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Clinical Utility of Intravascular Imaging and Physiology in Coronary Artery Disease

Short Title: Utility of Intravascular Imaging and Physiology

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Abstract

Available intravascular imaging and physiology techniques and technologies include fractional flow reserve; grayscale intravascular ultrasound (IVUS); IVUS radiofrequency tissue characterization; optical coherence tomography, the light analogue of IVUS; and near infrared spectroscopy that detects lipid within the vessel wall and that has recently been combined with grayscale IVUS in a single catheter as the first combined imaging device. They can be used to answer questions that occur during daily practice including 1) Is this stenosis significant? 2) Where is the culprit lesion? 3) Is this a vulnerable plaque? 4) What is the likelihood of distal embolization or peri-procedural myocardial infarction during stent implantation? 5) How do I optimize acute stent results? 6) Why did this stent thrombose or restenose? One of the legacies of coronary angiography is to assume that one technique will answer all of these questions, but that is not the current state-of-the-art.

Key words: Intravascular Ultrasound, Radiofrequency IVUS, Optical Coherence Tomography, Near Infrared Spectroscopy, Fractional Flow Reserve

Abbreviations

DES = drug-eluting stents

FFR = fractional flow reserve

ISR = in-stent restenosis

IVUS = intravascular ultrasound

LMCA = left main coronary artery

MI = myocardial infarction

MLA = minimum lumen area

OCT = optical coherence tomography

TCFA = thin-cap fibroatheroma

VH = virtual histology

It is more than two decades since Nico Pijls and Bernard DeBruyne introduced fractional flow reserve (FFR) as a way to assess coronary stenosis severity and since Paul Yock invented grayscale intravascular ultrasound (IVUS) that spawned second-generation intravascular imaging techniques such as

- 1) IVUS radiofrequency tissue characterization including virtual histology (VH)-IVUS, integrated backscatter-IVUS, and iMAP
- 2) Optical Coherence Tomography (OCT), the light analogue of IVUS
- 3) Near Infrared Spectroscopy that detects lipid within the vessel wall and that has recently been combined with grayscale IVUS in a single catheter as the first combined imaging device.

These are no longer just research tools. They are useful for answering questions that occur during daily practice including

- 1) Is this stenosis significant?
- 2) Where is the culprit lesion?
- 3) Is this a vulnerable plaque?
- 4) What is the likelihood of distal embolization or peri-procedural myocardial infarction (MI) during stent implantation?
- 5) How do I optimize acute stent results?
- 6) Why did this stent thrombose or restenose?

The subspecialty of interventional cardiology is data-driven. While correlations with histopathology are important, ultimately the issue is whether these techniques improve clinical diagnosis, treatment, and outcomes and whether patients benefit – irrespective of technical or histopathologic accuracy.

Is This Stenosis Significant?

Three randomized trials – DEFER, FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation)-I, and FAME-II – established FFR as the gold-standard to assess the significance of a non-left main coronary artery (LMCA) lesion. DEFER showed that it was safe to defer percutaneous coronary intervention of lesions with an FFR >0.75 .(1,2) FAME-I showed that treating lesions with an FFR >0.80 using mostly first generation drug-eluting stents (DES) was harmful while not treating such lesions was cost-saving.(3,4) FAME-II showed that treating lesions with an FFR <0.80 using optimal medical therapy alone was deleterious compared to optimal medical therapy plus DES implantation (5); while initially more expensive, the increased cost of “optimal medical therapy plus DES implantation” was halved one year later.(6) Many studies have attempted to identify invasive imaging criteria that are equivalent to FFR or non-invasive testing.

1) Although the IVUS minimum lumen area (MLA) in non-LMCA lesions is the parameter that best correlates with physiology, reported IVUS MLA cut-off thresholds range from 2.1mm^2 to 4.4mm^2 (Table 1, 7-25), are smaller in Asian than in Western studies, and the “most common” cut-off is approximately 3.0mm^2 .

2) Most IVUS studies show a relatively high negative predictive value, but a low positive predictive value indicating that using IVUS to justify the need for percutaneous intervention is wrong approximately half of the time.

3) There have been no randomized IVUS trials comparable to DEFER, FAME-I, or FAME-II or randomized trials of IVUS deferral vs FFR deferral; however, a recent propensity-matched study by de la Torre Hernandez suggests that clinical outcomes are similar whether IVUS or FFR is used to decide which lesions to stent or leave alone although a greater number of lesions are stented with IVUS compared to FFR (72% vs 51.2%, $p<0.0001$). (26)

4) Anatomic assessment of lesion severity is not improved with OCT although OCT-derived MLA cut-offs are smaller than with IVUS.(19,27-29)

5) While some studies have “corrected” for vessel size (12,16,17), none have factored in subtended viable myocardium.

In a recent substudy from PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), non-fibroatheromas were associated with very few events at three years of follow-up suggesting that tissue characterization and plaque composition may be an alternative way to predict lesion stability and defer intervention.(30)

LMCA lesions. Four angiographic studies – two historic (31,32) and two contemporary (33,34) – indicated that agreement among experts regarding the significance of a LMCA lesion can be as low as 30% (Figure 1). There have been two equivalent FFR and IVUS registry studies in patients with intermediate LMCA lesions in which an FFR >0.80 or an IVUS MLA $>6.0\text{mm}^2$ was used to defer revascularization with similar long term results compared to patients with an FFR <0.80 or an MLA $<6.0\text{mm}^2$ treated with revascularization (33,35). One IVUS vs FFR report from the United States indicated that an IVUS MLA of $<6\text{mm}^2$ in the LMCA best correlated with an FFR <0.80 (36) although a study in Korean patients suggested that 4.8mm^2 was the preferred IVUS MLA cut-off (37), again consistent with smaller MLA cut-offs in Asian compared to Western patients.

Both IVUS and FFR have limitations in assessing LMCA disease. Ideally when clinically indicated, IVUS should be performed from both the left anterior descending and left circumflex to define the MLA within the LMCA and to assess accurately disease at the left anterior descending and left circumflex ostia (38,39). Patients with LMCA disease have not typically been included in the many FFR validation studies, and FFR may have limitations in the setting of

a significant concomitant LAD stenosis.(40,41)

Where Is the Culprit Lesion?

Culprit lesions in acute coronary syndrome patients have plaque rupture in 60% to 65%, plaque erosion in 30% to 35%, and a calcified nodule in 5%; the final common pathway is thrombus formation.(42) Sometimes the culprit lesion is evident clinically; but as seen in the VANQWISH Trial, as many as 50% of these patients either have no identifiable culprit or have multiple potential culprits.(43)

Previous studies have shown that positive remodeling is more common in culprit lesions of patients presenting with acute coronary syndrome and is seen in association with plaque rupture, yellow plaque color, and thrombus formation; conversely, negative remodeling is more common in target lesions of patients presenting with stable symptoms (44-47). IVUS detects plaque ruptures in approximately half of ST-elevation MI culprit lesions (48-50). However, the superior resolution and the obligatory flushing when performing OCT sharply outline the plaque rupture cavity and residual fibrous cap fragment to optimize ruptured plaque identification (48); OCT can detect erosions (although there is some disagreement regarding the definition [48,51-53]); and OCT can identify and differentiate between red and white thrombus (54) although red thrombus, which is almost universal in these patients, can shadow and obscure underlying plaque morphology (Figure 2). Recent near infrared spectroscopy data indicate that a maximum lipid core burden index >400 within a 4mm long segment is a signature of plaques causing an ST-elevation MI.(55)

Other unusual culprit lesion morphologies that can be detected by both IVUS and OCT include calcific nodules (53,56) and spontaneous coronary artery dissections (Figure 3).(57,58)

Is This a Vulnerable Plaque?

