

# Diagnostic Accuracy of Microcatheter Derived Fractional Flow Reserve



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Microcatheter derived fractional flow reserve (FFR<sub>MC</sub>) system has an increased profile compared with pressure-wire derived fractional flow reserve (FFR<sub>W</sub>). Consequently, the FFR<sub>MC</sub> system itself may increase the degree of coronary artery stenosis and lower the measured FFR value. This can affect the diagnostic accuracy of the FFR<sub>MC</sub> system and inadvertently result in erroneous therapy for patients. Our aim was to evaluate the diagnostic accuracy FFR<sub>MC</sub> measurements and provide a means for clinicians to interpret individual FFR<sub>MC</sub> results with respect to FFR<sub>W</sub>. Correlation between FFR measurement techniques was analyzed in this lesion level analysis of 413 patients and 441 lesions from 6 studies. The reference standard to determine physiological significant stenosis was FFR<sub>W</sub> value  $\leq 0.80$ . The mean values for FFR<sub>MC</sub> and FFR<sub>W</sub> were  $0.80 \pm 0.11$  and  $0.83 \pm 0.09$ , respectively. Bland-Altman analysis demonstrated a bias toward overestimation of FFR by FFR<sub>MC</sub> (bias,  $-0.03$  [0.05]). The overall lesion level diagnostic accuracy of the FFR<sub>MC</sub> system was 80.4% (95% confidence interval [CI] 76.2% to 84.0%). The diagnostic accuracy for FFR<sub>MC</sub> values  $< 0.75$ ,  $0.75$  to  $0.85$  and  $> 0.85$  were 83.7% (95% CI 71.4% to 92.4%), 72.3% (95% CI 59.8% to 75.6%), and 99.2% (95% CI 94.8% to 99.8%), respectively. Using the FFR<sub>W</sub> threshold of  $\leq 0.80$ , 16.3% of lesions would have had inappropriate revascularization according to FFR<sub>MC</sub> measurements. Receiver-operating characteristics suggested the optimal cut-off value of FFR<sub>MC</sub> to determine ischemia was 0.78. In conclusion, the diagnostic accuracy of FFR<sub>MC</sub> varies markedly across the spectrum of disease with marked deterioration for values between 0.75 and 0.85. This may result in clinicians to inadvertently revascularize patients with FFR measurements  $> 0.80$ . © 2019 Published by Elsevier Inc. (Am J Cardiol 2019;124:183–189)

Measuring fractional flow reserve (FFR) has become the reference standard for assessing the functional significance of epicardial coronary artery disease in the cardiac catheterization laboratory.<sup>1–4</sup> All randomized controlled studies on the efficacy of FFR in determining the significance of stenosis have exclusively utilized dedicated pressure wires to determine the fractional flow reserve (FFR<sub>W</sub>). However, recently an alternative microcatheter derived fractional flow reserve (FFR<sub>MC</sub>) system (Navvus MicroCatheter; ACIST Medical Systems, Inc, Eden Prairie, Minnesota) has been developed.<sup>5</sup> The FFR<sub>MC</sub> is an optical pressure sensor which can be advanced over a standard 0.014" coronary guidewire, thereby negating the need to recross a lesion, which is required to check pressure-drift with FFR<sub>W</sub> systems and in cases where repeat measurements are

necessitated. The FFR<sub>MC</sub> system has an increased profile compared with FFR<sub>W</sub> system,  $0.025'' \times 0.020''$  across the lesion and  $0.027'' \times 0.036''$  at the level of the pressure sensor, compared with  $0.014''$  diameter for the FFR<sub>W</sub> system.<sup>5</sup> Consequently, a disadvantage of the FFR<sub>MC</sub> system is that the microcatheter itself may increase the degree of coronary artery stenosis and lower the measured FFR value. This can affect the diagnostic accuracy of the FFR<sub>MC</sub> system and inadvertently result in erroneous therapy for patients. To date, there have been few small studies<sup>5–10</sup> evaluating the correlation of FFR<sub>MC</sub> and FFR<sub>W</sub>, suggesting good overall diagnostic accuracy of FFR<sub>MC</sub>. However, it remains unclear how this correlation is influenced by physiological stenosis severity. In this study, we perform a systematic review comparing FFR<sub>MC</sub> and FFR<sub>W</sub>.

