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Determinants of functional significance of coronary bifurcation lesions and clinical outcomes after physiology-guided treatment

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ABSTRACT

Objectives: To determine the rate of functionally significant (fractional flow reserve, FFR $\leq$ 0.80) coronary bifurcation stenoses that are considered anatomically significant based on angiographic estimation and to define predictors of functional significance of stenoses in main vessel and side branch.
Background: To date, the rate of functionally significant stenoses in angiographic significant coronary bifurcation stenoses has not been specifically determined.
Methods: Patients with significant angiographic bifurcation lesions defined as diameter stenosis >50% in main vessel and/or side branch were included. FFR was performed in main vessel (MV) and side branch (SB) before and after percutaneous coronary intervention (PCI). The protocol was approved by the local ethics committee.
Results: Overall, 171 patients with bifurcation lesions were included. Mean FFR in MV was 0.80 $\pm$ 0.01 and 0.84 $\pm$ 0.09 in SB. 46% (n = 78) of bifurcation lesions were functionally significant when assessed with FFR. Diameter stenosis in main vessel, lesion length, side branch territory and SYNTAX score (SS) were found as predictors for lesion functional severity (main vessel FFR $\leq$ 0.80). At the time of follow-up, there were no differences between the treated and deferred group regarding rates of all-cause death, cardio-vascular death, MACEs and POCE.
Conclusion: Less than half of all angiographic significant bifurcation lesions were functionally significant when assessed with FFR. There was no difference in clinical outcomes at mean time of three years follow-up in treated and deferred lesion.

1. Introduction

Coronary bifurcation lesions represent nearly 20–25% of all percutaneous coronary interventions (PCI) [1,3]. Although during the last years significant progress has been made in interventional cardiology, bifurcation interventions remain a major therapeutic challenge with high early and late complication rates [2]. When compared with non-bifurcation interventions, bifurcation lesions have lower rate of procedural success and a higher rate of restenosis. This occurrence is more notable for the era of bare metal stents (BMS) and early generation drug-eluting stents (DES) [3]. The European Bifurcation Club recommends provisional single stent technique as the preferred strategy for most bifurcation lesions and recommends side branch (SB) stenting only if a significant flow limitation is present in a branch supplying a considerable myocardial territory [3]. Nevertheless, there is no established criterion as to which SB should be treated after main vessel stenting. Angiographic evaluation alone is sometimes imprecise and does not reflect the functional significance of lesions [4,5]. What is more, there are some specific difficulties in angiographic assessment of bifurcation lesions due to the image foreshortening, vessel overlapping and presence of stent struts across the branch [6,7]. Previous studies showed that

coronary angiography does not accurately predict the functional significance of the jailed side branches [8].

It is now accepted that measurements of fractional flow reserve (FFR) can identify haemodynamically significant lesions that require revascularisation [9]. Previous trials proved that FFR-guided PCI improved long-term outcomes in patients with stable coronary artery disease compared to angiography only or medical therapy [10,11]. Finally, the deferral of PCI in functionally non-significant lesions in DEFER trial was associated with favourable outcomes in short- and long-term follow-up [12,13].

To the best of our knowledge, there is no study that evaluates the hemodynamic severity of bifurcation lesion, assessing FFR at both MV and SB initially. The rate of functionally significant coronary bifurcation stenoses was not specifically explored previously. The aims of this hypothesis-generating study were to: 1) Determine the frequency of functionally significant (fractional flow reserve, FFR ≤ 0.80) coronary bifurcation stenoses considered significant on angiographic estimation,

2) Define predictors of functional significance of stenoses in main vessel and side branch, and 3) Report clinical outcomes in coronary bifurcation lesions treated based on FFR guidance.

