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Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses

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Aims The present analysis addresses the potential clinical and physiologic significance of discordance in severity of coronary artery disease between the angiogram and fractional flow reserve (FFR) in a large and unselected patient population.

Methods and results Between September 1999 and December 2011, FFR and percent diameter stenosis (DS) as assessed by quantitative coronary angiography were obtained in 2986 patients ($n = 4086$ coronary stenoses), in whom at least one stenosis was of intermediate angiographic severity. Fractional flow reserve correlated slightly but significantly with DS [−0.38 (95% CI: −0.41; −0.36); $P < 0.001$]. The sensitivity, specificity, and diagnostic accuracy of a ≥50% DS for predicting FFR ≤ 0.80 were 61% (95% CI: 59; 63), 67% (95% CI: 65; 69), and 0.64 (95% CI: 0.56; 0.72), respectively. In different anatomical settings, sensitivity and specificity showed marked variations between 35 to 74% and 58 to 76%, respectively, resulting in a discordance in 35% of all cases for these thresholds. For an angiographic threshold of 70% DS, the diagnostic performance by the Youden's index decreased from 0.28 to 0.11 for the overall population.

Conclusion The data confirm that one-third of a large patient population shows discordance between angiogram ≥50%DS and FFR ≤0.8 thresholds of stenosis severity. Left main stenoses are often underestimated by the classical 50% DS cut-off compared with FFR. This discordance offers physiologic insights for future trials. It is hypothesized that the discordance between angiography and FFR is related to technical limitations, such as imprecise luminal border detection by angiography, as well as to physiologic factors, such as variable minimal microvascular resistance.

Keywords Coronary artery disease • Quantitative coronary angiography • Fractional flow reserve

Introduction

Since its first description,[1] invasive coronary angiography (CA) has been uniformly accepted to define the presence and extent of obstructive coronary artery disease (CAD), and to guide revascularization. Seminal animal research has shown that hyperaemic flow starts to decline in the presence of a ≥50% diameter stenosis (DS).[2] This threshold value was therefore considered proof of 'significant' obstructive coronary atherosclerosis and became the cornerstone of the definition of CAD severity. Consequently, a ≥50% DS has been used to risk stratify patients,[3–6] to justify revascularization, to serve as an endpoint in studies on revascularization strategies,[7–14] and to validate non-invasive techniques.[15–18]

Novel diagnostic tools and concepts have shed new light on the accuracy and reliability assessing the severity of coronary narrowing.[19–23] Currently, pressure-derived fractional flow reserve (FFR) has become the standard of reference to define the ischaemic potential of epicardial stenoses of intermediate angiographic severity based on outcomes of randomized trials.[24,25] Nevertheless, in daily practice, the vast majority of decisions about revascularization are based on DS as gauged by visual estimation on CA.

Anatomic severity on CA is limited or 'one-dimensional' oversimplified measure of stenosis severity that do not account for all aspects of severity, especially for 'intermediate' stenosis. Accordingly, in the present study, we analysed the concordance or discordance between stenosis severity by CA and by FFR in a large unselected patient cohort.

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Methods

Study population

Between September 1999 and December 2011, 37 047 coronary angiograms and 14 989 PCIs were performed in the Cardiovascular Center Aalst, Aalst, Belgium. Among them, 2986 patients (1:5 relation when compared with PCIs) underwent *both* quantitative coronary angiography (QCA) and FFR measurements in at least one stenosis. Only stable coronary stenoses were considered (patients with stable CAD, or the non-culprit vessels of patient with acute CAD). Repeated measurements of the same lesion in the same setting were excluded. Measurements of multiple stenoses in the same patient could be included. These data were stored prospectively in the local database together with the clinical characteristics and constitute the basis of the present analysis. All subjects gave written informed consent approved by the local ethics committee prior to undergoing CA.

Table 1 Clinical characteristics of the investigated patient population

	***n* = 2986**
Age; mean ± SD	66.4 ± 10.4
Male gender; *n* (%)	1891 (63)
Hypertension; *n* (%)	1681 (56)
Hypercholesterolaemia; *n* (%)	1852 (62)
Diabetes mellitus; *n* (%)	1078 (36)
Body-mass index; mean ± SD	26.3 ± 10.3
Smoking; *n* (%)	1127 (38)

Coronary angiography

Coronary angiography was performed by a standard percutaneous femoral or radial approach with a 6 or 7 Fr diagnostic or guiding catheter. After administration of 200–300 μg intracoronary isosorbide dinitrate, the angiogram was repeated in the projection allowing the best possible visualization of the stenosis.

