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ORIGINAL ARTICLE

Outcomes Among Patients Undergoing Distal Left Main Percutaneous Coronary Intervention

Technique Analysis From the EXCEL Trial

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BACKGROUND: Distal left main (LM) coronary artery bifurcation disease increases percutaneous coronary intervention (PCI) procedural complexity and is associated with worse outcomes than isolated ostial/shaft disease. The optimal treatment strategy for distal LM disease is undetermined. We sought to determine whether outcomes after PCI of LM distal bifurcation lesions are influenced by treatment with a provisional 1-stent versus planned 2-stent technique, and if so, whether such differences are conditioned by the complexity of the LM bifurcation lesion.

METHODS AND RESULTS: The clinical and angiographic characteristics, procedural methods and outcomes, and clinical events through 3-year follow-up were compared in patients undergoing distal LM PCI with a 1-stent provisional versus planned 2-stent technique in the EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization). Among 529 patients undergoing planned distal LM PCI, 344 (65.0%) and 185 (35.0%) were treated with intended 1-stent provisional and planned 2-stent techniques, respectively. The primary composite end point rate of death, myocardial infarction, or stroke at 3 years was significantly lower in patients treated with the provisional 1-stent versus planned 2-stent method (14.1% versus 20.7%; adjusted hazard ratio, 0.55; 95% CI, 0.35–0.88; *P*=0.01), driven by differences in cardiovascular death (3.3% versus 8.3%, *P*=0.01) and myocardial infarction (7.7% versus 12.8%, *P*=0.06). The 3-year rate of ischemia-driven revascularization of the LM complex was also lower in the provisional group (7.2% versus 16.3%, *P*=0.001). In 342 patients with distal LM bifurcation disease that did not involve both major side branch vessels, the 3-year primary end point was lower with a provisional 1-stent versus planned 2-stent technique (13.8% versus 23.3%, *P*=0.04), whereas no significant difference was present in 182 patients with distal LM bifurcation disease that did involve both side branch vessels (14.3% versus 19.2%, *P*=0.36).

CONCLUSIONS: Among patients with distal LM bifurcation disease in the EXCEL trial randomized to PCI, 3-year adverse outcomes were worse with planned 2-stent treatment compared with a provisional 1-stent approach, a difference that was confined to patients without major involvement of both LM side branch vessels.

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Key Words: coronary artery disease ■ dilatation ■ everolimus ■ myocardial infarction ■ percutaneous coronary intervention

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WHAT IS KNOWN

- Among patients undergoing distal left main (LM) bifurcation percutaneous coronary intervention in the EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), important differences in bifurcation anatomy, procedural methods, and outcomes were observed in those treated with a provisional 1-stent versus a planned 2-stent strategy.
- Although early outcomes were similar with the 1-stent provisional and planned 2-stent techniques, at 3-year follow-up, the rates of cardiovascular death, myocardial infarction, ischemia-driven revascularization of the LM complex, and the composite primary end point of death, myocardial infarction, or stroke were more common with a planned 2-stent strategy, differences that persisted after multivariable adjustment for differences in clinical risk factors and coronary anatomy.
- These outcomes were importantly conditioned by whether both major side branches of the distal LM bifurcation were or were not involved.

WHAT THE STUDY ADDS

- With the wide variability in LM anatomy and disease distribution, as well as differences in stent types, technique, and operator expertise, no uniform recommendation about the best stenting strategy for LM distal bifurcation disease has prevailed. In this analysis, 3-year adverse outcomes were worse with planned 2-stent treatment compared with a provisional 1-stent approach, a difference that was confined to patients without major involvement of both LM side branch vessels.
- These results not only inform procedural technique about LM percutaneous coronary intervention but also advance our understanding of outcomes after LM percutaneous coronary intervention relative to treatment strategies.
- Especially in 2-stent strategies, further comparative study is needed to refine technique and outcomes in complex distal LM bifurcation disease.

Recent comparative studies of percutaneous and surgical revascularization for unprotected left main (LM) coronary artery disease have demonstrated clinical equipoise between the 2 revascularization modalities about the major outcomes of death, myocardial infarction (MI), and stroke.[1,2] On the basis of these results, percutaneous coronary intervention (PCI) may be considered an alternative to bypass surgery for selected patients with unprotected LM disease. However, the clinical outcomes of PCI may vary according to LM lesion site and complexity. Specifically, disease of the distal LM bifurcation increases PCI procedural complexity and is associated with worse clinical outcomes compared with disease limited to the LM ostial and shaft segments.[3,4] The optimal interventional approach when the distal LM bifurcation is involved remains uncertain, and although most non-LM bifurcation PCI studies have endorsed a provisional treatment strategy,[5–8] ≈40% of LM interventions are performed with an intentional 2-stent approach.[9–12] The wide variability in LM anatomy, coupled with differences in stent types, techniques, and operator expertise represented in prior studies have precluded reaching uniform recommendations as to the best stenting strategy for LM distal bifurcation disease. We therefore examined procedural methods and outcomes among patients undergoing distal LM PCI in the EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization).[13]

METHODS

Trial and Study Population

The design, enrollment criteria, and methods of the EXCEL trial have been previously reported.[14] EXCEL was an international, large-scale, open-label, multicenter trial in which 1905 patients with LM disease and low or intermediate SYNTAX scores (≤32) eligible for both PCI and coronary artery bypass surgery as assessed by a site-based heart team were randomized to treatment with cobalt-chromium alloy fluoropolymer-based everolimus-eluting stents (XIENCE; Abbott Vascular, Santa Clara, CA) or bypass graft surgery. The study was approved by the institutional review board or ethics committee at each enrolling site, and consecutive, eligible patients signed written informed consent before the revascularization assignment. At the time of the present report, the 3-year follow-up time point has been reached for all randomized patients.

