



Fractional Flow Reserve and Intravascular Ultrasound of Coronary Artery Lesions Beyond the Left Main: A Review of Literature

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Determining the severity of intermediate coronary artery lesions is a clinical dilemma. Physiologic assessment of these lesions can establish the presence of ischemia to justify percutaneous coronary intervention (PCI). Approximately 50% of patients undergo PCI without any non-invasive, cardiac, function testing to assess for myocardial ischemia. Intravascular ultrasound (IVUS) is a high-resolution, tomographic imaging modality used to identify vessel size, morphology, and its subsequent layers. The use of IVUS continues to evolve with applications in understanding plaque composition and burden, determination of reference diameter and appropriate stent placement after PCI, assessment for cardiac allograft vasculopathy after cardiac transplantation, and possible identification of vulnerable plaques which may lead to future coronary events. We review the literature related to the use of IVUS in intermediate, non-left main lesions of the coronary vasculature and its correlation with fractional flow reserve (FFR). Given the paucity of randomized controlled clinical trials in this area, it is difficult to make conclusions regarding the best cutoff value for IVUS which may correlate to ischemia producing lesions.

1. Introduction

Determining whether an intermediate coronary artery lesion is associated with ischemia poses a clinical dilemma. Approximately 50% of patients undergo percutaneous coronary intervention (PCI) without any noninvasive, cardiac function tests (Roy et al., 2008). The disconnect between coronary angiography, plaque burden, and functional significance is well recognized, especially in left main disease (Topol and Nissen., 1995) Physiologic assessment of these lesions can establish the burden of ischemia to identify who will benefit from PCI.

Two diagnostic modalities to help identify ischemia-producing lesions and optimize PCI include fractional flow reserve (FFR) and intravascular ultrasound (IVUS). Fractional flow reserve is

an easy, accurate, and reproducible physiological measure of ischemia in indeterminate (50-70%) lesions (De Bruyne et al., 2012). IVUS can help assess plaque composition and burden, determine reference diameter and appropriate stent placement after PCI, assess for cardiac allograft vasculopathy after cardiac transplantation, possibly identify vulnerable plaques which may lead to future coronary events, and facilitate the identification of ischemia causing lesions which may improve both clinical and procedural outcomes (Roy et al., 2008). Use of such modalities has been steadily increasing; from 2003 to 2009, the total IVUS procedures doubled from 0.77 to 1.53 per 1000 Medicare beneficiaries. However, this increase was small when compared to the total volume of PCI's performed in the United States (Riley et al., 2011). Randomized clinical trial data are lacking in terms of IVUS criteria for intermediate lesions in non-left main coronary artery. In a recent study by Barbin et al. have shown that majority of FFR's are performed in the left anterior descending artery (LAD) and is twice as likely to be positive as compared to the other arteries (Barbin et al., 2019). We systematically review the current evidence for intermediate coronary artery lesions in the context of IVUS measured alone versus with FFR and its diagnostic accuracy (Table. 1).

2. Percutaneous coronary intervention based on functional studies

Percutaneous coronary intervention is beneficial in patients with acute coronary syndrome, but the benefits of PCI for stable coronary artery disease have been debated (Boden et al., 2007; Group et al., 2009). The sensitivity of detecting and localizing multivessel coronary artery disease by noninvasive testing is limited (Emmett et al., 2002; Lima et al., 2003). These finding have led to the need for more direct and functional evaluation of coronary lesions to determine true functional and anatomic significance.

2.1. Fractional flow reserve

Fractional flow reserve is a pressure derived, lesion-specific, physiological index to determine the hemodynamic severity of in-

tracoronary lesions. FFR is measured by placing a pressure transducer across the lesion of interest and pharmacologically inducing maximal blood flow. It is then calculated in a comparison of distal mean coronary to aortic pressures during greatest hyperemia. FFR indicates the potential of a stenotic vessel to induce myocardial ischemia. FFR in a normal coronary artery is 1.0. An FFR value of 0.80 or less indicates significant coronary stenosis with an accuracy of more than 90% (De Bruyne et al., 2001; Pijls et al., 1996). The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) and FAME II trials demonstrated improved clinical outcomes including death, urgent revascularizations, and lower health care costs in patients with stable coronary artery disease that were selected from FFR-guided evaluation (De Bruyne et al., 2012; Tonino et al., 2009).

2.2. Intravascular ultrasound

Intravascular ultrasound uses high frequency sound waves to characterize the lumen of vessels including atherosclerotic plaques (Nissen et al., 1991). Based on Galgov's hypothesis of coronary remodeling, it is hypothesized that atherosclerotic plaques can grow into the elastic lamina of a vessel wall and cause minimal to no luminal narrowing until approximately 40% of the lumen is occupied (Glagov et al., 1987). Because IVUS provides a tomographic image of the lumen and vessel wall, it can identify low-grade plaques prior to causing luminal narrowing unlike the 2-dimensional images seen on coronary angiography which may not discern these lesions (Topol and Nissen., 1995).

3. IVUS lesion criteria in determining functional significance of coronary artery stenosis

Flow (volume/time) through a stenotic lesion correlates directly with the area of stenosis and the velocity. The diameter of stenosis may be misleading in determining area and flow since the luminal shape of a stenotic segment is not always perfectly circular. Intraluminal visualization and precise measurement of the stenosis have helped IVUS emerge as a leader in determining le-

sion characteristic and severity during coronary angiography.

IVUS offers the potential to identify vulnerable atherosclerotic lesions that may lead to acute coronary events. Unstable plaques have a large lipid core (> 40%) with only a thin overlying fibrinous cap (Falk et al., 1995). IVUS can characterize the plaque based on its echogenicity, offering the opportunity to assess both the quality and quantity of atherosclerotic lesions (Nissen, 2001). IVUS can help determine the severity of indeterminate left main coronary lesions, assess long lesions, apply the use of multiple stents, and evaluate in-stent restenosis (Jasti et al., 2004; Leesar et al., 2004).

