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Published in:
Journal of the American College of Cardiology

DOI (link to publication from Publisher):
[10.1016/j.jacc.2013.04.015](https://doi.org/10.1016/j.jacc.2013.04.015)

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Maeng, M., Holm, N. R., Erglis, A., Kumsars, I., Niemelä, M., Kervinen, K., Jensen, J. S., Galløe, A., Steigen, T. K., Wiseth, R., Narbute, I., Gunnes, P., Mannsverk, J., Meyerdierks, O., Rotevatn, S., Nikus, K., Vikman, S., Ravkilde, J., James, S., ... Nordic-Baltic Percutaneous Coronary Intervention Study Group (2013). Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: nordic bifurcation study 5-year follow-up results. *Journal of the American College of Cardiology*, 62(1), 30-4.
<https://doi.org/10.1016/j.jacc.2013.04.015>

Long-Term Results After Simple Versus Complex Stenting of Coronary Artery Bifurcation Lesions

Nordic Bifurcation Study 5-Year Follow-Up Results

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Objectives	This study sought to report the 5-year follow-up results of the Nordic Bifurcation Study.
Background	Randomized clinical trials with short-term follow-up have indicated that coronary bifurcation lesions may be optimally treated using the optional side branch stenting strategy.
Methods	A total of 413 patients with a coronary bifurcation lesion were randomly assigned to a simple stenting strategy of main vessel (MV) and optional stenting of side branch (SB) or to a complex stenting strategy, namely, stenting of both MV and SB.
Results	Five-year clinical follow-up data were available for 404 (98%) patients. The combined safety and efficacy endpoint of cardiac death, non-procedure-related myocardial infarction, and target vessel revascularization were seen in 15.8% in the optional SB stenting group as compared to 21.8% in the MV and SB stenting group ($p = 0.15$). All-cause death was seen in 5.9% versus 10.4% ($p = 0.16$) and non-procedure-related myocardial infarction in 4% versus 7.9% ($p = 0.09$) in the optional SB stenting group versus the MV and SB stenting group, respectively. The rates of target vessel revascularization were 13.4% versus 18.3% ($p = 0.14$) and the rates of definite stent thrombosis were 3% versus 1.5% ($p = 0.31$) in the optional SB stenting group versus the MV and SB stenting group, respectively.
Conclusions	At 5-year follow-up in the Nordic Bifurcation Study, the clinical outcomes after simple optional side branch stenting remained at least equal to the more complex strategy of planned stenting of both the main vessel and the side branch. (J Am Coll Cardiol 2013;62:30–4) © 2013 by the American College of Cardiology Foundation

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Cardiology, Falun Hospital, Falun, Sweden; †††Department of Cardiology, Odense University Hospital, Odense, Denmark; §§§Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland; |||||Division of Cardiology, Kuopio University Central Hospital, Kuopio, Finland; and the ¶¶¶Division of Cardiology, Turku University Central Hospital, Turku, Finland. The study was supported by an unrestricted grant from Cordis, a Johnson & Johnson company. Dr. Holm has received research grants and honoraria from Cordis; research grants, speaker's fees, and honoraria from St. Jude Medical; and speaker's fees and honoraria from Terumo. Dr. James has received research grants from Terumo, Medtronic, and Vascular Solutions. Dr. Thuesen is a physician proctor for Edwards Lifesciences Corporation. All other authors have reported they have no relationships relevant to the contents of this paper to disclose. Drs. Maeng and Holm contributed equally to this study.

Manuscript received January 14, 2013; revised manuscript received April 1, 2013, accepted April 9, 2013.

Using drug-eluting stents (DES) in coronary bifurcation lesions, the simple strategy of main vessel (MV) and optional side branch (SB) stenting has been compared to the more complex strategy of planned stenting of the MV and SB in a number of randomized studies with short-term follow-up (1-5). The general finding was that the optional SB stenting strategy resulted in comparable or better clinical outcomes, and was associated with shorter procedure and fluoroscopy times, and less use of contrast. Therefore, optional SB stenting has become the recommended bifurcation treatment strategy.

