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# Procedural Characteristics and Clinical Outcomes in Patients Undergoing Percutaneous Coronary Intervention for Left Main Trifurcation Disease: The EXCEL trial

**Running Title:** Left Main Trifurcation Disease in the EXCEL Trial

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## ABSTRACT

**Aims:** Limited data exist regarding procedural and clinical outcomes of percutaneous coronary intervention (PCI) in patients with trifurcation disease of the distal left main (LM) coronary artery.

**Methods and Results:** Patients with distal LM bifurcation disease randomized to PCI with everolimus-eluting stents in the EXCEL trial were categorized into those with and without trifurcation involvement. Angiographic and procedural characteristics in addition to clinical events through 5-year follow-up after PCI were compared. Among 605 patients with site-reported distal LM disease, 61 patients (10.1%) were identified with trifurcation anatomy. The 5-year primary composite endpoint of death, myocardial infarction, or stroke occurred in 16.6% of patients with trifurcation disease compared with 22.5% of patients with distal bifurcation disease only (p=0.32). Ischemia-driven target lesion revascularization rates were also similar (11.9% versus 12.0%, p=0.94). No significant differences in definite or probable stent thrombosis were observed between treatment groups (1.7% versus 2.3%, p=0.76).

**Conclusions:** Despite the greater inherent complexity, procedural and long-term clinical outcomes following PCI of distal LM trifurcations with everolimus-eluting stents in a modest-sized cohort from the EXCEL trial were similar compared with treatment of distal LM bifurcation disease without trifurcations. These findings support PCI as a treatment strategy for selected patients with distal LM trifurcation disease.



**Keywords:** left main, Drug-eluting stent, Clinical research

## CONDENSED ABSTRACT

Among 605 patients with site-reported distal LM disease in the EXCEL trial, 61 patients (10.1%) were identified with trifurcation anatomy. The 5-year primary composite endpoint of death, myocardial infarction, or stroke occurred in 16.6% of patients with trifurcation disease compared with 22.5% of patients with distal bifurcation disease only (p=0.32). Ischemia-driven target lesion revascularization rates were also similar (11.9% versus 12.0%, p=0.94). Despite the greater inherent complexity, similar early and long-term clinical outcomes observed following PCI of distal LM trifurcation and bifurcation only disease support PCI as a treatment strategy for selected patients with distal LM trifurcation disease.

## ABBREVIATIONS

DS=diameter stenosis

IDR=ischemia-driven repeat revascularization

LM=left main coronary artery

MI=myocardial infarction

PCI=percutaneous coronary intervention

TIMI=Thrombolysis in Myocardial Infarction

## INTRODUCTION

Coronary artery disease involving the distal left main (LM) coronary artery bifurcation increases procedural complexity of percutaneous coronary intervention (PCI) and is associated with worse outcomes compared with isolated ostial or shaft LM disease[1,2]. Despite extensive analysis of PCI techniques and clinical outcomes after distal LM bifurcation treatment, few reports have examined procedural strategy and outcomes in patients with trifurcation disease of the distal LM artery segment. Among such studies, procedural and early clinical outcomes appear favorable[3-6], yet late-term adverse event rates are high and correspond with increasing trifurcation disease complexity and number of stents used[5,6].

Whether contemporary outcomes in LM trifurcation PCI are similar to distal bifurcation disease using contemporary technique and drug-eluting stents has not been characterized. We therefore examined the procedural methods and early and late outcomes among patients undergoing distal LM trifurcation versus bifurcation PCI in the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.



## METHODS

**Trial and Study Population.** The design, enrollment criteria, methods and principal outcomes of the EXCEL trial have been previously reported[7]. 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 prior to the revascularization assignment.

Patients with site-reported distal LM disease (LM distal diameter stenosis [DS] >50%) were included in this analysis and compared relative to the presence of trifurcation versus "only" bifurcation disease as assessed by an independent angiographic core laboratory (Cardiovascular Research Foundation, New York, NY). Treatment approaches of LM trifurcation or bifurcation disease (e.g., use of single versus multiple stents, provisional 1-stent vs. planned 2-stent technique, pre- and post-dilation) were left to the discretion of the operator. If side branch post-dilation was required, the protocol recommended implanting an additional stent if, after a kissing balloon inflation, either a severe dissection (≥ grade B), Thrombolysis in Myocardial Infarction (TIMI) flow <3, or a severe stenosis was present (>70% angiographic 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 in cases of multiple stents or if side branch post-dilation was required.

**Study Endpoints and Data Management.** The primary endpoint was the composite rate of death, myocardial infarction (MI), or stroke at 3-year follow-up. Major secondary endpoints included death, MI, or stroke at 30 days, and the composite rate of death, MI, stroke, or ischemia-driven revascularization (IDR) at 3 years. Study endpoint definitions and qualifying criteria have been previously described[5]. 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 or trifurcation was involved (>50% visually assessed DS), the number of stents used to treat the LM segment. An independent clinical events committee adjudicated all primary and secondary endpoints following review of original source documents.

