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Quantitative flow ratio for the prediction of coronary events after percutaneous coronary intervention

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The Multivessel TALENT trial is an ongoing randomised controlled trial comparing 2 drug-eluting stents in patients with *de novo* three-vessel disease without left main disease[1]. The study design mandates an offline assessment of quantitative flow ratio (QFR) pre-percutaneous coronary intervention (PCI) to prospectively identify which lesions should be treated. The rationale of this study lies in the *post hoc* analysis of the SYNTAX II trial, which established that a post-PCI QFR ≥0.91 was the optimal cut-off for a lower risk of 2-year vessel-oriented composite endpoints (VOCE). ClinicalTrials.gov: NCT04390672.

The current study was a vessel-based analysis using the post-PCI QFR from the first 775 patients randomised in the Multivessel TALENT study and was conducted before event adjudication commenced to forecast the rate of VOCE at 2 years for the entire population.

The details of the Multivessel TALENT trial design have been previously published[1]. The powered secondary endpoint is a superiority comparison in the per-protocol analysis of VOCE, a composite of vessel-related cardiovascular death, vessel-related myocardial infarction, and clinically and physiologically indicated target vessel revascularisation at 24 months post-procedure[1].

QFR is an angiography-derived fractional flow reserve (FFR) technology which was analysed offline by either QAngio XA 3D QFR imaging software (Medis Medical) or AngioPlus Core software (Pulse Medical) with Murray law-based QFR analysis (μQFR), depending on whether there were one or two angiographic views available **(Supplementary Figure 1)**. Both systems have equivalent diagnostic performance[1,2,3]. Details of the analysis are described in **Supplementary Appendix 1**.

Based on previous reports describing the impact of post-PCI QFR values on 2-year VOCE[2], a favourable VOCE rate is expected when the post-PCI vessel QFR is ≥0.91.

To predict 2-year VOCE in the current study based on the QFR measurements available in this interim sample, we first fitted a logistic regression model to the SYNTAX II trial data, with 2-year VOCE as the binary response variable and post-procedure QFR as the continuous predictor variable. A restricted cubic spline was used to model the change in the log-odds of 2-year VOCE, with changes in QFR to flexibly model any non-linearity. The 95% prediction interval (PI) for the 2-year VOCE rate was obtained using the predicted probabilities in the interim sample and bootstrap resampling. The details are presented in **Supplementary Appendix 1**.

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This study included the first 775 consecutive patients randomised in the Multivessel TALENT trial. A total of 1,674 lesions were treated between September 2020 and February 2023. The mean number of vessels treated per patient was 2.32.

Baseline patient and lesion characteristics are presented in **Supplementary Table 1** and **Supplementary Table 2**, with comparisons to the SYNTAX II trial.

Analysable QFRs were available in 1,557 vessels pre-PCI and 1,403 vessels post-PCI **(Supplementary Figure 2)**. Details of non-analysability are presented in **Supplementary Appendix 1**.

Supplementary Figure 3 shows pre- and post-PCI QFRs presented as a cumulative distribution curve. Of note, 146 out of 1,557 vessels (9%) were treated even though the pre-PCI QFR was >0.8. A post-PCI QFR ≥0.91 was achieved in 1,072 of the 1,403 (76%) treated vessels.

