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Identification of Coronary Artery Side Branch Supplying Myocardial Mass That May Benefit From Revascularization

Hyung Yoon Kim, MD,[a] Joon-Hyung Doh, MD, PhD,[b] Hong-Seok Lim, MD, PhD,[c] Chang-Wook Nam, MD, PhD,[d] Eun-Seok Shin, MD, PhD,[e] Bon-Kwon Koo, MD, PhD,[f] Joo Myung Lee, MD,[g] Taek Kyu Park, MD,[g] Jeong Hoon Yang, MD, PhD,[g] Young Bin Song, MD, PhD,[g] Joo-Yong Hahn, MD, PhD,[g] Seung Hyuk Choi, MD, PhD,[g] Hyeon-Cheol Gwon, MD, PhD,[g] Sang-Hoon Lee, MD, PhD,[g] Sung Mok Kim, MD, PhD,[h] Yeonhyeon Choe, MD, PhD,[h] Jin-Ho Choi, MD, PhD[g,i]

ABSTRACT

OBJECTIVES The authors sought to identify whether a coronary side branch (SB) is supplying a myocardial mass that may benefit from revascularization.

BACKGROUND The amount of subtending myocardium and physiological stenosis is frequently different between the main vessel (MV) and SB.

METHODS In this multicenter registry, 482 patients who underwent coronary computed tomography angiography and fractional flow reserve (FFR) measurement were enrolled. The % fractional myocardial mass (FMM), the ratio of vessel-specific myocardial mass to whole myocardium, was assessed in 5,860 MV or SB consisting of 2,930 bifurcations. Physiological stenosis was defined by fractional flow reserve (FFR) <0.80. Myocardial mass that may benefit from revascularization was defined by %FMM ≥10%.

RESULTS In per-bifurcation analysis, MV supplied a 1.5- to 9-fold larger myocardial mass compared with SB. Unlike left main bifurcation (n = 482), only 1 of every 5 non-left main SB (n = 2,448) supplied %FMM ≥10% (97% vs. 21%; p < 0.001). SB length ≥73 mm could estimate %FMM ≥10% (c-statistic = 0.85; p < 0.001). In 604 vessels interrogated by FFR, diameter stenosis was similar (p = NS), but %FMM ≥10%, FMM/minimal luminal diameter, and frequency of FFR <0.80 was higher in MV compared with SB (p < 0.001, all). Generalized estimating equations modeling demonstrate that vessel diameter, left myocardial mass, and FFR were not (p = NS), but SB length ≥73 mm and left main bifurcation were significant predictors for %FMM ≥10% (p < 0.001).

CONCLUSIONS Compared with MV, SB supplies a smaller myocardial mass and showed less physiological severity despite similar stenosis severity. SB supplying a myocardial mass of %FMM≥10%, which may benefit revascularization could be identified by vessel length ≥73 mm. Pre-procedural recognition of these findings may guide optimal revascularization strategy for bifurcation. (J Am Coll Cardiol Intv 2017;10:571–81)

From the [a]Department of Medicine, Jeju University Hospital, Jeju National University School of Medicine, Jeju, Korea; [b]Department of Medicine, Inje University Ilsan-Paik Hospital, College of Medicine, Goyang, Korea; [c]Department of Cardiology, Ajou University School of Medicine, Suwon, Korea; [d]Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea; [e]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; [f]Department of Medicine, Seoul National University Hospital, Seoul, Korea; [g]Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [h]Department of Radiology, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; and the [i]Department of Emergency Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. This study was supported by Korean Society of Interventional Cardiology grant 2014-1, Samsung Biomedical Research Institute grant GL1B33211, and Heart Vascular and Stroke Institute of Samsung Medical Center. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. H.Y. Kim and J.H. Doh equally contributed to this work as first authors. Drs. J.H. Choi and J.H. Doh contributed equally to this work as co-corresponding authors.

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ABBREVIATIONS AND ACRONYMS

CAG = coronary angiography

CCTA = coronary computed tomography angiography

FFR = fractional flow reserve

FMM = fractional myocardial mass

LAD = left anterior descending coronary artery

LCX = left circumflex coronary artery

LV = left ventricular

MV = main vessel(s)

OM = obtuse marginal artery

PCI = percutaneous coronary intervention

PDA = posterior descending artery

PL = posterolateral artery

RCA = right coronary artery

SB = side branch(s)

The major role of percutaneous coronary intervention (PCI) is restoration of sufficient blood flow required to the supplying myocardium through the target vessel. Bifurcations are frequent in daily practice and account for 1 of 5 in PCI (1,2). Unlike nonbifurcations, coronary bifurcations supply 2 different territories of myocardium subtended by the main vessel (MV) and the side branch (SB), respectively (3). It often necessitates simultaneous 2-balloon dilation or stent implantation in both vessels. Despite advances in technology and devices, PCI of a bifurcation lesion is still limited by higher periprocedural myocardial infarction and long-term adverse events such as stent thrombosis, compared with a non-bifurcation lesion (4).

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The burden of myocardial ischemia is highly relevant to the clinical benefit of revascularization and long-term prognosis (5). Therefore, identification of a SB supplying a myocardial mass that benefits more from revascularization than optimal medical therapy may clarify the need of additional procedures for the SB, and may guide optimal revascularization strategy for bifurcation (6).

Recently, we established the concept of fractional myocardial mass (FMM), a vessel-specific amount of myocardium derived from coronary computed tomography angiography (CCTA) (7). We assessed the myocardial mass subtended by the MV and SB of each bifurcation and investigated how to identify SB supplying clinically meaningful myocardial mass as defined by ≥10% of the total myocardium (8) (**Figure 1**).

