Update on FFR, OCT, and IVUS

Expanded use of these modalities could overcome the limitations of coronary angiography.

BY KONSTANTINOS MARMAGKIOLIS, MD, MBA, FACC, FSCAI; MASSOUD LEESAR, MD, FACC, FSCAI; AND MEHMET CILINGIROGLU, MD, FSCAI, FACC, FESC, FAHA

Coronary angiography remains the most commonly used imaging modality to describe the degree and extent of coronary atherosclerosis during diagnostic cardiac catheterization and percutaneous coronary intervention (PCI). Its accuracy is affected by technical limitations, important interobserver variability, and its poor visualization of the vessel wall. Furthermore, it provides limited information about the functional significance of the lesion. Today, intravascular ultrasound (IVUS), fractional flow reserve (FFR), and optical coherence tomography (OCT) are extensively used to overcome the aforementioned limitations. Despite the increasing published data validating their advantages, IVUS, FFR, and OCT remain largely underutilized.[1]

FRACTIONAL FLOW RESERVE

FFR is the ratio of the mean coronary arterial pressure measured distal to the lesion of interest to the mean aortic pressure with pharmacologically induced maximum coronary hyperemia. It is now widely accepted as the gold standard for the evaluation of functional myocardial ischemia and as a reference for other invasive (IVUS, OCT) and noninvasive (SPECT-MPI, dobutamine echocardiography, and CMP-MPI) modalities.[2]

The initial DEFER study aimed to assess the appropriateness of stenting functionally nonsignificant intermediate coronary stenosis, used a cutoff of FFR < 0.75 for positivity of the test, and demonstrated excellent 5-year results, with a risk of cardiac death or myocardial infarction < 1% for the deferred group (nonstatistically significant compared to the PCI group).[3] After the FAME 1 and 2 trials, which investigated the outcomes of FFR-guided PCI in patients with multivessel coronary artery disease and stable coronary artery disease, respectively, a cutoff of < 0.8 is currently used for the positivity of the test, as recommended by the 2014 expert consensus statement by SCAI.[4] In a more recent trial, Depta et al showed that borderline FFR (0.8–0.85) carries the same risk as gray-zone FFR (0.75–0.8) regarding number of deferred lesion interventions and risk significantly higher than nonborderline FFR (> 0.85), raising the question whether the cutoff of 0.8 needs to be reconsidered.[5]

Intravenous adenosine has been used in most randomized trials as the main hyperemic agent. Intracoronary nicorandil, or sodium nitroprusside and intravenous regadenoson, have been found to induce similar hyperemic response and similar FFR results to adenosine, and they may be safer in selected subgroups.[6-9]

The instantaneous wave-free ratio (iFR) was developed as an alternative to FFR without the need for hyperemia. Using a high-fidelity pressure wire, iFR takes advantage of the "wave-free period," a specific period in diastole during which the pressure and flow are proportionally related (unlike different periods of the cardiac cycle). By averaging those measurements in three to five beats, the functional significance of coronary lesions may be assessed.

The ADVISE, VERIFY, CLARIFY, and RESOLVE trials showed variable correlation rates between iFR and FFR.[10-13] Despite its ease of use, debate regarding its reproducibility, accuracy, and correlation with FFR persists. To date, iFR is not a widely accepted alternative to FFR.

The RIPCORD study, which attempted to assess the impact of routine FFR at the time of diagnostic coronary angiograms, showed that the routine addition of FFR to the coronary angiogram may change the initial managing plan in 26% of patients.[14] Furthermore, FFR-guided coronary artery bypass grafting resulted in a lower number of graft anastomoses and on-pump surgeries, with similar event rates at 26-month follow-up compared to traditional coronary angiogram-guided PCI.[15] A FAME substudy showed that similar angiographic lesions in women may be less ischemia-producing than in men, suggesting increased use of FFR in women to prevent unnecessary PCI.[16] Furthermore, FFR use is cost effective and cost saving.[17-19] The routine use of FFR is associated with fewer stent implantations but no improvement in mortality compared to angiography-guided PCI, as shown by a recent large cohort study.[20]