## Methods

We performed a systematic review in accordance with guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.<sup>11</sup> A systematic search of MEDLINE & EMBASE (2011–2018 week 28) was performed for studies assessing the diagnostic accuracy of FFR<sub>MC</sub>. Title words used were monorail, microcatheter or ACIST and FFR. We also hand-searched the bibliographies of relevant selected studies and reviews to identify further eligible studies. Results were limited to publications in peer-reviewed journals. Duplicate studies and abstracts

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See page 188 for disclosure information.

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from scientific meetings were removed. Two independent investigators (O.M.D. and S.M.) reviewed all of the retrieved studies, including references, with disputes resolved by consensus following discussion with a third author (A.L.). Inclusion criteria were (1) assessment of the performance of  $FFR_{MC}$  compared with  $FFR_W$  as the standard procedure, (2) per-vessel data displayed in either a scatterplot or Bland-Altman plot of agreement between  $FFR_{MC}$  and  $FFR_W$  values.

From the included studies, to permit lesion-level systematic review, data were digitized from scatterplot plot using previously published methods of semiautomatic bitmap-to-digital software (Matlab, MathWorks Inc).<sup>12</sup> This was performed independently by 2 investigators (O.M.D and S.M.) to confirm accuracy of data. Digitized  $FFR_{MC}$  and  $FFR_W$  values were rounded to 2 decimal places. Results were dichotomized using 0.80 or less as the cut point for ischemia for both methods.  $FFR_W$  was used as the reference standard. Diagnostic accuracy was determined as a percentage value by binary  $FFR_{MC}$  predicting binary  $FFR_W$ .

The correlation between  $FFR$  groups was analyzed by calculating the Pearson's correlation coefficient ( $r$ ), and the agreement between  $FFR_W$  and  $FFR_{MC}$  was assessed using Bland-Altman plots of the relative differences. Homoscedasticity between  $FFR_W$  and  $FFR_{MC}$  was evaluated with Levene's test. The sensitivity, specificity, diagnostic accuracy, and positive and negative likelihood ratio of  $FFR_{MC}$  was calculated using  $FFR_W$  value of 0.80 or less as reference standard. In addition, diagnostic accuracy of  $FFR_{MC}$  at numerous cut-off values were evaluated, calculated using  $FFR_W$  value of 0.80 or less as reference standard. Continuous variables are described as means and standard deviations which were compared using paired Student's  $t$  Test. Receiver-operating curve analysis was performed to determine a cutoff of  $FFR_{MC}$  value to predict ischemia defined as  $FFR_W$  value of 0.80 or less. A  $p < 0.05$  was considered

statistically significant. All analyses were performed using SPSS 24.0 (IBM, Inc., New York) and Prism GraphPad 7.0 (GraphPad Software, Inc., California)

## Results

Our search strategy is outlined in [Figure 1](#). A total of 6 studies fulfilled inclusion criteria, these are outlined in [Table 1](#). All  $FFR_{MC}$  measurements were performed with the Navvus MicroCatheter system and all  $FFR_W$  were performed with a dedicated pressure wire system. The total study population included 413 patients and 441 lesions. Diletti et al,<sup>5</sup> reported preliminary clinical data in 15 patients but did not provide baseline patient or angiographic characteristics, except that patients had intermediate de novo disease in native coronary arteries. From the remaining 5 studies<sup>6-10</sup> the mean age was  $65.7 \pm 10.2$  years and 77% were male. Menon et al,<sup>6</sup> reported only median stenosis diameter and vessel diameter, 56% and 3.0 mm, respectively. From the remaining 4 studies, the mean stenosis diameter was  $48.6\% \pm 9.9\%$  and mean vessel diameter was  $2.9 \pm 0.5$  mm.

Mean  $FFR$  values for  $FFR_{MC}$  and  $FFR_W$  were  $0.80 \pm 0.11$  and  $0.83 \pm 0.09$  ( $p < 0.001$ ), respectively. Ischemic threshold using  $FFR$  value of 0.80 or less was observed in 48.3% of  $FFR_{MC}$  measurements and 34.9% of  $FFR_W$  measurements ( $p < 0.001$ ).