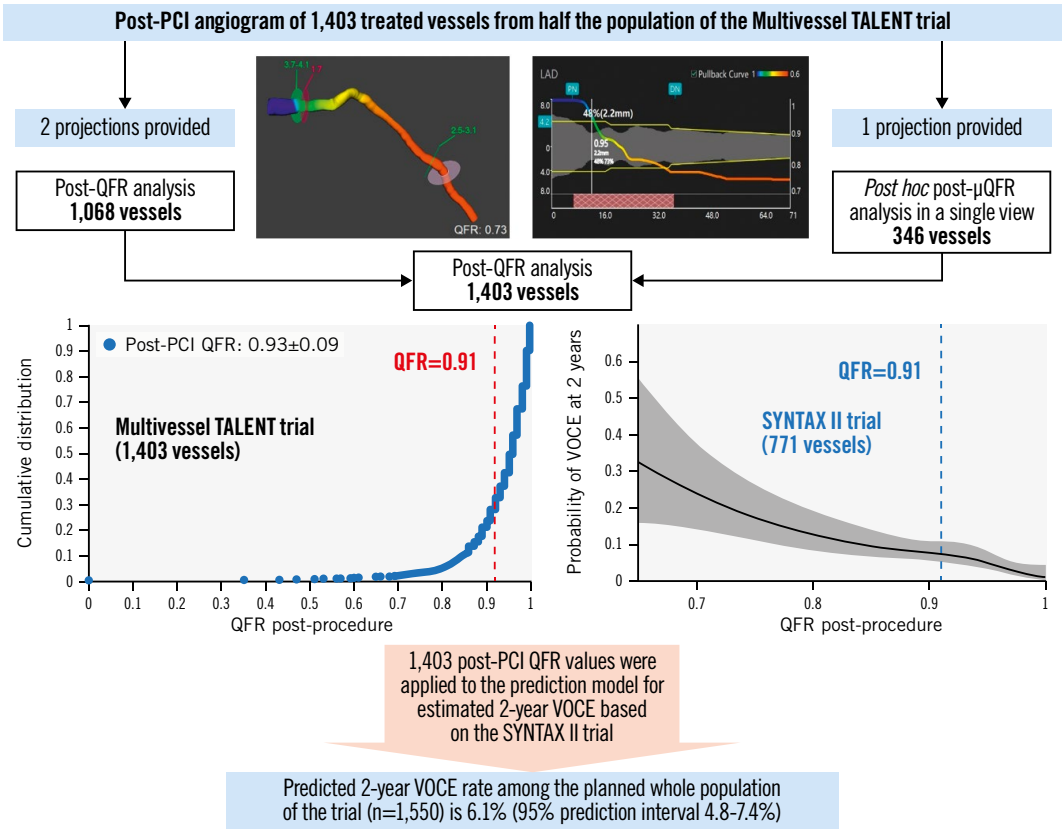
Based on predictions from the fitted SYNTAX II model and the available post-procedure QFRs in the interim Multivessel TALENT data, the predicted rate of 2-year VOCE in the trial was 6.1%, with a bootstrap 95% PI of 4.8% to 7.4% **(Supplementary Table 3, Supplementary Figures 4-6)**. The **Central illustration** summarises the scheme and the key results of this study.

The current analysis has been conducted on the first half of the planned study population in an attempt to ascertain (1) whether appropriate vessels are being selected for revascularisation and (2) whether PCI is being performed optimally. Its other main purpose was to reassure the steering committee and data and safety monitoring board on the validity of the statistical sample size assumptions.

A SYNTAX II substudy has established that a post-PCI QFR ≥0.91 significantly improves 2-year VOCE[2]. The current

EuroIntervention — Central **Illustration**

Prediction of 2-year VOCE for the whole population of the ongoing Multivessel TALENT trial based on post-PCI QFR results of half of the population.



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Two different offline angiography-derived FFR software were used, depending on whether there were one or two angiographic views available, in order to obtain the pre- and post-PCI QFR in the maximum number of participants in the ongoing Multivessel TALENT trial before event adjudication. In cases where only baseline or postprocedural QFR were available, µQFR analysis was added, pre- or post-PCI, in the same vessel. Eleven vessels were analysed with both techniques post-procedure. An optimal post-PCI QFR was obtained in 76% of the treated vessels. Based on the relationship between post-PCI QFR and 2-year VOCE in the SYNTAX II trial, the predicted 2-year VOCE in the entire Multivessel TALENT trial population would be 6.1%, with a boundary of 4.8% to 7.4%. FFR: fractional flow reserve; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; VOCE: vessel-oriented composite endpoint; µQFR: Murray law-based QFR

study has a similar number of vessels treated per patient to that seen in SYNTAX II. Given that 76% of vessels achieved the optimal threshold, we can reasonably assume that the 2-year VOCE of the Multivessel TALENT population could be 6.1%, with an acceptable PI.

