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ORIGINAL RESEARCH ARTICLE

Stepwise Provisional Versus Systematic Dual-Stent Strategies for Treatment of True Left Main Coronary Bifurcation Lesions

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BACKGROUND: The optimal coronary stenting technique for true left main bifurcation lesions is uncertain. EBC MAIN (European Bifurcation Club Left Main Trial) aimed to evaluate clinical outcomes of a stepwise provisional strategy compared with a systematic dual-stent approach.

METHODS: EBC MAIN was a randomized, investigator-initiated, open-label, multicenter, parallel-group trial conducted across 35 hospitals in 11 European countries. A total of 467 participants undergoing percutaneous coronary intervention for unprotected true left main bifurcation lesions were randomly assigned to the stepwise provisional strategy (n=230) or an upfront dual-stent approach (n=237). The mean (SD) age was 71 (10) years and 23% of participants were women. The primary end point was a composite of major adverse cardiac events, defined as all-cause mortality, all myocardial infarction, or clinically driven target lesion revascularization. Events were adjudicated by an independent clinical events committee and all analyses were by the intention-to-treat principle.

RESULTS: At 3 years, the primary end point occurred in 54 of 230 (23.5%) stepwise provisional and 70 of 237 (29.5%) dual-stent patients (hazard ratio, 0.75 [95% CI, 0.53–1.07]; *P*=0.11). There was no significant difference in all-cause mortality (10.0% versus 13.1%) or myocardial infarction (12.2% versus 11.0%). However, target lesion revascularization was significantly lower in the stepwise provisional group (8.3% versus 15.6%; hazard ratio, 0.50 [95% CI, 0.29–0.86]; *P*=0.013). In this population, the mean side vessel diameter by quantitative angiography was 2.9 mm, and median side vessel lesion length was 5 mm. Significant interactions were identified between the assigned bifurcation strategy and both side vessel diameter and lesion length with respect to the primary outcome (*P*=0.009 and *P*=0.005, respectively), with smaller vessels (<3.25 mm diameter) and shorter lesions (<10 mm length) favoring the provisional approach.

CONCLUSIONS: In a European population with true left main stem bifurcation coronary disease requiring intervention, there was no difference in major adverse cardiovascular events between stepwise provisional and systematic dual-stent strategies at 3 years. Target lesion revascularization was significantly less frequent with the stepwise provisional approach, which should be the default strategy for noncomplex left main bifurcation coronary intervention.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02497014.

Key Words: angiography ■ percutaneous coronary intervention ■ stents

Percutaneous coronary intervention (PCI) has been established as an effective treatment for left main disease, with 5-year mortality rates comparable to coronary artery bypass grafting (CABG) in patients with low to intermediate coronary disease complexity.[1] PCI is the only revascularization option in patients who are not

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Clinical Perspective

What Is New?

- European Bifurcation Club Left Main (EBC MAIN) is the first randomized controlled trial reporting 3-year outcomes of a stepwise provisional strategy compared with an upfront dual-stent approach for left main bifurcation disease in European patients.
- The primary composite end point of all-cause mortality, all myocardial infarction, or clinically driven target lesion revascularization was not significantly different between the 2 approaches.
- The secondary end point of target lesion revascularization favored the provisional strategy.
- Subgroup analysis suggested that branch vessel size and lesion length significantly influence outcomes, with a possible advantage for dual-stent techniques in larger-caliber branches and more extensive disease lengths.

What Are the Clinical Implications?

- These results suggest that the provisional strategy should be the default technique for the majority of left main bifurcation interventions involving low-complexity anatomy.
- Dedicated dual-stent techniques may have a role in patients with long segments of disease in large-caliber side branches.
- These findings should lead to refinement of the European Society of Cardiology guidelines supporting double-kissing crush as the preferred technique for left main intervention, instead recommending that dedicated dual-stent techniques be specifically used for complex anatomy.

Nonstandard Abbreviations and Acronyms

CABG	coronary artery bypass grafting
CONSORT	Consolidated Standards of Reporting Trials
DEFINITION	Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents
DK-crush	double-kissing crush
DKCRUSH	DK Crush Versus Culotte Stenting for the Treatment of Unprotected Distal Left Main Bifurcation Lesions
EBC MAIN	European Bifurcation Club Left Main Coronary Stent
HR	hazard ratio
KBI	kissing balloon inflation
LAD	left anterior descending
LCx	left circumflex
MACE	major adverse cardiac event
MI	myocardial infarction
PCI	percutaneous coronary intervention
SYNTAX	Synergy Between PCI With TAXUS and Cardiac Surgery
SV	side vessel
TIMI	Thrombolysis in Myocardial Infarction
TLR	target lesion revascularization

candidates for CABG. Whereas PCI is associated with lower procedural risks and a more rapid recovery, CABG is superior in terms of cardiac events during follow-up. Optimization of left main PCI is crucial for achieving surgical-like longer-term outcomes.

PCI of distal left main disease is associated with a poorer prognosis than PCI of ostial or midshaft lesions,[2] demonstrating that bifurcations remain a challenge for the interventionalist. Many stent implantation techniques have been described, with varying degrees of complexity and risk. Whereas there is an abundance of expert opinion regarding the optimal strategy, there is a paucity of long-term clinical data. The left main bifurcation is unique in that the vessels are of large caliber, the bifurcation angulation is wide, and the side vessels (SVs) are nearly always clinically important. These features limit the applicability of findings from non–left main bifurcation studies.