The linear correlation between the  $FFR_{MC}$  and  $FFR_W$  was 0.89 ([Figure 2](#)). Bland-Altman analysis demonstrated a bias toward overestimation of  $FFR$  by  $FFR_{MC}$  (bias,  $-0.03$  [0.05]) ([Figure 2](#)).

There was significant heteroscedasticity between  $FFR_{MC}$  and  $FFR_W$  values (Levene statistic ( $F$ ) = 7.7). Hence, to elucidate this heteroscedasticity, across the  $FFR$  disease spectrum, Bland-Altman analyses were repeated according to  $FFR_{MC}$  values and correlation of the difference in  $FFR$

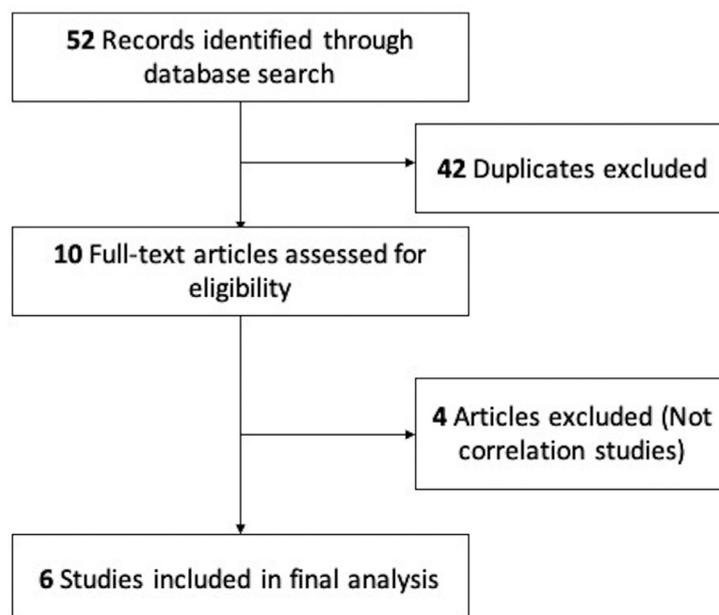


Figure 1. Search strategy and source of included studies.

Table 1  
Included study characteristics

Characteristics	Study					
	Diletti et al <sup>5</sup>	Menon et al <sup>6</sup>	Wijntjens et al <sup>7</sup>	Fearon et al <sup>8</sup>	Pouillot et al <sup>9</sup>	Ali et al <sup>10</sup>
Year	2015	2015	2016	2017	2018	2018
Design	Prospective, single-centre	Prospective, multicentre	Prospective, single-centre	Prospective, multicentre	Prospective, single-centre	Prospective, single-centre
Patients	15	50	28	169	77	74
Arteries	15	52	28	169	88	89
Patient baseline						
Age, mean (SD), years	-	66 (±9)	66 (±12)	68 (±9)	62 (±11)	64 (±11)
Men	-	40 (80%)	22 (79%)	133 (79%)	58 (75%)	54 (73%)
Hypertension	-	-	15 (54%)	140 (83%)	57 (74%)	71 (96%)
Hyperlipidemia	-	-	14 (50%)	127 (75%)	18 (23%)	73 (99%)
Smokers	-	-	6 (21%)	23 (14%)	24 (32%)	12 (16%)
Diabetes mellitus	-	-	7 (25%)	63 (37%)	34 (45%)	53 (72%)
Previous MI	-	-	4 (14%)	53 (31%)	23 (30%)	-
Previous PCI	-	-	8 (29%)	-	29 (38%)	-
Angiographic characteristics						
Mean stenosis diameter (%)	-	56 (median)	52.2 (±7.2)	47 (±9)	55 (±9)	44 (±10)
Mean vessel diameter (mm)	-	3.0 (median)	2.64 (±0.46)	2.8 (±0.5)	3.05 (±0.55)	2.84 (±0.54)
Coronary Artery interrogated						
LM	-	3 (6%)	0	4 (2%)	-	-
LAD	-	29 (56%)	21 (75%)	87 (52%)	-	47 (49%)
LCx	-	7 (13%)	4 (14%)	31 (18%)	-	23 (24%)
Right	-	13 (25%)	3 (11%)	44 (26%)	-	25 (26%)
Outcomes						
Hyperemic method	-	IV Adenosine (140 µg/kg/min)	IC Adenosine (bolus 100 µg)	IV Adenosine (140 µg/kg/min)	IV Adenosine (180 µg/kg/min)	IV Adenosine (140 µg/kg/min)
FFR <sub>w</sub> alone, mean (SD)	-	0.81 (0.11)	0.86 (0.06)	0.83 (0.1)	0.83 (0.1)	0.84 (IQR 0.78,0.89)
FFR <sub>MC</sub> , mean (SD)	-	0.79 (0.12)	0.82 (0.07)	0.81 (0.1)	0.80 (0.08)	0.79 (IQR 0.73, 0.85)
Significance of mean difference in FFR	-	p <0.001	-	p <0.001	p = 0.012	p <0.001
Correlation, r	0.95	0.87	0.88	0.90	0.85	0.82

