Visual and Quantitative Assessment of Coronary Stenoses at Angiography Versus Fractional Flow Reserve

The Impact of Risk Factors

Julien Adjedj, MD; Panagiotis Xaplanteris, MD, PhD; Gabor Toth, MD; Angela Ferrara, MD; Mariano Pellicano, MD; Giovanni Ciccarelli, MD; Vincent Floré, MD, PhD; Emanuele Barbato, MD, PhD; Bernard De Bruyne, MD, PhD

Background—The correlation between angiographic assessment of coronary stenoses and fractional flow reserve (FFR) is weak. Whether and how risk factors impact the diagnostic accuracy of angiography is unknown. We sought to evaluate the diagnostic accuracy of angiography by visual estimate and by quantitative coronary angiography when compared with FFR and evaluate the influence of risk factors (RF) on this accuracy.

Methods and Results—In 1382 coronary stenoses (1104 patients), percent diameter stenosis by visual estimation (DS_{VE}) and by quantitative coronary angiography (DS_{QCA}) was compared with FFR. Patients were divided into 4 subgroups, according to the presence of RFs, and the relationship between DS_{VE}, DS_{QCA}, and FFR was analyzed. Overall, DS_{VE} was significantly higher than DS_{QCA} ($P<0.0001$); nonetheless, when examined by strata of DS, DS_{VE} was significantly smaller than DS_{QCA} in mild stenoses, although the reverse held true for severe stenoses. Compared with FFR, a large scatter was observed for both DS_{VE} and DS_{QCA}. When using a dichotomous FFR value of 0.80, C statistic was significantly higher for DS_{VE} than for DS_{QCA} (0.712 versus 0.640, respectively; $P<0.001$). C statistics for DS_{VE} decreased progressively as RFs accumulated (0.776 for ≤1 RF, 0.750 for 2 RFs, 0.713 for 3 RFs and 0.627 for ≥4 RFs; $P=0.0053$). In addition, in diabetics, the relationship between FFR and angiographic indices was particularly weak (C statistics: 0.524 for DS_{VE} and 0.511 for DS_{QCA}).

Conclusions—Overall, DS_{VE} has a better diagnostic accuracy than DS_{QCA} to predict the functional significance of coronary stenosis. The predictive accuracy of angiography is moderate in patients with ≤1 RFs, but weakens as RFs accumulate, especially in diabetics. **(*Circ Cardiovasc Imaging*. 2017;10:e006243. DOI: 10.1161/CIRCIMAGING.117.006243.)**

Key Words: coronary angiography ■ coronary stenosis ■ diabetes mellitus ■ hyperemia ■ risk factors

Since the introduction of selective coronary angiography,[1] and the demonstration that coronary flow reserve starts to decline beyond the threshold of 50% diameter reduction,[2] the latter metric has been used to decide about the revascularization strategy in millions of patients. Moreover, the 50% diameter stenosis threshold, whether obtained by visual estimation (VE; eyeballing) or by quantitative coronary angiography (QCA), has been used in risk stratification models,[3] as study end points,[4,5] and to validate noninvasive techniques.[6–9] However, there is a growing awareness that the link between the angiographic metrics and the ischemic potential of a stenosis as expressed by fractional flow reserve (FFR) is elusive.[10–14]

See Editorial by Shaw and Min
See Clinical Perspective

Accordingly, the goal of this study was to compare, side-by-side, the diagnostic performance of angiography by VE and QCA to FFR and to investigate the effect of lesion location and risk factors on these diagnostic performances.

Methods

Study Population

In 1104 patients with stable coronary artery disease (patients with stable angina, or the nonculprit vessels of patient with an acute coronary syndrome), the values of percent diameter stenosis by VE (DS_{VE}), of percent diameter stenosis by QCA (DS_{QCA}), and of FFR were available in at least 1 epicardial artery with an isolated stenosis at angiography. We excluded patients with in-stent restenosis and coronary artery bypass graft. Sequential stenoses in the same vessel were excluded. These data were systematically collected and stored prospectively in the local database together with the clinical characteristics and risk factors to constitute the basis of the present analysis. Patients were divided into 4 subgroups, according to the presence of risk factors (none or 1, 2, 3, 4, and more). All subjects gave written informed consent before undergoing coronary angiogram as part of the local routine and in agreement with the local institutional review board.

Received January 28, 2017; accepted May 26, 2017.

From the Cardiovascular Center Aalst, Belgium (J.A., P.X., A.F., M.P., G.C., V.F., E.B., B.D.B.); and Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy (E.B.).

