

The Impact of Coronary Bifurcation Stenting Strategy on Health-Related Functional Status

A Quality-of-Life Analysis From the BBC One (British Bifurcation Coronary; Old, New, and Evolving Strategies) Study

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Objectives This study sought to assess the impact of coronary bifurcation stenting on health-related functional status, using the Seattle Angina Questionnaire (SAQ), for participants in the BBC ONE (British Bifurcation Coronary; Old, New, and Evolving Strategies) trial and to compare simple versus complex bifurcation stenting strategies in this regard.

Background Large randomized studies have examined outcomes from bifurcation stenting with drug-eluting stents. They have reported on major adverse cardiovascular events and angiographic follow-up. However, a principal goal of percutaneous coronary intervention is symptom control and improvement in quality of life, yet there are no published data from these trials on this aspect. Furthermore, it is unknown whether simple versus complex stenting strategies have different effects on angina control and quality of life.

Methods The BBC ONE study randomized 500 subjects to bifurcation stenting using either a simple (provisional T) or complex (crush or culotte) approach. Subjects completed the SAQ at baseline and at 9 months after percutaneous coronary intervention. Canadian Cardiovascular Society class and antianginal drug use were also evaluated.

Results Bifurcation stenting was associated with significant improvements on SAQ scales and in Canadian Cardiovascular Society class (baseline: 5.3% subjects were class 0; follow-up: 64.0% were class 0; $p < 0.001$) and a significant reduction in the number of antianginal drugs used (median decrease: 1; $p < 0.001$). Simple and complex strategies did not differ significantly for changes in the SAQ, actual SAQ scores, or use of antianginal drugs.

Conclusions Regardless of chosen strategy, bifurcation stenting produced significant functional improvements in angina-related health. No significant difference between simple and complex strategies was found in this regard. (*J Am Coll Cardiol Intv* 2013;6:139–45) © 2013 by the American College of Cardiology Foundation

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Lesions at coronary bifurcations have been associated with poorer outcomes from percutaneous coronary intervention (PCI) when compared with those not involving a branch, mostly due to problems affecting the side branch (1). The optimal strategy for treating bifurcations in the drug-eluting stent (DES) era has been examined in large randomized controlled trials (2–5). The BBC ONE (British Bifurcation Coronary; Old, New, and Evolving Strategies) trial randomized 500 patients to treatment of bifurcation lesions by either simple (planned main vessel only, T-stenting if required) versus complex (planned crush or culotte) strategies (3). The primary endpoint was a composite of death,

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myocardial infarction, or target vessel failure at 9-month follow-up and occurred significantly more often in the complex stenting group, driven principally by a greater number of myocardial infarctions. Inclusion of routine periprocedural enzyme measurements to diagnose myocardial infarctions may explain why more myocardial infarctions were seen with complex stenting than in the previously

Abbreviations and Acronyms

CCS = Canadian Cardiovascular Society

DES = drug-eluting stent(s)

IQR = interquartile range

PCI = percutaneous coronary intervention

SAQ = Seattle Angina Questionnaire

published large Nordic Bifurcation Study (2). A recent patient-level combined analysis of the Nordic and BBC ONE trials found more adverse clinical events with a complex stenting strategy, again driven by an excess of myocardial infarction (6). Other bifurcation studies comparing simple and complex approaches, such as the CACTUS (Coronary Bifurcations: Appli-

cation of the Crushing Technique Using Sirolimus-Eluting Stents) study and BBK (Bifurcations Bad Krozingen), did not include routine periprocedural enzyme measurements and did not find any major adverse cardiovascular event differences (4,5).

A major aim of PCI is symptom control and improvement in quality of life, yet the large published studies on bifurcation strategy have tended to focus on major adverse cardiovascular events and on angiographic out-

comes. Angiographic appearances are of minimal importance to most patients. From a patient perspective, an improvement in symptoms and, more generally, functional status relating to their coronary artery disease is usually the primary concern. There is a paucity of published data on this aspect for the treatment of bifurcation lesions, although such data could undoubtedly contribute to informed decision making by operators dealing with such lesions. Therefore, we present here a prospectively performed quality-of-life analysis for simple versus complex bifurcation treatment, undertaken as part of the multicenter BBC ONE study.

