Impact of Cutting Balloon Angioplasty (CBA) Prior to Bare Metal Stenting on Restenosis
— A Prospective Randomized Multicenter Trial Comparing CBA With Balloon Angioplasty (BA) Before Stenting (REDUCE III) —

Yukio Ozaki, MD1; Tetsu Yamaguchi, MD2; Takahiko Suzuki, MD3; Masato Nakamura, MD4; Michihiko Kitayama, MD5; Hideo Nishikawa, MD6; Teruo Inoue, MD7; Kazuhiro Hara, MD8; Fumihiko Usuba, MD9; Masami Sakurada, MD10; Kojiro Awano, MD11; Hitoshi Matsuo, MD12; Sugao Ishiwata, MD2; Tatsuya Yasukawa, MD13; Tevifik F. Ismail, MB BS, MRCP14; Hitoshi Hishida MD1; Osamu Kato, MD15

Background While stent restenosis and late thrombosis still occur even with drug-eluting-stents (DES), there remains a need to explore other strategies for preventing restenosis.

Methods and Results Five hundred and twenty-one patients were randomized: 260 to cutting-balloon angioplasty (CBA) before bare-metal stent (CBA-BMS) and 261 to balloon-angioplasty (BA) before BMS (BA-BMS). Intravascular ultrasound (IVUS)-guided procedures were performed in 279 (54%) patients and angiographic guidance was used in the remainder. Minimal lumen diameter was significantly greater in CBA-BMS than BA-BMS (2.65±0.40 mm vs 2.52±0.4 mm, p<0.01) and % diameter stenosis (%DS)-post was less in CBA-BMS than BA-BMS (14.0±5.9% vs 16.3±6.8%, p<0.01). %DS-follow-up was subsequently less in CBA-BMS than BA-BMS (32.4±15.1% vs 35.4±15.3%, p<0.05) associated with lower rates of restenosis in CBA-BMS than BA-BMS (11.8% vs 19.6%, p<0.05) and less target lesion revascularization (TLR) in CBA-BMS than BA-BMS (9.6% vs 15.3%, p<0.05). Patients were divided into 4 groups based on the device used before stenting and IVUS use (IVUS-CBA-BMS: 137 patients; Angio-CBA-BMS: 123; IVUS-BA-BMS: 142; and Angio-BA-BMS: 119). At follow-up IVUS-CBA-BMS had a significantly lower restenosis rate (6.6%) than Angio-CBA-BMS (17.9%), IVUS-BA-BMS (19.8%) and Angio-BA-BMS (18.2%, p<0.05).

Conclusions Restenosis and TLR were significantly lower in CBA-BMS than BA-BMS. This favorable outcome was achieved because of the lower restenosis rate conferred by the IVUS-guided-CBA-BMS strategy (6.6%). The restenosis rates obtained with this strategy were comparable to those achieved with DES. (Circ J 2007; 71: 1–8)

Key Words: Bare metal stent (BMS); Cutting balloon angioplasty (CBA); Drug-eluting stent (DES); Intravascular ultrasound (IVUS); Late stent thrombosis (LST); Quantitative coronary angiography (QCA)

Restenosis has been a major limitation to the success of percutaneous coronary intervention (PCI) over the past 2.5 decades. Although the advent of drug-eluting stents (DES) appeared to overcome the nemesis of restenosis, there are significant concerns about the long-term safety and efficacy of such devices.1–6 Recent major multicenter randomized studies, including RAVEL, SIRIUS, TAXUS and the PK study, have suggested that DES could drastically reduce 6-month restenosis rates to less than 10%.7–10 However, there is a paucity of long-term follow-up and safety data beyond 4 years.1,11–13 Recent US FDA public health reports citing reports from the RADAR project and others have warned that subacute thrombosis (SAT), late stent thrombosis (LST) and hypersensitivity reactions to sirolimus may have contributed to serious major adverse cardiac events (MACE) experienced in some patients treated with DES.3–6,14,15 Furthermore, a pathological study has also suggested that a hypersensitivity reaction to the polymer of the DES could cause LST. While the number of DES and the stent length required for each lesion is substantially increasing, based on the recent policy of full lesion coverage to avoid any potential injury at the stent edges, the increasing stent length could result in a relatively
higher restenosis rate. Based on a cost-effectiveness analysis, the recent BASKET study proposed that DES should not be used in all patients, only in selected patients. Long-term safety, efficacy and cost concerns highlight the need to continue to explore alternative strategies for reducing the occurrence of restenosis.