**Statistical Methods.** The present analysis was pre-specified in the original study protocol. All patients with site-assessed distal LM bifurcation and trifurcation disease randomized to and treated with PCI were included, and patient groups were compared according to intended treatment.

Baseline characteristics of study patients were summarized in terms of frequency and percentage for categorical variables and by mean with standard deviation for continuous variables. Categorical variables were compared by $\chi^2$ 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 two 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. Five-year clinical events were summarized as Kaplan-Meier estimates. Odds ratios, 95% confidence intervals and p values were determined using logistic regression including follow-up days as a log-transformed offset term. Multivariable analyses was performed in order to adjust for the influence of potential confounders on the relationship between distal LM anatomy and composite adverse events at 5 years using the following covariates: trifurcation versus no trifurcation, age, male sex, recent MI (<7 days), current smoker, diabetes, creatinine clearance <60 mL/min, SYNTAX score, concomitant LM ostial or shaft DS >50%, worst LM %DS, ostial left anterior descending %DS, ostial left circumflex %DS, TIMI flow <3 in either the left anterior descending or left circumflex artery, and left ventricular ejection fraction. All angiographic measures 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.** Among 605 patients with site-reported distal LM bifurcation disease (DS >50%), 61 patients (10.1%) had distal trifurcation anatomy. No significant differences were present in the baseline clinical or demographic characteristics between the groups other than a higher prevalence of prior PCI in the bifurcation only group and greater left ventricular ejection fraction in the trifurcation cohort (Table 1). Presentation with unstable angina or MI as well as a history of MI was non-significantly higher among bifurcation only patients. Approximately one-fourth of the overall study population had diabetes mellitus.

The baseline SYNTAX score was significantly higher among trifurcation patients by site estimation, but not by angiographic core laboratory assessment (Table 1). The presence of isolated LM disease was significantly more common in the trifurcation group, whereas the prevalence of LM and 3-vessel coronary artery disease was significantly more frequent in the bifurcation only group. Among those with trifurcation anatomy, disease involvement (DS ≥50%) of at least 3 segments was present in more than half of patients.

**Procedural Characteristics and Outcomes.** Six Fr guiding catheters were used more frequently in bifurcation only procedures, whereas 8 Fr guiding catheter use was more common in trifurcation cases (Table 2). Intravascular ultrasound guidance was used more frequently in bifurcation only cases. Use of hemodynamic support devices, procedure duration, and site-reported procedural complications did not differ between treatment groups. The average number of stents used to treat the LM complex (the distal LM, ostial LAD, ostial LCX and [in trifurcation disease] ostial ramus) was also similar among trifurcation and bifurcation only cases, although treatment with 3 or more stents was numerically higher in the trifurcation cohort (16.4% versus 9.6%, p=0.09). Despite differences in the prevalence of multivessel coronary

disease, there was no significant difference in the post-PCI residual SYNTAX score between groups.

**Clinical Outcomes.** Adverse event rates within 30 days were infrequent and not statistically different between the two groups (Table 3). At 5 years, no significant differences were identified between trifurcation and bifurcation only patients regarding the primary endpoint of death, MI, or stroke (16.6% versus 22.5%, p=0.32, respectively, Table 3 and Figure 1A) or the composite endpoint of death, MI, stroke or IDR (21.5% versus 32.6%, p=0.11, respectively, Table 3 and Figure 1B). The 5-year rates of IDR of the LM complex and any MI were also similar between groups. In multivariable analysis, the presence of trifurcation versus bifurcation only disease was not identified as a predictor of the composite primary endpoint but was a significantly negative predictor of death, MI, stroke or IDR at 5 years compared with bifurcation only disease (Table 4). Definite or probable stent thrombosis through 5 years occurred in 1.7% and 2.3% of trifurcation and bifurcation only patients, respectively (p=0.76). Adherence to dual antiplatelet therapy at 5 years was 45.8% among trifurcation patients and 57.1% in bifurcation only patients (p=0.13).



## DISCUSSION

Limited evidence exists to inform procedural methods and clinical outcomes using contemporary techniques and drug-eluting stents for patients with LM trifurcation disease. Among patients with distal LM disease randomized to PCI in the EXCEL trial, trifurcation involvement was identified in ~10% of cases. Despite greater lesion complexity associated with trifurcation anatomy, procedural and early clinical outcomes were similar to those undergoing PCI of the distal LM bifurcation only. Through 5 years, event-free survival also did not

significantly differ between trifurcation and bifurcation only groups, with late-term repeat revascularization rates among trifurcation patients representing a considerable improvement compared with historical studies. More specifically, over 5-year follow-up, rates of both all-cause and cardiovascular death in addition to the cumulative incidence of LM complex IDR and MI were similar to those treated for distal LM bifurcation only disease. In multivariable analysis, the presence of LM trifurcation disease compared with distal bifurcation only disease was associated with a significantly lower incidence of death, MI, stroke or IDR. Altogether, these findings support PCI as a treatment strategy for selected patients with distal LM trifurcation disease.

