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INTRAVASCULAR IMAGING (A.G. TRUESDELL, SECTION EDITOR)

Sex Differences in Intracoronary Imaging and Functional Evaluation of Coronary Arteries

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Abstract

Purpose Coronary artery disease encompasses broad pathologies beyond atherosclerosis such as spontaneous coronary artery dissection, myocardial infarction with non-obstructive coronary artery disease, and microvascular dysfunction. These diagnoses often warrant more detailed evaluations with intracoronary imaging or functional testing. In this review, we highlight the reported sex differences in intracoronary imaging and functional evaluation of the coronary arteries.

Recent Findings The diagnosis and treatment of women presenting with acute or chronic coronary syndromes have been fraught with disparities given the poor representation of women in trials addressing the role of conventional coronary angiography, intracoronary imaging, and coronary functional assessment. Most of the evidence for intravascular ultrasound and optical coherence tomography identified features unique to women; however, the published data do not establish validated references for women.

Summary Differences in vessel size, myocardial mass, microvascular function, hyperemic response, and plaque characteristics could explain the sex-based differences. Further evidence is required to define and validate cutoff values in women and ascertain clinical outcomes.

Keywords Intravascular ultrasound · Optical coherence tomography · Fractional flow reserve · Instantaneous wave-free ratio

Introduction

Despite progress in the management of coronary artery disease (CAD), cardiovascular disease remains the leading cause of mortality worldwide accounting for 35% of all deaths in 2019. [1] Women presenting with an acute myocardial infarction (AMI) are twice as likely as men to have myocardial infarction with non-obstructive coronary artery disease (MINOCA). [2] Furthermore, the diagnosis of CAD by conventional coronary angiography (CA) in women can be challenging with a lower positive predictive value for obstructive CAD. The WISE (The Woman's Ischemia Syndrome Evaluation) study revealed that many women have myocardial ischemia in the setting of non-obstructive CAD and either coronary endothelial dysfunction or microvascular dysfunction, or both, which further predicts adverse events during follow-up. [3] Other potential mechanisms for myocardial infarction (MI) in women with non-obstructive CAD include plaque disruption, plaque erosion with thrombosis, embolization, vasospasm, dissection, and supply–demand mismatch. [4•, 5] As such, further investigation with intracoronary (IC) imaging or physiology is necessary to diagnose and treat female patients appropriately. The purpose of this review is to summarize the available data on the utility of IC imaging and functional assessment in the diagnosis and treatment of CAD in women.

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This article is part of the Topical Collection on *Intravascular Imaging*

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Intracoronary Imaging in Women

IC imaging using intravascular ultrasound (IVUS) and optical coherence tomography (OCT), alone or in combination with other diagnostic modalities, has transformed our understanding of CAD and improved outcomes when used adjunctively with CA to guide percutaneous coronary interventions (PCI). [6••, 7, 8, 9•] IC imaging is capable of defining coronary pathology that is not visible by CA alone. This is of particular importance in women who have a higher incidence of non-obstructive CAD compared with men. However, data on outcomes of image-guided PCI specific to women is lacking.

Basics of Vessel Characteristics: Sex-Based Differences

There are inherent sex-based differences in coronary vessel size and plaque characteristics that cannot be identified by CA alone. IC imaging plays a significant role in identifying the differences in plaque morphology between men and women, and helps establish the diagnosis, particularly in women with non-obstructive CAD. [10•, 11–13]

Lumen Size

Sex is an independent predictor of coronary artery size with both CA and coronary computed tomography (CCT) studies showing smaller coronary artery diameters in women compared with men. [14–17] CA, however, cannot assess the arterial wall reliably as these may be confounded by eccentric lumens and angiographically silent diffuse atherosclerosis. IC imaging offers a more detailed evaluation of the coronary arterial wall and lumen size. In a retrospective analysis of CA with IVUS imaging of left main (LM) and left anterior descending arteries (LAD), Sheifer et al. noted smaller LM and LAD arteries in women compared with men independent of body size. [18]