The cutting balloon is a unique device that consists of a balloon catheter with 3–4 blades or atherotomes that create longitudinal incisions in the atherosclerotic lesion during balloon inflation. Although a previous multicenter study of the use of cutting balloon angioplasty (CBA) without stent implantation or intravascular ultrasound (IVUS) guidance failed to show a long-term advantage of CBA over balloon angioplasty (BA), another study has indicated some clinical benefit. The use of IVUS guidance and stent implantation could be essential for obtaining optimal results with PCI using CBA.

We hypothesized that CBA prior to bare metal stent (BMS) would assist in achieving full stent expansion with safety and improve accommodation of reactive intimal hyperplasia, thereby producing a favourable long-term outcome.

To test this hypothesis, we performed a prospective, randomized, multicenter trial to compare CBA with BA before stenting in 521 patients with and without IVUS guidance—the Restenosis Reduction by Cutting Balloon Angioplasty Evaluation (REDUCE III) study.

Methods

Study Design

The REDUCE III trial was designed as a prospective, multicenter, randomized study to compare CBA before BMS implantation and BA prior to stenting. Five hundred and twenty-one patients were randomly assigned to either CBA prior to stenting or BA before stenting in an envelope manner at 38 participating centers. To ensure an equal distribution of both treatments per center, the randomization sequence was developed on a site basis. IVUS-guided procedures (pre and post) and follow-up were performed in 22 centers and angiographic-guided procedures were done in the remaining 16. IVUS-guided procedures were performed in 279 (54%) patients, and angiographic-guided procedures were done in the remaining 242 (46%) patients.

Study Endpoints

The primary endpoint of this study was angiographic restenosis (defined as ≥50% diameter stenosis at follow-up by quantitative coronary angiography (QCA)) and subsequent target lesion revascularization (TLR) at follow-up. The principal clinical endpoint was a composite of MACE, including SAT (≤30 days after the procedure), LST (>30 days after the procedure), death, Q-wave and non-Q-wave myocardial infarction, and need for TLR.

Patient Selection

Patients with unstable or stable angina, a single target lesion in a native coronary artery with a vessel diameter less than 4 mm, and planned stent implantation with up to 2 stents and agreement to follow-up angiography were included. Patients were excluded from the study if they had (1) contraindication to anticoagulation and antiplatelet therapy; (2) graft disease; or (3) left main coronary artery disease. The study was approved by the local ethics committees and was carried out according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients.

PCI Procedures

CBA and BA prior to stent implantation were performed according to standard clinical practice with radial or femoral approaches using guide catheters 6F or greater in size to facilitate subsequent QCA analysis. A bolus of 8,000–10,000 IU of heparin (repeated if necessary) was administered during the procedure, followed by combination antiplatelet therapy. According to standard patient care, treatment with aspirin at a dose of 100–300 mg/day was started before the procedure and continued indefinitely, and treatment with ticlopidine at a dose of 200 mg/day was begun before or immediately after the procedure and continued for at least 2 weeks. Although BMS, including the NIR stent (Boston Scientific Co, Freemont, CA, USA) or Multilink stent (Guidant, Santa Clara, CA, USA), were recommended for use, the use of other types of BMS was left to the operator’s discretion. However, no DES were used in the REDUCE III study.

