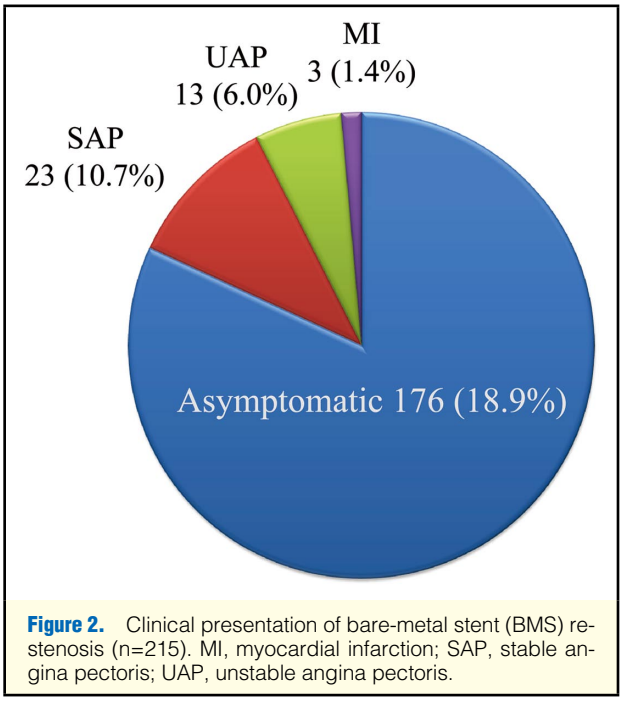


**Figure 2.** Clinical presentation of bare-metal stent (BMS) restenosis (n=215). MI, myocardial infarction; SAP, stable angina pectoris; UAP, unstable angina pectoris.

raphy in subjects with and without ISR.

## Primary Endpoint

The primary endpoints of the present study were major adverse cardiac events (MACE) defined as a composite of all-cause death, ACS and target lesion revascularization (TLR) during the follow-up period. The patients were clinically followed up by monitoring clinic attendance charts, via telephone contact and by sending questionnaires to the patients or their families. Mortality data were collected from the medical records of patients who died or who were treated at Juntendo University Hospital, and from other hospitals where patients were admitted (they were asked to provide details and causes of death). Mortality data were categorized as death from all causes or cardiovascular death including death from coronary artery disease (CAD), cardiogenic shock, stroke and sudden death. We defined ACS among patients with acute myocardial infarction (AMI) and unstable angina pectoris (UAP). AMI was defined as the presence of ischemic symptoms and a 2-fold increase in creatine kinase. UAP was diagnosed in the presence of ischemic symptoms regardless of ST-T changes. TLR was defined as repeat revascularization clinically driven by any lesion in the stented segment. First TLR at the time of follow-up angiography was excluded, therefore TLR in the present study included re-TLR with repeat revascularization

