Supplementary data

Core laboratory assessment of the quantitative flow ratio

All intermediate (diameter stenosis 40%-69%) nonculprit study lesions of the VULNERABLE trial were screened for quantitative flow ratio (QFR) analysis. Lesions were excluded from the analysis if: *a)* they were located < 3 mm from the aorta (ie, ostial lesion); *b)* they had a reference lumen diameter below 2.0 mm on visual estimation; *c)* there was vessel overlap of the segment of interest; or *d)* they had poor angiographic image quality that prevented correct contour delineation.

QFR (off-line) analysis was performed by certified analysts of the VULNERABLE trial core laboratory (BARCICORE-lab; Barcelona Cardiac Imaging Core Laboratory). The analysts selected the angiographic view with minimal vessel overlap in both the interrogated vessel and its side branch ostiums as the optimal angiographic view. The QFR and QCA analyses were performed in the same angiographic view. QFR calculation was performed using the artificial intelligence (AI)-aided AngioPlus Core software (version V2, Pulse Medical Imaging Technology, Shanghai, China). This software apllies a semiautomatic process that can summarized in the following steps: *a)* delineation of the interrogated epicardial coronary artery during contrast injection and calculation of the contrast flow velocity based on the centerline length divided by the contrast medium filling time; *b)* selection of the analysis frame with sharp lumen contour in the stenotic segment of the key frame; *c)* delineation of the lumen contour of the interrogated vessel and its side branches with diameters of ≥ 1.0 mm in the key frame based on convolutional neural network; *d)* reconstruction of the reference diameter function with a reduction size through

the bifurcations according to Murray's fractal law; *e)* modelling of the hyperemic flow velocity based on the contrast flow velocity and calculation of the pressure drop based on the fluid dynamics equations, assuming a blood density of 1.060 kg/m^3 and a viscosity of 0.0035 kg/(ms). Specifically, the pressure loss caused by friction loss along the lesion entrance and stenotic segment, as well as the inertial loss due to sudden expansion of flow out of the stenosis, based on the geometry of the stenosis and the hyperemic flow velocity.[1]

Translesional QFR was estimated as the pressure gradient across the coronary stenosis. This pressure drop depends on both the severity of the narrowing and the magnitude of blood flow through the stenosis. Its value is automatically calculated by the software.

Supplementary table 1. Comparison of QCA and QFR analysis between patients with positive and negative FFR

	All (N = 428[a])	FFR ≤ 0.80 (n = 97)	FFR > 0.80 (n = 329)	*P*
Lesion location				< .01
LAD	177 (41.4)	70 (72.2)	105 (31.9)	
LCF	153 (35.7)	14 (14.4)	139 (42.2)	
RCA	98 (22.9)	13 (13.4)	85 (25.8)	
Days from baseline to study procedure	5 (3-18)	5 (3-15)	5 (3-20)	.585
Invasive nonhyperemic index[b]	0.91 ± 0.10	0.80 ± 0.12	0.94 ± 0.06	< .01
Invasive FFR	0.86 ± 0.10	0.72 ± 0.08	0.89 ± 0.05	< .01
Invasive CFR[c]	2.97 ± 1.58	2.71 ± 1.14	3.03 ± 1.67	.137
Invasive IMR[c]	20.37 ± 13.64	15.38 ± 9.56	21.66 ± 14.25	< .01
QCA and QFR analyses at index (primary PCI) procedure				
Lesion length, mm	16.21 ± 6.94	17.17 ± 7.92	15.97 ± 6.62	.176
Minimal lumen diameter, mm	1.37 ± 0.37	1.24 ± 0.34	1.41 ± 0.37	< .01
Reference lumen diameter, mm	2.80 ± 0.59	2.64 ± 0.56	2.85 ± 0.59	< .01
Diameter stenosis, %	51.33 ± 8.04	52.94 ± 8.20	50.82 ± 7.94	.026
QFR vessel	0.85 ± 0.09	0.78 ± 0.09	0.87 ± 0.08	< .01
QFR translesional	0.10 ± 0.09	0.16 ± 0.10	0.08 ± 0.08	< .01
QCA and QFR analyses at staged study procedure				
Lesion length, mm	16.17 ± 6.94	17.36 ± 8.20	15.85 ± 6.36	.768
Minimal lumen diameter, mm	1.42 ± 0.35	1.34 ± 0.28	1.45 ± 0.37	< .01
Reference lumen diameter, mm	2.91 ± 0.57	2.80 ± 0.56	2.94 ± 0.57	.024
Diameter stenosis, %	50.54 ± 7.63	50.79 ± 8.38	50.52 ± 7.38	.768
QFR vessel	0.86 ± 0.09	0.76 ± 0.10	0.89 ± 0.06	< .01
QFR trans lesional	0.09 ± 0.09	0.18 ± 0.14	0.07 ± 0.05	< .01

CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LAD, left anterior descending; LCF, left circumflex; MI, myocardial infarction; RCA, right coronary artery.

[a]Two lesions in 2 patients did not have an invasive FFR value; [b]nonhyperemic value was only available in 338 lesions; [c]microcirculatory data were only available in 221 lesions.

Supplementary Table 2. Sensitivity and specificity analysis of index QFR cutoff values to assess positive FFR results at the staged procedure

Index QFR cutoff value	Sensitivity (%)	Specificity (%)	False negatives (negative QFR and positive FFR using this cutoff), No.% (1- sensitivity)	Youden index (sensitivity + Specificity - 1)[a]	Patients with negative index QFR using this cutoff, No. (%)[b]
≤ 0.74	35	96	63 (65)	0.31	378 (88)
≤ 0.75	37	95	61 (63)	0.33	375 (88)
≤ 0.76	41	93	57 (59)	0.35	364 (85)
≤ 0.77	47	93	51 (53)	0.41	358 (84)
≤ 0.78	67	92	42 (43)	0.49	346 (81)
≤ 0.79	64	91	35 (36)	0.55	335 (78)
≤ 0.80	72	91	27 (28)	0.63	327 (76)
≤ 0.81	74	87	25 (26)	0.61	311 (73)
≤ 0.82	77	84	22 (23)	0.61	298 (70)
≤ 0.83	79	79	20 (21)	0.58	279 (65)
≤ 0.84	80	74	19 (20)	0.54	262 (61)
≤ 0.85	82	66	17 (18)	0.49	235 (55)
≤ 0.86	83	61	16 (17)	0.44	215 (50)
≤ 0.87	86	55	14 (14)	0.40	194 (45)
≤ 0.88	87	48	13 (13)	0.35	171 (40)
≤ 0.89	89	41	11 (11)	0.30	146 (34)

[a]Youden Index ranges between 0 and 1, with 0 values indicating that a diagnostic test gives the same proportion of positive results for groups with and without the disease. A value of 1 indicates that there are no false positives or false negatives.

[b] Patients with negative index QFR should be treated with optimal medical therapy without need of staged procedure.

References:

1. Tu S, Echavarria-Pinto M, von Birgelen C, et al. Fractional flow reserve and coronary bifurcation anatomy: a novel quantitative model to assess and report the stenosis severity of bifurcation lesions. *JACC Cardiovasc Interv* 2015; **8**(4): 564-74.