IVUS-Guided and Angiographic-Guided Procedures

CBA, BA and stent sizes were determined by angiographic reference vessel diameter (RD) in the angiography-guided group, and by vessel dimension and plaque distribution detected by IVUS in the IVUS-guided group. The angiographic criteria for optimal stenting were a residual stenosis less than 30% and no flow limiting dissection. The IVUS criteria for optimal stenting were the common criteria originally derived from the MUSIC study: (1) good stent apposition with symmetric stent expansion; (2) full stent expansion with sufficient lumen area (LA) in the lesion segment (ie, LA 80% or greater of the average reference LA pre-intervention); and (3) the absence of major dissection. To fulfill these criteria, high-pressure intra-stent balloon inflation or additional stenting was performed. High-pressure intra-stent balloon inflation was done using conventional balloons (ie, stent balloon or greater sized balloon).

IVUS

Following selective coronary angiography after the intracoronary injection of nitrates, a mechanical intracoronary ultrasound imaging catheter (40-MHz, 2.5 Fr or 2.9 Fr, Boston Scientific Co, Freemont, CA, USA) was introduced over a 0.014-inch guidewire before, immediately after CBA or BA, after stenting, and at follow-up. After the imaging catheter was passed into and beyond the lesion, a motorized pullback was started to obtain an assessment of the target lesion. IVUS images were stored on super VHS videotape for off-line analysis.

Quantitative IVUS Assessment

Serial IVUS analysis pre-procedure, immediately after CBA or BA, post-stenting and at 7-month follow-up was performed at an independent core laboratory of Aichi Medical University and Fujita Health University. Cross-sectional luminal area was defined as the integrated area central to the intimal leading edge echo. The total vessel cross-sectional area (VA) was defined as the area inside the interface between the plaque—media complex and adventitia (area inside the external elastic membrane). VA, LA and plaque area were measured by the image analysis computer (Tapeasure, Index Systems, Mountain View,
The lesion segment was determined from pre-intervention images, including the frame with the smallest LA, whereas the proximal and distal reference segments were defined as the location of the least amount of disease before the emergence of any major side branches. The corresponding frames at post-intervention and follow-up were determined by using peri- and intra-coronary landmarks such as calcium deposits, side branches and venous structures.

QCA

QCA analyses were performed using the computer-based edge-detection coronary angiography analysis system (CAAS II, Pie Medical, Maastricht, Netherlands). Coronary angiograms were obtained in multiple views matched after the intracoronary injection of nitrates. Interpolated RD, minimal lumen diameter (MLD) and percent diameter stenosis were obtained at baseline (pre-), post-stenting and at follow-up using the guiding catheter as a scaling device. QCA measurements and subsequent QCA subanalysis were performed at an independent core laboratory of the Aichi Medical University and Fujita Health University. Restenosis was defined as ≥50% diameter stenosis at follow-up.

Statistical Analysis

Data were analyzed using the SAS statistical software package (SAS Institute, Cary, NC, USA). All continuous values are expressed as mean±SD. Differences in categorical variables were assessed using the chi-square test and Fisher’s exact test. The unpaired t-test was used to assess differences in continuous variables between 2 groups and ANOVA for 4 groups. Where a significant difference was detected by ANOVA, multiple comparison analysis was performed to disclose where the significance existed among the 4 values. All data were analyzed on an intention-to-treat basis. A 2-tailed value of p<0.05 was considered significant.

Results

Patient and Lesion Characteristics

Five hundred and twenty-one patients entered the study, of which 260 were randomized to CBA before bare metal stenting and 261 to BA prior to BMS implantation. The 2 groups were well matched without significant differences in baseline clinical and demographic characteristics (Table 1). Target coronary artery was similar between the 2 groups. Although no difference was seen in the American College Cardiology –American Heart Association lesion classification between the 2, the majority of the lesions were complex in both groups (type B2/C in CBA with BMS; 61.9%, type B2/C in BA with BMS; 65.2%).

