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Simple or Complex Stenting for Bifurcation Coronary Lesions

A Patient-Level Pooled-Analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study

Miles W. Behan, DM, MRCP; Niels R. Holm, MD; Nicholas P. Curzen, PhD, FRCP; Andrejs Erglis, MD; Rodney H. Stables, MD, FRCP; Adam J. de Belder, MD, FRCP; Matti Niemelä, MD; Nina Cooter, MSc; Derek P. Chew, MPH, FRACP; Terje K. Steigen, MD; Keith G. Oldroyd, MD, FRCP; Jan S. Jensen, MD; Jens Flensted Lassen, MD; Leif Thuesen, MD; David Hildick-Smith, MD, FRCP

Background—Controversy persists regarding the correct strategy for bifurcation lesions. Therefore, we combined the patient-level data from 2 large trials with similar methodology: the NORDIC Bifurcation Study (NORDIC I) and the British Bifurcation Coronary Study (BBC ONE).

Methods and Results—Both randomized trials compared simple (provisional T-stenting) versus complex techniques, using drug-eluting stents. In the simple group (n=457), 129 patients had final kissing balloon dilatation in addition to main vessel stenting, and 16 had T-stenting. In the complex group (n=456), 272 underwent crush, 118 culotte, and 59 T-stenting techniques. A composite end point at 9 months of all-cause death, myocardial infarction, and target vessel revascularization occurred in 10.1% of the simple versus 17.3% of the complex group (hazard ratio 1.84 [95% confidence interval 1.28 to 2.66], $P=0.001$). Procedure duration, contrast, and x-ray dose favored the simple approach. Subgroup analysis revealed similar composite end point results for true bifurcations (n=657, simple 9.2% versus complex 17.3%; hazard ratio 1.90 [95% confidence interval 1.22 to 2.94], $P=0.004$), wide-angled bifurcations >60 to 70° (n=217, simple 9.6% versus complex 15.7%; hazard ratio 1.67 [95% confidence interval 0.78 to 3.62], $P=0.186$), large (≥2.75 mm) diameter side branches (n=281, simple 10.4% versus complex 20.7%; hazard ratio 2.42 [95% confidence interval 1.22 to 4.80], $P=0.011$), longer length (>5 mm) ostial side branch lesions (n=464, simple 12.1% versus complex 19.1%; hazard ratio 1.71 [95% confidence interval 1.05 to 2.77], $P=0.029$), or equivalent sized vessels (side branch <0.25 mm smaller than main vessel) (n=108, simple 12.0% versus complex 15.5%; hazard ratio 1.35 [95% confidence interval 0.48 to 3.70], $P=0.57$).

Conclusions—For bifurcation lesions, a provisional single-stent approach is superior to systematic dual stenting techniques in terms of safety and efficacy. A complex approach does not appear to be beneficial in more anatomically complicated lesions.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00376571 and NCT 00351260.

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Key Words: coronary ■ bifurcation ■ stent

The treatment of bifurcation lesions presents a considerable challenge to interventional cardiologists. In the drug-eluting stent (DES) era, several trials have been published comparing a simple (provisional) strategy with a systematic 2-stent (complex) bifurcation strategy; yet controversies about the correct treatment choice remain.[1–6] Therefore, we combined the patient-level data from the 2 largest and most similar trials—BBC ONE and NORDIC I. These trials were almost identical in design and ran contemporaneously, therefore facilitating meaningful analysis. Other bifurcation trials were excluded because of their differing methodologies.[1–3] Both trials compared simple (provisional T-stenting) versus complex (culotte, crush, and T-stenting) techniques, using DES, with minimalist philosophy in the simple group. In this analysis we have therefore compared simple versus complex approaches both overall and in spe-

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cific subgroups; true bifurcations (>50% stenoses in both the main vessel [MV] and side branch [SB]), those lesions with bifurcation angles >60 to 70° (by visual estimation), those lesions with a large diameter SB (≥2.75 mm), those with ostial SB lesion length >5 mm, and those with equivalent sized vessels (SB <0.25 mm smaller than MV).

Clinical Perspective on p 64

Methods

The Studies

The NORDIC I study randomly assigned 413 patients with a bifurcation lesion to a simple strategy (n=207; stenting of MV with optional stenting of the SB) or to a complex strategy (n=206; stenting of both the MV and the SB) using sirolimus-eluting stents. The diameter of the MV and SB were required to be ≥2.5 mm and ≥2.0 mm, respectively, by visual estimation. Both 6- and 14-month follow-up have been reported.[4,6]

The BBC ONE study randomly assigned 500 patients with a bifurcation lesion to a simple strategy (n=250; stenting of the MV with optional kissing balloon dilatation/T-stent) or to a complex strategy (n=250; both vessels systematically stented with mandatory kissing balloon dilatation) with paclitaxel-eluting stents. The diameters of the MV and SB were required to be ≥2.5 mm and ≥2.25 mm, respectively, by visual estimation. Nine-month follow-up has been reported.[5]

Ethics Committee Approval

The BBC ONE study protocol was approved by the UK National Research Ethics Service and the Medicines and Healthcare products Regulatory Agency. The NORDIC I study protocol was approved by local ethics committees in all participating countries.