2. Methods

2.1. Study design

This is a single-centre prospective study of patients with stable coronary artery disease. The inclusion criteria were angiographic bifurcation lesions in a native coronary artery with diameter ≥ 2.5 mm and ≤ 4.5 mm and SB diameter ≥ 2.0 mm and percentage diameter stenosis (% DS) more than 50% in main vessel – either in the proximal MV or distal MV (MB). We excluded patients with acute coronary syndrome and those with non-cardiac co-morbid conditions with life expectancy of less than one year. Also, patients with left main coronary artery stenosis, total occlusion before occurrence of SB, lesion of interest located in infarct-related artery, subjects with LVEF < 40%, subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and patients with bundle branch blocks, atrial fibrillation/flutter with no identifiable isoelectric line were excluded. Another requirement was the normal range of troponin 24 h before percutaneous coronary intervention.

2.2. Definition of endpoints

A functionally significant bifurcation lesion was defined by stenosis in main vessel and/or side branch with measured FFR ≤ 0.80 in accordance with the latest recommendations [9,14]. Functionally significant lesion of main branch was considered as stenosis in main vessel with an FFR measured distally from bifurcation point (Supplmentary Figure 1). Side branch functionally significant stenosis was defined as stenosis in SB direction, which combines stenosis of SB and proximal main vessel.
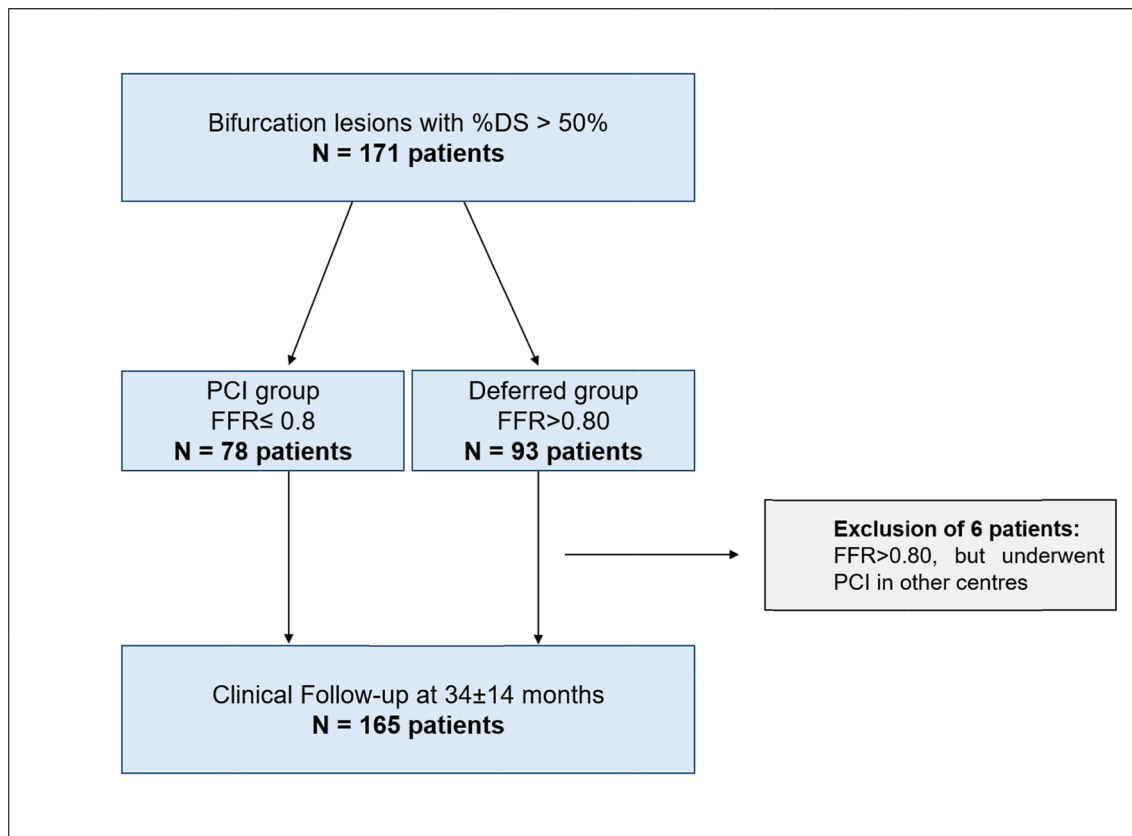

Fig. 1. Study flow chart.