Whether a 1-stent provisional approach or planned 2-stent approach to distal LM bifurcation disease was undertaken was left to the discretion of the operator. In patients undergoing a provisional approach, the decision to predilate and postdilate the side branch (usually the left circumflex coronary artery [LCX]) was left to operator discretion. If side branch postdilatation was required, the protocol recommended implanting a second stent if, after a kissing balloon inflation, either a severe dissection (≥grade B), thrombolysis in myocardial infarction flow <3, or a severe stenosis was present (>70% angiographic diameter stenosis [DS], minimal luminal area by intravascular ultrasound ≤4.0 mm^2 with plaque burden >60%, or fractional flow reserve ≤0.80). Proximal optimization and kissing balloon inflations were recommended for both techniques.

Study End Points and Data Management

The primary end point was the composite rate of death, MI, or stroke at a median follow-up period of 3 years. Major secondary end points included death, MI, or stroke at 30 days, and the composite rate of death, MI, stroke, or ischemia-driven revascularization (IDR) at a median follow-up of 3 years. Study end point definitions and qualifying criteria have been previously described.[14] The case report form collected site-assessed stenosis severity and location within

the different regions of the LM and in cases in which the distal LM bifurcation was involved (>50% visually assessed DS), whether the intent was to use a planned provisional 1-stent technique (with implantation of a second bailout stent reserved for a suboptimal result in the side branch) or a planned routine 2-stent technique. Details of crossover procedures and 2-stent methods were also collected.

All data were submitted to a central data coordinating facility (Cardiovascular Research Foundation, New York, NY). An independent clinical events committee adjudicated all primary and secondary end points after review of original source documents. Coronary angiograms performed at baseline were reviewed by an independent core laboratory (Cardiovascular Research Foundation). The data, analytic methods, and study materials are proprietary to the sponsor and will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Statistical Methods

The present analysis was prespecified in the original study protocol. All patients with site-assessed distal LM bifurcation disease randomized to and treated with PCI were included, and patient groups were compared according to intended treatment using a planned 1-stent provisional technique (regardless as to whether a second stent was implanted) or routine 2-stent method. To examine whether the complexity of the distal LM bifurcation lesion impacted the outcomes of the planned 1-stent provisional versus routine 2-stent technique, the treatment groups were also compared according to whether both side branches had an ostial lesion (within 3 mm of the distal LM bifurcation) with DS ≥50% by angiographic core laboratory analysis.

Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by means with SD for continuous variables. Categorical variables were compared by χ^2 or Fisher exact test if >20% of the expected cell frequencies were <5. For continuous variables that met the assumption of normality by the Shapiro–Wilk test, the 2 treatment groups were compared by the 2-sample *t* test. If the data failed to meet the assumption for normality, comparisons were made using the Wilcoxon rank-sum test. Three-year clinical events were summarized as Kaplan-Meier estimates and compared with the log-rank test. Hazard ratios and 95% CI were determined using Cox proportional hazards models. Multivariable analysis was performed using Cox stepwise regression to adjust for the influence of potential confounders on the relationship between planned technique and composite adverse events at 3 years. The list of covariates used included age, male sex, recent MI (<7 days), current smoker, diabetes mellitus, creatinine clearance <60 mL/min, SYNTAX score, concomitant LM ostial or shaft DS >50%, worst LM %DS, ostial left anterior descending [LAD] %DS, ostial LCX %DS, thrombolysis in myocardial infarction flow <3 in either the LAD or LCX, and left ventricular ejection fraction. Angiographic measures included in the model were determined by angiographic core laboratory assessment. A 2-sided *P* value of 0.05 was established as the level of statistical significance for all superiority tests. All analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Clinical and Angiographic Characteristics

PCI was the first procedure performed in 935 of the 948 patients randomized to PCI. Site-reported planned distal LM bifurcation PCI was performed in 529 of 925 patients (57.2%); in 10 additional cases, the procedural strategy was not recorded. Among the 529 patients with planned distal LM bifurcation disease, 344 patients (65.0%) were treated with a provisional 1-stent technique, and 185 patients (35.0%) underwent planned 2-stent bifurcation PCI. No significant differences were present in the baseline clinical or demographic characteristics between the groups other than a greater incidence of stable angina in the provisional 1-stent group (Table 1). Approximately one-third of patients had diabetes mellitus, and ≈40% of patients presented with unstable angina or recent MI.

Both the prevalence of non-LM disease and site-assessed SYNTAX score were similar between the provisional 1-stent and planned 2-stent treatment groups (Table 1); however, by angiographic core laboratory analysis, the overall SYNTAX score was significantly higher among patients in the planned 2-stent group. Similarly, patients undergoing planned 2-stent treatment were more likely to have distal LM bifurcation disease involving both the ostial LAD and ostial LCX coronary segments (Medina classification 1,1,1 or 0,1,1 by angiographic core laboratory analysis). Side branch lesion length (4.7±3.4 versus 8.8±7.6 mm, *P*<0.0001) and %DS (34.3±22.9% versus 59.7±22.3%, *P*<0.0001) were also significantly greater among planned 2-stent cases. No significant difference in the bifurcation angle separating the LAD and LCX was observed between the provisional 1-stent and planned 2-stent groups.