CBA, BA and Stent Implantation

Although balloon size prior to stenting was similar between the 2 groups, the inflated pressure was significantly lower with CBA than with conventional BA because of the limitation of maximal inflated pressure allowed with CBA.
Another patient also did not undergo stent implantation after CBA. Of the 261 patients randomized to BA with stenting, all patients subsequently received stents. Of the 521 patients, 271 (52.0%) had NIR stents, 209 (40.1%) had Multilink stents and 41 (7.9%) had other types of slotted tube stents. No significant difference was found between the 2 groups for the type of stent used (p=0.876) (Table 1). Nominal stent diameter and length used were also not different between the 2 groups (Table 1).

QCA Results
The overall angiographic follow-up rate was 87% (453 of 521 patients), with a mean angiographic follow-up period of 6.9 months. No significant difference was found in the angiographic follow-up rate, baseline reference vessel size (RD-pre), MLD-pre-procedure (MLD-pre) and lesion length between the 2 groups (Table 2). MLD-post procedure was significantly greater for CBA-BMS than BA-BMS (p=0.002) and was associated with significantly less residual diameter stenosis in the CBA-BMS group than in the BA-BMS group (p=0.001) (Table 2). This favorable effect for the CBA-BMS strategy carried over to follow-up. The residual diameter stenosis at follow-up was significantly less for CBA-BMS than for BA-BMS (p=0.001) (Table 2). This favorable effect for the CBA-BMS strategy carried over to follow-up. The residual diameter stenosis at follow-up was significantly less for CBA-BMS than for BA-BMS (p=0.001) (Table 2).

### Table 2 Serial (Pre, Post and Follow-up) QCA in 453 Patients and Serial (Pre, Post and Follow-up) IVUS in 141 Patients in REDUCE III

<table>
<thead>
<tr>
<th></th>
<th>CBA with BMS</th>
<th>BA with BMS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial QCA (n)</td>
<td>228</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>RD pre (mm)</td>
<td>2.83±0.47</td>
<td>2.82±0.47</td>
<td>0.754</td>
</tr>
<tr>
<td>MLD pre (mm)</td>
<td>1.05±0.32</td>
<td>1.01±0.30</td>
<td>0.100</td>
</tr>
<tr>
<td>MLD post (mm)</td>
<td>2.65±0.40</td>
<td>2.52±0.40</td>
<td>0.002</td>
</tr>
<tr>
<td>MLD follow-up (mm)</td>
<td>1.86±0.55</td>
<td>1.77±0.54</td>
<td>0.098</td>
</tr>
<tr>
<td>%DS pre</td>
<td>62.6±8.9</td>
<td>63.9±9.2</td>
<td>0.137</td>
</tr>
<tr>
<td>%DS post</td>
<td>14.0±5.9</td>
<td>16.3±6.8</td>
<td>0.001</td>
</tr>
<tr>
<td>%DS follow-up</td>
<td>32.4±15.1</td>
<td>35.4±15.3</td>
<td>0.039</td>
</tr>
<tr>
<td>Lesion length</td>
<td>14.5±5.3</td>
<td>14.7±4.6</td>
<td>0.126</td>
</tr>
<tr>
<td>Restenosis (n, %)</td>
<td>27 (11.8%)</td>
<td>44 (19.6%)</td>
<td>0.024</td>
</tr>
</tbody>
</table>
| **QCA, quantitative coronary angiography; IVUS, intravascular ultrasound; RD, reference vessel diameter; MLD, minimal lumen diameter; DS, diameter stenosis; VA, vessel area in the lesion segment; LA, lumen area in the lesion segment. Other abbreviations see in Table 1.**