Quantitative coronary angiography was performed based on the technology, described previously,[26–27] using one of the following software: Siemens Healthcare Axiom Artis VB35D110803 (Siemens Medical Solutions, Siemens AG; Forcheim, Germany); Siemens Healthcare ACOM.PC 5.01 System (Siemens Medical Solutions, Siemens AG); General Electric AW VolumeShare 6E (General Electric Inc., Fairfield, OH, USA). All measurements were obtained by an experienced technician, unaware of the FFR results. Data were introduced on a different page of the database. The projection was chosen to avoid, as far as possible, foreshortening or overlap of other arterial segments. The contrast-filled catheter was used for calibration. From an end-diastolic still-frame, reference diameter (RD, mm), minimum luminal diameter (MLD, mm), percent diameter stenosis (DS, %), and lesions length were calculated. The coronary arterial segments were defined according to the American Heart Association and modified for the ARTS I and II studies.[28] Segment 5 corresponds to the left main (LM) stem, and segments 4, 10, 13, 14, 15, 16, and 17 were considered 'distal'.

Pressure measurements

Fractional flow reserve was measured as previously described.[23] Briefly, after intracoronary administration of isosorbide dinitrate (200 μg), a pressure monitoring guide wire (St Jude Medical Inc., St Paul, MN, USA) was advanced distal to the coronary artery stenosis. Hyperaemia was obtained after administration of intravenous (continuous infusion of 140 μg/kg/min, 18% of all cases) or intracoronary (bolus of 50–150 μg, 79% of all cases) adenosine or intracoronary Papaverine (bolus of 10–20 mg, 3% of all cases). Fractional flow reserve was defined as

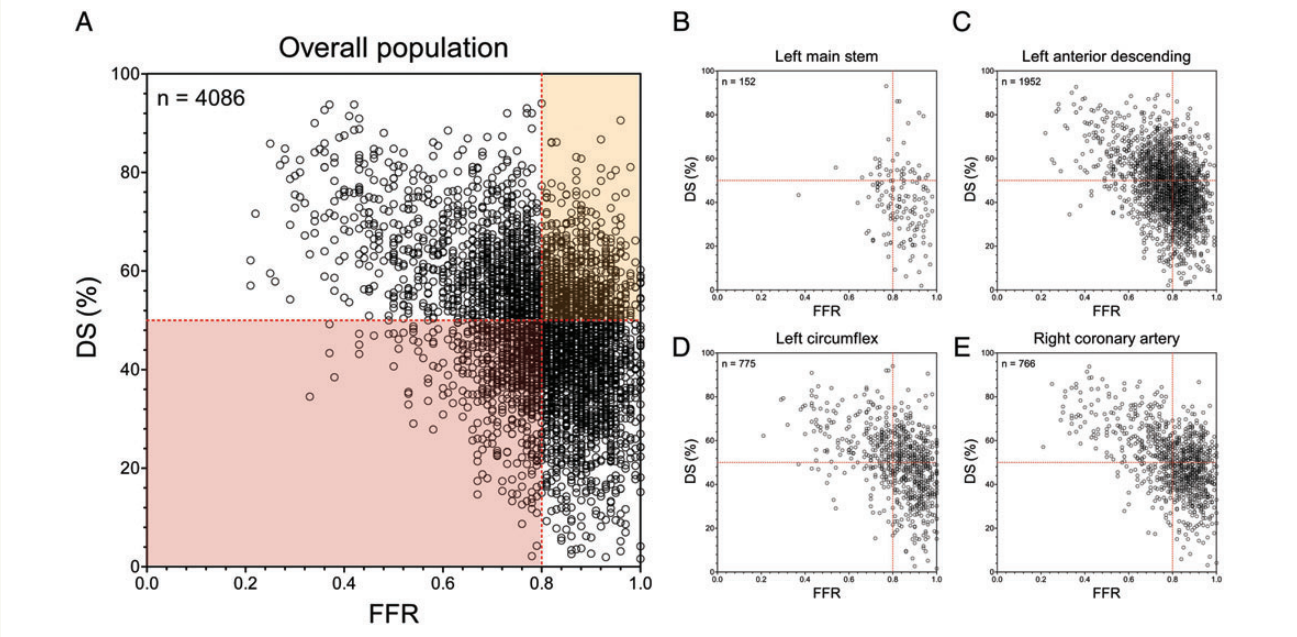

Figure 1 Correlation between diameter stenosis (DS) vs. fractional flow reserve (FFR) in the overall population (*A*) and specifically in the left main stem (*B*) and the three major branches (*C*–*E*). The *x*-axes indicate the functional metric (FFR), and the *y*-axes indicate the angiographic metrics (DS).