Procedural Outcomes

Radial artery access and 6F guiding catheters were used more frequently for provisional 1-stent procedures, whereas femoral artery access and 8F guiding catheter use were more common among planned 2-stent cases (Table 2). Despite significantly greater use of hemodynamic support devices with the planned 2-stent technique, site-reported procedural complications did not differ between treatment strategies. Planned 2-stent treatment was associated with longer procedural duration compared with a provisional method but with similar contrast utilization.

Among the 344 patients undergoing a planned provisional 1-stent method, treatment of the side branch was performed frequently (70.6%), most commonly with balloon angioplasty alone (Table 2). Rescue or bailout stenting of the side branch was required

Table 1. Baseline Clinical and Angiographic Characteristics According to the Planned Stent Approach in Patients With Left Main Distal Bifurcation Disease

	Provisional 1-Stent (n=344)	Planned 2-Stent (n=185)	*P* Value
Clinical characteristics			
Age, y	66.2±9.3	66.8±9.3	0.54
Male sex	275 (79.9)	141 (76.2)	0.32
Diabetes mellitus	99 (28.8)	64 (34.6)	0.17
Smoking history	221 (64.8)	118 (64.1)	0.88
Hypertension	254 (73.8)	141 (76.2)	0.55
Hyperlipidemia	251 (73.0)	129 (70.1)	0.49
Prior myocardial infarction	65 (19.2)	38 (20.8)	0.66
Prior percutaneous coronary intervention	69 (20.1)	42 (22.8)	0.46
Prior stroke or transient ischemic attack	16 (4.7)	15 (8.1)	0.11
Left ventricular ejection fraction, %	57.5±9.4	56.1±10.1	0.27
Clinical presentation			0.13
Stable angina	198 (57.9)	87 (47.3)	
Unstable angina	74 (21.6)	46 (25.0)	
Recent myocardial infarction*	50 (14.6)	36 (19.6)	
Angiographic characteristics			
Site assessed			
SYNTAX score, site assessed	21.2±6.1	22.2±5.8	0.07
SYNTAX score, categories			0.10
0–22 (low)	191 (55.5)	89 (48.1)	
23–32 (intermediate)	153 (44.5)	96 (51.9)	
LM ostial or shaft stenosis ≥50%	161 (47.9)	65 (37.1)	0.02
Ostial anterior descending artery ≥50%	170 (49.4)	126 (68.1)	<0.0001
Ostial left circumflex artery ≥50%	121 (35.2)	140 (75.7)	<0.0001
Angle between LAD and LCX, °	84.7±21.6	86.8±22.4	0.18
LM disease only	51 (14.8)	25 (13.5)	0.68
LM and 1-vessel disease	106 (30.8)	50 (27.0)	0.36
LM and 2-vessel disease	117 (34.0)	63 (34.1)	0.99
LM and 3-vessel disease	66 (19.2)	43 (23.2)	0.27
Angiographic core laboratory-assessed			
SYNTAX score (continuous)	27.8±8.8	30.7±8.7	0.0008
SYNTAX score			0.005
0–22 (low)	99/340 (29.1)	31/179 (17.3)	
23–32 (intermediate)	146/340 (42.9)	79/179 (44.1)	
≥33 (high)	95/340 (27.9)	69/179 (38.5)	
Medina classification†			<0.0001
1,0,0	65/210 (31.0)	9/118 (7.6)	
0,1,0	9/210 (4.3)	3/118 (2.5)	
1,1,0	63/210 (30.0)	13/118 (11.0)	
0,0,1	0/210 (0)	2/118 (1.7)	
1,0,1	26/210 (12.4)	22/118 (18.6)	
0,1,1	1/210 (0.5)	5/118 (4.2)	
1,1,1	45/210 (21.4)	64/118 (54.2)	
LM trifurcation disease present†	122/344 (35.5)	61/185 (33.0)	

Values are n/N (%) or mean±SD. LAD indicates left anterior descending coronary artery; LCX, left circumflex coronary artery; and LM, left main coronary artery.

*Within 7 days before randomization.

†Required diameter stenosis ≥50% by core laboratory measurement.

Table 2. Procedural Characteristics According to the Planned Stent Approach in Patients With Left Main Distal Bifurcation Disease

