Impact of Sirolimus-Eluting Stent Fracture on 4-Year Clinical Outcomes

Hisashi Umeda, MD, PhD; Tomoko Kawai, MD; Naoki Misumida, MD; Tomoyuki Ota, MD; Kazutaka Hayashi, MD; Mitsunori Iwase, MD, PhD, FACC; Hideo Izawa, MD, PhD; Shigeo Sugino, MD; Takeshi Shimizu, MD, PhD; Yasushi Takeichi, MD, PhD; Ryoji Ishiki, MD, PhD; Haruo Inagaki, MD, PhD; Yukio Ozaki, MD, PhD, FACC; Toyoaki Murohara, MD, PhD, FACC

Background—Although stent fracture (SF) after sirolimus-eluting stent (SES) implantation has been recognized as one of the predisposing factors of in-stent restenosis, it remains uncertain whether SF can increase the risk of major adverse cardiac events (MACE), especially beyond 1 year after SES implantation. The aim of this study was to assess the impact of SF relative to non-SF on 4-year clinical outcomes after treatment with SES of comparable unselected lesions.

Methods and Results—A total of 874 lesions in 793 patients undergoing SES implantation and subsequent angiography 6 to 9 months after index procedure were analyzed. At 6- to 9-month angiographic follow-up, SF was identified in 70 of 874 lesions (8.0%). In-stent late loss was significantly higher in SF lesions versus non-SF lesions (0.42±0.59 mm versus 0.13±0.49 mm, P<0.001), resulting in a significantly higher in-stent restenosis rate (21.4% versus 4.1%, P<0.001). At 4 years, SF versus non-SF was associated with a significantly higher MACE rate (23.2% versus 12.6%, P=0.014), mainly driven by significantly higher target-lesion revascularization (18.8% versus 10.2%, P=0.029). Adverse effects of SF on clinical outcomes occurred mostly within the first year (17.4% versus 6.6%, P=0.001), with similar MACE rate between 1 and 4 years (5.8% versus 5.9%, P=0.611). No significant differences between SF versus non-SF patients were observed in the cumulative frequency of very late stent thrombosis (2.9% versus 1.4%, P=0.281), death (0% versus 2.1%, P=0.252), or myocardial infarction (5.8% versus 2.9%, P=0.165).

Conclusions—SF of SES was associated with higher MACE rate up to 1 year, mainly driven by higher target-lesion revascularization, whereas no significant association was evident between years 1 and 4. (Circ Cardiovasc Interv. 2011;4:349-354.)

Key Words: angioplasty □ coronary disease □ follow-up studies □ restenosis □ stents

A number of trials documented that the use of sirolimus-eluting stents (SES) reduced restenosis and subsequent target-vessel revascularization rates, with similar safety compared with use of bare-metal stents,1-3 even in patients with off-label indications,4 resulting in widespread use of SES in clinical practice. On the other hand, the presence of stent fracture (SF) after SES implantation has been reported to be associated with an increased risk of in-stent restenosis, ranging from 15% to 60%,5-12 with higher cardiac event rates within a 1-year observation period.5-8,10,12 A recently published pathological study in 144 autopsy cases of patients who had received drug-eluting stents (DES) demonstrated that SF was detected in 29% of lesions, and the presence of SF with gap within the stent body was associated with a histological event, such as stent thrombosis or restenosis, in 67% of cases.13 Because the duration and severity of arterial responses at the site of SF, which may have an adverse effect on outcomes, as well as the time point at which the SF occurs after SES implantation remain uncertain, the clinical impact of SF on long-term outcomes should be evaluated. However, there are scant data on the clinical course of SF patients, particularly long-term follow-up data. Accordingly, the goal of the present study was to assess whether the presence of SF might influence long-term clinical outcomes, including rates of stent thrombosis, target-lesion revascularization (TLR), non-fatal myocardial infarction (MI), and death at 4 years, in routine clinical practice.

