

Unprotected Left Main Percutaneous Coronary Intervention: Integrated Use of Fractional Flow Reserve and Intravascular Ultrasound

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• or several decades, bypass surgery has been regarded as $oldsymbol{\Gamma}$ the treatment of choice for patients with unprotected left main coronary artery (LMCA) disease.^{1,2} However, because of easy anatomic accessibility and a relatively large vessel caliber, left main percutaneous coronary intervention (PCI) for LMCA disease has become an attractive option for cardiologists. In addition, technical advances in PCI and stent technology have emboldened physicians to test the feasibility of LMCA intervention and, coupled with the widespread availability of drug-eluting stents (DESs), has led to reevaluation of the role of PCI as a viable alternative treatment for unprotected LMCA disease.³ As a result, during the last decade, the prevalence of LMCA stenting has significantly increased worldwide. In addition, several recent large registries⁴⁻¹³ and randomized controlled trials¹⁴⁻¹⁷ have demonstrated that LMCA stenting yields mortality and morbidity rates comparable to coronary artery bypass grafting (CABG).

Hence, it is timely to now move the discussion forward on how to optimize PCI results, beyond the feasibility and safety issues with LMCA stenting. In this review, we briefly summarize the current status of LMCA stenting and discuss the concept of optimal LMCA stenting through integrated use of fractional flow reserve (FFR) and intravascular ultrasound (IVUS).

Current Status of LMCA Stenting

On the basis of increasing off-label experiences with stenting and clinical studies, 4^{-22} the American Heart Association/

J Am Heart Assoc. 2012;1:e004556 doi: 10.1161/JAHA.112.004556.

American College of Cardiology²³ and the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery.²⁴ recently updated the PCI guideline for the elective treatment of LMCA stenosis to include class IIa indications with a B level of evidence depending on the anatomical complexity of the coronary artery disease. Therefore, DES implantation is currently considered an alternative option for selected patients with unprotected LMCA disease. Table 1 summarizes key observational studies, meta-analyses, and randomized trials that compare PCI with DES and CABG.^{4–22} Detailed guidelines are summarized in Table 2. However, many unresolved technical issues remain, including how to assess the functional significance of intermediate LMCA stenosis and how to optimize procedural outcomes, especially for LMCA bifurcation lesion PCI. In this regard, daily practice has already changed to include more use of FFR and IVUS for LMCA stenting.25,26

Why Should We Consider FFR in Intermediate LMCA Stenosis?

Identification of significant stenosis of LMCA is of critical prognostic importance. Nevertheless, an angiographic stenosis diameter of 50% is still considered a cutoff value for significant LMCA stenosis. Hamilos et al²⁷ were the first to demonstrate the considerable discrepancy between coronary angiography and fractional flow reserve (FFR) in the evaluation of intermediate LMCA stenosis. Among the 213 patients in their study, 62 patients (29.1%) showed a "visual functional mismatch" between angiographic significance and functional significance, 13 patients had a diameter stenosis >50% while the FFR was >0.80, and 49 patients had a diameter stenosis <50% while the FFR was <0.80. It is interesting to note that the prevalence of "reverse mismatch," which refers to angiographically insignificant but functionally significant stenosis, was dominant and as high as 79.0% among the mismatched patients. Figure 1 demonstrates the discrepancy between coronary angiography and FFR.

In addition, noninvasive functional testing such as myocardial perfusion imaging is often noncontributive in the

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Table 1. Key Comparative Studies of PCI and CABG for Left Main Disease