	Provisional 1-Stent (344 Patients, 376 Procedures*)	Provisional 1-Stent (185 Patients, 208 Procedures*)	*P* Value
Maximum LM device diameter, mm	4.07±0.52	3.95±0.48	0.01
Poststent dilation	311/344 (90.4)	173/185 (93.5)	0.22
Guiding catheter size			<0.0001
6F	169/344 (49.1)	54/185 (29.1)	
7F	134/344 (39.0)	79/185 (42.7)	
8F	41/344 (11.9)	52/185 (28.1)	
Radial artery access	135/376 (35.9)	38/208 (18.3)	<0.0001
Intravascular ultrasound used	266/344 (77.3)	139/185 (75.1)	0.57
Fractional flow reserve used	31/344 (9.0)	14/185 (7.6)	0.57
Rotational atherectomy performed	24/344 (7.0)	11/185 (5.9)	0.65
Hemodynamic support used	12/375 (3.2)	21/208 (10.1)	0.0006
Unfractionated heparin used	317/373 (85.0)	160/206 (77.6)	0.03
Bivalirudin used	94/373 (25.2)	74/206 (35.9)	0.006
GP IIb/IIIa inhibitor used	28/376 (7.4)	18/208 (8.7)	0.60
Contrast volume, mL	264±131	270±122	0.30
Fluoroscopy time, min	24±15	28±17	0.0004
Procedural complications†	42/376 (11.2)	29/208 (13.9)	0.33
Provisional 1-stent approach			
Side branch treatment, any	243/344 (70.6)	…	…
Balloon angioplasty	207/243 (85.2)	…	…
Atherectomy	5/243 (2.1)	…	…
Stent	54/243 (22.2)	…	…
Side branch stent technique		…	…
T, modified T, or TAP	42/54 (77.8)	…	…
Culotte or reverse crush	8/54 (14.8)	…	…
Other	4/54 (7.4)	…	…
Planned 2-stent approach			
T, modified T, or TAP	…	92/185 (50.8)	…
Culotte	…	42/185 (23.2)	…
Crush or mini-crush	…	26/185 (14.4)	…
V stent	…	11/185 (6.1)	…
Simultaneous kissing stents	…	5/185 (2.8)	…
Other	…	5/185 (2.8)	…
Final kissing balloon inflation	189/344 (54.9)	156/185 (84.3)	<0.0001
Residual SYNTAX Score	7.0±6.9	6.3±6.5	0.39

Values are n/N (%) or mean±SD. GP indicates glycoprotein; LM, left main coronary artery; and TAP, T and protrusion.
*Includes staged procedures.
†Defined as chest pain or ECG changes lasting >10 min, slow flow, no reflow, distal embolization, abrupt closure, perforation, dissection, stent thrombosis, tamponade, cardiac arrest, stroke, bleeding, or severe arrhythmias.

in 54 (15.7%) of all provisional 1-stent procedures. T-stenting, modified T-stenting, and T-stent and protrusion were the most commonly used techniques in such bailout stent cases, as well as in the majority of the 185 intended 2-stent strategies, followed by culotte and crush techniques (Table 2).

Clinical Outcomes

Adverse event rates within 30 days were not statistically different between the 2 groups (Table 3). At 3 years, however, the primary end point of death, MI, or stroke occurred in significantly fewer patients treated with the provisional 1-stent approach compared with

Table 3. Thirty-Day and 3-Year Clinical Outcomes According to the Planned Stent Approach in Patients With Left Main Distal Bifurcation Disease

	Provisional 1-Stent (n=344)	Planned 2-Stent (n=185)	*P* Value
30-day adverse events			
Death	0.9% (3)	2.7% (5)	0.10
Cardiovascular death	0.9% (3)	2.7% (5)	0.10
Myocardial infarction	4.4% (15)	6.5% (12)	0.29
Stroke	0.3% (1)	1.6% (3)	0.09
Any IDR	0.9% (3)	1.1% (2)	0.81
LM complex* IDR	0.9% (3)	0.5% (1)	0.68
Any definite or probable stent thrombosis	0.6% (2)	1.6% (3)	0.24
LM definite or probable stent thrombosis	0.6% (2)	1.6% (3)	0.24
Death, myocardial infarction, or stroke	5.2% (18)	8.7% (16)	0.13
Death, myocardial infarction, stroke, or IDR	5.2% (18)	8.7% (16)	0.13
3-year adverse events			
Death	6.8% (23)	11.0% (20)	0.08
Cardiovascular death	3.3% (11)	8.3% (15)	0.01
Myocardial infarction	7.7% (26)	12.8% (23)	0.06
Stroke	1.8% (6)	3.4% (6)	0.24
Any IDR	12.0% (40)	16.7% (29)	0.14
LM complex* IDR	7.2% (24)	16.3% (28)	0.001
Any definite or probable stent thrombosis	1.5% (5)	3.3% (6)	0.16
Definite	0.9% (3)	1.1% (2)	0.78
Probable	0.6% (2)	2.2% (4)	0.10
LM definite or probable stent thrombosis	1.5% (5)	2.8% (5)	0.29
Definite	0.9% (3)	1.1% (2)	0.88
Probable	0.6% (2)	1.6% (3)	0.78
Death, myocardial infarction, or stroke	14.1% (48)	20.7% (38)	0.04
Death, myocardial infarction, stroke, or IDR	22.2% (76)	29.6% (54)	0.055

Values are Kaplan-Meier estimated rates % (n events). IDR indicates ischemia-driven revascularization; and LM, left main coronary artery.

*The LM complex consists of the distal LM, the ostial left anterior descending artery, and the ostial left circumflex coronary artery.

the planned 2-stent technique (14.1% versus 20.7%; multivariable-adjusted hazard ratio, 0.55; 95% CI, 0.35–0.88; *P*=0.01; Tables 3 and 4, and Figure 1A). The 3-year rate of IDR of the LM complex was also lower in the provisional group, as was the composite end point of death, MI, stroke, or IDR (Figure 1B). Definite or probable stent thrombosis occurred in 1.5% of provisional 1-stent patients and 3.3% of planned 2-stent patients (*P*=0.16). Dual antiplatelet therapy at 3 years was used in 61.8% and 57.2% of patients in the provisional 1-stent and planned 2-stent groups, respectively (*P*=0.34).