Randomized left main bifurcation trials with long-term follow-up have primarily focused on the double-kissing crush (DK-crush) technique. The DKCRUSH III trial (DK Crush Versus Culotte Stenting for the Treatment of Unprotected Distal Left Main Bifurcation Lesions) compared DK-crush with culotte, with 3-year follow-up demonstrating reduced major adverse cardiac events (MACEs) with DK-crush (8.2% versus 23.7%; $P<0.001$), driven by reduction of myocardial infarction (MI) and target vessel revascularization.[3] DK-crush was then compared with the provisional strategy in DKCRUSH V and showed less target lesion failure at 3 years (8.3% versus 16.9%; $P=0.005$) because of lower rates of target vessel MI and target lesion revascularization (TLR).[4] In both of these studies, the benefit of DK-crush was most apparent in complex lesions, as described by the DEFINITION (Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents) criteria.[5]

The EBC MAIN study (European Bifurcation Club Left Main Coronary Stent) randomized patients to either a stepwise provisional strategy or an upfront dual-stent approach, with no significant difference in MACEs (14.7% versus 17.7%; $P=0.34$) identified at 12 months.[6] Procedural time, radiation, and cost were significantly reduced in the provisional group. This article explores outcomes at 3 years.

METHODS

Trial Design and Oversight

EBC MAIN was an investigator-initiated, multicenter, open-label, randomized, parallel-group trial, designed and performed by the European Bifurcation Club. Participants were enrolled across 35 hospitals in 11 European countries (Denmark [2], France [7], Germany [2], Ireland [1], Italy [5], Latvia [1], Poland [4], Russia [1], Serbia [1], Spain [4], and the United Kingdom [7]). The study was approved by the relevant authorities in all countries involved. All patients provided written informed consent. The trial was performed in accordance with the principles of the Declaration of Helsinki. Randomization occurred through a 128-bit secure encrypted website and was stratified by center. Trial oversight was provided by the Cardiovascular European Research Center. All events were adjudicated by an independent clinical events committee and a data and safety monitoring board. Procedural details were analyzed by an independent core laboratory. Funding was provided through an educational and research grant from Medtronic Europe. The funders had no influence on the design or conduct of the trial and were not involved in data collection or analysis, in the writing of the manuscript, or in the decision to submit it for publication. The data that support the findings of this study are available from the corresponding author upon reasonable request. The authors assume responsibility for the accuracy of the data and for the fidelity of the trial to the protocol. All authors agreed to submit the manuscript for publication. This report follows the CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines.

Patients

Participants were eligible for inclusion if they were referred for PCI to treat clinically significant, unprotected, true distal left main bifurcation disease (Medina 1,1,1 or 0,1,1), in which both vessel reference diameters were ≥2.75 mm. Both chronic and acute coronary syndrome presentations were eligible (excluding ST-segment–elevation MI). Patients were required to have ischemic symptoms, positive noninvasive imaging for ischemia, a positive fractional flow reserve, or a left main minimal luminal area <6 mm^2 on intravascular ultrasound. A maximum of 2 additional lesions requiring revascularization could be present. The SYNTAX score (Synergy Between PCI With TAXUS and Cardiac Surgery) for lesions planned to be treated needed to be ≤32. Exclusion criteria included cardiogenic shock, chronic total occlusion of the left anterior descending (LAD) or left circumflex (LCx) artery, trifurcation disease with all limbs ≥2.75 mm diameter, or a left main diameter >5.75 mm.

Revascularization Procedure

A detailed outline is provided in the 12-month results publication.[6] In brief, the provisional strategy commenced with wire placement into both the LAD and LCx. It was recommended to avoid predilation of the designated SV to reduce the risk of dissection. The main vessel stent was sized to the distal main vessel and deployed with a jailed SV wire in situ. Proximal optimization technique was recommended before rewiring of the SV through a distal cell. Kissing balloon inflation (KBI) was mandatory and ideally performed with noncompliant balloons sized to the distal main vessel and SV. Sequential high-pressure inflations to optimize expansion were followed by a simultaneous low-pressure inflation to centralize the neocarina. Repeat proximal optimization technique could be performed with the kissing balloon pair or a short noncompliant balloon, ensuring the carina was not disturbed. After KBI, no further treatment was recommended unless SV flow was TIMI (Thrombolysis in Myocardial Infarction) <3, >90% ostial stenosis was present, or an SV dissection type >A was evident. In this case, the operator could continue to complete a dual-stent strategy of their preference.

In the systematic dual-stent group, operators could perform T-stenting, T-and-protrude, culotte, or DK-crush, according to the principles described in European Bifurcation Club recommendations.[7] For culotte, a repeat proximal optimization technique was required after second stent insertion before distal cell recrossing. Final KBI was mandated in all dual-stent strategies, with sequential and then simultaneous inflations as described earlier.

Participating operators were expected to be undertaking ≥150 PCI procedures per year. The Resolute Onyx zotarolimus-eluting coronary stent (Medtronic) was used. Patients received long-term aspirin and statin therapy. Clopidogrel, prasugrel, or ticagrelor were recommended for a minimum of 6 months.

Follow-Up

Adverse events were recorded from the time of randomization until death, loss to follow-up, or completion of the 3-year follow-up period. Participants underwent either telephone or in-person follow-up at 6, 12, and 36 months. Routine angiography was not performed. All revascularization events were reviewed by the core laboratory.