Procedural and Late Pharmacology

All patients were pretreated with aspirin and clopidogrel. Aspirin was continued indefinitely. Clopidogrel 75 mg daily was continued for 6 to 12 months in NORDIC I, and a minimum of 9 months in BBC ONE. Heparin was administered according to local hospital protocol in NORDIC I and at 70 IU/kg in BBC ONE. In both studies, glycoprotein receptor antagonists were used at the discretion of the operator. Percutaneous coronary intervention was undertaken via the access site of choice of the operator.

Simple Strategy

The MV and SB were pretreated at the operator's discretion. In the simple group both studies used a minimalist provisional 3-stage strategy:

NORDIC I: (i) stenting of the MV, (ii) SB dilation if there was thrombolysis in myocardial infarction (TIMI) flow <3 in the SB, (iii) SB stenting if the TIMI flow was 0 in the SB after dilation.

BBC ONE: (i) stenting of the MV, (ii) kissing balloon inflation if <TIMI 3 flow in the SB, severe ostial pinching of the SB (>90%), threatened SB vessel closure or SB vessel dissection > type A, (iii) T-stenting of the SB if < TIMI 3 flow in the SB, persistent ostial pinching of the SB (>70%), threatened SB vessel closure or SB dissection > type A.

In both studies, if the SB was stented, the operator was mandated to attempt a final kissing balloon inflation.

Complex Group

In the complex group the main treatment strategy was stenting of both the MV and SB. Specific bifurcation stenting techniques were used at the discretion of the operator (NORDIC I, crush, culotte, T, or other; BBC ONE, crush or culotte alone). The operator was mandated to attempt a final kissing balloon inflation in all cases after SB stenting.

End Points

The primary analysis was a composite of all-cause death, myocardial infarction (MI) (both periprocedural and subsequent MI), and target vessel revascularization (TVR).

Other analyses included the individual components of the primary end point and the incidence of stent thrombosis (ST).

Procedural end points included procedural success, in-hospital major adverse cardiovascular events (MACEs), procedure duration, fluoroscopy time, and contrast volume.

The NORDIC I study had planned repeat angiography for quantitative coronary assessment at 8-month follow-up, as well as clinical follow-up at 6 and 14 months (to avoid treatment based on angiography alone), whereas BBC ONE had clinical follow-up at 9 months only. For the purpose of this analysis, we have included clinical end points for both studies only. We had access to individual patient-level follow-up data from both trials; and, therefore, we were able to use 9-month clinical end points for our pooled analysis.

Definitions

Periprocedural MI

Cardiac enzymes were measured at the time of the procedure and after 12 to 18 hours (creatine kinase-MB [CK-MB] and troponin T/I in NORDIC I and CK and Troponin T/I in BBC ONE). Marker elevation of ≥3 the upper limit of normal was considered significant. For patients who already had an elevated cardiac enzyme level preprocedure, there had to be a rise to ≥50% previous value.

Subsequent MI

Subsequent MI is identified in the typical rise and fall of biochemical markers of myocardial necrosis with ischemic symptoms or ECG changes, as per the European Society of Cardiology/American College of Cardiology 2000 guidelines, >24 hours after the index procedure.[7]

TVR

TVR is defined as repeat attempted revascularization by percutaneous coronary intervention or coronary artery bypass grafting of the target vessel.

ST

This is an angiographically documented contrast filling defect of the target lesion in the presence of an acute coronary syndrome (Academic Research Consortium (ARC) definite).[8]

Procedural Success

If there is TIMI 3 flow and <30% stenosis in the main vessel, plus TIMI 3 flow in the side branch, the procedure is considered successful.

In-Hospital MACE

Death, MI, or coronary artery bypass grafting during the index admission are considered major adverse events.

Periprocedural MI Data

Different cardiac biomarkers were used to measure periprocedural MIs in each trial. In BBC ONE, CK was used, with additional measurement of troponin offering corroboration. In NORDIC I, to maximize the amount of diagnostic biomarker data available, CK-MB was used as the primary marker, and troponin-T or troponin-I only if CK-MB mass was not available. If an MI was confirmed or excluded by CK-MB, then the troponin data were not analyzed. If a normal postprocedure cardiac enzyme value was available (but no preprocedure value), then an MI was excluded. If no preprocedure cardiac enzyme level was available, but an abnormal postprocedure level was recorded, the diagnosis of periprocedural infarction was not made (ie, insufficient data).