the ratio of the simultaneously recorded mean arterial pressure distal to the stenosis and the mean aortic pressure at the tip of the guiding catheter during stable, steady state hyperaemia. An FFR value $\leq$0.80 was considered 'positive', i.e. likely to induce reversible myocardial ischaemia. An FFR value $>$0.80 was considered 'negative', i.e. unlikely to induce reversible myocardial ischaemia. The clinical relevance of this cut-off value is based on clinical outcome data.[29–37]

Statistical analysis

All analyses were performed with Prism GraphPad 5.0 (GraphPad Software Inc., CA, USA) and SPSS 20.0 (IBM Inc., New York, USA). Summary descriptive statistics are reported as mean $\pm$ standard deviation, median (inter quartile range) or counts (%), as appropriate. 95% confidence intervals (CI) are added, as appropriate. Normal distribution was tested with the D'Agostino–Pearson omnibus K2 test. Correlation among variables was determined by Pearson or Spearman correlation tests, as appropriate and expressed is *r*-value. Sensitivity, specificity, diagnostic accuracy, and optimal diagnostic cut-off value were defined from the calculated receiver operator characteristic curves, as appropriate. Receiver operator characteristics curves were compared as described by Hanley and McNeil.[38] The optimal diagnostic cut-off value was defined based on the Youden's index, calculated as [(sensitivity + specificity) − 1], namely where the sum of sensitivity and specificity is maximized. Logistic regression analysis was performed to assess the impact of various clinical and anatomical characteristics on the accuracy of 50% DS cut-off value in predicting FFR $\leq$ 0.80. *P* for interaction was calculated within all subgroups, as appropriate. A probability value of $P < 0.05$ was considered statistically significant.

Results

Data from 4086 coronary artery stenoses in 2986 patients were analysed. Patients' clinical characteristics are summarized in *Table 1*. The fractional flow reserve value was in median 0.82 (0.74; 0.88) DS was 48% (39; 57) and MLD was 1.40 mm (1.10; 1.71).

Table 2 Stratified analysis of the diagnostic accuracy of diameter stenosis for predicting an fractional flow reserve value ≤ 0.80 according to different patients' characteristics

Categories	*n* (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy AUC (95% CI)	OR (95% CI)	*P**
Age						
≥65years	2241 (55)	63.8 (60.1; 66.9)	66.0 (63.3; 68.6)	0.65 (0.63; 0.67)	3.557 (2.984; 4.240)	0.215
<65years	1845 (45)	58.6 (55.3; 61.9)	68.3 (65.3; 71.3)	0.64 (0.61; 0.66)	3.021 (2.497; 3.655)	
Gender						
Male	2611 (64)	60.1 (57.3; 62.7)	65.9 (63.3; 68.5)	0.63 (0.61; 0.65)	2.916 (2.486; 3.419)	0.017
Female	1475 (36)	64.2 (60.2; 68.1)	68.6 (65.4; 71.6)	0.66 (0.64; 0.69)	4.071 (3.260; 5.083)	
Hypertension						
Yes	2320 (57)	61.0 (58.0; 63.9)	65.1 (62.4; 67.8)	0.63 (0.61; 0.65)	2.978 (2.514; 3.528)	0.105
No	1766 (43)	61.8 (58.4; 65.2)	69.4 (66.4; 72.3)	0.66 (0.63; 0.68)	3.696 (3.032; 4.505)	
Hypercholesterolaemia						
Yes	2575 (63)	60.2 (57.4; 63.0)	68.1 (65.6; 70.6)	0.64 (0.62; 0.66)	3.248 (2.762; 3.820)	0.857
No	1511 (37)	63.3 (59.6; 66.9)	65.2 (61.8; 68.4)	0.64 (0.61; 0.67)	3.327 (2.691; 4.113)	
Diabetes mellitus						
Yes	1488 (36)	57.2 (53.6; 60.8)	65.8 (62.2; 69.2)	0.62 (0.59; 0.64)	2.589 (2.099; 3.194)	0.005
No	2598 (74)	64.1 (61.2; 66.9)	67.6 (65.2; 70.0)	0.66 (0.64; 0.88)	3.808 (3.231; 4.487)	
Smoking						
Yes	1710 (42)	59.7 (56.2; 63.1)	67.7 (64.5; 70.7)	0.64 (0.61; 0.66)	3.104 (2.546; 3.785)	0.500
No	2376 (58)	62.6 (59.6; 65.5)	66.5 (63.9; 69.1)	0.65 (0.62; 0.67)	3.396 (2.868; 4.022)	
Family history						
Yes	549 (13)	63.4 (57.2; 69.2)	70.0 (64.4; 75.3)	0.67 (0.62; 0.71)	4.096 (2.867; 5.851)	0.184
No	3537 (87)	61.0 (58.6; 63.4)	66.6 (64.4; 68.7)	0.64 (0.54; 0.73)	3.158 (2.751; 3.625)	
Body mass index (25 kg/m^2 or above)						
25 kg/m^2≤	2695 (66)	62.0 (59.3; 64.7)	65.9 (63.3; 68.3)	0.64 (0.62; 0.66)	3.241 (2.768; 3.795)	0.424
25 kg/m^2>	1210 (30)	61.3 (57.0; 65.5)	69.6 (66.0; 73.1)	0.66 (0.62; 0.69)	3.642 (2.867; 4.628)	