End Points

The primary end point was MACE, defined as the composite of all-cause mortality, all myocardial infarction, or clinically driven target lesion revascularization (TLR) at 3 years. Secondary end points included the individual components of the primary end point as well as angina status, angina medications, and stent thrombosis (definite and probable). All other secondary analyses were defined post hoc. The influence of patient and lesion variables, including SV reference diameter and SV lesion length, on the primary outcome was explored. To isolate clinical outcomes related directly to the study intervention, a composite of bifurcation-specific adverse cardiac events was examined. This included procedural or sudden death, periprocedural MI, target lesion stent thrombosis (definite or probable), target lesion type 4c MI, and TLR. DEFINITION criteria were used to grade lesion complexity.[5] Complex lesions were defined as those with ostial SV disease extending ≥10 mm with a diameter stenosis of ≥70%. In addition, ≥2 minor criteria were required (bifurcation angle <45 degrees or ≥70 degrees, main vessel reference diameter ≤2.5 mm, main vessel lesion length ≥25 mm, multiple bifurcations involved, thrombus, or moderate to severe calcification).

Definitions

MI was defined as per the Third Universal Definition of Myocardial Infarction,[8] except for the category of PCI-related periprocedural MI (Type 4a). For this, the more practical expert

consensus definition from the Society for Cardiovascular Angiography and Interventions was used.[9] Stent thrombosis was adjudicated on the basis of the Academic Research Consortium definition.[10] TLR referred to repeat intervention with balloon angioplasty, stents, or CABG for recurrent disease within the treated region, or in the adjacent 5 mm of vessel. The bifurcation angle refers to the angle subtended between the LAD and LCx.

Statistical Analysis

Power calculations were based on 12-month MACE estimates and have been previously published.[6] All analyses were performed on the intention-to-treat population. Continuous variables are described by mean and SD or median and 25th to 75th percentiles, and categorical data by raw numbers and percentages. Continuous variables were assessed with the independent samples *t* test or Mann-Whitney *U* test and categorical data with χ^2 or Fisher exact test. Kaplan-Meier curves were generated for the primary outcome and subgroups of interest. Cox regression analyses were used to calculate unadjusted hazard ratios (HRs) and *P* values for both primary and secondary end points. Analysis with stratification by site was also performed for the primary outcome. Two-sided *P* values of <0.05 were considered to indicate statistical significance. Clinically relevant patient and lesion variables were included as covariates to check for subgroup interactions. Schoenfeld residuals were used to confirm the proportional hazards assumption. The widths of the CIs of secondary end points were not adjusted for multiplicity and should therefore not be used to infer definitive treatment effects. Statistical analysis was performed with RStudio 2023.09.1 (Posit Software; survival, survminer, cmprsk and forestplot packages) and SPSS V26.0 (IBM SPSS Statistics; IBM Corp).

RESULTS

Baseline Characteristics and Interventions

A total of 467 patients were recruited between February of 2016 and November of 2020, of whom 230 were randomized to the provisional strategy, and 237 were randomized to systematic dual stenting. Six patients withdrew consent before completion of the study. Major protocol deviations occurred in 6 provisional and 12 dual-stent patients, including failure to undergo PCI in 8 and failure to use the Onyx stent in 4. One patient assigned to the provisional group and 2 assigned to dual stents were lost to follow-up over 3 years (Figure 1).

Demographic, lesion, and procedural characteristics are described in Tables 1 through 3. The mean age was 71 (10) years, and 23% were female. More than half of the lesions had a moderate or greater calcification burden, and the median SV disease length was 5 mm. Significantly more patients with SV disease length ≥10 mm were randomized to the dual-stent cohort. The mean SV reference diameter by quantitative coronary angiography across both groups was 2.9 mm, with a median implanted SV stent diameter of 3.5 mm. Only 7 patients (1.5%) fulfilled DEFINITION criteria for complexity.