Clinical Perspective on p 354

Methods

Patient Population and Procedural Protocol
From June 2004 to June 2006, a total of 925 patients who underwent successful implantation with only SES (Cypher; Johnson & Johnson, Miami Lakes, FL) at our institutions were followed prospectively.

Received July 3, 2010; accepted May 31, 2011.

From the Division of Cardiology, Toyota Memorial Hospital, Toyota, Japan (H.U., N.M., T.O., K.H., S.S., R.I., H.I.); the Department of Cardiology, Fujita Health University, Toyoake, Japan (T.K., Y.O.); the Division of Cardiology, Bantane Hospital, Fujita Health University, Toyoake, Japan (K.H.); the Department of Cardiology, Aichi Prefectural Cardiovascular and Respiratory Center, Ichinomiya, Japan (T.S.); and the Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan (T.M.).

Correspondence to Hisashi Umeda, MD, PhD, Division of Cardiology, Toyota Memorial Hospital 1-1 Heiwa-cho, Toyota 471-8513, Japan. E-mail hisashi_umedaa@mail.toyota.co.jp

© 2011 American Heart Association, Inc.

Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org

DOI: 10.1161/CIRCINTERVENTIONS.110.958306
Among 925 patients, 793 patients (85.7%) with 874 lesions who underwent follow-up angiography 6 to 9 months after initial procedure, irrespective of clinical symptoms, were enrolled in the study. In these patients, percutaneous coronary intervention was performed according to standard techniques. Before the procedure, 81 to 162 mg of aspirin was prescribed and 10,000 IU of heparin was given if not contraindicated. The decision to perform predilation and postdilation balloon inflations, as well as the use of intravascular ultrasound (IVUS), was left to the discretion of the operator. No platelet glycoprotein IIb/IIIa receptor inhibitors were used in the present study because they were not available in Japan. After the procedure, all patients were advised to continue on aspirin (81 to 162 mg daily) for life unless there were contraindications. Ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was also prescribed for at least 3 months after stent implantation. Follow-up coronary angiography was performed at 6 to 9 months or earlier if they had recurrent symptoms. Written informed consent was obtained from patients in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethics committees. All adverse events at 4 years were confirmed by reviewing the medical records of the patients followed at our institutions, by telephone contact with the patients or a next of kin, or from information from referring physicians when patients were followed up elsewhere. Complete follow-up data on clinical events at 4 years were available in 91% of SF and 93% of non-SF cases. All patients reported in this study had clinical follow-up. In patients in whom complete 4-year follow-up was not available, outcomes were included in all Kaplan-Meier analyses until the point they were lost to follow-up. No extramural funding was used to support this work.

Quantitative Angiographic Analysis and Definitions

The angiograms were reviewed as a single group by 2 experienced observers blinded to the clinical information. Quantitative coronary analysis was performed, using the Cardiovascular Measurement System (CMS-MEDIS Medical Imaging Systems, Nuenen, The Netherlands). Contrast-filled guiding catheters were used for magnification calibration. Each angiographic sequence was preceded by intracoronary injection of nitroglycerin. SF was defined as a complete separation of stent struts (partial fracture), as assessed by coronary angiography, plain fluoroscopy (30 frames/s), and/or IVUS at follow-up. In-stent restenosis was defined as a diameter stenosis >50% within the stented segment, and in-segment restenosis was defined as a diameter stenosis >50% either within the stented segment or within 5 mm proximal or distal to the stent segment measured with quantitative coronary analysis on the follow-up angiography. Renal insufficiency was defined as serum creatinine level >1.5 mg/dL. Before percutaneous coronary intervention, Nonfatal MI was defined by a new Q-wave >0.04 seconds or elevation of serum creatine kinase levels to greater than twice the upper limit of normal values, with an elevated myocardial band fraction and troponin I level associated with chest pain. TLR was defined as treatment for recurrent angina or signs of ischemia and a >50% diameter stenosis at the target lesion on follow-up angiogram. Major adverse cardiac events (MACE) were defined as death (all causes), nonfatal MI, and TLR during the hospital stay or at follow-up. Very late stent thrombosis (>360 days) was retrospectively classified by the Academic Research Consortium definition as definite, probable, or possible.16