Cut-off value for diameter stenosis was considered to be 50%.
AUC, area under the curve; OR, odds ratio.
**P* for interaction.

Overall relationship between angiographic metrics and fractional flow reserve

The relationship between DS and FFR was only modest but statistically significant [−0.38 (95% CI: −0.41; −0.36); $P < 0.001$] with marked scatter around the regression line (*Figure 1A*). A DS ≥50% correctly identified an FFR value ≤0.80 with a sensitivity of 61% (95% CI: 59; 63) and a specificity of 67% (95% CI: 65; 69), associated with a diagnostic accuracy of 0.64 (95% CI: 0.56; 0.72).

Similarly, the relationship between MLD and FFR was statistically significant [0.45 (95% CI: 0.42; 0.47) $P < 0.001$] with a large scatter of the data.

Influence of patients characteristics

Table 2 shows the stratified analysis of the sensitivity, specificity, diagnostic accuracy, and positive and negative likelihood ratios belonging to 50% DS for predicting an FFR value ≤ 0.80 according to the various patient characteristics. Two parameters, namely male gender ($P = 0.017$) and presence of diabetes ($P = 0.005$) negatively influenced the value of 50% DS in predicting significant FFR.

Influence of lesion characteristics

Table 3 shows the stratified analysis of the sensitivity, specificity, diagnostic accuracy, and positive and negative likelihood ratios of 50% DS cut-off value for predicting an FFR value ≤ 0.80 according to the lesion characteristics. Marked variation of the sensitivity and specificity values was observed, as illustrated in *Figure 2*.

Diagnostic performance of 50% vs. 70% diameter stenosis

Table 4 shows the stratified analysis of the sensitivity, specificity, diagnostic accuracy, and likelihood ratio of 70% DS cut-off value for predicting an FFR value ≤0.80 according to the lesion characteristics. *Figure 2* shows the Youden's index for the 50% DS cut-off vs. 70%

Table 3 Stratified analysis of the diagnostic accuracy of 50% diameter stenosis cut-off for predicting an FFR value ≤ 0.80 according to different lesions characteristics

Diameter stenosis cut-off value is set to 50%					
Categories	**Sensitivity**	**Specificity**	**Accuracy**	**LR+**	**LR−**
***n* (%)**	**% (95% CI)**	**% (95% CI)**	**AUC (95% CI)**		
Localization					
Overall					
4086 (100)	61.2 (59.0; 63.4)	66.9 (64.9; 68.8)	0.64 (0.56; 0.72)	1.87	0.57
LAD					
1952 (48)	55.5 (52.5; 58.4)	74.2 (71.1; 77.1)	0.65 (0.62; 0.67)	2.12	0.60
LCx					
775 (19)	73.5 (67.7; 78.8)	59.5 (55.1; 63.7)	0.67 (0.63; 0.71)	1.83	0.44
RCA					
766 (19)	73.0 (67.5; 77.0)	61.5 (56.9; 65.9)	0.67 (0.62; 0.71)	1.92	0.43
Supplied territory					
LM					
152 (4)	35.0 (23.1; 48.4)	75.8 (65.7; 84.2)	0.55 (0.46; 0.65)	1.58	0.83
Distal					
480 (12)	72.7 (65.8; 79.0)	57.7 (51.8; 63.4)	0.65 (0.60; 0.70)	1.71	0.46
Lesion length					
Short (≤12 mm)					
1364 (33)	60.9 (56.7; 65.0)	68.5 (65.2; 71.7)	0.65 (0.62; 0.68)	1.98	0.56
Long (≥20 mm)					
327 (8)	66.8 (59.9; 73.3)	60.8 (51.7; 69.4)	0.64 (0.58; 0.70)	1.68	0.55
Vessel size by tertiles of reference diameter					
Small					
1363 (33)	53.1 (49.4; 56.7)	72.7 (69.0; 76.2)	0.63 (0.60; 0.66)	1.98	0.64
Intermediate					
1406 (34)	64.2 (60.3; 68.0)	67.8 (64.3; 71.2)	0.66 (0.63; 0.69)	2.09	0.52
Large					
1294 (32)	69.3 (65.1; 73.3)	61.9 (58.5; 65.1)	0.66 (0.63; 0.69)	1.78	0.47