Outcomes According to Distal LM Side Branch Involvement

Angiographic core laboratory analysis was performed in 524 (99.1%) of the 529 patients with distal LM bifurcation disease. Among these 524 patients, both LM major side branches (LAD and LCX) had an ostial DS ≥50% in 182 cases (34.7%); a provisional 1-stent versus a planned 2-stent approach was used in 77 (42.3%) and 105 (57.7%) of these patients, respectively. Among the other 342 (65.3%) patients without an ostial DS of ≥50% in both LM side branches, 264 (77.2%) and 78 (22.8%) were treated with a provisional 1-stent versus a planned 2-stent approach, respectively. Among patients undergoing a provisional approach, a bailout stent was required in 22 (28.6%) of those with and 32 (12.1%) of those without ostial involvement of both side branches (*P*=0.0005). As shown in Tables 4 and 5 and Figure 2, in patients with distal LM bifurcation disease that did not involve the ostia of both side branch vessels, the 3-year occurrence of death, MI, or stroke was significantly lower among patients undergoing provisional 1-stent versus planned 2-stent PCI (13.8% versus 23.3%; multivariable-adjusted hazard

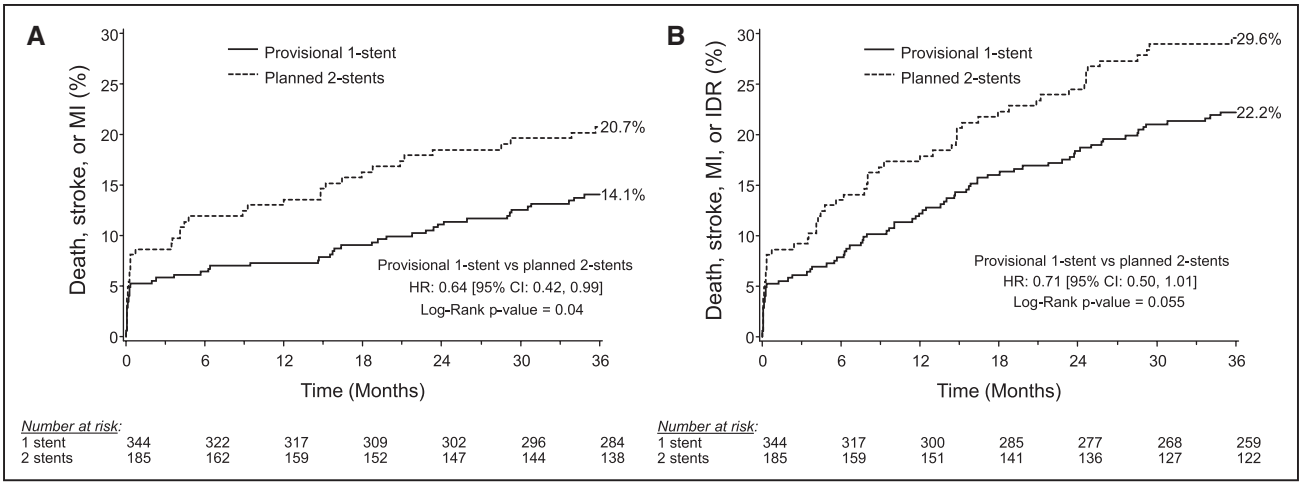

Figure 1. Time-to-first event curves in patients with distal left main bifurcation disease.
Patients were treated with a provisional 1-stent approach (blue curves) or a planned routine 2-stent approach (red curves). **A**, Time-to-first occurrence of death, myocardial infarction (MI), or stroke (the primary end point); (**B**) Time-to-first occurrence of death, MI, stroke, or ischemia-driven revascularization (IDR; the major secondary 3-year end point). For each of the 2 major 3-year end points, event rates were higher for patients treated with the planned routine 2-stent approach. HR indicates hazard ratio.

ratio, 0.53; 95% CI, 0.29–0.95; *P*=0.03). In comparison, among patients with distal LM bifurcation disease that did involve the ostia of both side branch vessels, no significant differences in 3-year outcomes between the provisional 1-stent and planned 2-stent methods were observed. Similarly, all-cause mortality was marginally lower in patients with distal LM bifurcation disease that did not involve both ostial side branch vessels treated with a provisional 1-stent approach versus a planned 2-stent approach (6.1% versus 13.0%; hazard ratio, 0.46; 95% CI, 0.21–1.01; log-rank *P*=0.04; Cox *P*=0.053), whereas survival rates were similar with both techniques in distal LM bifurcations with involvement of both ostial side branches (Table 5; Figure 2).

Table 4. Multivariable Correlates of the 3-Year Primary End Point of Death, Myocardial Infarction, or Stroke

Variable	Adjusted HR [95% CI]	*P* Value
All patients		
Provisional 1-stent vs planned 2-stent technique	0.55 [0.35–0.88]	0.01
Age (per year)	1.04 [1.01–1.07]	0.006
Male sex	0.61 [0.37–1.01]	0.055
Both LM ostial side branches with DS ≥50%*		
Provisional 1-stent vs planned 2-stent technique	0.86 [0.39–1.88]	0.70
Age (per year)	1.05 [1.00–1.10]	0.045
Recent myocardial infarction†	0.28 [0.07–1.20]	0.09
Creatinine clearance <60 mL/min	2.47 [0.96–6.32]	0.06
Hypertension, medically treated	0.52 [0.24–1.11]	0.09
0 or 1 LM ostial side branches with DS ≥50%*		
Provisional 1-stent vs planned 2-stent technique	0.53 [0.29–0.95]	0.03
Age (per year)	1.03 [1.00–1.06]	0.08

DS indicates diameter stenosis; HR, hazard ratio; and LM, left main coronary artery.
*Angiographic core laboratory measure.
†Within 7 days before randomization.