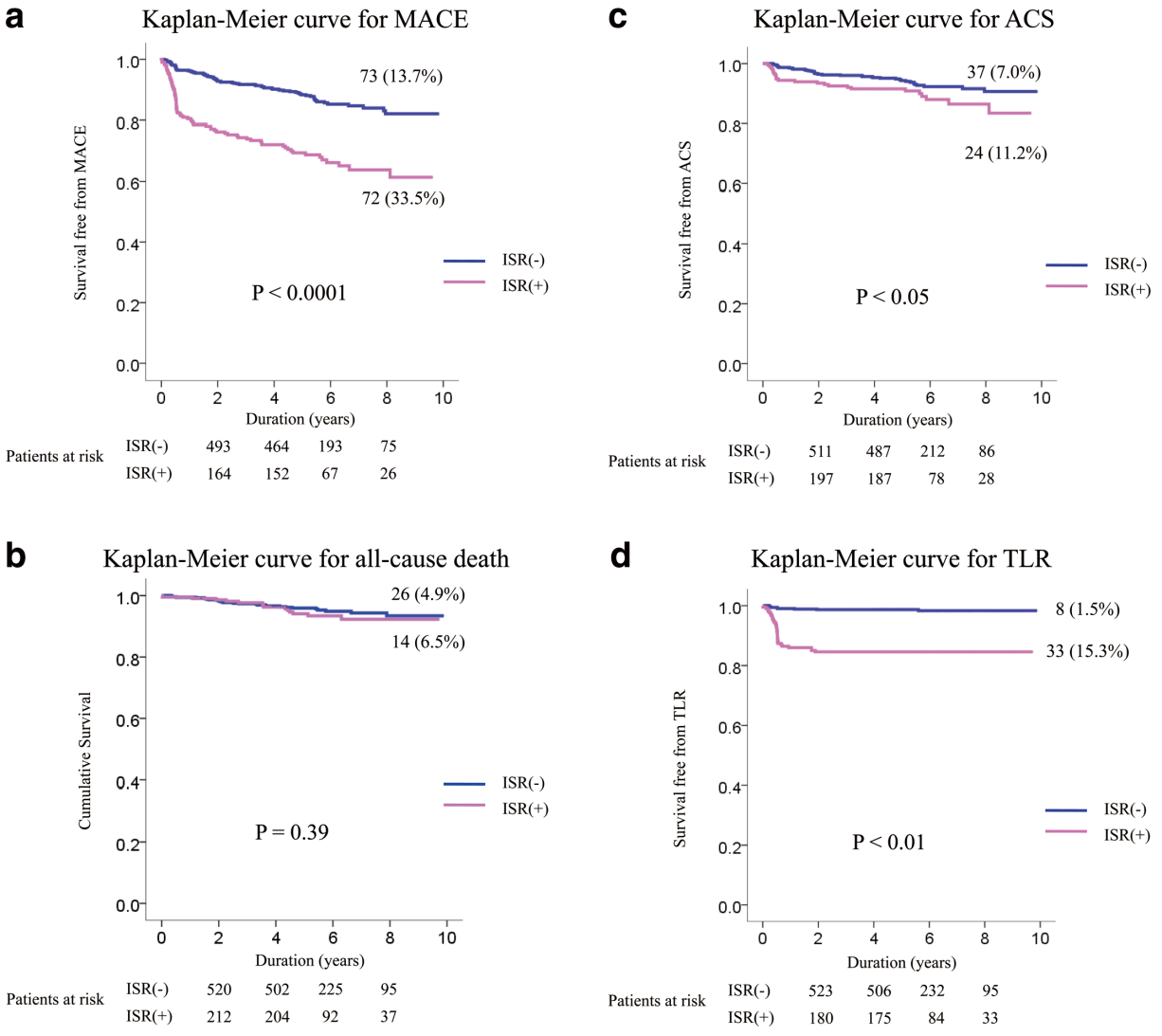


**Figure 3.** Kaplan–Meier curves for (**a**) major adverse cardiac events (MACE); (**b**) all-cause death; (**c**) acute coronary syndrome (ACS); and (**d**) target lesion revascularization (TLR). ISR, in-stent restenosis.

and late first TLR without repeat revascularization.

### Clinical Parameters

Clinical presentation, demographic data, coronary risk factors and medication use were recorded in the Juntendo University Hospital database. Blood samples were obtained during the early morning after an overnight fast. Blood pressure (BP) was measured at the time of admission. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) $<60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ calculated using the modification of diet in renal disease (MDRD) equation modified with a Japanese coefficient using baseline serum creatinine.[13] Diabetes mellitus was defined as fulfilling at least 1 criterion of either hemoglobin $A_{1c}$ ($HbA_{1c}$) >6.1% or undergoing treatment with anti-diabetic agents such as insulin or oral hypoglycemic drugs. Patients with BP>140/90 mmHg or taking anti-hypertensive drugs were regarded as hypertensive and those with total cholesterol >220, or taking statins and/or lipid-lowering agents were regarded as dyslipidemic. Written informed consent was obtained from all patients before coronary intervention. The internal review board approved the study, which proceeded according to the Declaration of Helsinki.

### Statistical Analysis

Quantitative data are presented as mean±SD. Patient characteristics were compared between the groups with and without ISR. Continuous variables were compared using an unpaired t-test or Mann–Whitney U-test. Categorical variables (presented as frequencies) were compared using either chi-squared statistics or Fisher's exact probability test. Event-free survival rates between the 2 groups were compared by constructing Kaplan–Meier curves and using the log-rank test. Multivariate Cox regression analysis was applied to determine whether ISR was associated with adverse events even after adjusting for confounding factors including age, multivessel disease, diabetes, current smoking, prior myocardial infarction, prior PCI, left ventricular ejection fraction, $HbA_{1c}$, eGFR and insulin usage. Marginally different characteristics (P<0.10) on uni-

**Table 3. Cumulative Incidence of Clinical Events**

| | ISR (n=215) | No ISR (n=531) | P value |
|---|---|---|---|
| **Death, n (%)** | 14 (6.5) | 26 (4.9) | 0.39 |
| **Cause of death** | | | |
| Cardiac death | 2 (14.3) | 9 (34.6) | |
| Non-cardiac death | 11 (78.6) | 11 (42.3) | |
| Unknown | 1 (7.1) | 6 (23.1) | |
| **ACS, n (%)** | 24 (11.2) | 37 (7.0) | <0.05 |
| **Culprit vessels of ACS** | | | |
| Target lesion related-ACS | 10 (41.7) | 5 (13.5) | |
| Non-target lesion related-ACS | 14 (58.3) | 32 (86.5) | |
| Indeterminate | 4 (16.7) | 6 (16.2) | |
| TLR, n (%) | 33 (15.3) | 8 (1.5) | <0.01 |

ACS, acute coronary syndrome; TLR, target lesion revascularization. Other abbreviations see in Table 1.

