# Long-term outcomes of rotational atherectomy in coronary bifurcation lesions

YUXIANG DAI[1,2], ATSUTOSHI TAKAGI[1], HAKUOH KONISHI[1], TETSURO MIYAZAKI[1], HIROSHI MASUDA[1], KAZUNORI SHIMADA[1], KATSUMI MIYAUCHI[1] and HIROYUKI DAIDA[1]

[1]Department of Cardiology, Juntendo University Hospital, Tokyo 113-8421, Japan;
[2]Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai 200032, P.R. China

Received September 9, 2014; Accepted July 23, 2015

DOI: 10.3892/etm.2015.2817

**Abstract.** The aim of the present study was to determine the long-term outcomes of bifurcation lesions following a rotational atherectomy (ROTA). In this retrospective study, patients that had undergone a ROTA of the bifurcation coronary lesions in Juntendo University Hospital (Tokyo, Japan) were enrolled between January 2007 and December 2009, and received follow-up for a median duration of 48 months (range, 12-84 months). A total of 337 patients were enrolled. Each patient was treated with an average of 1.2±0.4 ROTA burrs (mean size, 2.9±0.3 mm). Baseline lesion length, reference diameter, minimal lumen diameter (MLD) and percentage of diameter stenosis (%DS) prior to the procedure were comparable between the DM and non-DM patients. Furthermore, MLD, %DS and acute gain following the procedure were similar between the two groups. At follow-up, DM patients exhibited a significantly decreased MLD (1.97±0.92 vs. 2.26±0.73 mm; P=0.0038), increased %DS (27.9±21.3 vs. 20.2±13.3%; P=0.022) and late loss (0.70±0.45 vs. 0.42±0.36 mm; P=0.0047) compared with the non-DM patients. Follow-up examinations (mean duration, 52.2±19.4 months) revealed that the DM patients experienced significantly higher rates of target lesion revascularization (TLR) [28 (15.7%) vs. 8 (5.0%); P=0.0011], target lesion (TL) restenosis [46 (25.8%) vs. 20 (12.6%); P=0.0019] and major adverse cardiac events (MACE) [36 (20.2%) vs. 19 (12.0%), P=0.039] compared with the non-DM patients. Although the usage of ROTA and drug-eluting stent evidently improved long-term outcomes in patients with bifurcation lesions, DM remained an independent risk factor for TLR, TL restenosis and MACE. Therefore, the management of DM in bifurcation lesions treated with ROTA requires increased investigation in future clinical practice.

*Correspondence to:* Dr Hakuoh Konishi, Department of Cardiology, Juntendo University Hospital, 2-1-1 Hongo, Tokyo 113-8421, Japan
E-mail: hakuoh_konishi@yeah.net

*Abbreviations:* BA, balloon angioplasty; BMS, bare-metal stents; DES, drug-eluting stents; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; MI, myocardial infarction; MLD, minimum luminal diameter; PCI, percutaneous coronary intervention; ROTA, rotational atherectomy; TLR, target lesion revascularization; TVR, target vessel revascularization; %DS, percentage of diameter stenosis

*Key words:* rotational atherectomy, long-term outcomes, coronary bifurcation lesion

## Introduction

Coronary bifurcation lesions represent a complex lesion subtype, and treatment via a percutaneous coronary intervention (PCI) has been associated with reduced procedural success rates, an increased rate of restenosis and major adverse cardiovascular events (MACE) (1-4). In previous decades, considerable progress has occurred in the field of PCI, including the use of plaque debulking [rotational atherectomy (ROTA) or directional atherectomy and ablative lasers], cutting balloon, bare-metal stents (BMS), and particularly the development of drug-eluting stents (DES) (5-8). Previous studies have indicated that DES are able to significantly improve the incidence of myocardial infarction (MI), target vessel revascularization (TVR) and MACE following PCI of bifurcation coronary lesions, compared with BMS (9-12). Despite advances in device technology, the treatment of coronary bifurcation lesions remains a technically challenging field. An alternative to PCI is the coronary artery bypass graft; however, PCI is preferred due to minimal invasion (13).

It has been estimated that bifurcation lesions comprise 15-20% of all PCI procedures (14,15). Stenting of a bifurcation lesion may result in a significant reduction in the angiographic diameter of the ostium of the side branch (SB), primarily as a result of plaque shifting, ostial recoil and propagation of dissection (16,17). ROTA has been advocated for the treatment of bifurcation lesions as it appears to effectively remove plaque while minimizing injury to adjacent normal arterial segments to a greater extent compared with standard balloon angioplasty (BA), while additionally avoiding 'snow' plaque shifting (18,19). However, the role and long-term outcomes of ROTA for the treatment of bifurcation coronary lesions in the DES era remain unknown and require further investigation. Diabetes mellitus (DM) is a major contributor

to the development of coronary artery disease (CAD) as well as to the outcomes following various manifestations of the disease. DM patients have a higher prevalence of complex coronary lesions such as triple-vessel, bifurcation and ostial lesions. Therefore, the aim of the present study was to determine the long-term outcomes of bifurcation lesions following a ROTA.

## Materials and methods

*Study subjects*. This retrospective study enrolled 863 consecutive patients that had undergone elective PCI with bifurcation coronary lesions at Juntendo University Hospital (Tokyo, Japan) between January 2007 and December 2009. Finally, 337 patients met the inclusion criteria of the present study, which comprised the use of ROTA for the treatment of bifurcation coronary lesions. The baseline characteristics and follow-up clinical information of the patients were obtained from medical record reviews. The study was approved by the Ethics Committee of Juntendo University Hospital.

All laboratory measurements were performed immediately following patient admission. Renal function was evaluated via the estimated glomerular filtration rate (eGFR), which was calculated according to the simplified 'Modification of Diet in Renal Disease' equation, as follows: eGFR (ml/min/1.73 $m^2$) = 186 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742, if female), where Scr is the serum creatine level (20). All coronary angiograms obtained from the study patients were reviewed by board-certified interventional cardiologists.

