Impact of Left Ventricular Ejection Fraction on Procedural and Long-Term Outcomes of Bifurcation Percutaneous Coronary Intervention

IMPACT OF LEFT VENTRICULAR EJECTION FRACTION ON PROCEDURAL AND LONG TERM OUTCOMES OF BIFURCATION PERCUTANEOUS CORONARY INTERVENTION

Running title: **Impact of LV function on bifurcation PCI.**

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G.G., F.B., F.D.A., OD.F., B.K.K. and G.M.D.F. were involved in the conception and design of the study. G.G., M.D. and F.D.A performed the analysis and drafted the manuscript. All the authors contributed to the interpretation of data, critically revised the manuscript, approved it in its current form and are accountable for all aspects of the work.

ABSTRACT

Background

The association of left ventricular ejection fraction (LVEF) with procedural and long-term outcomes following state-of-the-art percutaneous coronary intervention (PCI) of bifurcation lesions remains unsettled.

Methods

5333 patients undergoing contemporary coronary bifurcation PCI were included in the intercontinental retrospective BIFURCAT (comBined Insights From the Unified RAIN and COBIS bifurcAtion regisTries) registry. Of 5003 (93.8%) patients with known baseline LVEF, 244 (4.9%) had LVEF <40% (BIFrEF group), 430 (8.6%) had LVEF 40%-49% (BIFmEF group) and 4329 (86.5%) had EF ≥50% (BIFpEF group). The primary endpoint was the Kaplan-Meier estimate of major adverse cardiac events (MACE, a composite of all-cause death, myocardial infarction and target vessel revascularization).

Results

Patients with BIFrEF had more complex clinical profile and coronary anatomy. No difference in procedural (30-day) MACE was observed across EF categories, also after adjustment for in-study outcome predictors (BIFrEF vs. BIFmEF: adj-HR=1.39, 95%CI 0.37-5.21, p=0.626; BIFrEF vs. BIFpEF: adj-HR=1.11, 95%CI 0.25-2.87, p=0.883; BIFmEF vs. BIFpEF: adj-HR=0.81, 95%CI 0.29-2.27, p=0.683). BIFrEF was independently associated with long-term MACE (median follow-up 21 months, interquartile range 10-21 months) as compared to both BIFmEF (adj-HR=2.20, 95%CI 1.41–3.41; p<0.001) and BIFpEF (adj-HR=1.91, 95%CI 1.41–2.60; p<0.001) groups, while no difference was observed between BIFmEF and BIFpEF groups (adj-HR=0.87, 95%CI 0.61–1.24; p=0.449).

Conclusions

Among patients undergoing PCI of a coronary bifurcation lesion according to contemporary clinical practice, reduced LVEF (<40%), while a strong predictor of long-term major adverse cardiovascular events, does not affect procedural outcomes.

KEY WORDS

Ejection fraction, bifurcation, percutaneous coronary intervention, clinical outcomes.

ABBREVIATIONS

ACS: acute coronary syndrome
CI: confidence interval
EF: ejection fraction
HR: hazard ratio
LV: left ventricle
MACE: major adverse cardiovascular events
MI: myocardial infarction
PCI: percutaneous coronary intervention
ST: stent thrombosis
TVR: target vessel revascularization

INTRODUCTION

The evolution of stent technologies and implantation techniques translated into improved clinical outcomes following percutaneous coronary intervention (PCI), also in complex anatomical and procedural settings as coronary bifurcation lesions(1–5). However, considerable risk of adverse events is still reported in real-life contemporary registries(6, 7), warranting careful consideration of risk-benefit trade-off when bifurcation PCI is considered.

Between 10 and 30% of patients undergoing clinically indicated PCI have left ventricular (LV) dysfunction(8). These patients are at higher absolute risk of long-term adverse events and may most benefit from revascularization, which is associated with improved pump function and long-term clinical benefit(9, 10). On the other side, they have reduced physiological reserve, with limited tolerance to hemodynamic stressors and ischemic complications during PCI, which may be particularly relevant in the setting of bifurcation lesions treatment in reason of the higher procedural complexity and risk.

Despite the potentially important clinical trade-off, no adequate clinical data is to date available to inform the choice of PCI among patients with a bifurcation lesion and LV dysfunction. Indeed, subjects with LV dysfunction were either excluded or strongly underrepresented among trials of bifurcation PCI strategies(11–15), and available real-world bifurcation PCI registries are mostly of modest sample size.