The Seattle Angina Questionnaire (SAQ) assesses a broader spectrum of disease effects than other measures, such as the Canadian Cardiovascular Society (CCS) score or the Duke Activity Status Index, do (7). It also provides a more disease-specific measure than, for example, the Duke Index, the Specific Activity Scale, or the short form 36. SAQ has been used in hundreds of published studies, including the recent COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trials (8,9). Therefore, it was chosen here to examine functional outcomes from bifurcation coronary stenting.

Methods

The methodology used in the BBC ONE study has been published elsewhere (3). Five hundred patients were randomized to either a simple or complex bifurcation stent strategy. The simple strategy involved planned stenting of main vessel only, with provisional treatment of the side branch. The complex strategy involved planned main vessel and side branch stenting from the outset, involving either culotte or crush technique based on operator preference. Baseline demographics of the study cohort are given in Table 1 of the original BBC ONE paper (3). Subjects entering the study received the standard 19-point SAQ, shown in Appendix 1 of that paper. They also underwent assessment of CCS score and documentation of the number of antianginal medications being taken. Baseline questionnaires were completed by the subjects before PCI. The same

Table 1. Nonparametric Testing Comparing Baseline and 9-Month Follow-Up Time Points for the Overall BBC ONE Study Cohort

Scale of SAQ	Pre-PCI Median, IQR, Range	9-Month Post-PCI Follow-Up Median, IQR, Range	Wilcoxon Signed-Rank Test for Pre-PCI vs. Post-PCI
Angina frequency scale	70, 40–90, 0–100	100, 80–100, 10–100	p < 0.001
Angina stability scale	50, 25–75, 0–100	100, 50–100, 0–100	p < 0.001
Physical limitation scale	63.9, 44.4–83.3, 0–100	88.9, 69.4–100, 0–100	p < 0.001
Treatment satisfaction scale	93.8, 81.3–100, 31.3–100	100, 87.5–100, 18.8–100	p = 0.22
Disease perception scale	41.6, 25.0–58.3, 0–100	83.3, 66.7–91.7, 0–100	p < 0.001

BBC ONE = British Bifurcation Coronary; Old, New, and Evolving Strategies; IQR = interquartile range; PCI = percutaneous coronary intervention; SAQ = Seattle Angina Questionnaire.

questionnaire format was used again at the mandated 9-month post-PCI follow-up visit.

SAQ comprises 5 scales that measure different aspects of the potential functional impact of coronary artery disease. These scales are: 1) physical activity; 2) angina stability; 3) angina frequency; 4) treatment satisfaction; 5) disease perception. The score for each scale is transformed to a value in the 0 to 100 range, with lower values reflecting lower levels of function for that particular scale. There is no summation score for all 5 scales because the scales measure different aspects of function that cannot be readily merged for the purposes of statistical analysis.

Statistical analysis. Data were analyzed using GraphPad Prism (version 4.01, GraphPad Software, Inc., La Jolla, California) and Minitab (version 15, Minitab Inc., State College, Pennsylvania). Nonparametric testing was employed to accommodate the distributional properties of the data.

For the overall study population (simple and complex groups combined), Wilcoxon signed-rank testing was used to analyze the change (in individual subjects) of SAQ scores, CCS scores, and number of antianginal medications between baseline and follow-up time points.

For assessing simple versus complex groups, Mann-Whitney *U* testing was used for between-group comparisons at baseline and at follow-up. Mann-Whitney *U* testing was also used to compare the change in SAQ scores (for each scale) between the 2 time points, for subjects in simple versus

complex groups. Chi-square testing was used to compare the proportions of patients in the 2 groups who were angina-free at follow-up.

Results

Baseline characteristics of the study cohort have been published previously and show excellent matching between the 2 study arms in terms of age, sex, coronary risk factors, presentation (acute vs. elective), number of diseased coronary territories, location of bifurcation lesion, and adverse anatomical factors.

Overall study population. Figures 1A to 1E show the scores on each of the 5 scales of SAQ for the overall BBC ONE study cohort at baseline (pre-PCI) compared with at the 9-month post-PCI follow-up. Maximum value on each scale is 100 and minimum is 0. On each scale, higher values represent better functional status. Statistical analysis is shown in Table 1. It is seen that scores for all scales other than treatment satisfaction score show a highly significant improvement after bifurcation PCI.