Diabetes mellitus (DM) was defined as the patient receiving active treatment with insulin or an oral antidiabetic agent, or if the patient exhibited an abnormal blood glucose level following overnight fasting or abnormal glucose tolerance test results according to the World Health Organization criteria (21). The patients were divided into DM and non-DM groups.

*Procedures*. All baseline, procedural, and follow-up angiograms were performed immediately following the administration of 200 $\mu$g intracoronary nitroglycerin, and the treated lesion was evaluated using two or more angiographic projections. The Cardiovascular Measurement System (Medis Medical Imaging Systems, Leiden, Netherlands) was used by two experienced angiographers to perform quantitative coronary angiography. The reference diameter, lesion length, % of diameter stenosis (%DS) and minimal lumen diameter (MLD) were measured using the view showing the smallest luminal diameter in the diastolic frames.

Lesions were classified according to the modified American College of Cardiology/American Heart Association grading system as type A, B1, B2 or C (22). Type A and B1 lesions were categorized as simple, while type B2 and C lesions were designated complex. The degree of coronary calcification was judged as follows: Grade 1, calcification difficult to recognize; grade 2, easily recognized; grade 3, recognized in >50% of a single coronary artery; and grade 4, recognized in nearly the entire length of a single coronary artery.

Louvard *et al* (23) defined a bifurcation lesion as 'a coronary artery narrowing occurring adjacent to, and/or involving, the origin of a significant SB'. A significant SB was defined as a branch (typically with a diameter of >1.5 mm) that would result in detrimental effects if lost, due to the associated symptoms, location of ischemia and loss of viability, collateral vessels and ventricular function (23). The diameter of SB was classified as small (≤2.0 mm), medium (2.0-2.5 mm) or large (≥2.5 mm). Lesion angulation was measured at baseline in a working view, which provided the optimal SB ostium visualization, by measuring the distal angle between the SB and the main vessel (MV) distal to the bifurcation. When angulation was <70˚, the bifurcation lesion was defined as Y-shape, while bifurcation lesions with angulation of >70˚ were defined as T-shape. The bifurcation lesion type was classified according to the classification of Medina *et al (*24).

A true bifurcation coronary lesion was defined as a coronary lesion with ≥50% luminal diameter stenosis in the parent vessel and the ostium of an SB arising from the lesion, which were observed to be ≥2.0 mm in diameter by visual estimation, in addition to specific plaque geography meeting the Medina classification *(*24), as follows: (1,1,1), (1,0,1), (0,1,1).

A simple stenting strategy was defined as stenting of the MV only, and provisional stenting of the SB only if bailout of the SB was necessary, while a complex stenting strategy was defined as routine stenting in the MV and SB using a variety of techniques, including crush, mini-crush, modified crush, culotte, simultaneous kissing stent and T-stent (25).

*Events***.** Acute gain and late loss were defined as the difference between pre- and post-procedural MLD, and between post-procedural and follow-up MLD. Procedural success was defined as the achievement of <30% angiographic residual stenosis in the MV, <50% in the SB by quantitative coronary angiography and thrombolysis in MI flow grade 3 in the MV and SB, with no periprocedural or in-hospital complications such as mortality, MI or emergent bypass surgery. MI was defined as the MB isoform of creatine kinase level was >3 times the normal value, with or without the occurrence of new abnormal Q-waves in ≥2 contiguous leads.

Acute thrombosis was defined as the occurrence of acute closure of the target vessel <24 h after the index procedure. Subacute thrombosis was defined as the occurrence of acute closure of the target vessel after 24 h but within 1 month, and late thrombosis was defined as the occurrence of acute closure ≥1 month after the index procedure (26).

Angiographic evaluations were performed at regular intervals. In addition, a repeat coronary angiography was scheduled within 5-9 months after the index procedure, unless earlier intervention was required due to symptoms or a history of myocardial ischemia. Follow-up was discontinued after December 2010.

Target lesion (TL) restenosis was defined as a stenosis diameter of ≥50% within the stented segment and the 5-mm proximal and distal persistent area at follow-up angiography. In addition, TL revascularization (TLR) was defined as any revascularization or bypass surgery of the original TL, which was performed in the presence of angiographic restenosis of ≥50% by quantitative angiography in the presence of ischemic symptoms or objective evidence of ischemia, or in the

Table I. Baseline demographics and risk factors in DM and non-DM patients.

| Parameter | DM group (n=178) | No DM group (n=159) | Total cohort (n=337) | P-value |
|---|---|---|---|---|
| Baseline demographics | | | | |
| Age (years)[a] | 68.7±8.8 | 67.4±9.3 | 68.1±9.1 | 0.19 |
| Gender (male)[b] | 148 (83.1) | 135 (84.9) | 283 (84.0) | 0.66 |
| Risk factors | | | | |
| BMI (kg/m$^2$)[c] | 22.9 (21.1-25) | 23.8 (21.6-25.2) | 23.3 (21.4-25.1) | 0.13 |
| Waist (cm)[c] | 85 (82-90) | 86 (82-90) | 86 (82-90) | 0.36 |
| Current smoking[b] | 78 (43.8) | 64 (40.2) | 142 (42.3) | 0.21 |
| Hypertension[b] | 132 (74.2) | 119 (74.8) | 251 (74.5) | 0.86 |
| Hyperlipidemia[b] | 131 (73.6) | 120 (75.5) | 251 (74.5) | 0.69 |
| MS[b] | 80 (44.9) | 55 (34.8) | 134 (40.0) | 0.06 |
| Family history[b] | 51 (28.7) | 50 (31.5) | 101 (30.0) | 0.58 |
| Previous PCI[b] | 17 (9.6) | 11 (6.9) | 28 (8.3) | 0.38 |
| Serum creatinine[c] | 0.88 (0.74-1.12) | 0.85 (0.74-1.00) | 0.86 (0.74-1.04) | 0.08 |
| eGFR[c] | 85.9 (67.7-102.5) | 92.3 (77.0-107.9) | 88.4 (72.1-105.1) | 0.03 |
| ESRD on hemodialysis[b] | 27 (15.2) | 12 (7.6) | 39 (11.6) | 0.03 |