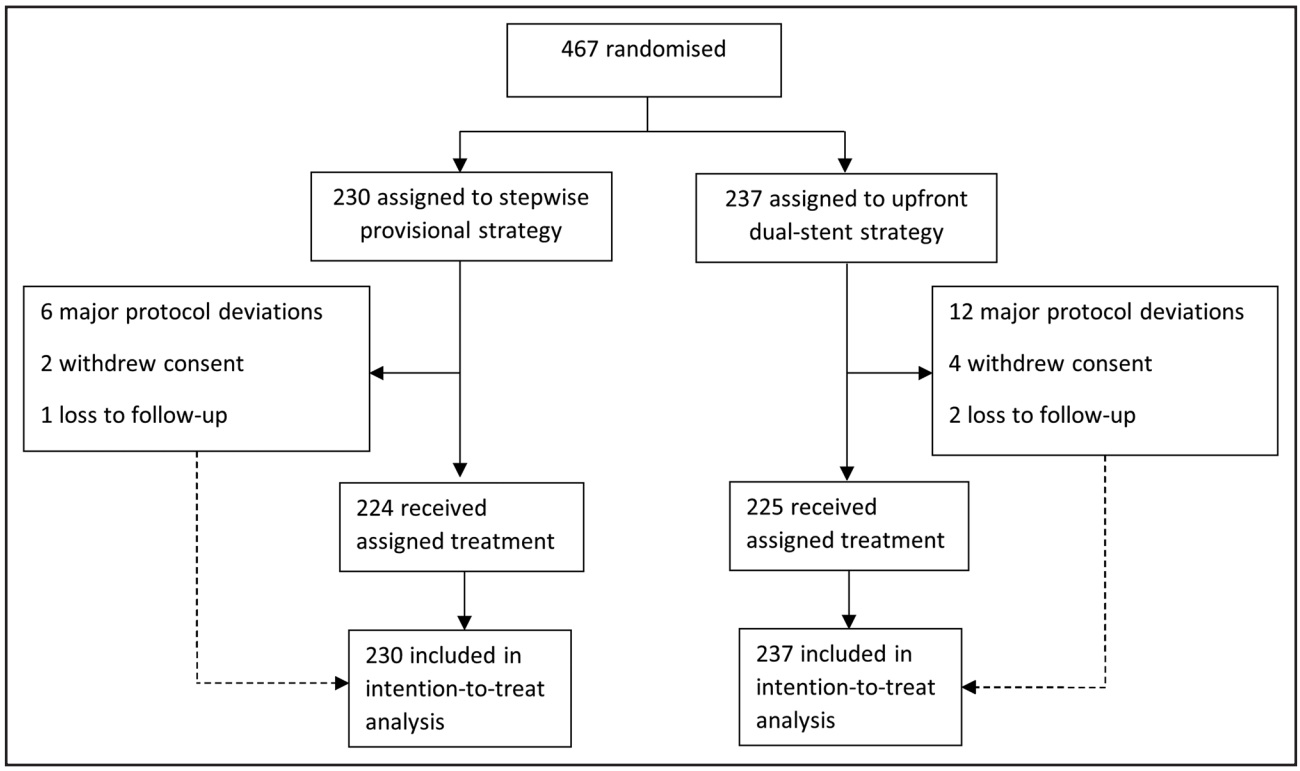

Figure 1. Randomization and follow-up.
Study flowchart.

Table 1. Demographic Characteristics and Clinical Variables

Variables	Provisional strategy (n=230)	Systematic dual-stent strategy (n=237)
Age, y	70.8±10.1	71.4±9.8
Female sex	48 (21)	60 (25)
BMI	28.6±5.5	28.4±5.5
Diabetes	66 (29)	62 (27)
Hypertension	180 (79)	190 (82)
Hypercholesterolemia	158 (70)	166 (72)
Smoking (current/past)	123 (54)	122 (53)
Family history	74 (33)	75 (33)
Previous MI	60 (26)	66 (28)
Previous PCI	93 (41)	99 (43)
LV function		
EF >50%	143 (63)	142 (62)
EF 30–50%	45 (20)	54 (23)
EF <30%	9 (4)	9 (4)
Unknown	30 (13)	27 (11)
Acute coronary syndrome	78 (33)	93 (40)
CCS class, mean (SD)		
Baseline	1.8 (1.1)	1.8 (1.2)
3 y	0.4 (0.8)	0.8 (0.9)
Angina medications, mean (SD)		
Baseline	1.5 (1.1)	1.3 (1.0)
3 y	0.8 (0.9)	0.8 (0.8)

Values are mean±SD or n (%). BMI indicates body mass index; CCS, Canadian Cardiovascular Society; EF, ejection fraction; LV, left ventricle; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Intravascular imaging was performed in 180 (39%) cases. Most of the dual-stent group was treated with culotte or T-stenting or T-and-protrude strategies. In the provisional group, a second stent was required in 51 cases (22%) and was inserted with a culotte technique in 26 patients (11%) and T-stenting or T-and-protrude in 24 (10%). Bystander lesions were treated in approximately half the cases. Use of dual antiplatelet and statin therapy was similar throughout follow-up.

Clinical Outcomes

The primary and secondary end points of the trial are shown in Figure 2 and Table 4. At 3 years, the primary end point had occurred in 54 (23.5%) stepwise provisional and 70 (29.5%) dual-stent patients (unadjusted hazard ratio, 0.75 [95% CI, 0.52–1.07]; *P*=0.11; stratified hazard ratio, 0.76 [95% CI, 0.53–1.09]; *P*=0.14). No significant differences were identified for all-cause mortality (10.0% versus 13.1%) or MI (12.2% versus 11.0%). However, TLR was significantly less frequent among stepwise provisional stenting patients (8.3% versus 15.6%; hazard ratio, 0.50 [95% CI, 0.29–0.86]; *P*=0.013). Bifurcation-specific adverse cardiac events were significantly lower with the provisional strategy (15.2% versus 22.4%; hazard ratio, 0.64 [95% CI, 0.42–0.99]; *P*=0.043). No difference was identified in periprocedural or type 4c MI. There was no penalty for provisional patients who proceeded to second stent insertion, with MACE rates of 25.0% with a single stent and 19.6% after SV stenting.

Subgroup analyses are detailed in Figure 3. Significant interactions were present between the bifurcation strategy and each of SV diameter and lesion length with respect to the primary outcome. Side vessel diameter <3.25 mm was associated with increased MACE within the dual-stent cohort (HR, 2.16 [95% CI, 1.13–4.12]), and SV disease length ≥10 mm was associated with increased MACE for the provisional group (HR, 2.74 [95% CI, 1.37–5.45]). In the event of SV stent implantation in either cohort, the use of ≥4-mm diameter stents was associated with significantly lower MACE (HR, 0.49 [95% CI, 0.28–0.86]).