METHODS

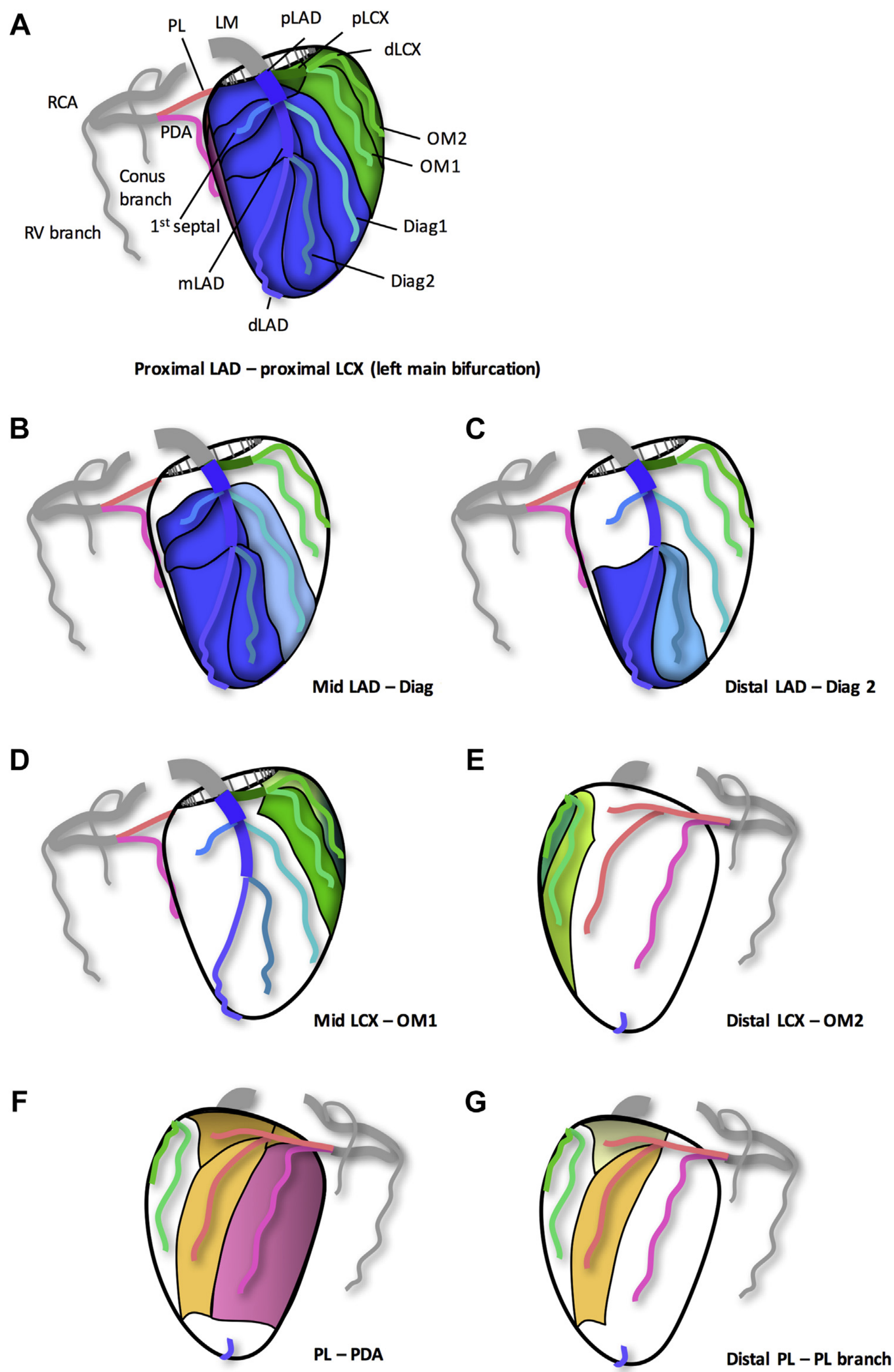
STUDY DESIGN. Data were derived from a prospective multicenter registry of 5 university teaching hospitals in Korea. From January 2010 to May 2015, 482 patients were enrolled who underwent clinically indicated CCTA and following elective invasive coronary angiography (CAG) with invasive fractional flow reserve (FFR) assessment without an intervening coronary event. Patients with ST-segment elevation myocardial infarction, uncompensated heart failure, bypass surgery with patent graft, contraindication to adenosine, complex structural or congenital heart disease, prosthetic valves, or any clinical instability or life-threatening disease were not included. The institutional review board at each institute approved the study protocol. Data were anonymized and analyzed independently by the core lab in the Samsung Medical Center.

FFR AND ANGIOGRAPHIC ANALYSIS. CAG and FFR measurement was performed according to the standard protocol of each institute (7). In brief, FFR was measured using a pressure wire (PressureWire Certus, St. Jude Medical Systems, St. Paul, Minnesota; ComboWire, Philips Healthcare, Amsterdam, the Netherlands) under maximal hyperemia induced by adenosine infusion. FFR has done on vessels that were visually estimated to have diameter stenosis ≥40% and to have clinical significance based on the interventionist's expertise. Quantitative CAG was done in vessels interrogated by FFR. A computer-assisted automatic arterial contour detection system (Centricity CA-1000, GE Healthcare, Little Chalfont, United Kingdom) was used to measure minimal luminal diameter, reference diameter, and diameter stenosis in the end-diastolic angiographic image with optimal projection showing minimal foreshortening of the lesion. Decision of revascularization strategy was made by agreement of attending physician and interventional cardiologist.

ACQUISITION AND ANALYSIS OF CCTA. CCTA data were obtained as described previously (7). In brief, multivendor computed tomography scanners equipped with 64 or higher detectors (Aquilion One or Aquilion 64, Toshiba Medical Systems, Otawara, Japan; SOMATOM Definition, Siemens Medical Solution, Erlangen, Germany; Lightspeed VCT, GE Healthcare) were used. Image dataset with 0.5- or 0.6-mm slices were processed by a dedicated workstation (iNtuition, TeraRecon, Foster City, California). The 3-dimensional coronary arterial tree model was segmented according to the modified American Heart Association classification of coronary artery anatomy. All major epicardial coronary arteries and 1st order branches ≥1.5 mm in diameter were tracked from ostium to distal end. The vessel central axis was determined and confirmed by reviewing all cross-sectional images from the proximal ostium to distal end. A total of 8,259 vessel segments were evaluated in length.