Moreover, despite older studies supported the adverse impact of LV dysfunction on early PCI outcomes(16, 17), this is inconsistent with more recent evidence(18), pointing at the potential modifying effect of PCI evolution on this relationship in contemporary practice(19).

The aim of this study is to describe the impact of LV dysfunction on procedural and long-term outcomes of bifurcation PCI in the BIFURCAT (comBined Insights From the

Unified RAIN and COBIS bifurcAtion regisTries) registry, which represents the largest available real-world experience of bifurcation PCI in contemporary clinical practice.

METHODS

Study design

The BIFURCAT registry is an intercontinental retrospective observational project deriving from the pre-specified merging of two real-world cohorts of patients undergoing clinically indicated PCI on a coronary bifurcation lesion: the COBIS III (Coronary Bifurcation Stenting Registry III, NCT01642992) and the RAIN (veRy Thin Stents for Patients With Left mAIn or bifurcatioN in Real Life, NCT03544294) registries.

COBIS III is a Korean multicenter retrospective registry, enrolling consecutive patients with coronary bifurcation lesions treated with a drug-eluting stent from January 2010 to December 2014.

RAIN is a Eurasian multicenter retrospective registry, enrolling consecutive patients with coronary bifurcation lesions or unprotected left main lesions treated with very-thin strut drug-eluting stent from June 2015 to December 2017. Detailed inclusion and exclusion criteria for both registries are reported in the supplementary appendix.

Out of 2648 and 2889 patients included in the COBIS III and RAIN registries, respectively, 5333 patients treated on a bifurcation lesion were finally included in the BIFURCAT registry. Data merging was conducted according to a prespecified data form, all variables were ultimately checked by 2 investigators from each group (JK, FDA; BKK, ODF) to assure accuracy and reproducibility of the data.

Of 5333 patients included in the BIFURCAT registry, pre-PCI LV ejection fraction (LVEF) was available for 5003 (93.8%), who were included in this analysis. In 674 (13.5%) patients, LVEF was <50%. These patients were categorized according to LVEF ranges

adopted from the heart failure terminology as follow: “bifurcation PCI with reduced ejection fraction (BIFrEF; LVEF<40%)”, “bifurcation PCI with mid-range ejection fraction (BIFmEF; LVEF 40-49%)”.

Study endpoints

The primary endpoint was major adverse cardiac events (MACE), a composite and mutual exclusive endpoint of all-cause death, myocardial infarction (MI) and target vessel revascularization (TVR). Secondary endpoints were the single components of MACE along with stent thrombosis (ST).

Study outcomes are presented as Kaplan-Meier estimates assessed at short-term (30-day, procedural outcomes) and long-term (max. follow-up censor 800-day) follow-up.

Statistical analysis

Categorical variables were reported as count and percentages, continuous variables as mean and standard deviations, or median and interquartile range (IQR). The presence of normal distribution was verified by Kolmogorov-Smirnoff test. The t-test was used to assess differences between parametric continuous variables, Man-Whitney U-test for non parametric variables and the chi-square test for categorical variables.

Kaplan-Meier and Cox proportional hazard models were performed to evaluate cumulative event rates of the study endpoints and results are presented as hazard ratio (HR) and 95% confidence intervals (CIs). To produce meaningful outcome estimates according to the observed number of patients at risk in the registry, maximum follow-up length was truncated at 800 days corresponding to the 75° percentile value of available follow-up length in the study population.

To assess the independent association of LVEF groups with MACE both multivariate

Cox proportional hazards analysis and propensity score matching were performed.

The multivariate Cox proportional model was constructed with all the variables associated with the long-term primary endpoint with a univariate p <0.10.

For the purpose of propensity score matching 28 clinical, anatomical and procedural covariates were considered (full list in the **Supplementary Appendix**). The PS matching was performed with the nearest neighbor method with a 1:1 ratio and a caliper width of 0.1. The covariate balance after PS matching was assessed by calculating the absolute standardized mean difference.

A p <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS (version 24.0, SPSS Inc., Chicago, Illinois, US).