All patients were followed up by telephone contact and/or clinical visit at 30 days and then monthly for vital status through National Insurance Institute. Cardiovascular death was defined as death with clearly determined cardiac origin or death from unknown reason. Myocardial infarction after hospitalization was diagnosed according to the Fourth definition of myocardial infarction [15] (as any rise in troponin or creatine-kinase MB more than 99th percentile of normal values in association with symptoms and/or documented ECG changes). Major adverse cardiac events (MACEs) were combination of cardiovascular death and myocardial infarctions. Patient oriented cardiac events (POCE) were summary of MACEs and target vessel failure rates. Target vessel failure was any intervention in target vessel beyond one month of initial vessel interrogation.

2.3. Procedures

Initial FFR was performed using the PrimeWire or PrimeWire Prestige (Volcano Corp., USA). For all FFR measurements, intracoronary adenosine was given in increasing doses of 60 mcg, 120 mcg, and 240 mcg. Check for drift of zero was performed before every segment measurement, as well as at the end of procedure. PCI was performed according to the current guidelines. Provisional stenting was the default PCI procedure in all patients. Predilatation of MV was mandatory. After stenting and proximal optimization balloon inflation (left on operator discretion) FFR was recorded in main and side branches. It was recommended that in case of SB FFR ≤ 0.80, a balloon dilatation of SB be performed. The SB was stented in case of flow less than TIMI 3, if visual diameter stenosis at ostium ≥ 70%, despite kissing balloon inflation (KBI), and if the patient was symptomatic. If none of the above was present and FFR > 0.80, the SB was left untreated. Final KBI or sequential balloon inflation were performed at the discretion of operator. All lesions were stented with second generation DES. Angiographic success was defined as end procedural MV %DS < 20% and SB stenosis < 70% without significant dissection and flow impairment. Procedure success included angiographic success in the absence of in-hospital MACE (death, stroke, and myocardial infarction). All patients received double antiplatelet therapy with aspirin 75–100 mg and P2Y2 inhibitor (clopidogrel, prasugrel or ticagrelor).

2.4. Angiographic analysis

Dedicated bifurcation quantitative coronary angiography (QCA) analysis was performed according to the recommendation of the consensus on QCA methods for bifurcation lesions [16]. True bifurcation lesions were defined as visual per cent diameter stenosis (%DS) > 50% at the SB. The minimal luminal diameter (MLD), reference vessel diameter (RVD) and %DS were measured for every segment of the bifurcation (i. e., proximal, and distal MV and SB) pre- and post-intervention. Lesion length was measured from proximal main vessel to distal main branch (i. e., we considered beginning and ending points where hypothetically the stent will be implanted). SB lesion length was measured from the ostium to the first normal appearing part of the vessel. All analyses were performed by two investigators (P.N. and G.D.) and in case of disagreement, a consensus was formed with additional analysis from the first author (D.V.). For assessment of territory at risk and relative contribution of bifurcation lesion to all territory at risk we calculated adapted Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index (BARI) score [17,18]. Bifurcation BARI score gives area at risk from the bifurcation of interest. Side branch BARI score gives the percentage myocardial area supplied by a side branch from coronary bifurcation stenosis. Absolute SB BARI score (percentage area at risk supplied by side branch) and relative SB BARI risk score (SB BARI risk score divided to bifurcation BARI score giving relative contribution of SB to total ischemic territory of bifurcation stenosis) were calculated as shown in Fig. 1. All analyses were performed with dedicated General Electric QCA software and additionally with MicroDicom QCA software.

Table 1
Functional significance of MV and SB according to the Medina bifurcation type.

Bifurcation type	Total N = 159 [*]	MV+/ SB+	MV+/ SB−	MV−/ SB+	MV−/ SB−
Medina 1-1-1	59	55	4	–	–
Medina 1-0-1	12	8	4	–	–
Medina 1-1-0	17	–	4	–	13
Medina 0-1-1	29	–	–	12	15
Medina 0-0-1	15	4	4	7	–
Medina 1-0-0	7	–	2	–	5
Medina 0-1-0	20	–	2	–	18

"+" FFR ≤ 0.80; "−" FFR > 0.80.
[*] 159 patients with FFR measurement in both MV and SB.