FFR = fractional flow reserve, FFR<sub>MC</sub> = microcatheter fractional flow reserve, FFR<sub>w</sub> = pressure wire fractional flow reserve, IC = intracoronary, IV = intravenous; IQR = interquartile range; LAD = left anterior descending; LCx = left circumflex; LM = left main; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

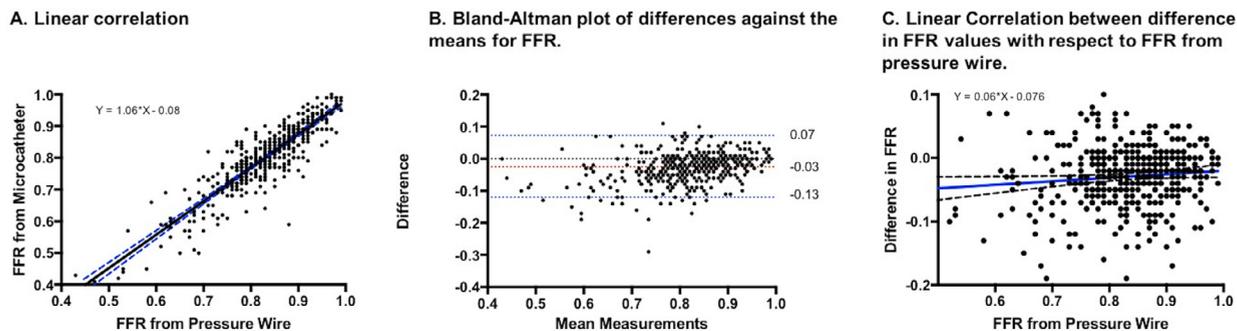


Figure 2. Scatterplot showing the overall association between FFR measured by microcatheter ( $FFR_{MC}$ ) and pressure wire ( $FFR_W$ ). (A) Linear correlation. The black line represents the line of best fit between  $FFR_{MC}$  and  $FFR_W$ . The dashed blue lines represents the 95% CI for the line of best fit;  $r^2 = 0.79$ ; 95% CI 0.87 to 0.91;  $p < 0.001$ . (B) Bland-Altman plot of differences against the means for FFR. The zero line is displayed in dashed black. The mean bias is represented by the dashed red line (with the 95% CI represented by the dashed blue lines). (C) Linear Correlation between difference in FFR values with respect to FFR from pressure wire. The blue line represents the line of best fit for difference between  $FFR_{MC}$  and  $FFR_W$ . The dashed black lines represents the 95% CI for the line of best fit;  $r^2 = 0.01$ ; 95% CI 0.004 to 0.2;  $p < 0.001$ .

values according to  $FFR_W$  were performed (Figure 2). For  $FFR_{MC}$  values  $< 0.75$  the Bland-Altman analysis demonstrated bias toward overestimation of FFR by  $FFR_{MC}$  (bias,  $-0.07$  [0.06]), with 95% limits of agreement ranging from 0.05 to  $-0.18$ ). For  $FFR_{MC}$  values between 0.75 and 0.85 the Bland-Altman analysis demonstrated bias toward overestimation of FFR by  $FFR_{MC}$  (bias,  $-0.03$  [0.04]), with 95% limits of agreement ranging from 0.05 to  $-0.11$ . For  $FFR_{MC}$  values  $> 0.85$  the Bland-Altman analysis demonstrated bias toward overestimation of FFR by  $FFR_{MC}$  (bias,  $-0.003$  [0.03]).