Subgroup Analysis

Bifurcation lesions were divided into subgroups by their anatomic characteristics to determine whether either strategy was more favorable with certain lesion properties (true bifurcations, those lesions with wide bifurcation angle (the angle formed by the SB and the

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vessel segment proximal to the SB origin) >60 to 70°, those lesions with a large diameter SB (≥ 2.75 mm), those with ostial SB lesion length >5 mm, and those with equivalent sized vessels. Bifurcation angles were classified as wide if they were greater, by visual estimation, than 60° (BBC ONE) or 70° (NORDIC I). For the purpose of our analysis, extreme angled lesions from the 2 trials were combined in a subgroup labeled "wide bifurcation angle >60° to 70°."

Statistical Analysis

Dichotomous variables are reported as counts and percentages of the total. Normally distributed variables are expressed as means (standard deviation); non-Gaussian factors are reported as medians (and interquartile ranges). χ^2 tests have been used for comparisons of binary outcomes between groups, whereas *t* tests, and Kruskal-Wallis testing have been used for normally distributed and nonnormally distributed data, respectively. Patient allocations to either simple or complex strategies were analyzed as randomized using the "intention to treat" principle. Aggregate data were used to assess heterogeneity between the studies with respect to the randomized strategy, and in-hospital and 9-month MACE using a random effects model. The Mantel-Haenszel estimate of heterogeneity of $P=0.890$ (I^2, 0%). Random effects meta-analysis of individual patient data was undertaken using Cox proportional hazards modeling, stratified by study. Exploratory analysis was undertaken to evaluate the impact of prerandomization and pharmacological differences between treatment groups through the development of a propensity score. Factors explored included age, sex, prevalence of diabetes, presentation with acute coronary syndromes, smoking status, prior revascularization, dyslipidemia, hypertension, vessel territory, left ventricular function, calcification, angulation, tortuosity, MV and SB diameter, and stenosis and use of glycoprotein IIb/IIIa inhibition. This propensity adjusted and stratified Cox model is presented. Event-free survival curves were generated using Kaplan-Meier methods. A probability value of <0.05 was considered statistically significant. All analyses were undertaken using STATA 10.1 software.

Results

A total of 913 patients were included in these 2 studies: 457 patients were treated with the simple strategy, and 456 with the complex strategy. There were no significant differences between the 2 groups for patient characteristics or clinical features (Table 1), with the exception that the use of glycoprotein inhibitors was more frequent in the complex group. The relative proportion of elective and urgent cases was the same in both groups. Four-fifths of cases involved left anterior descending coronary artery/diagonal bifurcations.

Bifurcation lesion characteristics are shown in Table 2. MV diameter, stenosis, lesion length, and stent diameter were similar in the 2 groups. MV stent length was significantly longer in the complex group. SB diameter, stenosis, and lesion length were significantly greater in the complex group. Seventy-two percent of cases were "true" bifurcations (ie, with >50% narrowing in both the MV and the SB).

Procedural characteristics are shown in Table 3. In the simple group, 128 patients (28%) underwent SB ballooning, 16 patients (3.5%) required a T-stent, and 129 patients (28.3%) underwent kissing balloon dilatation poststenting. In the complex group, 272 (59.6%) patients had crush stenting, 118 (25.9%) culotte stenting, and 342 (75.3%) had final kissing balloon inflation. Table 3 also demonstrates that procedural, fluoroscopy time, and contrast volumes were significantly greater in the complex group.

Clinical events for simple versus complex strategies are shown in Table 4. The incidence of the composite end point at 9 months of all-cause death, MI, and TVR occurred in 10.1% of the simple group, versus 17.3% of the complex group (hazard ratio [HR] 1.84 [95% confidence interval (CI) 1.28 to 2.66], $P=0.001$, propensity adjusted HR 1.92 [95% CI 1.27 to 2.91] $P=0.002$). The nature of the individual end point events are listed in Table 4. Most excess events in the complex group were because of MI; the majority of these events were periprocedural. The incidence of a separate, composite end point of all-cause death, subsequent MI alone, and TVR was 7.0% in the simple group versus 9.0% in the complex group, HR 1.38 (95% CI 0.87 to 2.20, $P=0.168$). Diagnostic postprocedure cardiac biomarker data were obtained in 92% of procedures (NORDIC I, 90%, and BBC ONE, 93%). There was no difference in the rates of TVR between the 2 groups, but TVR was more commonly undertaken by coronary artery bypass grafting rather than repeat intervention in the complex group. The incidence of

Table 1. Patient Characteristics and Clinical Features (Combined)