The precursor of the ruptured, thrombotic plaque is the thin-cap fibroatheroma (TCFA, the most common type of vulnerable plaque).(42) Although one early, small grayscale IVUS study suggested that a large eccentric plaque containing a shallow echolucent zone is at increased risk for instability (59), to date only VH-IVUS has been shown to predict future non-culprit events. In PROSPECT predictors of non-culprit events at three years were a VH-TCFA, an IVUS MLA $<4.0\text{mm}^2$, and an IVUS plaque burden $>70\%$.(60) These findings were supported by VIVA (VH-IVUS in Vulnerable Atherosclerosis) and ATHEROREMO-IVUS (European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound).(61,62)

While VH-IVUS can only infer the presence of a TCFA by the presence of a necrotic core abutting the lumen, OCT is able to identify many features of a TCFA including fibrous cap thickness <65 microns, macrophages in the fibrous cap, and an underlying lipid core.(51) However, only one small OCT study has showed that lesions with rapid progression (angiographic lumen loss $>0.4\text{mm}$ within seven months) have an increased frequency of intimal laceration, microvessels (which may be a source of blood extravasation and intraplaque hemorrhage), lipid pools, TCFAs, macrophages, and intraluminal thrombi.(63)

IVUS substudies of PROSPECT have highlighted the paradox between plaque ruptures or calcified nodules that cause ACS events vs. the benign nature of secondary, non-culprit plaque ruptures or calcified nodules that are detected incidentally.(64,65) Although positive remodeling was not an independent predictor of events in the PROSPECT, VIVA, or ATHEROREMO-IVUS studies, a substudy from PROSPECT showed that it is not just positive remodeling, but the extremes of positive and negative remodeling that predicted events.(66)

Whether or not routine invasive imaging to screen for vulnerable plaques as part of primary or

secondary prevention makes clinical sense is the subject of debate and depends on the prevalence of vulnerable plaques; how often and how rapidly they develop spontaneously, remain unstable, or stabilize (67,68); the impact of modern medical therapy on clinical events which in PROSPECT, VIVA, and ATHEROREMO-IVUS were mostly revascularization and not hard events of death or MI (60-62); and complications associated with routine three-vessel invasive imaging.(60) Currently we cannot predict plaques with a risk of complications high enough to warrant prophylactic therapy although a substudy within PROSPECT-II will attempt to address this issue.

What Is the Likelihood of Distal Embolization or Peri-Procedural MI During Stent Implantation?

Predictors of myonecrosis during stent implantation are a large grayscale IVUS attenuated plaque (“shadowing” in the absence of calcification), especially when shadowing begins closer to the lumen than to the adventitia (69-72) (Figure 4); a large VH-IVUS necrotic core or a VH-TCFA (73) or similar findings using integrated backscatter-IVUS (74,75) or iMAP (76); a large amount of OCT lipid or an OCT-TCFA (77-82); a large lipid rich plaque by near infrared spectroscopy (83-85); and the presence of plaque rupture whether detected by IVUS or OCT (86-90). The common denominator is the presence of a TCFA, with or without plaque rupture, that is responsible both for the imaging findings and for peri-procedural MI during stent implantation.(91-93) Conversely, the absence of these findings indicates a low probability of a peri-procedural MI.

How Do I Optimize Acute Stent Results?

In both bare metal stents and DES the IVUS predictors of early stent thrombosis or in-stent restenosis (ISR) are stent underexpansion (Figure 5) (94-111) and inflow/outflow track disease

(dissections, significant plaque burden, edge stenosis, etc) (98,103,104,106,107,112,113), but not acute stent malapposition (107,108,115-117) as long as the stent is well-expanded.

Underexpansion refers to the size of the stent while malapposition refers to the contact of the stent with the vessel wall; the two terms and concepts are not interchangeable, and the term “underdeployment” is imprecise and unclear. While bigger is better regarding stent expansion and less is more with respect to stent edge plaque burden, acceptable procedural endpoints are a minimum stent area (97,100,103,105,108,110,111) and stent-edge plaque burden (112,114) that maximize the probability of long-term stent patency while minimizing the risk of stent failure (Table 2).

Two meta-analyses of seven randomized IVUS vs. angiographic-guided bare metal stent implantation trials showed that IVUS guidance reduced restenosis, repeat revascularization, and major adverse cardiac events, but not death or MI.(118,119) Three meta-analyses of IVUS vs. angiographic-guided DES studies (the most recent involving three randomized trials and 14 observational studies with 26,503 patients) showed that IVUS guidance reduced stent thrombosis (120-122), MI (121,122), repeat revascularization (121,122), and mortality (120-122) despite using more stents and/or longer stents in IVUS-guided patients. This included a propensity-score matched analysis that was possible in nine studies (121); and there was no evidence of heterogeneity or publication bias. IVUS guidance was associated with using larger stents and achieving a larger post-procedure angiographic minimum lumen diameter with no evidence of increased peri-procedure MI. (123) Two studies questioned the value of IVUS guidance in MI patients undergoing primary percutaneous intervention (123,124); but ADAPT-DES suggested the opposite – that IVUS guidance had its greatest impact in MI patients.(125)

To date, there has been only one study of OCT vs. angiographic-guided DES implantation

showing benefits similar to the IVUS meta-analyses suggesting that it might not be the individual imaging technique, *per se*, but the increased information provided compared to angiography alone.(126) Advocates of OCT have cited superior resolution, enhanced imaging during flushing, ease of image interpretation, and detection of dissections, tissue protrusion, and malapposition not seen on IVUS.(127-129) However, unlike IVUS, there are no established concepts regarding stent sizing by OCT; and there is little data on OCT criteria for optimal stent implantation or predictors of adverse events. For example, there is no agreement whether an OCT-measured minimum stent area is larger, smaller, or the same as IVUS.(127-130) Enhanced OCT detection of stent edge dissections, tissue prolapse, thrombus, or stent-vessel wall malapposition is not associated with predicting adverse events.(131-134) One small, randomized and blinded IVUS-guided vs. OCT-guided DES implantation has showed that, because of its limited penetration, less aggressive OCT stent sizing is associated with more stent underexpansion and a larger reference segment plaque burden compared with IVUS.(130)

While it has a limited role in stent optimization, FFR is probably best to determine whether a jailed sidebranch is compromised after provisional bifurcation stenting.(135-139) Most of the time, the angiographic appearance of sidebranch ostial lumen compromise is an artifact; and FFR is >0.80 because lumen compromise is due to carina shift that is eccentric and focal and not due to plaque shift and because the amount of myocardium in jeopardy in most non-LMCA bifurcations is modest.

Why Did This Stent Thrombose or Restenose?

Table 3 shows causes of stent thrombosis and ISR that have been identified with intravascular imaging. While most of these have been elucidated with IVUS, they can also be detected with OCT; and the emergence of neoatherosclerosis as an important cause of late stent failure (140-

140) and observations regarding the relationship between lack of stent strut tissue coverage and late/very late ST (151,152) – neither of which can be identified using IVUS (142) – indicate that OCT may be the imaging technology of choice in this clinical setting. Neoatherosclerosis occurs earlier after DES than bare metal stents, occurs with greater frequency with many types of DES vs bare metal stents, can present as either ISR or very late stent thrombosis and may be responsible for the majority of very late stent thrombosis, and is associated with greater clinical instability at the time of presentation and peri-procedural MI at the time of treatment of ISR or stent thrombosis. However, it should be noted that OCT findings in stent thrombosis may depend on whether aspiration thrombectomy is performed before (148) or after OCT imaging (151) since aspiration will remove not only thrombus, but also fragments of atherosclerotic plaques such as foamy macrophages, cholesterol crystals, and a thin fibrous cap.(153) Other than neoatherosclerosis, the clinical impact of OCT patterns of neointimal tissue – ie., heterogeneous vs homogeneous vs layered vs peri-strut low intensity areas (154-163) – are not clear.