Data presented as [a]the mean ± SD, [b]n (%) and [c]mean (interquartile range). DM, diabetes mellitus; BMI, body mass index; MS, metabolism syndrome; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease.

presence of angiographic restenosis ≥70% with no evident ischemic symptoms or indications of ischemia. The TL was considered to be the area covered by the stent plus a 5-mm margin proximal and distal to the edges of the stent (27). Furthermore, TVR was defined as clinically driven PCI or coronary artery bypass grafting of the treated vessel. MACE was defined as a composite of clinical events including TLR, TL restenosis, non-fatal MI (Q- or non-Q-wave MI), acute thrombosis, subacute thrombosis and cardiac fatality (27).

*Statistical analysis*. Discrete variables are presented as frequency counts and percentages. Continuous variables were expressed as the mean ± standard deviation when normally distributed, or as the median with interquartile range if not.

The $\chi^2$ test, two-tailed independent Student's t-test and Wilcoxon/Kruskal-Wallis test were used to compare proportions and mean/median values. Independent predictors of long-term outcomes were identified using Cox's proportional hazards analysis and logistic regression analysis. Kaplan-Meier accumulated survival curves were drawn and log-rank values were calculated to assess their statistical significance.

Data analysis was performed using JMP software, version 8.0 (SAS Institute Inc., Cary. NC. USA). P≤0.05 was considered to indicate a statistically significant difference.

## Results

*Patient characteristics*. A total of 337 patients met the study criteria and were enrolled into the present study. The patients had a mean age of 68.1±9.1 years (age range, 52-86 years old), and 283 subjects (84.0%) were male. In total, 178 patients (52.8%) had a history of DM, 28 patients had a history of PCI and 39 patients were receiving hemodialysis treatment due to end-stage renal disease. Detailed baseline demographics and clinical risk factors in DM and non-DM patients are presented in Table I. Baseline patient characteristics were comparable between the two groups (P>0.05), with the exception of reduced eGFR and an increased number of hemodialysis patients in the DM group compared with the non-DM group.

*Angiographic and procedure characteristics*. A total of 211 cases (62.6%) exhibited severe calcification (grade 3 or 4) and 334 cases (99.1%) exhibited complex lesions (type B2 or C). Furthermore, 211 lesions (62.6%) had an angulation of >70˚, while 126 lesions (37.4%) exhibited an angulation of <70˚. The bifurcation of the left anterior descending artery/diagonal (193 lesions, 57.3%) and left main/left anterior descending/left circumflex artery (69 lesions, 20.5%) were among the most frequently involved locations. There were 202 cases (59.9%) with involvement of the MV and SB, with 155 cases (50.0%) classified as type (1,1,1), 20 cases (5.9%) as type (1,0,1) and 27 cases (8.0%) as type (0,1,1). In addition, there were 146 cases (43.3%) with a medium SB diameter, 100 cases (29.7%) with a large SB diameter and 152 cases (45.1%) with a true bifurcation lesion. Each case was treated with an average of 1.2±0.4 ROTA burrs, with a mean size of 2.9±0.3 mm. The mean values of MLD pre-PCI and post-PCI were 0.5±0.3 and 2.6±0.4 mm, respectively. There were 23 cases (6.8%) treated with BA (including cutting balloon), 46 cases (13.7%) with BMS and 268 cases (79.5%) with DES. A total of 287 cases (85.2%) were treated with a simple stenting technology and 29 cases (8.6%) with a complex stenting technology, with a mean total stent length was 33.0±16.9 mm. Furthermore, 43 cases (12.8%) received SB stents and 95 cases (28.3%) received final kissing-BA. In total, 319 cases (94.7%) exhibited immediate procedural success. Detailed angiographic and procedural characteristics

Table II. Angiographic and procedural characteristics in DM and non-DM patients.

A, Angiographic characteristics[a]

| Parameter | DM group (n=178) | No DM group (n=159) | Total cohort (n=337) | P-value |
|---|---|---|---|---|
| Severe calcification (Grade 3/4) | 113 (63.5) | 98 (61.6) | 211 (62.6) | 0.73 |
| Complex lesion (Type B2/C) | 178 (100.0) | 156 (98.1) | 334 (99.1) | 0.10 |
| Calcification severity (Grade 3/4) | 113 (63.5) | 98 (61.6) | 211 (62.6) | 0.73 |
| Bifurcation angulation | | | | 0.42 |
| Y (<70) | 115 (64.6) | 96 (60.4) | 211 (62.6) | |
| T (>70) | 63 (35.4) | 63 (39.6) | 126 (37.4) | |
| Bifurcation location | | | | 0.23 |
| LM, LAD, LCX | 30 (16.9) | 39 (24.5) | 69 (20.5) | |
| LM, intermediate branch, LAD | 1 (0.6) | 4 (2.5) | 5 (1.5) | |
| LAD, diagonal branch | 106 (59.6) | 87 (54.7) | 193 (57.3) | |
| LAD, septal branch | 7 (3.9) | 7 (4.4) | 14 (4.2) | |
| LCX, obtuse marginal branch | 14 (7.9) | 11 (6.9) | 25 (7.4) | |
| RCA, right ventricular branch | 20 (11.2) | 11 (6.9) | 31 (9.2) | |
| Bifurcation type | 109 (61.2) | 93 (58.5) | 202 (59.9) | 0.42 |
| (1,1,1) | 86 (48.3) | 69 (43.3) | 155 (50.0) | |
| (1,0,1) | 9 (5.1) | 11 (6.9) | 20 (5.9) | |
| (0,1,1) | 14 (7.9) | 13 (8.2) | 27 (8.0) | |
| (1,1,0) | 32 (18.0) | 36 (22.6) | 68 (20.2) | |
| (1,0,0) | 6 (3.4) | 2 (1.3) | 8 (2.4) | |
| (0,1,0) | 28 (15.7) | 21 (13.2) | 49 (14.5) | |
| (0,0,1) | 3 (1.7) | 7 (4.4) | 10 (3.0) | |
| Branch vessel size | | | | 0.24 |
| Medium (2.0-2.5 mm) | 83 (46.6) | 63 (39.6) | 146 (43.3) | |
| Large (≥2.5 mm) | 46 (25.8) | 54 (34.0) | 100 (29.7) | |
| True bifurcation lesions | 84 (47.2) | 68 (42.8) | 152 (45.1) | 0.42 |

