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FASTTRACK CLINICAL RESEARCH
Ischaemic heart disease

The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN)

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Background Patients with non-left-main coronary bifurcation lesions are usually best treated with a stepwise provisional approach. However, patients with true left main stem bifurcation lesions have been shown in one dedicated randomized study to benefit from systematic dual stent implantation.

Methods and results Four hundred and sixty-seven patients with true left main stem bifurcation lesions requiring intervention were recruited to the EBC MAIN study in 11 European countries. Patients were aged 71 ± 10 years; 77% were male. Patients were randomly allocated to a stepwise layered provisional strategy ($n = 230$) or a systematic dual stent approach ($n = 237$). The primary endpoint (a composite of death, myocardial infarction, and target lesion revascularization at 12 months) occurred in 14.7% of the stepwise provisional group vs. 17.7% of the systematic dual stent group (hazard ratio 0.8, 95% confidence interval 0.5–1.3; $P = 0.34$). Secondary endpoints were death (3.0% vs. 4.2%, $P = 0.48$), myocardial infarction (10.0% vs. 10.1%, $P = 0.91$), target lesion revascularization (6.1% vs. 9.3%, $P = 0.16$), and stent thrombosis (1.7% vs. 1.3%, $P = 0.90$), respectively. Procedure time, X-ray dose and consumables favoured the stepwise provisional approach. Symptomatic improvement was excellent and equal in each group.

Conclusions Among patients with true bifurcation left main stem stenosis requiring intervention, fewer major adverse cardiac events occurred with a stepwise layered provisional approach than with planned dual stenting, although the difference was not statistically significant. The stepwise provisional strategy should remain the default for distal left main stem bifurcation intervention.

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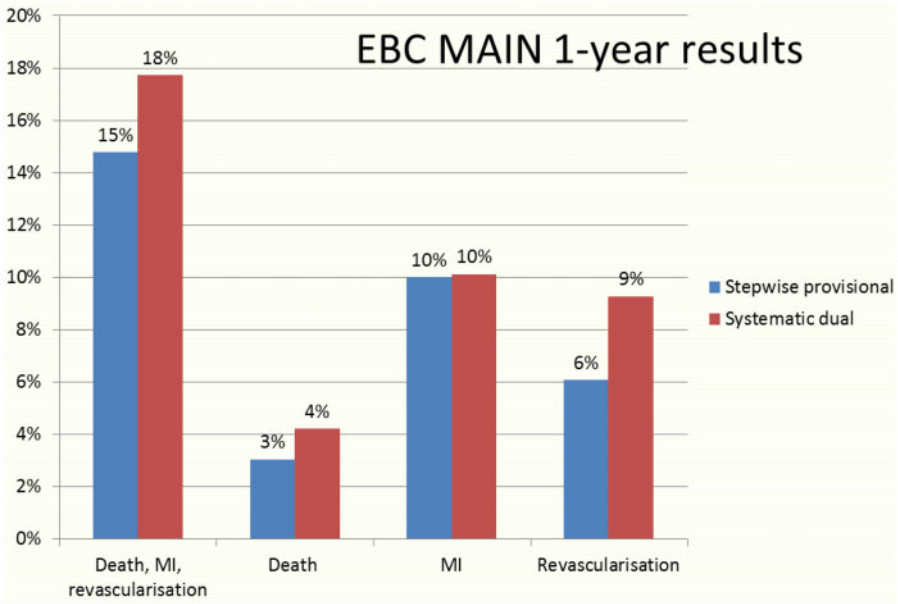
Graphical Abstract



Compared with a dual stent strategy, numerically (but not statistically) fewer major adverse cardiac events occurred with the stepwise provisional approach.

Keywords Angina • Bifurcation • Coronary artery • Left main stem • Stents

Introduction

Optimal treatment of coronary bifurcation anatomy remains a subject of debate, 15 years on from the publication of the first large randomized trial.[1] Trials of all-comer bifurcation lesions have demonstrated that there is no advantage to systematic dual drug-eluting stent strategies[1–3] and indeed that long-term mortality may be worse with a more complex approach.[4] For the left main stem, it might be expected that these differences would be magnified, given the wide angle of separation between the two vessels, the heavy calcification often involved and the fact that neither vessel is a side branch. Non-randomized data uniformly suggests that outcomes are worse with a two-stent strategy,[5–7] but randomized data support the double kissing (DK) crush technique for true bifurcation left main stem disease[8,9] and support it over culotte.[10] The European Bifurcation Club Left Main Coronary Stent Study (EBC MAIN) was designed to examine clinical outcomes in patients with distal bifurcation left main stem lesions undergoing intervention, randomly allocated to either a stepwise layered provisional stent strategy, or a systematic dual stenting strategy.[11]

Methods

The study was an investigator-led prospective randomized multicentre trial devised by and run through the European Bifurcation Club (www.bifurc.net) in 11 European countries. The trial was administered and overseen by a Clinical Research Organisation (CERC, Massy, France) and the data were seen, assessed, and adjudicated by a Clinical Events Committee and a Data and Safety Monitoring Board. All events were adjudicated by the Clinical Events Committee. An independent CoreLab analysed the procedural angiograms. The study was supported by an unrestricted educational grant from Medtronic. The study protocol was approved by the relevant authorities in all countries involved in the study. The trial was registered on ClinicalTrials.gov (NCT02497014).