Several trials have confirmed peri-procedural and clinical benefits of IVUS during and after PCI (Frey et al., 2000; Mudra et al., 2001; Oemrawsingh et al., 2003; Russo et al., 2009). Studies with IVUS-aided PCI have shown lower rates of stent thrombosis, urgent revascularizations, short- and long-term MI, and short- and long-term mortality (Roy et al., 2008; Kim et al., 2010).

In proximal coronary lesions with a reference vessel diameter of > 3 mm, an IVUS lumen area cutoff of 3 to 4 mm² is reported to accurately correlate with the functional stenosis as calculated by FFR (Abizaid et al., 1998; Briguori et al., 2001; Takagi et al., 1999). IVUS has also improved the assessment and understanding of both stent apposition and high pressure post-dilation in drug eluting (Roy et al., 2008; Hong et al., 2006) and bare metal stents (Oemrawsingh et al., 2003).

In the EXCELLENT trial, the use of IVUS during PCI was associated with more stents implanted, longer stenting, and bigger final stent diameter (Park et al., 2013). IVUS guidance was associated with increased risk of target lesion failure (4.3% vs. 2.4%; $p = 0.047$) and major cardiac adverse events (MACE) at 1 year almost exclusively due to increased risk of peri-procedural myocardial infarction (1.6% vs. 0.2%; $p = 0.050$). Conversely the rates of cardiac death, spontaneous myocardial infarction, and target lesion revascularization did not differ significantly between the two groups (Koo et al., 2011). However, the EXCELLENT trial relied upon QCA and did not use IVUS for deciding need for revascularization.

Table 1. Advantages and Disadvantages of IVUS vs FFR

	IVUS	FFR
Anatomy	Can show vessel in real-time	Not possible
Coronary Physiology	Cannot measure	Can measure functional significance
Need to cross lesion	Yes	Yes
Infusion of vasoactive drugs	No	Adenosine, Nicorandil, Sodium nitroprusside, Regadenoson
Prone to technical errors	No	Yes (Equalizing, drifts, infusion failure, tandem lesions)
Guidance for stent placement and evaluation	Yes with sizing, expansion, thrombosis	No
Plaque characteristics	Yes	No
Established Criteria	No definite criteria for non-left main lesions	< 0.80 associated with significant lesions
Guide complex coronary interventions	Yes, Wire crossing for bifurcation lesion and Chronic total occlusions (CTO's)	< Not possible
Ostial Left main disease	Set criteria < 6 mm ²	May miss aorto-ostia lesions

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Table 2. Summary of the study design of included studies.

Study	Type	N	FFR cut-off	FU (months)	Outcome	IVUS criteria for significance	Adverse Effects* in IVUS group	Summary
Excellent (Park et al., 2013)	nonrandomized observational	463 matched pairs	None	12	MACE	Not measured	Peri MI $p = 0.05$ Target lesion failure $p = 0.047$	IVUS guidance was associated with significantly increased risk of target lesion failure (4.3% vs. 2.4%; $p = 0.047$) and MACE at 1 year almost exclusively due to increased risk of periprocedural myocardial infarction (1.6% vs. 0.2%; $p = 0.050$)
Koo et al. (Koo et al., 2011)	multicenter, prospective registry	300	< 0.8		Functional	minimum lumen area (MLA), lesion location, vessel size	None reported	Proximal LAD MLA < 3, Mid LAD MLA < 2.75. Vessel size > 3 MLA < 3, VS < 3, MLA < 2.5, were significantly associated with prediction of functionally significant stenosis (FFR < 0.8)
Takagi et al. (Takagi et al., 1999)	Single center, non randomized	42	< 0.75		Functional	MLA IVUS, area stenosis IVUS, MLD QCA, percent diameter stenosis QCA	None reported	MLA IVUS < 3.0 mm ² and the area stenosis > 0.6 correlated with FFR of < 0.75 perfectly
Briguori et al. (Briguori et al., 2001)	Single center, non randomized	43	< 0.75		Functional	Area Stenosis, MLA, MLD	None reported	An area stenosis > 70%, MLD ≤ 1.8 mm, MLA ≤ 4.0 mm ² were the best cut-off values fitted to a FFR of < 0.75
Abizad et al. (Abizaid et al., 1998)	Single Center Non randomized, observational	86	CFR > 2		Functional	Cross sectional area (CSA), lesion length	None	IVUS minimum lumen CSA of > 4.0 mm ² had a diagnostic accuracy of 89% in identifying a CFR of > 2.0
Bendor et al. (De Bruyne et al., 2012)	Single center prospective registry	185	< 0.8	48	Functional	MLA, MLD, lesion length, area stenosis	None	They provide different cutoffs for different vessel diameters. MLA < 3.09 mm ² was the best threshold value for identifying FFR < 0.8
Kang et al. (Kang et al., 2012)	Single center retrospective non-randomized	692	< 0.8	12	Functional	Lesion length, Plaque rupture, Minimal lumen, Plaque burden	None reported	MLA < 2.4 mm ² was best cutoff for predicting FFR < 0.8, with accuracy of only 69%