Plaque Morphology and Vessel Remodeling

In addition to differences in vessel size, there are also inherent differences in the burden and composition of atherosclerotic plaque in women. Prior studies of patients dying after AMI reported disrupted plaque as the predominant pathology for the acute thrombotic event in 75% of patients. [19, 20] Interestingly, plaque erosion was seen in 38% of women who died following AMI compared to only 18% of men. [20] In a study utilizing IVUS, 38% of women with an AMI had less than 50% angiographic stenosis and were noted to have plaque disruption, the majority of whom had plaque rupture (29%) and only a few had plaque ulcerations (10%). [3] Importantly, plaque disruption rarely occurred at the site of largest vessel plaque and was often located in areas of the vessel that were angiographically normal—sites of outward plaque remodeling. The disrupted plaques were noted in fibrous or fibrofatty plaques and not in the typical regions of soft or eccentric and outwardly remodeled plaque. [21] Overall, plaque rupture is the predominant mechanism for plaque disruption in women > 50 years of age and men regardless of age, whereas plaque erosion is the predominant mechanism in younger women. [21]

Limitations of IC Imaging

There are some limitations to the use of IC imaging. IVUS is an ultrasound-based technology which operates at a wavelength of 40–50 µm. OCT has higher resolution, which is approximately 10 times greater than that of IVUS. However, IVUS has greater soft tissue penetration (5–6 mm) than OCT (1–2 mm) allowing full-thickness visibility of the vessel wall. A disadvantage of OCT is the need for contrast injections to clear blood for better imaging which can be a limiting factor in patients with impaired renal function. Another limitation of OCT is inadequate imaging of ostial lesions and imaging of large vessels. There are no limitations specific to women with IVUS or OCT.

Role of IC Imaging in Disease-Specific States in Women

The diagnosis of CAD by conventional CA in women can be challenging with a lower positive predictive value for obstructive CAD. Current guidelines recommend its use in special entities such as MINOCA and SCAD as well as atherosclerotic CAD. [22, 23]

Atherothrombotic Disease

The pattern of CAD is different in women, who, despite having a higher frequency of chest pain compared with men, have a lower prevalence of obstructive angiographic epicardial coronary artery stenosis. [10•, 11–13, 24, 25, 26•, 27] In a study by Khuddus et al., IVUS imaging in symptomatic women with suspected ischemia but no obstructive CAD revealed 80% mild to moderate atherosclerosis. There was a high prevalence of atherosclerosis with positive remodeling and preserved luminal area in women which explains the non-obstructive CAD by CA. [10•] Non-obstructive CAD is a predictor of mortality in women which is attributed to sex-specific differences in plaque burden and plaque remodeling [26•]. Thus, mild to moderate atherosclerosis does not obstruct coronary blood flow, but these lesions are substrates for future coronary events and hence there is a need for improved diagnostic and treatment options in women with CAD. [27]

Acute Plaque Rupture (MI)

Women experience higher mortality rates and more adverse outcomes after an AMI than men, despite less obstructive

CAD and plaque burden. [28] The WISE (The Woman's Ischemia Syndrome Evaluation) study revealed that many women have myocardial ischemia in the setting of non-obstructive CAD and either coronary endothelial dysfunction or microvascular dysfunction, or both, which further predicts adverse events during follow-up. [3] Other potential mechanisms for MI in women with non-obstructive CAD include plaque disruption, plaque erosion with thrombosis, embolization, vasospasm, dissection, and supply–demand mismatch. [5, 29] In a prospective, multicenter study including 697 patients (24% women) with acute coronary syndrome (ACS) in whom IVUS was performed after treatment of culprit lesions, women had a similar number of angiographically identified culprit lesions but fewer non-culprit lesions and similar plaque burden compared with men. [11] Interestingly, plaque rupture (6.6% vs 16.3%, $p = 0.002$) was less common and total necrotic volume was lower in women. It was noted that thin-cap fibrous atheromas and plaque burden were predictive of non-culprit major adverse cardiovascular events (MACE) at 3 years among women. Subsequent studies showed that plaque rupture was a frequent finding among women with an AMI and obstructive CAD at angiography. In a prospective study including women with MINOCA who underwent IVUS during CA, 16 of 42 (38%) had plaque disruption, 11 had plaque rupture, 4 had plaque ulceration, and 1 had both. Plaque disruption occurred in segments that were angiographically normal in more than half of the cases further supporting the long-held hypothesis of non-obstructive CAD as the cause of MI in women. [3]