In percutaneous coronary intervention (PCI), long-term clinical results are the ultimate assessment of different treatment modalities or devices (6,7). The present paper supplements our current knowledge on the short-term results of optional SB stenting versus MV plus SB stenting by presenting the 5-year clinical outcomes of the Nordic Bifurcation Study.

Methods

Patients and study design. This nonblinded randomized multicenter trial (NCT00376571) was conducted at 28 cardiology centers in Denmark, Sweden, Finland, Norway, and Latvia. The 413 patients were included from September 2004 to May 2005. The protocol was approved by ethics committees in all participating countries, and all participating patients gave written informed consent. The design of the Nordic Bifurcation Study has been published (1). In short, patients with stable, unstable, or silent angina pectoris and a de novo coronary bifurcation lesion were included. Diameter of the MV should be ≥ 2.5 mm and diameter of the SB ≥ 2.0 mm by visual estimate.

The sirolimus-eluting Cypher Select+ stent (Cordis, Johnson & Johnson, Bridgewater, New Jersey) was used in the study. The study lesion was pre-dilated and/or post-dilated at the discretion of the operator. In the optional SB stenting group, the main treatment principles were as follows: 1) stenting of MV; 2) SB dilation if SB TIMI (Thrombolysis In Myocardial Infarction) flow grade < 3 ; and 3) SB stenting if SB TIMI flow was 0 after dilation. In the stenting of the MV and the SB group, the main treatment principles were: 1) stenting of both the MV and SB applying the “crush technique” (8), “culotte technique” (9), or other techniques at the discretion of the operator; and 2) in all cases of SB stenting, the protocol required a “kissing balloon” dilation at the end of the procedure. The recommended clopidogrel treatment time was 6 to 12 months.

Five-year follow-up. Data on total death, cardiac death, myocardial infarction (MI), target lesion revascularization (TLR), target vessel revascularization (TVR), and angiographically verified definite stent thrombosis (ST) were obtained by yearly clinical control visits or telephone contacts to the patients. National registries and hospital files were used in case of death or admission to the hospital for a suspected cardiac event.

Study endpoints. We used the endpoint definitions reported in the primary publication (1). Endpoints were all-cause death, cardiac death, non-procedure-related MI, TLR, TVR, ST, and the combined endpoint of cardiac death, non-procedure-related MI, TVR by PCI or coronary artery bypass graft surgery (CABG), and ST. The endpoints up to 3 years were adjudicated blindly by an independent endpoint committee. Endpoints from 3 to 5 years were evaluated independently by 2 researchers (M.M. and N.R.H.). In case of discrepancies, consensus was obtained between the 2 researchers and a third senior interventional cardiologist (L.T.).

Statistical analysis. Differences in categorical variables between the 2 groups were analyzed using the chi-square test or Fisher exact test. Continuous variables were analyzed using Student *t* test or Mann-Whitney *U* test, and time-to-event data using the Kaplan-Meier method and the log-rank test. All *p* values were 2-sided. Level of significance was 5%. The analysis was performed on an intention-to-treat basis. All analyses were performed using Stata version 12 (StataCorp, College Station, Texas).

Results

A total of 413 patients were included in the study. Five-year clinical follow-up data were available for 404 (98%) patients, 202 in the MV group, and 202 in the MV plus SB group.

Abbreviations and Acronyms

- CABG** = coronary artery bypass graft operation
- DES** = drug-eluting stents
- MACE** = major adverse cardiac events
- MI** = myocardial infarction
- MV** = main vessel
- PCI** = percutaneous coronary intervention
- SB** = side branch
- ST** = stent thrombosis
- TLR** = target lesion revascularization
- TVR** = target vessel revascularization