Using the  $FFR_W$  threshold of 0.80 or less, the overall sensitivity, specificity, and diagnostic accuracy of  $FFR_{MC}$  was 91.7% (95% confidence interval [CI] 85.7% to 95.2%), 74.7% (95% CI 69.1% to 79.6%), 80.4%, (95% CI 76.2% to 84.0%), respectively. In addition, the positive-likelihood ratio was 5.08 and the negative-likelihood ratio was 0.17. The distribution of FFR values are displayed in Figure 3, which indicate that the population consisted predominately of lesions with mild severity. The histogram bars are colored according to agreement with  $FFR_W$  at threshold of 0.80 or less for functional significance.

Per range analysis for diagnostic accuracy of  $FFR_{MC}$  is outlined in Figure 4. Using the  $FFR_W$  threshold of 0.80 or less 16.3% of lesions would have had inappropriate revascularization and 2.8% inappropriately not revascularized according to  $FFR_{MC}$  measurements.

Receiver-operating characteristics were evaluated to define  $FFR_{MC}$  cut-off value to determine physiological significant stenosis, according to  $FFR_W$  dichotomous threshold of  $\leq 0.80$  ("true ischemia") or  $> 0.80$ . The cut-off value of  $FFR_{MC}$  to determine ischemia ("true ischemia") was 0.78. The receiver-operating characteristics were: Area under the curve 0.92 (95% CI 0.89 to 0.95); sensitivity 86%; and specificity 83%. If we were to use  $FFR_{MC}$  threshold of 0.78 to determine "true ischemia" there was reduction in rates inappropriate revascularization to 9%.

## Discussion

In the present study, we review the diagnostic performance of  $FFR_{MC}$  for the identification and exclusion of

ischemia-causing lesions compared with  $FFR_W$  as the reference standard.

Our analysis for the entire study population demonstrated good overall correlation between  $FFR_{MC}$  and  $FFR_W$ , similar to that observed in resting pressure derived coronary indices, including instantaneous fractional reserve and diastolic pressure ratios, in relation to  $FFR_W$ .<sup>13–15</sup> However, due to the potential hemodynamic impact of the  $FFR_{MC}$  system being dependent on stenosis severity, we performed analyses of the correlation of  $FFR_{MC}$  across a spectrum of  $FFR_W$  values. This revealed that  $FFR_{MC}$  values vary significantly across the FFR spectrum that was indeed dependent on the underlying physiological stenosis severity (Figure 2).

The evaluation of a continuous variable across a wide range has the potential to mask the presence of variation across the spectrum assessed. This is particularly true if the test in question has a dichotomous cut-off or a significant number of the population evaluated lie in the extreme end of the spectrum in relation to the cut-off value. These factors have the potential to have a detrimental impact on the actual utility of a test. To elucidate and rectify this, 2 methods can be utilized: (1) evaluation of the discordance of the variable across the continuous spectrum; (2) evaluating the accuracy of the test at a number of ranges ("per range analysis" for diagnostic accuracy of  $FFR_{MC}$  in our study).<sup>10</sup>