Table 2. Continued

Study	Type	N	FFR Cutoff	FU (months)	Outcome	IVUS criteria for significance	Adverse Effects* in IVUS group	Summary
Ideas (Lee et al., 2010)	Prospective center	94	< 0.75	24	Functional	MLA, Plaque Burden, lesion length	None	MLA of < 2.0 mm ² , was best cutoff for predicting FFR < 0.75 in intermediate lesions (RVD < 3 mm)
Phantom (Costa et al., 2007)	Multicenter Prospective	60	< 0.75	12	Functional	MLA, percent plaque obstruction	None	No correlation between IVUS indexes and FFR values, for vessels with < 2.8 mm diameter
Kang et.al (Kang et al., 2012)	Single center Prospective	55	< 0.8, < 0.75	12	Functional	MLA, Plaque burden	None	MLA of < 4.8 and < 4.1 was best cutoff for determining FFR of < 0.8 and < 0.75 respectively for intermediate Left main lesions
Koh .et al (Koh et al., 2012)	Single center	77	< 0.8	24	Functional	MLA, Plaque burden, percent diameter stenosis, percent area stenosis only for Major epicardial vessel lesions	None	IVUS parameters and FFR were different between MV and SB ostial lesions but had > 80% NPV thus helpful in excluding ischemic vessels
Nam et.al (Nam et al., 2010)	Single center, retrospective	167	< 0.8	22	MACE	MLA, Minimal stent area, percent diameter stenosis	Not significant between 2 groups	Incidence of MACE and target vessel revascularization was similar, 3 x PCI's were done in IVUS group as compared to the FFR group
Yang et. al (Yang et al., 2014)	Single center, prospective	206	< 0.8	36	MACE	MLA, lesion length	Not reported	Lesions with MLA referenced to the lesion location and lesion length > 20 mm, 80.7% of lesions had FFR < 0.80
Han et.al (Han et al., 2014)	Multicenter, prospective, pooled	822	< 0.8		Functional	MLA, Lesion Location	Not reported	MLA of 2.75 mm ² had the best correlation with FFR < 0.8 (95% CI 0.609-0.685)
Naganuma (Naganuma et al., 2014)	Single Center, prospective	109	< 0.8	60	Functional	MLA, Plaque burden	Not reported	In the entire cohort MLA < 2.70 mm ² had a 77.3% accuracy for predicting an FFR < 0.8

Table 2. Continued

Study	Type	N	FFR Cutoff	FU (months)	Outcome	IVUS criteria for significance	Adverse Effects* in IVUS group	Summary
FIRST (Waksman et al., 2013)	multicenter, prospective, international registry	350	< 0.8	18	Functional	MLA, plaque burden, lesion length and LAD lesions	Not reported	MLA < 3.07 mm ² is the best overall threshold value for identifying ischemic FFR
CUI et.al (Cui et al., 2013)	Single center prospective study	141	< 0.8	30	Functional	MLA, Plaque burden	Not reported	MLA of 3.15 mm ² predicted FFR < 0.80 with an overall diagnostic accuracy of 73.6% (AUC = 0.709)
De la Torre et.al (de la Torre Hernandez et al., 2013)	Two center, randomized prospective study	800	< 0.8	24	Functional and IVUS guided	MACE	Not significant	MACE not different at 1 or 2 years in the IVUS or FFR group ($p = 0.35$)

*Adverse Events: target lesion failure (TLF), a composite of cardiac death, target-vessel-related myocardial infarction (MI), clinically-driven target lesion revascularization (TLR), at 1 year. in-segment binary restenosis at 9 months as measured by QCA, all-cause death, cardiac death, all-cause MI, target vessel-related MI, target vessel revascularization, and definite or possible stent thrombosis.

Limited data exist from randomized clinical trials that have evaluated the role of IVUS as the sole decision making modality for revascularization. One reason for this is the lack of a universally accepted IVUS determined criteria to demonstrate physiologically significant stenosis.

4. Studies using IVUS and FFR/CFR for inter-mediated coronary lesions (Table. 2)

Determination of an IVUS cutoff for physiologically significant stenosis was first reported using coronary flow reserve (CFR) ≤ 2 as a marker of ischemia (Abizaid et al., 1998). Only three left main lesions were included. An IVUS minimum lumen cross sectional area of 4.0 mm^2 predicted a CFR of 2.0 with a diagnostic accuracy of 89%. The minimum lumen cross sectional area ($r = 0.771$, $p < 0.0001$) and minimum lumen diameter ($r = 0.782$, $p < 0.0001$) correlated best with the measured CFR. A moderate correlation between CFR and QCA minimum lumen diameter ($r = 0.552$) and diameter stenosis ($r = 0.454$) was found.

Takagi et al demonstrated a significant relationship between the minimum lumen area (MLA) on IVUS and FFR values ($r^2 = 0.62$, $p < 0.0001$) (Takagi et al., 1999). The area of stenosis, calculated by dividing the reference luminal area minus MLA by the reference luminal area, was inversely correlated to the FFR ($r^2 = 0.60$, $p < 0.0001$). The IVUS cutoffs that had the best sensitivity and specificity were MLA's $< 3.0 \text{ mm}^2$ (sensitivity = 83.0%; specificity = 92.3%) and area of stenosis > 0.6 (sensitivity = 92.0%; specificity = 88.5%). With combined MLA's $< 3.0 \text{ mm}^2$ and areas of stenosis > 0.6 , all lesions, had an FFR < 0.75 . In the multivariate regression analysis, the area of stenosis by IVUS was independently correlated with FFR of < 0.75 .

Briguori et al. introduced minimal luminal diameter and percent of stenosis that increased the sensitivity and specificity of the IVUS cutoffs (Briguori et al., 2001). FFR of < 0.75 was best predicted by a stenotic area $> 70\%$ (sensitivity 100%, specificity 68%), an MLD $\leq 1.8 \text{ mm}$ (sensitivity 100%, specificity 66%), and an MLA $\leq 4.0 \text{ mm}^2$ (sensitivity 92%, specificity 56%). Half of the lesions with an area of stenosis $> 70\%$ had an FFR < 0.75 . However, an MLD $\leq 1.8 \text{ mm}$ was always associated with an FFR of < 0.75 . The combination of the percent of the stenotic area and the MLD increased the sensitivity (100%) and specificity (76%) of IVUS.

In a single center prospective registry, FFR and IVUS were measured in 205 intermediate lesions (40%–70% stenosis) including 12 left main lesions (De Bruyne et al., 2012). A statistically significant correlation was observed between FFR and MLA in lesions with reference vessel diameters of 3–3.5 mm and $> 3.5 \text{ mm}$ ($r = 0.44$, $p < 0.001$ and $r = 0.43$, $p = 0.01$, respectively). Correlation between FFR and IVUS was poor as 65% of the lesions with an MLA $< 4 \text{ mm}^2$ had an FFR > 0.8 (non-ischemic). They demonstrated that as the reference vessel diameter changed, the MLA threshold for FFR also changed which emphasized that other factors like lesion length, flow, and size of the vessel should also be taken into account.