Study population

Patients requiring percutaneous coronary intervention (PCI) were eligible for the study if they were aged ≥18 years and had 'true' unprotected bifurcation left main stem coronary artery disease (Medina type 1,1,1 or 0,1,1—both main vessel and side vessel >50% narrowed) in which both vessel reference diameters were ≥2.75 mm. In order to be included in the study, patients had to have either ischaemic symptoms, positive non-invasive imaging for ischaemia, a positive fractional flow reserve or a left main stem intravascular ultrasound (IVUS)-derived minimum luminal area of <6 mm^2. Patients with ≤2 additional coronary lesions could be included in the study. The main exclusion criteria were: acute ST-elevation myocardial infarction; cardiogenic shock; chronic total occlusion of either vessel; left main trifurcation with all three vessels ≥2.75 mm diameter; left main stem diameter >5.75 mm; patient life expectancy <12 months; or known relevant allergies. Patients who consented to the study were randomized via a 128-bit secure encrypted dedicated website

using standard random number generation methodology with stratification by centre.

Revascularization procedure

Pre-percutaneous coronary intervention

Patients were assessed for angina status (Canadian Cardiovascular Society—CCS) and extent of anti-anginal medication (angina index). Serum creatine kinase (CK) and high sensitivity troponin were measured pre-procedure. Operators were expected to be undertaking ≥150 PCI procedures per year. Antiplatelet regimen of choice was at the operator's discretion. Antiplatelet loading was to be made ≥3 h before the procedure to antiplatelet-naïve patients.

Percutaneous coronary intervention procedure

Intravenous unfractionated heparin 70 IU/kg was given at the start of the procedure to maintain an activated clotting time of ≥250 s. Access site, use of glycoprotein inhibitors and use of IVUS or optimal coherence tomography was at the discretion of the operator. The Onyx® zotarolimus-eluting coronary stent (Medtronic) was used in the study. This stent has 4.5 mm and 5 mm diameter options which can be valuable in the left main.

Stepwise provisional single stent group

The protocol specified the procedural steps for this group of patients. Coronary guide wires were passed to the left anterior descending (LAD) and circumflex (Cx)/intermediate arteries, respectively. One was designated the main vessel and one the side vessel. Lesion preparation was undertaken as required but side vessel predilatation was discouraged unless considered essential by the operator, to reduce the risk of an unsecured dissection. Stenting of the main vessel was undertaken with a wire jailed in the side vessel to preserve side vessel flow and access. Stent diameter was chosen according to the diameter of the main vessel immediately distal to the bifurcation. Following stenting of the left main into the main vessel, the left main stent was dilated to the carina with a short non-compliant balloon of appropriate size for the left main stem (proximal optimization technique, POT). Following this, the side vessel was rewired through a distal stent strut where possible, and a kissing balloon inflation was undertaken. Kissing balloon sizes were chosen according to the diameter of the distal main and side vessel respectively, with individual higher pressure inflation followed by a final lower pressure kiss dilatation. The left main stent was then dilated using either low pressure dilatation of the kissing balloon pair or a separate individual balloon. For these dilatations, non-compliant balloons were preferred to limit the risk of dissection through uneven expansion. Following kissing dilatation, the side vessel was not to be treated further unless there was one of the following: <TIMI 3 flow in the side vessel, severe (>90%) ostial pinching of the side vessel, threatened side-vessel closure or side-vessel dissection >type A. Under these circumstances, the operator could choose to implant a side vessel stent in a manner of their choosing (e.g. T, TAP, culotte). Following implantation of a second stent, repeat POT followed by recrossing and repeat kissing balloon inflation was mandatory, again using non-compliant balloons as above, with individual very high pressure inflations at the stent bifurcations followed by final kissing balloons at lower pressures. Further treatment to proximal or distal aspects of the main vessel or side vessel could be continued at the discretion of the operator in the event of, for example, proximal or distal dissections.

Systematic planned two-stent group

The protocol specified the procedural steps for this group of patients. Coronary guide wires were passed to the LAD and Cx/intermediate arteries, respectively. One was designated the main vessel and one the side vessel. Lesion preparation was undertaken as considered necessary in both limbs. The stent technique was at the discretion of the operator but could be one of culotte, DK-minicrush, T or TAP. Stent diameter was made according to the diameter of the vessel immediately distal to the bifurcation. Specific practical steps varied according to the technique chosen. In the culotte strategy, after the first stent was implanted and POT done, the second vessel was rewired (ideally distally), predilated and a stent placed with a short overlap only to the main vessel stent. A second POT was made and the main vessel rewired. A final kiss was made with high pressure individual dilatations at the bifurcation of the stents followed by a lower pressure kiss at the neocarina. A final POT or low-pressure inflation of the two kissing balloons was made back to the proximal edge of the left main stem stent to ensure full apposition. Similar procedural steps, with appropriate variations, were required for the T, TAP, and DK-minicrush procedures, according to the principles laid out in previous European Bifurcation Club recommendations.[12,13] Further treatment to the proximal or distal aspects of the main vessel or side vessel could be made at the discretion of the operator. At any stage, proximal or distal dissections could be treated as required with further stent implantations.