The magnitude of disagreement between  $FFR_{MC}$  and  $FFR_W$  was observed to be proportional to the severity of the underlying stenosis. Hence, it is not feasible to have a universal correction factor for  $FFR_{MC}$  to negate its effect, especially in values around the 0.8 ischemia threshold. Due to this nonuniform discordance between  $FFR_{MC}$  and  $FFR_W$ , we evaluated the diagnostic accuracy of  $FFR_{MC}$  across a range of FFR values. The diagnostic accuracy of  $FFR_{MC}$  is highly precise in vessels where the underlying FFR value is at either end of the spectrum, severe stenosis (highly negative FFR values) or mild stenosis (highly positive FFR values). For vessels with  $FFR_{MC}$  values  $> 0.90$  the diagnostic accuracy was 100%, and at the other end of the spectrum vessels with  $FFR_{MC}$  values  $< 0.60$  and 0.60 to 0.70 the diagnostic accuracy was 95.2% and 90.9%, respectively. However, in between these values, the diagnostic accuracy of

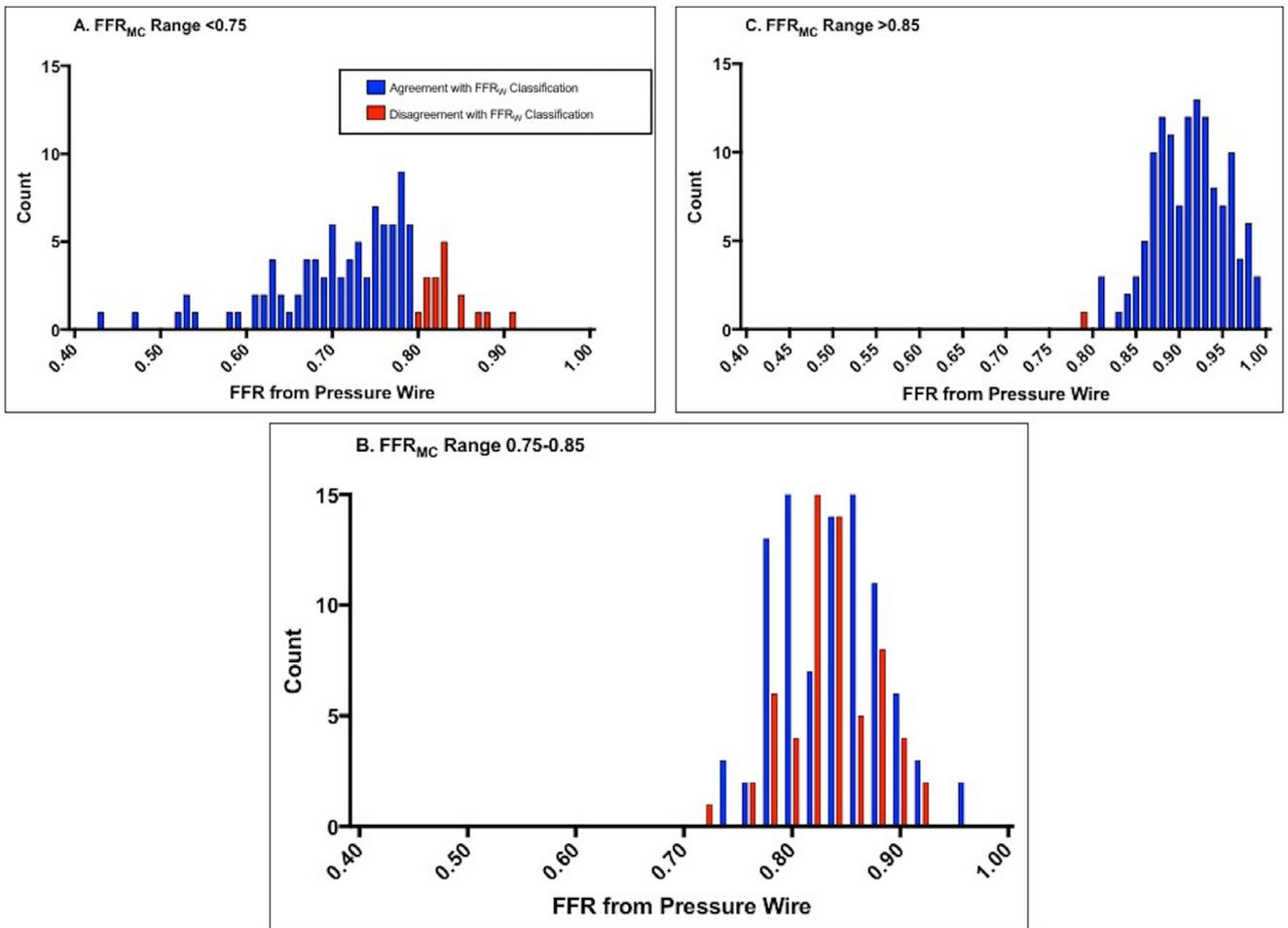
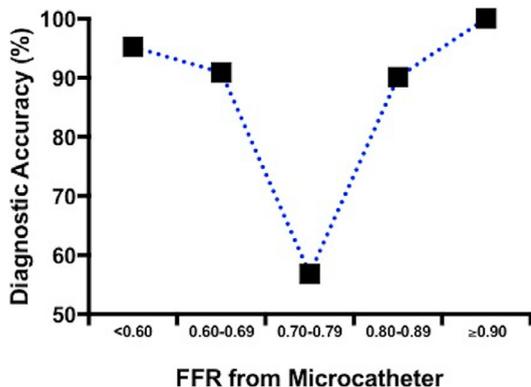