A multicenter, prospective registry conducted at 4 Korean centers performed IVUS and FFR on 267 stenotic lesions in 252 patients to determine the functional significance of the stenosis (Koo

et al., 2011). They advocated proposing different IVUS criteria according to the lesion location and coronary anatomy rather than the size of the vessel. The best cutoff value (BCV) of MLA to define the functional significance was 3.0 mm^2 (area under the curve [AUC]: 0.81, 95% confidence interval [CI]: 0.68 to 0.91) for proximal left anterior descending artery (LAD) lesions. MLA $< 3 \text{ mm}^2$ and plaque burden $> 75\%$ had a moderate sensitivity and specificity of 75% and 79% respectively for determining functional significance.

In the IDEAS trial, IVUS and FFR were performed on small coronary arteries with diameters $< 3 \text{ mm}$ to determine the IVUS derived anatomic criteria for functionally significant lesions (Lee et al., 2010). They randomized 94 patients with an average reference vessel diameter of 2.72 mm. FFR criteria of < 0.75 was used to define functionally significant stenosis. In the multivariate analysis, factors that correlated well with a FFR of < 0.75 were MLA of $< 2.0 \text{ mm}^2$ (sensitivity 82.35%, specificity 80.77%), plaque burden of $> 80\%$ (sensitivity 87.9%, specificity 78.9%), and lesion length of $> 20 \text{ mm}$ (sensitivity 63.6%, specificity 78.9%). 95.5% (Oemrawsingh et al., 2003) of patients who had all three of the above mentioned criteria also had an FFR < 0.75 .

Kang et al analyzed 692 consecutive patients with 784 coronary lesions by IVUS and FFR before PCI (Kang et al., 2012). IVUS criteria which were significantly related to an FFR of < 0.8 were, left anterior descending coronary artery location, proximal segments, lesion length, averaged RLD, plaque rupture, MLA, and plaque burden. Subgroup analyses for MLA were performed taking into account clinical factors, vessel type, lesion location, and vessel size. Combined best cut-off IVUS MLA was 2.4 mm^2 (CI: 2.3–2.5) with a poor diagnostic accuracy of 69% and moderate sensitivity and specificity of 84% and 63% respectively for FFR < 0.8 . They observed different cutoffs for different vessels, lesion location (proximal, mid, or distal), and reference vessel diameters, and all had a diagnostic accuracy $< 80\%$.

In the PHANTOM trial, which included 60 patients, there was no correlation between various angiographic indices, IVUS, and FFR for reference vessels of $< 2.8 \text{ mm}$ diameter and $< 20 \text{ mm}$ length (Costa et al., 2007). A jeopardy score was also used to calculate the amount of myocardium, at risk beyond the plaque (Califf et al., 1985). Poor inverse correlation was observed between FFR and jeopardy score ($p = 0.01$, $R = -0.32$) and none between jeopardy score and IVUS. Per the authors, the jeopardy score could be hypothesized as a way of determining the hemodynamic significance of moderate stenosis in small caliber coronaries.

Koh et al conducted a trial to study the relationship of coronary angiography, IVUS, and FFR < 0.80 between major epicardial vessels (MV) and side branches (SB) with intermediate ostial lesions in 77 patients (93 lesions) (MV: 38, SB: 55) (Koh et al., 2012). SB's had a reference diameter $> 2.25 \text{ mm}$ and vessel length $> 40 \text{ mm}$. Only MLA ($r = 0.55$, $p < 0.001$) and percent plaque burden ($r = -0.42$, $p = 0.011$) significantly correlated with an FFR of < 0.8 for MV but not for SB. MV lesion $> 3.5 \text{ mm}^2$ had a positive predictive value of 69% and specificity of 75%, but for SB ostial lesions the positive predictive value for all IVUS parameters was $\leq 50\%$. The negative predictive value for both lesions was $> 80\%$. Thus, the relationship between IVUS parameters and FFR was different be-

tween MV and SB ostial lesions, and had poor diagnostic accuracy in predicting the functional significance of SB ostial lesions.

In the FIRST registry, a multicenter, prospective, international registry of patients with intermediate coronary lesions, 350 patients with 367 lesions were enrolled at 10 U.S. and European sites (Waksman et al., 2013). MLA of 3.07 mm² for the entire cohort had a sensitivity of 64.0% and specificity of 64.9% for predicting FFR of < 0.8. There was an increase in correlation as the diameter of the vessel increased. The weakest correlation was for RVDs of 2.5 to 3.0 mm ($r = 0.22$, $p = 0.003$), then 3.0 to 3.5 mm ($r = 0.27$, $p = 0.01$), and the best with > 3.5-mm vessels ($r = 0.34$, $p = 0.007$). Plaque burden was not significantly associated with FFR.

Cui et al performed IVUS on 141 patients with 165 intermediate coronary lesions in vessels ≥ 2.50 mm in diameter (Cui et al., 2013). MLA of 3.15 mm² predicted FFR < 0.80 with an overall diagnostic accuracy of 73.6% (AUC=0.709). When taken together as a binary variable, MLA < 3.15 mm² and PB $\geq 65.45\%$, were independent predictors of FFR < 0.8. However, the diagnostic accuracy was reduced to 73.1%.

In a study by Yang et al, 206 patients with intermediate LAD lesions were divided into two groups by using an FFR cutoff of < 0.8 (Yang et al., 2014). In addition to conventional IVUS parameters, they measured plaque volume (PV) and percent atheroma volume (PAV). Lesions with minimal lumen area (MLA) > 4 mm² had an FFR > 0.8 in 91% of cases with a strong negative predictive value. However, with an MLA < 4 mm², the relationship to FFR was poor with 51% having an FFR < 0.8. Independent predictors of FFR < 0.80 included lesion length, MLA, and lesion location. PV and PAV were inversely related to FFR but only marginally improved the diagnostic accuracy of IVUS.

Han et al conducted an international, large-scale, pooled analysis of 11 centers with 882 patients for determining the best cut-off value (BCV) of IVUS MLA in intermediate coronary stenosis of functional significance (Han et al., 2014). BCV of IVUS MLA of 2.75 mm² (AUC 0.646, 95% CI 0.609–0.684) correlated with FFR < 0.8 with a positive predictive value of 73%. No reliable MLA cut-off value was found for lesions other than proximal and mid LAD lesions. Additional differences in MLA cut-off values between Asian and western populations were also found.