Post-percutaneous coronary intervention

Creatine kinase and troponin were measured 6–24 h post-PCI. Aspirin 75 mg daily was continued long term. Clopidogrel 75 mg daily was given for a minimum of 6 months (or appropriate dose of prasugrel or ticagrelor). Discontinuation of antiplatelet agents for soft indications was strongly discouraged. Statin therapy was continued for the duration of the study. Procedural angiograms were sent to the CoreLab for analysis.

Follow-up

Patients were followed up by telephone or in person pre-discharge, at 6 months (±15 days) and 12 months (±30 days). At the 6-month follow-up, patient symptoms and wellbeing were established. Significant symptoms triggered further investigation as required. At 1-year follow-up, symptoms, angina index, adverse events, and endpoints were assessed. Follow-up could be made by telephone if necessary. Adverse event tracking began at randomization and continued to the end of the 12-month follow-up period in a cohort block. All revascularization and possible stent thrombosis cases were reviewed by the CoreLab.

Endpoints

Primary endpoint

The primary endpoint of the study was a composite of all-cause death, myocardial infarction, and target lesion revascularization at 12 months.

Secondary endpoints

These were the individual components of the primary endpoint, angina status, angina medication, and adjudicated stent thrombosis.

Definitions

Myocardial infarction

The Universal Definition of Myocardial Infarction (Revision 2013) was used to define myocardial infarction in this study, except for the category of PCI-related myocardial infarction (Type 4a) or coronary artery bypass graft-related myocardial infarction (Type 5). Under these circumstances, the more practical expert consensus definition from Society for Cardiovascular Angiography and Interventions (SCAI) was used.[14] Therefore, in patients who are stable on admission, the peak biomarker measured post-PCI will need to rise to 10× the local laboratory upper limit of normal (ULN) for CK [5× with new persistent left bundle branch block (LBBB) or Q waves] or 70× the local laboratory ULN for troponin (35× with new persistent LBBB or Q waves). In patients with an acute

coronary presentation and raised biomarkers on admission, the peak biomarker measured post-PCI will need to rise to an absolute increase of 10× the local laboratory ULN for CK (5× with persistent LBBB or Q waves) or an absolute increase of 70× the local laboratory ULN for troponin (35× with persistent LBBB or Q waves).

Target vessel revascularization

If either main vessel or side vessel requires or undergoes attempted repeat revascularization with either balloon angioplasty, stenting, or coronary artery bypass grafting, within the previous treated vessel area (balloon or stent) or within 5 mm adjacent to this area.

Technical success

Completion of stent placement, balloon dilatation, rewiring, and final kissing balloon therapy as required by the protocol.

Procedure success

Placement of stents as per randomization with TIMI 3 flow and <30% stenosis in any stented vessel and TIMI 3 flow in any unstented vessel.

Angina index

Angina medication scoring system, scoring 1 each for glyceryl trinitrate spray; oral nitrate; β-blocker; calcium antagonist; nicorandil or other (max score 5).

Statistical methods

Descriptive data analyses were conducted depending on the nature of the considered criteria. For quantitative data, this included number of observed values (and missing values, if any), mean, standard deviation, median, first and third quartiles, and minimum and maximum. For qualitative data, this included the number of observed and missing values and the number and percentage of patients per class. Comparisons between treatment groups were assessed with chi-square or the Fisher's exact test for categorical variables and the Student's *t*-test or Wilcoxon test for quantitative variables. Normality of variables was graphically confirmed.

The statistical analysis method for the primary endpoint was based on Kaplan–Meier methods and the log-rank test was used to test for treatment group differences. Furthermore, the treatment effect was estimated as well as its accuracy (estimate of the hazard ratio and 95% confidence interval) using a Cox hazard proportional regression model with treatment group as the only covariate. The hypothesis for the study was that left main coronary true bifurcation lesions (type 1,1,1 or 0,1,1: both LAD and Cx >2.75 mm diameter) would be best treated with a planned single stent stepwise strategy rather than a planned dual stent strategy, with respect to death, target lesion revascularization and myocardial infarction at 1 year. At the time of protocol development, left main stem bifurcation data from published studies suggest that the primary endpoint might be reached in 14% (single) vs. 25% (dual) patients at 1 year. Using these estimates, a two-sided significance (1-alpha) of 95% and 80% power, a sample size of 404 patients was developed. Allowing for a 10% loss-to-follow-up rate, the study was powered for 450 randomizations. One interim analysis was planned for the primary endpoint. This was undertaken at the first/third recruitment stage and allowed for stopping the trial early for positive efficacy using an alpha-spending function if needed. Analyses were done on an intention-to-treat basis using SAS 9.4 software.

Results

Between February 2016 and November 2019, 467 patients were randomized into the EBC MAIN study at 31 sites in 11 European countries. Two hundred and thirty patients were randomized to the stepwise layered provisional approach, 237 to the systematic dual stent approach. There were major protocol deviations in 6 single and 12 dual patients, respectively [including failure to undergo PCI ($n = 8$) and failure to use the Onyx stent ($n = 4$)]; all remained in the analysis on an intention-to-treat basis. Patient demographics and clinical features are shown in *Table 1*. Patients were aged 71 ± 10 years. 77% were male and 28% were diabetic. Two-thirds of patients were treated electively.