	Simple (n=457)	Complex (n=456)	*P* Value
Age (years) mean (SD)	63.8 (9.9)	63.1 (11.0)	0.424
Male (%)	351 (77%)	355 (78%)	0.766
Height (cm) mean (SD)	171.8 (8.8)	172.0 (9.0)	0.834
Weight (kg) mean (SD)	86.2 (62.6)	86.3 (62.6)	0.757
Diabetes	63 (13.7%)	59 (12.9%)	0.534
Hypertension	252 (55.1%)	273 (59.8%)	0.171
Hypercholesterolemia	349 (76.4%)	338 (74.1%)	0.398
Smoking (current)	99 (21.7%)	91 (20%)	0.508
Family history	223 (48.8%)	214 (46.9%)	0.593
Previous PCI	94 (20.6%)	93 (20.4%)	0.935
Previous CABG	13 (2.8%)	9 (2.0%)	0.388
Left ventricular function			0.111
Good (EF >50%)	319 (86.7%)	305 (81.1%)	
Moderate (30%–50%)	47 (12.8%)	69 (18.4%)	
Poor (<30%)	2 (0.5%)	2 (0.5%)	
Presentation			0.360
Elective	309 (67.6%)	297 (65.1%)	
ACS	144 (31.5%)	157 (34.4%)	
Site of bifurcation disease			0.432
LAD	353 (77.2%)	362 (79.4%)	
Circumflex	71 (15.5%)	66 (14.5%)	
RCA	24 (5.3%)	25 (5.5%)	
Other	9 (2%)	3 (0.7%)	
Adverse lesion features			
Calcification ≥ moderate	133 (29.1%)	127 (27.9%)	0.706
Tortuosity ≥ moderate	33 (7.2%)	43 (9.4%)	0.219
Bifurcation angle >60°–70°	115 (25.1%)	102 (22.4%)	0.321
Antiplatelet therapy			
Glycoprotein inhibitor use	176 (38.5%)	215 (47.5%)	0.008
Aspirin	447 (98%)	451 (99.3%)	0.194
Clopidogrel	428 (94%)	433 (95.5%)	0.396

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft; ACS, acute coronary syndrome; LAD, left anterior descending coronary artery; RCA, right coronary artery.

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Table 2. Bifurcation Characteristics

	Simple (n=456)	Complex (n=454)	*P* Value
Main vessel diameter, n (%)			0.995
>2.5 mm	37 (8%)	32 (7%)	
>2.75 mm	62 (13.6%)	63 (13.8%)	
>3.0 mm	195 (42.6%)	199 (43.6%)	
>3.5 mm	138 (27.7%)	129 (28.1%)	
>4 mm	28 (6.1%)	24 (5.2%)	
>4.5 mm	7 (1.5%)	7 (1.5%)	
Main vessel mean stenosis (%)	77.0	76.1	0.821
Main vessel lesion length, n (%)			0.105
0–5 mm	5 (1.1%)	10 (2.2%)	
5–10 mm	81 (17.8%)	74 (16.2%)	
10–15 mm	121 (26.5%)	108 (23.7%)	
15–20 mm	121 (26.5%)	126 (27.6%)	
20–30 mm	90 (19.7%)	109 (23.9%)	
30–50 mm	29 (6.3%)	29 (6.4%)	
>50 mm	0 (0%)	7 (1.5%)	
Main vessel mean stent diameter (mm, SD)	3.1 (0.4)	3.1 (0.4)	0.802
Main vessel stent length (mm, SD)	21.9 (7.3)	22.8 (6.9)	0.010
Side branch			
Side branch diameter, n (%)			0.018
>2.25 mm	116 (25.3%)	90 (19.7%)	
>2.5 mm	222 (48.6%)	204 (44.8%)	
>2.75 mm	45 (9.8%)	68 (14.9%)	
>3.0 mm	57 (12.5%)	82 (18.0%)	
>3.25 mm	3 (0.6%)	2 (0.4%)	
>3.5 mm	9 (2%)	8 (1.7%)	
>4 mm	2 (0.4%)	0 (0%)	
Side branch mean stenosis (%)	59.2	65	0.027
Side branch lesion length, n (%)			<0.001
0–5 mm	250 (54.7%)	199 (43.6%)	
5–10 mm	123 (26.9%)	134 (29.4%)	
10–15 mm	31 (6.8%)	70 (15.4%)	
15–20 mm	26 (5.7%)	34 (7.5%)	
20–30 mm	5 (1.1%)	13 (2.9%)	
30–50 mm	0 (0%)	3 (0.6%)	
>50 mm	6 (1.3%)	2 (0.4%)	
Side branch stent length (mm, SD)	. . .	13.4	. . .
True bifurcation n (%)	316 (69.1%)	341 (74.7%)	0.058

Table 3. Procedure Characteristics

	Simple (n=457)	Complex (n=456)	*P* Value
Side branch stented, n (%)	16 (3.5%)	421 (92.3%)	<0.001
Crush technique, n (%)	. . .	272 (59.6%)	
Culotte technique, n (%)	. . .	118 (25.9%)	
Other complex technique n (%)	16 (3.5%)	59 (12.9%)	
Final kissing balloons, n (%)	129 (28.3%)	342 (75.3%)	<0.001
Procedural success, n (%)	435 (95.4%)	429 (94.5%)	0.430
Procedural time (min, SD)	59.1 (39.1)	77.4 (34.4)	0.001
Fluoroscopy time (min, SD)	15.1 (11.1)	21.5 (11.4)	<0.001
Contrast volume (mL, SD)	243.2 (108.1)	297.9 (129.3)	<0.001

stent thromboses was not significantly different between the 2 groups. In-hospital MACE was more common in the complex group. Cumulative risk of the primary outcome, MI, and TVR are shown in Figure 1A, 1B, and 1C, respectively.