Design	Contributing Studies	PCI (n)	CABG (n)	Follow-up Duration	Adjusted Risk for Death	Adjusted Risk for TVR/TLR
Observational study	MAIN-COMPARE ⁴	784	690	5 years	HR 1.00 (0.73 to 0.37) <i>P</i> =0.99	HR 6.45 (3.75 to 11.09) <i>P</i> =0.34
	Lee et al ⁵	153	50	6.7 months	4% for PCI 13% for CABG <i>P</i> =0.18	7% for PCI 1% for CABG <i>P</i> =0.22
	Chieffo et al ⁶	107	142	1 year	OR 0.33 (0.06 to 1.40) <i>P</i> =0.17	OR 4.22 (1.49 to 14.55) <i>P</i> =0.005
	Palmerini et al ⁷	94	154	1.2 years	HR 0.99 (0.47 to 2.07) <i>P</i> =0.97	25.5% for PCI 2.6% for CABG <i>P</i> =0.0001
	Sanmartin et al ⁸	96	245	1 year	5.2% for PCI 8.4% for CABG <i>P</i> =0.34	5.2% for PCI 0.8% for CABG <i>P</i> =0.004
	Makikallio et al ⁹	49	238	1 year	4% for PCI 11% for CABG <i>P</i> =0.14	4% for PCI 2% for CABG <i>P</i> =0.29
	Cheng et al ¹⁰	94	216	3 years	12.1% for PCI 21.1% for CABG <i>P</i> =0.01	16.0% for PCI 6.1% for CABG <i>P</i> =0.002
	Wu et al ¹¹	131	245	3 years	HR 0.22 (0.06 to 0.81) <i>P</i> =0.02	HR 2.69 (1.30 to 5.57) <i>P</i> =0.008
	Park et al ¹²	205	257	3 years	OR 1.20 (0.70 to 2.08) <i>P</i> =0.51	OR 5.56 (2.85 to 10) <i>P</i> <0.001
	CUSTOMIZE ¹³	222	361	1 year	HR 1.1 (0.4 to 3.0) <i>P</i> =0.81	HR 8.0 (2.2 to 28.7) <i>P</i> =0.001
Meta-analysis	Takagi et al ¹⁹	1006	1175	3 months to 3 years	OR 0.99 (0.69 to 1.43) <i>P</i> =0.97	OR 5.05 (3.07 to 8.30) <i>P</i> <0.001
	Lee et al ²⁰	1236	1669	1 year	OR 0.83 (0.64 to 1.25)	OR 2.27 (1.69 to 3.13)
	Naik et al ²¹	1659	2114	1 to 3 years	OR 1.27 (0.83 to 1.94)	OR 3.30 (0.96 to 11.33)
	Capodanno et al ²²	809	802	1 year	OR 0.74 (0.43 to 1.29) <i>P</i> =0.29	OR 2.25 (1.54 to 3.29) <i>P</i> <0.001
Randomized controlled trial	Buzman et al ¹⁴	52	53	1 year	1.9% for PCI 7.5% for CABG <i>P</i> =0.37	9.7% for PCI 9.4% for CABG <i>P</i> =0.97
	SYNTAX substudy ¹⁵	357	348	1 year	4.2% for PCI 4.4% for CABG <i>P</i> =0.88	6.5% for PCI 11.8% for CABG <i>P</i> =0.02
	Boudriot et al ¹⁶	100	101	1 year	5.0% for PCI 7.98% for CABG	5.9% for PCI 14.0% for CABG
	Park et al ¹⁷	300	300	1 year	4.4% for PCI 4.7% for CABG <i>P</i> =0.83	9.0% for PCI 4.2% for CABG <i>P</i> =0.02

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting; TVR, target-vessel revascularization; TLR, target-lesion revascularization; SYNTAX, the Synergy between PCI with Taxus and Cardiac Surgery.

diagnosis of patients with intermediate LMCA stenosis. Perfusion defects are often seen in only 1 vascular territory, or tracer uptake may be reduced in all vascular territories ("balanced ischemia") giving rise to false-negative studies, especially when the right coronary artery is significantly diseased. $^{\rm 28}$ This is another reason why we should measure FFR for intermediate LMCA stenosis.