2.5. Statistical analysis

Differences between groups were examined with paired or unpaired t-tests as appropriate. Otherwise, the Wilcoxon sign-ranked test and Mann-Whitney U-tests were used. Chi-square tests were applied for qualitative data. The area under the receiving operating characteristics curve (AUC) was used to assess the diagnostic accuracy of the test. Correlation analysis was performed (Pearson or Spearman test depending on type of data) between FFR values and possible predictors. Multiple logistic regression analysis was performed to identify independent predictors of functionally significant bifurcation lesion, as well as functionally significant stenoses in main branch and side branch directions. The proportion of functionally positive coronary bifurcation lesions was compared with the data from FAME trial, giving frequency data of functionally significant non-bifurcation lesions [10]. Multivariate Cox regression analysis was performed for identification of independent predictors of all-cause death, cardiovascular death, MACEs and POCEs. The study was investigator initiated, funded by the local institution (Alexandrovska University Hospital, Sofia, Bulgaria). The local ethics committee approved the study. All statistical calculations were performed via SPSS version 23 (SPSS, USA).

Table 2
Demographic and risk factor characteristics of the patients.

Patient characteristics	All patients	FFR ≤ 0.80 n = 78	FFR > 0.80 n = 93	P-value
Age (years)	67 ± 10	66 ± 11	67 ± 10	0.349
Sex – males, n (%)	113 (66)	55 (71)	58 (62)	0.169
Family history for ASCVD, n (%)	22 (13)	16 (21)	6 (7)	0.010
Hyperlipidemia, n (%)	157 (92)	69 (88)	89 (96)	0.076
Diabetes, n (%)	63 (37)	34 (44)	30 (32)	0.129
Renal failure, n (%)	51 (30)	23 (29)	29 (31)	0.464
Carotid artery disease, n (%)	10 (6)	9 (12)	2 (2)	0.019
Peripheral artery disease, n (%)	15 (9)	8 (10)	8 (9)	0.713
Smoking, n (%)	79 (46)	40 (52)	37 (40)	0.143
Previous myocardial infarction, n (%)	32 (19)	19 (24)	14 (15)	0.132
Previous PCI, n (%)	87 (51)	42 (54)	46 (49)	0.570
Clinical presentation				0.311
Angina class CCS I, n (%)	3	1 (1.3)	2 (2.2)	
Angina class CCS II, n (%)	10	4 (5.1)	6 (6.5)	
Angina class CCS III, n (%)	46	21 (26.9)	24 (25.8)	
Angina class CCS IV, n (%)	112	52 (66.7)	61 (65.6)	
Beta blocker, n (%)	149 (87)	70 (90)	78 (84)	0.262
ACE inhibitor/ ARB, n (%)	147 (86)	69 (88)	85 (91)	0.259
Calcium antagonist, n (%)	80 (47)	54	41	0.092
Atrial fibrillation, n (%)	39 (23)	17	28	0.080
LV ejection fraction, %	57 ± 7	56 ± 7	58 ± 7	0.169

Renal failure defined as calculated glomerular filtration rate according to MDRD formula < 60 ml/min. ASCVD – atherosclerotic cardio-vascular disease.

Table 3

Angiographic characteristics of patients.

Parameters	FFR MB ≤ 0.80 n = 78	FFR MB > 0.80 n = 93	P-value
Target vessel:			
LAD	60	77	0.218
LCX	13	11	
RCA	5	5	
SYNTAX score	12 ± 4	8 ± 3	0.001
MV RVD, mm	3.29 ± 0.31	3.30 ± 0.45	0.975
MV %DS, %	61 ± 21	30 ± 19	0.001
MB RVD, mm	2.94 ± 0.26	2.83 ± 0.32	0.018
MB %DS, %	70 ± 13	36 ± 22	0.001
SB RVD, mm	2.41 ± 0.32	2.40 ± 0.37	0.974
SB %DS, %	56 ± 25	43 ± 24	0.001
Lesion length, mm	43 ± 19	19 ± 7	0.001
SB lesion length, mm*	6.4 ± 4.45	9.8 ± 3.1	0.002
All BARI score, %	48 ± 16	42 ± 9	0.009
SB BARI score, %	15 ± 6	13 ± 5	0.007
Bifurcation BARI score, %	44 ± 10	42 ± 7	0.245
Multivessel disease, n (%)	38 (49)	33 (35)	0.082

All BARI score – percentage area at risk of left ventricle, based on all stenoses equal or>50% in diameter; bifurcation BARI risk score – area at risk supplied from bifurcation stenosis of interest; SB BARI score – percentage area at risk supplied from a side branch.