Myocardial Infarction with Non-obstructive Coronary Artery Disease (MINOCA)

MINOCA is a diagnosis of exclusion in patients with AMI with no obstructive CAD and no alternate diagnosis to explain the clinical presentation. [5] Plaque disruption on IVUS was noted in one-third of patients with MINOCA. [3, 30] In a recent multicenter study of 301 women with MINOCA, an identifiable cause was observed in 85% with the combination of intracoronary OCT imaging and CMR, which showed 75% had an ischemic etiology and 25% were non-ischemic. [31] A definitive or a possible culprit lesion was identified by OCT in 46% which was most commonly atherosclerotic plaque disruption including plaque rupture, intra-plaque cavity, or layered plaque. The proportion of patients with an identifiable culprit lesion was higher than that in earlier studies using IVUS and can be attributed to the improved sensitivity of OCT. [31, 32] Given that MINOCA patients can have plaque disruption that is not visible by CA, imaging with IVUS or OCT must be performed in the workup of these patients. [5, 30–32]

Spontaneous Coronary Artery Dissection (SCAD)

Spontaneous coronary artery dissection (SCAD) is a non-atherosclerotic mechanism of MI seen in up to 35% of women < 50 years of age. [33•, 34] The CA appearance may range from near normal to diffuse stenosis. A definitive diagnosis can be made using IC imaging with IVUS or OCT. Because of its superior resolution, OCT may be the preferred imaging modality when evaluating a patient with suspected SCAD, although care must be taken to avoid extending the dissection plane with contrast injections. The role of IC imaging in the follow-up of SCAD has not been ascertained yet. [34] An example is provided in Fig. 1.

Role of IC Imaging in PCI

Several studies have shown the superiority of IC imaging compared with angiography alone in improving outcomes of PCI by permitting appropriate sizing, defining plaque morphology and need for atherectomy, assessment of stent expansion, edge dissections, etc. Figure 2 is an example of the utility of IVUS in determining the significance of disease in the LM artery and further revascularization.

IVUS Studies

The ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial demonstrated that IVUS-guided PCI significantly improved clinical outcome in all-comers, particularly for patients who had an IVUS-defined optimal procedure, compared with angiographic guidance. [35••] At 3 years follow-up, the IVUS group had lower target vessel failure (TVF) compared with the CA group (6.6% vs 10.7%, $p = 0.01$). [36] The ADAPT-DES (Assessment of Dual Anti-platelet Therapy With Drug-Eluting Stents) registry, enrolling 8582 all-comers, found that the benefits of IVUS guidance during PCI increased from 1 to 2 years, especially in reducing target vessel MI and revascularization. [37] It has also been established that IVUS guidance improves the 1-year clinical benefit in various complex lesion subsets including long lesions, chronic total occlusions, and bifurcation lesions undergoing DES implantation. [38–44] A recent meta-analysis including 9 randomized trials and 4724 patients demonstrated that IVUS-guided DES implantation reduced the risk of cardiac death, coronary revascularization, and stent thrombosis compared with angiographic guidance alone. [45]

OCT Studies

In the ILUMIEN III study, OCT-guided PCI using external elastic lamina (EEL)-based stent optimization strategy was