Summary and Barriers to Implementation

There are three main barriers to implementing an intravascular imaging and physiology program: cost, expertise, and convincing interventional cardiologists of the limitations of relying on coronary angiography alone. In some countries the cost of these techniques can dwarf that of the other materials used during percutaneous intervention. Education is problematic; and interpretation is not intuitive – not even with OCT (164); and like all medical imaging techniques requires an understanding of artifacts, limitations, and confounders. One of the legacies of coronary angiography is to assume that one technique will answer all questions, but that is not the current state-of-the-art. While there may be few randomized trials, the utility of these techniques to answer routine clinical questions is undeniable.

ACCEPTED MANUSCRIPT

References

1. Berger A, Botman KJ, MacCarthy PA, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *J Am Coll Cardiol* 2002;46:438-42.
2. 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;49:2105-11.
3. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
4. 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;122:2545-50.
5. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
6. Fearon WF, Shilane D, Pijls NH, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary disease and abnormal fractional flow reserve. *Circulation*. 2013;128:1335-40.
7. Abizaid A, Mintz GS, Pichard AD, et al. Clinical, intravascular ultrasound, and quantitative angiographic determinants of the coronary flow reserve before and after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1998;82:423-8.
8. Nishioka T, Amanullah AM, Luo H, et al. Clinical validation of intravascular ultrasound imaging for assessment of coronary stenosis severity: comparison with stress myocardial perfusion imaging. *J Am Coll Cardiol* 1999;33:1870-8.

9. Takagi A, Tsurumi Y, Ishii Y, Suzuki K, Kawana M, Kasanuki H. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation*. 1999;100:250-5.
10. Briguori C, Anzuini A, Airolidi F et al. Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and comparison with fractional flow reserve. *Am J Cardiol* 2001;87:136-41.
11. Takayama T, Hodgson JM. Prediction of the physiologic severity of coronary lesions using 3D IVUS: validation by direct coronary pressure measurements. *Catheter Cardiovasc Interv*. 2001;53:48-55.
12. Lee CH, Tai BC, Soon CY, et al. New set of intravascular ultrasound-derived anatomic criteria for defining functionally significant stenoses in small coronary arteries (results from Intravascular Ultrasound Diagnostic Evaluation of Atherosclerosis in Singapore [IDEAS] study). *Am J Cardiol* 2010;105:1378-84.
13. Kang SJ, Lee JY, Ahn JM, et al. Validation of intravascular ultrasound-derived parameters with fractional flow reserve for assessment of coronary stenosis severity. *Circ Cardiovasc Interv* 2011;4:65-71.
14. Kang SJ, Ahn JM, Song H, et al. Usefulness of minimal luminal coronary area determined by intravascular ultrasound to predict functional significance in stable and unstable angina pectoris. *Am J Cardiol* 2012;109:947-53.
15. Ahn JM, Kang SJ, Mintz GS, et al. Validation of minimal luminal area measured by intravascular ultrasound for assessment of functionally significant coronary stenosis comparison with myocardial perfusion imaging. *JACC Cardiovasc Interv* 2011;4:665-71.

16. Ben-Dor I, Torguson R, Gaglia MA Jr, et al. Correlation between fractional flow reserve and intravascular ultrasound lumen area in intermediate coronary artery stenosis. *EuroIntervention* 2011;7:225-33.
17. Ben-Dor I, Torguson R, Deksissa T, et al. Intravascular ultrasound lumen area parameters for assessment of physiological ischemia by fractional flow reserve in intermediate coronary artery stenosis. *Cardiovasc Revasc Med* 2012;13:177-82.
18. Koo BK, Yang HM, Doh JH, et al. Optimal intravascular ultrasound criteria and their accuracy for defining the functional significance of intermediate coronary stenoses of different locations. *JACC Cardiovasc Interv* 2011;4:803-11.
19. Gonzalo N, Escaned J, Alfonso F, et al. Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. *J Am Coll Cardiol* 2012;59:1080-9
20. Waksman R, Legutko J, Singh J, et al. FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. *J Am Coll Cardiol* 2013;61:917-23
21. Stone GW. VERDICT/FIRST: prospective, multicenter study examining the correlation between IVUS and FFR parameters in intermediate lesions. (Accessed September 3, 2013 at <http://www.tctmd.com/show.aspx?id=114442>)
22. Kwan TW, Yang S, Xu B, et al. Optimized quantitative angiographic and intravascular ultrasound parameters predicting the functional significance of single de novo lesions in the left anterior descending artery. *Chin Med J (Engl)*. 2012;125:4249-53.
23. Chen SL, Xu B, Chen JB, et al. Diagnostic accuracy of quantitative angiographic and intravascular ultrasound parameters predicting the functional significance of single de novo lesions. *Int J Cardiol*. 2013;168:1364-9.

24. Yang HM, Tahk SJ, Lim HS, et al. Relationship between intravascular ultrasound parameters and fractional flow reserve in intermediate coronary artery stenosis of left anterior descending artery - intravascular ultrasound volumetric analysis. *Catheter Cardiovasc Interv*. 2013 Jun 27. [Epub ahead of print]
25. Kang SJ, Ahn JM, Han S, et al. Sex differences in the visual-functional mismatch between coronary angiography or intravascular ultrasound versus fractional flow reserve. *JACC Cardiovasc Interv*. 2013;6:562-8.
26. de la Torre Hernandez JM, Lopez-Palop R, Garcia Camarero T, et al. Clinical outcomes after intravascular ultrasound and fractional flow reserve assessment of intermediate coronary lesions. Propensity score matching of large cohorts from two institutions with a differential approach. *EuroIntervention*. 2013;9:824-30.
27. Shiono Y, Kitabata H, Kubo T, et al. Optical coherence tomography-derived anatomical criteria for functionally significant coronary stenosis assessed by fractional flow reserve. *Circ J*. 2012;76:2218-25.
28. Reith S, Battermann S, Jaskolka A, et al. Relationship between optical coherence tomography derived intraluminal and intramural criteria and haemodynamic relevance as determined by fractional flow reserve in intermediate coronary stenoses of patients with type 2 diabetes. *Heart*. 2013;99:700-7.
29. Pawlowski T, Prati F, Kulawik T, Ficarra E, Bil J, Gil R. Optical coherence tomography criteria for defining functional severity of intermediate lesions: a comparative study with FFR. *Int J Cardiovasc Imaging*. 2013;29:1685-91
30. Dohi T, Mintz GS, McPherson JA, et al. Non-fibroatheroma lesion phenotype and long-term clinical outcomes: A substudy analysis from the PROSPECT Study. *JACC Cardiovasc Imaging*.

2013;6:908-16.

31. Fisher LD, Judkins MP, Lesperance J, et al. Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS). *Cathet Cardiovasc Diagn*. 1982;8:565-75.
32. Cameron A, Kemp HG Jr, Fisher LD, et al. Left main coronary artery stenosis: angiographic determination. *Circulation*. 1983;68:484-9.
33. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 2009;120:1505-12.
34. Lindstaedt M, Spiecker M, Perings C, et al. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? *Int J Cardiol* 2007;120:254-61.
35. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leeser MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation*. 2004;110:2831-6.
36. de la Torre Hernandez JM, Hernández 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;58:351-8.
37. Kang SJ, Lee JY, Ahn JM, et al. Intravascular ultrasound-derived predictors for fractional flow reserve in intermediate left main disease. *JACC Cardiovasc Interv* 2011;4:1168-74.
38. Oviedo C, Maehara A, Mintz GS, et al. Intravascular ultrasound classification of plaque distribution in left main coronary artery bifurcations: where is the plaque really located? *Circ Cardiovasc Interv*. 2010;3:105-12
39. Oviedo C, Maehara A, Mintz GS, et al. Is accurate intravascular ultrasound evaluation of the

left circumflex ostium from a left anterior descending to left main pullback possible? *Am J Cardiol.* 2010;105:948-54

40. Daniels DV, van't Veer M, Pijls NH, et al. The impact of downstream coronary stenoses on fractional flow reserve assessment of intermediate left main disease. *JACC Cardiovasc Interv* 2012;5:1021-5.