AUC, area under the curve; LR, positive and negative likelihood ratios.
Each comparison within the categories is non-significant.

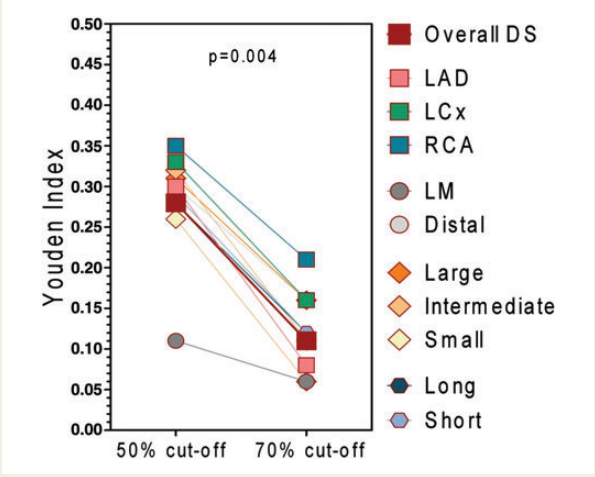

Figure 2 Youden's index for the 50% diameter stenosis (DS) cut-off vs. 70% DS cut-off in various anatomical subsets of lesions.

DS cut-off for the various subsets of lesions. The overall diagnostic performance of angiography is significantly weaker when a 70% DS is considered as cut-off value [0.30 (0.28; 0.32) vs. 0.08 (0.06; 0.12), respectively; $P = 0.004$]. Specifically, Youden's index decreased from 0.28 to 0.11 for the overall population, and showed an absolute decrease of 0.16 $\pm$ 0.05 in the various anatomical subsets.

Optimal angiographic cut-off values for percent diameter stenosis

The diagnostic accuracy and the corresponding optimal cut-off values were defined for several, clinically relevant anatomical settings. Detailed analysis is shown in *Table 5*. Comparison between LM ($n = 152$), the overall population ($n = 4086$), and the distal segments ($n = 472$) is depicted in *Figure 3*. The optimal cut-off values of DS for predicting FFR $\leq$0.80 were markedly different: 43% for the LM, 51% for the global population, and 55% for the small vessels. However, the corresponding accuracies remained low for all the three groups [0.65 (95% CI: 0.56; 0.74) vs. 0.69 (95% CI: 0.60; 0.78) vs. 0.72 (95% CI: 0.67;

Table 4 Stratified analysis of the diagnostic accuracy of 70% diameter stenosis cut-off for predicting an FFR value $\leq$ 0.80 according to different lesions characteristics

Diameter stenosis cut-off value is set to 70%					
Categories *n* **(%)**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**Accuracy AUC (95% CI)**	**LR+**	**LR−**
Localization					
Overall					
4086 (100)	12.6 (11.2; 14.2)	97.9 (97.2; 98.4)	0.55 (0.48; 0.63)	6.75	0.89
LAD†					
1952 (48)	8.7 (7.1; 10.5)	98.8 (97.9; 99.4)	0.54 (0.51; 0.56)	7.77	0.92
LCx					
775 (19)	19.1 (14.5; 24.5)	96.5 (94.6; 97.9)	0.58 (0.53; 0.62)	5.57	0.84
RCA†					
766 (19)	21.3 (16.8; 26.4)	99.2 (97.8; 99.8)	0.60 (0.56; 0.65)	25.56	0.79
Supplied territory					
LM					
152 (4)	6.7 (1.9; 16.2)	98.9 (94.0; 100.0)	0.53 (0.43; 0.62)	6.31	0.94
Distal segments					
480 (12)	20.1 (14.6; 26.6)	95.5 (92.5; 97.6)	0.56 (0.52; 0.63)	4.58	0.83
Lesion length					
Short ($\leq$12 mm)					
1364 (33)	14.5 (11.7; 17.7)	97.7 (96.4; 98.7)	0.56 (0.53; 0.59)	7.98	0.87
Long ($\geq$20 mm)					
327 (8)	14.9 (10.3; 20.5)	96.8 (92.0; 99.1)	0.56 (0.50; 0.62)	4.70	0.88
Vessel size by tertiles of reference diameter					
Small††					
1363 (33)	9.0 (7.1; 11.3)	97.4 (95.8; 98.5)	0.53 (0.50; 0.56)	3.65	0.93
Intermediate					
1406 (34)	11.9 (9.5; 14.7)	98.6 (97.5; 99.3)	0.55 (0.52; 0.58)	9.63	0.89
Large††					
1294 (32)	18.8 (15.4; 22.5)	97.5 (96.2; 98.5)	0.58 (0.55; 0.61)	9.71	0.72