B, Procedural characteristics

| Parameter | DM group (n=178) | No DM group (n=159) | Total cohort (n=337) | P-value |
|---|---|---|---|---|
| ROTA number[b] | 1.2±0.4 | 1.3±0.4 | 1.2±0.4 | 0.26 |
| ROTA size[b] | 2.9±0.3 | 2.9±0.3 | 2.9±0.3 | 0.14 |
| MLD pre-PCI[b] | 0.5±0.3 | 0.5±0.3 | 0.5±0.3 | 0.25 |
| MLD post-PCI[b] | 2.7±0.4 | 2.6±0.4 | 2.6±0.4 | 0.71 |
| Total stent length (mm)[b] | 33.1±18.4 | 32.8±15.0 | 33.0±16.9 | 0.88 |
| PCI strategy[a] | | | | 0.30 |
| Balloon angioplasty | 11 (6.2) | 12 (7.6) | 23 (6.8) | |
| Bare-metal stents | 29 (16.3) | 17 (10.7) | 46 (13.7) | |
| Drug-eluting stents | 138 (77.5) | 130 (81.8) | 268 (79.5) | |
| Stenting strategy[a] | | | | 0.63 |
| Simple stenting technology | 153 (86.0) | 134 (84.3) | 287 (85.2) | |
| Complex stenting technology | 13 (7.3) | 16 (10.1) | 29 (8.6) | |
| Use of side-branch stents | 17 (9.6) | 26 (16.4) | 43 (12.8) | 0.06 |
| Final kissing-balloon angioplasty | 45 (25.3) | 50 (31.4) | 95 (28.3) | 0.21 |
| Procedural success | 171 (96.1) | 148 (93.1) | 319 (94.7) | 0.23 |

Presented as [a]n (%) and [b]mean ± SD. DM, diabetes mellitus; LM, left main; LAD, left anterior descending artery; LCX, left circumflex artery; ROTA, rotational atherectomy; MLD, minimum luminal diameter; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table III. Quantitative coronary angiographic data of DM and non-DM patients.

| Parameter | DM group (n=178) | No DM group (n=159) | Total cohort (n=337) | P-value |
|---|---|---|---|---|
| Lesion length (mm) | 21.8±6.5 | 23.1±6.4 | 22.4±6.4 | 0.07 |
| Reference diameter (mm) | 2.73±0.36 | 2.75±0.33 | 2.74±0.35 | 0.55 |
| Minimal lumen diameter (mm) | | | | |
| Pre-PCI | 0.48±0.28 | 0.45±0.31 | 0.47±0.29 | 0.44 |
| Post-PCI | 2.66±0.42 | 2.64±0.39 | 2.65±0.41 | 0.71 |
| Follow-up | 1.97±0.92 | 2.26±0.73 | 2.11±0.85 | <0.01 |
| Diameter stenosis (%) | | | | |
| Pre-PCI | 82.4±10.1 | 83.4±11.4 | 82.9±10.7 | 0.41 |
| Post-PCI | 5.2±4.0 | 5.7±4.6 | 5.5±4.3 | 0.60 |
| Restudy | 27.9±21.3 | 20.2±13.3 | 24.3±18.1 | 0.02 |
| Acute gain (mm) | 2.18±0.47 | 2.19±0.48 | 2.18±0.47 | 0.87 |
| Late loss (mm) | 0.70±0.45 | 0.42±0.36 | 0.57±0.41 | <0.01 |

Data presented as the mean ± SD. DM, diabetes mellitus; PCI, percutaneous coronary intervention.

Table IV. Long-term outcomes in DM and non-DM patients.

| Long-term outcome | DM group (n=178) | No DM group (n=159) | Total cohort (n=337) | P-value |
|---|---|---|---|---|
| Mean follow-up (months)[a] | 53.7±19.1 | 50.5±19.8 | 52.2±19.4 | 0.13 |
| Cardiac mortality | 8 (4.5) | 8 (5.0) | 16 (4.7) | 0.82 |
| TLR | 28 (15.7) | 8 (5.0) | 36 (10.7) | <0.01 |
| TVR | 7 (3.9) | 12 (7.6) | 22 (6.5) | 0.15 |
| Target lesion restenosis | 46 (25.8) | 20 (12.6) | 66 (19.6) | <0.01 |
| Non-fatal MI | 0 (0.0) | 1 (0.6) | 1 (0.3) | 0.47 |
| SAT | 0 (0.0) | 2 (1.3) | 2 (0.6) | 0.22 |
| MACE | 36 (20.2) | 19 (12.0) | 55 (16.3) | 0.04 |

[a]Data presented as the mean ± SD. All other fields presented as n (%). DM, diabetes mellitus; TLR, target lesion revascularization; TVR, target vessel revascularization; MI, myocardial infarction; SAT, subacute thrombosis; MACE, major adverse cardiovascular events.

in the DM and non-DM patients were comparable (P>0.05) and are presented in Table II.