RESULTS

Baseline characteristics

Baseline characteristics of the study population stratified as BIFrEF (n=244), BIFmEF (n=430) and bifurcation PCI with preserved LVEF (BIFpEF, n=4329) are presented in **Table 1**. Overall, a graded increase in age, in the burden of cardiovascular risk factors, prior coronary events and comorbidities was observed from the BIFpEF to the BIFrEF groups. Patients with BIFrEF and BIFmEF more frequently presented with either non-ST-elevation acute coronary syndrome or ST-elevation MI, and with a left main coronary bifurcation as compared to BIFpEF patients. True bifurcations were similarly represented among groups. Femoral access was more frequently undertaken among patients with BIFrEF and BIFmEF. Two-stent techniques were similarly adopted among groups.

Outcomes

Survival curves for the study outcomes stratified by LVEF categories are presented in **Figure 1**. The Kaplan Meier estimates for procedural (30-day) MACE were similar across LVEF categories (BIFrEF vs. BIFmEF vs. BIFpEF: 4.7% vs. 0.9%. vs 1.1%, p= ns for all paired comparisons). Similarly, no difference in the 30-day estimated rate for any of the secondary endpoints was observed, a part for ST which was more common among BIFrEF patients as compared to BIFpEF patients (1.3 % vs 0.2% vs 0.3%, p for BIFrEF vs BIFpEF=0.035, p=ns for other paired comparisons).

Long-term (median follow-up 21 months, interquartile range 10-21 months) MACE estimate was significantly higher among patients with BIFrEF (26.7%) as compared to patients with BIFmEF (8.9%) and BIFpEF (11.5%) (p for both comparisons <0.001), while no difference in MACE between BIFmEF and BIFpEF was observed (p=0.683). Results were similar for all-cause mortality (16.9% vs 5.3% vs 4.8%, p for BIFrEF vs BIFmEF/BIFpEF both <0.001, p for BIFmEF vs BIFpEF=0.532) and for ST (3.9% vs 1.3% vs 1.1%, BIFrEF vs BIFmEF: p=0.026, BIFrEF vs BIFpEF: p=0.003; BIFmEF vs BIFpEF: p=0.664). TVR was more frequent in patients with BIFrEF vs BIFmEF (9.4% vs 3.6%, p=0.006) and in patients with BIFpEF vs BIFmEF (7.9% vs 3.6%, p=0.012). No difference in MI occurrence among LVEF categories was observed.

After adjusting for in-study outcome predictors (**Table 2**), BIFrEF remained significantly associated with long-term MACE as compared to both BIFmEF (adj-HR=2.20, 95%CI 1.41–3.41; p<0.001) and BIFpEF (adj-HR=1.91, 95%CI 1.41–2.60; p<0.001) patients, while no difference was observed between BIFmEF and BIFpEF categories (adj-HR=0.87, 95%CI 0.61–1.24; p=0.449). Similar results were observed for long-term all-cause mortality (BIFrEF vs BIFmEF: HR=1.88, 95%CI 1.07 – 3.33; p=0.029; BIFrEF vs BIFpEF: HR=2.00, 95%CI 1.32 - 3.01; p<0.001; BIFmEF vs BIFpEF: HR=1.05, 95%CI 0.65 – 1.69; p=0.848). No difference in the adjusted risk of the procedural primary and

secondary endpoints was observed among groups. Unadjusted and adjusted HR for all study endpoints at 30-day and long-term follow-up are presented in **Table 3**. Results were similar in the propensity matching analysis (**Supplementary Table 1**). Results were consistent irrespective of clinical features (diabetes, chronic kidney disease history, clinical presentation), of coronary anatomy (lesion site, true bifurcation, severely calcificied lesions, diffusely diseased coronary tree) and of stenting technique (**Figure 2**).

DISCUSSION

The present study aims to describe the impact of LVEF on procedural and long-term outcomes of coronary bifurcation PCI in a large intercontinental population of unselected patients treated according to contemporary clinical practice. The main finding of this study is that reduced LVEF (<40%), while a strong predictor of long-term MACE, does not affect procedural outcomes following contemporary bifurcation PCI. This is consistent regardless of the patient's clinical profile, coronary anatomy or PCI procedural features.