LM trifurcation anatomy introduces unique technical and procedural challenges beyond bifurcation disease alone given variability in disease distribution (1 to 4 diseased segments), side branch angulation, and implications of carinal shift. In the present study, >70% of patients had significant disease involving ≥3 segments of the trifurcation, and the additive contribution of trifurcation disease to anatomic complexity is reflected by a similar overall SYNTAX score to patients with distal bifurcation disease despite a lower incidence of multivessel disease among trifurcation patients. As a result of the differential plaque burden in trifurcation disease, stent number and performance of 2-step kissing balloon inflation or triple kissing inflation is variable. However, consistent with contemporary bifurcation strategies that favor a provisional single stent approach[8-10], the average number of stents to treat the LM complex was similar among the trifurcation and bifurcation only groups, demonstrating operator intent to avoid multiple stents if possible.

Previous studies examining outcomes following LM trifurcation PCI have reported rates of major adverse events ranging from 19% to 34% over a follow-up period of approximately 1 to

5 years (Supplemental Table 1)[3-6,14,15]. In most prior studies first-generation drug-eluting stents were predominantly used, and the composite endpoint was principally driven by repeat revascularization that occurred in 19% to 32% of patients. In selected studies, the likelihood for repeat revascularization escalated with increasing trifurcation disease complexity and number of stents used[5,6]. In comparison, the 11.9% rate of LM repeat revascularization over 5 years is not only similar to the observed rate for bifurcation only disease, but it also represents a considerable improvement by indirect comparison with historical reports. It is likely that the use of contemporary thin-strut everolimus-eluting stents contributed to these favorable outcomes, although greater application of the provisional strategy and other unmeasured variables may also be related. Surprisingly, use of intravascular ultrasound was less common among trifurcation cases, an unexpected observation given the potential for multiple overlapping stent segments and increased likelihood for comprised luminal dimensions secondary to carinal shift[11]. Even better outcomes may have been achieved had intravascular ultrasound guidance been used more frequently[12,13].

**Study Limitations.** The EXCEL trial has many strengths, including its large size and international representation, use of contemporary devices and techniques, complete patient monitoring, and utilization of independent angiographic core laboratories and clinical event committees to rigorously assess outcomes. Nonetheless (and consistent with prior reports), the modest-sized cohort of LM trifurcation patients limits definite conclusions related to low frequency events. Whether the absence of difference in outcome between trifurcation and bifurcation groups was influenced by a significantly higher incidence of three vessel disease and trend toward higher residual SYNTAX score in the bifurcation cohort is undetermined. Indeed, in multivariable analysis, trifurcation disease was associated with significantly lower composite

outcome of death, MI, stroke or IDR despite similar rates of LM-specific IDR between cohorts. In addition, the present analysis was performed principally from the operator's perspective to be relevant to catheterization laboratory decisions, and treatment strategy and procedural methods were exclusively investigator determined. The potential influence of selected procedural methods that were not recorded in the database (e.g. stent technique [culotte, double kiss crush, T-stent] or use of proximal optimization technique) cannot be determined. Similarly, patients with site-reported LM trifurcation disease were included in this report and therefore subject to limitations of angiographic interpretation of complex distal left main anatomy. Further, despite multivariable analysis, differences in outcomes may have been influenced by unmeasured confounders not collected in the case report form. Finally, the EXCEL trial restricted enrollment to selected patients with LM disease and a SYNTAX score ≤32. In addition, the trifurcation lesions enrolled in EXCEL were carefully selected as those which the operators estimated a high likelihood of procedural success. The present results may therefore not be applicable to patients with high SYNTAX scores and highly complex LM trifurcations not represented in this trial.



## CONCLUSIONS

In summary, in the EXCEL trial, despite the inherent complexity of PCI in distal LM lesions with trifurcation involvement, the PCI procedural technique (including the number of stents used) was similar to treatment of bifurcation only disease. Event rates including cardiac death, IDR, stent thrombosis and the primary composite endpoint of death, MI, or stroke were similar in patients with trifurcation and bifurcation only disease of the distal LM at 30-day and 5-year follow-up. These findings support PCI as an acceptable treatment strategy for selected patients with distal LM trifurcation disease.