Angina based on Canadian Cardiovascular Society class remained significantly improved from baseline at

Table 2. Lesion Characteristics

Variables	Provisional strategy (n=230)	Systematic dual-stent strategy (n=237)	*P* value
SYNTAX score	19 (16–25.8)	21 (17–27)	0.018
Medina			0.809
1,1,1	204 (90)	206 (89)	
0,1,1	23 (10)	25 (11)	
Calcification* (moderate or severe)	140 (62)	160 (69)	0.101
Bifurcation angle B >70 deg*	136 (61)	131 (58)	0.516
Reference diameter, mm*			
Proximal main vessel	3.9±0.8	3.9±0.7	0.605
Distal main vessel	3.0±0.5	3.1±0.6	0.077
Side vessel	2.9±0.6	2.9±0.6	0.925
Percent stenosis*			
Proximal main vessel	53.2±20.5	55.8±20.8	0.453
Distal main vessel	58.8±13.8	56.4±17.0	0.190
Side vessel	51.9±18.5	55.4±15.7	0.028
Lesion length, mm*			
Proximal main vessel	5.8 (4.2–8.2)	5.8 (4.3–8.0)	0.735
Distal main vessel	6.2 (4.6–10.7)	6.6 (4.1–10.3)	0.714
Side vessel	4.7 (3.3–7.0)	5.7 (4.0–10)	<0.001
SV lesion length* ≥10 mm	20 (9)	56 (25)	<0.001
Main vessel			0.953
LAD	174 (77)	176 (77)	
LCx	53 (23)	54 (23)	

Values are median (25th–75th percentile), n (%), or mean±SD. LAD indicates left anterior descending; LCx, left circumflex; and SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery.

*Core laboratory measurements.

Table 3. Procedural Details

Variables	Provisional strategy (n=230)	Systematic dual-stent strategy (n=237)	*P* value
IVUS or OCT	92 (40)	88 (37)	0.524
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)	
Stent deployment			–
Main vessel	226 (99)	229 (99)	
Side vessel	51 (22)	217 (94)	
Stent size, mm			
Main vessel	3.8±0.5	3.6±0.6	0.001
Side vessel	3.5±0.6	3.6±0.6	0.178
Final stent technique			–
Single stent	176 (77)	12 (5)	
Culotte	26 (11)	121 (53)	
Crush (double-kissing)	1 (0.4)	11 (5)	
T-stenting or TAP	24 (10)	76 (32)	
Unstated	–	10 (4)	
Missing data	3 (1)	7 (3)	
POT after first stent	194 (85)	199 (87)	0.657
Final POT	184 (81)	192 (84)	0.636
KBI after first stent	202 (89)	15 (6)	–
KBI after second stent	51 (100)	217 (93)	–
Additional bystander lesion stented	103 (45)	118 (51)	0.205
Fluoroscopy duration, min	18 (12.5–26.0)	21 (14–28)	0.023

Values are n (%), mean±SD, or median (25th–75th percentile). IVUS indicates intravascular ultrasound; KBI, kissing balloon inflation; OCT, optical coherence tomography; POT, proximal optimization technique; and TAP, T-and-protrude.

3 years in both cohorts ($P<0.001$). No significant differences in angina severity or number of anti-anginal medications were seen between strategies at the trial conclusion.

DISCUSSION

EBC MAIN shows no significant difference in MACEs between the stepwise provisional and systematic dual-stent strategies at 3 years in patients with low complexity, true bifurcation, left main coronary disease. The stepwise provisional strategy was associated with a lower risk of TLR; all-cause mortality and MI did not differ between the groups. Only 22% of the provisional cohort proceeded to SV stenting after KBI, with no observed penalty in clinical event rate. Subgroup analyses supported provisional stenting for SV disease lengths <10 mm, and SV diameters <3.25 mm. Systematic dual-stent strategies may be favorable among patients with larger-caliber SVs and longer SV disease. Relief from angina was excellent in both cohorts.

Clinical outcomes after bifurcation PCI are influenced by multiple variables beyond technique, including comorbidities, clinical presentation, and anatomy. Important lesion characteristics include vessel size, SV lesion length, and calcium burden. It is important for trials to recruit participants representative of those encountered in standard clinical practice. The population in EBC MAIN is typical of European patients undergoing PCI for distal left main disease, with an average age of ≈70 years and a third presenting with an acute coronary syndrome. Patients had low to intermediate complexity coronary disease, most had moderate or severe calcification, and the median SV lesion length was 5 mm. In this cohort, the 3-year incidences of all-cause mortality (11.6%) and MI (11.6%) were relatively low. This was achieved with a single stent in 77% of provisional patients, demonstrating that most true left main bifurcation lesions encountered in routine practice can be effectively managed with a stepwise provisional approach.

The higher rate of TLR in the dual-stent cohort may be a surprise to operators who favor a 2-stent strategy. There are several possible mechanisms in play. Restenosis predominantly involved the ostium of the left circumflex artery, in which low shear stress related to vessel angulation and size may promote atherosclerosis.[11] Bifurcation PCI simulations also show improved hemodynamics with main vessel stenting±SV angioplasty, compared with dual-stent implantation.[12] In addition, the angulation into the LCx artery from the left main demands considerable mechanical stent deformation. Bench testing has demonstrated the potential for restricted stent expansion and malapposition at the SV ostium in this setting.[13] Whereas meticulous use of KBI can optimize stent geometry, worse clinical outcomes have been reported for 2-stent strategies (including both culotte and crush) in wide-angled bifurcations.[14–16] T-stenting may be a valid alternative in these situations but remains prone to geographic miss or exaggerated protrusion into the main vessel.