In a study by Naganuma et al 109 patients with 132 intermediate stenoses were assessed by FFR, IVUS, and quantitative angiography to find IVUS parameters that correlated with functional significance (FFR < 0.8) (Naganuma et al., 2014). MLA of 2.70 mm² (95% CI 0.745–0.898) correlated best with FFR < 0.80 in the entire lesion cohort with a sensitivity of 79.5% and a specificity of 76.3%, 2.84 mm² in vessels with RVD ≥ 3.0 mm and 2.59 mm² in those with RVD > 3.0 mm. Plaque morphology, however, did not affect the FFR.

4.1. Studies evaluating clinical outcomes using IVUS

Nam et al evaluated clinical outcomes of FFR-guided PCI compared with IVUS-guided PCI for intermediate coronary lesions (40–70%) and reference vessel diameter of > 2.5 mm in 167 patients at one year (Nam et al., 2010). The incidence of MACE and target vessel revascularization was similar; PCI was performed less often in the FFR-guided group compared to IVUS group (33.7% vs. 91.5%, $p < 0.001$). Authors noticed that by de-

creasing MLA from 4 mm² to < 3 mm², the incidence of PCI would be similar in both groups. They concluded that FFR- and IVUS-guided PCI in patients with intermediate coronary lesions both provided acceptable clinical outcomes though neither was associated with statistically significant MACE.

In a randomized trial by de la Torre et al 400 patients were enrolled over a six-year period by dividing them into two groups for possible PCI in non-LM intermediate lesions (de la Torre Hernandez et al., 2013). 488 lesions in the IVUS group and 463 lesions in the FFR group were included, with the primary outcome being MACE in either strategy. PCI was performed when FFR was < 0.75 or MLA < 4 mm² in vessels > 3 mm, and < 3.5 mm² in vessels 2.5–3 mm along with plaque burden > 50%. More interventions were performed in the IVUS group as compared to the FFR group (48.8% vs. 28%; $p < 0.001$). Similar MACE free survival over 2 years was observed in both groups (97.7% at one year and 93.1% at two years in the FFR group and 97.7% at one year and 95.6% at two years in the IVUS group; $p = 0.35$), as well as, in the no intervention cohorts.

In a recent meta-analysis by Ahn et al. which included 3 randomized trials and 14 observational studies with a total of 26,503 patients, 12,499 patients underwent IVUS guided PCI (Ahn et al., 2014). Over a follow-up period of 1 to 4 years, IVUS was associated with a significant reduction in the risk of mortality (39%, 95% CI 0.48 to 0.79, $p < 0.001$), TLR (19%, 95% CI 0.66 to 1.00, $p < 0.046$), MI (OR 0.57, 95% CI 0.44 to 0.75, $p < 0.001$), and stent thrombosis (41%, 95% CI 0.47 to 0.75, $p < 0.001$). The risk of periprocedural MI was not increased.

4.2. Effect of reference vessel size and lesion length on the cut-off value

Looking at the Bernoulli equation, the pressure difference across an area of narrowing is inversely related to both the area and length of the area in conjunction with the velocity of flow. Although different studies have different criteria, we hypothesize that additional IVUS criteria should be taken into account to accurately predict the functional significance of the lesion including the vessel involved which may suggest the amount of myocardium at risk, size of the vessel, flow velocities, lesion lengths, plaque burden, and plaque rupture (Lee et al., 2010; Kang et al., 2012). Nishioka et al showed that reference vessel size did not play an important role in determining cut-offs. (Sensitivity of the lesion's lumen area slightly improved from 88% to 92% without decreasing in specificity.) (Nishioka et al., 1999). This is in contrast with studies by Kang et al (Califf et al., 1985) and Naganuma et al (de la Torre Hernandez et al., 2013) where the size of the reference vessel affected the cut-off values and their correlation with a physiologically significant stenosis. A study by Lopez-Palop et al, 103 patients with lesion length of > 20 mm (mean 28.7 ± 10.6 mm), had a sensitivity and specificity of 74.5 and 74.6% respectively and was strongly correlated with an FFR of < 0.8 (AUC 0.78 95% CI 0.69–0.87, $p < 0.0005$). The authors suggest that long lesions may have different morphologies of stenosis such that parameters including only the mean or maximal area of stenosis, with no consideration of lesion length, may not accurately quantify such stenotic lesions (Lopez-Palop et al., 2013).

4.3. IVUS-guided measures of plaque burden and natural history of CAD

Two studies have prospectively examined the natural history of CAD using IVUS guidance to look at coronary plaques. In the PROSPECT trial, tracked 678 patients with acute coronary syndrome who underwent three-vessel coronary angiography, grayscale, and radiofrequency intravascular ultrasonographic imaging after percutaneous coronary intervention, for a median of 3.4 years (Stone et al., 2011) 3 year cumulative rate of MACE was 20.4%, and half of the events occurred in the non-culprit lesions. Plaque burden > 70% (HR 5.03 95% CI 2.51–10.11, $p < 0.001$), thin-cap fibroatheromas (HR 3.35 95% CI 1.77–6.36, $p < 0.001$), and MLA $\leq 4.0 \text{ mm}^2$ HR 3.21 95% CI 1.61–6.42, $p = 0.001$) were three IVUS parameters independently associated with MACE in non-culprit lesions. When all three were combined, the hazard ratio was 11.05. The PREDICTION trial followed 506 patients who presented with ACS treated for 1 year (Stone et al., 2012). They measured coronary hemodynamic and IVUS-guided plaque morphology. Plaque burden was the most relevant independent factor, and when combined with low endothelial shear stress, it had a 41% positive predictive value for plaque progression and luminal obstruction treated with PCI.