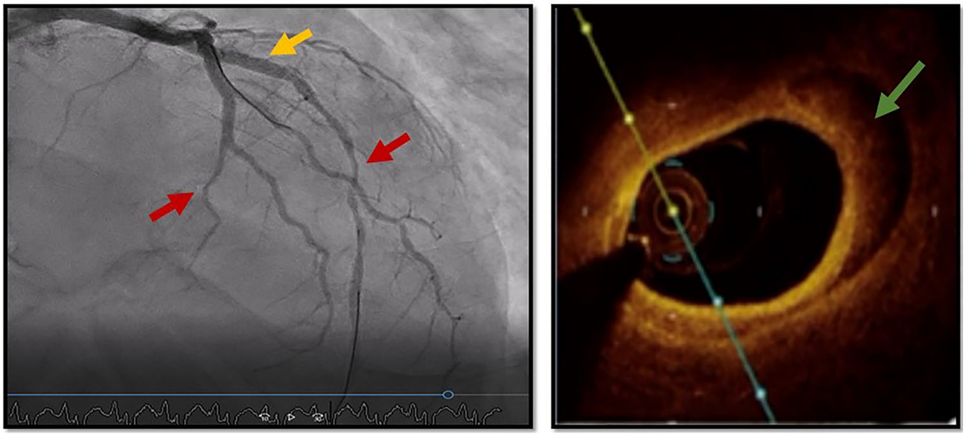

Fig. 1 Example of spontaneous coronary artery dissection. A 51-year-old woman presenting with chest pain and dynamic electrocardiographic changes. A coronary angiogram in right anterior oblique cranial projection demonstrates dissection of the distal segments of the obtuse marginal branch and proximal and mid segments of the left anterior descending (LAD) artery (red arrow). An intramural hematoma with luminal narrowing is confirmed by optical coherence tomography (green arrow) This patient's proximal LAD dissection was treated with drug eluting stents (yellow arrow) and the mid-segment was managed conservatively

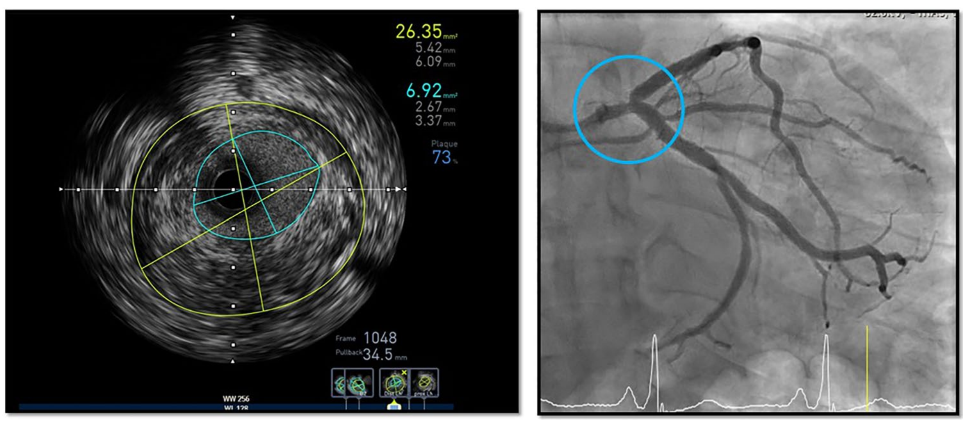

Fig. 2 Measurement of the MLA defined by IVUS in a patient with LM disease

found to be non-inferior to IVUS-guided PCI for achieving minimum stent area (MSA) in the overall population. In addition, OCT-guided PCI resulted in superior stent expansion and procedural success compared with angiography-guided PCI, and fewer untreated major dissections and areas of major stent malapposition. [46] The efficacy of OCT-guided PCI with stent optimization protocols to improve event-free survival after PCI will be evaluated in the upcoming large-scale, randomized pivotal ILUMIEN IV trial. [47••] Fig. 2 demonstrates the utility of IVUS in ascertaining the minimum lumen area of LM disease. An example of OCT to optimize drug-eluting stent underexpansion and to assess bioresorbable scaffolds is provided in Fig. 3.