Therefore, the decision about whether the treatment of intermediate LMCA stenosis should be performed or deferred should not be determined by coronary angiogram alone, and

Guidelines	COR	LOE			
2011 ACC/AHA Guidelines ²³	Ila—For SIHD when both of the following are present:				
	Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score of \leq 22, ostial or trunk left main stenosis)	В			
	Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality \geq 5%)				
	Ib—For SIHD when both of the following are present:				
	Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (eg, low-intermediate SYNTAX score of <33, bifurcation left main stenosis)	В			
	Clinical characteristics that predict an increased risk of adverse surgical outcomes (eg, moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality >2%)				
	III—For SIHD in patients (vs performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	В			
2010 ESC Guidelines ²⁴	Ila-Left main (isolated or 1VD, ostium/shaft)	В			
	IIb—Left main (isolated or 1VD, bifurcation)/left main+2VD or 3VD, SYNTAX score ≤32				
	IIIb—Left main+2VD or 3VD, SYNTAX score ≥33	В			

ACC indicates American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; COR, class of recommendation; LOE, level of evidence; SIHD, stable ischemic heart disease; SYNTAX, the Synergy between PCI with Taxus and Cardiac Surgery; STS, Society of Thoracic Surgeons; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; VD, vessel disease.



Figure 1. Representative case of visual–functional mismatch in LMCA stenosis. A, Visually estimated percentage diameter stenosis was \approx 60%, but FFR was 0.86. B, Visually estimated percentage diameter stenosis was \approx 20%, but FFR was 0.70. LM indicates left main; MLA, minimal lumen area; FFR, fractional flow reserve; LMCA, left main coronary artery.

FFR measurement for intermediate LMCA evaluation should be required, especially in cases of ostial and shaft LMCA disease. FFR measurement could avoid unnecessary LMCA stenting or bypass surgery. Revascularization of a nonsignificant stenosis in the LMCA may lead to early occlusion of the conduits, especially when internal mammary arteries are used.²⁹ In addition, when significant LMCA stenosis is highly suspected in a noninvasive functional study in patients with angiographically mild LMCA stenosis, FFR measurement reduced the risk that functionally significant LMCA stenosis remained unrevascularized.

FFR>0.80 Is a Good Predictor of Favorable Prognosis in Intermediate LMCA Stenosis

An FFR>0.75 to 0.80 has been suggested as a strong predictor of favorable survival and low event rates in patients with intermediate LMCA disease, making it useful for the identification of patients in whom deferral of revascularization is associated with favorable clinical outcomes. In an evaluation of patients with intermediate LMCA stenosis, patients with an FFR>0.80 treated medically had survival rates comparable to patients with an FFR<0.80 who underwent CABG. Therefore, FFR-guided decision making for the treatment of intermediate LMCA stenosis is associated with favorable prognosis, and intermediate LMCA disease with an FFR>0.75 to 0.80 could be safely deferred. Table 3 summarizes key studies that demonstrate FFR-guided decision making in intermediate LMCA stenosis stenosis.^{27,30–33}

Conceptual Limitations of FFR in Intermediate LMCA Stenosis and a Practical Approach

FFR measurement of intermediate ostial and shaft stenosis of LMCA provides accurate information about the functional status of angiographic intermediate stenosis (Figure 2A). However, many physicians have raised questions about the reliability of FFR measurement for the intermediate bifurcation stenosis of LMCA, as they consider the distal LMCA bifurcation as the tandem lesion interposing the large side branch.^{34,35} Therefore, FFR of intermediate LMCA stenosis tends to be under- or overestimated because of additional disease in the left anterior descending artery (LAD) and left circumflex artery (LCX) (Figure 2B); thereby, accurate assessment of functional status of intermediate LMCA stenosis itself would not be possible. However, this is only a conceptual limitation. Determining the functional significance and planning for treatment strategy are different issues. Recent IVUS analysis demonstrated the diffuse nature of atherosclerosis involving both the parent (LMCA) segment and both flow dividers (LAD and LCX).³⁶ Atherosclerotic plaques extend