Procedural characteristics are shown in *Table 2*. Most patients had a transradial approach, with 6 F guiding catheters. Intravenous antiplatelet agents were rarely used. In three-quarters of patients, the LAD was designated the main continuation vessel. Among those randomized to the stepwise provisional approach, side vessel predilatation was undertaken in about half of cases. In those who were randomized to a planned two-stent strategy, half had treatment directed into the main vessel first, half into the side vessel. The culotte was the most commonly used two-stent technique. Five percent of patients allocated to the dual stent strategy had only a single stent implanted. Twenty-two percent of patients in the stepwise provisional group had a second bifurcation stent implanted (the final path of the stepwise strategy).

Utilization of consumables is shown in *Table 3*. More balloons and stents were used in the systematic dual stenting group, and the total stented length was greater. Procedure duration, fluoroscopy time, and X-ray dose were higher in the dual-stent group. Technical success was lower in the provisional group but procedural success was higher in the provisional group. The procedural sequence of events is shown in *Table 4*, to delineate the flow of procedures in each group.

The primary and secondary endpoints of the trial are shown in *Table 5*. One patient was lost to follow-up in each group. There was no difference between groups at 1 year in terms of death, myocardial infarction, target lesion revascularization, or the composite of the three (the primary endpoint). Periprocedural myocardial infarction outcomes were underscored by recording of CK ($n = 279$), CK-MB ($n = 152$), or troponin ($n = 198$). 85% of patients had appropriate cardiac enzyme measurement.

The trial results are shown diagrammatically in *Figure 1*, and in Kaplan–Meier form in *Figure 2*. Symptomatic relief was good in both groups with a mean improvement in CCS class from 1.8 to 0.5, and a mean improvement in angina index from 1.4 to 0.8 (*Table 6*).

Quantitative coronary angiography results from the CoreLab (Pie Medical CERC) are shown in *Table 7*. Proximal main vessel and side vessel minimal luminal diameter post-procedure were both larger in the systematic dual stenting group.

Discussion

In this study, we have found that stent treatment for true left main stem bifurcation lesions can be undertaken with low 1-year adverse event rates employing either the stepwise provisional approach or a

systematic dual stenting technique (*Graphical abstract*). Symptomatic improvement and reduction in use of anti-anginal medications were highly significant in both groups. Procedure duration, X-ray dose and consumables were reduced. The results support a default stepwise provisional strategy for true left main stem bifurcation lesions requiring intervention.

The vast majority (78%) of the patients in the stepwise provisional approach received a single stent. The advantage of the stepwise strategy is therefore that it does not prejudge the anatomical requirements. The approach is layered and sequential and the procedure is complete when a good result is obtained at any stage in the sequence.

The main study of comparison is the DKCRUSH-V[8] trial published in 2017. In this comprehensive study, the DK crush and provisional stenting strategies were compared. At 1 year, the primary endpoint (a composite of cardiac death, target vessel myocardial infarction, and target lesion revascularization) occurred in 10.7% of provisional cases and 5.0% of DK crush cases ($P = 0.02$). This compares with the primary endpoint (a composite of death, myocardial infarction, and target lesion revascularization) of 14.7% and 17.7% in our study. Why are the results different in the two studies?

Firstly, the definitions in the studies were different. The DKCRUSH-V study used cardiac death and target vessel-related myocardial infarction rather than death and myocardial infarction and this will have reduced the overall number of events. Secondly, the coronary anatomy was different. The respective SYNTAX scores were 31 (DK crush) vs. 23 (EBC MAIN) and the side-vessel lesion lengths were 16 mm (DK crush) vs. 7 mm (EBC MAIN—although the measurement methodology may have differed between the studies). Therefore, the extent of disease was greater in the DKCRUSH-V study and indeed 45% of patients in the provisional group had implantation of two stents vs. 22% in EBC MAIN.

Thirdly, the philosophical approach varied between the two trials. The DK crush technique was pioneered by the Chinese Cardiology teams who undertook the DKCRUSH-V trial,[15] whereas the stepwise provisional approach has been championed by the European Bifurcation Club since its inception.[16] Hence unconscious biases are likely to have played a part in both trials. Attention to detail with regard to the specific technical aspects of each procedure likely differed in the two studies, and results may have varied slightly as a result. For example, in the DKCRUSH-V study, the POT was not described as a part of the procedure after initial stent placement in the main vessel, and therefore wire passage behind stent struts may have occurred in some cases, whereas in EBC MAIN it was required and was undertaken in 85%. It is of note that the stent thrombosis rate in the two trials was seen to be 2.5% (DK) vs. 1.7% (EBC) for the provisional group and 0.4% (DK) vs. 1.3% (EBC) for the systematic group.

Angiographic follow-up was undertaken in the DKCRUSH-V study. This was scheduled for 13 months (after planned ascertainment of the 12-month primary endpoint); however, there was a sudden spike in target lesion revascularization at 12 months (from 3.0% to 7.4% in the provisional group) related to early angiography-based revascularization (mean angiography time 367 ± 49 days). This may have been a factor in the unconscious biases noted above as operators could not be blinded to the previous treatment.