### Table 3 Comparison of MACE Between the 4 Subgroups of the 521 Patients in REDUCE III

<table>
<thead>
<tr>
<th></th>
<th>CBA with BMS (n=260)</th>
<th>BA with BMS (n=261)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAT (n, %)</td>
<td>0 (0%)</td>
<td>1 (0.4%)*</td>
<td>0.336</td>
</tr>
<tr>
<td>LST (n, %)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Death (n, %)</td>
<td>1 (0.4%)</td>
<td>2 (0.8%)</td>
<td>0.564</td>
</tr>
<tr>
<td>Cardiac (n, %)</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
<td>0.997</td>
</tr>
<tr>
<td>Non-cardiac (n, %)</td>
<td>0 (0%)</td>
<td>1 (0.4%)</td>
<td>0.317</td>
</tr>
<tr>
<td>MI (n, %)</td>
<td>2 (0.8%)</td>
<td>1 (0.4%)*</td>
<td>0.560</td>
</tr>
<tr>
<td>TLR (n, %)</td>
<td>25 (9.6%)</td>
<td>40 (15.3%)*</td>
<td>0.048</td>
</tr>
<tr>
<td>PCI (n, %)</td>
<td>25 (9.6%)</td>
<td>39 (14.9%)*</td>
<td>0.064</td>
</tr>
<tr>
<td>CABG (n, %)</td>
<td>0 (0%)</td>
<td>1 (0.4%)</td>
<td>0.317</td>
</tr>
<tr>
<td>Overall MACE (n, %)</td>
<td>30 (11.5%)</td>
<td>44 (16.8%)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

*One patient had SAT, which resulted in acute MI. This was subsequently treated by PCI.
#PCI was performed for a de novo lesion in a different vessel from the original target vessel.
^The numbers given for any major adverse cardiac event are therefore not equal to the cumulative numbers given in each event, because some patients had more than 1 event.
MACE, major adverse cardiac events; SAT, subacute stent thrombosis; LST, late stent thrombosis; TLR, target lesion revascularization; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting. Other abbreviations see in Table 1.
Clinical Outcomes

Clinical follow-up was obtained in all 521 patients (100%). In the CBA with BMS group 1 patient was lost to angiographic follow-up and died of a ventricular arrhythmia 12 months after the procedure, and 2 patients experienced procedure-related acute myocardial infarction (Table 3). TLR was done by PCI in 25 (9.6%) patients, and PCI at follow-up was done for newly developed lesions in different vessels from the target vessels in 2 (0.8%) patients in the CBA-BMS group (Table 3). The event-free survival was therefore 88.5% at follow-up.

In the BA with BMS group, 1 patient experienced SAT with myocardial infarction 4 days after the procedure but underwent emergency PCI and Thrombolysis in Myocardial Infarction III flow was quickly restored (Table 3). One patient died of heart failure 4 months after the procedure (cardiac death) and 1 without follow-up angiography died of lung cancer 12 months after the procedure (non-cardiac death). A further 39 (14.9%) patients had TLR by PCI, and 1 (0.4%) underwent coronary artery bypass grafting. The event-free survival per patient was therefore 83.9% at follow-up. Late thrombosis was not observed in any group after the procedure.

The TLR rate was significantly lower in the CBA-BMS group than in the BA-BMS group (p=0.048). The incidence of MACE tended to be lower for CBA-BMS but this trend did not reach statistical significance (p=0.082) (Table 3).

Comparison of Restenosis Rate Among the 4 Groups

Of the 260 patients with CBA and BMS, 137 patients underwent CBA and BMS under IVUS-guidance (IVUS-CBA-BMS) and 123 under angiographic-guidance alone (Angio-CBA-BMS). Of the 261 patients with BA and BMS, 123 patients underwent BA under IVUS-guidance (IVUS-BA-BMS) and the remaining 119 under angiographic-guidance alone (Angio-BA-BMS). Angiographic follow-up was done in 122 (89.1%) of 137 patients with IVUS-CBA-BMS, in 106 (86.2%) of 123 patients with CBA-BMS, 126 (88.7%) of 142 patients with IVUS-BA-BMS, and 99 (83.1%) of 119 patients with Angio-BA-BMS (Table 4). No difference was found in the angiographic follow-up rate.