Statistical Analysis

Statistical analysis was performed using the SPSS 11.0 software program (SPSS Inc, Chicago, IL). Data were expressed as mean±SD for continuous variables and as percentages for discrete variables. Student unpaired t test or Mann-Whitney U test was used to compare continuous variables between groups. Categorical variables were compared by χ² test or Fisher exact test, as appropriate. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. The log-rank tests and hazard ratios were used to test for differences between SF and non-SF incidence curves. Cox proportional hazard regression analysis was performed to adjust for confounders. A 2-sided probability value of <0.05 was considered statistically significant.

Results

Coronary angiography was repeated 7.6±4.0 months after the index procedure. Baseline characteristics of the 793 patients with follow-up angiography included in this report were not significantly different from those of the 132 patients without angiography (data not shown). At follow-up, SF was present in 70 of 874 lesions (8.0%) and in 69 of 793 patients (8.7%). In 51 of 70 lesions (72.9%), SF was found at a single point, whereas SF occurred in 2 or more points per lesion in 19 lesions (27.1%). As a result, a total of 93 fractures in 70 lesions, for an average of 0.11 fractures per lesion, were observed. Of the 93 points in which stent fracture occurred, 63 fracture points (67.7%) were located within 5 mm proximal or distal to the margins of stent overlap.

Table 1. Baseline Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Fracture (n=69)</th>
<th>Nonfracture (n=724)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesions</td>
<td>70</td>
<td>804</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.8±10.6</td>
<td>65.8±9.7</td>
<td>0.331</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>79.7</td>
<td>80</td>
<td>0.959</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5±3.6</td>
<td>24.2±2.9</td>
<td>0.572</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>40.6</td>
<td>42.3</td>
<td>0.786</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>71</td>
<td>66.7</td>
<td>0.467</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>63.8</td>
<td>62.3</td>
<td>0.809</td>
</tr>
<tr>
<td>Renal insufficiency, %</td>
<td>8.7</td>
<td>14.6</td>
<td>0.175</td>
</tr>
<tr>
<td>Hemodialysis, %</td>
<td>0</td>
<td>4.1</td>
<td>0.062</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>47.8</td>
<td>36.9</td>
<td>0.073</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>82.6</td>
<td>64.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior infarction, %</td>
<td>40.6</td>
<td>38.1</td>
<td>0.688</td>
</tr>
<tr>
<td>Previous angioplasty, %</td>
<td>47.8</td>
<td>49.2</td>
<td>0.831</td>
</tr>
<tr>
<td>Previous bypass surgery, %</td>
<td>8.7</td>
<td>9.9</td>
<td>0.739</td>
</tr>
<tr>
<td>Clinical status, %</td>
<td>66.7</td>
<td>70.0</td>
<td>0.408</td>
</tr>
<tr>
<td>Stable angina</td>
<td>10.1</td>
<td>13.7</td>
<td>0.519</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>15.9</td>
<td>12.3</td>
<td>0.809</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>7.2</td>
<td>4.0</td>
<td>0.085</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>57.5±11.3</td>
<td>56.4±11.4</td>
<td>0.408</td>
</tr>
<tr>
<td>Medical treatment, %</td>
<td>97.1</td>
<td>99.0</td>
<td>0.181</td>
</tr>
<tr>
<td>Aspirin</td>
<td>98.4</td>
<td>97.4</td>
<td>0.519</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>39.1</td>
<td>39.1</td>
<td>0.995</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>20.3</td>
<td>30.2</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or percentages.

For confounders. A 2-sided probability value of <0.05 was considered statistically significant.
more likely to have multivessel disease, right coronary artery lesions, and lesions with tortuosity and chronic total occlusion. There was a lower incidence of left anterior descending artery lesions and lesions produced by in-stent restenosis in SF patients than in non-SF patients.