To date, the enrollment of women in randomized trials evaluating the role of IC imaging to optimize PCI such as the ULTIMATE and ILUMIEN III trials was very low. As such, results from these trials do not permit adjustment of reference diameters and cutoff values of EEL and MSA according to sex nor was a sub-analysis of outcomes by sex performed.

Future Directions

There are inherent sex-based differences in the severity, burden, and presentation of CAD in women compared with men. IC imaging is a helpful tool in establishing the diagnosis of CAD where CA alone is insufficient. In addition, IC imaging also improves outcomes when used to optimize PCI. However, female sex-specific vessel measurements are currently lacking and future randomized trials must enroll more women to provide references that guide PCI.

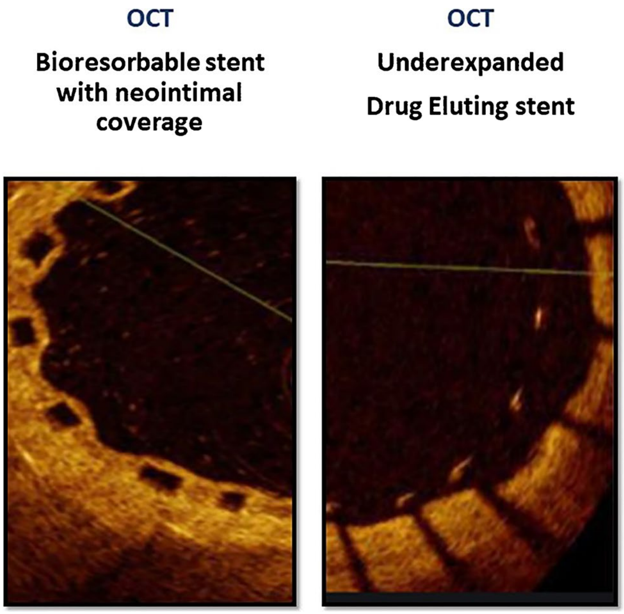

Fig. 3 **A** OCT of an expanded bioresorbable scaffold (green = scaffold struts). **B** IVUS of an underexpanded drug-eluting stent (red = stent struts)

Intracoronary Physiology in Women

FFR (fractional flow reserve) and iFR (instantaneous wave-free ratio) are well-established and validated tests of the hemodynamic significance of epicardial coronary stenoses. Although hemodynamically guided PCI is guideline indicated, gaps exist in understanding the physiologic sex-based differences between men and women and the impact on management decisions. [48, 49••, 50••]

Fractional Flow Reserve

In a seminal study, Pijls et al. showed an FFR ≤ 0.74 reliably discriminated ischemia. [51] Subsequent studies showed an FFR < 0.75 was associated with inducible ischemia (100% specificity) while an FFR > 0.8 was associated with absence of inducible ischemia (sensitivity 90%). [52]

The predictive value of FFR was investigated in several landmark trials including DEFER, FAME, and FAME 2. DEFER demonstrated that routine PCI of lesions with FFR ≥ 0.75 was not superior to optimal medical therapy (OMT) for major adverse cardiac events (MACE) at 5 years, and at 15 years was associated with a higher risk of MI than OMT alone. [53••, 54] FAME demonstrated lower MACE rates when PCI performed on lesions with FFR ≤ 0.80 with sustained benefit at 5 years. [55–57] FAME 2 was halted early due to significantly higher MACE rates in the OMT alone arm, suggesting that hemodynamically significant lesions with FFR ≤ 0.80 should be treated with PCI upfront [58]. Following FAME, the higher cutoff value of FFR > 0.80 became the standard for excluding ischemia at the risk of reduced specificity. The "gray zone" between 0.75 and 0.8 remains a diagnostic dilemma. In a retrospective study at Mayo Clinic, deferral of PCI in patients within this zone was associated with increased MACE rates. Women had higher rates of death and MI. Men had higher revascularization rates. [56–58]