* SB lesion length reported for 84 patients with true bifurcation lesion (37 with FFR ≤ 0.80 and 47 with >0.80).

3. Results

From January 2015 to December 2019, 171 patients met inclusion criteria for the study. From those, 78 (46%) had functionally significant bifurcation stenosis versus 93 (54%) with non-significant stenosis based on FFR. (Fig. 1.) Six patients had functionally non-significant lesions, which were intervened in other institutions in the following 3 months after the initial procedure. In one patient, it was impossible to cross main vessel stenosis with pressure wire, but side branch stenosis was interrogated. In 9 patients (5%), it was impossible to measure initial FFR in the SB but the main vessel FFR was strongly significant. The left anterior descending artery was the target vessel in 81% of cases (n = 139). The true bifurcation stenoses (with SB ostial stenosis more than 50%, Medina xx1) were 49% (n = 84), Table 1. Mean FFR in MV was 0.80 ± 0.01 and 0.84 ± 0.09 in SB. 46% (n = 78) of bifurcation lesions were functionally significant when assessed with FFR. Mean FFR post-PCI in MV was 0.89 ± 0.03 and 0.84 ± 0.06 in SB. When compared with data from FAME study, used as reference for rate of functionally significant lesions detected by FFR [10], there was a significant difference in frequencies of functionally significant lesions – 46% vs 63%, n = 171 (95% CI: 38.37–53.78%, z-statistic = 4.604, p = 0.001). Thus, the percentage of angiographically significant coronary bifurcation lesions that were also functionally significant, was notable lower than in non-bifurcation stenoses.