Figure 3. Distributions of the invasive FFR<sub>W</sub> corresponding to bands of FFR<sub>MC</sub> values. (A) FFR<sub>MC</sub> Range <0.75. (B) FFR<sub>MC</sub> Range 0.75 to 0.85. (C) FFR<sub>MC</sub> Range >0.85. Distributions of the FFR<sub>W</sub> corresponding to bands of FFR<sub>MC</sub> values. Diagnostic accuracy (above vs below the FFR<sub>MC</sub> ≤0.80 cut point) is displayed for these bands of FFR<sub>MC</sub>.

**A. Diagnostic accuracy of FFR from microcatheter according to incremental increase stenosis severity.**



**B. Diagnostic accuracy of FFR from microcatheter at diagnostic “grey-zone”.**

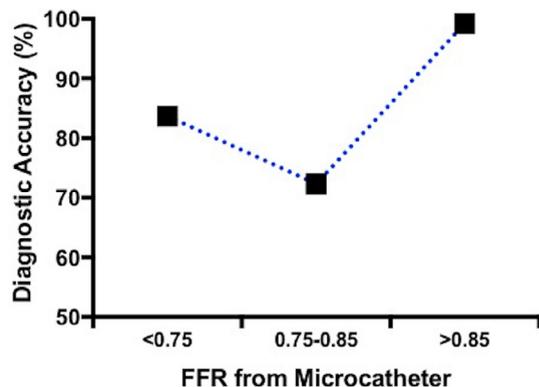


Figure 4. Diagnostic accuracy of FFR measurements from microcatheter. (A) Diagnostic accuracy of FFR from microcatheter according to incremental increase stenosis severity. For vessels with FFR<sub>MC</sub> values below 0.60 (5% of lesions), 0.60 to 0.70 (8% of lesions), 0.70 to 0.80 (28% of lesions), 0.80 to 0.90 (41% of lesions), and above 0.90 (18% of lesions), diagnostic accuracy of FFR<sub>MC</sub> was 95.2%, 90.9%, 56.8%, 90.1%, and 100%, respectively. (B) Diagnostic accuracy of FFR from microcatheter at diagnostic “gray-zone”. For vessels with FFR<sub>MC</sub> values between 0.75 and 0.85 (41% of lesions), so-called diagnostic gray zone’, the diagnostic accuracy was 72.3%. In addition, the diagnostic accuracy of FFR<sub>MC</sub> values <0.75 (24% of lesions) and >0.85 (35% of lesions) were 83.7% and 99.2%, respectively.