41. Yong AS, Daniels D, De Bruyne B, et al. Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. *Circ Cardiovasc Interv* 2013;6:161-5.

42. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I and Part II. *Circulation* 2003;108:1664-1672 and 1772-8.

43. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ. Revisiting the culprit lesion in non-Q-wave myocardial infarction. Results from the VANQWISH trial angiographic core laboratory. *J Am Coll Cardiol* 2002;39:1456-63.

44. Gyongyosi M, Yang P, Hassan A, et al. Arterial remodeling of native human coronary arteries in patients with unstable angina pectoris: a prospective intravascular ultrasound study. *Heart* 1999;82:68-74.

45. Takano M, Mizuno K, Okamatsu K, Yokoyama S, Ohba T, Sakai S. Mechanical and structural characteristics of vulnerable plaques: analysis by coronary angioscopy and intravascular ultrasound. *J Am Coll Cardiol* 2001;38:99-104.

46. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation* 2000;101:598-603.

47. Nakamura M, Nishikawa H, Mukai S, et al. Impact of coronary artery remodeling on clinical

presentation of coronary artery disease: an intravascular ultrasound study. *J Am Coll Cardiol* 2001;37:63-9.

48. Kubo T, Imanishi T, Takarada S, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angiography. *J Am Coll Cardiol* 2007;50:933-9.

49. Hong MK, Mintz GS, Lee CW, et al. Comparison of coronary plaque rupture between stable angina and acute myocardial infarction: a three-vessel intravascular ultrasound study in 235 patients. *Circulation*. 2004;110:928-33

50. Hong YJ, Jeong MH, Choi YH, et al. Differences in intravascular ultrasound findings in culprit lesions in infarct-related arteries between ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction. *J Cardiol*. 2010;56:15-22

51. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012;59:1058-72

52. Prati F, Uemura S, Souteyrand G, et al. OCT-based diagnosis and management of **STEMI** associated with intact fibrous cap. *JACC Cardiovasc Imaging*. 2013;6:283-7

53. Jia H, Abtahian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol*. 2013;62:1748-58.

54. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial thrombus by optical coherence tomography. *Am J Cardiol* 2006;97:1713-7.

55. Madder RD, Goldstein JA, Madden SP, et al. Detection by near-infrared spectroscopy of

large lipid core plaques at culprit sites in patients with acute ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2013;6:838-46.

56. Duissailant GR, Mintz GS, Pichard AD, et al. Intravascular ultrasound identification of calcified intraluminal lesions misdiagnosed as thrombi by coronary angiography. *Am Heart J* 1996;132:687-9.

57. Maehara A, Mintz GS, Castagna MT, et al. Intravascular ultrasound assessment of spontaneous coronary artery dissection. *Am J Cardiol* 2002;89:466-8.

58. Alfonso F, Paulo M, Gonzalo N, et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *J Am Coll Cardiol* 2012;59:1073-9.

59. Yamagishi M, Terashima M, Awano K, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol* 2000;35:106-11.

60. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364: 226-35.

61. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. *JACC Cardiovasc Imaging* 2011;4:894-901.

62. Cheng JM, Garcia-Garcia HM, de Boer SP, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. *Eur Heart J*. 2013 Nov 19. [Epub ahead of print]

63. Uemura S, Ishigami K, Soeda T, et al. Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur Heart J* 2012; 33:78-85.

64. Xie Y, Mintz GS, Yang J, et al. Frequency, morphology, and clinical outcome of non-culprit plaque ruptures in patients with acute coronary syndrome in the PROSPECT study. *JACC Cardiovasc Imaging*, in press.
65. Xu Y, Mintz GS, Tam A, et al. Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). *Circulation* 2012;126:537-45.
66. Inaba S, Mintz GS, Farhat H, et al. Impact of Positive and Negative Lesion Site Remodeling on Clinical Outcomes: Insights From PROSPECT. *JACC Cardiovasc Imaging*, in press.
67. Kubo T, Maehara A, Mintz GS, et al. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. *J Am Coll Cardiol* 2010;55:1590-7.
68. Zhao Z, Witzenbichler B, Mintz GS, et al. Dynamic nature of nonculprit coronary artery lesion morphology in STEMI: a serial IVUS analysis from the HORIZONS-AMI trial. *JACC Cardiovasc Imaging* 2013;6:86-95.
69. Okura H, Taguchi H, Kubo T, et al. Atherosclerotic plaque with ultrasonic attenuation affects coronary reflow and infarct size in patients with acute coronary syndrome: an intravascular ultrasound study. *Circ J* 2007;71:648-53.
70. Lee SY, Mintz GS, Kim SY, et al. Attenuated plaque detected by intravascular ultrasound: clinical, angiographic, and morphologic features and post-percutaneous coronary intervention complications in patients with acute coronary syndromes. *JACC Cardiovasc Interv.* 2009;2:65-72.
71. Wu X, Mintz GS, Xu K, et al. The relationship between attenuated plaque identified by

intravascular ultrasound and no-reflow after stenting in acute myocardial infarction: the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv* 2011;4:495-502.

72. Shiono Y, Kubo T, Tanaka A, et al. Impact of attenuated plaque as detected by intravascular ultrasound on the occurrence of microvascular obstruction after percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2013;6:847-53.

73. Claessen BE, Maehara A, Fahy M, Xu K, Stone GW, Mintz GS. Plaque composition by intravascular ultrasound and distal embolization after percutaneous coronary intervention. *JACC Cardiovasc Imaging* 2012;5:S111-8.

74. Uetani T, Amano T, Ando H et al. The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation. *Eur Heart J* 2008;29:1714-20.

75. Shibuya M, Okamura A, Hao H et al. Prediction of distal embolization during percutaneous coronary intervention for unstable plaques with grayscale and integrated backscatter intravascular ultrasound. *Catheter Cardiovasc Interv* 201;81:E165-72

76. Utsunomiya M, Hara H, Sugi K, Nakamura M. Relationship between tissue characterisations with 40MHz intravascular ultrasound imaging and slow flow during coronary intervention. *EuroIntervention* 2011;7:340-6.

77. Tanaka A, Imanishi T, Kitabata H, et al. Lipid-rich plaque and myocardial perfusion after successful stenting in patients with non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study. *Eur Heart J* 2009;30:1348-55.

78. Yonetsu T, Kakuta T, Lee T, et al. Impact of plaque morphology on creatine kinase-MB

elevation in patients with elective stent implantation. *Int J Cardiol* 2011;146:80-5.

79. Lee T, Yonetsu T, Koura K, et al. Impact of coronary plaque morphology assessed by optical coherence tomography on cardiac troponin elevation in patients with elective stent implantation. *Circ Cardiovasc Interv* 2011;4:378-86.

80. Porto I, Di Vito L, Burzotta F, et al. Predictors of periprocedural (type IVa) myocardial infarction, as assessed by frequency-domain optical coherence tomography. *Circ Cardiovasc Interv* 2012;5:89-96.

81. Imola F, Occhipinti M, Biondi-Zoccai G, et al. Association between proximal stent edge positioning on atherosclerotic plaques containing lipid pools and postprocedural myocardial infarction (from the CLI-POOL Study). *Am J Cardiol* 2013;111:526-31.