- Multiple comparisons also revealed significant differences in MLD-post; p<0.05 in A1*) vs B1*) , A1*) vs C1*) , A1*) vs D1*) ; %DS post; p<0.05 in A2)* vs C2)* , A2)* vs D2)* .

Abbreviations see in Tables 1,2.

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baseline RD-pre, MLD-pre or lesion length between the 4 groups (Table 4). MLD-post procedure was significantly greater in the IVUS-CBA-BMS group compared with Angio-CBA-BMS, IVUS-BA-BMS and Angio-BA-BMS (p=0.001 by ANOVA, p<0.05 by multiple comparisons respectively) and the group had significantly less residual diameter stenosis than the other groups (p=0.001 by ANOVA) (Table 4). This favorable effect produced by the IVUS-CBA-BMS strategy carried over to follow-up. The residual diameter stenosis at follow-up was significantly less in the IVUS-CBA-BMS group than in the others (p=0.016 by ANOVA) (Table 4). Similarly, a significant difference was observed following multiple comparison analysis between IVUS-CBA-BMS and IVUS-BA-BMS (p<0.05) and between IVUS-CBA-BMS and Angio-BA-BMS (p<0.05) (Table 4).

The difference in residual diameter stenosis at follow-up subsequently conferred a significant difference in restenosis rates. The restenosis rate in the IVUS-guided CBA with stent group (6.6%; 8 of 122 patients) was lower than that in the angiographic-guided CBA with stent groups (17.9%; 19 of 106 patients); the IVUS-guided BA with stent group (19.8%; 25 of 126 patients); and that in angiographic-guided BA with stent group (18.2%; 18 of 99 patients, p=0.016) (Table 4). The favorable outcome for the CBA-BMS group (ie, combined IVUS-CBA-BMS and Angio-CBA-BMS groups) was mainly conveyed by the low restenosis rate produced by the IVUS-guided-CBA-BMS strategy (restenosis rate: 6.6%).

Multivariate Analysis Results

Multivariate analyses to evaluate the respective contributions of the clinical, angiographic and IVUS variables to restenosis indicated that the use of BA (but not of CBA), smaller vessel area on IVUS, diabetes, left anterior descending (LAD) lesion and total stent length were independent predictors for stent restenosis at follow-up (Table 5). Minimal LA post stenting by IVUS tended to be a significant (p=0.072) but not a significant independent predictor.

Discussion

This prospective multicenter randomized study (REDUCE III) has demonstrated that using a CBA strategy prior to BMS implantation could provide significantly greater MLD-post (p=0.002) with less residual percentage diameter stenosis post procedure (p=0.001) than BA with BMS (Table 2). This strategy subsequently resulted in significantly less percentage diameter stenosis at follow-up (p=0.039), conferring a substantially lower restenosis rate and lower incidence of TLR than in the BA with BMS group (Tables 2,3). The greater lumen diameter obtained by an IVUS-guided CBA strategy could have contributed to the favorable long-term outcomes observed. Multivariate analysis indicated that the use of BA, but not CBA, small vessels, diabetes, LAD lesion location and longer stent length were independent predictors for restenosis at follow-up.

Role of IVUS Guidance in CBA and BA Prior to BMS

Previous studies investigating the benefit of an IVUS-guided PCI strategy have yielded conflicting evidence. Although Fitzgerald et al24 found that IVUS-guided stenting resulted in more effective stent expansion and subsequently a lower restenosis rate in comparison with angiographic guidance alone, Mudra et al reported that optimizing stent implantation by IVUS failed to show beneficial effects on long-term outcome29 The latter suggested that those with extensive experience with IVUS obtained similar final results to those not using IVUS guidance. More recently however, Oemrawsingh et al revealed that angiographic and clinical outcome after stenting for long lesions guided by IVUS is superior to that performed using angiography alone30