Quantitative coronary angiographic data in the two groups are presented in Table III. Baseline lesion length, reference diameter, MLD and %DS prior to the procedure were comparable between the DM and non-DM patients (P>0.05). MLD, %DS and acute gain following the procedure were also comparable between two groups. DM patients exhibited a significantly reduced MLD value (1.97±0.92 vs. 2.26±0.73 mm; P=0.0038), increased %DS value (27.9±21.3 vs. 20.2±13.3%; P=0.022) and late loss (0.70±0.45 vs. 0.42±0.36 mm; P=0.0047) compared with the non-DM patients.

*Clinical events for long-term outcomes.* Mean clinical follow-up periods were 53.7±19.1 and 50.5±19.8 months in the DM and non-DM groups, respectively (P=0.13). Cumulative clinical events for long-term outcomes are shown in Table IV. During the follow-up period, there were 8 cases of cardiac fatality in each group, no cases of acute thrombosis in either group, 1 case of non-fatal MI and 2 cases of subacute thrombosis in the non-DM group. The rates of TLR [28 (15.7%) vs. 8 cases (5.0%), P=0.0011], TL restenosis [46 (25.8%) vs. 20 cases (12.6%), P=0.0019] and MACE [36 (20.2%) vs. 19 cases (12.0%), P=0.039] were significantly higher in the DM group compared with the non-DM group.

Kaplan-Meier survival curves indicated that the rates of TLR and MACE were significantly higher in the non-DES group (Fig. 1A and B; log-rank P<0.0001) and DM group (Fig. 2A and B; log-rank P<0.05).

Multivariate Cox proportional hazard analysis (Table V) showed that, following adjustment, DM (HR, 3.06; 95%CI, 1.41-7.36; P=0.0039), current smoker status (HR, 2.25; 95%CI, 1.03-4.73; P=0.043) and DES (HR, 0.40; 95%CI, 0.23-0.69; P=0.0013) were independent predictors of TLR, while DM and DES were independent predictors of MACE. In addition, logistic regression analysis demonstrated that

Table V. Multivariate Cox proportional hazard models for TLR and MACE.

| | TLR (multivariate, adjusted) | | MACE (multivariate, adjusted) | |
|---|---|---|---|---|
| Parameter | HR (95%CI) | P-value | HR (95%CI) | P-value |
| Age (10 year increase) | 1.13 (0.75, 1.75) | 0.56 | 1.38 (0.78, 2.52) | 0.27 |
| Gender (female) | 0.65 (0.19, 1.87) | 0.44 | 0.74 (0.29, 1.76) | 0.51 |
| Metabolism syndrome | 1.98 (0.93, 4.26) | 0.077 | 1.59 (0.87, 2.88) | 0.13 |
| Diabetes mellitus | 3.06 (1.41, 7.36) | 0.0039 | 1.55 (1.10, 2.22) | 0.01 |
| Hypertension | 1.02 (0.48, 2.19) | 0.97 | 1.51 (0.82, 2.71) | 0.18 |
| Hyperlipidemia | 1.98 (0.94, 4.10) | 0.073 | 1.85 (0.97, 3.40) | 0.06 |
| Current smoker | 2.25 (1.03, 4.73) | 0.043 | 1.61 (0.88, 2.99) | 0.12 |
| ESRD on hemodialysis | 1.10 (0.37, 2.78) | 0.85 | 2.16 (0.94, 4.42) | 0.07 |
| True bifurcation | 1.07 (0.51, 2.26) | 0.87 | 1.20 (0.66, 2.21) | 0.54 |
| Bifurcation angulation (>70˚) | 0.74 (0.33, 1.57) | 0.44 | 0.85 (0.46, 1.56) | 0.61 |
| Calcified severity | 1.20 (0.58, 2.60) | 0.64 | 1.26 (0.68, 2.30) | 0.46 |
| Simple stent strategy | 1.16 (0.44, 2.88) | 0.76 | 1.16 (0.54, 2.42) | 0.70 |
| Final kissing-balloon angioplasty | 0.98 (0.41, 2.58) | 0.97 | 0.87 (0.43, 1.86) | 0.70 |
| PCI strategy (DES) | 0.40 (0.23, 0.69) | 0.0013 | 0.41 (0.26, 0.63) | <0.01 |

TLR, target lesion revascularization; MACE, major adverse cardiovascular events; CI, confidence interval; HR, hazard ratio; ESRD, end stage renal disease; PCI, percutaneous coronary intervention; DES, drug-eluting stents.

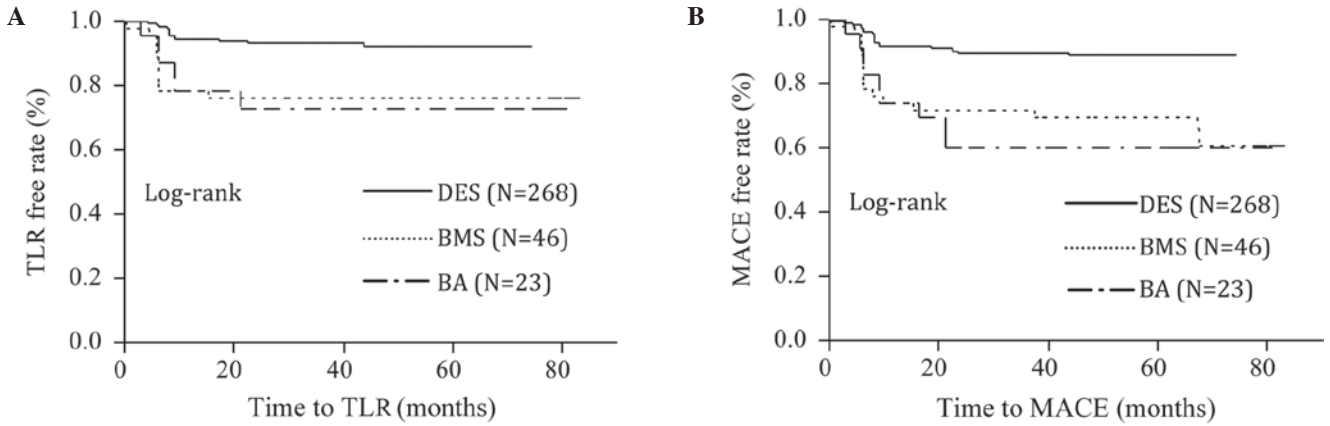


Figure 1. Kaplan-Meier survival curves for (A) TLR and (B) MACE in the BA, BMS and DES groups. TLR, target lesion revascularization; MACE, major adverse cardiovascular events; BA, balloon angioplasty; BMS, bare-metal stent; DES, drug-eluting stent.