Procedural and Angiographic Results

Table 3 compares the procedural characteristics and quantitative coronary analysis results of the 2 study groups. In SF patients, the number of stents per lesion was significantly larger (P<0.001) and total stent length was significantly longer (P<0.001) than that of non-SF patients. No significant differences were observed between the 2 groups in terms of stent size, maximum inflation pressure or frequency of IVUS use, or direct stenting. At baseline, SF patients had longer lesion (P<0.001) and higher diameter stenosis (P=0.004), whereas mean vessel size and minimal lumen diameter were similar in the 2 groups. At follow-up, SF patients showed significantly lower in-stent minimal lumen diameter (P=0.001) and higher late lumen loss in the stented segment (P<0.001) compared with those of non-SF patients. As a result, in-stent restenosis occurred more frequently in SF patients (21.4%) as compared with non-SF patients (4.1%, P<0.001). In SF, restenosis was observed at SF sites in 13 of 15 restenotic lesions (86.7%). Additionally, the differences in restenosis rates remained significant when outcomes were compared in the in-segment zone (22.9% versus 7.6%, P<0.001).

Clinical Outcomes

The cumulative cardiac event rates at 1 and 4 years after the procedure are presented in Table 4 and Figures 1, 2, and 3. At 1 year, the cumulative incidence of TLR was significantly higher in SF patients than in non-SF patients (P=0.005), whereas there were no statistically differences in rates of death and nonfatal MI between the 2 groups. As a result, SF versus non-SF was associated with a significantly higher 1-year MACE rate (P=0.001). Similarly, the 4-year cumulative risk rates of TLR and MACE were significantly increased in SF patients (P=0.029 and 0.014, respectively). There were no significant differences in the 4-year cumulative rates of death and nonfatal MI between the 2 groups. During the clinical follow-up from 1 to 4 years, increases in the rates of death, nonfatal MI, TLR, and MACE were similar between SF and non-SF patients. The difference in the 4-year cumulative risk rates of TLR and MACE peaked at approximately 1 year and remained constant through 4 years of follow-up (Figure 1).

Cox proportional hazards regression analysis was performed to adjust for confounders. After adjusting for the factors that are seen as clinically important for MACE, namely, age, diabetes, renal insufficiency, multivessel disease, prior infarction, acute MI, and left ventricular ejection fraction, the association of SF and MACE at 4 years remained significant (hazard ratio, 1.91; 95% confidence interval, 1.10 to 3.33; P=0.023). Similarly, when all group differences with P<0.10 (hemodialysis, current smoking, multivessel disease, the use of β-blockers, right coro-
nary artery, in-stent restenosis, tortuosity, chronic total occlusion, and total stent length) were forced in the model, the association of SF and MACE at 4 years remained significant (hazard ratio, 1.96; 95% confidence interval, 1.02 to 3.76; \( P = 0.043 \)).

Table 5 summarizes the frequency of very late stent thrombosis up to 4 years. According to the Academic Research Consortium definitions, the cumulative incidence of any very late stent thrombosis during 4 years was not different between the 2 groups. No significant differences were observed in rates of very late stent thrombosis when the events were assessed as “definite” or “probable” in the 2 groups. Very late stent thrombosis (1 to 4 years) occurred in 2 patients (2.9%) in the SF group at 999 and 1218 days after the index procedure and in 10 patients (1.4%) in the non-SF group at 441, 484, 570, 627, 895, 990, 1157, 1318, 1404, and 1457 days (\( P = 0.281 \)). In addition, frequencies of early cessation of thienopyridine therapy within 6 months after the index procedure were similar in the 2 groups, at 19.4% in the SF group and 13.6% in the non-SF group (\( P = 0.567 \)).

**Discussion**

The major findings of the present study are as follows: (1) patients with SF after SES implantation had significantly higher...
late loss and significantly higher rates of restenosis at 6- to 9-month angiographic follow-up and TLR and MACE at 1 year compared with non-SF patients; (2) at 4 years, moreover, SF versus non-SF patients had significantly higher rates of TLR and composite MACE, without an increased risk of very late stent thrombosis; (3) between 1 and 4 years, however, stent thrombosis, MI, death, and TLR were uncommon and occurred with similar frequency in SF and non-SF patients.