Our REDUCE III study results indicate that despite similar vessel size and lesion severity, IVUS-guided CBA with BMS produced significantly greater MLD-post (p=0.001) with less residual percentage diameter stenosis-post (p=0.001) and resulted in significantly less percentage diameter stenosis at follow-up (p=0.016), as well as a lower restenosis rate (p=0.016) (Table 4). Without IVUS guidance, the interventional operator systematically tends to select undersized devices because of fears about the inherent danger of vessel perforation. This may negate the benefits of CBA and result in a suboptimal smaller LA similar to that which might be achieved with BA alone.

However, we did not have an IVUS blinded arm (IVUS playing a spectator role), unlike the CRUISE study24 Therefore, all the information provided by IVUS could have affected the subsequent PCI procedure for both IVUS-guided CBA-BMS and IVUS-guided BA-BMS. We speculate that IVUS-guidance CBA facilitated the use of larger cutting balloon sizes and gave the operator increased confidence and latitude with balloon sizing. This favourable effect of IVUS could play a more important role in CBA rather than with simple BA. IVUS-guided CBA would have minimized vessel injury and risk of complications while maximising the achieved MLD.

Impact of the IVUS-Guided CBA-BMS Strategy in the Era of DES

Our REDUCE III study has demonstrated that the use of an IVUS-guided CBA strategy prior to stent implantation can achieve acceptably low restenosis rates (6.6%) that are comparable to those achieved with DES (Table 4). Although the First experience In Man and the RAVEL studies indicated complete inhibition of restenosis, the broader application of DES in the SIRIUS and TAXUS-IV studies demonstrated that they markedly reduced but did not eliminate the problem of restenosis.7–9,11,12 Substantial growth in the real-life clinical use of DES has revealed some potentially significant limitations. A recent US FDA public health notification, including data from the RADAR project, has warned that the occurrence of SAT, LST and hypersensitivity reactions to sirolimus may have significantly contributed to serious adverse cardiac events experienced by some patients.2,6,15 Both subacute and LST have been associated with non-fatal myocardial infarction or death2–6,14,15,31 Recently, Jakovou et al reported that subacute and LST occurred in 29 of 2,229 patients (1.3%) and the incidence in “real-world” patients was substantially higher than the rate reported in clinical trials.

Furthermore, Rodriguez et al revealed that stent thrombosis occurred in 7 (3.1%) of 225 patients following DES and 4 (1.8%) of them had LST9 In the present study, SAT occurred in 1 patient in the angiographic-guided BA and BMS group and LST was not observed in any patient. Long-term safety data beyond 5 years have not yet been available for DES, whereas conventional stent use has a history spanning nearly 2 decades. Therefore, until long-term safety...
concerns have been allayed, there remains a need to explore alternative strategies for improving the outcomes achieved with conventional stent technologies.

**Independent Predictors for Stent Restenosis**

Several independent predictive factors for restenosis have been proposed from multicenter randomized studies or large sample studies. Although Kastrati et al revealed that diabetes, small MLD-post and multiple stents were predictors for stent restenosis, de Feyter et al indicated that MLD area on IVUS and stent length were independent predictors for stent restenosis. Kasaka et al showed that longer stent length, smaller vessel size, MLD-post and post stent LA on IVUS were strong predictors for stent restenosis, but Carrozza et al disclosed that stenting of the LAD was the strongest predictor of restenosis in their multivariate model.

We initially used multivariate analysis to examine the clinical, angiographic and IVUS predictors for restenosis in patients undergoing CBA and BA prior to BMS, and our multivariate model clearly demonstrated that the use of BA (but not of CBA) was the strong independent predictor for restenosis, in addition to conventional restenosis predictors such as small vessels, diabetes, LAD lesion location and longer stent length. The importance of using CBA, but not BA, prior to stenting on the reduction of stent restenosis were reconfirmed by both univariate analysis and the multivariate model.