Subgroup Analysis (see Figure 2)

True Bifurcations

A total of 657 (72%) cases were "true" bifurcations, in which the incidence of the combined end point of all-cause death, MI, and TVR was 9.2% in the simple group versus 17.3% in the complex group (HR 1.90 [95% CI 1.22 to 2.94], $P=0.004$). The nature of the individual clinical events is listed in Table 5.

Wide Bifurcation Angle (>60 to 70°)

A total of 217 (24%) cases had bifurcation angle >60° to 70°, in which the incidence of the combined end point of all-cause death, MI, or TVR was 9.6% in the simple group versus 15.7% in the complex group (HR 1.67 [95% CI 0.78 to 3.62], $P=0.186$). The nature of the individual clinical events is listed in Table 5.

SB ≥2.75 mm Diameter

A total of 281 (31%) of cases had a SB ≥2.75 mm, in which the incidence of the combined end point of all-cause death, MI, or TVR was 10.4% in the simple group versus 20.7% in the complex group (HR 2.42 [95% CI 1.22 to 4.80], $P=0.011$). The nature of the individual clinical events is listed in Table 5.

SB Lesion Length >5 mm

A total of 464 (51%) cases had a SB lesion length >5 mm, in which the incidence of the combined end point of all-cause death, MI, or TVR was 12.1% in the simple group versus 19.1% in the complex group (HR 1.71 [95% CI 1.05 to 2.77], $P=0.029$). The nature of the individual end point events is listed in Table 5.

SB Diameter ≥2.75 mm and Lesion Length >5 mm

A total of 137 (15%) cases had a SB diameter ≥2.75 mm and a SB lesion length >5 mm. In this group, the incidence of the combined end point of all-cause death, MI, or TVR was 11.6% in the simple group versus 19.5% in the complex group (HR 1.84 [95% CI 0.68 to 4.97], $P=0.229$). The frequency of the individual clinical events is listed in Table 5.

Equivalent Sized MV and SB Diameter

A total of 108 (11.8%) cases had a SB diameter that was <0.25 mm smaller than the MV. In these cases, the incidence of the combined end point of all-cause death, MI, or TVR was 12.0% in the simple group versus 15.5% in the complex group (HR 1.35 [95% CI 0.48 to 3.70], $P=0.57$). The frequency of the individual clinical events is listed in Table 5.

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Table 4. Trial End Points Simple vs Complex Total

	Simple (n=457)	Complex (n=456)	HR (95% CI)	*P* Value
All-cause death, myocardial infarction (periprocedural and subsequent) or target vessel revascularization at 9 months	46 (10.1%)	79 (17.3%)	1.84 (1.28–2.66)	*P*=0.001
All-cause death, myocardial infarction (subsequent alone) or target vessel revascularization at 9 months	32 (7.0%)	41 (9.0%)	1.38 (0.87–2.20)	0.168
All-cause death	5 (1.0%)	5 (1.0%)		0.99
Periprocedural	2 (0.4%)	3 (0.6%)		
Subsequent	3 (0.6%)	2 (0.4%)		
Myocardial infarction	22 (4.8%)	56 (12.3%)		<0.001
Periprocedural	16 (3.5%)	45 (9.9%)		<0.001
Subsequent	6 (1.3%)	11 (2.4%)		0.22
Target vessel revascularization	26 (5.7%)	33 (7.2%)		0.34
PCI	24 (5.3%)	20 (4.4%)		0.54
CABG	2 (0.4%)	13 (2.9%)		0.004
Stent thrombosis (ARC definite)	3 (0.7%)	6 (1.3%)		0.31
In-hospital				
Death	2 (0.4%)	3 (0.6%)		0.65
Myocardial infarction	17 (3.7%)	45 (9.9%)		<0.001
CABG	0 (0%)	4 (0.8%)		0.04

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft; ARC, academic research consortium.