82. Ikenaga H, Ishihara M, Inoue I, et al. Longitudinal extent of lipid pool assessed by optical coherence tomography predicts microvascular no-reflow after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Cardiol*. 2013;62:71-6

83. Goldstein JA, Maini B, Dixon SR, et al. Detection of lipid-core plaques by intracoronary near-infrared spectroscopy identifies high risk of periprocedural myocardial infarction. *Circ Cardiovasc Interv* 2011;4:429-37.

84. Raghunathan D, Abdel-Karim AR, et al. Relation between the presence and extent of coronary lipid core plaques detected by near-infrared spectroscopy with postpercutaneous coronary intervention myocardial infarction. *Am J Cardiol* 2011;107:1613-8.

85. Brilakis ES, Abdel-Karim AR, Papayannis AC, et al. Embolic protection device utilization during stenting of native coronary artery lesions with large lipid core plaques as detected by near-infrared spectroscopy. *Catheter Cardiovasc Interv* 2012;80:1157-62.

86. Ohshima K, Ikeda S, Kadota H, et al. Cavity volume of ruptured plaque is an independent

predictor for angiographic no-reflow phenomenon during primary angioplasty in patients with ST-segment elevation myocardial infarction. *J Cardiol*. 2011;57:36-43.

87. Endo M, Hibi K, Shimizu T, et al. Impact of ultrasound attenuation and plaque rupture as detected by intravascular ultrasound on the incidence of no-reflow phenomenon after percutaneous coronary intervention in ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2010;3:540-9.

88. Hong YJ, Jeong MH, Choi YH, et al. Predictors of no-reflow after percutaneous coronary intervention for culprit lesion with plaque rupture in infarct-related artery in patients with acute myocardial infarction. *J Cardiol*. 2009;54:36-44.

89. Yonetsu T, Kakuta T, Lee T, et al. Impact of plaque morphology on creatine kinase-MB elevation in patients with elective stent implantation. *Int J Cardiol*. 2011;146:80-5.

90. Hong YJ, Jeong MH, Choi YH, et al. Positive remodeling is associated with more plaque vulnerability and higher frequency of plaque prolapse accompanied with post-procedural cardiac enzyme elevation compared with intermediate/negative remodeling in patients with acute myocardial infarction. *J Cardiol*. 2009;53:278-87.

91. Wu X, Maehara A, Mintz GS, et al. Virtual histology intravascular ultrasound analysis of non-culprit attenuated plaques detected by grayscale intravascular ultrasound in patients with acute coronary syndromes. *Am J Cardiol* 2010;105:48-53.

92. Lee T, Kakuta T, Yonetsu T, et al. Assessment of echo-attenuated plaque by optical coherence tomography and its impact on post-procedural creatine kinase-myocardial band elevation in elective stent implantation. *JACC Cardiovasc Interv* 2011;4:483-91.

93. Kubo T, Matsuo Y, Ino Y, et al. Optical coherence tomography analysis of attenuated plaques detected by intravascular ultrasound in patients with acute coronary syndromes. *Cardiol Res*

Pract. 2011;Epub 2011 Sep 15.

94. Kasaoka S, Tobis JM, Akiyama T, et al. Angiographic and intravascular ultrasound predictors of in-stent restenosis. *J Am Coll Cardiol* 1998;32:1630-5.
95. de Feyter PJ, Kay P, Disco C, Serruys PW. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. *Circulation* 1999;100:1777-83.
96. Castagna MT, Mintz GS, Leiboff BO, et al. The contribution of "mechanical" problems to in-stent restenosis: An intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions. *Am Heart J* 2001;142:970-4.
97. Morino Y, Honda Y, Okura H, et al. An optimal diagnostic threshold for minimal stent area to predict target lesion revascularization following stent implantation in native coronary lesions. *Am J Cardiol* 2001;88:301-3.
98. Ziada KM, Kapadia SR, Belli G, et al. Prognostic value of absolute versus relative measures of the procedural result after successful coronary stenting: importance of vessel size in predicting long-term freedom from target vessel revascularization. *Am Heart J* 2001;141:823-31.
99. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. *Circulation* 2003;108:43-7.
100. 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;43:1959-63.
101. Fujii K, Mintz GS, Kobayashi Y, et al. Contribution of stent underexpansion to recurrence after sirolimus-eluting stent implantation for in-stent restenosis. *Circulation* 2004;109:1085-8.
102. 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;45:995-8.

103. Hong MK, Mintz GS, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J* 2006;27:1305-10.

104. Okabe T, Mintz GS, Buch AN, et al. Intravascular ultrasound parameters associated with stent thrombosis after drug-eluting stent deployment. *Am J Cardiol* 2007;100:615-20.

105. Doi H, Maehara A, Mintz GS, et al. Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv* 2009;2:1269-75.

106. Liu X, Doi H, Maehara A, et al. A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. *JACC Cardiovasc Interv* 2009;2:428-34.

107. Choi SY, Witzenbichler B, Maehara A, et al. Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy. *Circ Cardiovasc Interv* 2011;4:239-47.

108. Kang SJ, Ahn JM, Song H, et al. Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv* 2011;4:562-69.

109. Choi SY, Maehara A, Cristea E, et al. Usefulness of minimum stent cross sectional area as a predictor of angiographic restenosis after primary percutaneous coronary intervention in acute myocardial infarction (from the HORIZONS-AMI Trial IVUS substudy). *Am J Cardiol* 2012;109:455-60.

110. 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*. 2012 Jul 19.[Epub ahead of print]
111. Hahn JY, Song YB, Lee SY, et al. Serial intravascular ultrasound analysis of the main and side branches in bifurcation lesions treated with the T-stenting technique. *J Am Coll Cardiol*. 2009;54:110-7.
112. Sakurai R, Ako J, Morino Y, et al. Predictors of edge stenosis following sirolimus-eluting stent deployment (a quantitative intravascular ultrasound analysis from the SIRIUS trial). *Am J Cardiol* 2005;96:1251-3.
113. Costa MA, Angiolillo DJ, Tannenbaum M, et al. Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). *Am J Cardiol* 2008;101:1704-11.
114. Liu J, Maehara A, Mintz GS, et al. An integrated TAXUS IV, V, and VI intravascular ultrasound analysis of the predictors of edge restenosis after bare metal or paclitaxel-eluting stents. *Am J Cardiol* 2009;103:501-6.
115. Kimura M, Mintz GS, Carlier S, et al. Outcome after acute incomplete sirolimus-eluting stent apposition as assessed by serial intravascular ultrasound. *Am J Cardiol* 2006;98:436-42.
116. Steinberg DH, Mintz GS, Mandinov L, et al. Long-term impact of routinely detected early and late incomplete stent apposition: an integrated intravascular ultrasound analysis of the TAXUS IV, V, and VI and TAXUS ATLAS workhorse, long lesion, and direct stent studies. *JACC Cardiovasc Interv* 2010;3:486-94.
117. Guo N, Maehara A, Mintz GS, et al. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial

infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. *Circulation* 2010;122:1077-84.

118. Casella G, Klauss V, Ottani F, Siebert U, Sangiorgio P, Bracchetti D. Impact of intravascular ultrasound-guided stenting on long-term clinical outcome: a meta-analysis of available studies comparing intravascular ultrasound-guided and angiographically guided stenting. *Catheter Cardiovasc Interv* 2003;59:314-21.

119. Parise H, Maehara A, Stone GW, Leon MB, Mintz GS. 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;107:374-32.

120. Zhang Y, Farooq V, Garcia-Garcia HM, et al. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention* 2012;8:855-65.