Correspondence to Bernard De Bruyne, MD, PhD, Cardiovascular Center Aalst, OLV-Clinic, Moorselbaan, 164, B-9300 Aalst, Belgium. E-mail bernard.de.bruyne@olvz-aalst.be

Coronary Angiogram

Coronary angiography was performed by a standard percutaneous femoral or radial approach with a 6F or 7F guiding catheter. After administration of 200 to 300 µg intracoronary isosorbide dinitrate, the angiogram was repeated in the projection allowing the best possible visualization of the stenosis. DS_{VE} was assessed by the interventional cardiologist. QCA was performed based on the technology, described previously,[15,16] using one of the following softwares: Siemens Healthcare Axiom Artis VB35D110803 (Siemens Medical Solutions, Siemens AG, Forchheim, Germany); Siemens Healthcare ACOM.PC 5.01 System (Siemens Medical Solutions, Siemens AG); and General Electric AW Volume Share 6E (General Electric Inc, Fairfield, OH). An experienced technician, unaware of the FFR results, obtained all measurements. 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 (mm), minimum luminal diameter (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 (Arterial Revascularization Therapies Studies) I and II.[17]

Pressure Measurements

FFR was measured as previously described.[18] A pressure monitoring guidewire (St Jude Medical Inc, St Paul, MN) was advanced distal to the coronary artery stenosis. Hyperemia was obtained after administration of intravenous (continuous infusion of 140 µg kg^{-1} min^{-1}) or intracoronary (bolus of 100–200 µg)[19] of adenosine. FFR was defined as the ratio of the simultaneously recorded mean arterial pressure distal:the stenosis and the mean aortic pressure at the tip of the guiding catheter during stable, steady-state hyperemia. An FFR value ≤0.80 was considered as hemodynamically significant, and FFR value >0.80 was considered as nonhemodynamically significant.[20] The clinical relevance of this cutoff value is based on clinical outcome data.[21–31]

Statistical Analysis

Normal distribution was tested with the Shapiro–Wilk test. Summary descriptive statistics are reported as mean and SD, median (interquartile range), or counts (%) as appropriate. The Kruskal–Wallis test with Dunn correction for multiple comparisons was used to compare continuous variables among the 4 risk factors subgroups, and the Mann–Whitney test was used to compare diabetics versus nondiabetics. Categorical variables were compared with the Pearson χ^2 test. Correlation among variables was determined by calculating Spearman ρ correlation coefficient. Receiver operator characteristic (ROC) analysis was used to assess the diagnostic capability of the angiographic indices to detect hemodynamically significant stenoses (FFR with a cutoff of 0.80 as the gold standard). The areas under the ROC curves (C statistics) were compared as described by Hanley and McNeil.[32] All analyses were performed with Prism GraphPad 5.0 (GraphPad Software Inc, CA) and SPSS 21.0 (IBM Inc, NY).

Results

VE and QCA Versus FFR

During the study period, we included and analyzed 1382 coronary stenoses in 1104 patients. The median FFR was 0.81 (25th, 75th percentile: 0.73, 0.88), the median DS_{QCA} was 50% (25th, 75th percentile: 39%, 60%), and the mean DS_{VE} was 50% (25th, 75th percentile: 40%, 65%). A significant but weak correlation was found between DS_{VE} and FFR (ρ=−0.418; $P<0.001$) and between DS_{QCA} and FFR (ρ=−0.282; $P<0.001$). DS_{VE} tended to be larger than DS_{QCA}, <60% DS, whereas the opposite was true >70% DS (Figure 1). The C statistic of the DS_{QCA} ROC curve was significantly lower than that of DS_{VE} (0.640 versus 0.712, respectively; $P<0.001$; Figure 2).

Impact of Lesion Location

The location of the analyzed coronary lesions is presented in Table 1. The C statistics of the DS_{VE} ROC curves for lesions located at the left main (LM), left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) were 0.824, 0.699, 0.780, and 0.738, respectively. In pairwise comparisons, a statistically significant difference was noted between the LM-LAD ($P<0.001$) and the LAD-LCx ($P=0.02$) DS_{VE} ROC curves.

Similarly, for DS_{QCA}, the C statistics of the ROC curves for lesions at the LM, LAD, LCx, and RCA were 0.511,