DISCUSSION

Among patients undergoing distal LM bifurcation PCI in the EXCEL trial, important differences in bifurcation anatomy, procedural methods, and outcomes were observed in those treated with a provisional 1-stent versus a planned 2-stent strategy. Although early outcomes were similar with the 1-stent provisional and planned 2-stent techniques, at 3-year follow-up, the rates of cardiovascular death, MI, IDR of the LM complex, and the composite primary end point of death, MI, or stroke were more common with a planned 2-stent strategy, differences that persisted after multivariable adjustment for differences in clinical risk factors and coronary anatomy. These outcomes were importantly conditioned by whether both major side branches of the distal LM bifurcation were or were not involved. Specifically, all-cause mortality was lower and event-free survival was superior with a 1-stent provisional compared with a planned 2-stent technique in distal LM bifurcation lesions in which both major side branches were not involved (ie, when the DS within 3 mm of the distal LM bifurcation was <50% by angiographic core laboratory analysis in at least 1 major side branch). In contrast, if both distal LM major side branches had an ostial DS ≥50%, mortality and event-free survival at 3 years were similar in patients treated with a provisional 1-stent and planned 2-stent technique.

Most patients randomized to PCI in the EXCEL trial had distal LM bifurcation or trifurcation disease, the majority of whom were treated with an intended

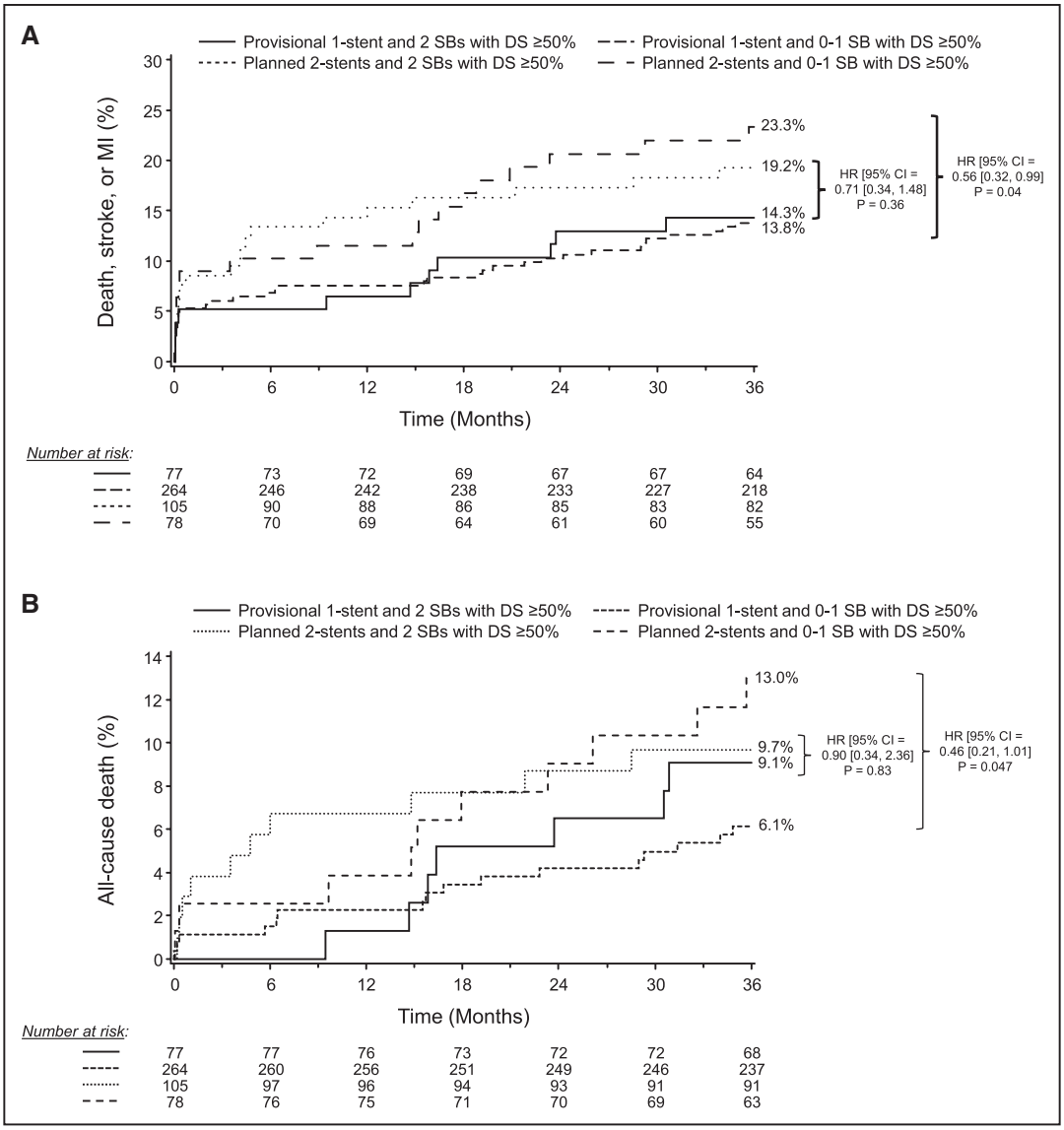

Figure 2. Three-year outcomes among patients with versus without involvement of the major side branch of the left main complex.
A, The composite rate of death, myocardial infarction (MI), or stroke; (**B**) all-cause mortality. Event-free survival was lower and mortality was higher for the provisional 1-stent technique compared with the planned 2-stent technique in patients without major ostial involvement of both side branches of the distal left main (LM) bifurcation, but not when both side branches were diseased (ostial diameter stenosis ≥50%). DS indicates diameter stenosis; HR, hazard ratio; and SB, side branch.