AUC, area under the curve; LR, positive and negative likelihood ratios.
Each comparison within the categories is non-significant, except †$p = 0.011$ and ††$p = 0.032$.

Table 5 Diagnostic performance of the optimal cut-off values in the overall population and in segments with large (left main) or small (distal segments) supplied myocardial territories

DS in different segments; *n* (%)						
Correlation *r* **(95% CI)**	**Cut-off %**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**Accuracy AUC (95% CI)**	**LR+**	**LR−**
Overall; 4086 (100)						
−0.38 (−0.41; −0.36)	51.2	57.9 (55.7; 60.2)	70.8 (68.8; 72.7)	0.69 (0.60; 0.78)	1.99	0.59
LM; 152 (4)						
−0.28 (−0.43; −0.13)	43.0	60.0 (46.5; 72.4)	68.5 (58.0; 77.8)	0.65 (0.56; 0.74)	1.96	0.57
Distal segments; 480 (12)						
−0.43 (−50; −0.35)	54.5	63.0 (55.6; 70.0)	70.5 (64.8; 75.6)	0.72 (0.67; 0.77)	2.12	0.52
MLD in different segments; *n* (%)						
Correlation *r* (95% CI)	Cut-off mm	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy AUC (95% CI)	LR+	LR−
Overall; 4086 (100)						
0.45 (0.42; 0.47)	1.49	75.2 (73.1; 77.1)	57.5 (55.4; 59.6)	0.72 (0.58; 0.86)	1.73	0.43
LM; 152 (4)						
0.32 (0.17; 0.46)	1.60	37.3 (25.0; 50.9)	90.1 (82.1; 95.4)	0.65 (0.56; 0.74)	3.30	0.69
Distal segments; 480 (12)						
0.48 (0.41; 0.55)	1.17	65.6 (58.2; 72.4)	73.4 (67.9; 78.4)	0.74 (0.69; 0.78)	2.40	0.46

AUC, area under the curve; LR, positive and negative likelihood ratios.

0.77), respectively]. The corresponding optimal cut-off values of MLD are 1.6, 1.5, and 1.1 mm, respectively.

Discussion

Coronary angiography remains central to diagnosis and treatment of CAD. However, the present data from a large patient population emphasizes that reliance on the angiogram needs to be modified by physiologic measures of severity for intermediate stenosis of which FFR is a better guide for intervention based on randomized trials: as much as one-third of the decisions based on the 50% cut-off value about angiographically intermediate stenoses are discordant with the FFR. In contrast with previous work,[39] present data were based on a quantitative assessment of the angiogram.

Traditionally, angiographic management of CAD has been based on the threshold of 50% DS.[40] Validation of patient risk-stratification, non-invasive testing, and studies of revascularization have used this criterion as standard of reference.[3–18] However, the 50% DS threshold was derived from animal experiments which showed that hyperaemic myocardial flow reserve myocardial flow started to decline below 4.0 when DS was ≥50%[2] or below 3.0 for DS ≥ 70%DS as fluid dynamic endpoints unrelated to ischaemia, LV function, or clinical outcomes.[2] In humans with proven atherosclerosis, a similar relationship between DS and myocardial blood flow has been confirmed, although this relationship is substantially diminished by a very large scatter[41] or even absent,[42] again with no relation to ischaemia, LV function, or clinical outcomes.