CCS scores at baseline showed an approximately bell-shaped distribution with median of 2, interquartile range (IQR) of 1 to 3, and full range of 0 to 4. In contrast, CCS scores at 9-month follow-up showed a left-skewed distribution with median of 0, IQR of 0 to 1, and full range of 0 to 4. The median decrease in CCS score between the 2 time

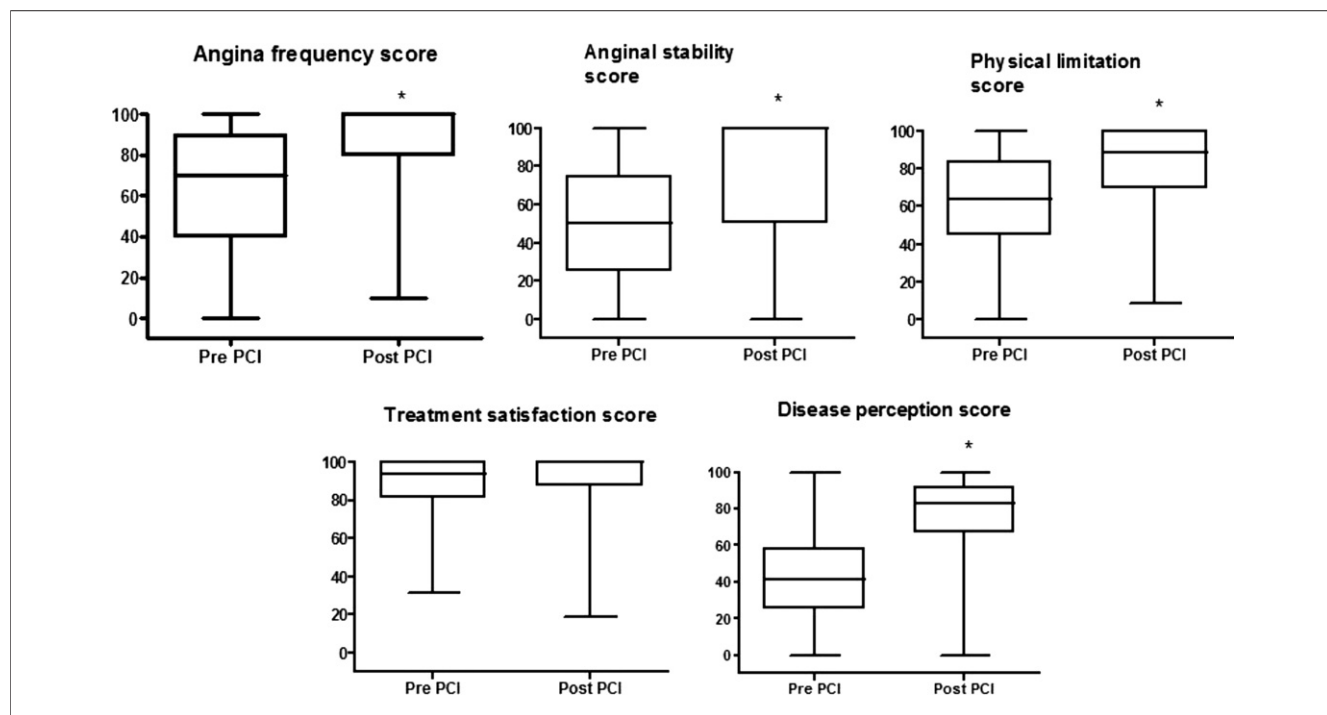


Figure 1. Seattle Angina Questionnaire Scores for the Overall BBC-ONE Study Cohort

Scores at baseline and at nine months post-PCI are shown. * Significant difference between pre- and post-PCI scores. Bifurcation PCI significantly improved scores on 4 out of the 5 SAQ scales. PCI = percutaneous coronary intervention.