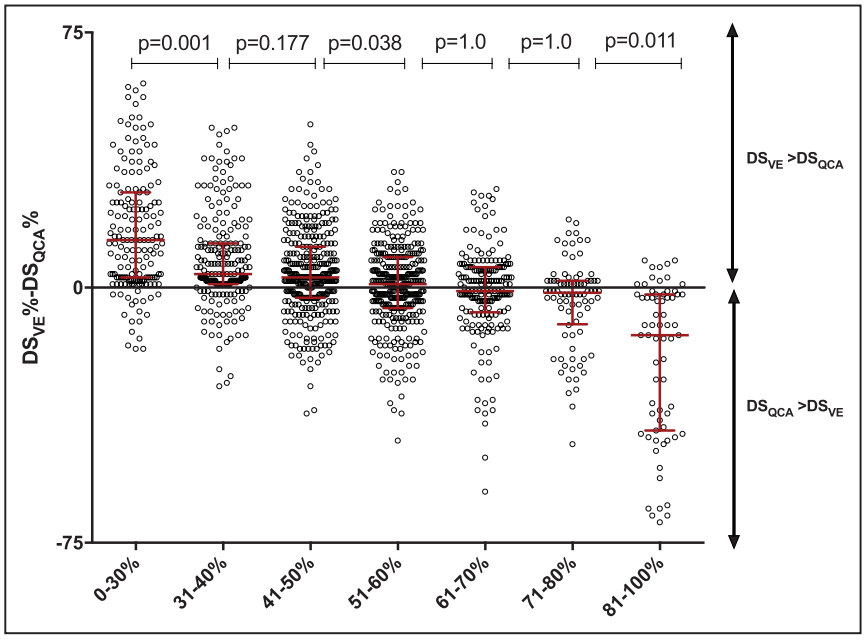

Figure 1. Individual values of the diameter stenosis by visual estimate (DS_{VE})/diameter stenosis by quantitative coronary angiography (DS_{QCA}) difference plotted per strata of DS.. The difference of DS_{VE} and DS_{QCA} (*y* axis) is plotted against their average value (*x* axis). DS_{VE} tended to be larger than DS_{QCA} <60% diameter stenosis, whereas the opposite was true >70% diameter stenosis. *P* values for between-groups comparisons with the Kruskal–Wallis test with Dunn correction. Error bars present the median (25th–75th value) of the DS_{VE}%–DS_{QCA}% difference for each strata.

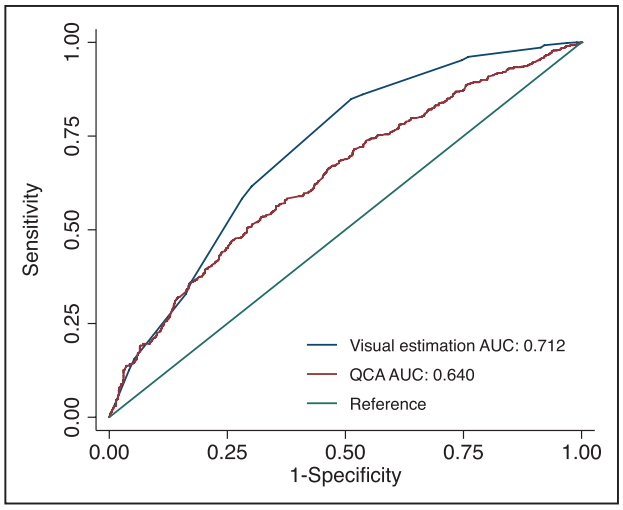

Figure 2. Receiver operating characteristic curves for diameter stenosis by visual estimation (DS_{VE}) and diameter stenosis by quantitative coronary angiography (DS_{QCA}) for the entire group. AUC indicates area under the curve.

0.636, 0.693, and 0.692, respectively. In pairwise comparisons, a statistically significant difference was noted between the LM-LCx (P=0.02) and the LM-RCA (P=0.02) DS_{QCA} ROC curves.

In subgroup analysis according to lesion location, the C statistics of the DS_{VE} ROC curves for lesions located at the proximal, mid, and distal part of the vessel were, respectively, 0.740, 0.699, and 0.704. The respective C statistics of the DS_{QCA} curves were 0.629, 0.626, and 0.658. Pairwise comparisons did not reveal significant differences of C statistics according to lesion location for the DS_{VE} and DS_{QCA} ROC curves.

Impact of Risk Factors

In our study population, 124 (11%) patients had no or only 1 risk factor, 338 patients (31%) had 2, 398 patients (36%) had 3, and 244 patients (22%) had ≥4 risk factors (Table 1). Angiographic indices (DS, reference diameter, and minimum lumen diameter) did not differ across subgroups (Table 2). The ROC curve C statistic for DS_{VE} diminished significantly with the accumulation of risk factors (0.776 for 0–1 risk factor, 0.750 for 2 risk factors, 0.713 for 3 risk factors, and 0.627 for ≥4 risk factors, respectively; P=0.005; Figure 3).

Impact of Diabetes Mellitus

In our study population, 97 (9%) patients had diabetes mellitus, and 1007 (91%) did not have diabetes mellitus. Both groups were similar in terms of baseline and angiographic characteristics, with the exception of higher prevalence of dyslipidemia, family history of coronary artery disease, and higher body mass index in the diabetic group (Table 3). FFR was significantly higher in the diabetic group compared with the nondiabetic group (0.83 [0.76, 0.90] versus 0.81 [0.73, 0.88]; P=0.013). In ROC analyses, the DS_{VE} curve for the diabetic group had a lower C statistic compared with the nondiabetic group (0.524 versus 0.729; P<0.001; Figure 4).