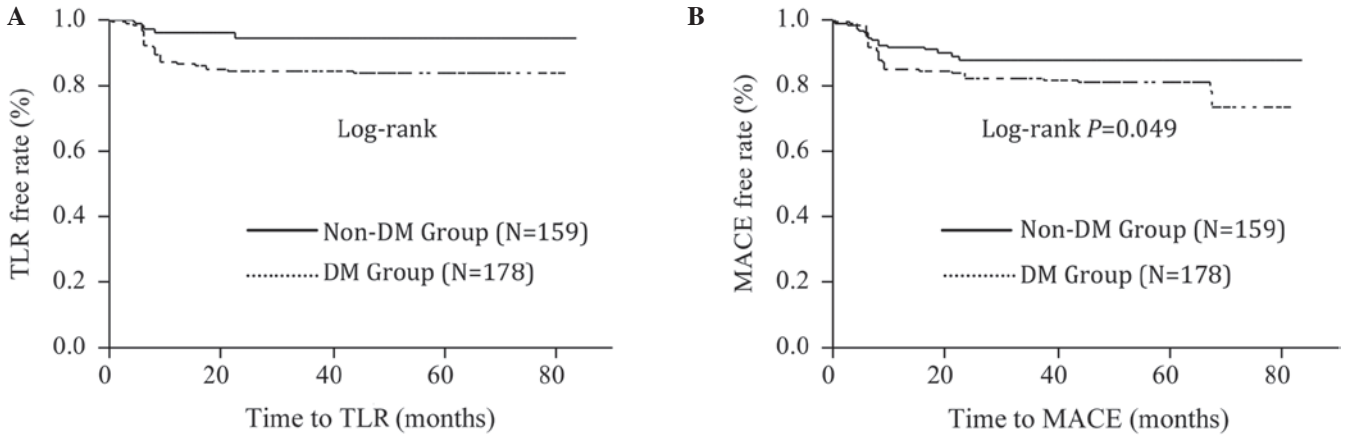


Figure 2. Kaplan-Meier survival curves for (A) TLR and (B) MACE in the DM and non-DM patients. TLR, target legion revascularization; MACE, major adverse cardiovascular events; DM, diabetes mellitus.

Table VI. Logistic regression analysis for target lesion restenosis at restudy.

| Parameter | Estimated coefficient | P-value |
|---|---|---|
| Age | 0.02 | 0.35 |
| Gender (female) | -0.94 | 0.07 |
| Metabolism syndrome | 0.08 | 0.82 |
| Diabetes mellitus | 0.47 | 0.01 |
| Hypertension | 0.09 | 0.80 |
| Hyperlipidemia | 0.55 | 0.14 |
| Current smoker | 0.98 | 0.01 |
| ESRD on hemodialysis | 0.01 | 0.98 |
| True bifurcation | 0.20 | 0.55 |
| Bifurcation angulation (>70˚) | -0.17 | 0.62 |
| Severe calcification | 0.04 | 0.91 |
| Complex stenting strategy | -0.79 | 0.09 |
| Final kissing-balloon angioplasty | 0.62 | 0.17 |
| PCI strategy (DES) | 1.51 | <0.01 |

ESRD, end stage renal disease; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

DM (P=0.0053), current smoker status (P=0.0059) and DES stenting (P<0.0001) were independent predictors of TL restenosis at follow-up (Table VI).

## Discussion

The results of the present study indicated that in bifurcation lesions treated with ROTA, patients that have undergone non-DES and DM patients exhibited higher rates of TLR and MACE. Bifurcation coronary lesion represents a complex lesion subtype and remains a major interventional challenge, despite the advances associated with DES. The complexity of treating bifurcations arises from a number of technical and clinical challenges, including variations in bifurcation anatomy (different bifurcation location, type and angulation) and dynamic differences in anatomy during treatment (plaque shifting and dissection causing flow problems), as well as time-consuming and technically challenging managements, including wire trapping and subsequent requirement of wire replacement, stent deformation, incomplete lesion coverage, stent overlap and large metal burden in the arteries (2,14,15,28).

Previous studies have indicate that DES is superior to BMS in the treatment of bifurcation lesions with lower in-stent restenosis or TLR (9,11,12,29). In the present study, significant reductions in TLR rates (15.7 vs. 5.0%; P=0.0011) and MACE rates (20.2 vs. 12.0; P=0.039) were observed in the DES group compared with the BA and BMS groups, and the use of DES was an independent protector for TLR and MACE. DES has emerged as the preferred stent platform for the treatment of coronary bifurcations. However, due to the aforementioned causes, PCI for bifurcation remains technically challenging, with reduced procedural success rates and worse clinical outcomes compared with non-bifurcation lesions, despite recent advances in interventional cardiology and the introduction of DES (30).