%FRACTIONAL MYOCARDIAL MASS. Transport of vital materials such as oxygen or glucose in hierarchical fractal-like branching network plays a key role in the metabolism of life. Therefore, the anatomy of the coronary artery tree would meet the principle of efficiency or minimum energy loss in transportation. Allometric scaling law is a universally observed logarithmic relationship among anatomic dimension, physiological function, and energy expenditure in

FIGURE 1 Concept of FMM in Bifurcation Vessels



(A to G) Schematic illustration of myocardial territory or fractional myocardial mass (FMM) subtended by bifurcation vessels. Arterial segments that do not directly perfuse LV myocardium were excluded from calculation of FMM **(gray)**. d = distal; Diag = diagonal artery; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main artery; m = mid; OM = obtuse marginal artery; p = proximal; PDA = posterior descending artery; PL = posterolateral artery; RCA = right coronary artery; RV = right ventricle.

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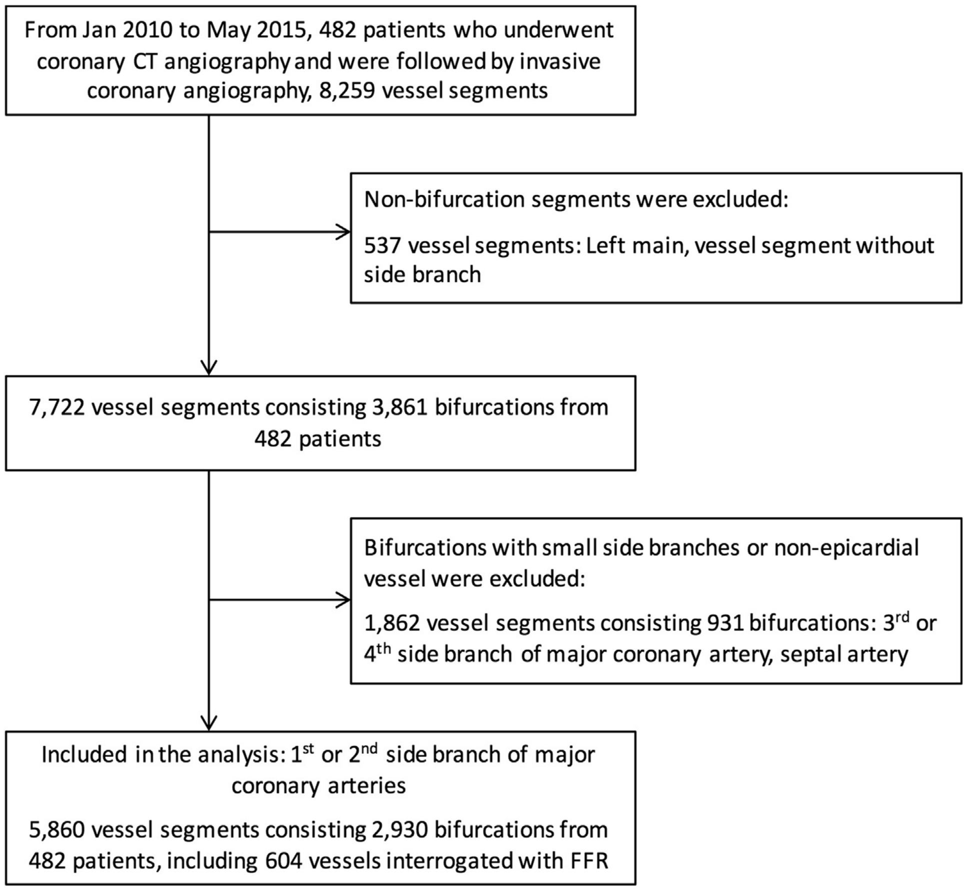
FIGURE 2 **Study Enrollment**



FFR = fractional flow reserve; CT = computed tomography.

living organisms. It also successfully explains the mismatch between anatomic coronary artery stenosis and physiological severity of stenosis (7).

We computed FMM using a stem-and-crown model based on the allometric scaling between length of coronary arterial tree and left ventricular (LV) myocardial mass (7). Each stem and crown was defined by a corresponding vessel segment and arterial tree distal to the stem. Left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA) were defined as major arteries. First septal artery, diagonal branches, obtuse marginal branches (OM), posterior descending artery (PDA) and posterolateral (PL) branches were defined as 1st order branches of major arteries. Arterial segments that do not directly perfuse LV myocardium were excluded, which were the RCA segment from the ostium to the distal RCA, right ventricular branches, and left main segment (**Figures 1A to 1G**, gray-colored vessels). FMM of each vessel segment was calculated by total LV myocardial mass and the fraction of corresponding cumulative arterial tree length to total arterial tree length adjusted by power of the $4/3^{rd}$ (7). FMM of the RCA and left main was calculated by sum of FMM of the PDA and PL branches, and by the sum of FMM of the LAD, LCX, and ramus arteries if existed, respectively. %FMM, a fraction of the myocardium at risk subtended by the specific vessel segment, was defined as % fraction of FMM to total myocardial mass. The amount of SB-specific myocardium that may benefit from revascularization was defined as %FMM ≥10% based on the mortality risk by optimal medical therapy or revascularization in single-photon emission computed tomography studies (8).

DEFINITION OF MV AND SB IN BIFURCATION. Left main bifurcation was defined by proximal LAD and proximal LCX as MV and SB, respectively (**Figure 1C**). In non-left main bifurcations, we selected 2 SB for each major coronary artery. For LAD, mid-LAD-1st diagonal and distal LAD-2nd diagonal; for LCX, mid-LCX-1st OM and distal LCX-2nd OM; for RCA, PL-PDA and distal PL-1st PL, respectively (**Figures 1C to 1G**).