Discussion

In this study, we combined and analyzed patient-level data of 2 contemporary randomized trials comparing 2 strategies for the DES treatment of bifurcation lesions. We have produced the largest patient-level data set of randomized bifurcation stenting trials, allowing meaningful subgroup analysis. We found that a simple step-wise provisional T-stent approach is superior to a complex technique, in terms of the main clinical end- point (a composite of death, TVR, and MI at 9 months). Most of this difference was driven by a higher rate of

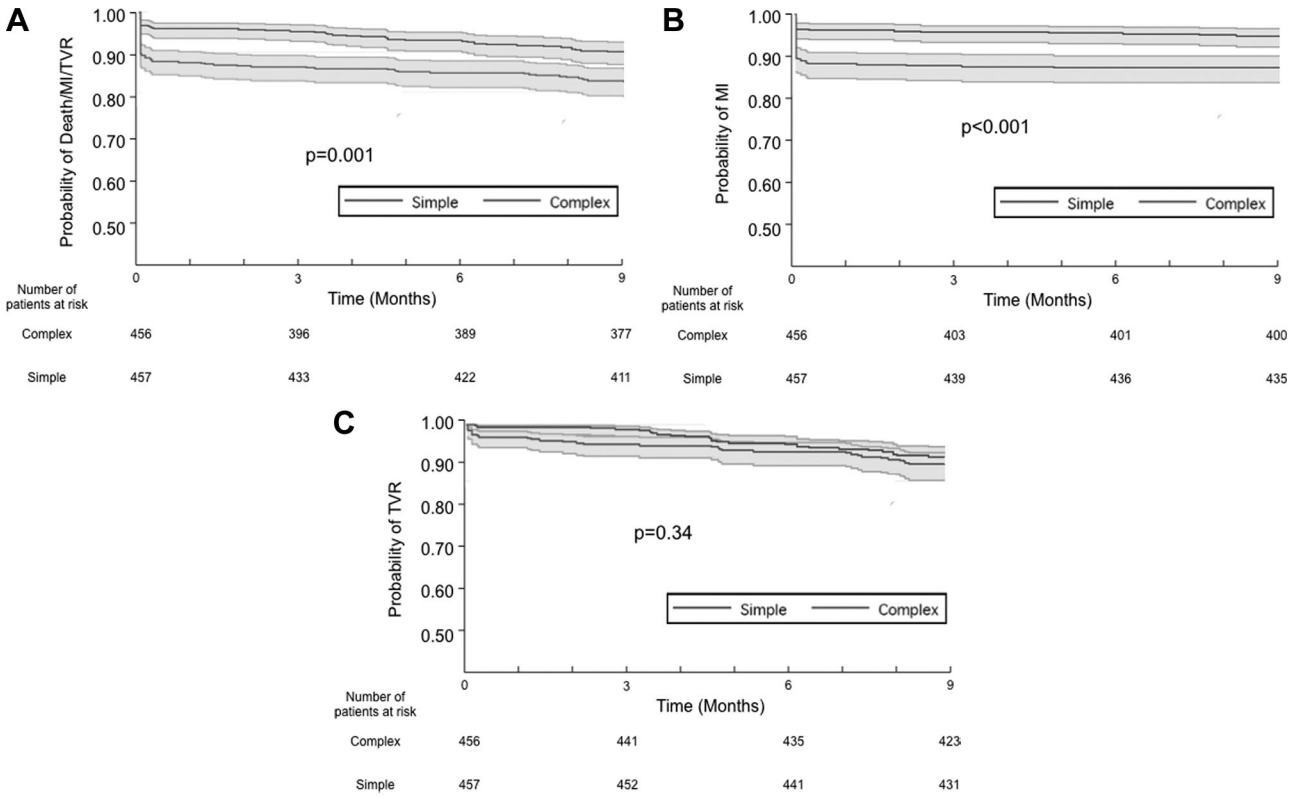

Figure 1. Kaplan-Meier freedom from the composite event (A), MI (B), and TVR (C) by strategy. MI indicates myocardial infarction; TVR, target vessel revascularization.

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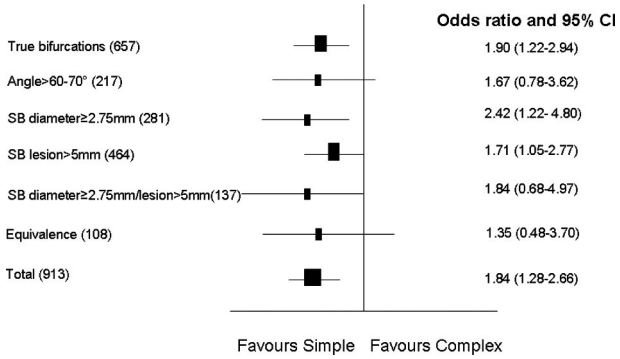

Figure 2. Odds ratio plot of the primary outcome for individual subgroups. Equivalence indicates that the SB is <0.25 mm smaller than the MV. Size of data markers indicates the number of patients in that subgroup. SB indicates side branch; MV, main vessle; CI, confidence interval.

periprocedural MI. We found no significant differences in the individual end points of death, TVR, subsequent MI, or ST at 9 months between the simple and complex strategy. Surgical TVR was significantly higher in the complex group.