3. Clinical Outcomes of LMCA Stenosis Managed by FFR-Guided Decision Making

Table

Hami	ilos et al ²⁷	Bech et a	al ³⁰	Courtis et al ³¹		Lindstaedt e	t al ³²	Jasti et al ³³	
Age, y 64±	<u>-</u> 9 68±11	63±9	6一0	61土10	63±10	61±10	64±9	6 2±11	
Mean follow-up, months 35±	-25	29±15		13土10	14土12	29±18	29土14	38	
No. of patients 75	138	30	24	60	82	27	24	14	37
FFR cutoff value <0.8	30 ≥0.80	<0.75	≥0.75	<0.75*	>0.80	<0.75*	>0.80	<0.75	≥0.75
Treatment CAB	G Medicatio	n [†] CABG	Medication*	Revascularization (CABG 54, PCI 6)	Medication	CABG	Medication [†]	Revascularization (CABG 7, PCI 7)	Medication
Clinical outcomes									
Death, n (%) 7 (9.	.6) 9 (6.5)	-	0	3 (5)	3 (4)	4 (14.8)	0	0	3 (NC)
Myocardial infarction, n (%) 0	-	-	0	1 (2)	4 (5)	1 (3.7)	0	0	0
Revascularization, n (%) 4 (5.	.5) 17 (12.3)	2	5	0	9 (11)	1 (3.7)	6 (25) [‡]	0	4



Figure 2. Practical approach for the evaluation of functional significance of left main coronary artery stenosis. LAD indicates left anterior descending artery; LCX, left circumflex artery.

from the LMCA to the LAD in 90% of patients and LCX in 62% of patients, which suggests distal LMCA bifurcation could not be treated separately and considered as a "single disease unit" (Figure 2C). Therefore, if both FFRs of LAD and LCX side are >0.80, distal LMCA bifurcation is functionally insignificant. If any FFR of LAD and LCX side is \leq 0.80, practically, distal LMCA bifurcation PCI as suggested below should be considered, without consideration of the functional significance of intermediate stenosis of the LMCA.

Another reason why the FFR of intermediate LMCA stenosis should be interpreted with caution is that isolated LMCA stenoses are very rare, with most stenoses associated with disease in the LAD and/or LCX, both of which tend to increase FFR measured across the LMCA stenosis. Therefore, in this case, the reassessment for the functional significance of intermediate LMCA stenosis is recommended after the correction of distal coronary artery stenosis.

Complementary Roles of Intravascular Ultrasound in Functional Evaluation of LMCA Stenosis

Because of the limitations of the conventional coronary angiogram in assessing the severity of LMCA stenosis, there have been several attempts to compare the anatomical parameter assessed by intravascular ultrasound (IVUS) with the corresponding FFR measurement.

Jasti et al³³ reported that an MLA of 5.9 mm² had the highest sensitivity and specificity (93% and 95%, respectively) for determining a significant LM stenosis, compared with FFR as the gold standard. Recently, clinical application of an MLA criterion for treatment decision making for intermediate LMCA stenosis was tested.³⁷ In the LITRO study, a total of 354 patients with intermediate LMCA stenoses were enrolled.

In patients with an MLA<6 mm², revascularization were performed, and in patients with an MLA≥6 mm², revascularization was deferred. In a 2-year follow-up period, there were no statistical between-group differences regarding the incidence of death (2.3% versus 4.5%, respectively; *P*=0.5) and any event (12.7% versus 19.4%, respectively; *P*=0.3). Therefore, they suggested an MLA ≥6 mm² was a safe value for deferring revascularization of the LMCA.

We recently addressed these issues in 55 patients with isolated intermediate LMCA stenosis who underwent preinterventional IVUS and FFR measurements to determine the IVUS MLA criterion corresponding to an FFR<0.80.38 We found that the IVUS MLA value within the LMCA that best predicted FFR<0.80 was <4.8 mm² (89% sensitivity, 83% specificity, 86% accuracy; AUC 0.90, 95% CI 0.788 to 0.964, P < 0.001). It is interesting to note that that the positive predictive value of IVUS-measured MLA<4.8 mm² is acceptably high at 82%, in contrast with non-LMCA stenosis (Figure 3).³⁸ This might be explained by the simplicity of morphological characteristics of pure LM lesions, uniformly large vessel size, short lesion length, and lack of side branch and other anatomical factors that could potentially affect FFR. Therefore, in the evaluation of intermediate LMCA stenosis, anatomical parameter provided by IVUS appeared to be correlated well with functional significance of LMCA stenosis.