Although women comprised a minority of the patients (25%) in these trials, a sub-study of FAME evaluating sex differences noted that for similar rates of angiographic stenoses, women have fewer ischemic lesions by FFR compared with men. [55, 59••] In this analysis, women were older with more hypertension and unstable angina compared to men with smaller coronary vessel diameter. Women also had fewer angiographically significant lesions with significantly lower SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores. In angiographically intermediate lesions, a lower proportion was functionally significant by FFR in women. Despite these differences, 2-year MACE rates were similar in men and women irrespective of treatment strategy. In FAME 2, 22% of the study population were women, but there is no sex-based sub-analysis. [60••, 61••, 62].

Instantaneous Wave-Free Ratio

Instantaneous wave-free ratio (iFR) is a non-hyperemic pressure-derived index of stenosis severity. [61••] Data from the ADVISE study showed agreement between FFR 0.8 and iFR at a cutoff value of 0.89. [62] Subsequently, DEFINE-FLAIR and iFR SWEDEHEART concluded that iFR-guided PCI was non-inferior to FFR with regard to MACE events at 1-year follow-up. [63, 64] In a sub-study of physiological measurements in the LAD artery, iFR had a superior negative predictive value driven by lower rates of unplanned revascularization in the iFR group. [65]

A post hoc analysis of DEFINE-FLAIR of sex-based differences between FFR and iFR revascularization strategies and compared 1-year MACE rates (composite of death, non-fatal myocardial infarction, or unplanned revascularization) showed that women had higher mean FFR values than men and lower rates of revascularization regardless of modality, without sex-specific differences in mean iFR values or MACE outcomes at 1 year. In light of the FAME sub-study, iFR measurement may add to the physiologic assessment in women. [66••]

Theories for Sex Differences

Sex-based differences in vessel lumen size, myocardial mass, microvascular function, diastolic function, and plaque characteristics could explain higher FFR values in women for similar rates of angiographic stenosis, resulting in less hyperemic flow and smaller pressure drop across a given stenosis. [60••, 67–69, 70••, 71–73] The pivotal Women's Ischemia Syndrome Evaluation (WISE) study noted that a surrogate marker of microvascular dysfunction in women may be an attenuated coronary volumetric flow augmentation in response to adenosine. [74] The relative impairment of endothelium-dependent vasodilation in adenosine-mediated hyperemia may partly explain sex-specific differences in FFR but not iFR. Importantly, the index of microcirculatory resistance (IMR) is similar by sex, but women have lower coronary flow reserve (CFR), owing principally to faster mean transit time (Tmn) consistent with increased resting coronary flow. [74, 75] This higher resting coronary flow may relate to the unexplained differences in epicardial coronary blood flow in women.

Excess microvascular dysfunction among menopausal women and varying estrogen levels contribute to both endothelium-dependent and endothelium-independent coronary vasodilation. [76–78] Large population-based data from the Women's Health Initiative demonstrated excess harm from routine estrogen replacement with a complex risk–benefit profile. [79] Further investigation into sex-based differences in the pathophysiology of ischemia is necessary.

FFR-iFR Discordance

Although cutoffs of FFR ≤ 0.8 and iFR ≤ 0.89 are useful for decision making, discordance occurs in 20% of cases. [80–83] Lee et al. studied 849 vessels from 590 patients (70% men) and reported differences in the vasodilatory capacity between low-iFR-high FFR and high iFR-low FFR groups (higher CFR corresponding with higher iFR). This discordance was not associated with increased patient-oriented composite outcomes (POCO) in deferred lesions. [84, 85] Only the concordant low iFR-low FFR group had higher POCO rates than high iFR-high FFR group at 5 years. Predictors of discordance include lesion location (left main or proximal LAD), degree of stenosis, heart rate, age, and beta blocker use. iFR low-FFR high discordance was higher in women, while iFR high-FFR low discordance was higher in men [86–89]. The sex-specific differences in outcomes of discordant lesions remain unknown. An example of discordance is provided in Fig. 4.