In the pre-DES era, SF was considered a rare event typically observed with the use of stents in anatomic locations associated with unique implant technique or when exposed to traumatic extravascular forces. In the current era, however, a 1.9% to 16.0% incidence of SF after SES implantation has been recognized as one of the clinically relevant contributors to focal in-stent restenosis. In the current study, SF patients had a significantly higher rate of in-stent restenosis at 6 to 9 months, as compared with non-SF patients. An increase in mechanical stimulation of the vessel wall, the loss of mechanical scaffolding of the stent, and a decrease in local drug delivery may have predominantly contributed to the higher rates of in-stent restenosis.

Moreover, the analyses of several single-center studies showed that SF resulted in higher frequencies of TLR and/or MACE at 6 to 12 months (5 to 7, 10 to 12). In 382 patients who underwent follow-up angiography 6 to 9 months after the index procedure, we previously reported that the occurrence of SF after SES implantation did not lead to an increased risk of TLR or MACE at 450 days, despite a higher incidence of in-stent restenosis. In this study, SF versus non-SF patients had significantly increased rates of TLR and composite MACE at 1 year, which was consistent with some observations reported by others, but was different from our previous results. One of the possible explanations for different outcomes was that with a larger number of patients/events, their power to detect differences increased in the current study compared with their previous one.

Although several large-scale registries raised concerns on the long-term safety and efficacy of DES as compared with bare-metal stents, recent reports demonstrated that the use of SES versus bare-metal stents had superior efficacy in terms of a reduction of the need for repeat revascularization without an increase in rates of death, MI, or stent thrombosis for up to 5 years. Fortunately, the issue of SF was not assessed or described in these trials, and it was uncertain whether SF could exert a detrimental effect on long-term outcomes, especially beyond 1 year after SES implantation. At present, moreover, long-term arterial responses at the site of SF as well as timing of SF have not been well clarified. Once SF occurs in the coronary artery, however, an increase in local mechanical stimulation caused by the broken struts, incomplete coverage of unstable plaque, and stent compression at the fracture site may permanently persist, all of which can increase the likelihood of late restenosis and/or clinical events, even in the long term after stent implantation in this particular population. There has been only 1 small retrospective and observational study concerning long-term outcomes of SF patients. In 273 consecutive patients including 18 SF cases, Lio et al. compared clinical outcomes at 2 time points after the index procedure between patients with and without SF. Although SF versus non-SF was associated with significantly higher TLR rates at 6- to 9-month follow-up, SF patients had no cardiac events such as death, TLR and stent thrombosis during 2 years after the initial follow-up. In agreement with their observation, our results demonstrate that SF versus non-SF is associated with a significantly higher 1-year MACE rate, mainly driven by a significantly higher TLR rate; however, increases in the rates of TLR and MACE were gradual and relatively low after the first year in SF and non-SF patients. This translates into equally low MACE rates up to 4 years in SF and non-SF patients who did not have repeat revascularization or any other cardiac events within 1 year. Importantly, our study also showed that the presence of SF did not increase risk of very late stent thrombosis. These observations therefore suggest that even if SF is identified, repeat revascularization should be considered carefully, dependent on clinical symptom, extent, and/or severity of myocardial ischemia on functional testing and associated anatomic severity of coronary lesions. Finally, no optimal intervention strategy (balloon angioplasty, bare-metal stents, homogenous DES, or heterogeneous DES) of in-stent restenosis at fracture sites to date has been well established because there have been few studies on the topic of this issue. Avoidance of unnecessary long and/or overlapping SES implantation for lesions at high-risk for SF might help prevent restenosis.