The clinical and angiographic patient characteristics are presented in Tables 2 and 3. All patients had history of hypertension or were on antihypertensive treatment. The treated and deferred groups had
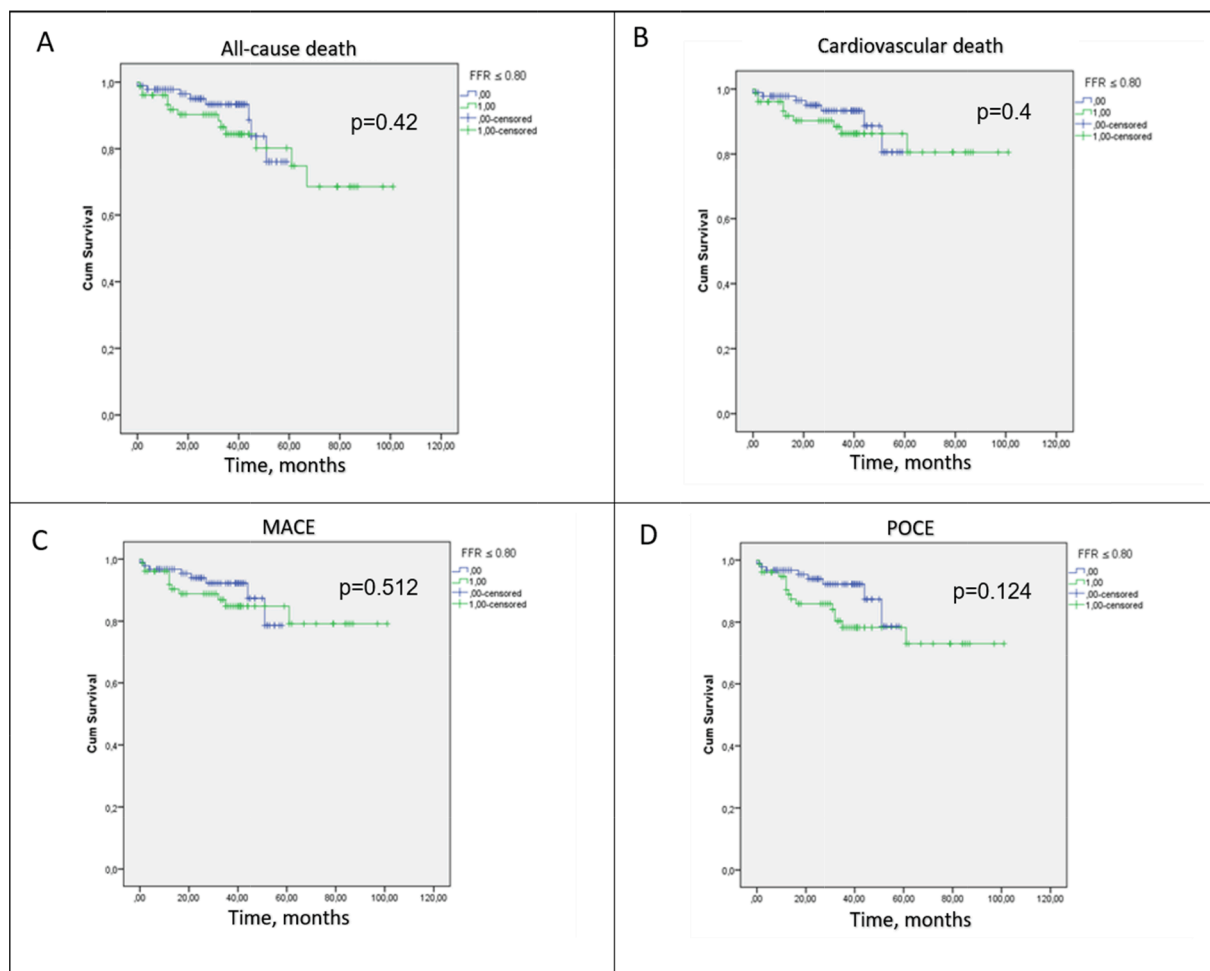

Fig. 2. Survival curves for adverse events: A) All-cause death, B) Cardiovascular death, C) Major adverse cardiac events (MACE), D) Patient oriented cardiac events (POCE).

relatively equal distribution of risk factors, apart from family history for atherosclerotic vascular disease (ASVD) which was more frequent in the group with FFR ≤ 0.80.

The angiographic analysis demonstrated notable differences between groups with functional significance and those without. Stenoses were more severe, and lesions were longer in patients with FFR ≤ 0.80, while SB lesion length was longer in patients with non-functionally significant stenosis (Table 3). The following cut-off values were defined: main vessel stenosis ≥ 55% (AUC = 0.857, p < 0.001), main branch stenosis ≥ 65% (AUC = 0.898, p < 0.001), SB stenosis ≥ 50% (AUC = 0.645, p < 0.001) and main vessel lesion length ≥ 25 mm (AUC = 0.903, p < 0.001). Patients with functionally significant bifurcation stenoses had more severe atherosclerotic disease illustrated by higher SYNTAX score, as well as larger amount of myocardial mass at risk (higher All BARI score). A cut-off value for SYNTAX score ≥ 11 was proved to be associated with functionally significant bifurcation stenosis (AUC = 0.837, p < 0.001).

The territory supplied by SB with functionally significant stenoses was substantially larger as seen from higher SB BARI score. Interestingly, territory-based BARI indexes correlated significantly with lowest detectable FFR value in bifurcation stenosis (SB BARI r = −0.210, p = 0.007; Bifurcation BARI r = −0.214, p = 0.006, All BARI r = −0.282, p < 0.001; SB BARI AUC = 0.625, p = 0.005; Bifurcation BARI AUC = 0.603, p = 0.023; All BARI AUC = 0.640, p = 0.002). The cut-off values were identified accordingly – SB BARI ≥ 12% (sensitivity 69%, specificity 75%, p = 0.006), All BARI ≥ 44%, sensitivity = 66%, specificity = 66%, p = 0.005 (the values for Bifurcation BARI were identical). We assessed the relative contribution of side branch to whole territory at risk posed from bifurcation stenosis as a ratio SB BARI/Bifurcation BARI which correlated significantly with FFR values (r = 0.167, p = 0.031). By ROC-analysis a cut-off value of 0.25 was defined (c-statistics = 0.591, p = 0.043). Additionally, as a marker for territory at risk distributed within bifurcation lesion region we observed a significant correlation between main branch/proximal main vessel reference diameter ratio with functional severity of the stenosis (r = 0.201, p = 0.009), with a cut-off value of ≥0.85 (AUC = 0.615, p = 0.010). Surprisingly, there were no significant relationship between functional significance and side branch reference diameter, or ratio of SB diameter and main vessel sizes.