STATISTICAL ANALYSIS. Analysis was done on a per-vessel basis due to the presence of multiple bifurcations in a heart. Data were not normally distributed, and nonparametric statistics were applied. Categorical variables are presented with frequencies and percentages. Continuous variables are presented with median with 1st and 3rd quartiles. FFR and quantitative angiography data were treated as continuous scale. FFR <0.80 and %FMM ≥10% were used as dichotomized parameters for physiologically significant stenosis and clinically relevant amount of myocardium that may benefit more from revascularization than optimal medical therapy, respectively. Dose-response relation between FMM and vessel location was assessed by Cochran-Armitage test for trend. Diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were presented with proportions and 95% confidence intervals. Performance of vessel length for discrimination of %FMM ≥10% was evaluated by receiver-operating characteristics with DeLong's method and multivariate regression. To adjust clustered nature of branches and intrapatient autocorrelation, 5 variables that might be related to %FMM ≥10% including SB length, left main bifurcation, reference vessel diameter, LV mass, and FFR were selected. Dichotomous cutoffs were calculated by deLong's method and used in generalized estimating equations predicting independent parameters for %FMM ≥10% with an assumed binomial family distribution. A 2-tailed $p < 0.05$ was considered statistically significant. R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) was used.

RESULTS

BIFURCATIONS. A total of 8,259 vessel segments from 482 patients were enrolled. Nonbifurcation vessel segments (n = 537) and bifurcations that were not targets for revascularization such as a SB having reference diameter <1.5 mm or nonepicardial septal branches (n = 1,862) were excluded. Finally, 5,860 vessel segments consisting of 2,930 bifurcations, which also included 604 vessels interrogated by FFR, were included in the analysis (**Figure 2**).

TABLE 1 Clinical Characteristics

Age, yrs	64 (58–70)
Male	352 (76)
Body mass index (kg/m^2)	24.6 (23.0–26.4)
Diagnosis	
Stable angina	320 (69.2)
Silent ischemia	53 (11.4)
Unstable angina	90 (19.4)
Diabetes	174 (37.6)
Hypertension	283 (61.1)
Dyslipidemia	129 (27.9)
Prior history of smoking	183 (39.5)
Family history of coronary artery disease	30 (6.4)
Prior myocardial infarction	40 (8.6)
Prior percutaneous coronary intervention	69 (14.9)
Chronic kidney disease	5 (0.1)
Prior stroke	7 (1.5)
Left ventricular ejection fraction (%)	65 (59–69)
Hemoglobin	14.0 (12.9–14.7)
Creatinine	0.93 (0.79–1.01)
Total cholesterol	170 (137–202)
LDL-cholesterol	102 (73–129)
HDL-cholesterol	48 (42–57)
Triglyceride	111 (76–147)

Values are mean (interquartile range) or n (%).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

STUDY POPULATION AND CLINICAL CHARACTERISTICS. Most patients had symptomatic angina (89%). The median interval between CCTA and CAG was 17 (1st and 3rd quartile: 7 to 37) days (**Table 1**).

%FMM OF BIFURCATION VESSELS. The median LV mass was 106 g (92 to 126 g). The amount of myocardium supplied by the SB was different between the left main and non-left main bifurcations. %FMM of non-left main bifurcation SB (n = 2,448) was significantly smaller compared with %FMM of left main bifurcation SB (n = 482) ($p < 0.001$, all) (**Figure 3A**, Online Table 1). The ratio between the amount of myocardium supplied by the MV and SB was also different between left main and non-left main bifurcations (1.5-fold vs. 3.7-fold; $p < 0.001$). The ratio was also highly variable according to bifurcation location, from 1.9-fold in PL-PDA bifurcation to 8.8-fold in mid LAD-2nd diagonal branch bifurcation (**Figure 3B**, Online Table 1).

Most left main bifurcation SB supplied a myocardial mass with %FMM ≥10% (97%; n = 467). However, the frequency of non-left main bifurcation SB supplying %FMM ≥10% varied according to the bifurcation location. Only 21% (n = 510) of non-left main bifurcation SB supplied %FMM ≥10% ($p < 0.001$) (**Figure 3C**, Online Table 1).

The optimal cutoff of arterial length for %FMM ≥10% was ≥73 mm and showed good predictive