How to Perform Unprotected LMCA Stenting

From a technical perspective, it would be easy to perform a single-stent procedure for ostial and shaft LM disease; published long-term clinical outcomes are excellent.^{39–41} The current PCI guideline was updated as mentioned before.^{23,24} For LMCA bifurcation disease, unresolved



Figure 3. Correlation between minimal lumen area and fractional flow reserve in intermediate left main coronary artery stenosis. FFR indicates fractional flow reserve. With permission from Kang et al.³⁸

technical issues remain. The single-stent technique clearly shows more favorable long-term clinical outcomes compared with the 2-stent technique, even in bifurcation LM disease.^{42–45} Therefore, in real practice, the single-stent crossover technique has been used more frequently, in as many as \approx 60% of all LMCA bifurcation treatments.⁴² Selection of a single- or 2-stent technique should be based on disease involvement of the LCX ostium, because side-branch compromise after stent crossover is frequent in the setting of significant ostial disease of the side branch (Table 4). Thus, to determine the choice of a single- or 2-stent strategy, IVUS provides accurate information for both main- and side-branch

Table 4. Favorable or Unfavorable Anatomical Features for Single-Stent Crossover Stenting in Treatment of Unprotected Left Main Coronary Artery Stenosis⁵⁴

	Anatomical Features
Favorable	Insignificant stenosis at the ostial LCX with Medina classification 1,1,0 or 1,0,0
	Diminutive LCX with <2.5 mm in diameter; right dominant coronary system
	Wide angle with LAD
	No concomitant disease in LCX
	Focal disease in LCX
Unfavorable	Insignificant stenosis at the ostial LCX with Medina classification 1,1,1; 1,0,1; or 0,1,1
	Large size of LCX with ≥2.5 mm in diameter; left dominant coronary system
	Narrow angle with LAD
	Concomitant disease in LCX
	Diffuse disease in LCX

LCX indicates left circumex artery; LAD, left anterior descending artery. Table is adapted with permission from Moussa et al. $^{\rm 54}$



Figure 4. Geometric changes in left main coronary artery bifurcation after main-branch stenting. Longitudinal image reconstruction demonstrated carina shift into the LCX poststenting (arrow). EEM indicates external elastic membrane; P+M, plaque area plus media area; LAD, left anterior descending artery; LCX, left circumflex artery. Adapted with permission from Kang et al.⁴⁷

disease status and vascular remodeling in LMCA bifurcation lesions. In addition, if possible, direct imaging from the LCX is necessary for accurate assessment of the side branch, including its ostium, because IVUS evaluation of a sidebranch ostium from the main vessel is only moderately reliable.⁴⁶

After main-stent crossover from the proximal left anterior descending artery (LAD) to LM, geometric changes in the LCX ostium were related mainly to carina shift, reduction of MLA, and increased eccentricity of the external elastic membrane and carina angle between the LAD and the LCX (Figure 4).⁴⁷ However, an important issue is being unable to predict the functional significance of the stenosis with only the degree of jailed LCX ostium, no matter how big or small. Therefore, in cases in which the LCX ostium is significantly compromised (>50%) after simple crossover stent implantation from LM to LAD, we should consider FFR measurement first before further treatment of the LCX.

IVUS Minimal Stent Area Criteria Optimizing the Clinical Outcomes

Optimal stent expansion was considered one of the most important factors in preventing restenosis or adverse clinical outcomes.^{48,49} However, there are no data suggesting the optimal minimal stent area (MSA) cutoff for prediction of

restenosis and long-term clinical outcome after DES implantation for LMCA stenosis.