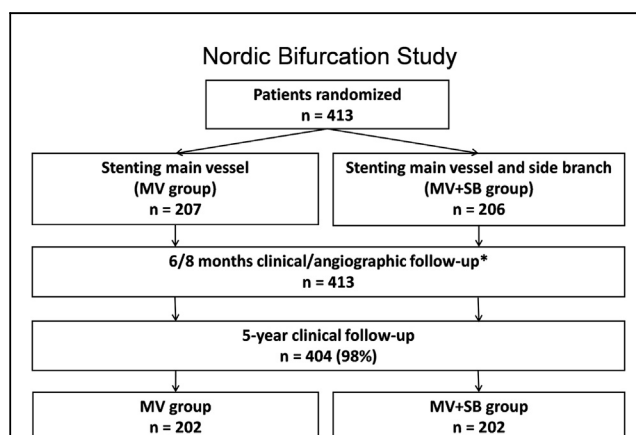


Figure 1 5-Year Follow-Up Patient Flow Chart of the Nordic Bifurcation Study

*A total of 307 patients had a quantitative coronary assessment at the index procedure and after 8 months. MV = main vessel; SB = side branch.

Table 1 Baseline Clinical Characteristics of 5-Year Follow-Up Cohort of the Nordic Bifurcation Study

	MV (n = 202)	MV+SB (n = 202)	p Value
Age, yrs	63 ± 10	63 ± 10	0.49
Male	76	78	0.63
Indication			
Stable angina pectoris	66	65	
Unstable angina pectoris	32	34	
Silent ischemia	2	1	
Vessel treated			
Left anterior descending artery	73	74	
Circumflex artery	17	18	
Right coronary artery	7	6	
Left main	2	1	
Diabetes mellitus	13	12	0.65
Hypercholesterolemia	78	72	0.14
Hypertension	54	58	0.42
Family history	58	54	0.59
Prior PCI	25	25	1.00
Prior CABG	4	3	0.58
Aspirin	99.5	98.5	0.32
Clopidogrel	100	99.5	0.31
Glycoprotein IIb/IIIa inhibitors	51	51	0.92

Values are mean ± SD or %.

CABG = coronary artery bypass graft surgery; MV = main vessel; PCI = percutaneous coronary intervention; SB = side branch; SD = standard deviation.

Eight patients were lost to follow-up, and 1 patient withdrew consent. Figure 1 shows the patient flow diagram.

The 2 groups were well balanced regarding baseline clinical variables (Table 1) and procedural characteristics (Table 2). There was no significant difference between the

Table 2 Procedural Characteristics of 5-Year Follow-Up Cohort of the Nordic Bifurcation Study

	MV (n = 202)	MV+SB (n = 202)	p Value
Median lesion length*			
MV, mm	16 (12-24)	16 (12-20)	0.76
SB, mm	5 (3-8)	5 (4-8)	0.15
Median stent length			
MV, mm	23 (18-28)	23 (18-28)	0.89
Reference diameter,* proximal			
MV, mm	3.3 ± 0.4	3.3 ± 0.4	0.91
SB, mm	2.6 ± 0.6	2.6 ± 0.3	0.98
True bifurcation lesion	77	67	0.026
Angulation <70°	63	66	0.46
Visible calcification	60	47	0.14
Tortuous proximal vessel	4	8	0.09
MV stented	99.5	98.5	0.37
SB stented	4.4	95.0	<0.0001
Final kissing balloon	32	74	<0.0001
Procedural success	97	94	0.24
Procedure time, min	55 (35-75)	70 (55-90)	<0.0001
Fluoroscopy time, min	13 (9-20)	19 (14-26)	<0.0001
Contrast volume, ml	210 (160-280)	265 (200-330)	<0.0001

Values are % (interquartile range), mean ± 1 SD or %. *Visual assessment. Abbreviations as in Table 1.

Table 3 Clinical Endpoints at 5-Year Follow-Up of the Nordic Bifurcation Study

	MV	MV+SB	p Value
All-cause death	5.9	10.4	0.16
Cardiac death	2.5	4.0	0.40
Myocardial infarction	4.0	7.9	0.09
Target lesion revascularization	11.3	15.3	0.24
Target vessel revascularization	13.4	18.3	0.14
Target vessel revascularization by CABG	2.0	3.5	0.38
Stent thrombosis*	3.0	1.5	0.32

Values are %. *Angiographically verified stent thrombosis.