Whether LVEF is associated with procedural outcomes following PCI remains a matter of debate. Older studies reported an association between worsening LV systolic function and early mortality and MACE following PCI (16, 17). However, the evolution in stent technologies, invasive imaging, procedural techniques and periprocedural pharmacologic and non-pharmacologic treatments may have strongly modified this relationship. This is supported by the difference in the early post-PCI mortality rates of patients with reduced LVEF reported in older registries ranging from 10% (LVEF <30%)(8) to 3% (LVEF <40%) (16) as opposed to the observed 1.6% early mortality rate in BIFrEF patients in the current analysis, despite the selected bifurcation PCI setting.

Thus, our results fit the evidence of positive temporal trends in PCI outcomes (19)

and further extend these observations by suggesting that modern PCI management is able to blunt the adverse consequences of impaired systolic function, even in a complex PCI setting as the investigated one. Our findings are backed by similar data from the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, in which LVEF <40% (with the limit of comprising only a small group of 43 patients) was not a determinant of procedural outcomes following left main PCI(18).

Because of limited clinical evidence regarding bifurcation PCI in patients with LV dysfunction, a higher threshold to intervene in this subset may be kept by many operators in clinical practice. This is highlighted by the low prevalence (4.9%) of patients with reduced LVEF in the BIFURCAT registry (as opposed to 10-30% in unselected PCI real-world registries) which is a cross-section of contemporary intercontinental real-world practice in bifurcation PCI. Notwithstanding this low prevalence, the current analysis represents the largest evidence-base currently available to inform decision-making regarding bifurcation PCI treatment in patients with reduced LVEF. Specifically, our findings suggest that, with contemporary PCI management, reduced LVEF is not a determinant of procedural outcomes and should not negatively affect the decision to perform bifurcation PCI. This is of paramount clinical relevance, as reduced LVEF patients are likely those with the greatest prognostic benefit from revascularization. In the PROTECT II trial, 51% of the patients with reduced LVEF undergoing high-risk PCI improved their pump function, and improvement in pump function was associated with sustained long-term clinical benefit(9). In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, patients with reduced LVEF (35% to 45%) or heart failure undergoing initial revascularization had reduced cardiovascular death or MI as compared to conservatively treated patients(10).

In keeping with previous studies(8, 18), patients with reduced LVEF had a higher burden of cardiovascular risk factors and comorbidities, along with more complex coronary anatomy and lesional features. These factors all contribute to the adverse long-term prognosis observed in BIFrEF as compared to BIFmEF/BIFpEF patients. However, the persistent association of reduced LVEF with long-term adverse outcomes following adjustment once again suggests the direct detrimental contribution of pump failure to the natural history of ischemic cardiomyopathy(20). LV function keeps to strongly feature as a central prognostic predictor in contemporary risk stratification models of coronary artery disease (21) and reclassifies risk over the coronary anatomy and the clinical profile, with each 10% increase in LVEF being associated with a 44% reduction in 4-year post-PCI mortality(22). Our findings are consistent and circumscribe the validity of this concept to the bifurcation PCI setting. Besides, and similarly to the findings from EXCEL(18), outcomes in BIFmEF patients were similar to those of BIFpEF patients highlighting the inherent physiopatological and clinical differences of BIFmEF from BIFrEF patients and indirectly substantiating current heart failure terminology and classification.

Interestingly, not only patient-oriented, but also device-oriented outcomes at long-term follow-up were more frequently observed among BIFrEF patients as also previously reported(23). Specifically, BIFrEF patients experienced a significant 2.6-fold higher adjusted-risk of TVR as compared to BIFmEF patients and a significant 2.5-fold higher adjusted-risk of ST as compared to BIFpEF patients. The reason underlying this finding is likely multifactorial. BIFrEF patients presented a higher burden of prior MI events along with more frequent acute index presentation pointing at a prothrombotic milieu potentially entailing higher ST predisposition(24). Furthermore, BIFrEF patients presented with more complex coronary anatomy including higher prevalence of calcified lesions which may have in theory affected the procedural results translating into an excess of late

ST or TVR events. Speculatively, the attitude of the operator for a faster procedure in a perceived more fragile patient may have further contributed.