The systematic dual stent techniques used in the two trials were different. In the DKCRUSH-V trial, the DK crush approach was used throughout. In the EBC MAIN trial, the majority of dual-stent procedures were culotte (53%) or T/TAP (33%). Chen *et al.*[10] have previously published a randomized trial showing better outcomes with the

Table 1 Patient characteristics and clinical features

	Stepwise provisional ($n = 230$)	Systematic dual ($n = 237$)
Age (years), mean (SD)	70.8 (10.1)	71.4 (9.8)
Male sex (%)	182 (79%)	177 (74%)
Ischaemic symptoms	223 (97%)	224 (95%)
+ve non-invasive imaging	91 (40%)	100 (42%)
+ve FFR	47 (20%)	47 (20%)
IVUS <6 mm^2	77 (34%)	72 (30%)
BMI (kg/m^2), mean (SD)	28.6 (5.5)	28.4 (5.5)
Diabetes	66 (29%)	62 (27%)
Hypertension	180 (79%)	190 (82%)
Hypercholesterolaemia	158 (70%)	166 (72%)
Current smoker	36 (16%)	30 (13%)
Family history	74 (33%)	75 (33%)
Previous MI	60 (26%)	66 (28%)
Previous PCI	93 (41%)	99 (43%)
Previous stroke	16 (7%)	17 (7%)
Peripheral vascular disease	31 (14%)	37 (16%)
Renal failure[a]	12 (5%)	9 (4%)
Left ventricular function		
Good (EF > 50%)	143 (63%)	142 (62%)
Moderate (30–50%)	45 (20%)	54 (23%)
Poor (<30%)	9 (4%)	9 (4%)
Unknown	30 (13%)	27 (11%)
Presentation		
Stable coronary disease	149 (66%)	139 (60%)
CCS 0	25	32
CCS 1	31	19
CCS 2	49	42
CCS 3	35	38
CCS 4	8	7
Acute coronary syndrome	78 (33%)	93 (40%)
SYNTAX score, mean (SD)	22.6 (5.9)	23.2 (6.0)
0–22	72 (30%)	62 (26%)
22–32	132 (56%)	134 (57%)
Missing	36 (15%)	40 (17%)
Medina classification		
1,1,1	204 (90%)	206 (89%)
0,1,1	23 (10%)	25 (11%)
Adverse lesion features		
Trifurcation	13 (5%)	10 (4%)
Calcification ≥moderate	101 (44%)	125 (54%)
Tortuosity ≥moderate	43 (19%)	56 (24%)
Angle between LAD and Cx	80.4 (20.1)	82.3 (22.8)

CCS, Canadian Cardiovascular Society; Cx, circumflex coronary artery; EF, ejection fraction; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.
[a]Creatinine >200 mg/dL or equivalent.

Table 2 Procedural characteristics

	Stepwise provisional (*n* = 230)	Systematic dual (*n* = 237)
Access site		
Femoral	64 (28%)	68 (29%)
Radial	161 (71%)	160 (70%)
Sheath gauge		
6F	138 (61%)	136 (59%)
≥7F	71 (31%)	83 (36%)
Antiplatelets	230 (100%)	237 (100%)
Aspirin	216 (95%)	222 (96%)
Clopidogrel	147 (66%)	155 (67%)
Ticagrelor	48 (22%)	47 (20%)
Prasugrel	11 (5%)	13 (6%)
Glycoprotein inhibitor use	11 (5%)	9 (4%)
Bivalirudin use	2 (1%)	1 (0%)
Main vessel LMS/LAD	174 (77%)	176 (77%)
Main vessel LMS/Cx	53 (23%)	54 (23%)
Preparation of main vessel	199 (88%)	204 (88%)
Balloon	147 (65%)	163 (69%)
Cutting balloon	25 (12%)	22 (10%)
Rotablation	28 (13%)	27 (12%)
Lithotripsy	4 (2%)	0 (0%)
Preparation of side vessel	112 (49%)	190 (83%)
Balloon	96 (43%)	159 (69%)
Cutting balloon	12 (6%)	18 (8%)
Rotablation	11 (6%)	16 (7%)
Lithotripsy	1 (0%)	0 (0%)
Vessel stented first		
Main	226 (100%)	119 (51%)
Side	0 (0%)	110 (49%)
Stent to main/first vessel	226 (99%)	229 (99%)
No stent	1 (0%)	1 (0%)
Missing data	3[a] (1%)	7[b] (2%)
Stent diameter main/first vessel, mm (SD)	3.8 (0.5)	3.6 (0.6)
Stent length to main/first vessel, mm (SD)	22.1 (7.0)	21.8 (7.0)
Implantation technique		
Stepwise provisional	226 (99%)	12 (5%)
Culotte	—	121 (53%)
Crush (DK)	—	11 (5%)
T or TAP	—	76 (32%)
Unstated	—	10 (4%)
Missing data	3 (1%)	7 (3%)
Wire jail after first stent	185 (82%)	187 (82%)
TIMI flow in side vessel after 1st stent		
0	2 (1%)	0 (0%)
1	2 (1%)	1 (1%)
2	8 (3%)	7 (3%)
3	215 (95%)	182 (77%)
Missing data	3 (1%)	47 (19%)
Proximal optimization after first stent	194 (85%)	199 (87%)
Rewiring second vessel		
Yes	212 (93%)	219 (95%)
No	15 (6%)	3 (1%)
Missing	3 (1%)	7 (4%)
Kissing balloons after first stent		
Yes	202 (89%)	15 (6%)
No	25 (11%)	—
Missing	3 (1%)	—
Further treatment to side vessel needed?		
Yes	59 (26%)	—
No	168 (74%)	—
Missing	3 (1%)	—
Stent to side/second vessel		
Yes	51 (22%)	217 (94%)
No	8 (4%)	12 (5%)
Missing	3	7
Second stent implantation technique		
Culotte	26 (11%)	121 (53%)
Crush (DK)	0 (0%)	11 (5%)
T or TAP	24 (11%)	76 (33%)
Not applicable	176 (78%)	22 (10%)
Missing data	3	7
Reason for second stent		
Dissection	22 (10%)	—
Residual stenosis	26 (12%)	—
Impaired flow	1 (1%)	—
Other	2 (1%)	—
Stent diameter side/second vessel, mm (SD)	3.5 (0.6)	3.6 (0.6)
Stent length to side/second vessel, mm (SD)	17.6 (6.9)	19.3 (6.7)
Kissing balloon inflations after 2nd stent?		
Yes	51 (22%)	217 (93%)
No	0 (0%)	13 (6%)
Not applicable	176 (78%)	—
Missing	3	7
Final POT		
Yes	184 (81%)	192 (84%)
No	43 (19%)	38 (17%)
Missing	3	7