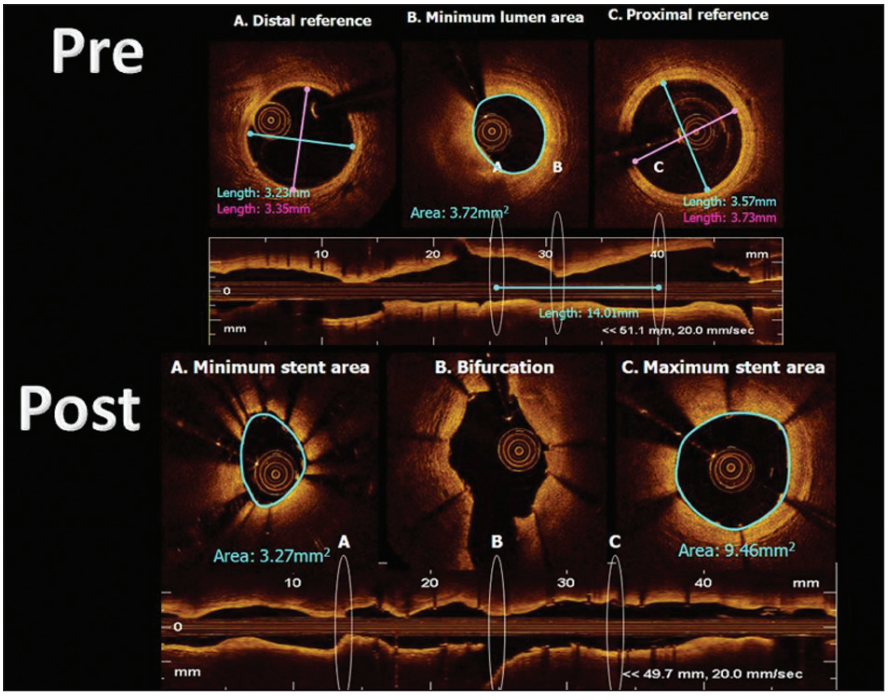

Figure 1. Example of OCT-guided PCI. Preintervention OCT clearly estimates the distal reference area (top row A), the minimum lumen area (top row B), and the proximal reference area (top row C). Postintervention OCT assesses the minimum stent area (bottom row A), the patency of the side branch at the site of the bifurcation (bottom row B), and the maximal stent area (bottom row C).

FFR has not been used in saphenous vein grafts due to the presumed limited response of the vein grafts to adenosine. Di Serafino et al demonstrated that FFR-guided PCI for moderate graft lesions resulted in improved major adverse cardiac and cerebrovascular event rates, with reduced cost compared to angiography-guided PCI.[21]

In an effort to perform a completely noninvasive FFR, FFR(CT) was developed based on computational fluid dynamic techniques. A special software technique using physical laws of mass conservation and momentum balance has managed to estimate fluid pressure and velocity and achieve improved discrimination of hemodynamically significant lesions. FFR(CT) increased the accuracy of regular computed coronary angiography in the NXT, DEFACTO, and DISCOVER-FLOW trials.[22-24]

OPTICAL COHERENCE TOMOGRAPHY

OCT technology uses near-infrared light to produce excellent in vivo imaging of the vessel wall, with an axial resolution of 10 to 15 µm. One of the limitations of OCT is penetration depth of 2 to 4 mm, as well as the requirement of a blood-free environment for optimal imaging.

Before percutaneous intervention, OCT allows accurate description of the vessel size and the extent of the atherosclerotic plaque; identification and characterization of lipid-rich plaques, thin-cap fibroatheroma, calcification, and fibrous cap thickness; distinction between white and red thrombus; and calculation of total thrombus burden.[25] OCT ensures optimal sizing and complete stent coverage of the vulnerable plaque. In prospective, nonrandomized cohorts with serial OCT evaluations in patients with STEMI or acute coronary syndromes, it has been suggested that thrombectomy without angioplasty or stent placement may be sufficient.[26,27]

After PCI, OCT provides detailed description of the stent strut coverage, edge dissections, stent protrusion or fracture, residual thrombus, restenosis, or thrombosis. Data about the long-term clinical consequences of those OCT findings are currently unavailable.