LIMITATIONS

The findings of this study should be interpreted in the light of several limitations. First, the BIFURCAT registry derives from the merging of two retrospective datasets. Accordingly, as an inherent limitation of retrospective data, LVEF was calculated as per clinical practice. While more accurate homogeneous measurements may have carried somewhat more accurate results, this approach is pragmatic and establishes the real value of routinely assessed LVEF. Second, we did not collect important outcome procedural metrics which may have been of relevance to the current analysis including acute kidney injury, bleeding outcomes and length of in-hospital stay. However, the procedural and long-term hard outcomes analyzed somewhat resume the clinical implications of these softer endpoints. Third, we did not explore the prognostic impact of very low EF values (mean EF among BIFrEF patients: 32.9 ± 5.0%): this is inherent to the contemporary clinical practice represented by the present registry and limits our findings to the explored range of EF values. Fourth, the information regarding cardiogenic shock presentation and mechanical circulatory support during PCI was not collected. Fifth, we cannot exclude type II error due to the inherently limited number of BIFrEF patients. However, as already discussed, the current analysis represents the largest outcome study to inform clinical decision-making for BIFrEF patients.

CONCLUSIONS

Among patients undergoing PCI of a coronary bifurcation lesion according to contemporary clinical practice, reduced LVEF (<40%), while a strong predictor of long-term

major adverse cardiovascular events, does not affect procedural outcomes. Patients with reduced LVEF should not be denied bifurcation PCI if a clinical long-term benefit may be expected.

REFERENCES

1. Bangalore S, Kumar S, Fusaro M, et al. Short-and long-term outcomes with drug-eluting and bare-metal coronary stents: A mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873–2891.

2. von Birgelen C, Kok MM, van der Heijden LC, et al. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. Lancet 2016;388:2607–2617.

3. Biolè C, Huczek Z, Nuñez-Gil I, et al. Daily risk of adverse outcomes in patients undergoing complex lesions revascularization: A subgroup analysis from the RAIN-CARDIOGROUP VII study (veRy thin stents for patients with left mAIn or bifurcatioN in real life). Int. J. Cardiol. 2019;290:64–69. Available at: https://doi.org/10.1016/j.ijcard.2019.03.038.

4. D'Ascenzo F, Omedè P, De Filippo O, et al. Impact of Final Kissing Balloon and of Imaging on Patients Treated on Unprotected Left Main Coronary Artery With Thin-Strut Stents (From the RAIN-CARDIOGROUP VII Study). Am. J. Cardiol. 2019;123:1610–1619. Available at: https://doi.org/10.1016/j.amjcard.2019.02.013.

5. Gaido L, D'Ascenzo F, Imori Y, et al. Impact of Kissing Balloon in Patients Treated With Ultrathin Stents for Left Main Lesions and Bifurcations: An Analysis From the RAIN-CARDIOGROUP VII Study. Circ. Cardiovasc. Interv. 2020;13:e008325.

6. D'Ascenzo F, Chieffo A, Cerrato E, et al. Incidence and Management of Restenosis After Treatment of Unprotected Left Main Disease With Second-Generation Drug-Eluting Stents (from Failure in Left Main Study With 2nd Generation Stents–Cardiogroup III Study). Am. J. Cardiol. 2017;119:978–982. Available at: http://dx.doi.org/10.1016/j.amjcard.2016.12.005.

7. Naganuma T, Chieffo A, Meliga E, et al. 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). JACC Cardiovasc. Interv. 2013;6:1242–1249.
8. Mamas MA, Anderson SG, O'Kane PD, et al. Impact of left ventricular function in relation to procedural outcomes following percutaneous coronary intervention: Insights from the British Cardiovascular Intervention Society. Eur. Heart J. 2014;35:3004–3012.
9. Daubert MA, Massaro J, Liao L, et al. High-risk percutaneous coronary intervention is associated with reverse left ventricular remodeling and improved outcomes in patients with coronary artery disease and reduced ejection fraction. Am. Heart J. 2015;170:550–558. Available at: http://dx.doi.org/10.1016/j.ahj.2015.06.013.
10. Lopes RD, Alexander KP, Stevens SR, et al. Initial Invasive Versus Conservative Management of Stable Ischemic Heart Disease in Patients with a History of Heart Failure or Left Ventricular Dysfunction: Insights from the ISCHEMIA Trial. Circulation 2020.
11. Chen SL, Santoso T, Zhang JJ, et al. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions. J. Am. Coll. Cardiol. 2011;57:914–920.
12. Ferenc M, Gick M, Comberg T, et al. Culotte stenting vs. TAP stenting for treatment of de-novo coronary bifurcation lesions with the need for side-branch stenting: The Bifurcations Bad Krozingen (BBK) II angiographic trial. Eur. Heart J. 2016;37:3399–3405.
13. Kim YH, Lee JH, Roh JH, et al. Randomized comparisons between different stenting approaches for bifurcation coronary lesions with or without side branch stenosis. JACC Cardiovasc. Interv. 2015;8:550–560.
14. Behan MW, Holm NR, Curzen NP, et al. Simple or complex stenting for bifurcation coronary lesions : A patient-level pooled-analysis of the nordic bifurcation study and the