Cx, circumflex coronary artery; DK, double kissing; LAD, left anterior descending coronary artery; LMS, left main stem; POT, proximal optimization technique; SD, standard deviation.
[a]Three patients did not undergo percutaneous coronary intervention.
[b]Five patients did not undergo percutaneous coronary intervention.

DK crush technique than culotte with a composite major adverse cardiac event rate of 6% vs. 16% at 1 year. Some of the caveats mentioned above may also apply.

Revascularization after a systematic two-stent strategy is usually more complex than after a single-stent approach. As was seen in the

Table 3 Procedural summary characteristics

	Stepwise provisional ($n = 230$)	Systematic dual ($n = 237$)	*P*-values
No. guide catheters used	1.2 (0.5)	1.2 (0.6)	$P = 0.4$
No. guidewires used	3.0 (1.4)	3.2 (1.5)	$P = 0.07$
No. balloons used	4.9 (2.1)	5.4 (2.2)	$P = 0.004$
No. stents deployed at bifurcation	1.6 (1.1)	2.3 (0.8)	$P < 0.001$
IVUS	81 (36%)	71 (31%)	$P = 0.3$
Single vessel	46 (20%)	19 (8%)	
Both vessels	35 (15%)	52 (19%)	
Reintervention resulting	28 (12%)	14 (6%)	
OCT	11 (4%)	17 (7%)	$P = 0.3$
FFR	12 (4%)	2 (1%)	$P = 0.006$
Stented length (mm)	25.4 (13)	31.7 (18)	$P = <0.001$
Additional vessels stented	103 (45%)	118 (51%)	$P = 0.3$
LAD	61	80	
Cx	29	22	
RCA	13	16	
Additional stents	1.6 (1.1)	1.7 (1.1)	$P = 0.4$
Total no. stents implanted	2.9 (1.3)	3.7 (1.1)	$P < 0.001$
Procedure duration, min (SD)	74 (35)	80 (39)	$P = 0.049$
Fluoroscopy duration, min (SD)	21 (12)	24 (16)	$P = 0.02$
X-ray dose (cGy.cm^2)	7060 (7320)	7470 (6560)	$P = 0.02$
Air Kerma (Gy)	0.70 (1.30)	0.82 (1.34)	$P = 0.02$
Contrast volume (mLs, SD)	215 (92)	225 (96)	$P = 0.3$
Technical success	202 (88%)	211 (89%)	$P = 0.5$
Procedural success	224 (97%)	219 (92%)	$P = 0.8$
In-hospital complications	20 (9%)	29 (13%)	$P = 0.4$
Death	2	3	
Myocardial infarction	11	11	
Target vessel revasc.	0	2	
Stent thrombosis	1	0	
Other	6	13	

Cx, circumflex coronary artery; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; OCT, optical coherence tomography; RCA, right coronary artery; SD, standard deviation.

BBC ONE trial,[3] revascularization after a two-stent strategy was numerically more likely to require coronary artery bypass grafting rather than PCI.

Stent thrombosis rates were low in both groups. The two-stent strategy has frequently been associated with higher stent thrombosis rates in the literature[17]; however, in both the DKCRUSH-V and EBC MAIN studies, stent thrombosis rates at 1 year were low, and undifferentiated between the two groups. The low incidence of stent thrombosis is reassuring and may reflect thinner-strut second and third generation stents along with improved understanding of optimal implantation characteristics.

In the provisional group, there was no POT (15%), no rewiring of the second vessel (6%) and no kissing balloon inflation made (11%). Whether this was largely because the operator felt it was not needed is not clear. For the two-stent strategy, there was no POT (13%), no rewiring of the second vessel (1%) and no second stent (5%) and therefore it is clear that operators still have technical difficulties in a minority of cases.