## CONFLICT OF INTEREST STATEMENT

David Kandzari: grants and personal fees from Biotronik, Medtronic, and Boston Scientific. Patrick Serruys: personal fees from Abbott Laboratories, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Philips/Volcano, St Jude Medical, Qualimed, and Xeltis, Martin Leon: grants and personal fees from Medtronic, Boston Scientific, Abbott, personal fees from Gore Medical, Meril Lifescience, grants from Edwards Lifesciences. Charles Simonton: employee of Abbott. Nicholas Lembo: personal fees from Abbott Vascular, non-financial support from Boston Scientific, Medtronic Vascular, and Abiomed. Samer Mansour: grants and personal fees from Abbott Vascular. Manel Sabaté; grants from Abbott Vascular. Joseph Sabik: personal fees from Medtronic, grants from Edwards and Abbott. Arie Pieter Kappetein: employee of Medtronic. Gregg Stone: grants from Abbott, personal fees from Terumo, Amaranth, Shockwave, Valfix, TherOx, Reva, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Matrizyme, Miracor, Neovasc, V-wave, Abiomed, Claret, Sirtex, SpectraWaveAncora, Qool Therapeutics, MAIA Pharmaceuticals, Orchestra Biomed, and Novartis; equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, MedFocus family of funds, SpectraWave, Orchestra Biomed, and Aria.

## IMPACT ON DAILY PRACTICE

Despite greater lesion complexity associated with trifurcation anatomy, early and late clinical outcomes following PCI with everolimus-eluting stents were similar compared with those undergoing PCI of distal LM bifurcation disease without trifurcations. These findings support PCI as an acceptable treatment strategy for selected patients with distal LM trifurcation disease.

## REFERENCES


1. Gershlick AH, Kandzari DE, Banning A, Taggart DP, Morice MC, Lembo NJ, Brown WM 3rd, Banning AP, Merkely B, Horkay F, van Boven AJ, Boonstra PW, Dressler O, Sabik JF 3rd, Serruys PW, Kappetein AP, Stone GW. Outcomes after left main percutaneous coronary intervention versus coronary artery bypass grafting according to lesion site: results from the EXCEL Trial. *JACC Cardiovasc Interv.* 2018;11:1224-33.
2. Naganuma T, Chieffo A, Meliga E, Capodanno D, Park SJ, Onuma Y, Valgimigli M, Jegere S, Makkar RR, Palacios IF, Costopoulos C, Kim YH, Buszman PP, Chakravarty T, Sheiban I, Mehran R, Naber C, Margey R, Agnihotri A, Marra S, Capranzano P, Leon MB, Moses JW, Fajadet J, Lefevre T, Morice MC, Erglis A, Tamburino C, Alfieri O, Serruys PW, Colombo A. Long-term clinical outcomes after percutaneous coronary intervention for ostial/mid-shaft lesions versus distal bifurcation lesions in unprotected left main coronary artery: the DELTA Registry (drug-eluting stent for left main coronary artery disease): a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv.* 2013;6:1242-49.
3. Tamburino C, Tomasello SD, Capodanno D, Di Salvo ME, Marzà F, Ruggero Galassi A. Long-term follow-up after drug-eluting stent implantation in left main trifurcations. *EuroIntervention.* 2009;5:432-7.
4. Shammas NW, Shammas GA, Jerin M, Parikh A, Coin K, Dippel E, Sharis P, Robken J. Treatment of left main coronary trifurcation lesions with the paclitaxel drug-eluting stent: Mid-term outcomes from a tertiary medical center. *J Invasive Cardiol.* 2009;21:321–5.

5. Sheiban I, Gerasimou A, Bollati M, Biondi-Zoccai G, Sciuto F, Omedé P, Sillano D, Trevi GP, Moretti C. Early and long-term results of percutaneous coronary intervention for unprotected left main trifurcation disease. *Catheter Cardiovasc Interv.* 2009;73:25-31.
6. Ielasi A, Takagi K, Latib A, Basavarajaiah S, Figini F, Carlino M, Montorfano M, Chieffo A, Nakamura S, Colombo A. Long-term clinical outcomes following drug-eluting stent implantation for unprotected distal trifurcation left main disease: the Milan-New Tokyo (MITO) Registry. *Catheter Cardiovasc Interv.* 2014;83:530-8.
7. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med.* 2016;375:2223–35.
8. Palmerini T, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Santarelli A, Bartorelli A, Briguori C, Vignali L, Di Pede F, Ramondo A, Inglese L, De Carlo M, Falsini G, Benassi A, Palmieri C, Filippone V, Sangiorgi D, Barlocco F, De Servi S. Impact of bifurcation technique on 2-year clinical outcomes in 773 patients with distal unprotected left main coronary artery stenosis treated with drug- eluting stents. *Circ Cardiovasc Interv.* 2008;1:185–92.
9. Song YB, Hahn JY, Yang JH, Choi SH, Choi JH, Lee SH, Jeong MH, Kim HS, Lee JH, Yu CW, Rha SW, Jang Y, Yoon JH, Tahk SJ, Seung KB, Oh JH, Park JS, Gwon HC. Differential prognostic impact of treatment strategy among patients with left main versus

non–left main bifurcation lesions undergoing percutaneous coronary intervention: results from the COBIS (Coronary Bifurcation Stenting) Registry II. *JACC Cardiovasc Interv.* 2014;7:255–63.