british bifurcation coronary study. Circ. Cardiovasc. Interv. 2011;37:57–64.

15. Hildick-Smith D, Behan MW, Lassen JF, et al. The EBC TWO Study (European Bifurcation Coronary TWO): A Randomized Comparison of Provisional T-Stenting Versus a Systematic 2 Stent Culotte Strategy in Large Caliber True Bifurcations. Circ. Cardiovasc. Interv. 2016;9:1–9.

16. Keelan PC, Johnston JM, Koru-Sengul T, et al. Comparison of in-hospital and one-year outcomes in patients with left ventricular ejection fractions ≤40%, 41% to 49%, and ≥50% having percutaneous coronary revascularization. Am. J. Cardiol. 2003.

17. Wallace TW, Berger JS, Wang A, Velazquez EJ, Brown DL. Impact of Left Ventricular Dysfunction on Hospital Mortality Among Patients Undergoing Elective Percutaneous Coronary Intervention. Am. J. Cardiol. 2009.

18. Thuijs DJFM, Milojevic M, Stone GW, et al. Impact of left ventricular ejection fraction on clinical outcomes after left main coronary artery revascularization: results from the randomized EXCEL trial. Eur. J. Heart Fail. 2020;22:871–879.

19. Sundaram V, Bloom C, Zakeri R, et al. Temporal trends in the incidence, treatment patterns, and outcomes of coronary artery disease and peripheral artery disease in the UK, 2006–2015. Eur. Heart J. 2020;41:1636–1649.

20. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur. Heart J. 2016;37:2129-2200m.

21. D'Ascenzo F, Filippo O De, Gallone G, et al. Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled datasets. Lancet 2021;397:199–207.

22. Farooq V, Vergouwe Y, Räber L, et al. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: The Logistic Clinical SYNTAX score. Eur. Heart J. 2012.

23. Sardi GL, Gaglia MA, Maluenda G, et al. Outcome of percutaneous coronary intervention utilizing drug-eluting stents in patients with reduced left ventricular ejection fraction. Am. J. Cardiol. 2012.
24. Gallone G, Baldetti L, Pagnesi M, et al. Medical Therapy for Long-Term Prevention of Atherothrombosis Following an Acute Coronary Syndrome. J. Am. Coll. Cardiol. 2018;72:2886–2903.

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FIGURE LEGENDS

Figure 1. Kaplan Meier estimates and adjusted hazard ratios for long-term outcomes following bifurcation PCI according to LVEF categories

Abbreviations as in table 1.

Figure 2. Adjusted hazard ratios for procedural and long-term major adverse cardiovascular events according to LVEF categories in relevant clinical and coronary anatomy subgroups

Abbreviations as in table 1.

TABLES

Table 1. Baseline characteristics according to left ventricular ejection fraction