121. Jang JS, Song YJ, Kang W, et al. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. *JACC Cardiovasc Interv*, in press

122. Ahn JM, Kang SJ, Yoon SH, et al. Meta-analysis after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized and fourteen observation studies. *Am J Cardiol*, in press.

123. Maluenda G, Lemesle G, Ben-Dor I, et al. Impact of intravascular ultrasound guidance in patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2010;75:86-92.

124. Ahmed K, Jeong MH, Chakraborty R, et al. Role of intravascular ultrasound in patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Am J Cardiol*.

2011;108:8-14.

125. Witzenbichler B, Maehara A, Weisz G, et al. Relationship Between Intravascular Ultrasound Guidance and Clinical Outcomes After Drug-Eluting Stents: The ADAPT-DES Study. *Circulation*, in press.

126. Prati F, Di Vito L, Biondi-Zoccai G, et al. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention* 2012;8:823-9.

127. Bezerra HG, Attizzani GF, Sirbu V, et al. Optical coherence tomography versus intravascular ultrasound to evaluate coronary artery disease and percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2013;6:228-36.

128. Fujino Y, Bezerra HG, Attizzani GF, et al. Frequency-domain optical coherence tomography assessment of unprotected left main coronary artery disease-a comparison with intravascular ultrasound. *Catheter Cardiovasc Interv.* 2013 Jan 29 [Epub ahead of print]

129. Kubo T, Akasaka T, Shite J, et al. OCT Compared With IVUS in a Coronary Lesion Assessment: The OPUS-CLASS Study. *JACC Cardiovasc Imaging.* 2013 Aug 31 [Epub ahead of print]

130. Habara M, Nasu K, Terashima M, et al. Impact of frequency-domain optical coherence tomography guidance for optimal coronary stent implantation in comparison with intravascular ultrasound guidance. *Circ Cardiovasc Interv* 2012;5:193-201.

131. Kume T, Okura H, Miyamoto Y, et al. Natural history of stent edge dissection, tissue protrusion and incomplete stent apposition detectable only on optical coherence tomography after stent implantation – preliminary observation. *Circ J.* 2012;76:698-703.

132. Chamié D, Bezerra HG, Attizzani GF, et al. Incidence, predictors, morphological characteristics, and clinical outcomes of stent edge dissections detected by optical coherence tomography. *JACC Cardiovasc Interv.* 2013;6:800-13
133. Kawamori H, Shite J, Shinke T, et al. Natural consequence of post-intervention stent malapposition, thrombus, tissue prolapse, and dissection assessed by optical coherence tomography at mid-term follow-up. *Eur Heart J Cardiovasc Imaging.* 2013;14:865-75
134. Im E, Kim BK, Ko YG, et al. The incidences, predictors, and clinical outcomes of acute and late stent malapposition detected by optical coherence tomography after drug-eluting stent implantation. *Circ Cardiovasc Interv.* in press.
135. Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol.* 2005;46:633-7.
136. Koo BK, Park KW, Kang HJ, et al. Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve. *Eur Heart J.* 2008;29:726-32
137. Nam CW, Hur SH, Koo BK, et al. Fractional flow reserve versus angiography in left circumflex ostial intervention after left main crossover stenting. *Korean Circ J.* 2011;41:304-7
138. Ahn JM, Lee JY, Kang SJ, et al. Functional assessment of jailed side branches in coronary bifurcation lesions using fractional flow reserve. *JACC Cardiovasc Interv.* 2012;5:155-61
139. Kang SJ, Ahn JM, Kim WJ, et al. Functional and morphological assessment of side branch after left main coronary artery bifurcation stenting with cross-over technique. *Catheter Cardiovasc Interv.* 2013 Jun 13 [Epub ahead of print]
140. Takano M, Yamamoto M, Inami S, et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by

intracoronary optical coherence tomography. *J Am Coll Cardiol*. 2009;55:26-32

141. Lee CW, Kang SJ, Park DW, et al. Intravascular ultrasound findings in patients with very late stent thrombosis after either drug-eluting or bare-metal stent implantation. *J Am Coll Cardiol*. 2010;55:1936-42

142. Hou J, Qi H, Zhang M, et al. Development of lipid-rich plaque inside bare metal stent: possible mechanism of late stent thrombosis? An optical coherence tomography study. *Heart*. 2010;96:1187-90.

143. Kang SJ, Mintz GS, Akasaka T, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation*. 2011;123:2954-63

144. Habara M, Terashima M, Nasu K, et al. Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study. *Circ Cardiovasc Interv*. 2011;4:232-8

145. Yonetsu T, Kim JS, Kato K, et al. Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography. *Am J Cardiol*. 2012;110:933-9

146. Yonetsu T, Kato K, Kim SJ, et al. Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry. *Circ Cardiovasc Imaging*. 2012;5:660-6

147. Habara M, Terashima M, Nasu K, et al. Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study. *Eur Heart J Cardiovasc Imaging*. 2013;14:276-84

148. Kang SJ, Lee CW, Song H, et al. OCT analysis in patients with very late stent thrombosis.

JACC Cardiovasc Imaging. 2013;6:695-703

149. Amabile N, Souteyrand G, Ghostine S, et al. Very late stent thrombosis related to incomplete neointimal coverage or neoatherosclerotic plaque rupture identified by optical coherence tomography imaging. *Eur Heart J Cardiovasc Imaging*. 2013;15:24-31

150. Ali ZA, Roleder T, Narula J, et al. Increased Thin-Cap Neoatheroma and Periprocedural Myocardial Infarction in Drug-Eluting Stent Restenosis: Multimodality Intravascular Imaging of Drug-Eluting and Bare-Metal Stents. *Circ Cardiovasc Interv* 2013;6:507-17.

151. Guagliumi G, Sirbu V, Musumeci G, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv* 2012;5:12-20.

152. Won H, Shin DH, Kim BK, et al. Optical coherence tomography derived cut-off value of uncovered stent struts to predict adverse clinical outcomes after drug-eluting stent implantation. *Int J Cardiovasc Imaging*. 2013;29:1255-63

153. Yamaji K, Inoue K, Nakahashi T, et al. Bare metal stent thrombosis and in-stent neoatherosclerosis. *Circ Cardiovasc Interv*. 2012;5:47-54

154. Lee SJ, Kim BK, Kim JS, et al. Evaluation of neointimal morphology of lesions with or without in-stent restenosis: an optical coherence tomography study. *Clin Cardiol*. 2011;34:633-9

155. Kwon SW, Kim BK, Kim TH, et al. Qualitative assessment of neointimal tissue after drug-eluting stent implantation: comparison between follow-up optical coherence tomography and intravascular ultrasound. *Am Heart J*. 2011;161:367-72

156. Choi JH, Granada JF, Kim JS, et al. OCT-verified peri-strut low-intensity areas and the extent of neointimal formation after 3 years following stent implantation. *JACC Cardiovasc Imaging*. 2012;5:1156-60

157. Kim JS, Hong MK, Shin DH, et al. Quantitative and qualitative changes in DES-related neointimal tissue based on serial OCT. *JACC Cardiovasc Imaging*. 2012;5:1147-55
158. Hou J, Jia H, Liu H, et al. Neointimal tissue characteristics following sirolimus-eluting stent implantation: OCT quantitative tissue property analysis. *Int J Cardiovasc Imaging*. 2012;28:1879-86
159. Otake H, Shite J, Ikeno F, et al. Evaluation of the peri-strut low intensity area following sirolimus- and paclitaxel-eluting stents implantation: insights from an optical coherence tomography study in humans. *Int J Cardiol*. 2012;157:38-42
160. Ishibashi K, Tanaka A, Kitabata H, et al. Clinical significance of low signal intensity area surrounding stent struts identified by optical coherence tomography. *Int Heart J*. 2013;54:7-10.
161. Ino Y, Kubo T, Kitabata H, et al. Difference in neointimal appearance between early and late restenosis after sirolimus-eluting stent implantation assessed by optical coherence tomography. *Coron Artery Dis*. 2013;24:95-101
162. Nagoshi R, Shinke T, Otake H, et al. Qualitative and quantitative assessment of stent restenosis by optical coherence tomography: comparison between drug-eluting and bare-metal stents. *Circ J*. 2013;77:652-60.
163. Goto K, Takebayashi H, Kihara Y, et al. Appearance of neointima according to stent type and restenotic phase: analysis by optical coherence tomography. *EuroIntervention*. 2013;9:601-7.
164. Abnoui F, Waseda K, Kume T, et al. Variability in quantitative and qualitative analysis of intravascular ultrasound and frequency domain optical coherence tomography. *Catheter Cardiovasc Interv*. 2013;82:E192-9.