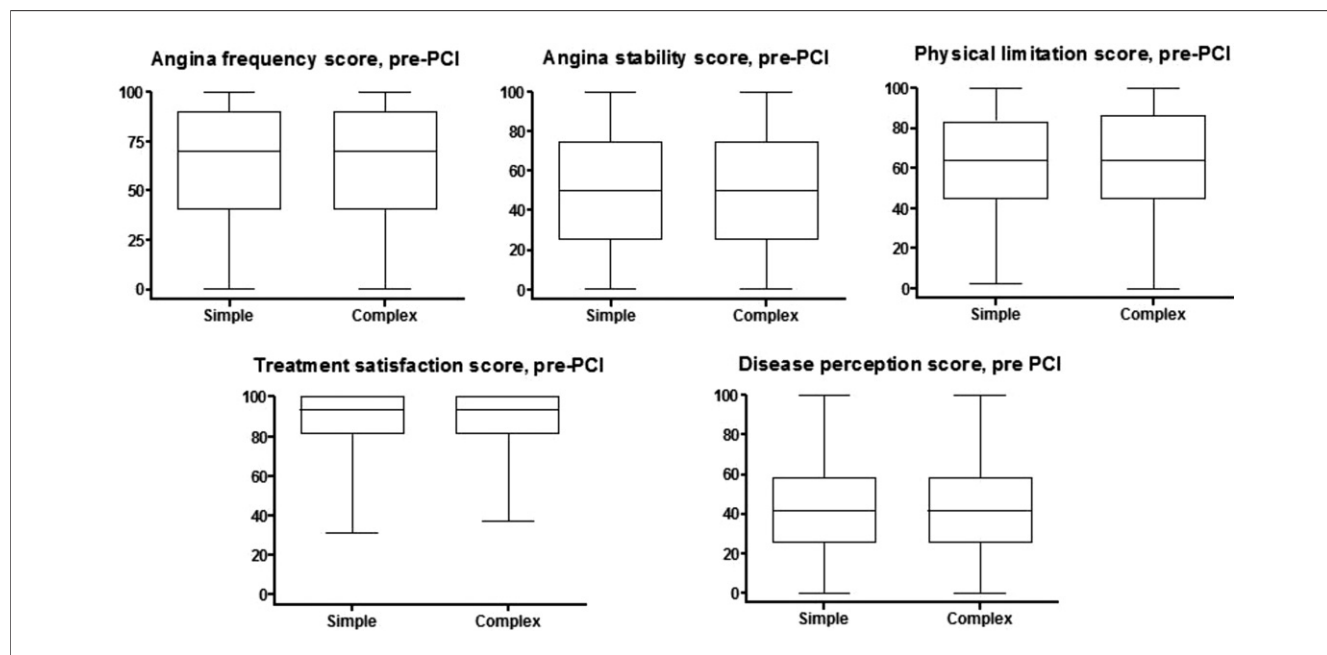


Figure 2. Baseline (Pre-PCI) Scores on SAQ for Simple and Complex Groups

Interquartile range shown in boxed region, full range within whisker bars. The pre-PCI scores did not differ significantly between the 2 groups for any of the SAQ scales. Abbreviation as in Figure 1.

points was 2 (IQR 1 to 2), with Wilcoxon signed-rank testing confirming significant evidence for improvement in angina class at follow-up ($p < 0.001$).

The number of antianginal agents at baseline was median 2, IQR 1 to 3, and full range 0 to 5. At follow-up, this had fallen to median 1, IQR 1 to 2, and full range 0 to 5. Wilcoxon signed-rank