5. Limitations of FFR

Accurate utilization of FFR depends upon the ability to abolish microvascular resistance completely and thus to achieve maximal hyperemic trans-stenotic flow in the vessel of interest. However, conditions such as acute myocardial infarction, diffuse coronary artery disease, serial stenosis, previous MI (scar tissue), microvascular disease, high systemic venous pressures, and left ventricular hypertrophy/dysfunction may prevent total abolition of microvascular resistance. Thus, maximal trans-stenotic flow rates may not be achieved leading to inaccurate FFR values (Blows and Redwood., 2007).

6. New modalities

Instantaneous wave free ratio (iFR) and optical coherence tomography (OCT) have emerged as new physiologic and intracoronary imaging, techniques in the recent years. iFR measures the relative distal pressure from mid-to-end diastole at rest in the coronary bed as coronary flow occurs predominantly in diastole, pressure gradients are higher than during the lower flow period of systole. iFR operated on the theoretical basis that diastolic resting myocardial resistance equals mean hyperemic resistance. Two recently published randomized controlled trials comparing FFR and iFR in intermediate coronary lesion have shown non-inferiority of iFR in terms of all-cause mortality, non-fatal MI and unplanned revascularization (Davies et al., 2017; Gotberg et al., 2017). Patients who underwent iFR also reported less discomfort, has less rates of PCI and shorter procedural times in the secondary outcomes. Recent appropriate use criteria have endorsed the use of both iFR and FFR to access intermediate coronary artery lesions with cutoff for being iFR < 0.89 (Blows and Redwood., 2007). OCT is another intracoronary imaging modality which uses near-infrared technology for vessel visualization (Jang et al., 2002). OCT has a better axial and lateral resolution than IVUS and can characterize plaque, vessel wall and stents better than

IVUS (Yabushita et al., 2002). OCT can identify intimal thickening in the early phases of atherosclerosis, quantify plaque burden and characterize the type of plaque (Yabushita et al., 2002). IVUS has better tissue penetration than OCT which leads to better assessment of plaque burden and vessel remodeling (Kume et al., 2009). OCT requires vessel opacification with contrast media to acquire good quality pictures and can be a limiting factor in patients with renal impairment. ILUMIEN III: OPTIMIZE PCI trial was a RCT comparing OCT, IVUS and routine angiography, showed that OCT was non-inferior to IVUS in achieving minimal stent area (MSA) (one-sided 97.5% CI -0.70 mm^2 ; $p = 0.001$) and but not superior to routine angiography (Ali et al., 2016). As of now there are not set criteria or guidelines for the use of OCT in patients undergoing PCI. Technological advances have now allowed functional assessment of epicardial coronary arteries using contrast computer tomography (CTA). FFR-CT has now emerged as a new technology to potentially quantify FFR non-invasively using CTA measurements. PROMISE (Schneider et al., 1993) trial sub study included 181 patients who underwent CTA, coronary angiography and FFR-CT. They found that patients with an FFRCT ≤ 0.80 were significantly more likely to undergo PCI and to meet the composite endpoint of major adverse cardiac events (MACE) or revascularization than those with FFRCT > 0.8 . FFRCT was compared with CTA alone for assessment of lesion severity and patient management in 200 patients with stable chest pain in the FFRCT RIPCORDER study (Curzen et al., 2016). Independent cardiologists CTA reviewed data and made clinical decisions, pre and post knowledge of the FFR-CT. The endpoint was the difference between management plans based on the CTA alone or FFRCT data which happened in 72 patients in the cohort. In the PLATFORM study (Douglas et al., 2016) 584 patients were divided into invasive ($n = 287$) vs CTA ($n = 297$ with 177 FFRCT). The authors found that the strategy of using FFR-CT was more cost effective and had better QoL metrics as compared to other invasive and non-invasive testing. Gaur et al (Gaur et al., 2017) performed coronary CTA with FFR calculation and invasive coronary angiogram with FFR on patients with multivessel CAD one month after a STEMI. The study evaluated 124 non-culprit vessels from 60 patients and found that the diagnostic performance of FFRCT for ischemia evaluation in post STEMI population was moderate and the authors did not recommend this a modality ready for prime time in this patient subset. Currently FFR-CT can be used as an adjunctive tool to evaluate intermediate coronary lesions however is affected by all the limitation inherent to any CT scan including artifacts, image quality and needing invasive coronary angiography to as a tie breaker for indeterminate/borderline results.

7. Discussion

The relationship between IVUS parameters and FFR in intermediate non-left main coronary lesions has not yet been fully evaluated. Nonetheless, recent studies suggest limited efficacy of IVUS parameters in predicting functional significance of coronary stenosis, as well as, significant variation in the diagnostic accuracies due to lesion location (Kang et al., 2012; Costa et al., 2007). IVUS imaging may be of limited benefit in small caliber arteries due to the diameter of the catheter itself, vessel spasm, doppler

effect, and unreliable image quality. However, angiographically difficult to visualize lesions and high-risk lesions such as ostial, side branch, bifurcation, or overlapping segment can be readily visualized by IVUS providing information that can guide therapy. It is also useful for accessing optimal stent size, expansion, and apposition thus leading to reduced rates of in-stent stenosis, MI, and MACE (Roy et al., 2008; Oemrawsingh et al., 2003; Witzenbichler et al., 2014). Additionally, many non-cluprit lesions are responsible for acute coronary events as demonstrated in several studies, and the identification of such vulnerable, thin-cap fibromas is possible through the use of IVUS (Stone et al., 2011, 2012; Naghavi et al., 2003a,b).

The lack of a systematic, randomized trial prohibits us from making clear recommendations for the use of IVUS and the related adverse events. In the EXCELLENT trial, MACE were higher in the IVUS group exclusively driven by periprocedural MI's and target lesion failures (Park et al., 2013). However, some studies have shown no difference in MACE, but more PCI's were performed in the IVUS group (Nam et al., 2010; de la Torre Hernandez et al., 2013), and the recent meta-analysis of PCI with IVUS-guided therapy, reduced MACE including the risk of death and MI (Ahn et al., 2014).