Characteristics	LVEF <40% HFrEF (n=244)	LVEF 40-49% HFmEF (n=430)	LVEF ≥50% Preserved (n=4329)	p-value
Female sex (%)	57/244 (23.4)	83/430 (19.3)	1041/4329 (24.0)	0.087
Age (years)	69.4 ± 12.4	66.3 ± 12.3	66.2 ± 11.2	< 0.001
Clinical characteristics				
LVEF (%)	32.9 ± 5.0	44.3 ± 2.9	60.6 ± 6.4	< 0.001
Hypertension (%)	168/244 (68.9)	239/430 (55.6)	2928/4329 (67.6)	< 0.001
Hyperlipidemia (%)	103/244 (42.2)	154/430 (35.8)	2251/4329 (52.0)	< 0.001
Diabete Mellitus (%)	100/244 (41.0)	142/430 (33.0)	1421/4329 (32.8)	0.031
Smoke (%)	60/244 (24.6)	146/430 (34.0)	1061/4329 (24.5)	< 0.001
eGFR≤60 ml/min (%)	60/240 (25.0)	48/428 (11.2)	560/4270 (13.1)	< 0.001
Previous PCI (%)	45/244 (18.4)	66/430 (15.3)	1009/4329 (23.3)	< 0.001
Previous CABG (%)	6/244 (2.5)	5/430 (1.2)	131/4329 (3.0)	0.080
Previous MI (%)	78/244 (32.0)	79/430 (18.4)	723/4329 (16.7)	< 0.001
Clinical presentation				
CCS (%)	69/244 (28.3)	105/430 (24.4)	1891/4329 (43.7)	< 0.001
NSTE-ACS (%)	106/244 (33.4)	325/430 (42.8)	2438/4329 (44.1)	
STEMI (%)	69/244 (28.3)	141/430 (32.8)	528/4329 (12.2)	
Coronary anatomy				
LM bifurcation (%)	95/244 (38.9)	138/430 (32.1)	1223/4329 (28.3)	0.001
True bifurcation (%)	106/244 (43.4)	190/430 (44.2)	1721/4329 (39.8)	0.120
Severely calcified (%)	69/244 (28.3)	95/430 (22.1)	691/4329 (16.0)	< 0.001
Diffuse disease (%)	115/244 (47.1)	163/430 (37.9)	1592/4329 (36.8)	0.005
Procedural characteristics				
Main branch diameter (mm)	3.2 ± 0.5	3.1 ± 0.4	3.1 ± 0.5	0.565
Main branch lenght (mm)	24.9 ± 10.4	26.9 ± 12.2	25.8 ± 11.8	0.092
2-stent strategy (%)	51/244 (20.9)	80/430 (18.6)	750/4329 (17.3)	0.308
Final kissing Balloon (%)	181/244 (74.2)	437/430 (80.7)	2900/4329 (67.0)	< 0.001
POT only (%)	63/244 (25.8)	83/430 (19.3)	1429/4329 (33.0)	< 0.001
Antiplatetel regimen				
Potent P2Y12-i (%)	68/237 (28.7)	78/435 (18.4)	937/4299 (21.8)	0.008
DAPT duration				
6 months (%)	50/244 (20.5)	59/430 (13.7)	414/4329 (9.6)	< 0.001
12 months (%)	104/244 (42.6)	124/430 (28.8)	2159/4329 (49.9)	< 0.001
> 12 months (%)	90/244 (36.9)	247/430 (57.4)	1756/4329 (40.6)	< 0.001

Values are expressed as % patients or mean ± standard deviation.
Abbreviations: BIFrEF, bifurcation PCI with reduced ejection fraction; BIFmEF, bifurcation PCI with mid-range ejection fraction; BIFpEF, bifurcation PCI with preserved ejection fraction; CABG, coronary artery bypass graft; CCS, Chronic coronary syndrome; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular

filtration rate; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 2. Multivariate model of in-study predictors of the primary outcome at 800-day follow-up after bifurcation PCI

Variables	HR (95% CI)	p-value
Age	1.01 (1.00 - 1.02)	**0.001**
Diabete Mellitus	1.46 (1.20 -1.77)	**< 0.001**
Renal Disease	2.94(2.35 – 3.69)	**< 0.001**
Previous PCI	1.05(0.83 - 1.33)	0.702
Previous CABG	1.06 (0.69 - 1.63)	0.782
Previous MI	0.90 (0.69 - 1.17)	0.442
Distal LM	1.67 (1.37 – 2.02)	**< 0.001**
Severe Calcification	0.93 (0.74 - 1.23)	0.530
Two-stent strategy	1.32 (1.06 - 1.65)	**0.014**
DAPT <12 vs ≥12 months	1.71 (1.38 – 2.11)	**< 0.001**
BIFrEF vs BIFmEF	2.20(1.41 - 3.41)	**<0.001**
BIFrEF vs BIFpEF	1.91(1.41 - 2.60)	**<0.001**
BIFmEF vs BIFpEF	0.87 (0.61 - 1.24)	0.449

Values are expressed as HR (95%CI). Abbreviations as in table 1.