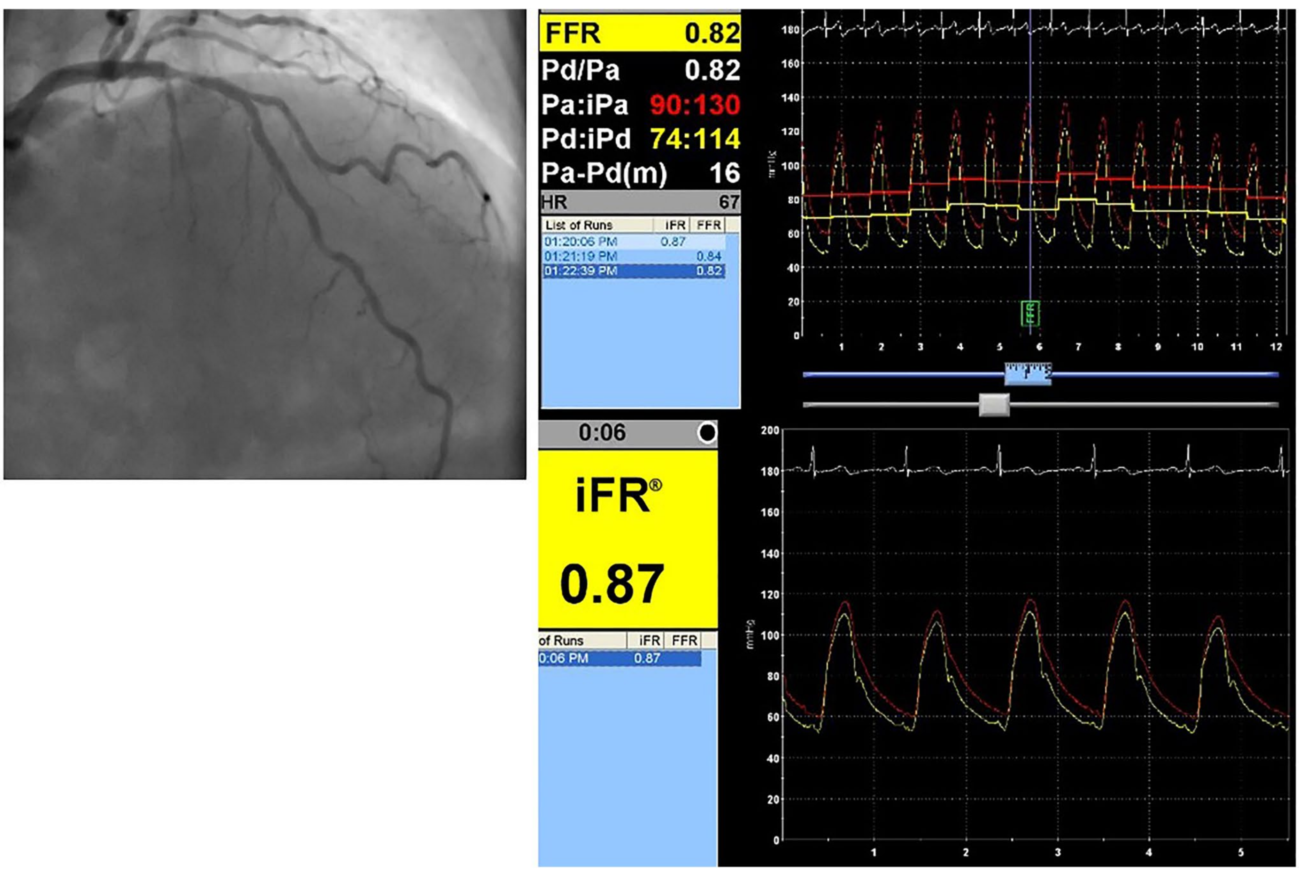

Fig. 4 Example of iFR – FFR discordance. A 74-year-old woman presenting with chest pain and myocardial perfusion imaging with small- to medium-sized, mild intensity, reversible perfusion defect in the mid to apical anterior and true apical walls