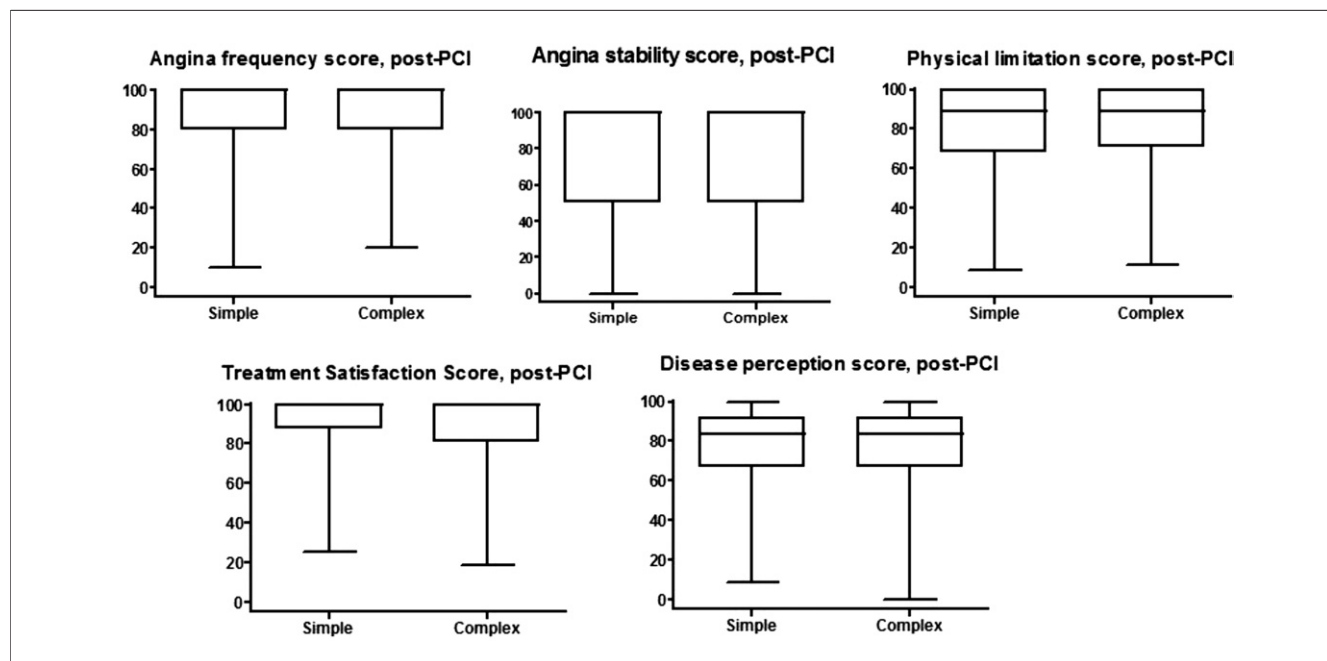


Figure 3. 9-Month Post-PCI Scores on SAQ for Simple and Complex Groups

Interquartile range shown in boxed region, full range within whisker bars. The post-PCI scores did not differ significantly between the two groups for any of the SAQ scales. Abbreviation as in Figure 1.

testing demonstrated a significant reduction (median 1) in the number of antianginal drugs being used at follow-up compared to baseline ($p < 0.001$).

Simple versus complex treatment groups. Figures 2A to 2E illustrate box plots for the 2 study groups for each of the 5 scales of the SAQ at baseline. The 2 study arms were very closely matched in terms of baseline functional status, as is expected with large subject numbers and randomized treatment allocation.

Figures 3A to 3E show data for the 5 SAQ scales at the 9-month follow-up. Statistical analysis of the group data for simple and complex cohorts is given in Table 2.

The corresponding graphs for simple and for complex approaches appear very similar to each other for every scale on the SAQ. This is borne out statistically, with no significant difference emerging between the groups for any scale at either time point.

Analysis of change in individual patients' scores on each SAQ scale (between baseline and follow-up) allowed a more powerful statistical assessment of any potential difference in outcomes between simple and complex groups. Score changes (i.e., a subject's 9-month post-PCI score minus their baseline score) did not differ significantly between simple and complex groups, for any of the 5 scales (angina frequency score: $p = 0.65$; angina stability score: $p = 0.75$; physical limitation score: $p = 0.60$; treatment satisfaction score: $p = 0.84$; disease perception scale: $p = 0.93$). Figure 4 gives an indication of the proportions of patients in each group whose scores improved, remained unchanged, or deteriorated between baseline and follow-up, for each scale of the SAQ. The close similarity between simple and complex groups in this regard is apparent in this figure.

The proportions of patients who were free of angina at follow-up (score of 100 on angina frequency score on SAQ) was 65.1% in the simple treatment group and 59.7% in the complex group, which was not significant on chi-squared testing ($p = 0.23$).

The number of antianginal drugs at baseline in the simple group was median 2, IQR 1 to 3, and full range 0 to 5. Median, IQR, and full range were identical in the complex group at baseline. A Mann-Whitney U test confirmed no significant evidence for difference between the 2 groups in terms of baseline antianginal use ($p = 0.67$). At 9-month follow-up, the average number of antianginal drugs had dropped in the simple group to median 1, IQR 1 to 2, and full range 0 to 4. For the complex group at follow-up, median number of drugs was 1, IQR 1 to 2, and full range 0 to 5. Mann-Whitney U analysis again demonstrated no significant evidence for a difference between simple and complex groups in antianginal use at follow-up ($p = 0.96$).