ROTA may provide a safe and effective means of treating this difficult lesion subtype. ROTA is performed using a high-speed rotating burr containing diamond chips, which selectively ablates calcified plaque within the coronary artery while deflecting normal elastic tissue away from the burr, resulting in a near circular lumen with a focally smooth and polished surface (31,32). The small particles are able to pass harmlessly through the distal myocardial capillary bed (33). This technique has been particularly useful for heavily calcified lesions that cannot be easily approached using BA or directional atherectomy (34). In the present study, 62.6% of the subjects had severe calcified lesions (grade 3 or 4). A number of previous studies have reported the use of ROTA for the treatment of bifurcation lesions. Nageh *et al* (35) evaluated the role of ROTA in a non-randomized study and observed that the ROTA group exhibited a higher success rate and lower in-hospital event rate. Furthermore, during a mean follow-up period of 15 months, ROTA was associated with reduced cardiac events and target lesion revascularization compared with BA. Furthermore, Dauerman *et al* (36) compared the clinical outcomes between mechanical debulking (directional or rotational coronary atherectomy) and BA for true bifurcation lesions. At the 1-year follow-up, the incidence of TVR was markedly reduced in the debulking group compared with the BA group. In addition, Ito *et al* (28) have demonstrated the safety and feasibility of ROTA and provisional SB stenting to treat SB ostial lesions of true severe bifurcation coronary artery disease. The authors suggested that ROTA of an SB ostium prior to MV stenting may be performed in patients undergoing complex bifurcation lesion angiography (28).

Based on the aforementioned findings of previous studies, the combination of ROTA and DES placement appears to be a promising approach for the treatment of bifurcation lesions. In the present study, which included a mean follow-up period of 52.2±19.4 months, the rates of TLR and MACE were 10.7 and 16.3%, respectively, in all cohorts, and 7.1 and 10.8% in DES group, respectively. Considering the extended period of follow-up, it appears to be a low incidence of TLR and MACE.

The results of previous studies have indicated that DM is a consistent clinical predictor of worse outcomes following BA, BMS and DES implantation (37-39). Patients with DM exhibit a higher risk of mortality and elevated restenosis rates following stenting compared with patients without DM, despite the application of DES. In the present study, increased rates of TLR (15.7 vs. 5.0%; P=0.0011), target lesion restenosis (25.8 vs. 12.6%; P=0.0019) and MACE (20.2 vs. 12.0%; P=0.039) were observed in the DM group compared with the non-DM group. After adjusting for other factors, DM remained an independent risk factor of TLR, TL restenosis and MACE.

Diabetes is associated with hormonal and vascular abnormalities that promote the proliferation of smooth muscle cells after vascular injury, including injury from catheter-based interventions, including BA, stenting implantation and ROTA (40). Increased smooth muscle proliferation

in diabetic patients may by induced by mitogens, such as platelet-derived growth factor and insulin-like growth factor, that stimulate cell growth and deleterious vascular effects, including endothelial dysfunction and excessive extracellular matrix production (41). In addition, DM is markedly associated with the loss of endothelial cells, increased platelet activation, hypercoagulability and the release of vasoconstrictive substances (42). This may explain why DM remained the 'Achilles' heel' of bifurcation lesions following the introduction of DES and ROTA (43). Therefore, patients with DM that receive ROTA and DES for bifurcation lesions may require adjunctive systemic pharmacotherapy to modify the underlying pathophysiological mechanisms responsible for neointimal formation and atherosclerosis progression.

There were a number of limitations in the present study. It was a retrospective and single-institution study with no randomization. Furthermore, the ROTA procedure and stenting strategy were performed at the operator's discretion. A large, randomized, multicenter clinical study is required for more accurate evaluation of this interventional approach.

In conclusion, the results of the present study demonstrate that, although ROTA and DES evidently improved long-term outcomes in patients with bifurcation lesions, DM remained an independent risk factor for TLR, TL restenosis and MACE. In the future, more emphasis should be placed on the management of DM in bifurcation lesions treated with ROTA. Intensive and systemic pharmacotherapy to control neointimal formation and atherosclerosis progression may be required for treating this particular patient population.