Abbreviations as in Table 1.

2 groups with respect to vessel size or severity of stenosis as assessed by the operator. Genuine bifurcations were more prevalent in the MV group, whereas the bifurcation lesion characteristics of SB angulation <70°, vessel calcification, and proximal vessel tortuosity were evenly distributed.

Five-year clinical outcomes are presented in Table 3. The rates of the efficacy parameters, TLR and TVR, were numerically lower in the MV group, but the differences were not statistically different. The safety parameters, all-cause death, cardiac death, and ST did not differ significantly between the 2 groups. Angiographically verified ST occurred in 6 patients in the MV group (3% [acute, n = 0; subacute, n = 1; late, n = 3; and very late, n = 2]), and in 3 patients in the MV plus SB group (1.5% [acute, n = 0; subacute, n = 0; late, n = 1; and very late, n = 2]).

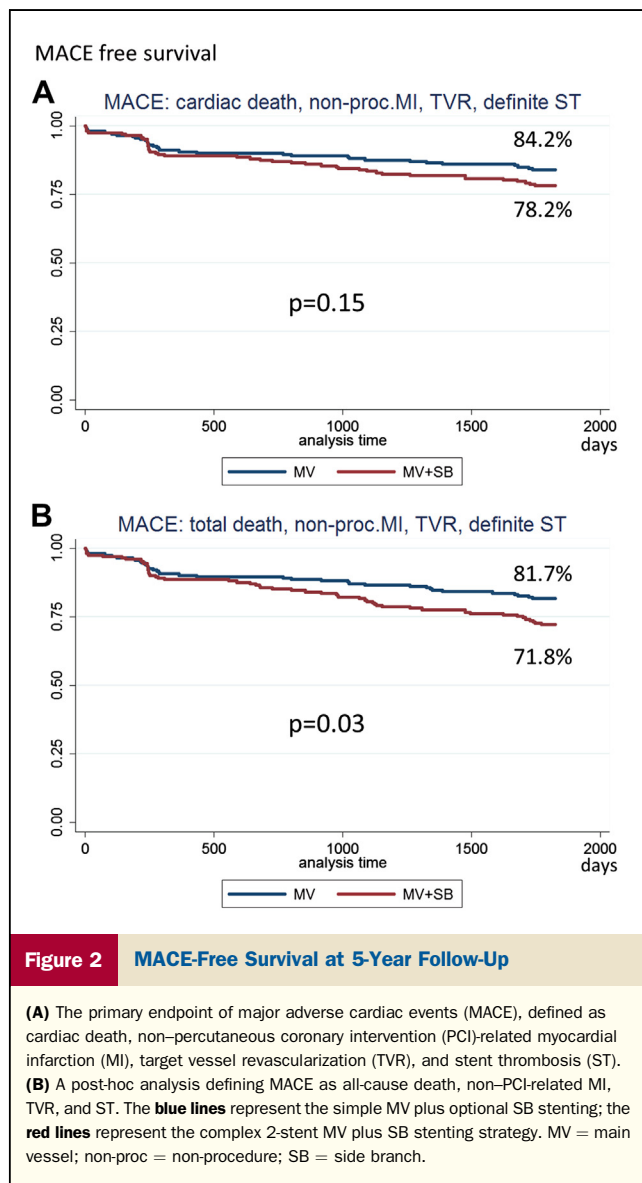
The Kaplan-Meier curves for major adverse cardiac events (MACE)-free survival did not differ significantly between the groups, with the 5-year MACE-free survival being 84.2% in the MV group versus 78.2% in the MV plus SB group (p = 0.12) (Fig. 2A).

Including total death in a post-hoc MACE analysis (all-cause death, non-procedure-related MI and TVR), event-free survival rates were 81.7% in the MV group versus 71.8% in the MV plus SB groups (p = 0.03) (Fig. 2B). In patients with genuine “true” bifurcation lesions, MACE rates were 19.9% versus 30.1% (p = 0.044) in the MV versus the MV plus SB group.