Recently, the use of OCT has been successfully evaluated in saphenous vein grafts, as well as carotid, renal, iliac, superficial femoral, and transplanted coronary arteries.[28-33]

To date, there are no randomized trials supporting the use of OCT to guide PCI. An example of OCT-guided PCI is seen in Figure 1. The DOCTORS trial will assess the use of OCT to optimize results in patients with NSTEMI.[34]

A novel OCT-derived FFR is under investigation, which combines OCT's excellent resolution with FFR's assessment of functional significance based on the calculation of blood flow resistance and hyperemic microvascular resistance.[35]

OCT today has emerged as a user-friendly, fast, and safe imaging modality that offers instant, high-resolution 2D or 3D intravascular images. The main disadvantages are the inability to visualize ostial lesions because of the difficulty of clearing the blood in the coronary ostia and the absence of large randomized trials to assess the clinical significance of the numerous OCT findings. The previously reported OCT drawback of the inability to visualize larger vessels has been overcome with the use of novel OCT technology, and the need for contrast injections, which may be important in patients with kidney disease, can be overcome with use of dextran.

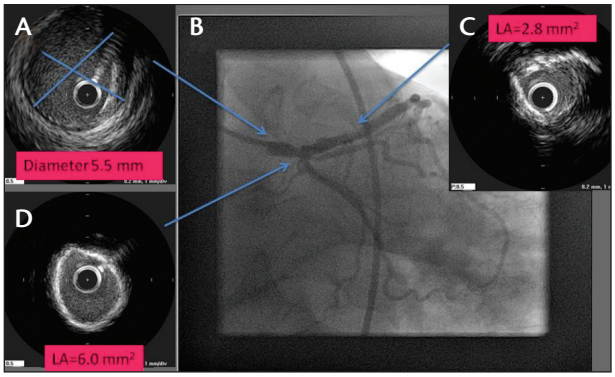

Figure 2. Example of IVUS-guided PCI. IVUS of the ostial left main coronary artery (LMCA) (average diameter = 5.5 mm) (A). Coronary angiography demonstrates tandem lesions of the proximal left anterior descending coronary (LAD) artery and distal LMCA (B). IVUS of the LAD (lumen area = 2.8 mm²; significant) (C). IVUS of the distal LMCA (lumen area = 6 mm²; not significant) (D). The patient underwent stenting of the LAD.

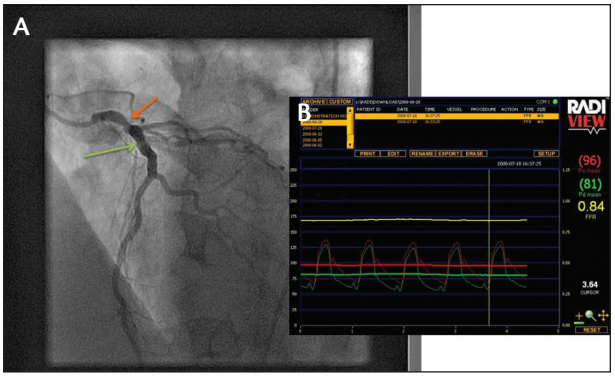

Figure 3. Repeat coronary angiography 2 years later shows a patent stent in the LAD (A), but the LMCA appears significantly stenosed (B). FFR was 0.84, indicating that the LMCA stenosis is not hemodynamically significant (C).