Figure legends

Figure 1: Artifactual Ostial LMCA “Lesion”: This patient was admitted to a coronary care unit because of chest pain, underwent diagnostic angiography, and then had bypass surgery (left internal mammary artery to the left anterior descending and saphenous vein graft to the left circumflex artery) for an ostial left main stenosis similar to the one shown by the white arrow in this angiogram. He did well for approximately one month, developed recurrent pain, was readmitted to the coronary care unit, underwent repeat angiography which showed closure of both the internal mammary artery and saphenous vein grafts, and had repeat bypass surgery this time using saphenous vein grafts to both the left anterior descending and left circumflex arteries. He again did well for about a month before developing recurrent chest pain. At this time he was referred for an IVUS study of the ostial left main stenosis. The pre-IVUS angiogram and its ostial stenosis (white arrow) are shown. The IVUS imaging run shows no left main disease or lumen compromise. There is at most mild intimal thickening (“a”). Note the shadowing caused by the aortic wall (“b”). The guiding catheter has been retracted and is out of view. (reprinted by permission of CRF Press from Intracoronary Ultrasound by Gary S. Mintz)

Figure 2: Identification of a Culprit Lesion: This middle-aged man presented with an acute coronary syndrome. Angiography (2A) showed two potential culprit lesions – one in the left anterior descending (“a”) and one in the left circumflex (“b”) arteries. OCT imaging of the left anterior descending (2B) showed plaque rupture (“c”), but no thrombus formation. OCT imaging of the left circumflex showed thrombus (“d”, identifying it as the culprit lesion) and presumed erosion. (Illustration courtesy of Takashi Kubo MD and Takashi Akasa MD of Wakayama Medical University, Wakayama, Japan)

Figure 3: Spontaneous coronary artery dissection: This post-partum female was admitted due to chest pain. Coronary angiography (A) showed a severe stenosis from proximal to distal left anterior descending artery (double-headed black arrow). Corresponding IVUS imaging (B-F with duplicated and annotated images B’-F’) shows a spontaneous dissection (double-headed white arrow), intramural hematoma (“a”) and contrast retention (“b”). The gray areas on the annotated frames (B’-F’) indicate the true lumen, the white areas indicate the false lumen, and the black area indicates contrast retention. The non-dissected image slice (B) shows a nonatherosclerotic coronary artery that is typical for spontaneous coronary artery dissection.

Figure 4: Extensive attenuated plaque in the LMCA. Coronary angiography (A) showed intermediate stenosis in the middle of the LMCA. Cross-sectional images (B-D) show extensive attenuated plaque (“a”) over 270° of the arterial circumference (B) that begins near the lumen (dotted white line). The longitudinal re-constructed (B) indicates the length of the attenuated plaque (double-headed arrow, “b”) in relationship to the length of the LMCA (double-headed arrow, “c”). The minimum lumen area measured by IVUS was 4.4mm² (C). During the stent implantation procedure, the patient developed prolonged no-reflow.

Figure 5: Very late stent thrombosis with aneurysm and stent fracture. The left anterior descending artery was treated using two Cypher stents 1.5 years ago. Coronary angiogram (A-B) shows stent thrombosis (white arrow in Panel A) with stent fracture (white arrow in Panel B). IVUS imaging (C-E) revealed aneurysm formation (“a”) that is better seen in the longitudinal

reconstruction (“B” in Panel F) and absence of stent struts (Panel E) confirming stent fracture. The external elastic membrane area in the proximal reference (C) measured 14.1mm^2 , and the external elastic membrane area at the site of the aneurysm (D) measured 31.4mm^2 .

Table 1. IVUS MLA cut-offs that have been associated with ischemia

References	7	8	9	10	11	12	13, 14	15	16, 17	18	21	20	21	22	23	24	25
N	112	70	51	53	14	94	236	170	205	267	47	304	544	169 LAD	323	206 LAD	700 LAD
Comparison technique	CFR	SPECT	FFR	FFR	FFR	FFR	FFR	SPECT	FFR	FFR	FFR	FFR	FFR	FFR	FFR	FFR	FFR
% abnormal	40%	65%	49%	23%	50%	40%	21%	26%	26%	33%	46%	28%	31%	59%	54%	44%	38%
IVUS																	
Mean MLA (mm²)	4.4	4.3	3.9	3.9	3.5	2.3	2.6	2.1	3.5	3.0	2.6	3.5	3.3	3.0	2.9	3.1	2.5
MLA Cut-off (mm²)	4.0	4.0	3.0	4.0	n/a	2.0	2.4	2.1	3.1	2.8	2.4	3.0	2.9	3.0	3.0	3.2 prox 2.5 mid	2.5
Other IVUS determinants of ischemia	LL				MLA/L L	PB LL	PB LAD	PB	Vessel size	Prox vs Mid LAD		PB	LAD EEM	PB LL	PB LL LAD	LL Prox vs Mid PB	LL PB

Abbreviations: CFR=coronary flow reserve, EEM=external elastic membrane, FFR=fractional flow reserve, LAD=left anterior descending, LL=lesion length, Mid=middle, MLA=minimum lumen area, PB=plaque burden, Prox=proximal, SPECT=single photon emission computed tomography

Table 2. IVUS studies and cut-point minimum stent area, stent length, and edge plaque burden predictors of adverse events after BMS or DES implantation

Reference	N	Follow-up Endpoint	Stent	Acute Endpoint	MSA Location	Cut-off	Sensitivity	Specificity
94	543	TLR	BMS	MSA		6.5mm ₂	PPV=17%, NPV=94%	
97	60	IVUS MLA <4mm ²	BMS	MSA		6.5mm ₂	63%	78%
	72		SES			5.0mm ₂	76%	83%
100	543	Angiographic in-stent restenosis	SES	MSA		5.5mm ₂	67%	67%
				Stent length		40mm	81%	78%
102	482	Angiographic in-stent restenosis	BMS	MSA		6.4mm ₂	c statistic=0.64	
	1098		PES			5.7mm ₂	c statistic=0.64	
105	403	Angiographic in-stent restenosis	SES	MSA	LM	8.2mm ₂	80%	81%
					POC	7.2mm ₂	100%	78%
					LAD ostium	6.3mm ₂	73%	85%
					LCX ostium	5.0mm ₂	78%	78%
107	541	Angiographic in-stent restenosis	SES	MSA		5.5mm ₂	72%	66%
	229		EES			5.4mm ₂	60%	60%
	220		ZES			5.3mm ₂	57%	62%

108	106	IVUS MLA <4mm ²	DES	MSA	Main vessel	6.1mm ₂	PPV=91%
					Side branch	4.8mm ₂	PPV=70%
111	255	Angiographic edge restenosis	BMS	Edge plaque burden		48%	c statistic=0.70
	276		PES			47%	c statistic=0.69

Abbreviations: BMS=bare metal stent, DES=drug-eluting stent, EES=everolimus-eluting stent, IVUS=intravascular ultrasound, LAD=left anterior descending, LCX=left circumflex, LM=left main, MSA=minimum stent area, PES=paclitaxel-eluting stent, POC=polygon of confluence, TLR=target lesion revascularization, ZES=zotarolimus-eluting stent.

