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 non-invasive, 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 artery pressure with 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 Galglov’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 lesion 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 fibrous 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; Madra 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 mm²                     | May miss aorto-ostia lesions             |

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| Study                  | Type                          | N     | FFR Cut-off | FU (months) | Outcome  | IVUS criteria for significance | Adverse Effects* in IVUS group | Summary                                                      |
|-----------------------|-------------------------------|-------|-------------|-------------|----------|-------------------------------|-------------------------------|-------------------------------------------------------------|
| Excellent             | nonrandomized observational   | 463   | None        | 12          | MACE     | Not measured                  | Peri procedural MI \( p = 0.05 \) Target lesion failure \( p = 0.047 \) and MACE at 1 year almost exclusively due to increased risk of periprocedural myocardial infarction \((1.6\% \text{ vs. } 0.2\%; \ p = 0.050)\) | IVUS guidance was associated with significantly increased risk of target lesion failure \((4.3\% \text{ vs. } 2.4\%; \ p = 0.047)\) and MACE at 1 year almost exclusively due to increased risk of periprocedural myocardial infarction \((1.6\% \text{ vs. } 0.2\%; \ p = 0.050)\) |
| Koo et al.            | 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 \((\text{FFR} < 0.8)\) |
| Takagi et al.         | 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.       | 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 itted to a FFR of < 0.75 |
| Abizaid et al.        | 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.         | Single center prospective registry | 185   | <0.8        | 48          | Functional | MLA, MLD, lesion length, area stenosis | None reported | 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.           | 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. Summary of the study design of included studies.
| Study               | Type               | N   | FFR Cutoff | FU (months) | Outcome          | IVUS criteria for significance | Adverse Effects* in IVUS group | Summary                                                                 |
|---------------------|--------------------|-----|------------|-------------|------------------|------------------------------|--------------------------------|--------------------------------------------------------------------------|
| Ideas (Lee et al., 2010) | Prospective two center | 94  | <0.75      | 24          | Functional       | MLA, Plaque Burden, lesion length | None                          | MLA of < 2.0 mm², 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 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 mm² had the best correlation with FFR < 0.8 (95% CI 0.69:0.685) |
| 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 mm² had a 77.3% accuracy for predicting an FFR < 0.8 |
| 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 mm² 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 mm² 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 intermediately 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 mm² 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 (r² = 0.552) and diameter stenosis (r = 0.454) was found.

Agrawal 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 mm² (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 mm² 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 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 mm² (sensitivity 82.35%, specificity 80.77%), plaque burden of > 80% (sensitivity 87.9%, specificity 78.9%), and lesion length of > 20 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 mm² (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 mm diameter and < 20 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 mm and vessel length > 40 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 mm² 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 ≤ 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 \(\geq 2.50\) 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 decreasing 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, \(p = 0.006\)), 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 ≤ 4.0 mm² 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 mm²; 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 FRR 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 RIPCORD 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 FFT-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 instent stenosis, MI,
and MACE (Roy et al., 2008; Oemrawsingh et al., 2003; Witzend-
bichler 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 fibro-
mas is possible through the use of IVUS (Stone et al., 2011, 2012;
Naghaei 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 tar-
get 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 cur-
rently published data, IVUS MLA cut-off of < 3 mm$^2$ correlates
strongly with the FFR of < 0.8 to < 0.75 in non-left main lesions
for reference vessel diameters > 3 mm (Fig. 1 and Fig. 2). For ref-
erence vessels < 3 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 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 as-
essment 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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Figure 1. (A) Angiogram shows Mid LAD lesion (50-70%). (B) IVUS
of Mid LAD lesion shows MLA > 3 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 mm$^2$. (C)
FFR of the same area shows a value of 0.74 which is physiologically
significant.