In many early studies that have shaped our understanding of the relationship between CAD, revascularization, and clinical outcome, the threshold of 70% DS has been used for assessing prognosis or accuracy of non-invasive imaging.[7,8,43] Present data show that increasing the threshold to 70% improved the specificity (i.e. will decrease the trend of CA to overestimate lesion severity) but decreased sensitivity (i.e. will increase the number of stenoses underestimated by CA) so that the overall diagnostic performance of DS in predicting FFR ≤0.80 actually decreased when compared 50% cut-off value. Both types of misclassifications may have important clinical consequences. Recent outcome studies have demonstrated that revascularization of non-significant stenoses can be safely deferred,[29] and that the revascularization of non-significant lesions is inappropriate with adverse procedure risk without offsetting benefit.[30] Conversely, denying revascularization to patients with haemodynamically significant stenoses is detrimental.[31]

The present data also show that the optimal diagnostic threshold of DS is markedly lower in coronary segments supplying larger myocardial area than in segments supplying small myocardial area. At first glance, this phenomenon is surprising, since DS factors in myocardial mass to be perfused by a given segment. Seiler *et al.*[44] showed that the normal coronary diameter (the denominator of DS) correlates linearly with myocardial mass. In atherosclerotic vessels, this relation is flatter than in normal arteries. This observation might explain why a less severe DS is associated with a lower FFR in large vs. small arteries. Reciprocally, a small artery may have higher FFR than a large artery for comparable anatomic stenosis, thereby indicating that FFR depends to some extent on the downstream mass. Practically, this finding implies that a LM stenosis may reach haemodynamic significance (FFR ≤ 0.80) for a lesser degree of DS than a distal arterial segment. Thus, in the present data, the underestimation by the