The deployment of any stent is not a benign intervention and carries a long-term risk of adverse events. Analysis of pooled patient-level data from multiple randomized trials identified a target lesion failure rate of 7.7% between 1 and 5 years after second-generation drug-eluting stent implantation.[17] This 1.9% annual risk

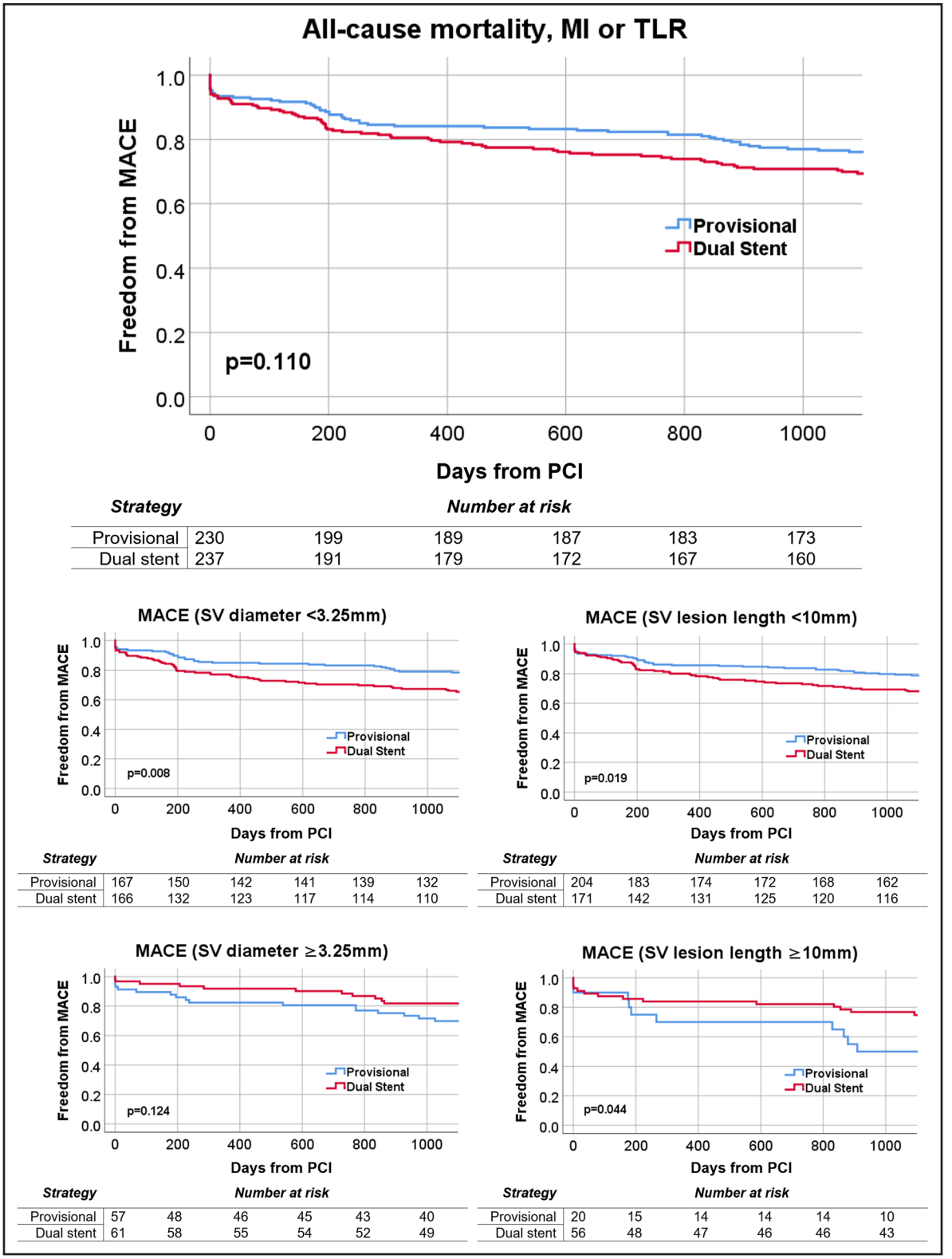

Figure 2. Results.
No significant between-group difference was noted at 3 years for the primary composite major adverse cardiac event (MACE) end point: provisional 23.5% vs dual-stent 29.5% (P=0.110). Side vessel (SV) diameter (<3.25 or ≥3.25 mm) $P_{interaction}$=0.009. SV lesion length (<10 mm or ≥10 mm) $P_{interaction}$=0.005. MI indicates myocardial infarction; PCI, percutaneous coronary intervention; and TLR, target lesion revascularization.