INTRAVASCULAR ULTRASOUND

Stent underexpansion, smaller postprocedure lumen dimensions, residual reference segment stenosis, and the presence of thrombus or dissection have been reported to be the IVUS predictors of restenosis or stent thrombosis.[36,37] A number of studies have demonstrated that IVUS-derived minimum stent area (MSA) after stent deployment is a predictor of in-stent restenosis. In this respect, in the SIRIUS IVUS substudy,[38] an MSA of 5 mm² after deployment of sirolimus-eluting stents highly predicted stent patency, which was defined as an MSA > 4 mm by IVUS at follow-up. Likewise, a recent large study[39] showed that poststenting MSA was the only independent predictor of angiographic in-stent restenosis in patients who underwent zotarolimus-eluting, everolimus-eluting, and sirolimus-eluting stent implantation. The best cutoff values of MSA for predicting ISR were 5.3 mm², 5.4 mm², and 5.5 mm² for zotarolimus-, everolimus-, and sirolimus-eluting stents, respectively.

A meta-analysis of randomized trials demonstrated that stenting with a bare-metal stent guided by IVUS, compared with angiography, significantly reduced major adverse cardiac events.[40] Furthermore, another meta-analysis of 18,707 patients from three randomized studies comparing IVUS-guided stenting with angiography and other studies showed that IVUS guidance reduced the rates of mortality, myocardial infarction, and stent thrombosis, but not the rate of revascularization.[41] Along the same lines, a recently published large-scale prospective, multicenter, nonrandomized ADAPT-DES study of 8,583 patients showed IVUS guidance compared to angiography reduced the risk of stent thrombosis, myocardial infarction, and major adverse cardiac events within 1 year after drug-eluting stent (DES) implantation.[42] Although the ADAPT-DES study supports IVUS-guided DES implantation, large randomized trials are warranted to confirm the utility of IVUS for reduction of event rates because current randomized trials have been underpowered to definitively assess the clinical utility of IVUS guidance.

IVUS is a valuable tool for the assessment of the left main coronary artery (LMCA) stenosis. An example of IVUS-guided PCI is described in Figures 2 and 3. In an analysis of 55 patients, Jasti et al[43] reported that an IVUS minimum lumen area (MLA) of 5.9 mm² and a minimum lumen diameter of 2.8 mm strongly predicted FFR < 0.75. The LITRO study,[44] which enrolled 354 patients with intermediate LMCA lesions, reported that an IVUS MLA > 6 mm² was safe for deferring revascularization. In the 2-year follow-up period, there was no significant difference between the deferred and revascularized groups in terms of cardiac death-free survival and event-free survival. Recently, the Society of Cardiovascular Angiography and Interventions recommended using an IVUS MLA cutoff value of 6 mm² for a decision-making strategy regarding revascularization in patients with an LMCA stenosis. However, the use of IVUS should be discouraged when evaluating non-left main lesions,[4] because the diagnostic performance of IVUS MLA to predict FFR is not high enough to reliably exclude lesions that are hemodynamically significant.

CONCLUSION

FFR has emerged as a valuable tool in the cath lab to determine the functional significance of intermediate coronary lesions and appropriately guide treatment strategies. For that reason, it has been upgraded to a class IA in the European guidelines for multivessel PCI and class IIa in the 2013 SCAI consensus document to assess angiographic

intermediate coronary lesions (50%–70%).[4,45] Although registry studies and meta-analyses support IVUS-guided DES implantation, large randomized trials are warranted to confirm the utility of IVUS for reduction of event rates. The SCAI endorsed using an IVUS MLA cutoff value of 6 mm^2 for a decision-making strategy regarding revascularization in patients with an LMCA stenosis. OCT is a promising novel imaging technology that provides a large amount of data regarding the vessel wall and atherosclerotic plaque. Larger studies are needed to investigate the clinical value of this information. ■

Konstantinos Marmagkiolis, MD, MBA, FACC, FSCAI, is Medical Director, STEMI Program at Citizens Memorial Hospital in Bolivar, Missouri. He stated that he has no financial interests related to this article.

Massoud Leesar, MD, FACC, FSCAI, is Professor of Medicine; Section Head, Interventional Cardiology; and Baker-Dean Endowed Professor in Interventional Cardiology at University of Alabama-Birmingham in Birmingham, Alabama. He stated that he has no financial interests related to this article.