provisional 1-stent approach and with intravascular ultrasound guidance. These practices are consistent with registry reports demonstrating the increasing use over time of the provisional approach and imaging guidance during LM intervention, reflecting emerging evidence.[12,15,16] Nevertheless, a planned 2-stent technique is often necessary in cases in which the disease in both side branches is severe or when marked side branch angulation may compromise future access. As evidenced in this trial, a provisional 1-stent strategy was preferentially (but not exclusively) selected for patients with noncomplex bifurcation disease. The rate of and scenarios for use of a planned 2-stent approach, however, are operator dependent, and the relative outcomes of a provisional 1-stent versus planned 2-stent technique according to bifurcation lesion complexity continue to be debated. Other uncertainties include whether and when side branch treatment is necessary during provisional treatment and the optimal technique to select when a second stent is required either for provisional bailout use or during a routine 2-stent case.

Such uncertainties were reflected in the contemporary EXCEL trial, in which some general recommendations were provided, but ultimate procedural decisions were left to operator discretion. Although approximately two-thirds of all distal LM bifurcations undergoing PCI were treated with a provisional approach, a planned 2-stent technique was chosen more commonly when both major side branches had ostial involvement. Even when angiographic core laboratory analysis confirmed that both side branches were involved, a provisional 1-stent approach was still chosen in ≈42% of

Table 5. Three-Year Outcomes of Distal Left Main Bifurcation Treatment According to Lesion Complexity and Technique Strategy

Angiographic Core Laboratory Classification	Both LM Side Branches With Ostial DS ≥50%			0 or 1 LM Side Branches With Ostial DS ≥50%		
	Provisional 1-Stent (n=77)	Planned 2-Stent (n=105)	Hazard Ratio [95% CI]	Provisional 1-Stent (n=246)	Planned 2-Stent (n=78)	Hazard Ratio [95% CI]
Death, MI, or stroke	14.3% (11)	19.2% (20)	0.71 [0.34–1.48]	13.8% (36)	23.3% (18)	0.56 [0.32–0.99]
Death, MI, stroke, or IDR	26.0% (20)	29.9% (31)	0.82 [0.47–1.44]	21.0% (55)	29.8% (23)	0.68 [0.42–1.10]
Death	9.1% (7)	9.7% (10)	0.90 [0.34–2.36]	6.1% (16)	13.0% (10)	0.46 [0.21–1.01]
Cardiovascular	4.1% (3)	7.8% (8)	0.49 [0.13–1.83]	3.1% (8)	9.1% (7)	0.33 [0.12–0.91]
MI	6.6% (5)	13.6% (14)	0.47 [0.17–1.31]	7.8% (20)	12.1% (9)	0.64 [0.29–1.40]
Stroke	0% (0)	2.0% (2)	…	2.4% (6)	5.3% (4)	0.42 [0.12–1.50]
IDR	14.7% (11)	19.3% (19)	0.72 [0.34–1.52]	10.9% (28)	13.8% (10)	0.80 [0.39–1.65]
LM complex IDR	6.7% (5)	18.5% (18)	0.33 [0.12–0.90]	6.2% (16)	14.0% (10)	0.45 [0.20–0.99]
Definite or probable stent thrombosis	0% (0)	2.9% (3)	…	2.0% (5)	4.0% (3)	0.48 [0.11–2.00]
LM definite or probable stent thrombosis	0% (0)	1.9% (2)	…	2.0% (5)	4.0% (3)	0.48 [0.11–2.00]

Values are Kaplan-Meier estimated rates % (n). DS indicates diameter stenosis; IDR, ischemia-driven revascularization; LM, left main coronary artery; and MI, myocardial infarction.

cases, suggesting differences in operator assessment of the angiographic severity and complexity of disease or procedural comfort with bailout techniques. Conversely, when both side branches did not have major involvement (according to the core laboratory), planned 2-stent treatment was still undertaken in ≈23% of cases, perhaps reflecting challenges in visual assessment of the LM bifurcation, additional downstream disease in the LCX, clinical equipoise, or other factors. Moreover, despite evidence suggesting the infrequent need for side branch intervention based on published data for angiographic or fractional flow reserve assessment[17,18] and evidence that discourage routine side branch postdilation in non-LM bifurcation provisional stenting,[19] in the present study, treatment of the LM side branch was common with the provisional technique (most often with balloon angioplasty alone). Moreover, bailout stenting during the provisional approach was not uncommon (performed in ≈1 in 6 cases), although it was needed more frequently when the second major side branch (usually the LCX) had versus did not have an ostial lesion with DS ≥50% (28.6% versus 12.1%, respectively). The high rate of intervention in the side branch even when the provisional approach was undertaken likely reflects the fact that the LCX lumen in cases with a narrow bifurcation angle is often compromised after main branch stenting because of carina shift.[20] However, side branch fractional flow reserve was rarely performed in EXCEL, which otherwise may have provided reassurance to not dilate or stent the side branch in provisional cases.