Table 3. Unadjusted and adjusted hazard ratios for procedural and long-term outcomes following bifurcation PCI according to LVEF categories

EF CATEGORIES	30-DAY OUTCOMES				LONG-TERM OUTCOMES			
	HR (95% CI)	p-value	Adj-HR (95% CI)	p-value	HR (95% CI)	p-value	Adj-HR (95% CI)	p-value
MACE								
BIFrEF vs BIFmEF	2.21 (0.59 - 8.26)	0.236	1.39 (0.37 - 5.21)	0.626	3.10 (2.00 - 4.79)	**< 0.001**	2.22 (1.45 - 3.44)	**<0.001**
BIFrEF vs BIFpEF	1.85 (0.74 - 4.65)	0.189	1.11 (0.25 - 2.87)	0.883	2.47 (1.85 - 3.31)	**< 0.001**	1.82 (1.35 - 2.50)	**<0.001**
BIFmEF vs BIFpEF	0.84 (0.30 - 2.32)	0.732	0.81 (0.29 - 2.27)	0.683	0.80 (0.56 - 1.14)	0.214	0.81 (0.57 - 1.15)	0.246
Death								
BIFrEF vs BIFmEF	0.88 (0.08 - 9.71)	0.918	2.00 (0.36 - 10.99)	0.427	3.16 (1.81 - 5.56)	**< 0.001**	1.88 (1.07 - 3.33)	**0.029**
BIFrEF vs BIFpEF	0.63 (0.09 - 4.65)	0.653	1.03 (0.35- 3.02)	0.963	3.68 (2.49 - 5.41)	**< 0.001**	2.00 (1.32 - 3.01)	**0.001**
BIFmEF vs BIFpEF	0.61 (0.15 - 2.53)	0.495	0.54 (0.13 - 2.30)	0.406	1.16 (0.73 - 1.85)	0.532	1.05 (0.65 - 1.69)	0.848
Myocardial Infarction								
BIFrEF vs BIFmEF	1.57 (0.22-11.63)	0.653	0.59 (0.05 - 6.58)	0.667	1.47 (0.62 - 3.48)	0.383	0.98 (0.41 - 2.34)	0.958
BIFrEF vs BIFpEF	1.39 (0.33-5.85)	0.610	0.53 (0.07 - 4.03)	0.540	1.50 (0.76 - 2.97)	0.240	1.20 (0.59 - 2.42)	0.617
BIFmEF vs BIFpEF	0.72 (0.17 - 3.01)	0.651	0.88 (0.20 - 3.75)	0.857	1.02 (0.56 - 1.86)	0.941	1.22 (0.66 - 2.23)	0.523
Target Vessel Revascularization								
BIFrEF vs BIFmEF	NA	0.982	NA	0.987	2.88 (1.39 - 6.17)	**0.006**	2.60 (1.12 - 5.59)	**0.014**
BIFrEF vs BIFpEF	2.96 (0.36 - 24.40)	0.315	1.27 (0.14 - 11.63)	0.830	1.37 (0.81 - 2.32)	0.237	1.31 (0.77 - 2.25)	0.318
BIFmEF vs BIFpEF	NA	0.616	NA	0.989	0.48 (0.27 - 0.85)	**0.012**	0.50 (0.29 - 0.90)	**0.021**
Stent Thrombosis								
BIFrEF vs BIFmEF	5.32 (0.55 - 50.00)	0.147	3.98 (0.41 - 38.46)	0.232	3.91 (1.18 - 12.99)	**0.026**	2.83 (0.85 - 9.52)	0.092
BIFrEF vs BIFpEF	3.83 (1.10 - 13.33)	**0.035**	2.71 (0.74 - 9.90)	0.132	3.12 (1.47 - 6.58)	**0.003**	2.53 (1.15 - 5.56)	**0.021**
BIFmEF vs BIFpEF	0.72 (0.09 - 5.46)	0.749	0.71 (0.09 - 5.49)	0.739	0.80 (0.29 - 2.22)	0.664	0.87 (0.31 - 2.46)	0.794

Values are expressed as HR (95%CI). Adj-HR are adjusted for in-study outcome predictors. Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; NA, not available; other abbreviations as in table 1