QFR identifies stenotic vessels with a pressure-derived FFR ≤0.80 with good diagnostic accuracy, without need for a pressure wire or induction of pharmacological hyperaemia. Recently, FAVOR III China demonstrated significantly fewer myocardial infarctions and ischaemia-driven revascularisations in one- and two-year major adverse cardiac events in the QFR versus the angiography-guided group[4,5].

For 24% of the lesions, single-view software was used, so post-PCI QFR analyses were ultimately analysable in 84% of the cohort.

The stated assumptions that (1) the available QFR data of these initial patients will be representative of the eventual full trial sample and that (2) the relationship between QFR and VOCE in Multivessel TALENT is similar to SYNTAX II, whilst plausible, can only be verified upon completion of the study.

Favourable post-PCI QFRs were obtained in 76% of patients, resulting in an expected overall favourable VOCE rate of 6.1%, with a boundary of 4.8% to 7.4%.

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Conflict of interest statement

K. Ninomiya reports a grant from Abbott Medical Japan outside the submitted work. S. Tu reports receiving research grants and consultancy fees from Pulse Medical. M. Sabaté has received consultancy fees from Abbott and iVascular, outside the submitted work. H. Möllmann reports speaker honoraria from Abbott, Boston Scientific, and SMT. P. Serruys reports personal consultation fees from Philips/Volcano, SMT, Novartis, Xeltis, and Meril Life, outside the submitted work. J. Reiber is Chief Scientific Officer at Medis Medical Imaging Systems. The other authors have no conflicts of interest to declare.

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00561

Supplementary data

Supplementary Appendix 1. Methods.

The Multivessel TALENT study (ClinicalTrials.gov, NCT04390672) is a prospective, randomized, equal allocation, controlled, multi-centre, open-label study comparing clinical outcomes between SUPRAFLEX Cruz and SYNERGY stents in 60 sites from 8 European countries.

Patients with de novo 3VD and without left main disease had QFR of their invasive coronary angiograms analysed by an independent Core lab (CORRIB Lab, Galway) before PCI. State-of-the-art PCI encompasses: 1) legitimization of PCI treatment in multi-vessel disease based on SYNTAX Score II treatment recommendations; 2) functional evaluation with QFR (central Core lab) of each stenotic lesion prior to treatment [ESC guidelines (GL) Class IA]; 3) intravascular ultrasound (IVUS)/optical coherence tomography (OCT) optimization (ESC GL, Class IIa, B); 4) use of contemporary chronic total occlusion (CTO) techniques performed by an on-site accredited expert. In the Global Leaders study P2Y12 monotherapy after one month of dual antiplatelet therapy with optimal medical therapy was associated with better outcome in patients with complex CAD. In addition, a recent meta-analysis comparing P2Y12 with Aspirin tends to demonstrate the superiority of P2Y12 over aspirin in secondary prevention. The primary endpoint of this trial is a non-inferiority comparison of the patient-oriented composite endpoint (POCE), a composite of any death, stroke, MI or repeat revascularization, between the Supraflex Cruz and SYNERGY cohort at 12 months post-procedure. The powered secondary endpoint is a superiority comparison in the per-protocol analysis - at vessel level - of VOCE, a composite of vessel-related cardiovascular death, vessel-related MI, or clinically and physiologically indicated target vessel revascularisation, at 24 months post-procedure, consistent with the previous TALENT trial methodological approach.

All primary and secondary clinical endpoints, together with stent thrombosis and bleeding events will be adjudicated by an independent Clinical Events Committee blinded to stent allocation.

QFR analysis in core lab

QFR is an angiography-derived fractional flow reserve (FFR) technology which was analysed off-line by either QAngio XA 3D/QFR® imaging software (Version 2.0.60.6 Medis medical imaging system, Leiden, The Netherlands) or AngioPlus Core software with Murray-law

based QFR (μQFR) analysis (version V2, Pulse Medical, Shanghai, China) depending on the availability of one or two angiographic views **(Supplementary Figure 1)**.

Following informed consent, and before randomization, the central core lab identified functionally significant lesions. These QFR results, as well as the recommended length and diameter of stents to be used, were then forwarded to investigators in a deck of approximately 10 PowerPoint slides. The anatomical SYNTAX score was calculated on-site and by the independent Core lab. Post-PCI QFR analysis was performed retrospectively by the Core lab.