In the subgroup analyses (true bifurcations, lesions with wide bifurcation angles >60° to 70°, large diameter SB (diameter ≥2.75 mm), those with long ostial SB lesions (length >5 mm), a combination of large SB with long lesion (diameter ≥2.75 mm and length >5 mm) and equivalent-sized vessels), we found that there remained an increased risk of the primary end point associated with the complex group (see Figure 2).

A systematic 2-stent approach represents a more complex procedure. The increased rate of periprocedural MI seen in complex procedures probably reflects the longer duration of vessel instrumentation with more frequent balloon and stent passage and dilation. Periprocedural MI, however, may be important as an adverse prognostic indicator,[9] although not all studies have reached the same conclusion in this respect.[10] We feel that it is important to include periprocedural MI in the composite analysis (this was the case in BBC ONE but not NORDIC I) because of its probable prognostic significance and as a marker of overall uncomplicated clinical success. Without the procedural biomarker data, there is no significant difference between the strategies in major end points (death, TVR, or non-procedure-related MI), but procedure duration, fluoroscopy time, and contrast volume still favor the simple group.

Excluding periprocedural MI, adverse events were infrequent in both groups. Mortality rates were low and similar to other previous studies.[1–3,11] ST was seen in relatively few cases overall, with no statistical difference between the groups; thus, procedural complexity did not appear to be associated with increased risk of ST. High-pressure stent deployment and mandatory kissing balloon inflation in dual-stented lesions may account for the low rate of ST compared with early studies.[12]

Different DES types were used in NORDIC I (sirolimus) and BBC ONE (paclitaxel). These stent types have been compared in 2 previous studies of bifurcation stenting. Chen et al compared paclitaxel and sirolimus crush stenting in a registry of 252 patients and found MACE rates of 18% versus 8%, respectively, for the 2 stent types at 8 months.[13] Pan et al randomly assigned 205 patients to paclitaxel or sirolimus provisional T-stenting and found TVR rates of 13% versus 4%, respectively, at 24 months.[14] There is, therefore, evidence to suggest that sirolimus-coated stents provide superior results at coronary bifurcation lesions.

We found much higher rates of surgical TVR in the complex group compared with the simple group. This is likely because of physician reluctance to reintervene on in-stent restenosis lesions that may already have 2 or 3 layers of metal. It is a disadvantage if the complex strategy renders a patient only suitable for surgical revascularization in the setting of recurrent ischemia.

Koo et al demonstrated that apparently significant angiographic lesions at the origin of SBs are often overestimated.[15] Using fractional flow reserve, he showed that only 30% of lesions that appear >75% on quantitative coronary angiography are in fact physiologically significant. It is notable that with a "minimalist" provisional strategy a very similar number to this (28%) required further intervention on the SB after MV stenting.

There was a high proportion of "true" bifurcations that formed a subgroup analysis. In non-true bifurcations, because

Table 5. Trial End Points for Different Subgroups

Group	Total (n=913)	True Bifurcation (n=657)	SB ≥2.75 mm (n=281)	Bifurcation Angle >60–70° (n=217)	SB Lesion Length >5 mm (n=464)	SB Diameter ≥2.75 mm+Lesion Length >5 mm (n=137)	Equivalence (n=108)
Composite end point	10.1% vs 17.3%*	9.2% vs 17.3%†	10.4% vs 20.7%†	9.6% vs 15.7%	12.1% vs 19.1%†	11.6% vs 19.15%	12.0% vs 15.5%
Death	1.0% vs 1.0%	0.6% vs 0.9%	0.8% vs 1.9%	0.9% vs 1.0%	1.4% vs 2.0%	0% vs 3.2%	0% vs 1.7%
MI (total)	4.8% vs 12.3%*	4.6% vs 12.6%*	6.1% vs 13.2%	6.1% vs 11.8%	4.8% vs 14%*	6.98% vs 14.89%	8.0% vs 12.1%
TVR	5.7% vs 7.2%	5.5% vs 7.3%	4.3% vs 8.2%	4.3% vs 2.9%	7.2% vs 7.4%	4.65% vs 4.26%	6.0% vs 6.9%
ST	0.7% vs 1.3%	0.6% vs 1.1%	0.0% vs 1.9%	0% vs 0%	1.0% vs 1.2%	0% vs 1.3%	0% vs 5.0%

Values shown are percentages of each subgroup (simple vs complex). Equivalence indicates that the side branch is <0.25 mm smaller than the main vessel. The composite end point includes all-cause death, both periprocedural and subsequent MIs and TVR. MI indicates myocardial infarction; TVR, target vessel revascularization; ST, stent thrombosis.

*Denotes $P \leq 0.001$ for comparison between the strategy types.

†Denotes $P < 0.05$ for comparison between the strategy types.