10. Kandzari DE, Gershlick AH, Serruys PW, Leon MB, Morice MC, Simonton CA, Lembo NJ, Banning AP, Merkely B, van Boven AJ, Ungi I, Kappetein AP, Sabik JF 3rd, Généreux P, Dressler O, Stone GW. Outcomes among patients undergoing distal left main percutaneous coronary intervention: technique analysis from the EXCEL trial. *Circ Cardiovasc Interv.* 2018;11: e007007.
11. Kang SJ, Mintz GS, Kim WJ, Lee JY, Oh JH, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Changes in left main bifurcation geometry after a single-stent crossover technique: an intravascular ultrasound study using direct imaging of both the left anterior descending and the left circumflex coronary arteries before and after intervention. *Circ Cardiovasc Interv.* 2011;4:355-61.
12. de la Torre Hernandez JM, Baz Alonso JA, Gómez Hospital JA, Alfonso Manterola F, Garcia Camarero T, Gimeno de Carlos F, Roura Ferrer G, Recalde AS, Martínez-Luengas IL, Gomez Lara J, Hernandez Hernandez F, Pérez-Vizcayno MJ, Cequier Fillat A, Perez de Prado A, Gonzalez-Trevilla AA, Jimenez Navarro MF, Mauri Ferre J, Fernandez Diaz JA, Pinar Bermudez E, Zueco Gil J; IVUS-TRONCO-ICP Spanish study. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. *JACC Cardiovasc Interv.* 2014;7:244-54.
13. Andell P, Karlsson S, Mohammad MA, Götberg M, James S, Jensen J, Fröbert O, Angerås O, Nilsson J, Omerovic E, Lagerqvist B, Persson J, Koul S, Erlinge D.

Intravascular ultrasound guidance is associated with better outcome in patients undergoing unprotected left main coronary artery stenting compared with angiography guidance alone. *Circ Cardiovasc Interv.* 2017;10:e004813.

14. Kubo S, Kadota K, Sabbah M, Otsuru S, Hasegawa D, Habara S, Tada T, Tanaka H, Fuku Y, Katoh H, Goto T, Mitsudo K. Clinical and angiographic outcomes after drug-eluting stent implantation with triple-kissing-balloon technique for left main trifurcation lesion: comparison of single-stent and multi-stent procedures. *J Invasive Cardiol.* 2014;26:571-8.
15. Gil RJ, Bil J, Kern AK, Garcia LAI, Formuszewicz R, Dobrzycki S. Five-year clinical outcomes following drug-eluting stent implantation in left main trifurcations. *Postepy Kardiol Interwencyjnej.* 2019;15:116-9.

## FIGURE LEGEND

**Figure 1. Five-Year Outcomes Following Percutaneous Coronary Intervention for Patients with Distal Left Main Trifurcation Disease Versus Bifurcation Only Disease**

(A) The composite rate of death, myocardial infarction (MI), or stroke; (B) composite rate of death, MI, stroke, or ischemia-driven repeat revascularization. CI=confidence interval; HR=hazard ratio.

**Table 1. Baseline Clinical and Angiographic Characteristics Among Patients with Distal Left Main Trifurcation and Bifurcation Disease**

| | Trifurcation (n=61) | Bifurcation (n=544) | p Value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age, years | 65.2±9.5 | 66.2±9.1 | 0.37 |
| Male sex | 50 (82.0) | 429 (78.9) | 0.57 |
| Diabetes mellitus | 13 (21.3) | 162 (29.8) | 0.17 |
| Smoking history | 33 (54.1) | 350 (64.7) | 0.10 |
| Hypertension | 46 (75.4) | 414 (76.1) | 0.90 |
| Hyperlipidemia | 39 (63.9) | 390 (71.8) | 0.20 |
| Prior myocardial infarction | 5 (8.3) | 98 (18.2) | 0.054 |
| Prior percutaneous coronary intervention | 6 (9.8) | 112 (20.7) | 0.04 |
| Prior stroke or transient ischemic attack | 1 (1.6) | 28 (5.2) | 0.35 |
| Left ventricular ejection fraction, % | 59.7±7.7 | 56.8±9.9 | 0.02 |
| Clinical presentation | | | |
| Stable angina | 40 (65.6) | 289 (53.4) | 0.07 |
| Unstable angina | 11 (18.0) | 126 (23.3) | 0.35 |
| Recent myocardial infarction* | 5 (8.2) | 85 (15.7) | 0.12 |
| Angiographic characteristics | | | |
| SYNTAX score, site-assessed | 23.3±6.0 | 21.4±6.1 | 0.02 |
| 0-22 (low) | 23 (38.3) | 299 (55.0) | 0.01 |
| 23-32 (intermediate) | 37 (61.7) | 245 (45.0) | 0.01 |
| SYNTAX score, angiographic core laboratory-assessed | 28.4±7.0 | 28.5±8.8 | 0.92 |
| 0-22 (low) | 13 (22.0) | 136 (25.5) | 0.56 |
| 23-32 (intermediate) | 32 (54.2) | 234 (43.8) | 0.13 |
| ≥33 (high) | 14 (23.7) | 164 (30.7) | 0.27 |
| LM disease only† | 19 (31.1) | 85 (15.7) | 0.002 |
| LM and 1-vessel disease† | 21 (34.4) | 151 (27.8) | 0.28 |
| LM and 2-vessel disease† | 16 (26.2) | 194 (35.7) | 0.14 |
| LM and 3-vessel disease† | 5 (8.2) | 107 (19.7) | 0.03 |
| LM ostial stenosis ≥50%† | 8 (13.1) | 99 (18.7) | 0.28 |
| Ostial anterior descending artery ≥50%† | 43 (70.5) | 286 (52.7) | 0.008 |
| Ostial left circumflex artery ≥50%† | 37 (60.7) | 251 (46.2) | 0.03 |
| Trifurcation segments† | | | |
| 1 segment involved | 7 (12.7) | — | — |
| 2 segments involved | 14 (25.5) | — | — |
| 3 segments involved | 15 (27.3) | — | — |
| 4 segments involved | 19 (34.5) | — | — |