Table 1. Clinical and Lesion Characteristics of the Study Population

Clinical characteristics	
Patients, n	1104
Age, y	67 (58, 75)
Male sex, n (%)	774 (70)
Body mass index, kg/m^2	26.9 (24.5, 29.8)
Diabetes mellitus, n (%)	97 (9)
Hypertension, n (%)	626 (57)
Dyslipidemia, n (%)	711 (64)
Current smoker, n (%)	143 (13)
Family history of coronary artery disease, n (%)	84 (8)
No. of risk factors	
0–1 risk factors, n (%)	124 (11)
2 risk factors, n (%)	338 (31)
3 risk factors, n (%)	398 (36)
≥4 risk factors, n (%)	244 (22)
Angiographic characteristics (lesions)	n=1382
Diameter stenosis by visual estimation, %	50 (40, 65)
Diameter stenosis by quantitative coronary angiography, %	50 (39, 60)
Reference diameter, mm	2.70 (2.30, 3.20)
Minimum lumen diameter, mm	1.35 (1.00, 1.70)
Lesion length, mm	12 (9, 15)
Fractional flow reserve	0.81 (0.73, 0.88)
Left ventricular ejection fraction, %	71 (61, 80)
Lesion location	n (%)
Left main	67 (5)
Left anterior descending artery	744 (54)
	Proximal: 261 (19), mid: 387 (28), distal: 96 (7)
Left circumflex artery	248 (18)
	Proximal: 92 (7), distal: 156 (11)
Right coronary artery	323 (23)
	Proximal: 91 (7), mid: 136 (10), distal: 96 (7)

Discussion

Even though coronary angiography will remain central to the diagnosis and treatment of coronary artery disease, the relation between the angiographic severity, typically expressed in percent DS, remains elusive.[33] In the present analysis, we compared side-by-side VE and QCA to FFR and studied the effect of risk factors on these relationships.

The main findings of this study can be summarized as follows: (1) when compared with QCA, VE underestimates mild stenoses and overestimates tight stenoses; (2) VE predicts

Table 2. Clinical and Angiographic Characteristics Across Risk Factor Subgroups

Risk Factors Subgroups	0–1 Risk Factors	2 Risk Factors	3 Risk Factors	≥4 Risk Factors	*P* Value
Clinical characteristics					
Patients, n	124	338	398	244	
Age, y	62 (51, 76)	66 (58, 74)	68 (61, 75)	66 (59, 73)	0.003
Male sex, n (%)	78 (63)	221 (65)	273 (69)	203 (83)	<0.0001
Body mass index, kg/m^2	25.7 (23.4, 30.0)	26.2 (24.1, 29.1)	27.3 (24.6, 30.1)	27.6 (25.6, 30.8)	<0.0001
Diabetes mellitus, n (%)	1 (1)	4 (1)	25 (6)	91 (37)	<0.0001
Hypertension, n (%)	4 (3)	133 (40)	272 (68)	215 (88)	<0.0001
Dyslipidemia, n (%)	8 (6)	146 (43)	322 (81)	234 (96)	<0.0001
Current smoker, n (%)	8 (6)	36 (11)	53 (13)	46 (19)	<0.0001
Family history of coronary artery disease, n (%)	2 (2)	4 (1)	18 (5)	61 (25)	<0.0001
Angiographic characteristics					
Lesions, n	162	416	488	316	
Diameter stenosis by visual estimation, %	50 (40, 60)	50 (40, 70)	50 (40, 70)	50 (40, 60)	0.94
Diameter stenosis by quantitative coronary analysis, %	49 (40, 60)	50 (39, 62)	50 (38, 59)	50 (38, 60)	0.72
Reference diameter, mm	2.7 (2.3, 3.1)	2.6 (2.2, 3.1)	2.7 (2.3, 3.2)	2.7 (2.3, 3.2)	0.34
Minimum lumen diameter, mm	1.3 (1.0, 1.7)	1.3 (1.0, 1.7)	1.4 (1.0, 1.8)	1.4 (1.1, 1.7)	0.18
Lesion length, mm	12 (9, 18)	12 (8, 15)	12 (9, 15)	12 (9, 15)	0.40
Fractional flow reserve	0.78 (0.70, 0.87)	0.81 (0.73, 0.89)	0.82 (0.73, 0.89)	0.81 (0.74, 0.87)	0.17
Left ventricular ejection fraction, %	75 (64, 81)	71 (58, 78)	72 (63, 80)	66 (56, 80)	0.017

better the FFR value than does QCA; and (3) the diagnostic accuracy of angiography in predicting FFR decreases with accumulating risk factors, particularly so in diabetic patients.