The reference vessel diameter and lesion location significantly affected the IVUS cut-off value for the given FFR. Based on currently published data, IVUS MLA cut-off of $< 3 \text{ mm}^2$ correlates strongly with the FFR of < 0.8 to < 0.75 in non-left main lesions for reference vessel diameters $> 3 \text{ mm}$ (Fig. 1 and Fig. 2). For reference vessels $< 3 \text{ mm}$, however, no recommendation can be made due to the lack of data, and functional tests should be considered in decision making during PCI in both cases. MLA of $> 4 \text{ mm}^2$ can safely be assumed to predict a non-significant coronary lesion, and PCI can be deferred. Finally, minimal luminal diameter may be more useful in ruling out significant coronary artery disease than determining the need for revascularization. iFR and OCT are newer modalities and can be combined with IVUS to help in better decision making. At this time, use of IVUS for angiographic assessment of non-left main intermediate coronary arteries (50% to 70% diameter stenosis) is considered a class IIb recommendation (level of evidence B) (Lotfi et al., 2014; Levine et al., 2011).

Conflict of interest

The authors declare no competing interests.

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References

- 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. *The American journal of cardiology*. 1998;82:423-428.
- Ahn JM, Kang SJ, Yoon SH, et al. Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. *The American journal of cardiology*. 2014;113:1338-1347.

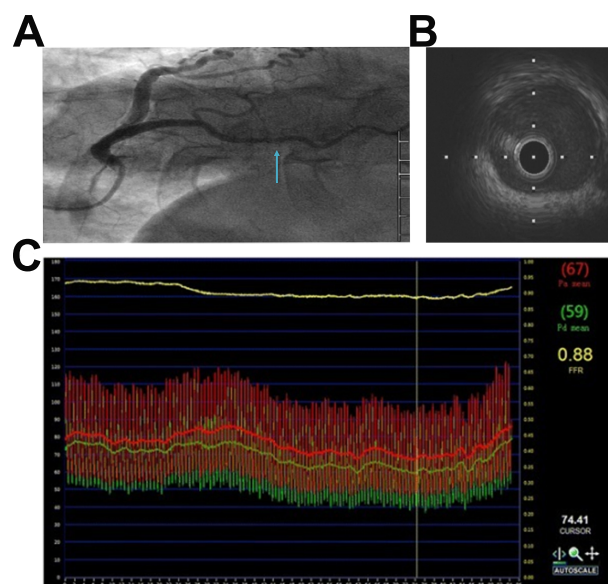


Figure 1. (A) Angiogram shows Mid-LAD lesion (50-70%). (B) IVUS of Mid LAD lesion shows MLA $> 3 \text{ mm}^2$. (C) FFR of the same area shows a value of 0.88 which is physiologically negative.

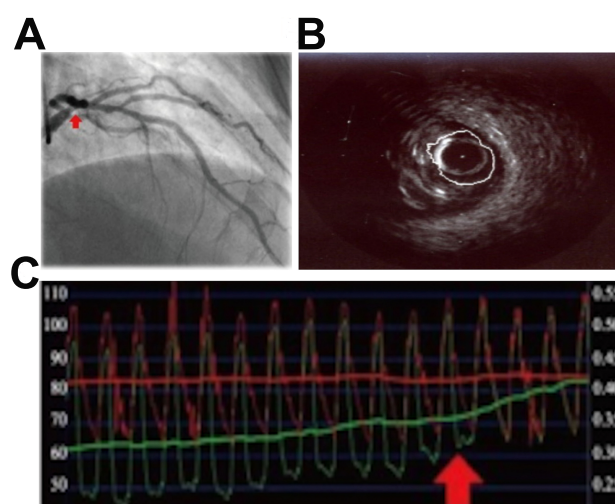


Figure 2. (A) Angiogram reveals intermediate proximal LAD lesion (50-70%). (B) IVUS of Proximal LAD lesion shows MLA $< 3 \text{ mm}^2$. (C) FFR of the same area shows a value of 0.74 which is physiologically significant.

- Ali ZA, Maehara A, Genereux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet*. 2016;388:2618-2628.
- Barbin CM, Vasudevan A, Choi JW, et al. Frequency of abnormal fractional flow reserve measurements among major coronary arteries. *Cardiovasc Revasc Med*. 2019;20:143-146.
- Blows LJ, Redwood SR. The pressure wire in practice. *Heart*. 2007;93:419-422.
- Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *The New England*