Table 4. Primary and Secondary End Points

End points	Provisional strategy (n=230), n (%)	Systematic dual-stent strategy (n=237), n (%)	Hazard ratio (95% CI)	*P* value
Primary end point (MACE)				
All-cause mortality, MI, and TLR	54 (23.5)	70 (29.5)	0.75 (0.52–1.07)	0.110
Secondary end points				
Mortality				
All-cause mortality	23 (10.0)	31 (13.1)	0.74 (0.43–1.27)	0.269
Procedural or sudden death*	8 (3.5)	12 (5.1)	0.67 (0.27–1.63)	0.375
MI				
All	28 (12.2)	26 (11.0)	1.09 (0.64–1.86)	0.749
Periprocedural*	9 (3.9)	11 (4.6)	0.84 (0.35–2.03)	0.700
Type 4c*	8 (3.5)	8 (3.4)	1.01 (0.38–2.69)	0.983
Revascularization				
TLR	19 (8.3)	37 (15.6)	0.50 (0.29–0.86)	0.013
Stent thrombosis				
Definite or probable	5 (2.2)	3 (1.3)	1.69 (0.40–7.08)	0.471
Bifurcation-specific adverse cardiac events*				
Procedural or sudden death, periprocedural MI, definite or probable stent thrombosis, T4c MI, and TLR	35 (15.2)	53 (22.4)	0.64 (0.42–0.99)	0.043

MACE indicates major adverse cardiac event; MI, myocardial infarction; and TLR, target lesion revascularization.
*Post hoc analysis.

did not plateau through follow-up, suggesting persistence beyond 5 years. Therefore, avoidance of stent insertion when possible may result in cumulative benefit with time. The extended follow-up SYNTAX trial bifurcation substudy revealed increased revascularization rates with 2-stent techniques compared with one stent at 5 years (33.3% versus 23.7%; HR, 1.60 [95% CI, 1.12–2.28]; *P*=0.010) and higher mortality rates with 2-stent techniques at 10 years (33.3% versus 25.9%; HR, 1.51 [95% CI, 1.06–2.14]; *P*=0.021).[18] The same mortality disadvantage for planned dual-stent implantation was also seen in long-term follow-up of randomized non–left main stem bifurcation studies.[19] These long-term results contrast with a meta-analysis of studies with shorter follow-up, which showed no difference in MACEs between provisional and 2-stent approaches at 2 years.[20]

The effect of SV diameter on bifurcation strategy outcomes is novel but expected, as smaller vessel size is a recognized risk factor for stent failure in nonbifurcation lesions. Even with drug-eluting stents, a 0.5 mm smaller vessel size is associated with an adjusted odds ratio of 1.65 (95% CI, 1.22–2.23) for TLR.[21] This relationship was also observed in EBC MAIN, with an SV diameter <3.25 mm by quantitative coronary angiography corresponding to increased MACEs in the dual-stent cohort at 3 years follow-up. In patients who received an SV stent, improved outcomes were seen with use of ≥4.0-mm diameter stents. Avoidance of stent placement in smaller left main SVs with an acceptable angiographic result after KBI may be advantageous. In addition, outcomes after treatment of in-stent restenosis are worse than for native vessel lesions,[22] and therefore restenosis of an unstented SV may be easier to treat effectively than restenosis of a stented SV. Given these limitations of stents, attention is turning towards an alternative approach, with drug-coated balloon therapy for bifurcation lesions.[23]

DKCRUSH V was a similar-sized randomized study (n=482) comparing provisional and 2-stent techniques for true left main bifurcation disease. At 3 years, in contrast to the results of EBC MAIN, less target lesion failure (composite of cardiac death, target vessel MI, and TLR) was seen with DK-crush when compared with a provisional strategy (8.3% versus 16.9%; *P*=0.005). This was driven by both TLR (5.0% versus 10.3%; *P*=0.029) and target vessel MI (1.7% versus 5.8%; *P*=0.017). Several factors need to be considered when directly comparing these trials. Patients with SYNTAX scores >32 were not recruited into EBC MAIN, whereas they comprised >40% of patients in DKCRUSH V. Mean main vessel lesion lengths were 15 mm in EBC MAIN compared with 23 mm in DKCRUSH V. Mean SV lesion lengths were 7 mm versus 16 mm. Complex lesions (as per DEFINITION criteria) were found in 1.5% and 32% of cases in the 2 trials, respectively. SV stent deployment in the provisional cohorts was 22% versus 47%. Therefore, the 2 studies are anatomically distinct despite apparently studying the same disease process and its treatment. Other relevant factors in DKCRUSH V are that proximal optimization technique and KBI were performed more often in the DK-crush than the provisional cohort, and that the use of routine follow-up angiography influenced TLR rates.