Discussion

This is the first publication of long-term follow-up data from a randomized comparison of coronary bifurcation treatment strategies comparing the simple strategy of MV stenting plus optional SB stenting versus the more complex planned stenting of MV plus SB. We found no significant differences regarding clinical safety and efficacy in the 2 study groups, although a trend toward superior results in patients treated with the simple strategy was observed.

Coronary bifurcations represent a challenging lesion subset. Balloon angioplasty of bifurcation lesions was associated with poor results, and restenosis frequently complicated bare-metal stent implantation, especially if



2 stent techniques were used (10,11). DES treatment gave rise to optimistic reports on low rates of acute events and minimal problems with restenosis (12). Later, a high rate of ST was reported in complex coronary lesions, especially in bifurcations (13,14). The potential high risk of ST was a concern when we designed the Nordic Bifurcation Study because multiple layers of stents, deformation of stent architecture, stent strut malapposition, and SB stent jail were thought to predispose to early and late thrombotic events. Such architectural changes were likely to be more pronounced after the complex MV and SB stenting using culotte, crush, or T techniques. After 5 years, the rates of ST, cardiac death, all-cause death, and non-procedure-related MI were similar in the 2 treatment groups, albeit numerically greater after the use of MV plus SB stenting with the exception of ST. Thus, our data demonstrate a high

degree of long-term safety irrespective of the bifurcation stenting strategy used, but do support the simple bifurcation strategy whenever feasible.

Although the Kaplan-Meier curves of the combined safety and efficacy endpoint (MACE) separated over time, showing an absolute 6% difference in favor of the simple strategy at 5-year follow-up, this difference was not statistically different. However, a post-hoc analysis, substituting cardiac death with all-cause death in the MACE analysis, resulted in significantly more events in the MV plus SB group and added further support to the simple MV stenting plus optional SB stenting approach. Using all-cause death instead of cardiac death may be relevant, as late-occurring fatal events in elderly patients may be difficult to classify correctly.

Study limitations. First, only 72% of the patients had a genuine bifurcation lesion with stenosis in both the MV and the SB. However, even patients with genuine “true” bifurcation lesions had significantly better outcomes when treated with the simple approach. Second, the results in the MV plus SB group may in part reflect a learning curve in complex bifurcation stenting. In this first Nordic Bifurcation Study, 74% of the patients treated with a complex stenting strategy had final kissing balloon dilation (1). In the Nordic Stent Technique Study, this number had increased to 85% in the crush group and 92% in the culotte group (15). Third, various 2-stent strategies were used in the complex group. We have previously shown that the crush technique approximately doubled the risk of angiographic in-stent restenosis in comparison to the culotte technique (10.5% vs. 4.5%, $p = 0.046$), although this observation did not impact MACE rates (4.3% vs. 3.7%, $p = 0.87$) (15). Although we did not find major differences between the crush and the culotte techniques, we cannot exclude the possibility that use of the culotte technique, or another 2-stent strategy in the majority of patients, could have had an impact on clinical outcomes.

Conclusions

At the 5-year follow-up of the Nordic Bifurcation Study, the clinical outcomes after simple MV plus optional SB stenting remained at least equal to the more complex strategy of stenting both the MV and the SB. The simple approach thus remains the recommended bifurcation treatment strategy.

Acknowledgments

The authors thank the study coordinators: Helle Bargsteen, medical secretary, Pia Ottosen, RN, Lars Raballovich Jørgensen, research coordinator. Data monitoring and safety: members of the steering committee. Statistical support: Niels Ramsing Holm, Aarhus University Hospital, Skejby, Denmark. Clinical endpoint committee: Kristian Thygesen, MD, Aarhus University Hospital, Aarhus, Denmark; Jan Ravkilde, MD, Aarhus University Hospital, Aalborg,

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Key Words: bifurcation ■ drug-eluting stent ■ randomized ■ restenosis ■ stent thrombosis.