Table 2. Nonparametric Testing for Comparison of SAQ Scores Between Simple and Complex Groups, at Baseline and at 9-Month Follow-Up

Scale of SAQ	Simple, Pre-PCI		Complex, Pre-PCI		Mann-Whitney U Test, p Value for Simple vs. Complex Groups at Baseline (Pre-PCI)		Simple, Post-PCI		Complex, Post-PCI		Mann-Whitney U Test, p Value for Simple vs. Complex Groups at 9-Month Post-PCI Follow-Up	
	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range	Median, IQR, Range
Angina frequency scale	70, 40–90, 0–100	70, 40–90, 0–100	70, 40–90, 0–100	70, 40–90, 0–100	0.50	0.50	100, 80–100, 10–100	100, 80–100, 20–100	100, 80–100, 20–100	100, 80–100, 20–100	0.40	0.40
Angina stability scale	50, 25–75, 0–100	50, 25–75, 0–100	50, 25–75, 0–100	50, 25–75, 0–100	0.72	0.72	100, 50–100, 0–100	100, 50–100, 0–100	100, 50–100, 0–100	100, 50–100, 0–100	0.51	0.51
Physical limitation scale	63.9, 44.4–83.3, 2.8–100	63.9, 44.4–86.1, 0–100	63.9, 44.4–86.1, 0–100	63.9, 44.4–86.1, 0–100	0.69	0.69	88.9, 68.1–100, 8.3–100	88.9, 70.8–100, 11.1–100	88.9, 70.8–100, 11.1–100	88.9, 70.8–100, 11.1–100	0.83	0.83
Treatment satisfaction scale	93.8, 81.3–100, 31.3–100	93.8, 81.3–100, 37.5–100	93.8, 81.3–100, 37.5–100	93.8, 81.3–100, 37.5–100	0.64	0.64	100, 87.5–100, 25.0–100	100, 81.3–100, 18.8–100	100, 81.3–100, 18.8–100	100, 81.3–100, 18.8–100	0.65	0.65
Disease perception scale	41.7, 25.0–58.3, 0–100	41.7, 25.0–58.3, 0–100	41.7, 25.0–58.3, 0–100	41.7, 25.0–58.3, 0–100	0.66	0.66	83.3, 66.7–91.7, 0–100	83.3, 66.7–91.7, 0–100	83.3, 66.7–91.7, 0–100	83.3, 66.7–91.7, 0–100	0.56	0.56

Abbreviations as in Table 1.