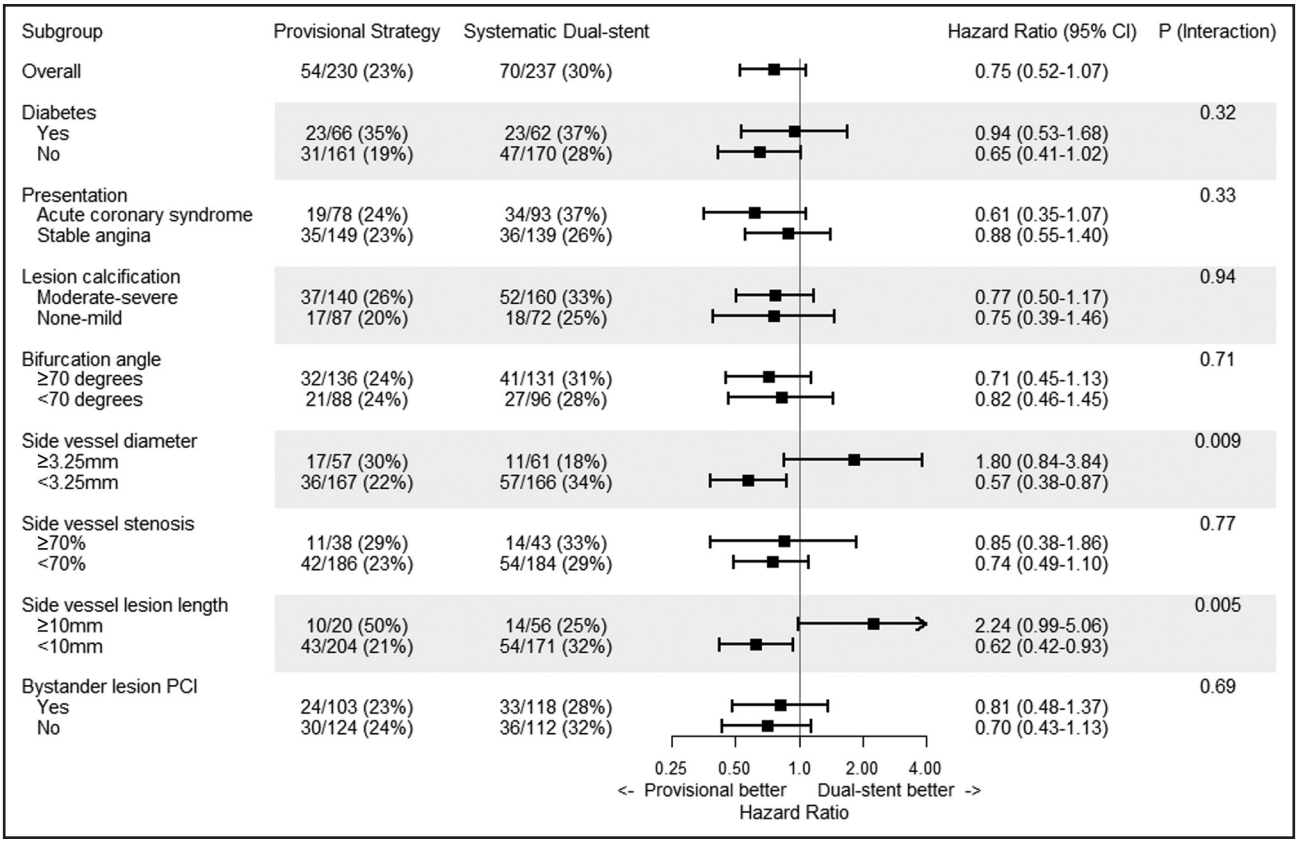

Figure 3. Subgroup analyses.
Subgroup analyses of the primary end point (major adverse cardiac event). PCI indicates percutaneous coronary intervention.

Keeping these differences in mind, both trials report consistent results when anatomic complexity is accounted for. Whereas there were insufficient numbers of patients meeting the full DEFINITION criteria for complexity in EBC MAIN for subanalysis, SV disease length is a major component of this classification and showed significant influence on outcomes. The finding that systematic dual-stent techniques are unnecessary, and possibly harmful, for many SV lesions <10 mm is in line with the previously discussed data regarding long-term risks of stent failure. Shorter SV lesions were underrepresented in the DKCRUSH V cohort, and overrepresented in EBC MAIN, so care must be taken when interpreting the apparent differences in outcomes. There was a trend for improved outcomes with systematic dual-stent techniques for longer lengths of SV disease in EBC MAIN, as the results of the provisional strategy declined in this subgroup. This is concordant with results reported from a large network meta-analysis of bifurcation studies, demonstrating clinical benefit with dual-stent techniques for SV lesion lengths ≥10 mm.[24]

In summary, the available data suggest that there is not one uniform approach for all left main bifurcation anatomy. We therefore suggest that the Class IIb recommendation for DK-crush as the stenting strategy of choice in true left main bifurcations[25] be revised to specify use for complex lesions only. The provisional method should be preferred in most patients with less complex disease. Before any revascularization, patients with left main coronary disease should undergo heart team discussion, as recommended in the 2024 European Society of Cardiology chronic coronary syndrome guidelines.[26]

A primary limitation of both EBC MAIN and DKCRUSH V remains a lack of follow-up beyond 3 years. This is important given the prognostic significance of left main disease and the evidence of the long-term risk of stent failure. Whereas EBC MAIN is one of the largest randomized trials of bifurcation PCI in the left main, there remains a chance the neutral primary outcome is a type II error. In addition, in both trials, use of intracoronary imaging was not mandated and was undertaken in only ≈40% of cases. Increasing evidence supports the use of intracoronary imaging,[27] particularly in left main PCI,[28] and therefore it is likely that outcomes could have been improved with routine use. Indeed, intracoronary imaging now carries a class IA recommendation for percutaneous treatment of the left main or true bifurcation lesions in the European Society of Cardiology chronic coronary syndrome guidelines.[26] Functional or physiologic assessment of the LCx and LAD was not mandated, and it is therefore possible that not all lesions were of

hemodynamic significance. Core laboratory quantitative coronary angiography measurements indicated that 35% of cases had a stenosis diameter in the SV of <50%. Data on participant race or ethnicity were not available. Adjustment for multiple testing on secondary analyses was not performed, and subgroups are of limited size. Those results should be considered hypothesis generating.

Conclusions

Three-year follow-up from EBC MAIN demonstrates that MACE rates were similar between systematic dual-stent and stepwise provisional strategies in true left main bifurcation lesions of relatively low anatomic complexity. The dual-stent approach increased procedural complexity and cost, and led to significantly more TLR. The stepwise provisional approach should remain the default strategy for noncomplex left main bifurcation coronary interventions.

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