## References


1. Garot P, Lefèvre T, Savage M, *et al*: Nine-month outcome of patients treated by percutaneous coronary interventions for bifurcation lesions in the recent era: A report from the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial. J Am Coll Cardiol 46: 606-612, 2005.
2. Melikian N and Di Mario C: Treatment of bifurcation coronary lesions: a review of current techniques and outcome. J Interv Cardiol 16: 507-513, 2003.
3. Al Suwaidi J, Yeh W, Cohen HA, *et al*: Immediate and one-year outcome in patients with coronary bifurcation lesions in the modern era (NHLBI dynamic registry). Am J Cardiol 87: 1139-1144, 2001.
4. Al Suwaidi J, Berger PB, Rihal CS, *et al*: Immediate and long-term outcome of intracoronary stent implantation for true bifurcation lesions. J Am Coll Cardiol 35: 929-936, 2000.
5. Delhaye C, Wakabayashi K, Maluenda G, Ben-Dor I, Torguson R, Xue Z, Suddath WO, Satler LF, Pichard AD, Kent KM, *et al*: Safety and efficacy of bivalirudin for percutaneous coronary intervention with rotational atherectomy. J Interv Cardiol 23: 223-229, 2010.
6. Tang Z, Bai J, Su SP, Wang Y, Liu MH, Bai QC, Tian JW, Xue Q, Gao L, An CX, *et al*: Cutting-balloon angioplasty before drug-eluting stent implantation for the treatment of severely calcified coronary lesions. J Geriatr Cardiol 11: 44-49, 2014.
7. Liu Y, Zhou X, Jiang H, Gao M, Wang L, Shi Y and Gao J: Percutaneous coronary intervention strategies and prognosis for graft lesions following coronary artery bypass grafting. Exp Ther Med 9: 1656-1664, 2015.
8. Toutouzas K, Anousakis-Vlachochristou N and Tousoulis D: Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease. N Engl J Med 373: 580, 2015.
9. Pendyala L, Jabara R, Hou D, *et al*: Review of percutaneous therapy for bifurcation lesions in the era of drug-eluting stents. Minerva Cardioangiol 56: 89-105, 2008.
10. Chen JL, Gao RL, Yang YJ, *et al*: Short and long-term outcomes of two drug eluting stents in bifurcation lesions. Chin Med J (Engl) 120: 183-186. 2007.
11. Galassi AR, Colombo A, Buchbinder M, *et al*: Long-term outcomes of bifurcation lesions after implantation of drug-eluting stents with the mini-crush technique. Catheter Cardiovasc Interv 69: 976-983. 2007.
12. Pan M, Suárez de Lezo J, *et al*: Drug-eluting stents for the treatment of bifurcation lesions: A randomized comparison between paclitaxel and sirolimus stents. Am Heart J 153: 15.e1-e7, 2007.
13. Lassen JF, Holm NR, Stankovic G, Lefèvre T, Chieffo A, Hildick-Smith D, Pan M, Darremont O, Albiero R, Ferenc M and Louvard Y. Percutaneous coronary intervention for coronary bifurcation disease: consensus from the first 10 years of the European Bifurcation Club meetings. EuroIntervention 10: 545-560, 2014.
14. Colombo A. Bifurcation lesions. Ital Heart J 6: 475-488, 2005.
15. Sharma SK, Sweeny J and Kini AS: Coronary bifurcation lesions: a current update. Cardiol Clin 28: 55-70, 2010.
16. Dauerman HL, Higgins PJ, Sparano AM, *et al*. Mechanical debulking versus balloon angioplasty for the treatment of true bifurcation lesions. J Am Coll Cardiol 32: 1845-1852, 1998.
17. Dzavik V: Progress in percutaneous management of coronary bifurcation lesions. Minerva Cardioangiol 53: 379-401, 2005.
18. Villanueva EV, Wasiak J and Petherick ES: Percutaneous transluminal rotational atherectomy for coronary artery disease. Cochrane Database Syst Rev 4: CD003334, 2003.
19. Nageh T, Kulkarni NM, Thomas MR: High-speed rotational atherectomy in the treatment of bifurcation-type coronary lesions. Cardiology 95: 198-205, 2001.
20. Levey AS, Bosch JP, Lewis JB, *et al*: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130: 461-470, 1999.
21. World Health Organization: Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. World Health Organization, Geneva, 1999.
22. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB III, Loop FD, Peterson KL, Reeves TJ, Williams DO and Winters WL Jr: Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation 78: 486-502, 1988.
23. Louvard Y, Thomas M, Dzavik V, Hildick-Smith D, Galassi AR, Pan M, Burzotta F, Zelizko M, Dudek D, Ludman P, *et al*: Classification of coronary artery bifurcation lesions and treatments: Time for a consensus! Catheter Cardiovasc Interv 71: 175-183, 2008.
24. Medina A, Suárez de Lezo J and Pan M: A new classification of coronary bifurcation lesions. Rev Esp Cardiol 59: 183, 2006.
25. Zhang F, Dong L and Ge J: Simple versus complex stenting strategy for coronary artery bifurcation lesions in the drug-eluting stent era: A meta-analysis of randomised trials. Heart 95: 1676-1681, 2009.
26. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R and Cutlip DE: Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 356: 1020-1029, 2007.
27. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW and Leon MB: Angiographic patterns of in-stent restenosis: Classification and implications for long-term outcome. Circulation 100: 1872-1878, 1999.
28. Ito H, Piel S, Das P, *et al*: Long-term outcomes of plaque debulking with rotational atherectomy in side-branch ostial lesions to treat bifurcation coronary disease. J Invasive Cardiol 21: 598-601, 2009.
29. Stinis CT, Hu SP, Price MJ, *et al*: Three-year outcome of drug-eluting stent implantation for coronary artery bifurcation lesions. Catheter Cardiovasc Interv 75: 309-314, 2010.
30. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, *et al*: 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 124: 2574-2609, 2011.
31. Bersin RM and Simonton CA: Rotational and directional coronary atherectomy. Catheter Cardiovasc Interv 58: 485-499, 2003.
32. Saland KE, Cigarroa JE, Lange RA, *et al*: Rotational atherectomy. Cardiol Rev 8: 174-179, 2000.

33. Reisman M: Technique and strategy of rotational atherectomy. Cathet Cardiovasc Diagn (Suppl 3): 2-14, 1996.
34. Kaufmann UP and Meyer BJ: Atherectomy (directional, rotational, extractional) and its role in percutaneous revascularization. Curr Opin Cardiol 10: 412-419, 1995.
35. Nageh T, Kulkarni NM and Thomas MR: High-speed rotational atherectomy in the treatment of bifurcation-type coronary lesions. Cardiology 95: 198-205, 2001.
36. Dauerman HL, Higgins PJ, Sparano AM, *et al*: Mechanical debulking versus balloon angioplasty for the treatment of true bifurcation lesions. J Am Coll Cardiol 32: 1845-1852, 1998.
37. Smith SC Jr, Faxon D, Cascio W, *et al*: Prevention Conference VI: Diabetes and Cardiovascular Disease. Writing Group VI: Revascularization in diabetic patients. Circulation 105: e165-e169, 2002.
38. Elezi S, Kastrati A, Pache J, *et al*: Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 32: 1866-1873, 1998.
39. Ortolani P, Balducelli M, Marzaroli P, *et al*: Two-year clinical outcomes with drug-eluting stents for diabetic patients with de novo coronary lesions: results from a real-world multicenter registry. Circulation 117: 923-930, 2008.
40. Kornowski R, Mintz GS, Kent KM, *et al*: Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. A serial intravascular ultrasound study. Circulation 95: 1366-1369, 1997.
41. Sobel BE: Acceleration of restenosis by diabetes: pathogenetic implications. Circulation 103: 1185-1187, 2001.
42. Iijima R, Ndrepepa G, Mehilli J, *et al*: Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. Am Heart J 154: 688-693, 2007.
43. Diletti R, Garcia-Garcia HM, Bourantas CV, van Geuns RJ, Van Mieghem NM, Vranckx P, Zhang YJ, Farooq V, Iqbal J, Wykrzykowska JJ, *et al*; RESOLUTE All Comers Investigators: Clinical outcomes after zotarolimus and everolimus drug eluting stent implantation in coronary artery bifurcation lesions: Insights from the RESOLUTE All Comers Trial. Heart 99: 1267-1274, 2013.