Values are n/N (%) or mean±standard deviation. *Within 7 days prior to randomization; †angiographic core laboratory measurement. LM=left main coronary artery.

**Table 2. Procedural Characteristics Among Patients with Distal Left Main Trifurcation and Bifurcation Disease**

| | Trifurcation (n=61) | Bifurcation (n=544) | p Value |
|---|---|---|---|
| Maximum LM device diameter, mm | 4.12±0.52 | 4.01±0.51 | 0.11 |
| Guiding catheter size | | | |
| 6 Fr | 15 (24.6) | 246 (45.2) | 0.002 |
| 7 Fr | 27 (44.3) | 213 (39.2) | 0.44 |
| 8 Fr | 19 (31.1) | 85 (15.6) | 0.002 |
| Radial artery access | 14 (21.5) | 179 (29.7) | 0.17 |
| Intravascular ultrasound used | 37 (60.7) | 416 (76.5) | 0.007 |
| Fractional flow reserve used | 5 (8.2) | 44 (8.1) | 1.0 |
| Rotational atherectomy performed | 2 (3.3) | 40 (7.4) | 0.30 |
| Hemodynamic support used | 3 (4.6) | 33 (5.5) | 1.0 |
| Unfractionated heparin used | 49 (76.6) | 473 (79.4) | 0.60 |
| Bivalirudin used | 22 (34.4) | 191 (32.0) | 0.71 |
| Glycoprotein IIb/IIIa inhibitor used | 4 (6.2) | 47 (7.8) | 0.81 |
| Contrast volume, mL | 275 ± 140 | 256 ± 129 | 0.51 |
| Fluoroscopy time, minutes | 28 ± 22 | 25 ± 16 | 0.61 |
| Staged procedure planned | 4 (6.2) | 60 (10.3) | 0.32 |
| Procedural complications* | 6 (9.2) | 67 (11.1) | 0.64 |
| Number of stents in the LM complex | 1.7±0.8 | 1.6±0.7 | 0.46 |
| None | 1 (1.6) | 3 (0.6) | |
| 1 | 30 (49.2) | 290 (53.3) | |
| 2 | 20 (32.8) | 199 (36.6) | |
| ≥3 | 10 (16.4) | 52 (9.6) | |
| Post-stent dilation | 57 (93.3) | 497 (91.3) | 0.59 |
| Residual SYNTAX Score | 5.2±5.6 | 6.9±6.6 | 0.06 |

Values are n/N (%) or mean±standard deviation. *Defined as chest pain or electrocardiogram changes lasting >10 min, slow flow, no reflow, distal embolization, abrupt closure, perforation, dissection, stent thrombosis, tamponade, cardiac arrest, stroke, bleeding, or severe arrhythmias. LM=left main coronary artery.