FFR<sub>MC</sub> declined remarkable to 56.8% for values from 0.70 to 0.80. Consequently, the overall diagnostic accuracy of FFR<sub>MC</sub> is not uniform across different FFR ranges. The delineation of this phenomenon is imperative as all studies to-date have correlated FFR<sub>MC</sub> measurements with FFR<sub>W</sub> and there is no clinical outcome data established for FFR<sub>MC</sub> measurements. Moreover, we evaluated the diagnostic accuracy of FFR<sub>MC</sub> for values between 0.75 and 0.85, where overestimation may have greatest effect on diagnostic accuracy: diagnostic accuracy between 0.75 and 0.85 was 72.3% (Figure 4). This is important as a significant proportion of FFR measurements are between 0.75 and 0.85.<sup>16</sup>

Current international guidelines give FFR a Class I and Evidence Level A for guiding revascularization.<sup>3,4</sup> However, these are based on studies that exclusively utilized FFR<sub>W</sub> systems to determine the ischemic cut-off for revascularization. Hence, the widespread adoption of the FFR<sub>MC</sub> system in cardiac catheterization laboratories is not supported by clinical outcome studies.

The results from our analysis demonstrate that the diagnostic accuracy of FFR<sub>MC</sub> is not uniform and its performance deteriorates remarkably around the “FFR<sub>MC</sub> diagnostic gray-zone.” Hence, clinicians need to be aware that FFR<sub>MC</sub> values in the “FFR<sub>MC</sub> diagnostic gray-zone” may result in inadvertent erroneous decision for revascularization. Indeed, this occurred in 16.3% of lesions in our study. Moreover, our analysis demonstrated that the optimal cut-off value to determine “true ischemia” was FFR<sub>MC</sub> value of 0.78. Resonating the good diagnostic accuracy of FFR<sub>MC</sub> system when FFR<sub>MC</sub> values are <0.75 or >0.85 (Figure 4). Future iterations of the FFR<sub>MC</sub> system need to overcome the shortcomings for inaccurate FFR measurements in the “FFR<sub>MC</sub> diagnostic gray-zone.” Our study presents some limitations. The FFR<sub>MC</sub> and FFR<sub>W</sub> data points were extracted from scatterplots from studies using digitization software. However, digitization error was tested by 2 independent investigators (O.M.D. & S.M) performing extraction independently. Patients included in studies forming our analysis included patient populations that had either low vessel calcification and tortuosity, or the angiographic vessel characteristics/complexity were not included. Hence, the performance of the FFR<sub>MC</sub> system in patients with high vessel complexity has not been evaluated. Pouillot et al,<sup>9</sup> reported 12% failure in crossing lesion with FFR<sub>MC</sub> system, mainly due to tortuous and/or calcified arteries. Consequently, the performance of FFR<sub>MC</sub> system in a real-world all-comers population, especially in patients with high vessel complexity, remains poorly defined. Despite all FFR measurements being performed with adenosine administration, the method utilized for achieving hyperemia varied between studies. Hence, if maximal hyperemia was not achieved, in particular with intracoronary bolus of adenosine, then the overestimation by the FFR<sub>MC</sub> system may be less than stated by current studies. Inclusion criteria for studies included in this analysis required reference vessel diameter >2.5 mm, therefore physiological assessment of side branch or distal stenosis using FFR<sub>MC</sub> has not been evaluated. Furthermore, due to lack of data on angiographic characteristics from baseline studies, it is unclear how FFR<sub>MC</sub> system performs in vessels with tandem lesions. Our per-lesion analysis was unable to

determine whether vessel diameter or stenosis location within the vessel influenced the diagnostic accuracy of the FFR<sub>MC</sub> measurement. Only 2 studies reported study population vessel characteristics, from which Ali et al,<sup>10</sup> reported that distal reference vessel diameter was an independent predictor of discordance between FFR<sub>MC</sub> and FFR<sub>W</sub>.

In conclusion, the diagnostic accuracy of FFR<sub>MC</sub> varies markedly across the spectrum of disease: good diagnostic accuracy when FFR values are at either end of the spectrum but marked deterioration for FFR values between 0.75 and 0.85 (“FFR<sub>MC</sub> diagnostic gray-zone”). The performance of FFR<sub>MC</sub> needs to be evaluated in a large prospective study that includes patients with moderate and high-vessel complexity to establish the real-world diagnostic utility compared with FFR<sub>W</sub> and whether different cut-off values should be considered in lesions that are in the “FFR<sub>MC</sub> diagnostic gray-zone.” Otherwise, users may inadvertently revascularize patients with FFR measurements >0.80.

## Disclosures

Dr Azeem Latib is a consultant for Medtronic and Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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