Study Limitations
Several potential limitations must be mentioned. First, it is a retrospective study on a limited number of patients, especially those with SF. Therefore, the selection bias may exist in these 2 groups, and it may lead to a biased conclusion. Nevertheless, to the best of our knowledge, this study has the largest sample size of SES fracture and the longest follow-up periods. Confirmatory studies with a larger number of patients for longer concomitant study periods are required to clarify this issue. Second, IVUS at follow up was not performed in all patients. In our study, 61% of SF was confirmed by using IVUS as well as careful plain fluoroscopic examination, which was reported to be useful for detecting SF of SES because of its radiopacity and better fluoroscopic visualization. On the other hand, sensitivity of plain fluoroscopic examination and IVUS to identify SF is limited, and it is possible that fracture or separation of a single-strut filament has not been identified, dependent on conditions of the examination. Third, the time point at which SF occurs after SES implantation was not assessed in the current study. It may play a crucial role in the occurrence of restenosis in patients with SF because the efficacy of SES on restenosis is closely related to the release of an active therapeutic compound. It is possible that SF can occur after the onset of early events as well as after 6- to 9-month angiographic evaluation of SF.

Table 5. Very Late Stent Thrombosis According to ARC Definitions

<table>
<thead>
<tr>
<th>ARC Definitions</th>
<th>Fracture</th>
<th>Nonfracture</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>2 (2.9)</td>
<td>6 (0.8)</td>
<td>0.148</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>2 (0.3)</td>
<td>0.833</td>
</tr>
<tr>
<td>Possible</td>
<td>0</td>
<td>2 (0.3)</td>
<td>0.833</td>
</tr>
<tr>
<td>Definite or</td>
<td>2 (2.9)</td>
<td>8 (1.1)</td>
<td>0.214</td>
</tr>
<tr>
<td>probable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ARC event</td>
<td>2 (2.9)</td>
<td>10 (1.4)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

ARC indicates Academic Research Consortium. Values are expressed as n (%).
Fourth, this study does not elucidate whether extended dual antiplatelet therapy should be considered in SF patients because of lack of available data for long-term antiplatelet therapy. Finally, SF can occur in other type of DES and bare-metal stents as well as SES. Our results apply only to SES and may not be generalized to all DES types.

Conclusions

The present study suggests that although SF patients have a higher MACe rate at 4 years compared with non-SF patients, the increases in the rates of the events (very late stent thrombosis, MI, death, and TLR) between years 1 and 4 are low and not significantly different between the 2 groups.

Acknowledgments

We thank Roberto Patarca and Shoko Takahashi for assistance with thrombosis, MI, death, and TLR) between years 1 and 4 are increases in the rates of the events (very late stent thrombosis, MI, death, and TLR) between years 1 and 4 are low and not significantly different between the 2 groups.

Disclosures

None.

References


CLINICAL PERSPECTIVE

The presence of stent fracture (SF) after sirolimus-eluting stent implantation has been reported to be associated with an increased risk of in-stent restenosis and major adverse cardiac events rates within a 1-year observation period. However, it remains uncertain whether SF can increase the risk of major adverse cardiac events beyond 1 year after sirolimus-eluting stent implantation. Accordingly, we sought to evaluate whether SF might influence long-term clinical outcomes, including rates of stent thrombosis, target-lesion revascularization, nonfatal myocardial infarction, and death at 4 years. We found that patients with SF had higher rates of restenosis at 6- to 9-month angiographic follow-up and subsequent target-lesion revascularization and major adverse cardiac events at 1 year than those without SF. Between 1 and 4 years, however, stent thrombosis, myocardial infarction, death, and target-lesion revascularization were uncommon and occurred with similar frequency in SF and non-SF patients.
Impact of Sirolimus-Eluting Stent Fracture on 4-Year Clinical Outcomes
Hisashi Umeda, Tomoko Kawai, Naoki Misumida, Tomoyuki Ota, Kazutaka Hayashi, Mitsunori Iwase, Hideo Izawa, Shigeo Sugino, Takeshi Shimizu, Yasushi Takeichi, Ryoji Ishiki, Haruo Inagaki, Yukio Ozaki and Toyoaki Murohara

Circ Cardiovasc Interv. 2011;4:349-354; originally published online August 2, 2011; doi: 10.1161/CIRCINTERVENTIONS.110.958306
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/4/4/349

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org/subscriptions/