**Table 3. Thirty-Day and 5-Year Clinical Outcomes According to Distal Left Main Trifurcation or Bifurcation Disease**

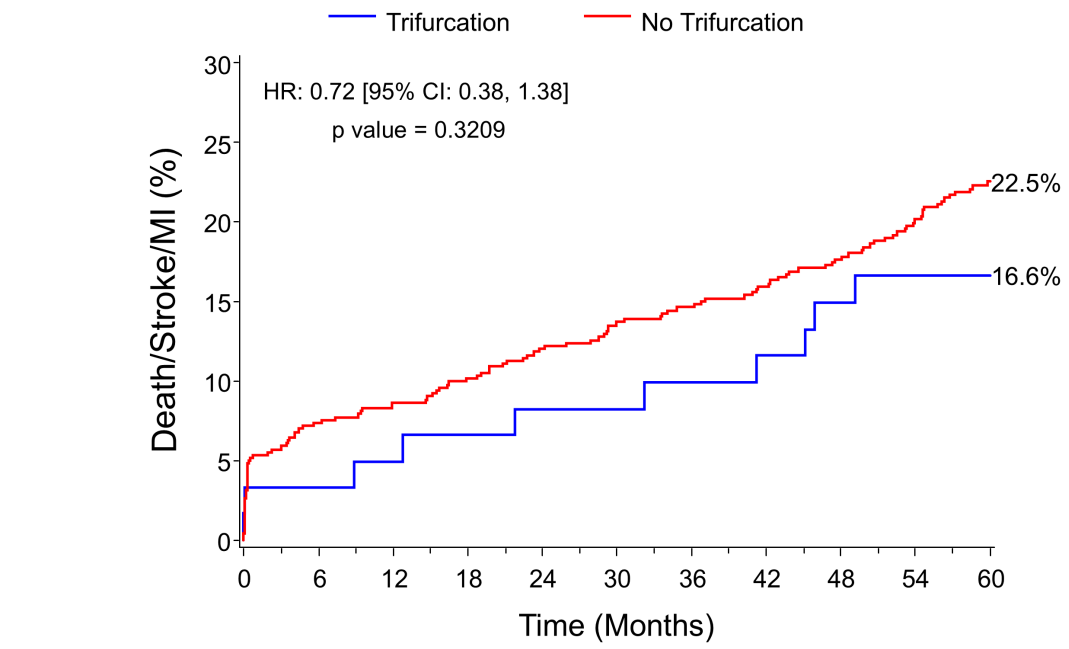
| | Trifurcation (n=61) | Bifurcation (n=544) | p Value | Odds Ratio (95% CI) |
|---|---|---|---|---|
| 30-Day events | | | | |
| Death | 0 | 1.5% (8) | 0.97 | — |
| Cardiovascular | 0 | 1.5% (8) | 0.97 | — |
| Myocardial infarction | 1.6% (1) | 4.2% (23) | 0.34 | 0.37 (0.05-2.82) |
| Stroke | 1.6% (1) | 0.6% (3) | 0.35 | 2.98 (0.31-29.15) |
| Any IDR | 0 | 0.9% (5) | 0.98 | — |
| LM complex* IDR | 0 | 0.7% (4) | 0.98 | — |
| Any definite or probable ST | 0 (0) | 1.1% (6) | 0.98 | — |
| LM definite or probable ST | 0 (0) | 1.1% (6) | 0.98 | — |
| Death, myocardial infarction, or stroke | 3.3% (2) | 5.3% (29) | 0.49 | 0.60 (0.14-2.56) |
| Death, myocardial infarction, stroke, or IDR | 3.3% (2) | 5.3% (29) | 0.49 | 0.60 (0.14-2.56) |
| 5-year events | | | | |
| Death | 11.9% (7) | 12.9% (68) | 0.80 | 0.90 (0.39-2.06) |
| Cardiovascular | 7.3% (4) | 6.9% (36) | 0.97 | 0.98 (0.34-2.86) |
| Myocardial infarction | 7.0% (3) | 10.6% (41) | 0.37 | 0.62 (0.22-1.77) |
| Stroke | 1.6% (1) | 2.7% (14) | 0.65 | 0.63 (0.08-4.84) |
| Any IDR | 13.5% (8) | 17.3% (89) | 0.49 | 0.76 (0.35-1.66) |
| LM complex* IDR | 11.9% (7) | 12.0% (62) | 0.99 | 1.00 (0.43-2.29) |
| Any definite or probable ST | 1.7% (1) | 2.3% (12) | 0.77 | 0.73 (0.09-5.74) |
| LM complex definite or probable ST | 1.7% (1) | 2.1% (11) | 0.83 | 1.26 (0.16-9.93) |
| Death, myocardial infarction, or stroke | 16.6% (6) | 22.5% (120) | 0.29 | 0.68 (0.33-1.38) |
| Death, myocardial infarction, stroke, or IDR | 21.5% (13) | 32.6% (174) | 0.08 | 0.56 (0.30-1.07) |

Values are Kaplan-Meier estimated rates % (n events). *Consists of the distal LM, the ostial left anterior descending artery, ostial left circumflex coronary artery and [in trifurcation disease] ostial ramus artery. CI=confidence interval; IDR=ischemia-driven revascularization; LM=left main coronary artery; ST=stent thrombosis.