**Table 4. Univariate and Multivariate Cox Hazard Model for MACE**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | P value | HR | 95%CI | P value |
| ISR | 2.82 | 2.04–3.91 | <0.01 | 2.81 | 2.01–3.94 | <0.01 |
| Age | 1.02 | 1.00–1.03 | 0.054 | 1.01 | 0.99–1.03 | 0.50 |
| Multivessel disease | 2.12 | 1.50–2.98 | <0.01 | 1.91 | 1.34–2.76 | <0.01 |
| Diabetes | 1.67 | 1.21–2.31 | <0.01 | 1.03 | 0.65–1.64 | 0.89 |
| Current smoking | 0.64 | 0.42–0.97 | <0.05 | 0.77 | 0.50–1.18 | 0.23 |
| Prior MI | 1.55 | 1.07–2.24 | <0.05 | 0.99 | 0.66–1.49 | 0.96 |
| Prior PCI | 1.93 | 1.35–2.77 | <0.01 | 1.43 | 0.96–2.14 | 0.08 |
| LVEF | 0.99 | 0.98–1.00 | 0.098 | 0.99 | 0.98–1.00 | 0.20 |
| $HbA_{1c}$ | 1.19 | 1.08–1.32 | <0.01 | 1.18 | 0.99–1.39 | 0.06 |
| eGFR | 0.99 | 0.98–0.998 | <0.01 | 0.99 | 0.99–1.00 | 0.13 |
| Insulin usage | 1.74 | 1.10–2.76 | <0.05 | 0.93 | 0.52–1.67 | 0.79 |

MACE, major adverse cardiac events; HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

variate analysis were defined as confounding factors. All variables were simultaneously adjusted in 1 step. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. P<0.05 was considered to indicate statistical significance. All data were analyzed using SPSS version 18.0 for Windows (SPSS, Chicago, IL, USA).

## Results

### Baseline and Procedural Characteristics

The median follow-up period was 2,214 days (interquartile range, 1,878–2,806 days). Of the 746 patients included in the final analysis, 215 (28.8%) had ISR at follow-up angiography (ISR group). Table 1 lists the baseline clinical characteristics of the 2 groups. Patients in the ISR group were significantly older (64.7±9.5 years vs. 63.1±10.1 years, P<0.05) and had a higher prevalence of diabetes (44.7% vs. 33.0%, P<0.01). Clinical parameters did not significantly differ except for $HbA_{1c}$ (6.14±1.48 vs. 5.85±1.26, P<0.01). Table 2 lists medication and angiographic characteristics. More patients in the ISR group used insulin (32.4% vs. 21.0%, P<0.05), oral hypoglycemic agents (31.6% vs. 24.3%, P<0.05) and aspirin (99.1% vs. 93.6%, P<0.01). The reference lumen diameter and minimum lumen diameter after the procedure were significantly smaller in the ISR group (3.01±0.44 vs. 3.18±0.47, P<0.01; and 2.73±0.53 vs. 2.91±0.49, P<0.01, respectively). Of 215 patients with angiographic ISR, 136 patients (63.3%) underwent repeat revascularization. Most patients with repeat revascularization were treated with plain old balloon angioplasty (POBA), 22 patients were treated with BMS implantation, and only 2 patient had DES implantation.

### Clinical Outcomes

At clinical presentation of 215 ISR, 81.9% of patients were asymptomatic, 10.7% had stable angina pectoris, 6.0% had UAP and 1.4% had MI (Figure 2). Figure 3 shows Kaplan–Meier survival curves. Overall total death rates did not significantly differ between the 2 groups. During long-term follow-up, 40 patients died (ISR vs. non-ISR: 14 [6.5%] vs. 26 [4.9%], P=0.39). Table 3 lists the cumulative incidence of clinical events. The cause of death was cardiac in 11 patients (27.5%), non-cardiac in 22 patients (55.0%) and unknown in 7 patients (17.5%). The cumulative incidence of ACS was significantly higher in the ISR group than in the non-ISR group (7.0% vs. 11.2%, P<0.05). The rate of TLR was significantly higher in the ISR group (1.5% vs. 15.3%, P<0.01). The results of univariate and multivariate Cox hazard regression analyses are given in Table 4. Adjusted models for baseline confounding factors showed that ISR was significantly associated with MACE, ACS and TLR itself (adjusted HR for MACE, ACR and TLR: 2.81, 95%CI: 2.01–3.95, P<0.01; 1.84, 95%CI: 1.08–3.13, P<0.05; and 11.7, 95%CI: 5.12–26.8, P<0.0001, respectively).