Comparison of VE and QCA With DS Severity

Our study showed that VE underestimates mild stenoses and overestimates tight stenosis compared with QCA. Our results were similar and confirm in a larger population previous studies describing the difference observed between VE and QCA.[34–36]

Correlation of VE Versus QCA With Physiology

Several studies have indicated that the reproducibility of QCA was significantly better than that of VE.[37] Both inter- and intraobserver variability are reduced by QCA. This justifies the adoption of QCA in trial setting. Yet, the present data indicate that the diagnostic accuracy of VE to predict a positive or negative FFR value was significantly higher than that of QCA and actually justifies the lack of adoption of QCA for clinical decision-making. Our study showed better diagnosis accuracy expressed as AUCs in LM assessed with VE compared with FFR, whereas QCA evaluation for the same stenoses is markedly low and significantly lower than AUCs of QCA compared with FFR in LCx (P=0.02) and in RCA (P=0.02). Of note, AUCs of VE compared with FFR in LAD lesions was lower compared with LCx (P=0.02) and to LM (P<0.001). No difference in terms of AUCs of VE or QCA compared with FFR was observed according to lesion location between proximal, mid, and distal coronary segments. The reasons for this apparent paradox remain speculative. QCA is largely operator independent. In contrast, VE—often called eyeballing—is largely operator dependent and subjective. It is likely that when evaluating the percent DS the operator unconsciously incorporates many other factors not directly related to the dimensions of the lumen but known to play a role on transstenotic hemodynamics: myocardial mass, segmental wall motion, filling pressures, prognostic significance of the stenotic segment, general morphology of the coronary vasculature, and bifurcation. These factors influence the FFR values but are not accounted for by QCA. In addition, operator's knowledge of results of noninvasive

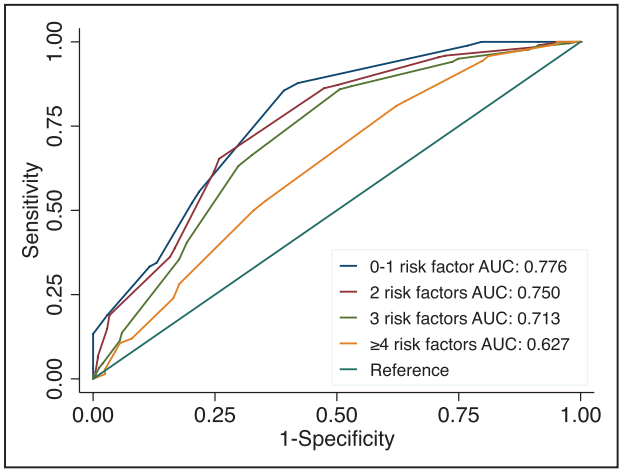

Figure 3. Receiver operating characteristic curves for diameter stenosis by visual estimation (DS_{VE}) according to the presence of risk factors. AUC indicates area under the curve.

Table 3. Clinical and Angiographic Characteristics of Diabetic Versus Nondiabetic Patients

	Diabetic Patients	Nondiabetic Patients	*P* Value
Clinical characteristics			
Patients, n	97	1007	
Age, y	65 (58, 72)	67 (58, 75)	0.34
Male sex, n (%)	67 (69)	707 (70)	0.82
Body mass index, kg/m^2	27.8 (25.5, 31.0)	26.8 (24.4, 29.7)	0.005
Hypertension, n (%)	60 (62)	566 (56)	0.34
Dyslipidemia, n (%)	75 (77)	636 (63)	0.005
Current smoker, n (%)	42 (43)	447 (44)	0.92
Family history of coronary artery disease, n (%)	15 (15)	69 (7)	<0.001
Angiographic characteristics			
Lesions, n	123	1,222	
Diameter stenosis by visual estimation, %	50 (50, 60)	50 (40, 65)	0.24
Diameter stenosis by quantitative coronary analysis, %	51 (38, 61)	49 (39, 60)	0.78
Reference diameter, mm	2.7 (2.2, 3.2)	2.7 (2.3, 3.2)	0.87
Minimum lumen diameter, mm	1.4 (1.1, 1.6)	1.4 (1.0, 1.7)	0.62
Lesion length, mm	12.3 (9.1, 15.2)	12.0 (9.0, 15.2)	0.25
Fractional flow reserve	0.83 (0.76, 0.90)	0.81 (0.73, 0.88)	0.013
Left ventricular ejection fraction, %	65 (54, 82)	71 (61, 80)	0.19

stress test may contribute to the subjective evaluation of a stenosis. Similar factors probably contribute to the fact that the operator tends to underestimate mild stenoses and to overestimate mild stenoses. When gauging a severe stenosis, cardiologists are still used to speak of a 90% stenosis, which is actually often a misnomer. Indeed, in a 3-mm artery, a 90% DS corresponds to a 99% area reduction that is not compatible with Thrombolysis In Myocardial Infarction grade 3 flow, stable angina, and a normal segmental wall motion in the absence of collaterals.

Influence of Risk Factors

This study indicates a weaker correlation between angiography and FFR with accumulating risk factors, in particular with diabetes mellitus. Risk factors are associated with diffuse epicardial atherosclerosis and with microvascular disease that may blur the relation between FFR and the angiographic appearance. In the presence of diffuse epicardial disease, the percent DS will tend to be underestimated because both stenotic segment and reference segment are infiltrated by atherosclerosis. On the other hand, microvascular dysfunction will lead to a lesser degree of vasodilation, and in turn to a reduced hyperemic flow and a higher FFR. From a clinical point of view, the present results indicate that the more the risk factors, the more both FFR and angiography together are needed to understand myocardial circulation in individual patients and for optimal clinical decision-making.