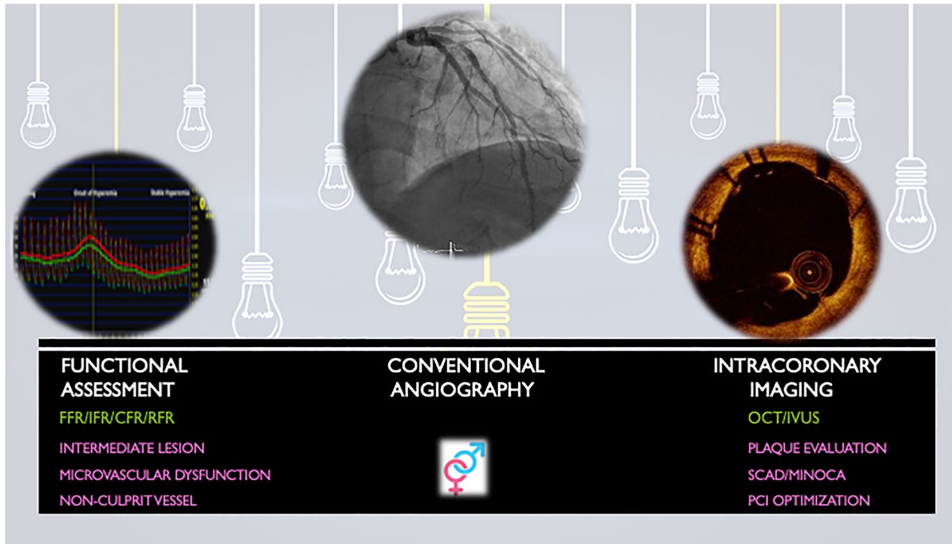

Fig. 5 Central illustration—intracoronary functional assessment and imaging are complementary to conventional coronary angiography

Future Directions

The combination of FFR with anatomic assessment using cardiac computed tomography (FFR_{CT}) is a novel modality that permits better detection of obstructive disease on CA and increases the frequency of revascularization. Fairbairn et al. examined the role of FFR_{CT} in women in the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) registry including 4737 participants (34% female). A post hoc analysis was consistent with prior studies confirming women had less severe CAD, with lower rates of both intermediate (50% to 69%) and severe (≥ 70%) stenoses. Women had higher FFR_{CT} values than men and underwent less CA and revascularization. Angiographically, women with a reduced FFR_{CT} were less likely to have obstructive (> 50% stenosis) disease and underwent less revascularization than men (31% vs. 36%). [90•] These findings parallel invasively measured FFR. As use of FFR_{CT} increases, it will be important to further understand these sex-specific differences.

Correlating imaging and functional testing is key to decision making. A very recent study by ElHajj et al. evaluated iFR in LM disease and referenced it to body surface area (BSA). In those with intermediate LM stenosis, an iFR of ≤ 0.89 correlated with IVUS MLA < 6 mm^2 regardless of BSA. This small study refutes the theory that women who generally have a smaller BSA may have different iFR and MLA cutoffs. It does, however, indicate the pressing need to correlate and determine references of significance in both imaging and physiology. [90•] Fig. 5 is a central illustration representative of the additive value of intracoronary imaging and functional assessment in the management of the various coronary pathologies.

Conclusion

Intracoronary assessment using imaging and physiology complements invasive coronary angiography. It permits more accurate diagnosis, better optimization of PCI, and improved patient outcomes. The representation of women in landmark trials defining the role of IC imaging and functional testing has been poor. In order to provide sex-specific recommendations based on cardiovascular outcomes, better rates of enrollment of women in such clinical trials are imperative.

Declarations

Conflict of Interest None of the authors has any relevant conflicts of interest pertinent to this manuscript. This manuscript was not funded.

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•• Of major importance

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