Lesions were excluded from the analysis if they: 1) had a reference luminal diameter on visual assessment <2 mm; 2) were partially out of the range of the cine angiogram in the end-diastolic phase; 3) were filmed without isocenter calibration information; 4) had severe vessel overlap at the site of the stenosis. The QFR of occluded vessels (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0/1) was assumed to be zero. The QFR calculation was based either on the 3-dimensional quantitative coronary angiogram reconstructed from 2 angiographic projections with angles >25 degrees apart (QAngio XA 3D) or on a single angiographic view (AngioPlus Core) whenever two appropriate views were not available. The volumetric flow rate was assessed by contrast bolus frame count as described in the literature. When only 1 angiographic projection was available either pre- or post-procedure, software relying on a single view was used for the matched paired analysis, pre- and post-procedure. Comparable diagnostic accuracies have been reported when comparing the respective validations of the two software against pressure-derived FFR by the two respective vendors, as well as by an independent assessment by our academic core lab. Compared Core lab assessments of both QFR software outputs relying on either one or two angiographic views with respect to a benchmark of 325 iFR and FFR measurements has been recently published[11].

Lesion QFR was defined as the QFR of a stenotic lesion in the target vessel that was automatically detected by the software on the baseline angiogram. The cut-off value of QFR for physiological significance was ≤0.80.

Vessel QFR was analysed from the ostia of the main vessels (right coronary artery [RCA], left anterior descending [LAD], and left circumflex coronary arteries [LCX]) to an anatomic landmark (e.g., side branch) located distal to the lesion. If an anatomical landmark was not

present in the post-procedural angiogram, the distal point was set 10 mm distal to the stent edge. Delta QFR across the stent was measured and regarded as "in-stent QFR" drop. Information about the anatomical SYNTAX score (including lesion characterization such as bifurcation, heavy calcification, and total occlusion) and implanted stents (number of stents, stent diameter and length) were collected in an electronic case report form (eCRF).

Based on previous reports describing the impact of post-PCI QFR values on 2-year VOCE, a favourable VOCE is expected when the post-PCI vessel QFR is ≥0.91.

Statistical analysis

To predict 2-year VOCE in the current study based on the QFR measurements available in this interim sample, we first fitted a logistic regression model in the SYNTAX II trial data, with the 2-year VOCE as the binary response variable and post-procedure QFR as the continuous predictor variable. A restricted cubic spline was used to model the change in the log odds of 2-year VOCE with changes in QFR to flexibly model any non-linearity. Once the model was fitted, it was possible to predict a probability for 2-year VOCE for each treated vessel in the interim sample, based on their measured post-procedure QFR. The 95% prediction interval (PI) for the rate of 2-year VOCE was obtained using the predicted probabilities in the interim sample and bootstrap resampling.

A bootstrap sample was made by randomly selecting vessel data from the interim sample and then simulating a single VOCE event based on each vessel's predicted probability of 2-year VOCE. Sampling was with replacement, meaning the data of the same patient could be included multiple times. Bootstrap resampling was performed at the patient level (clustered bootstrap). This clustered resampling approach accounted for the sampling/recruitment of lesions at patient level. A total of 10,000 bootstrap samples and simulations were made to ensure a high degree of resampling precision. The 2.5th and 97.5th percentiles of 2-year VOCE across these samples were used to estimate the 95% PI.

The validity of these predictions relies on the following assumptions:

1. the relationship between post-PCI QFR and the probability of 2-year VOCE is similar for patients in SYNTAX II and the Multivessel TALENT trial.

2. the distribution of post-PCI QFR values available in half of the population in this interim analysis of the Multivessel TALENT trial will be similar to that seen in the final per-protocol sample of 1,550 randomized patients.

QFR values, and the proportions of lesions with post-PCI QFR≥0.91, were further summarised by lesion location (RCA, LAD, LCX). Kruskal-Wallis tests and Chi-square tests were used to compare QFR distributions and proportions across these three groups.