3.1. Follow-up results

A total of 165 patients were followed-up for 34 ± 14 months. Six FFR negative cases received PCI in the following months after the initial interrogation and were not included in this analysis. All-cause mortality rate was 12.5% (n = 20), with cardiovascular death rate of 9.7% (n = 16). Three out of these 16 patients (3/165, 1.8%) with cardiovascular death were in fact with undetermined cause of death. Two patients had spontaneous myocardial infarctions (1.2%). Two patients had in-stent restenosis and four additional patients had target vessels revascularizations – in total, target vessel failure rate was 3.6%. MACE rate was 11% (n = 18) and the rate of POCE – 13% (n = 22).

At the time of follow-up there were no differences regarding rates of all-cause death, cardio-vascular death, MACEs and POCE between the positive FFR group that underwent PCI and the deferred group (Fig. 2). For the period of the whole follow-up, 31 patients (18.8%) were rehospitalized in cardiology unit as a result of symptom occurrence. From these, 14 patients (8%) were with functionally significant stenosis and 17 patients (10%) with non-functionally significant stenosis.

4. Discussion

The main findings of our study can be summarized as follows: (1) the proportion of functionally significant bifurcations is less than half of the number of angiographic significant coronary bifurcation stenosis. (2) Diameter stenosis in main vessel, lesion length, side branch territory and

SYNTAX score (SS) were found as predictors for lesion functional severity (main vessel FFR ≤ 0.80). (3) Patients from the group with deferred PCI have low MACE rate at 3 years follow-up. This is in accordance with FAME studies results where the MACE rate in deferred patients was 10% [19,20]. In FAME, the population with coronary bifurcation lesions was not specifically addressed and explored, however, our study may give contribution to that area.

The number of functionally significant lesions in our study is statistically lower, when compared with the data from FAME I trial [10]. While the reason for this finding is not entirely clear, it is possible that SB creates more favorable flow conditions at the MV stenosis site, thus improving local perfusion. The occurrence of side vessel at stenosis side "steals" some flow from the main vessel, which can result into two main consequences. First, the proportion of subtended myocardium in distal main vessel is less than expected if no SB appears, meaning that less blood is needed for that region. Second, the increased resistance in distal MV, because of smaller diameter after branching, will result in higher distal pressure and higher values of FFR. This hypothesis needs further investigation but is particularly important as it rises question of the necessity of intervention in these patients. We suggest that lesion should be assessed by virtue of FFR, and intervention should be performed only in case of functional severity. The intervention can safely be deferred without influencing the outcome in the next 3 years.

We demonstrated that angiographically significant stenosis in bifurcation region could be largely misleading when taking 50% stenosis as a cut-off value for performing PCI. Our data is in accordance with the current guidelines for treatment of chronic coronary syndrome recommending performance of functional assessment by means of FFR in lesions less than 70% diameter stenosis [9]. However, these recommendations did not particularly consider coronary bifurcation lesions and our findings are confirmatory in this regard. We identified different threshold for significance in proximal main vessel (≥55%) and distal main branch (≥65%), after the division with side branch. This is logical as the territory obeyed from MB is smaller than the one supplied by proximal main vessel [20].