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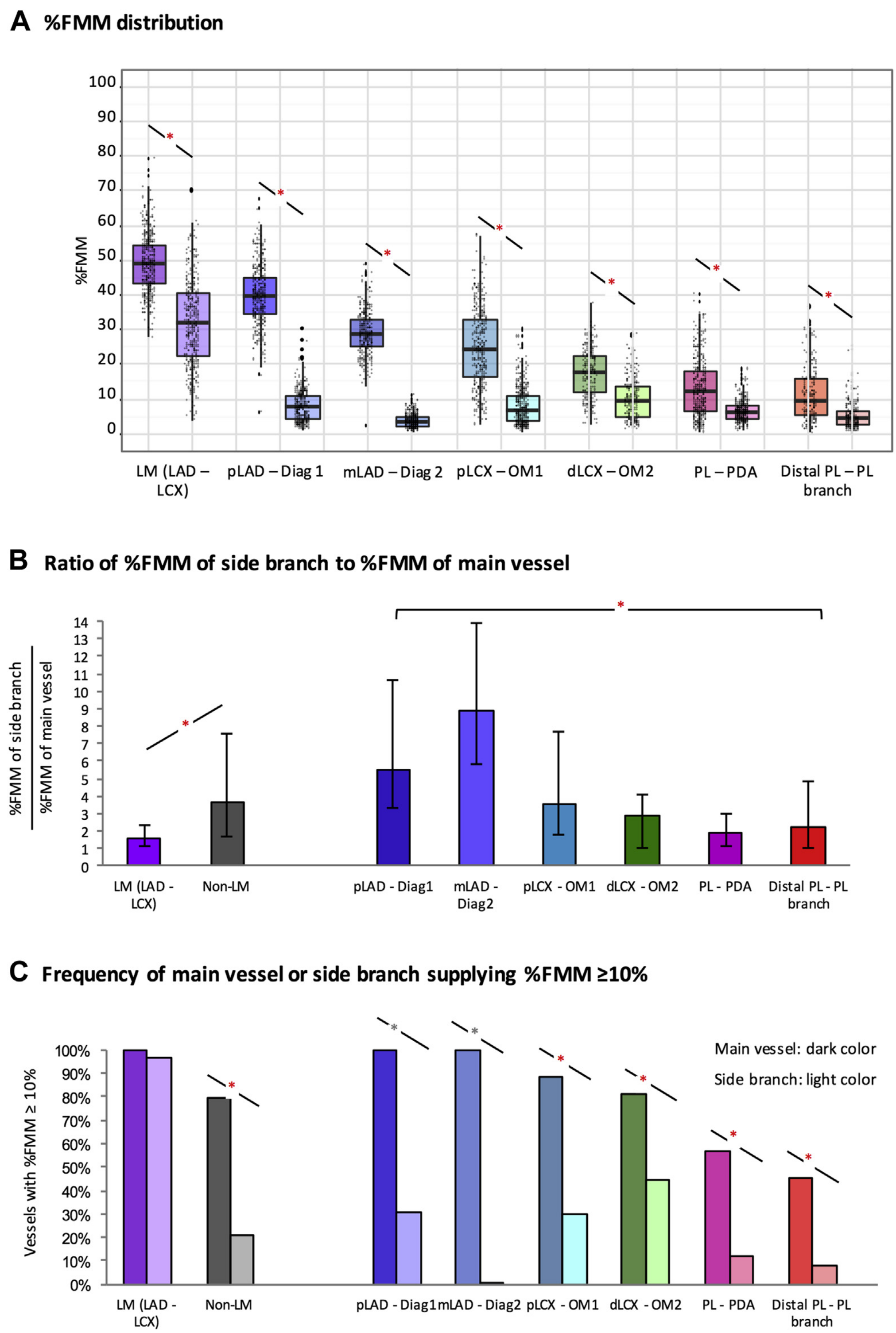
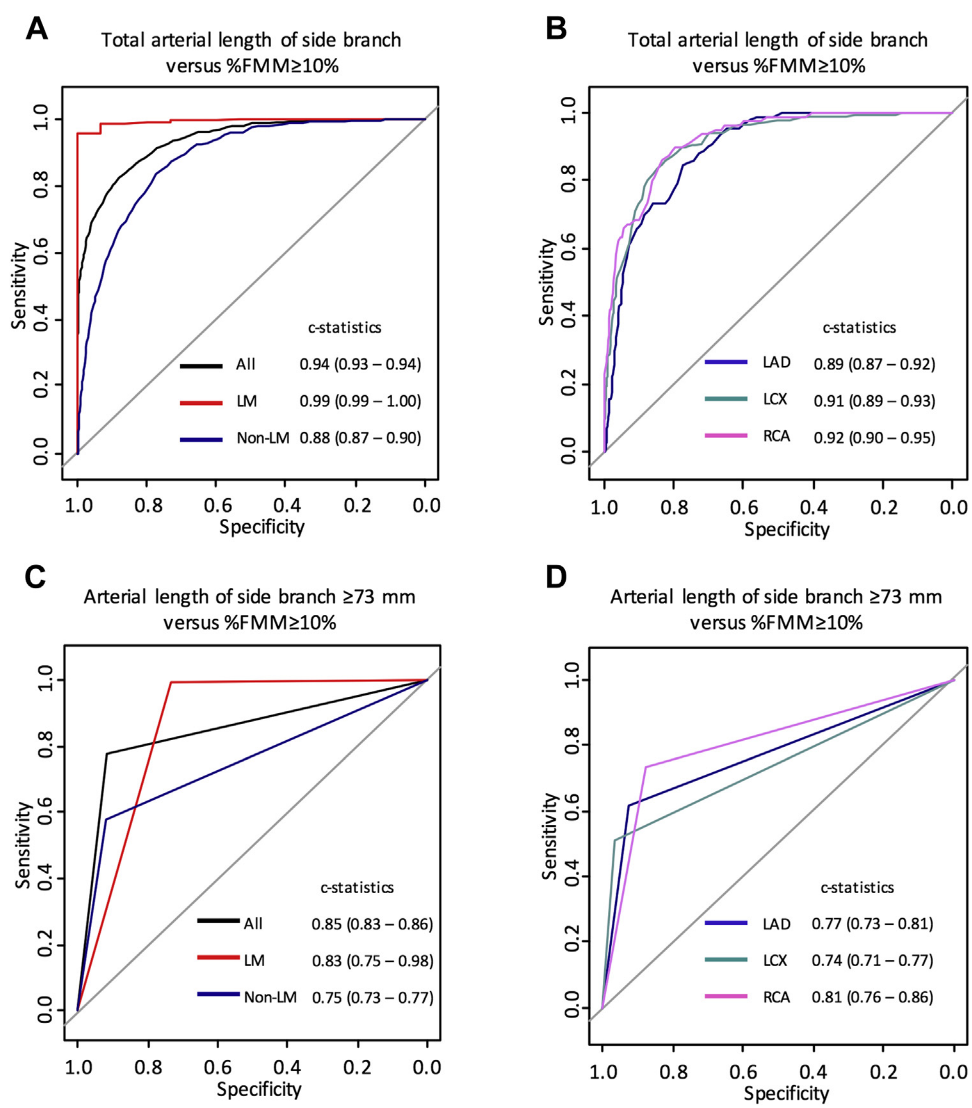
FIGURE 3 FMM of MV and SB



(A) %FMM of left main bifurcation and 6 non-left main bifurcations. %FMM of SB was significantly lower compared with %FMM of MV in all bifurcations ($p < 0.001$, all). Boxes and whiskers indicate respectively median with 1st to 3rd quartiles and 1.5-fold of interquartile ranges. **(B)** Highly various ratio of myocardium supplied by MV to myocardium supplied by SB. **(C)** Unlike left main bifurcation **(violet)**, only 1 of 5 non-left main bifurcation **(gray)** SB supplied %FMM ≥10%. *$p < 0.05$. MV = main vessel(s); SB = side branch(s); other abbreviations as in Figure 1.