We established a weaker correlation with the accumulation of risks factors between angiographic assessments of coronary stenosis compared with FFR. This might be related to the influence of microcirculation disease in patients with risks factors compared with those without. It is noteworthy that for comparable coronary stenosis assessed with angiography FFR was significantly different according to the presence of age–sex[38] and diabetes mellitus. Those factors seem to be involved in coronary microvascular disease. The impact of diabetes mellitus on FFR seems to significantly increase the FFR value compared with a similar stenosis in patients without diabetes mellitus. This study confirms that VE and QCA are both limited to assess functional significance of coronary stenosis. Moreover, more patients had risk factors; less reliability of VE and QCA is present; and more FFR evaluation is needed.

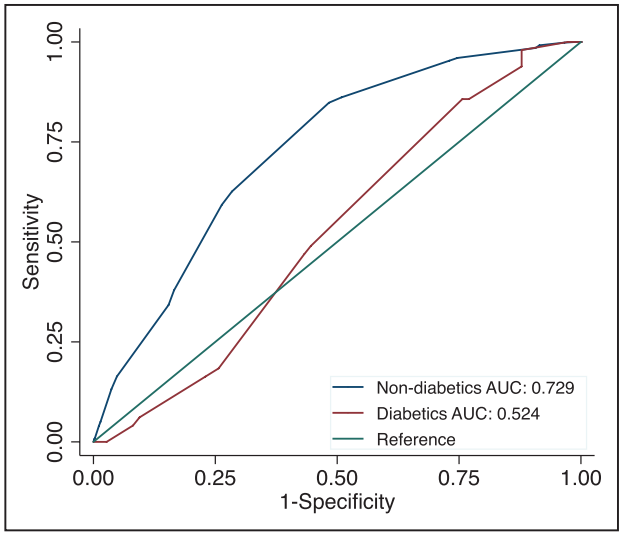

Figure 4. Receiver operating characteristic curves for diameter stenosis by visual estimation (DS_{VE}) in diabetic and nondiabetic patients. AUC indicates area under the curve.

Limitations

Many limitations have to be considered. First, in the present study cohort, there is a relatively low incidence of diabetes mellitus (9%) when compared with the classical 25% to 30% incidence in most percutaneous coronary intervention trials. This is likely related to the fact that many diabetic patients were not included when lesions were not suitable for QCA analysis such as diffusely diseased coronary lesions or sequential lesions which might impact the hemodynamic evaluation assessed with FFR and diabetic patients with previous coronary artery bypass graft were therefore excluded. Lesion characteristics between diabetic patients and nondiabetic patients are not significantly different, which allow a good reliability of our results. Second, this is a retrospective analysis from a single center database. There were several different operators to perform FFR measurements and to assess the lesion by VE and several technicians who performed the QCA analysis. Nevertheless, it represents real-world clinical practice in which no core laboratory is involved.

Third, we did not perform propensity matched or multivariate analyses because of the relatively low number of diabetic patients.

Conclusions

This study confirms the weak correlation between angiographic metrics and FFR and indicates that, despite its subjectivity, VE is more accurate in predicting physiology than QCA. The presence of risk factors markedly blur this relationship: the more risk factors, the weaker the potential of angiography to assess physiology, particularly so in diabetics. In these patients—even more than in others—a combined angiographic and functional approach is mandated for optimal clinical decision-making about revascularization.

Disclosures

Drs De Bruyne and Barbato report that their institution receives grant support and consulting fees on their behalf from St. Jude Medical, Opsens, and Boston Scientific. Dr Toth reports receiving consulting fee from St. Jude Medical. The other authors report no conflicts.