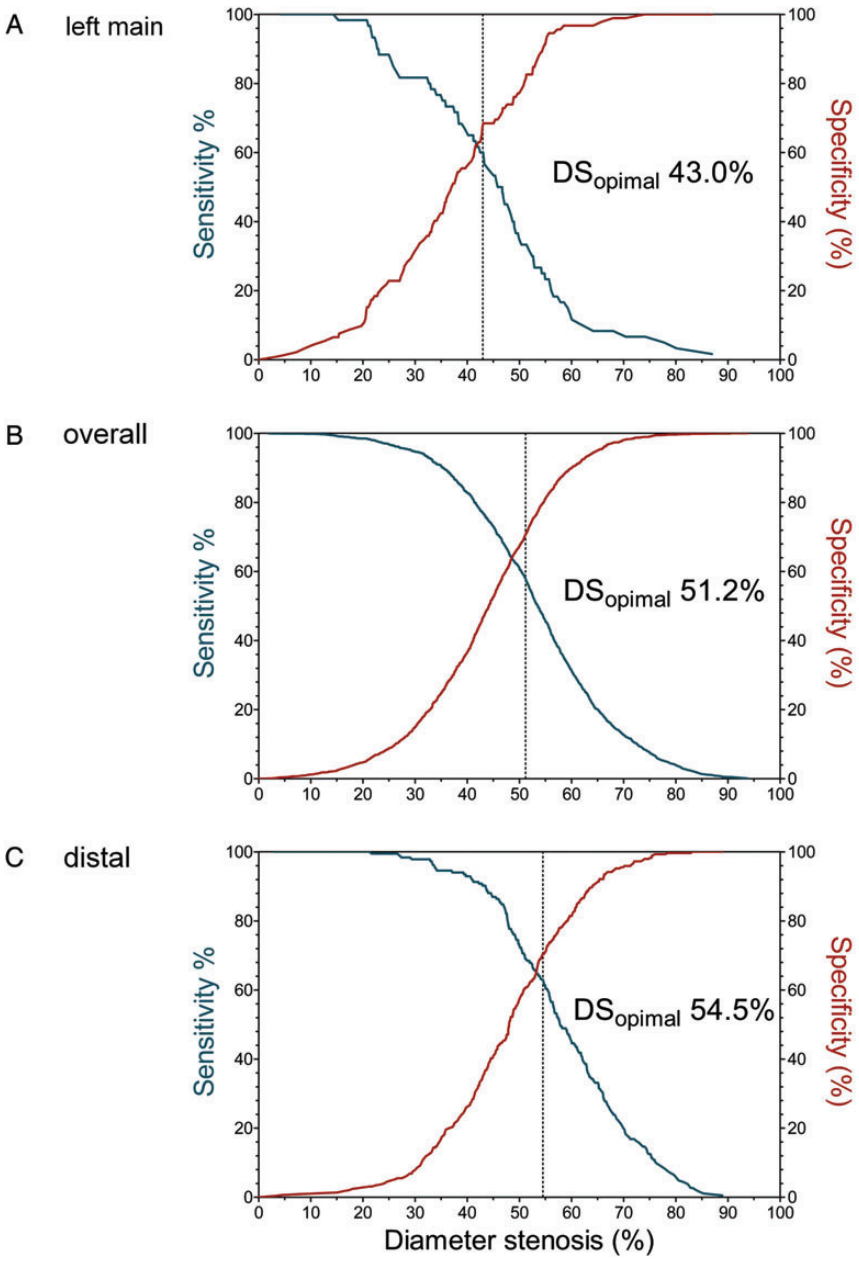

Figure 3 Determination of the optimal cut-off values for diameter stenosis ($DS_{optimal}$) in different localization with different supplied myocardial territories, namely the left main stem (*A*), the overall population (*B*), and the distal segments (*C*), as defined in the text above.

angiographic 50% cut-off was markedly more frequent among LM stenoses than in distal segments.

Many factors, including technical limitations as well as physiologic conditions may contribute to explain the poor correlation between angiographic indices and FFR. First, both QCA and FFR suffer inherent measurements uncertainties and imperfect repeatability that limit the expected correlation. The lack of standardization of FFR measurements and recordings, especially in the beginning of the experience, may account for some scatter. Angiographic border detection can be difficult in patients with diffuse CAD, especially when calcifications are present. Overlap with other arterial segments, foreshortening of the segment, bifurcation and ostial stenoses, and expansive vessel remodelling may further complicate the calculation of DS. The MLD, which consists of one single measurement, should be less influenced by technical inaccuracies. Yet, this advantage is offset by the fact that the physiological impact of MLD is also related to the downstream myocardial mass to be perfused. Mass dependence may explain the threefold difference between the optimal cut-off value of cross-sectional area between the LM and the distal segments. Combining DS and MLD might confer more precision to angiography as suggested by Fischer *et al.* who found that no patient with stenosis $<$ 60% or minimal luminal diameter $>$1.4 mm had FFR $<$0.75,[45]

however still suffering all the limitations of a solely anatomic approach. All techniques aiming at quantifying a single luminal measurement (MLD or cross-sectional area) face the same intrinsic limitation of being segment related. Second, and most importantly, both approaches are different in nature.

Therefore for reasons noted here, coronary anatomy alone—even with the highest resolution and a perfect repeatability—will never be sufficient to predict physiological behaviour of a single stenosis.[46,47] The main unknowns are the myocardial mass depending from the stenotic segment and the microvascular function. Both will determine maximal myocardial blood flow which is essentially measured by FFR. In contrast, FFR is a flow index. As such, its value is influenced and integrates hyperaemic flow, which itself depends on stenosis severity, myocardial mass, and its microvascular function. Since mass and microvascular function are not likely to change in a given patients before and after revascularization, FFR indicates to what extent hyperaemic myocardial flow will increase after PCI (i.e. normalization of the epicardial resistance). Therefore, FFR can be considered specific to the epicardial segment which constitutes the basis of its clinical utility. From the previous discussion, it can be hypothesized that measurements of absolute myocardial blood flow are the major missing link to explain the fundamental discordance between angiography and FFR (the red and yellow quadrants on *Figure 1*).

A number of limitations should be acknowledged. The majority of the cases in the data set were chosen when the anatomy could not give the clinical answers, and was the indication for FFR. Therefore, some 'referral bias' cannot be avoided and the conclusions should be limited to intermediate stenoses by visual assessment (i.e. between 30 and 70%DS). Second, the data were collected over a long period of time and were analysed retrospectively. This might have affected the accuracy of the angiographic measurements, as several technicians performed the measurements. Third, QCA analysis was not done by a dedicated corelab but by highly experienced technicians. Fourth, angiographic analysis was performed in one, the most severe projection only. Since coronary stenoses are asymmetrical, it is likely that a three-dimensional reconstruction of the artery would provide better correlations.[48]

In conclusions, the present data confirm that in comparison with FFR, CA underestimates, or overestimates physiologic stenosis severity in a large proportion of angiographically intermediate stenoses that may trigger inappropriate decisions about revascularization. It is hypothesized that this discordance relates, at least in part, to differences in microvascular function. The clinical 'truth' of more complete descriptors combining coronary flow reserve and FFR to guide PCI must be determined by randomized intervention trials. Until such trials, FFR remains the only clinical measure of intermediate stenosis severity to guide interventions that is proven in randomized trials. At greater or lesser severities, the objectively quantified angiogram may be appropriate but remains unproven by angiogram driven, randomized intervention trials.

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