## Discussion

The major findings in the present study on long-term outcomes

in patients with ISR were as follows. ISR identified a group of patients who were at high risk of future events in the long term (>6 years); the rates of ACS and TLR were consistently higher in the ISR group and the association between ISR after BMS implantation and long-term clinical outcomes remained statistically significant even after adjusting for potential confounding factors.

The restenosis of BMS has historically been regarded as a benign clinical process. Some recent reports, however, have found that ACS occurs in approximately 50% of patients with BMS restenosis.[14,15] The rate of ACS at presentation of restenosis, although relatively low (3.8–18%) in Japan (which might be associated with the routine follow-up angiography and frequent use of intravascular ultrasound for PCI), is nevertheless frequent.[16,17] The present study found that the rate of ACS at presentation among 215 ISR patients was 7.4%, which is comparable to previous reports from Japan.

Neointimal hyperplasia peaked up to 6 months after BMS implantation (early restenosis phase), then regressed (intermediate regression phase), and then a late luminal narrowing phase occurred after 4 years.[8,18] A very long-term clinical and angiographic follow-up after BMS implantation has suggested that luminal re-narrowing of stented segments is a process that develops over 10 years; this corresponds to the rate of late TLR that increases at 15 years (24.7%).[19] In addition, that study also found that 38% of late TLR was driven by severe angina or AMI. One report describes a 10-year incidence of clinical restenosis of 18.1% and a 2.1% incidence of presenting with AMI.[20] The present study found a consistently higher rate of ACS in the ISR group. Several possible explanations for this should be considered. The accumulation of smooth muscle cells within neointimal hyperplasia leads to plaque expansion by an increase in the extracellular matrix and thrombus formation, which plays an important role in ACS.[21] Another possible mechanism of ACS presentation might be a rapid conformational change in a lesion due to the proliferation of smooth muscle cells that could contribute to a relatively rapid and abrupt onset of luminal narrowing. With regard to ACS that arises during the late phase, emerging histopathological evidence supports the formation of late neoatherosclerotic plaque within stented segments after 5 years;[22] and unstable lesions characterized as thin-cap fibroatheromas or plaque rupture have also been observed.[23] Coronary imaging using optical coherence tomography has shown that neointima within BMS transforms into lipid-laden tissue at >5 years after stent implantation and that neovascularization expanding into the intra-intima might contribute to the atherosclerotic progression of neointima.[24] These findings suggest that BMS restenosis presenting with ACS long after implantation might be attributable to plaque rupture within the neointima.

The cumulative incidence of TLR after follow-up coronary angiography reached a plateau after 1 year in the present study, suggesting that the cause of ACS was predominantly a non-target lesion (**Table 3**). In addition, the higher TLR rate was observed in patients with repeat revascularization in the ISR group (30/136, 22%) compared with ISR patients without repeat revascularization (3/79, 3.8%), suggesting that higher TLR in the ISR group was predominantly due to re-restenosis. After the introduction of DES with remarkable efficacy for restenosis, DES has become the treatment of choice for BMS restenosis patients.[25,26] In most of the present study period, however, DES was not available in Japan. Therefore, POBA, especially cutting balloon, was widely used for BMS restenosis, which resulted in a relatively higher TLR rate. We also confirmed that the established classical risks of BMS restenosis such as age and diabetes were significantly higher in the ISR group. In particular, the presence of diabetes affects mortality rates due to CAD more than its absence.[27,28] Others have demonstrated that diabetes mellitus is associated with accelerated development of atherosclerosis characterized by small vessels, long lesions and a greater plaque burden. Restenosis and disease progression equally contribute to repeated revascularization in diabetic patients.[29] Multivariate Cox regression analysis showed that ISR is a more powerful predictor of long-term clinical outcomes than diabetes after adjusting for confounding factors. Therefore, we believe that ISR should be considered as a high-risk clinical entity and a possible predictor of atherosclerotic progression, as well as diabetes, and that careful management and more aggressive intervention are required to improve long-term prognosis.

### Study Limitations

This was a single-center, retrospective observational study of a small patient cohort, and thus unknown confounding factors might have affected the outcomes regardless of the adjusted analysis. We might not have captured all adverse events, which could have resulted in underestimation of events during follow-up. In addition, the duration of follow-up was relatively shorter than that in some published reports.

## Conclusions

The ISR of BMS was significantly associated with long-term adverse clinical outcomes, suggesting that this is not a benign clinical entity, although these patients had optimal medical treatment with evidence-based medicine, as did patients without ISR. Careful consideration of the risks of ISR for future cardiovascular events is required.


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## Disclosure

None.

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