Table 3. Causes of stent failure detected with intravascular imaging

	Bare Metal Stents				Drug-eluting Stents				
	Stent Thrombosis		Restenosis		Stent Thrombosis			Restenosis	
	<30d	>1y	<5y	>5y	<30d	30d - 1y	>1y	<18m	>18m
Procedure-related complications including underexpansion, edge plaque burden or dissection, geographic miss, etc	x		x		x			x	
Intimal hyperplasia			x					x	
Neoatherosclerosis		x		x			x		x
Late malapposition or aneurysm formation							x		
Stent fracture	x	x			x		x		x
Uncovered stent struts						x	x		

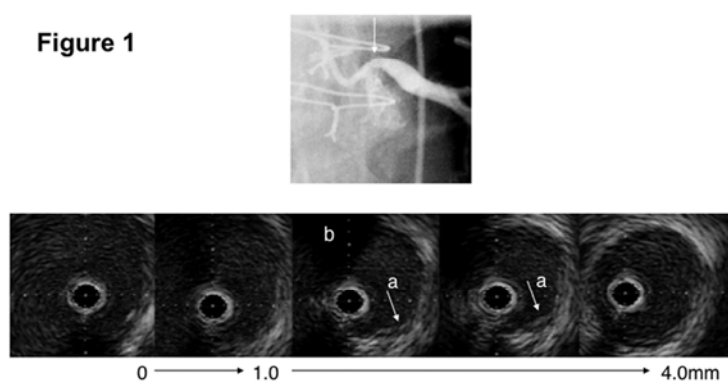
Figure 1

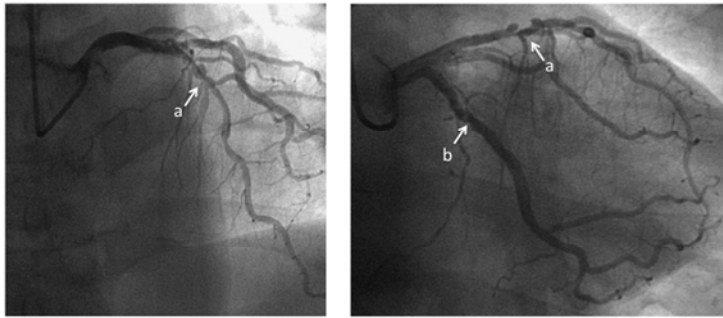
Figure 2A

Figure 2B

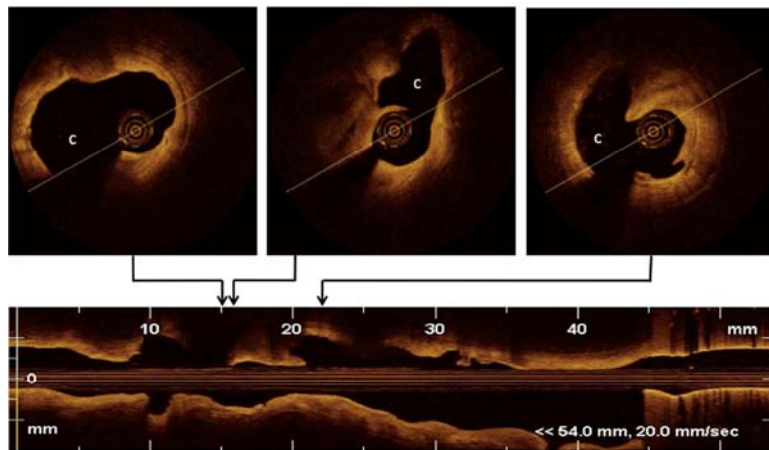


Figure 2C

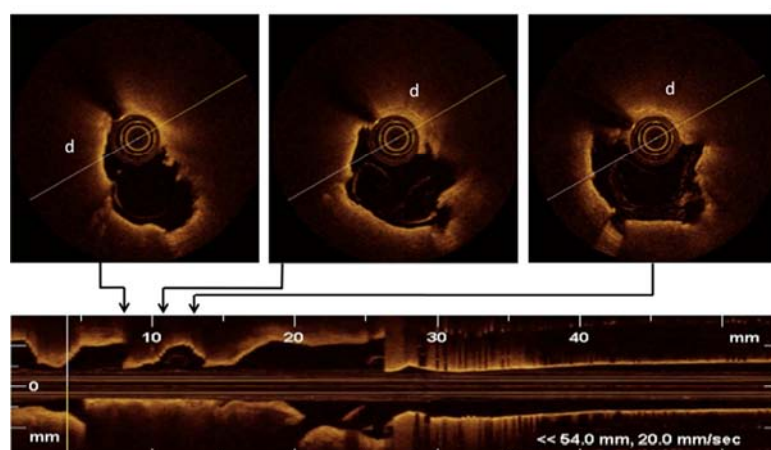


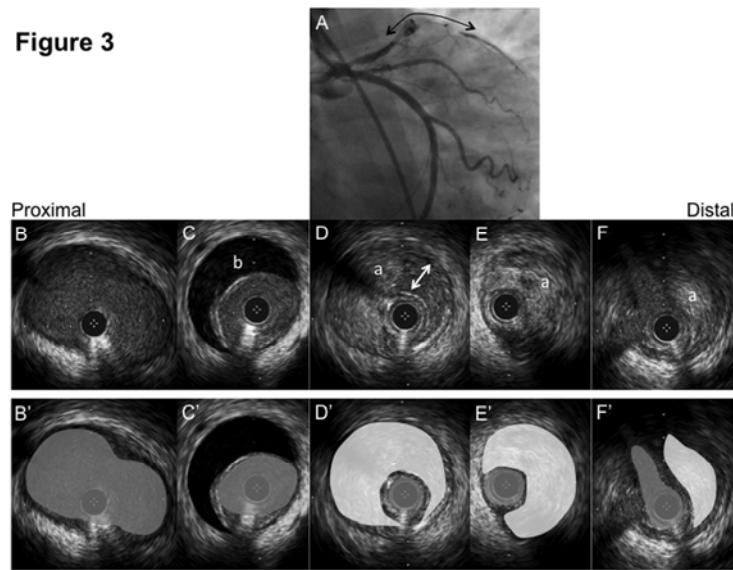
Figure 3

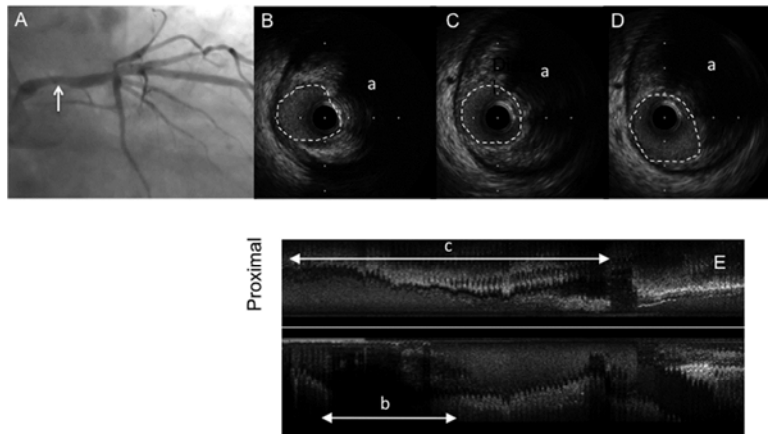
Figure 4

Figure 5