The studies investigating FFR in coronary bifurcations have demonstrated a substantial disparity between the angiographic and functional assessments, especially when evaluating SB stenosis after MV stenting [21–23]. Koo et al. [21] revealed that during provisional SB intervention strategy, angiographic assessment overestimates the severity of jailed side-branch lesions compared to physiological evaluation via fractional flow reserve. Another study comparing QCA analysis with visual estimation and FFR for jailed SB lesions showed discrepancy between the angiographic and functional evaluation of SB lesions and that the severity of jailed SB lesion was overestimated when assessed visually [22].

To assess correlation between functional significance of side branches and vessel size, we used several parameters besides vessel diameter. The BARI score is a well-established tool to estimate the relative territory covered from a given vessel [22]. It can establish the territory at risk of side branch stenosis (estimated by SB BARI score), as well as its relative contribution to global ischemic potential of a bifurcation stenosis (assess by SB BARI/Bifurcation BARI ratio). It appeared, that the absolute myocardial mass at risk, reflected by higher SB BARI score is more important contributor to functional stenosis significance than its relative impact. This is in line with basic coronary physiology principles. Moreover, the SB BARI score gives a priory a measure for importance of a side branch. The calculation of SB BARI considers the whole coronary vessel tree and relative contribution of a given vessel to whole left ventricle myocardium blood supply. It could be calculated in any catheterization laboratory as it did not require any dedicated software. As seen from our results, the patients included in our study had quite large side vessel territory, despite that vessel calibers were not larger than reported in the literature [24–26]. This demonstrates that side vessel reference diameter and its stenosis could not be used for reliable measurement of the functional importance of this stenosis.
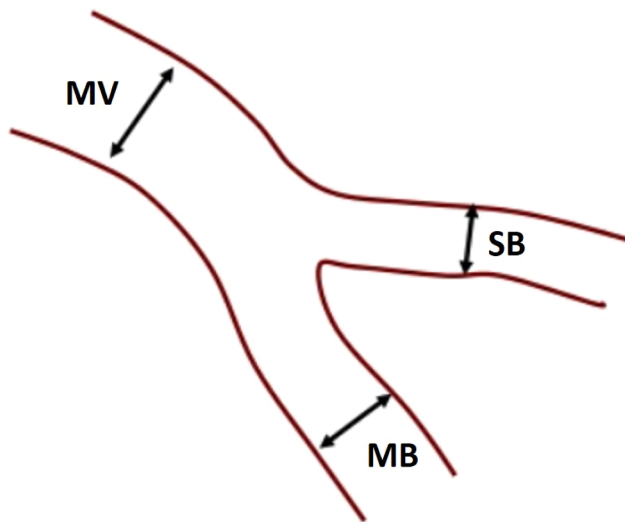
Fig. 3. Coronary bifurcation. MV – proximal main vessel, MB – main branch (distal main vessel), SB – side branch.

5. Limitations

The main limitation of our study is the sample size albeit it was unexpected that such a large proportion of patients will have functionally non-significant lesion. Also, this is a single centre study with no independent adjudication and some restrictions considering cost limitations, due to price of pressure wires. We carefully selected patients, however, and to the best of our knowledge, this is the largest study in this patient population. The calculation of BARI score also required some training of the staff making angiographic analysis. After the first 10 patients, however, the differences between operators became negligible and this confirms the applicability of the findings. Another limitation is the possible overestimation of the rate of cardiovascular death. However, we were following the current recommendations to classify any death from unknown origin as cardiovascular death for the endpoint definitions [27].

6. Conclusions

Severity of coronary bifurcation lesions is often overestimated based on angiographic assessment. When assessed with FFR only half of all angiographically significant lesions were functionally significant. Different degree of stenosis in proximal main vessel and distal side branch, lesion length, side branch territory and SYNTAX score were predictive for lesion functional significance. There was no difference in clinical outcomes at mean time of three years follow-up in treated and deferred lesions, giving assurance of FFR-guided strategy.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Carlos Collet reports receiving research grants from Biosensor, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, Cathworks, Boston Scientific, Siemens, HeartFlow Inc. and Abbott Vascular; and consultancy fees from Heart Flow Inc, Opsens, Abbott Vascular and Philips Volcano. The other co-authors have no conflict of interest related to this manuscript.

Supplementary data

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