Table 4 Procedural flow

	Stepwise provisional ($n = 230$)	Systematic dual ($n = 237$)
Main vessel preparation	199 (88%)	204 (88%)
Side vessel preparation	112 (49%)	190 (83%)
Stent to main vessel	226 (99%)	229 (99%)
POT	194 (85%)	199 (87%)
Kissing	202 (89%)	—
Stent to side vessel	51 (22%)	217 (95%)
Kissing	51 (22%)	217 (95%)
Final POT	184 (81%)	192 (84%)

POT, proximal optimization technique.

Differences in technical and procedural success rates relate to the definitions. Technical success required completion of stent

Table 5 Trial endpoints

	Stepwise provisional ($n = 230$)	Systematic dual ($n = 237$)	Hazard ratio (95% CI) and *P*-value
Primary endpoint			
Death, myocardial infarction or target lesion revascularization at 12 months	34 (14.7%)	42 (17.7%)	HR 0.8 (0.5–1.3), $P = 0.34$
Secondary endpoints			
Death	7 (3.0%)	10 (4.2%)	HR 0.7 (0.3–1.9), $P = 0.48$
Myocardial infarction	23 (10.0%)	24 (10.1%)	
Peri-procedural	9 (4%)	11 (5%)	HR 0.9 (0.5–1.7), $P = 0.9$
Subsequent	12 (5%)	13 (6%)	
Target lesion revascularization	14 (6.1%)	22 (9.3%)	
PCI	13	19	HR 0.6 (0.3–1.2), $P = 0.16$
CABG	1	3	
Stent thrombosis (definite/probable)	4 (1.7%)	3 (1.3%)	
Acute	1	0	
Subacute	1	1	HR 0.9 (0.4–1.9), $P = 0.9$
Late	2	2	

CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.

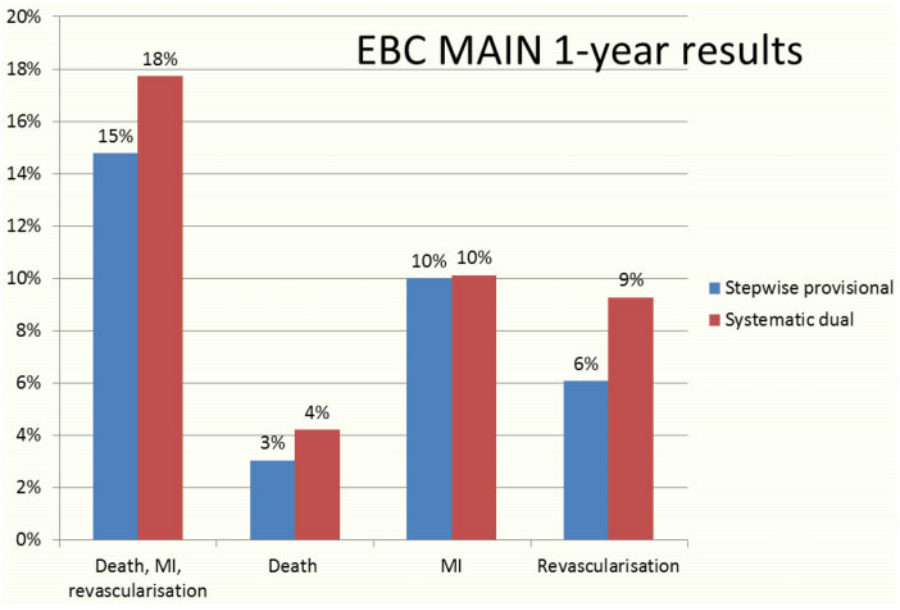


Figure 1 Graphical representation of the primary endpoint. MI, myocardial infarction.

placement, balloon dilatation, rewiring, and final kissing balloon therapy as required by the protocol. Procedural success required placement of stents as per randomization with TIMI 3 flow and <30% stenosis in any stented vessel and TIMI 3 flow in any unstented vessel. Therefore technical success was numerically lower in the stepwise provisional technique because a minority of cases did not have a kissing balloon inflation (probably as it was thought not necessary). However, procedural success was numerically lower in the systematic dual-stent strategy due to the number of patients in whom a second stent could not be placed.

Intravascular imaging was used in ~40% of cases. It was used equally common in the stepwise provisional strategy as in the systematic two-stent approach. In the DKCRUSH-V trial, IVUS use was similar at 41%.