References

1. Sones FM Jr, Shirey EK. Cine coronary arteriography. *Mod Concepts Cardiovasc Dis*. 1962;31:735–738.
2. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974;33:87–94.
3. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. 1979;300:1350–1358. doi: 10.1056/NEJM197906143002402.
4. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, Galema TW, Meijboom WB, Mollet NR, de Feyter PJ, Cademartiri F, Maffei E, Dewey M, Zimmermann E, Laule M, Pugliese F, Barbagallo R, Sinitsyn V, Bogaert J, Goetschalckx K, Schoepf UJ, Rowe GW, Schuijf JD, Bax JJ, de Graaf FR, Knuuti J, Kajander S, van Mieghem CA, Meijs MF, Cramer MJ, Gopalan D, Feuchtner G, Friedrich G, Krestin GP, Hunink MG; CAD Consortium. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J*. 2011;32:1316–1330. doi: 10.1093/eurheartj/ehr014.
5. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219–227.
6. Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. Different degrees of ischemic threshold stratified by the dipyridamole-echocardiography test. *Am J Cardiol*. 1987;59:71–73.
7. Stewart RE, Schwaiger M, Molina E, Popma J, Gacioch GM, Kalus M, Squicciarini S, al-Aouar ZR, Schork A, Kuhl DE. Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease. *Am J Cardiol*. 1991;67:1303–1310.
8. Baer FM, Voth E, Theissen P, Schicha H, Sechtem U. Gradient-echo magnetic resonance imaging during incremental dobutamine infusion for the localization of coronary artery stenoses. *Eur Heart J*. 1994;15:218–225.
9. Ravipati G, Aronow WS, Lai H, Shao J, DeLuca AJ, Weiss MB, Pucillo AL, Kalapatapu K, Monsen CE, Belkin RN. Comparison of sensitivity, specificity, positive predictive value, and negative predictive value of stress testing versus 64-multislice coronary computed tomography angiography in predicting obstructive coronary artery disease diagnosed by coronary angiography. *Am J Cardiol*. 2008;101:774–775. doi: 10.1016/j.amjcard.2007.10.044.
10. White CW, Wright CB, Doty DB, Hiratza LF, Eastham CL, Harrison DG, Marcus ML. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med*. 1984;310:819–824. doi: 10.1056/NEJM198403293101304.
11. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, Camici PG, Cerqueira MD, Chow BJ, Di Carli MF, Dorbala S, Gewirtz H, Gropler RJ, Kaufmann PA, Knaapen P, Knuuti J, Merhige ME, Rentrop KP, Ruddy TD, Schelbert HR, Schindler TH, Schwaiger M, Sdringola S, Vitarello J, Williams KA Sr, Gordon D, Dilsizian V, Narula J. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol*. 2013;62:1639–1653. doi: 10.1016/j.jacc.2013.07.076.
12. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA*. 2005;293:477–484. doi: 10.1001/jama.293.4.477.
13. Marzilli M, Merz CN, Boden WE, Bonow RO, Capozza PG, Chilian WM, DeMaria AN, Guarini G, Huqi A, Morrone D, Patel MR, Weintraub WS. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! *J Am Coll Cardiol*. 2012;60:951–956. doi: 10.1016/j.jacc.2012.02.082.
14. Colombo A, Panoulas VF. Diagnostic coronary angiography is getting old! *JACC Cardiovasc Imaging*. 2015;8:11–13. doi: 10.1016/j.jcmg.2014.11.003.
15. Reiber JH, Kooijman CJ, Slager CJ, Gerbrands JJ, Schuurbiers JC, Den Boer A, Wijns W, Serruys PW, Hugenholtz PG. Coronary artery dimensions from cineangiograms methodology and validation of a computer-assisted analysis procedure. *IEEE Trans Med Imaging*. 1984;3:131–141. doi: 10.1109/TMI.1984.4307669.
16. Reiber JH, van der Zwet PM, Koning G, von Land CD, van Meurs B, Gerbrands JJ, Buis B, van Voorthuisen AE. Accuracy and precision of quantitative digital coronary arteriography: observer-, short-, and medium-term variabilities. *Cathet Cardiovasc Diagn*. 1993;28:187–198.
17. Serruys PW, Unger F, van Hout BA, van den Brand MJ, van Herwerden LA, van Es GA, Bonnier JJ, Simon R, Cremer J, Colombo A, Santoli C, Vandormael M, Marshall PR, Madonna O, Firth BG, Breeman A, Morel MA, Hugenholtz PG. The ARTS study (Arterial Revascularization Therapies Study). *Semin Interv Cardiol*. 1999;4:209–219. doi: 10.1006/siic.1999.0107.
18. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703–1708. doi: 10.1056/NEJM199606273342604.
19. Adjedj J, Toth GG, Johnson NP, Pellicano M, Ferrara A, Floré V, Di Gioia G, Barbato E, Muller O, De Bruyne B. Intracoronary adenosine: dose-response relationship with hyperemia. *JACC Cardiovasc Interv*. 2015;8:1422–1430. doi: 10.1016/j.jcin.2015.04.028.
20. Adjedj J, De Bruyne B, Floré V, Di Gioia G, Ferrara A, Pellicano M, Toth GG, Bartunek J, Vanderheyden M, Heyndrickx GR, Wijns W, Barbato E. Significance of intermediate values of fractional flow reserve in patients with coronary artery disease. *Circulation*. 2016;133:502–508. doi: 10.1161/CIRCULATIONAHA.115.018747.
21. De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, Van Crombrugge P, Heyndrickx GR, Wijns W. Fractional flow reserve in patients with prior myocardial infarction. *Circulation*. 2001;104:157–162.
22. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*. 2001;103:2928–2934.
23. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow

reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224. doi: 10.1056/NEJMoa0807611.
24. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001. doi: 10.1056/NEJMoa1205361.
25. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371:1208–1217. doi: 10.1056/NEJMoa1408758.
26. Berger A, Botman KJ, MacCarthy PA, Wijns W, Bartunek J, Heyndrickx GR, Pijls NH, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *J Am Coll Cardiol*. 2005;46:438–442. doi: 10.1016/j.jacc.2005.04.041.
27. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, Nelis O, Bartunek J, Vanderheyden M, Wyffels E, Barbato E, Heyndrickx GR, Wijns W, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation*. 2009;120:1505–1512. doi: 10.1161/CIRCULATIONAHA.109.850073.
28. Muller O, Mangiacapra F, Ntalianis A, Verhamme KM, Trana C, Hamilos M, Bartunek J, Vanderheyden M, Wyffels E, Heyndrickx GR, van Rooij FJ, Witteman JC, Hofman A, Wijns W, Barbato E, De Bruyne B. Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior descending coronary artery stenosis. *JACC Cardiovasc Interv*. 2011;4:1175–1182. doi: 10.1016/j.jcin.2011.09.007.
29. Puymirat E, Mangiacapra F, Peace A, Sharif F, Conte M, Bartunek J, Vanderheyden M, Wijns W, de Bruyne B, Barbato E. Long-term clinical outcome in patients with small vessel disease treated with drug-eluting versus bare-metal stenting. *Am Heart J*. 2011;162:907–913. doi: 10.1016/j.ahj.2011.07.024.
30. Li J, Elrashidi MY, Flammer AJ, Lennon RJ, Bell MR, Holmes DR, Bresnahan JF, Rihal CS, Lerman LO, Lerman A. Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice. *Eur Heart J*. 2013;34:1375–1383. doi: 10.1093/eurheartj/eht005.
31. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, Erbel R, Legrand V, Gwon HC, Remkes WS, Stella PR, van Schaardenburgh P, Bech GJ, De Bruyne B, Pijls NH. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J*. 2015;36:3182–3188. doi: 10.1093/eurheartj/ehv452.
32. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983;148:839–843. doi: 10.1148/radiology.148.3.6878708.
33. Toth G, Hamilos M, Pyxaras S, Mangiacapra F, Nelis O, De Vroey F, Di Serafino L, Muller O, Van Mieghem C, Wyffels E, Heyndrickx GR, Bartunek J, Vanderheyden M, Barbato E, Wijns W, De Bruyne B. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J*. 2014;35:2831–2838. doi: 10.1093/eurheartj/ehu094.
34. Fleming RM, Kirkeeide RL, Smalling RW, Gould KL. Patterns in visual interpretation of coronary arteriograms as detected by quantitative coronary arteriography. *J Am Coll Cardiol*. 1991;18:945–951.
35. Nallamothu BK, Spertus JA, Lansky AJ, Cohen DJ, Jones PG, Kureshi F, Dehmer GJ, Drozda JP Jr, Walsh MN, Brush JE Jr, Koenig GC, Waites TF, Gantt DS, Kichura G, Chazal RA, O'Brien PK, Valentine CM, Rumsfeld JS, Reiber JH, Elmore JG, Krumholz RA, Weaver WD, Krumholz HM. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. *Circulation*. 2013;127:1793–1800. doi: 10.1161/CIRCULATIONAHA.113.001952.
36. Anderson RD, Pepine CJ. Coronary angiography: is it time to reassess? *Circulation*. 2013;127:1760–1762. doi: 10.1161/CIRCULATIONAHA.113.002566.
37. Beauman GJ, Vogel RA. Accuracy of individual and panel visual interpretations of coronary arteriograms: implications for clinical decisions. *J Am Coll Cardiol*. 1990;16:108–113.
38. Lim HS, Tonino PA, De Bruyne B, Yong AS, Lee BK, Pijls NH, Fearon WF. The impact of age on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial substudy. *Int J Cardiol*. 2014;177:66–70. doi: 10.1016/j.ijcard.2014.09.010.

CLINICAL PERSPECTIVE

Fractional flow reserve is an invasive index quantifying the ratio of maximal myocardial flow with and without epicardial stenosis and has become the standard of reference of coronary stenosis severity. Nevertheless, the majority of decisions about treatment in patients with coronary artery disease are based on the angiographic diameter stenosis. In the present work, we compare the diameter stenosis obtained by visual estimate and by quantitative coronary angiography to fractional flow reserve. We show that the diagnostic performance of both visual estimate and quantitative coronary angiography is poor, but that visual estimate performs slightly better than quantitative coronary angiography. In addition, the diagnostic performance of diameter stenosis decreases as risk factors accumulate. This is particularly the case in diabetic patients.

Circulation
Cardiovascular Imaging

Visual and Quantitative Assessment of Coronary Stenoses at Angiography Versus Fractional Flow Reserve: The Impact of Risk Factors

Julien Adjedj, Panagiotis Xaplanteris, Gabor Toth, Angela Ferrara, Mariano Pellicano, Giovanni Ciccarelli, Vincent Floré, Emanuele Barbato and Bernard De Bruyne

Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.117.006243
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080