FIGURE 4 Performance of Arterial Length for Prediction of SB %FMM ≥10%



Both total arterial length and arterial length ≥73 mm predicted %FMM ≥10% in all vessels, including the LAD, LCX, and RCA. Abbreviations as in Figures 1 and 3.

performance; c-statistic = 0.85 (95% confidence interval: 0.83 to 0.86), sensitivity = 78% (75% to 80%), specificity = 82% (90% to 93%), positive predictive value = 82% (80% to 85%), negative predictive value = 89% (88% to 90%), and accuracy = 87% (86% to 88%). The good-to-fair performance of arterial length ≥73 mm for %FMM ≥10% could be maintained in all bifurcations (c-statistic = 0.70 to 0.99) (Figure 4, Online Table 1). Representative cases of SB having %FMM ≥10% or %FMM <10% are shown in Figure 5.

%FMM OF BIFURCATION VESSELS INTERROGATED BY FFR. The impact of %FMM on the functional significance of stenosis was investigated by subgroup analysis of 604 vessels interrogated by FFR. Compared with MV (n = 462), SB (n = 142) showed similar angiographic diameter stenosis (SB 53% [44% to 64%]; MV 55% [45% to 66%]; p = 0.27), minimal luminal diameter (SB 1.31 mm [0.94 to 1.77]; MV 1.32 mm [0.97 to 1.71]; p = 0.79), and slightly smaller reference diameter (SB 2.81 [2.33 to 3.48]; MV 2.99 mm [2.60 to 3.41]; p = 0.044). However, SB