**Table 4. Multivariable Correlates of the 5-Year Composite Outcomes**

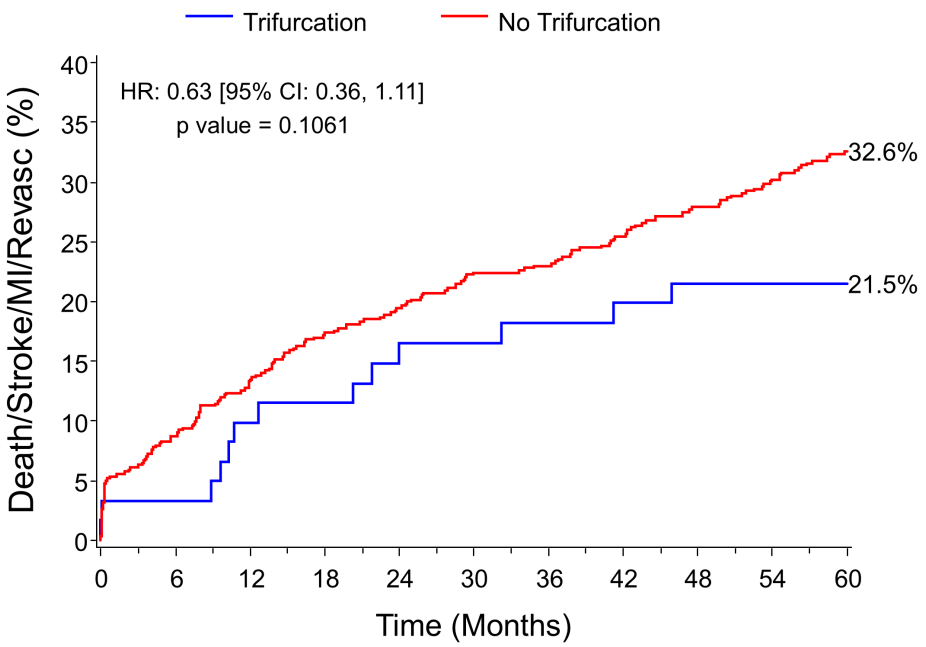
| Endpoint/Variable | Adjusted Hazard Ratio [95% Confidence Interval] | p Value |
|---|---|---|
| Death, myocardial infarction, or stroke | | |
| Trifurcation versus bifurcation only | 0.56 (0.25–1.27) | 0.17 |
| Age (per year) | 1.06 (1.03–1.10) | 0.0001 |
| LVEF (percent) | 0.96 (0.94–0.99) | 0.001 |
| Death, myocardial infarction, stroke, or IDR | | |
| Trifurcation versus bifurcation only | 0.46 (0.23–0.95) | 0.04 |
| Age (per year) | 1.04 (1.02–1.07) | 0.002 |
| Ostial LCX >50% stenosis | 1.01 (1.00–1.01) | 0.03 |
| LVEF (percent) | 0.97 (0.95–0.99) | 0.002 |
| Recent MI (<7 days) | 0.52 (0.29-0.93) | 0.03 |
| Baseline TIMI flow <3 in LCX or LAD | 0.51 (0.29–0.88) | 0.02 |

IDR=ischemia-driven revascularization; LAD=left anterior descending artery; LCX=left circumflex artery; LVEF=left ventricular ejection fraction; MI=myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.




*Number at risk:*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trifurcation | 61 | 59 | 58 | 56 | 55 | 55 | 54 | 53 | 50 | 47 | 35 |
| No Trifurcation | 544 | 503 | 494 | 483 | 471 | 461 | 454 | 445 | 434 | 415 | 274 |




*Number at risk:*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trifurcation | 61 | 59 | 55 | 53 | 50 | 50 | 49 | 48 | 46 | 44 | 32 |
| No Trifurcation | 544 | 496 | 469 | 445 | 431 | 414 | 409 | 394 | 379 | 361 | 241 |

**Supplemental Table 1. Left Main Trifurcation PCI Studies**

| Study | Year | N | Follow-up Duration | Cardiac Death | Myocardial Infarction | Left Main Target Lesion Revascularization |
|---|---|---|---|---|---|---|
| Shammas et al.[4] | 2009 | 52 | Mean 9.8 months | 2.1 | 15.4 | 31.9 |
| Tamburino et al.[3] | 2009 | 11 | Mean 32 months | 0 | 9.1 | 27.0 |
| Sheiban et al.[5] | 2009 | 27 | Mean 28 months | 15.0 | 4.0 | 19.0 |
| Ielasi et al.[6] | 2014 | 84 | Median 47 months | 1.2 | 7.1 | 24.1 |
| Kubo et al.[14] | 2014 | 72 | 3 years | 8.9* | 0 | 14.5 |
| Gil et al.[15] | 2019 | 67 | 5 years | 1.5 | 2.9 | 14.9 |
| EXCEL[7] | 2019 | 61 | 3 years | 0 | 5.1 | 10.1 |

Data expressed as percent. *Indicates all-cause mortality.