**Study Limitations**

First, we successfully reached the primary endpoints (ie, angiographic restenosis, as well as TLR), but we could not show a statistical difference in MACE, even though the incidence of MACE tended to be lower for CBA with BMS (11.5%) than for BA with BMS (16.8%, p=0.082).

Second, we did not perform a direct comparison of IVUS-guided CBA-BMS and DES. A prospective randomized study including a DES arm with a greater overall sample size is required to confirm whether the IVUS guided CBA-BMS strategy can really provide a similar clinical outcome to that for DES.

**Conclusions**

Despite tackling complex lesion morphology (ie, angiographic restenosis, as well as TLR), but we could not show a statistical difference in MACE, even though the incidence of MACE tended to be lower for CBA with BMS (11.5%) than for BA with BMS (16.8%, p=0.082).

Second, we did not perform a direct comparison of IVUS-guided CBA-BMS and DES. A prospective randomized study including a DES arm with a greater overall sample size is required to confirm whether the IVUS guided CBA-BMS strategy can really provide a similar clinical outcome to that for DES.

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**Appendix 1**

**REDUCE III Investigators**

Tetsu Yamaguchi (Toranomon Hospital); Takahiko Suzuki (Toyohashi Heart Center); Michihiko Kitayama (Kanazawa Medical University Hospital); Hideo Nishikawa (Yamada Red Cross Hospital, Mie Heart Center); Teruo Inoue (Dokkyo University Koshigaya Hospital, Saga Medical University); Kazuhiro Haru (Matsui Memorial Hospital); Fumihiko Usuba (Tomei Atsugi Clinic, Kikuna Memorial Hospital); Masami Sakurada (Sekishinkai Sayama Hospital, Tokorozawa Heart Center); Kojiro Awano (Miki City Hospital); Hitoshi Matsuo (Gifu Prefectural Hospital); Sugao Ishiwata, (Toranomon Hospital); Osamu Kato (Kyoto Katsura Hospital, Toyohashi Heart Center); Takatoshi Hayashi (Himeji Cardiovascular Center); Yutaka Hikichi (Shin Koga Hospital); Ichiro Michishita (Yokohama Sakae Kyoai Hospital); Yoshishia Kinoshita (Matsue Municipal Hospital); Masato Nakamura (Toho University Medical Center Hohashi Hospital); Fumitsugu Oida (Dokkyo University Hospital); Yoshikazu Hiasa (Tokushima Red Cross Hospital); Masunori Morii (Ako City Hospital); Mikihiro Kijima (Hoshi General Hospital); Tetsuo Matsubara (Nagoya Kyoritsu Hospital); Haruo Hirayama (Nagoya Dai-ni Red Cross Hospital); Mikiyaka Murakami (Showa University Hospital); Taizo Kondo (Komaki City Hospital); Hiroaki Hosokawa (National Toyohashi Higashi Hospital); Yoshinori Yasaka (Toyooka Hospital); Toru Kobayashi (Osaka Medical Center for Cancer and Cardiovascular Diseases); Wakatomi Chin (Osaka National Hospital); Tetsuya Sumiyoshi (Sakakibara Heart Institute); Itabashi Central Hospital); Toshihiko Muramatsu (Kawasaki Social Insurance Hospital); Kyoichi Mizuno (Nippon Medical School Chiba Kuoosu Hospital); Hiroyuki Takada (Tama Nambu Chiki Hospital); Yasuyuki Kurimoto (Yodogawa Christian Hospital); Takashi Uchiyama (Tokyo Medical University Hachioji Medical Center); Yasushi Asakura (Keio University Hospital); Yasuhiro Hayashi (Tuchiya General Hospital); Tatsuya Yasukawa (Yasukawa Clinic, Aichi Medical University Hospital); Yukio Ozaki (Fujita Health University Hospital, Aichi Medical University Hospital).