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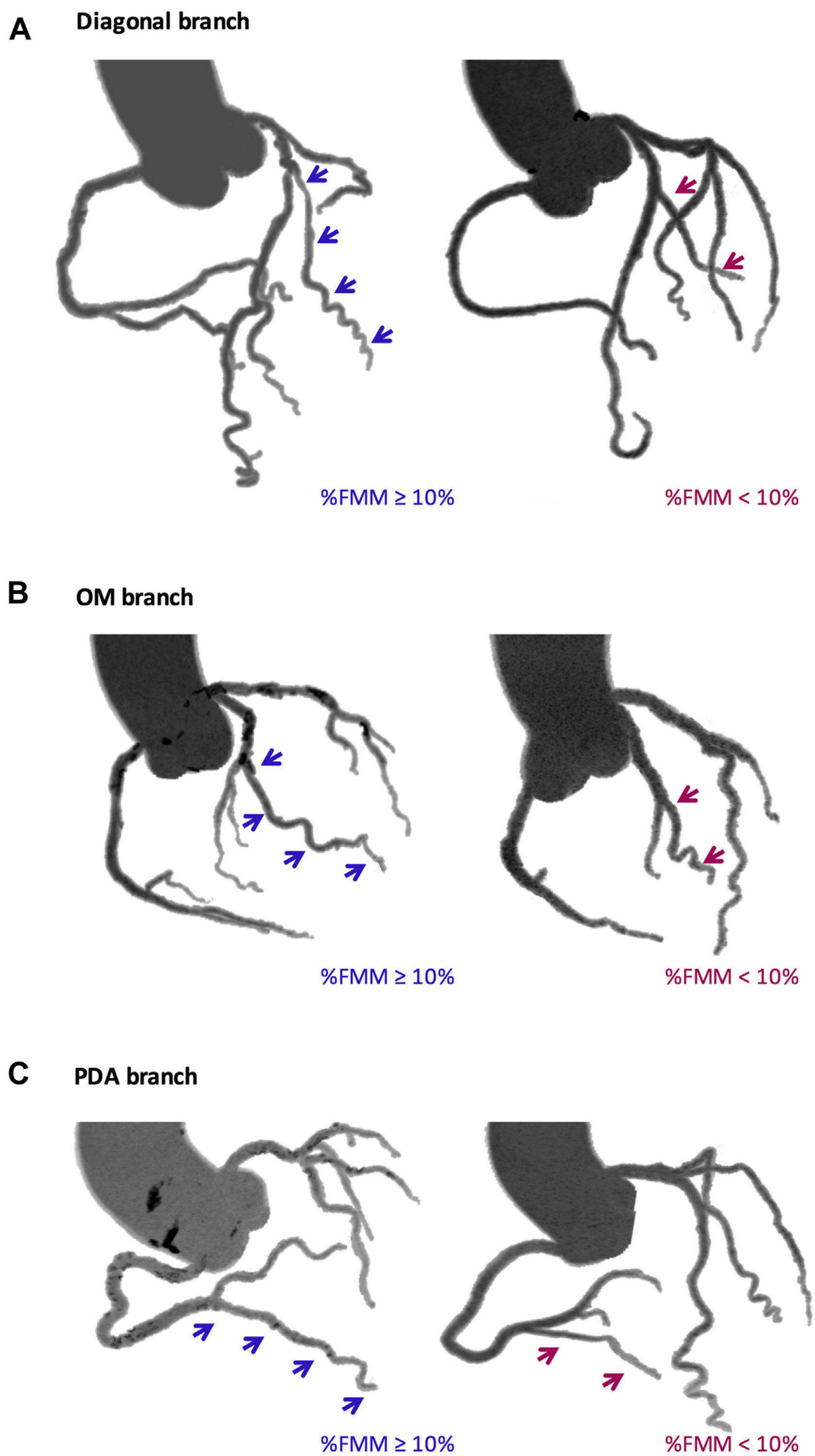
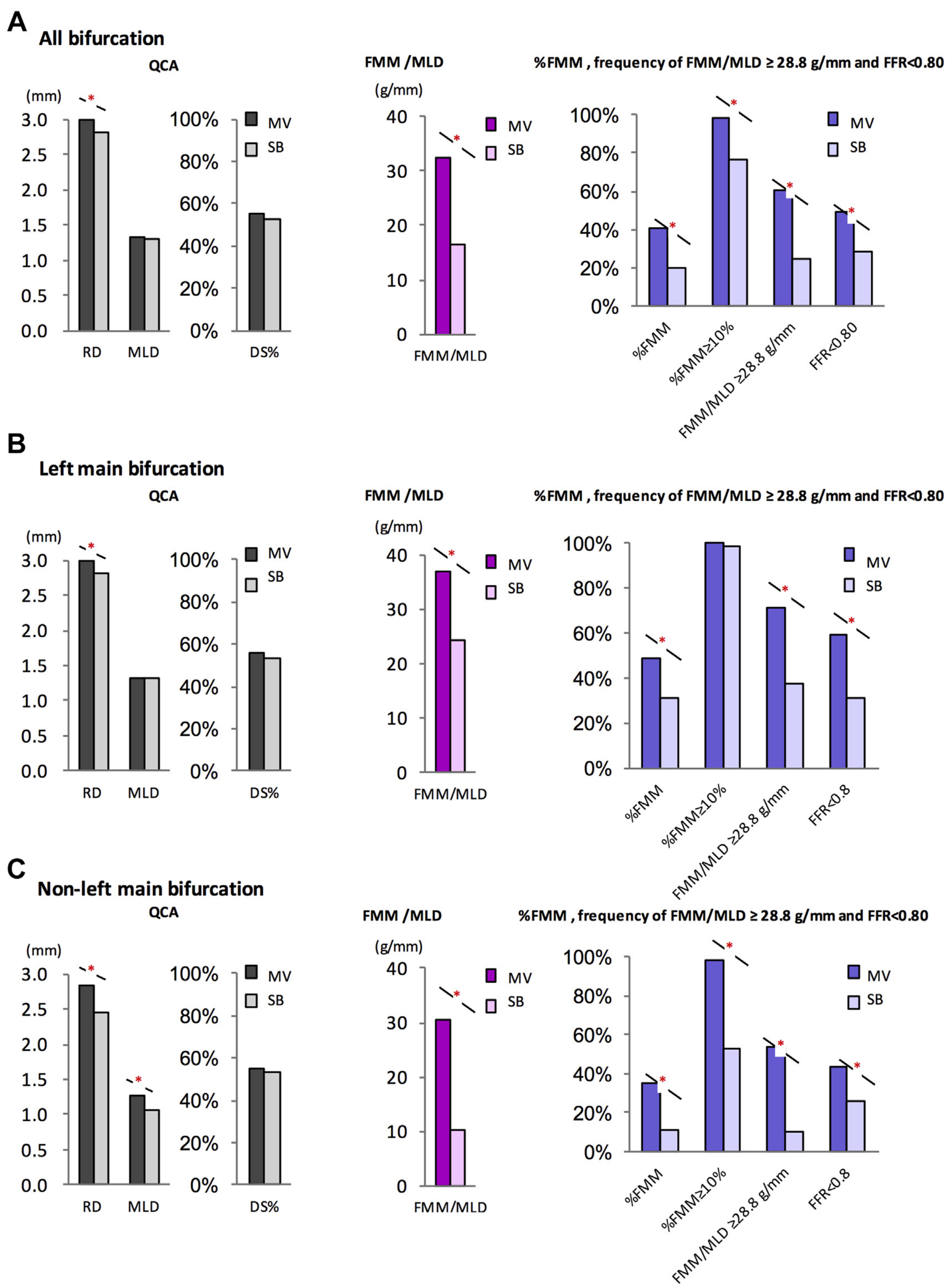
FIGURE 5 Representative Cases of SB With %FMM ≥10% and SB With %FMM <10%



Simulated angiography images derived from coronary computed tomography angiography (CCTA). **Colored arrows** indicate SB with %FMM ≥10% **(blue)** or <10% **(pink)**. Abbreviations as in Figures 1 and 3.

FIGURE 6 **Comparison of Anatomic and Physiological Assessment Between MV and SB**



%FMM, FMM/minimal luminal diameter (MLD), the frequency of FMM/MLD ≥28.8 g/mm, and the frequency of FFR <0.80 were lower in SB compared with MV. Both left main and non-left main showed similar results. *p < 0.05. See Online Table 2 for detailed results. QCA = quantitative coronary angiography; RD = reference diameter; other abbreviations as in **Figures 1 and 3**.

TABLE 2 Multivariate Generalized Estimating Equations Modeling for Prediction of %FMM ≥10%

	Odds Ratio ± SE	p Value
Side branch length ≥73 mm	41.9 ± 2.1	<0.001
Left main bifurcation	345.2 ± 2.9	<0.001
Reference vessel diameter ≥2.68 mm	1.5 ± 1.9	0.73
Left ventricular mass >104.8 g	1.4 ± 1.8	0.61
Fractional flow reserve <0.80	2.3 ± 2.2	0.24

Multivariate generalized estimating equations modeling was performed using optimal cutoffs of each parameters predicting % fractional myocardial mass (%FMM) ≥10%. The respective c-statistics of left main bifurcation, reference vessel diameter ≥2.68 mm, left ventricular mass >104.8 g, and fractional flow reserve <0.80 were 0.820, 0.734, 0.609, and 0.526 ($p < 0.05$, all).

showed significantly lower %FMM (SB 20% [11% to 31%]; MV 41% [32% to 49%]), higher FFR (SB 0.88 [0.77 to 0.93]; MV 0.80 [0.70 to 0.87]), and lower frequency of FFR <0.80 (SB 50%; MV 28%) compared with MV ($p < 0.001$, all). FMM/minimal luminal diameter and frequency of FMM/minimal luminal diameter ≥28.8 g/mm, which are validated as FMM-derived parameters for ischemia (7), were also lower in SB compared with MV (SB 17 g/mm [10 to 21]; MV 33 g/mm [24 to 44], SB 25%; MV 61%; $p < 0.001$, all). These findings were consistent in both left main and non-left main bifurcations (**Figure 6**, Online Table 2).