Recently, we studied the optimal IVUS-MSA criteria for prevention of in-stent restenosis (ISR) in 403 patients undergoing sirolimus-eluting stent implantation for LMCA disease.⁵⁰ We classified the LMCA into 4 segments: the LCX ostium, LAD ostium, polygon of confluence (POC), and LMCA above the POC. The best IVUS-MSA criteria that predicted angiographic ISR on a segmental basis were 5.0 mm² for the LCX ostium, 6.3 mm² for the LAD ostium, 7.2 mm² for the POC, and 8.2 mm² for the proximal LMCA above the POC (Figure 5).⁵⁰ Using these criteria, 133 patients (33.8%) experienced underexpansion ≥ 1 of the prespecified segments. In addition, underexpansion was more frequent in the 2-stent group than in the single-stent group (54% versus 27%, respectively, P=0.001). In the 2-stent group, the LCX ostium was the most common site of underexpansion (37%), which may explain the greater risk of ISR when LMCA bifurcation lesions are treated with a 2-stent strategy. Overall, angiographic ISR was more frequent in lesions with underexpansion than in lesions without underexpansion (24.1% versus 5.4%, respectively; P=0.001). Even in the 2-stent group, lesions with complete expansion at all sites showed only 6% of the ISR rate, which was similar to that of the single-stent group (6.3%) or in nonbifurcation LMCA lesions (4.5%). Furthermore, a smaller IVUS-MSA predicted angiographic ISR 9 months after DES implantation for treatment of LMCA disease, and poststenting underexpansion was an independent predictor of 2-year adverse clinical outcomes, especially repeat revascularization.



Figure 5. Cutoff values of minimal stent area for the prediction of angiographic in-stent restenosis on a segmental basis. LM indicates left main; POC, polygon of confluence; LAD, left anterior descending artery; LCX, left circumflex artery. Adapted with permission from Kang et al.⁵⁰

Impact of IVUS Guidance for LMCA Stenting

Although IVUS guidance has been useful in stenting unprotected LMCA stenoses, its impact on long-term mortality is still unclear. In 201 matched pairs from the MAIN-COMPARE registry, there was a tendency of lower risk for 3-year mortality with IVUS guidance compared with angiography guidance (6.0% versus 13.6%, respectively; log-rank P=0.063; hazard ratio 0.54).²⁶ In particular, for 145 matched pairs of patients receiving DES, the 3-year mortality was significantly lower for IVUS guidance compared with angiography guidance (4.7% versus 16.0%, respectively; log-rank P=0.048; hazard ratio 0.39). It is interesting to note that the mortality rate started to diverge beyond 1 year after the procedure. In contrast, the use of IVUS did not reduce the risk of mortality in 47 matched pairs of patients receiving a bare-metal stent (8.6% versus 10.8%, respectively; log-rank P=0.35; hazard ratio 0.59). Therefore, despite inherent limitations of nonrandomized registry design, this study indicated that IVUS guidance may play a role in reducing very late stent thrombosis and subsequent long-term mortality.

IVUS guidance has provided more information on negative remodeling, reference vessel size, and morphologic complexity of ostial or bifurcation lesions in preintervention evaluation, stent underexpansion, incomplete lesion coverage, small stent area, large residual plaque, and incomplete stent apposition in postinterventional evaluation.^{51–53} For LMCA lesions, in particular, the use of IVUS is helpful in determining treatment strategy and in optimizing the stent procedure. Therefore, we strongly recommend mandatory use of IVUS in PCI for unprotected LMCA.



Figure 6. Integrated use of FFR and IVUS in left main stenting. LMCA indicates left main coronary artery; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MLA, minimal lumen area; MSA, minimal stent area.

Conclusions

FFR-guided PCI can help to select appropriate patients and lesions for treatment, avoid unnecessary procedures, reduce medical costs, and improve clinical outcomes. Furthermore, IVUS can be used to secure the PCI procedure by preinterventional lesion assessment and postinterventional stent optimization. We propose the concept of the integrated use of FFR and IVUS in LMCA stenting (Figure 6). Despite several limitations of this approach including cost, procedural time, and availability of trained personnel, FFR-guided complex PCI, which is supported by IVUS, can give us better insights into LMCA disease and may improve the clinical outcomes of patients who undergo LMCA stenting.

Sources of Funding

This study was supported by funds from the CardioVascular Research Foundation, Seoul, Korea, and a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (A102065).

Disclosure

None.

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Key Words: fractional flow reserve • intravascular ultrasound • left main stenosis • stent