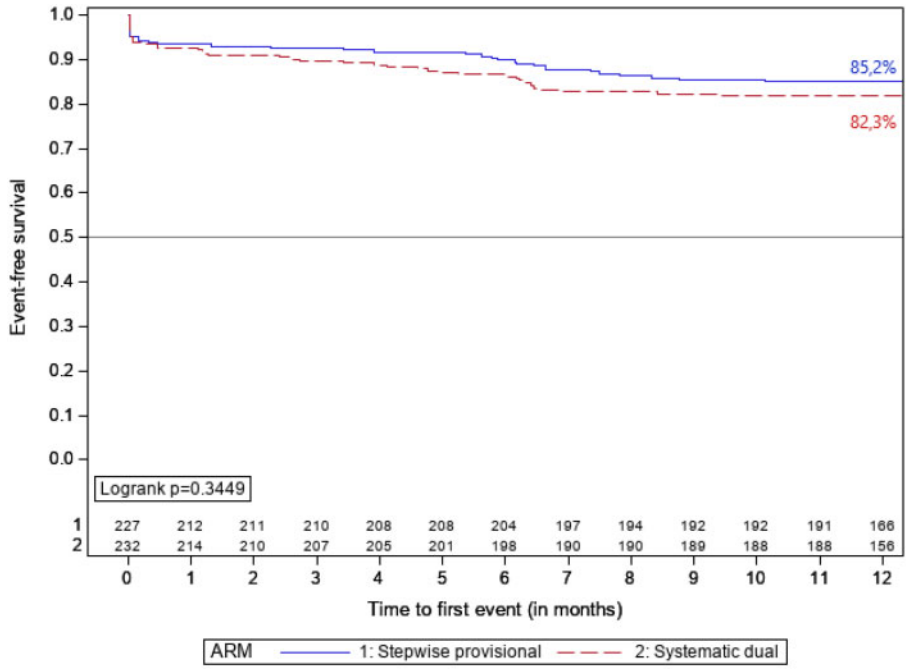


Figure 2 Kaplan–Meier curve for primary endpoint at 12 months.

Table 6 Symptom status

	Stepwise provisional (n = 230)	Systematic dual (n = 237)	P-value
CCS class pre	1.8 (1.1)	1.8 (1.2)	0.01 (pre to 1 year)
CCS class 1 year	0.4 (0.8)	0.5 (0.8)	
Angina index pre	1.5 (1.1)	1.3 (1.0)	0.02 (pre to 1 year)
Angina index 1 year	0.9 (1.0)	0.8 (0.8)	
Antiplatelets at 1 year			
Aspirin	195 (89%)	200 (90%)	
Clopidogrel, prasugrel or ticagrelor	170 (77%)	160 (72%)	

CCS, Canadian Cardiovascular Society.

One-year follow-up alone is not adequate and the study will progress to 3-year follow-up in due course. At 1 year, there were numerically more revascularizations in the dual stent group and it will be interesting to see if this trend expands or contracts over time. It is worth noting that longer-term follow-up of the NORDIC and BBC ONE studies demonstrated a mortality difference between the two techniques that was not present on shorter follow-up.[4] The EBC TWO study is due to report final outcomes soon[18] and along with the DEFINITION II trial,[9] the longer-term outcomes will be of considerable interest.

Study limitations

This trial had an open design that meant the operators and patients were aware of received treatment. This could have led to theoretical bias in interpreting clinical outcomes. The study event rates were lower than anticipated and therefore the study was underpowered to detect a significant difference between the two groups.

Conclusions

Stent treatment of true bifurcation left main stem coronary artery disease is safe and effective. Patients are treated equally well with a stepwise layered provisional approach, starting with a single stent, as with a more complex dual-stent implantation procedure. When a provisional stepwise approach was used, only one-fifth of patients required a second stent. The provisional approach should remain the

Table 7 Quantitative coronary angiography analysis

	Stepwise provisional ($n = 230$)	Systematic dual ($n = 237$)	*P*-value
Reference diameter (mm), mean (SD)			
Proximal main vessel	3.82 (0.79)	3.82 (0.70)	
Distal main vessel	2.77 (0.44)	2.87 (0.57)	
Side vessel	2.69 (0.59)	2.67 (0.52)	
Minimum lumen diameter (mm), mean (SD)			
Proximal pre	1.79 (0.89)	1.56 (0.78)	
Proximal post	3.81 (0.54)	3.95 (0.51)	<0.01
Distal pre	1.14 (0.43)	1.25 (0.54)	0.02
Distal post	2.92 (0.42)	2.95 (0.47)	
Side pre	1.29 (0.58)	1.19 (0.51)	
Side post	2.24 (0.61)	2.71 (0.51)	<0.01
% Stenosis, mean (SD)			
Proximal pre	53.2 (20.5)	55.8 (20.8)	
Proximal post	12.3 (12.4)	10.2 (6.6)	<0.01
Distal pre	58.8 (13.8)	56.4 (17.0)	
Distal post	9.3 (7.7)	10.1 (7.8)	
Side pre	51.9 (18.5)	55.4 (15.7)	0.03
Side post	20.2 (14.4)	11.8 (10.2)	<0.01
Lesion length (mm), mean (SD)			
Proximal main	6.4 (3.2)	6.3 (2.8)	
Distal main	8.4 (6.1)	8.0 (5.1)	
Side vessel	5.8 (4.0)	7.9 (5.7)	<0.01

SD, standard deviation.

philosophy of choice in the majority of left main stem true bifurcation procedures.

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Conflict of interest: D.H.-S. Proctor/Advisory to Boston, Abbott, Medtronic, Terumo, Edwards, Occlutech, Gore; CERC. A.C.: Consultant Abiomed, Biosensor, Magenta; Speakers fees Abbott vascular, Abiomed, Boston Scientific, Cardinal Health. T.L.: Abbott Proctoring, Edwards Proctoring, Lectures, Boston scientific, Terumo Proctoring, lectures. M.-C.M.: CERC CEO. M.P.: Lecture fees Abbott, Boston. J.F.L.: Lecturing and Honoraria for Medtronic, Boston Scientific, Biotronik, Biosensors. A.B.: Lecture fees Boston. O.D.: Lecture fees for Boston and Edwards. All other authors report no conflicts of interest.

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