Mehmet Cilingiroglu, MD, FSCAI, FACC, FESC, FAHA, is Professor of Medicine at Koç University School of Medicine in Istanbul, Turkey, and Medical Director of Peripheral Vascular Institute at Arkansas Heart Hospital in Little Rock, Arkansas. He has stated that he has no financial interests related to this article. Dr. Cilingiroglu may be reached at mcilingiroglu@yahoo.com.

1. Dattilo PB, Prasad A, Honeycutt E, et al. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. J Am Coll Cardiol. 2012;60:2337-2339.
2. Kamiya K, Sakakibara M, Asakawa N, et al. Cardiac magnetic resonance performs better in the detection of functionally significant coronary artery stenosis compared to single-photon emission computed tomography and dobutamine stress echocardiography. Circ J. 2014 Aug 11. [Epub ahead of print]
3. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49:2105-2111.
4. Lotfi A, Jeremias A, Fearon WF, et al. Expert consensus statement on the use of fractional flow reserve, intravascular ultrasound, and optical coherence tomography: a consensus statement of the Society of Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. 2014;83:509-518.
5. Depta JP, Patel JS, Novak E, et al. Outcomes of coronary stenoses deferred revascularization for borderline versus nonborderline fractional flow reserve values. Am J Cardiol. 2014;113:1788-1793.
6. Prasad A, Zareh M, Doherty R, et al. Use of regadenoson for measurement of fractional flow reserve. Catheter Cardiovasc Interv. 2014;83:369-374.
7. Kato D, Takashima H, Waseda K, et al. Feasibility and safety of intracoronary nicorandil infusion as a novel hyperemic agent for fractional flow reserve measurements. Heart Vessels. 2014 April 19. [Epub ahead of print]
8. Arumugham P, Figueredo VM, Patel PB, Morris DL. Comparison of intravenous adenosine and intravenous regadenoson for the measurement of pressure-derived coronary fractional flow reserve. EuroIntervention. 2013;8:1166-1171.
9. Wang X, Li S, Zhao X, et al. Effects of intracoronary sodium nitroprusside compared with adenosine on fractional flow reserve measurement. J Invasive Cardiol. 2014;26:119-122.
10. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol. 2012;59:1392-1402.
11. Berry C, van 't Veer M, Witt N, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. J Am Coll Cardiol. 2013;61:1421-1427.
12. Jeremias A, Maehara A, Genereux P, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. J Am Coll Cardiol. 2014;63:1253-1261.
13. Sen S, Asrress KN, Nijjer S, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). J Am Coll Cardiol. 2013;61:1409-1420.
14. Curzen N, Rana O, Nicholas Z, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORD study. Circ Cardiovasc Interv. 2014;7:248-255.
15. Toth G, De Bruyne B, Casselman F, et al. Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. Circulation. 2013;128:1405-1411.
16. Kim HS, Tonino PA, De Bruyne B, et al. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. JACC Cardiovasc Interv. 2012;5:1037-1042.
17. Siebert U, Arvandi M, Gothe RM, et al. Improving the quality of percutaneous revascularisation in patients with multivessel disease in Australia: cost-effectiveness, public health implications, and budget impact of FFR-guided PCI. Heart Lung Circ. 2014;23:527-533.
18. Fearon WF, Shilane D, Pijls NH, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. Circulation. 2013;128:1335-1340.
19. Fearon WF, Bornschein B, Tonino PA, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. Circulation. 2010;122:2545-2550.
20. Frohlich GM, Redwood S, Rakhit R, et al. Long-term survival in patients undergoing percutaneous interventions with or without intracoronary pressure wire guidance or intracoronary ultrasonographic imaging: a large cohort study. JAMA Intern Med. 2014;174:1360-1366.
21. Di Serafino L, De Bruyne B, Mangiacapra F, et al. Long-term clinical outcome after fractional flow reserve- versus angio-guided percutaneous coronary intervention in patients with intermediate stenosis of coronary artery bypass grafts. Am Heart J. 2013;166:110-118.
22. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014;63:1145-1155.
23. Nakazato R, Park HB, Berman DS, et al. Noninvasive fractional flow reserve derived from computed tomography angiography for coronary lesions of intermediate stenosis severity: results from the DeFACTO study. Circ Cardiovasc Imag. 2013;6:881-889.
24. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol. 2011;58:1989-1997.
25. Lowe HC, Narula J, Fujimoto JG, Jang IK. Intracoronary optical diagnostics current status, limitations, and potential. JACC Cardiovasc Interv. 2011;4:1257-1270.
26. Souteyrand G, Amabile N, Combaret N, et al. Invasive management without stents in selected acute coronary syndrome patients with a large thrombus burden: a prospective study of optical coherence tomography guided treatment decisions. EuroIntervention. 2014 Jul 19. pii: 20130704-03. doi: 10.4244/EIJY14M07_18. [Epub ahead of print]
27. Cervinka P, Spacek R, Bystron M, et al. Optical coherence tomography-guided primary percutaneous coronary intervention in ST-segment elevation myocardial infarction patients: a pilot study. Can J Cardiol. 2014;30:420-427.
28. Jones MR, Attizzani GF, Given CA 2nd, et al. Intravascular frequency-domain optical coherence tomography assessment of carotid artery disease in symptomatic and asymptomatic patients. JACC Cardiovasc Interv. 2014;7:674-684.
29. Sanchez-Recalde A, Moreno R, Jimenez-Valero S. Renal artery fibromuscular dysplasia: in vivo optical coherence tomography insights. Eur Heart J. 2014;35:931.
30. Marmagkiolis K, Lendel V, Leesar MA, et al. Use of optical coherence tomography during superficial femoral artery interventions. J Invasive Cardiol. 2014;26:220-223.
31. Tanaka A, Suzuki K, Inoue N, Meguro T. Optical coherence tomography images of iliac artery fibromuscular dysplasia. Eur Heart J. 2014 Jun 10. pii: ehu233. [Epub ahead of print]
32. Khandhar SJ, Yamamoto H, Teuteberg JJ, et al. Optical coherence tomography for characterization of cardiac allograft vasculopathy after heart transplantation (OCTCAV study). J Heart Lung Transplant. 2013;32:596-602.
33. Roleder T, Parma Z, Smolka G, et al. Optical coherence tomography imaging of everolimus-eluting bioresorbable vascular scaffold implanted into coronary vein graft at 3-month follow-up. Eur Heart J. 2014;35:2207.
34. Meneveau N, Ecarnot F, Souteyrand G, et al. Does optical coherence tomography optimize results of stenting? Rationale and study design. Am Heart J. 2014;168:175-181 e2.
35. Zafar H, Sharif F, Leahy MJ. Feasibility of intracoronary frequency domain optical coherence tomography derived fractional flow reserve for the assessment of coronary artery stenosis. Int Heart J. 2014;55:307-311.
36. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol. 2005;45:995-998.
37. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation. 2003;108:43-47.
38. Sonoda S, Morino Y, Ako J, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the SIRIUS trial. J Am Coll Cardiol. 2004;43:1959-1963.
39. Song HG, Kang SJ, Ahn JM, et al. Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. Catheter Cardiovasc Interv. 2014;83:873-878.
40. Parise H, Maehara A, Stone GW, et al. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. Am J Cardiol. 2011;107:374-382.
41. Klersy C, Ferlini M, Raisaro A, et al. Use of IVUS guided coronary stenting with drug eluting stent: a systematic review and meta-analysis of randomized controlled clinical trials and high quality observational studies. Int J Cardiol. 2013;170:54-63.
42. Witzenbichler B, Maehara A, Weisz G, et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. Circulation. 2014;129:463-470.
43. Jasti V, Ivan E, Yalamanchili V, et al. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. Circulation. 2004;110:2831-2836.
44. de la Torre Hernandez JM, Hernandez Hernandez F, Alfonso F, et al. Prospective application of pre-defined intravascular ultrasound criteria for assessment of intermediate left main coronary artery lesions results from the multicenter LITRO study. J Am Coll Cardiol. 2011;58:351-358.
45. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010;31:2501-2555.