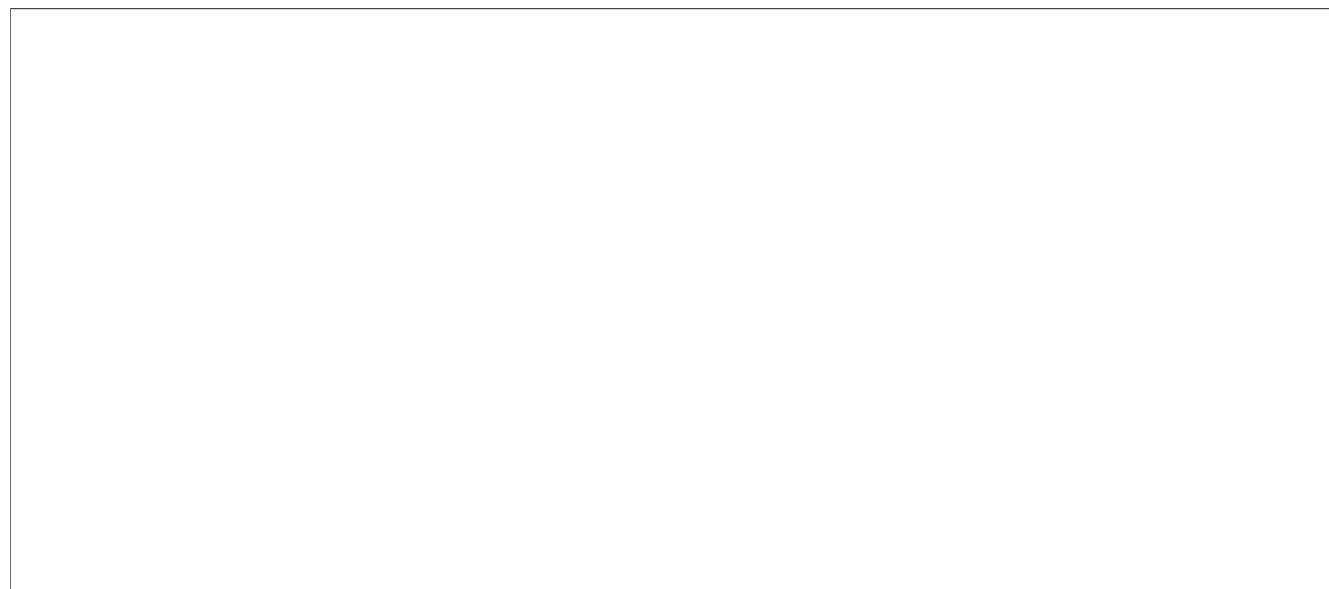


Figure 4. Direction of Change in Individual Patients' Scores on SAQ

Patients' scores at baseline (pre-PCI) and at 9 month follow-up were compared. The graphs indicate the proportions of patients who improved, deteriorated, and remained unchanged over this period, for each of the SAQ scales. A close similarity between findings in the simple and complex groups was again evident. Abbreviations as in Figure 1.

Discussion

Coronary bifurcation lesions are frequently encountered in interventional practice, due to a predilection for atheroma development at sites of turbulent flow, such as arterial branch points (10). Outcomes have been worse for PCI to lesions at these sites when compared with nonbifurcation lesions. The arrival of DES offered the prospect of more complex treatment to both distal limbs of bifurcations without the prohibitive in-stent restenosis rate seen with bare-metal stents in this context (11). Several large randomized studies comparing simple and complex stenting approaches have been performed in the DES era. There has been a signal for increased major adverse cardiovascular events with complex stenting in some of these studies, as discussed. Additionally, and consistent across all these studies, simple stent strategies have clear benefits in terms of lower procedural duration, procedural (equipment) costs, contrast usage, and fluoroscopy exposure.

The 2 main aims of PCI in general are: 1) symptom control and/or functional improvement; and, in some settings and 2) a reduction in the risk of future events. For stable patients undergoing elective treatment, it is the first of these for which PCI is of clear proven benefit; hence, strategies should be based on evidence of impact on this. Such data in the context of bifurcation lesions have been lacking. The data shown here demonstrate that bifurcation stenting (irrespective of simple or complex strategy) is associated with a highly significant and sustained improvement in health-related functional status and quality of life.

The lack of difference in functional status between simple and complex groups contrasts with a difference in the primary endpoint of the main BBC ONE study. The primary endpoint difference was driven particularly by periprocedural enzyme rises, documented on mandated blood tests. These events are frequently associated with minimal symptoms and are often of debatable clinical relevance (12). This might be reflected in our SAQ findings.

These findings counter the intuitive suggestion that a simple strategy leaving a "pinched" side branch ostium creates a substrate for future symptoms related to ischemia in the side branch territory. The findings here fit with data provided by Koo et al. (13) and more recently by Ahn et al. (14), who demonstrated that many of these apparently pinched side branch ostia are not functionally significant on fractional flow reserve assessment. This is also in keeping with "real-world" clinical experience, wherein only a minority of patients treated with a simple approach requires further intervention due to ongoing angina symptoms at subsequent review.

Study limitations. The time course of follow-up was 9 months after PCI, and it is possible that a difference between groups would have emerged if patients had been tracked for a longer duration after the procedure. This may be relevant for in-stent restenosis and/or late or very late stent thrombosis. Indeed, restenosis and stent thrombosis were numerically greater for complex stenting although there was no statistically significant difference when compared with a simple strategy. This study used Taxus

stents (Boston Scientific, Natick, Massachusetts), which are known to have greater late lumen loss and in-stent restenosis (and stent thrombosis rate) than do second-generation everolimus-eluting stents (15). This might have disadvantaged the complex (2-stent) approaches where restenosis is likely to be a greater problem than for simple procedures.

Conclusions

The findings presented here fill an important gap in our knowledge regarding outcomes after bifurcation stenting in the DES era. A clear improvement in health-related functional status and quality of life is seen with bifurcation PCI, regardless of the technique employed. The lack of difference in symptomatic and functional outcomes between simple and complex approaches strengthens the argument that a default simple strategy is preferable in most cases, given its other proven advantages (reduced procedural duration, radiation dose, equipment costs, and so on).

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Key Words: bifurcation ■ coronary ■ crush ■ culotte ■ provisional stent ■ quality of life ■ Seattle angina questionnaire ■ stent.