Because multiple bifurcations exist in a patient, generalized estimating equations modeling using dichotomous parameters was performed to find independent parameters predicting %FMM >10%. Reference vessel diameter ≥2.68 mm, LV mass >104.8 g, and FFR <0.80 were not (p = NS), but SB length ≥73 mm (odds ratio: 42 ± 2; $p < 0.001$) and LM bifurcation (odds ratio: 345 ± 3; $p < 0.001$) were independent predictors for %FMM >10% (**Table 2**).

DISCUSSION

Here, we showed the specific values for regional myocardial mass subtended by each MV and SB of 2,930 bifurcations. Unlike left main bifurcation, only 1 of every 5 non-left main bifurcation SB supplied myocardium mass with %FMM ≥10%, in which revascularization may lead to better clinical outcomes than optimal medical therapy (8). Such potentially clinically important SB could be reasonably identified by vessel length ≥73 mm in all major coronary arteries, including the LAD, LCX, and RCA. In subgroup analysis of vessels interrogated by FFR (n = 604), SB showed similar angiographic stenosis, but lower %FMM and lower prevalence of physiologically significant stenosis, which explains the less functional significance of angiographic stenosis in SB. To our knowledge, this study is the first successful demonstration with robust quantitative data that utilized the concept of regional myocardial mass for anatomy and physiology of bifurcation vessels.

NEEDS OF ASSESSING ISCHEMIC BURDEN IN BIFURCATION DISEASE. Mismatch between anatomic and physiological stenosis is common in bifurcation lesions (3,4). Provisional interventional strategy for SB was comparable to or more favorable than pre-dilation of SB or aggressive 2-stenting strategy (2,9). Occluded SB causes less chest pain and electrocardiographic changes than occluded MV. These findings can be best explained by the intuitive fact that SB supplies a much lower amount of myocardium, which is frequently clinically not relevant, compared with MV. However, there has been no well-established quantitative definition of clinically relevant SB that need revascularization (10). Our study provides a single cutoff value (vessel length ≥73 mm) for a clinically relevant amount of myocardium defined as %FMM ≥10% as well as quantitative amount of myocardium supplied by SB (8). Our result also explains the low frequency of ischemia in SB compared with MV. Recognition of these findings by pre-procedural CCTA may help to select optimal strategy for bifurcation PCI (2,6,9).

Semiquantitative angiographic scoring systems, including Duke Jeopardy, APPROACH, or Syntax score, have been used to estimate the amount of ischemic burden. However, little has been investigated with respect to the estimation of ischemic burden in bifurcation vessels. Also, angiographic scoring systems do not account for the individual anatomic variation of the arterial tree or myocardial mass. FMM enables direct assessment of the vessel-specific amount of ischemic myocardium or myocardium to be saved by revascularization, which may overcome the current limitation of scoring systems. Future studies will be needed to interrogate the prognostic implication of FMM or change of FMM after revascularization of bifurcation disease compared with angiographic scoring systems.

STUDY LIMITATIONS. Vessel-specific amount of myocardium has been investigated based the Voronoi tessellation or allometric scaling law similar to our study (3,7,11,12). These mathematical models have been tested against animal or human models but still do not account for collateral supplies or microvascular function that may affect the actual vessel-specific burden of myocardium. FFR was not interrogated in all bifurcation vessels. FFR is usually not tested for vessels without stenosis or with severe stenosis. However, vessels without stenosis confer low chance of ischemia or risk and do not need any evaluation. Contrarily, highly stenotic vessels do not benefit from invasive physiology for a therapeutic decision. Although we provided representative cases, a vessel length ≥73mm is easily measured in CCTA, but may be challenging in CAG, which projects 3-dimensional arterial course onto 2-dimensional plane. The prognostic implication of measured %FMM was not investigated but is currently under investigation.

CONCLUSIONS

%FMM correlated well with angiographic scores and showed comparable PCI predicting performance. %FMM may be used as an alternative to the angiographic scores in a noninvasive and quantitative manner. PCI was likely to be performed respecting both the amount of jeopardized myocardium and severity of stenosis.

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ADDRESS FOR CORRESPONDENCE: Dr. Jin-Ho Choi, Sungkyunkwan University School of Medicine, Department of Internal Medicine, Department of Emergency Medicine, Samsung Medical Center, 81 Irwon-Ro, Gangnam-Gu, Seoul, 135-710 Korea. E-mail: jhchoimd@gmail.com. OR Dr. Joon-Hyung Doh, Division of Cardiology, Department Internal Medicine, Ilsan-Paik Hospital, Inje University College of Medicine, Juwha-ro 170, Ilsanseo-gu, Goyang-si, Gyeonggi-do 10380, Korea. E-mail: joon.doh@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? In bifurcation percutaneous coronary intervention, a side branch supplying a clinically relevant amount of myocardium may deserve aggressive treatment. However, identification of such a side branch is challenging.

WHAT IS NEW? Only one-fifth of non-left main bifurcation side branches supplied a myocardial mass ≥10%, which could be reasonably identified by vessel length ≥73 mm.

WHAT IS NEXT? Pre-procedural recognition of myocardial mass subtended by the main vessel and side branch may guide an optimal revascularization strategy for bifurcation.

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KEY WORDS bifurcation, fractional myocardial mass, side branch ischemia

APPENDIX For supplemental tables, please see the online version of this article.