- journal of medicine. 2007;356:1503-1516.
- 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. *The American journal of cardiology*. 2001;87:136-141.
- Califf RM, Phillips HR, 3rd, Hindman MC, et al. Prognostic value of a coronary artery jeopardy score. *Journal of the American College of Cardiology*. 1985;5:1055-1063.
- Costa MA, Sabate M, Staico R, et al. Anatomical and physiologic assessments in patients with small coronary artery disease: final results of the Physiologic and Anatomical Evaluation Prior to and After Stent Implantation in Small Coronary Vessels (PHANTOM) trial. *American heart journal*. 2007;153:296 e1-e7.
- Cui M, Zhu D, Guo LJ, et al. Usefulness of lumen area parameters determined by intravascular ultrasound to predict functional significance of intermediate coronary artery stenosis. *Chinese medical journal*. 2013;126:1606-1611.
- Curzen NP, Nolan J, Zaman AG, et al. Does the Routine Availability of CT-Derived FFR Influence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone? The FFRCT RIPCORT Study. *JACC Cardiovasc Imaging*. 2016;9:1188-1194.
- Davies JE, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *The New England journal of medicine*. 2017;376:1824-1834.
- 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: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2013;9:824-830.
- De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *The New England journal of medicine*. 2012;367:991-1001.
- De Bruyne B, Pijls NH, Bartunek J, et al. Fractional flow reserve in patients with prior myocardial infarction. *Circulation*. 2001;104:157-162.
- De Bruyne B, Pijls NH, Kalesan B, et al. Intravascular ultrasound lumen area parameters for assessment of physiological ischemia by fractional flow reserve in intermediate coronary artery stenosis. *Cardiovascular revascularization medicine: including molecular interventions*. 2012;13:177-182.
- Douglas PS, De Bruyne B, Pontone G, et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. *J Am Coll Cardiol*. 2016;68:435-445.
- Emmett L, Iwanochko RM, Freeman MR, et al. Reversible regional wall motion abnormalities on exercise technetium-99m-gated cardiac single photon emission computed tomography predict high-grade angiographic stenoses. *Journal of the American College of Cardiology*. 2002;39:991-998.
- Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657-671.
- Frey AW, Hodgson JM, Muller C, et al. Ultrasound-guided strategy for provisional stenting with focal balloon combination catheter: results from the randomized Strategy for Intracoronary Ultrasound-guided PTCA and Stenting (SIPS) trial. *Circulation*. 2000;102:2497-2502.
- Gaur S, Taylor CA, Jensen JM, et al. FFR Derived From Coronary CT Angiography in Nonculprit Lesions of Patients With Recent STEMI. *JACC Cardiovasc Imaging*. 2017;10:424-433.
- Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. *The New England journal of medicine*. 1987;316:1371-1375.
- Gotberg M, Christiansen EH, Gudmundsdottir U, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *The New England journal of medicine*. 2017;376:1813-1823.
- Group BDS, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *The New England journal of medicine*. 2009;360:2503-2515.
- Han JK, Koo BK, Park KW, et al. Optimal intravascular ultrasound criteria for defining the functional significance of intermediate coronary stenosis: an international multicenter study. *Cardiology*. 2014;127:256-262.
- Hong MK, Mintz GS, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *European heart journal*. 2006;27:1305-1310.
- 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.
- Jang IK, Bouma BE, Kang DH, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. *Journal of the American College of Cardiology*. 2002;39:604-609.
- 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. *The American journal of cardiology*. 2012;109:947-953.
- Kim SH, Kim YH, Kang SJ, et al. Long-term outcomes of intravascular ultrasound-guided stenting in coronary bifurcation lesions. *The American journal of cardiology*. 2010;106:612-618.
- Koh JS, Koo BK, Kim JH, et al. Relationship between fractional flow reserve and angiographic and intravascular ultrasound parameters in ostial lesions: major epicardial vessel versus side branch ostial lesions. *JACC Cardiovascular interventions*. 2012;5:409-415.
- 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 Cardiovascular interventions*. 2011;4:803-811.
- Kume T, Okura H, Yamada R, et al. Frequency and spatial distribution of thin-cap fibroatheroma assessed by 3-vessel intravascular ultrasound and optical coherence tomography: an ex vivo validation and an initial in vivo feasibility study. *Circ J*. 2009;73:1086-1091.
- 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). *The American journal of cardiology*. 2010;105:1378-1384.
- Leesar MA, Masden R, Jasti V. Physiological and intravascular ultrasound assessment of an ambiguous left main coronary artery stenosis. *Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions*. 2004;62:349-357.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Journal of the American College of Cardiology*. 2011;58:e44-e122.
- Lima RS, Watson DD, Goode AR, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. *Journal of the American College of Cardiology*. 2003;42:64-70.
- Lopez-Palop R, Carrillo P, Cordero A, et al. Effect of lesion length on functional significance of intermediate long coronary lesions. *Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions*. 2013;81:E186-E94.
- Lofi 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. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2014;83:509-518.
- Mudra H, di Mario C, de Jaegere P, et al. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS Study). *Circulation*. 2001;104:1343-1349.
- Naganuma T, Latib A, Costopoulos C, et al. The role of intravascular ultrasound and quantitative angiography in the functional assessment of intermediate coronary lesions: correlation with fractional flow reserve. *Cardiovascular revascularization medicine : including molecular interventions*. 2014;15:3-7.
- 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. *Circulation*. 2003;108:1664-1672.
- Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation*. 2003;108:1772-1778.
- Nam CW, Yoon HJ, Cho YK, et al. Outcomes of percutaneous coronary intervention in intermediate coronary artery disease: fractional flow reserve-guided versus intravascular ultrasound-guided. *JACC Cardiovascular interventions*. 2010;3:812-817.
- 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. *Journal of the American College of Cardiology*. 1999;33:1870-1878.
- Nissen SE, Gurley JC, Grines CL, et al. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. *Circulation*. 1991;84:1087-1099.
- Nissen SE. Clinical images from intravascular ultrasound: coronary disease, plaque rupture, and intervention-the inside view. *The American journal of cardiology*. 2001;88:16K-18K.
- Oemrawsingh PV, Mintz GS, Schali J, et al. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenoses: final results of a randomized comparison with angiographic guidance (TULIP Study). *Circulation*. 2003;107:62-67.
- Park KW, Kang SH, Yang HM, et al. Impact of intravascular ultrasound guidance in routine percutaneous coronary intervention for conventional lesions: data from the EXCELLENT trial. *International journal of cardiology*. 2013;167:721-726.
- Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology*. 2017;69:2212-2241.
- Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. *The New England journal of medicine*. 1996;334:1703-1708.
- Riley RF, Don CW, Powell W, et al. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circulation Cardiovascular quality and outcomes*. 2011;4:193-197.
- Roy P, Steinberg DH, Sushinsky SJ, et al. The potential clinical utility of intravascular ultrasound guidance in patients undergoing percutaneous coronary intervention with drug-eluting stents. *European heart journal*. 2008;29:1851-1857.
- Russo RJ, Silva PD, Teirstein PS, et al. A randomized controlled trial of angiography versus intravascular ultrasound-directed bare-metal coronary stent placement (the AVID Trial). *Circulation Cardiovascular interventions*. 2009;2:113-123.
- Schneider C, Reck T, Greskott KR, et al. [Cystic pancreatic tumors]. *Langenbecks Arch Chir*. 1993;378:281-287.
- Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *The New England journal of medicine*. 2011;364:226-235.
- Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. *Circulation*. 2012;126:172-181.
- Takagi A, Tsurumi Y, Ishii Y, et al. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation*. 1999;100:250-255.
- Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *The New England journal of medicine*. 2009;360:213-224.
- Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation*. 1995;92:2333-2342.
- Waksman R, Legutko J, Singh J, et al. FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. *Journal of the American College of Cardiology*. 2013;61:917-923.
- 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.
- Yabushita H, Bouma BE, Houser SL, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002;106:1640-1645.
- 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. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2014;83:386-394.