The excellent 30-day and 3-year results after PCI of distal LM bifurcation disease in EXCEL reflect the improved outcomes that can be achieved with everolimus-eluting stents, use of intravascular ultrasound guidance in most cases, and operators with advanced technical skills and ability to select cases appropriately. These favorable results notwithstanding, the 3-year rates of cardiovascular death, LM complex IDR, and the primary end point of death, MI, or stroke were significantly more common with a planned 2-stent treatment strategy than with a provisional 1-stent strategy, and stent thrombosis and MI rates tended to be higher, suggesting room for improvement in technique, stent properties, and adjunctive technologies. In most prior studies of PCI for non-LM bifurcation disease, 2-stent treatment has been associated with higher rates of periprocedural MI and stent thrombosis.[5–8] Observational studies of distal LM bifurcation PCI also have reported higher rates of cardiovascular death, MI, target lesion revascularization, and stent thrombosis with 2-stent approaches.[21,22] The higher risks associated with 2-stent methods may relate to side branch stent underexpansion[23] and overlying layers of bifurcating stents.[21] The relative outcomes of a planned 2-stent strategy versus a provisional 1-stent approach may depend on the bifurcation angle[24] and complexity of disease being treated. The DEFINITION study (Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents) reported lower individual rates of cardiac death and MI in complex LM bifurcation disease (Medina 1,1,1 or 0,1,1) treated with 2 stents compared with a provisional strategy.[25] In EXCEL, the 3-year clinical event rates with planned 2-stent use compared with the provisional approach were comparable if both LM side branches had significant ostial disease but were inferior (including higher rates of death) if one or both major side branch had an ostial DS <50%. When applying DEFINITION[25] trial criteria of LM complexity to EXCEL patients with true bifurcation lesions, overall no significant differences in outcomes were observed between treatment strategy and LM complexity except for higher

LM target lesion revascularization with a planned 2-stent technique in noncomplex Medina 1,1,1 or 0,1,1 lesions (Table I in the Data Supplement).

Although these results are compelling in recommending a provisional 1-stent approach in most cases in which the major side branch is not involved, the outcomes of a planned 2-stent approach may vary according to the technique used. In the randomized DKCRUSH trial (Double Kissing Crush Versus Culotte Stenting for the Treatment of Unprotected Distal Left Main Bifurcation Lesions)-III and DKCRUSH-V trial, the DK crush 2-stent method provided superior clinical outcomes compared with both a planned culotte 2-stent technique[26,27] and a provisional 1-stent strategy[27] in patients with true distal LM bifurcation disease. Unfortunately, DK crush use in EXCEL was captured under the general category of crush techniques and not selectively recorded; however, all crush techniques represented <15% of all planned 2-stent cases, and thus, DK crush was not widely used in EXCEL. The extent to which the overall outcomes of EXCEL (and specifically the results in the planned 2-stent group) may have been improved with more widespread usage of the DK crush technique is unknown. The strategy of a planned 2-stent versus a provisional 1-stent PCI technique in complex LM bifurcation disease is the focus of the ongoing EBC MAIN study (European Bifurcation Club Left Main; NCT02497014).

Limitations

The EXCEL trial, performed at 126 centers in 17 countries, reflects the clinical outcomes that may be expected from contemporary distal LM bifurcation treatment (in the context of a randomized trial) by experienced operators; however, the decision to use a provisional 1-stent versus a planned 2-stent technique was not randomized, and despite multivariable analysis, differences in outcomes may have been influenced by unmeasured confounders not collected in the case report form. The influence of selected procedural methods that were not recorded in the database, such as proximal optimization technique, also cannot be determined. In addition, although EXCEL is the largest LM trial to date and the present analysis was prespecified, the study was not statistically powered for comparison of outcomes in subgroups. For these reasons, the results should be considered hypothesis generating. Finally, operator assessment and angiographic core laboratory measures of LM bifurcation lesion severity, length, and angulation often vary. The present analysis was performed principally from the operator's perspective to be relevant to catheterization laboratory decisions, although it was supplemented by core laboratory measurements to provide objectivity in assessing techniques and outcomes according to whether the major side branch was truly diseased.

Conclusions

Among patients undergoing distal LM bifurcation PCI with everolimus-eluting stents in the EXCEL trial, differences in bifurcation disease complexity influenced procedural treatments and outcomes with a provisional 1-stent versus a planned 2-stent strategy. During 3-year follow-up, rates of cardiac death, IDR of the LM complex, and the primary composite end point of death, MI, or stroke were significantly increased with a planned 2-stent strategy compared with a 1-stent provisional technique. However, these differences were confined to patients without major ostial involvement of both LM side branch vessels. In true LM bifurcation lesions in which both side branches had major involvement, no statistically significant difference in outcomes between the 1-stent provisional and planned 2-stent approaches was observed. These results support a provisional 1-stent strategy in most cases when both distal LM side branch vessels are not involved (eg, Medina 1,0,0; 1,1,0; or 1,0,1). Further studies are required to determine the optimal approach to true Medina 1,1,1 or 0,1,1 distal LM bifurcation lesions.

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