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atheroma at the carina is rare, there should be a low risk of SB occlusion in comparison with true bifurcations.[16,17] Therefore, the complex strategy might confer an advantage in true bifurcations because it provides scaffolding of the ostium of the SB. Previous studies have compared the strategies in true bifurcations.[12,18] The CACTUS investigators failed to demonstrate that the crush technique was superior to provisional T-stenting in these lesions.[1] We found that in "true" bifurcations the simple approach was still associated with lower rates of the combined end point at 9 months, with no difference in TVR rates. There were also lower rates of in-hospital MACE with the simple strategy.

It has been postulated that, because a complex strategy provides total lesion coverage, it might be preferable in longer SB lesions.[19] However, we found a lower composite end point with the simple strategy, significantly fewer MIs, and no difference in TVR between the groups. Furthermore, Latib et al recommended that an intentional "two-stent" strategy be reserved for bifurcations with a SB that has a relatively large diameter and disease that extends beyond the ostium.[20] From our subgroup analysis, we found no benefit of a complex strategy in these situations, individually or in combination.

There have been other published meta-analyses of randomized bifurcation stenting trials (which have included NORDIC I and BBC ONE).[21–24] Unlike our analysis, these studies did not have access to individual patient data.

Limitations

Although NORDIC I has reported longer term, our pooled analysis has only midterm follow-up.[6] Later outcomes following discontinuation of dual-antiplatelet therapy will be interesting. Platelet function testing to ensure adequate antiplatelet response was not conducted.

Periprocedural MIs were diagnosed using different cardiac biomarkers for each trial (CK and CK-MB). Our method of analyzing periprocedural MIs meant that diagnostic cardiac biomarker data were available for 90% of patients overall, compared with the original Nordic article in which data for only 67% were reported.[4]

To facilitate more meaningful pooled analysis, we used 9-month clinical end points for both trials from individual patient-level data, whereas the original NORDIC 1 reported only 6-month clinical end points with 8-month angiographic follow-ups. This raises the possibility that NORDIC I TVR end points between 8 and 9 months could be angiographically driven, rather than clinically (there would be no effect on MI or death). Any effect would be equally applied to both simple and complex groups. Indeed, in our analysis only 5 NORDIC I TVR end points occurred at planned 8-month angiographic follow-up: 4 in the simple group, and 1 in the complex group.

Despite the use of pooled analysis to increase the number of events, it is not possible to significantly identify which morphological substrate is best suited to which strategy. The subgroup analysis is exploratory and illustrative but is not an attempt to find a morphological substrate best treated by a particular strategy. The subgroup analysis shows consistency of the strategy effect rather than identification of a particular group.

The SB diameter, stenosis, and lesion length were significantly greater in the complex group. All these parameters were estimated visually, and this allows for operator bias. Planned treatment of the SB is likely to cause an overestimation of the length and severity of the SB lesion (as opposed to the MV in which the parameters were the same in both groups). There was a trend to an increased number of "true" bifurcations in the complex group, and it is likely that this also reflects operator overestimation of SB stenosis.

In both studies, (ARC)-definite criteria were used to define ST. More events might have been recorded if probable and possible also were used.

Whereas a high rate of kissing balloon inflation was achieved in the complex group (>75%), ideally this should be carried out in all complex stenting procedures.

Clinical Implications

A provisional T-stenting strategy appears to have equal efficacy, better safety, and greater economic benefit than a planned 2-stent strategy in most circumstances. These benefits remain in those anatomic situations that have previously been argued as advantageous for a complex strategy.

Conclusions

The results of this pooled analysis of the NORDIC I and BBC ONE trials show that the simple strategy is associated with lower rates of the composite end point of death, MI, and TVR at 9 months. In addition, the simple strategy resulted in reduced procedure duration, fluoroscopy times, contrast volume, and risk of periprocedural MI. The advantage of this strategy is also apparent in "true" bifurcations, those with large SBs, long SB lesions, and lesions with wide bifurcation angles.

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CLINICAL PERSPECTIVE

Controversy persists regarding the correct strategy for the treatment of coronary bifurcation lesions. We have carried out a pooled analysis of patient-level data of 913 patients enrolled in 2 randomized trials comparing a simple stenting strategy (stenting of main vessel and provisional treatment of side branch) with a complex strategy (stenting both main vessel and side branch) using drug-eluting stents. Clinical follow-up of these 2 groups to 9 months showed a 10.1% major adverse event rate in the simple group versus a 17.3% major adverse event rate in the complex group. The difference was largely driven by periprocedural myocardial infarction. Procedure duration, contrast volume, and x-ray dose exposure favored the simple group. In addition, a subgroup analysis of more anatomically complicated lesions demonstrated no benefit of a complex strategy. This study, therefore, suggests that the usual strategy for the treatment of bifurcation lesions should be the simple provisional strategy.

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