Supplementary Appendix 2. Additional results.

QFRs were not analysable in 2% of vessels at baseline and 4% post-procedure for one or more of the following reasons: an isocenter issue in the DICOM data; inadequate angiograms including missing final shot, incomplete contrast filling, inappropriate projection angle or table movement caused foreshortening and/or overlapping; or out of the frame target vessels including poor resolution or a lower frame rate per second than the software requirements (12.5 frames).

Figure S4 shows the estimated relationship between 2-year VOCE and post-procedure QFR in the SYNTAX II trial based on the fitted logistic regression model with a restricted cubic spline. There is a monotonic decrease evident in the risk of 2-year VOCE with an increase in QFR. The rate of VOCE was 3.7% in the 487 vessels that achieved a post-PCI QFR≥0.91, and 12.0% in the 284 vessels with a post-PCI QFR<0.91.

The distribution of post-procedure QFRs in the available Multivessel TALENT data and SYNTAX II are shown in **Supplementary Figure 5**. The proportion of patients with a post-PCI QFR≥0.91 was higher in the interim Multivessel TALENT data compared to SYNTAX II (76% vs 63%).

The pre- and post-PCI QFR results for the three major epicardial vessels are presented in **Supplementary Table 3** and **Supplementary Figure 6**. The LAD was the most frequently treated vessel; however, it had the lowest mean post-PCI QFR (0.91 ± 0.09, p<0.001) and the lowest rate of a post-PCI QFR≥0.91 (66%, p<0.001) compared to the RCA and LCX (Table S3). No intra-stent QFR drop* was seen in 67% of the lesions.

*The definition of "intra-stent QFR drop" is a delta QFR of ≥0.01 between the proximal edge and the distal edge of the stent. If multiple stents were implanted serially in one target vessel, the sum of the delta QFR in-stent≥0.01 needs to be judged as having an "intra-stent QFR drop".

Supplementary Table 1. Baseline patient characteristics.

	Multivessel TALENT	***SYNTAX II***		
	N=775	N=393	95% CI of the difference	P-value
Age	68.2 ± 9.1	66.6 ± 9.8	0.4 to 2.7	0.006
Gender (male)	587 (75.7%)	364 (92.6%)	-20.9% to -12.9%	<0.001
BMI	28.2 ± 4.9	29.0 ± 4.7	-1.4 to -0.2	0.008
Current smoker	153 (19.9%)	36 (14.7%)	-0.05% to 10.5%	0.052
COPD	56 (8.0%)	45 (11.5%)	-7.3% to 0.2%	0.067
Hypertension	587 (76.4%)	295 (76.4%)	-5.2% to 5.2%	0.998
Dyslipidaemia	553 (72.0%)	297 (77.1%)	-10.4% to 0.1%	0.057
Medically treated diabetes	269 (35.1%)	108 (27.7%)	1.8% to 13.0%	0.009
Insulin use	76 (9.9%)	34 (8.7%)	-2.3% to 4.7%	0.502
Previous MI	35 (4.6%)	48 (12.3%)	-11.3% to -4.1%	<0.001
History of PVD	64 (8.3%)	30 (7.6%)	-2.6% to 4.0%	0.671
Precious stroke	35 (4.6%)	21 (5.3%)	-3.4% to 2.0%	0.604
Acute coronary syndrome	226 (29.4%)	98 (25.0%)	-0.9% to 9.8%	0.106
Chronic coronary syndrome	542 (70.6%)	294 (75.0%)	-9.8% to 0.9%	0.106
LVEF, %	54.8 ± 10.0	58.3 ± 8.1	-4.5 to -2.1	<0.001
CrCl, ml/min	86.3 ± 33.4	81.8 ± 27.2	0.7 to 8.3	0.021
SYNTAX score	22.1 ± 8.7	20.6 ± 6.4	0.5 to 2.5	0.025

Abbreviations: QFR, quantitative flow ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; MI, myocardial infarction; PVD, peripheral vascular disease; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme blocker; ARB, angiotensin II receptor blocker.

Supplementary Table 2. Baseline lesion and procedural characteristics of lesions and vessels.

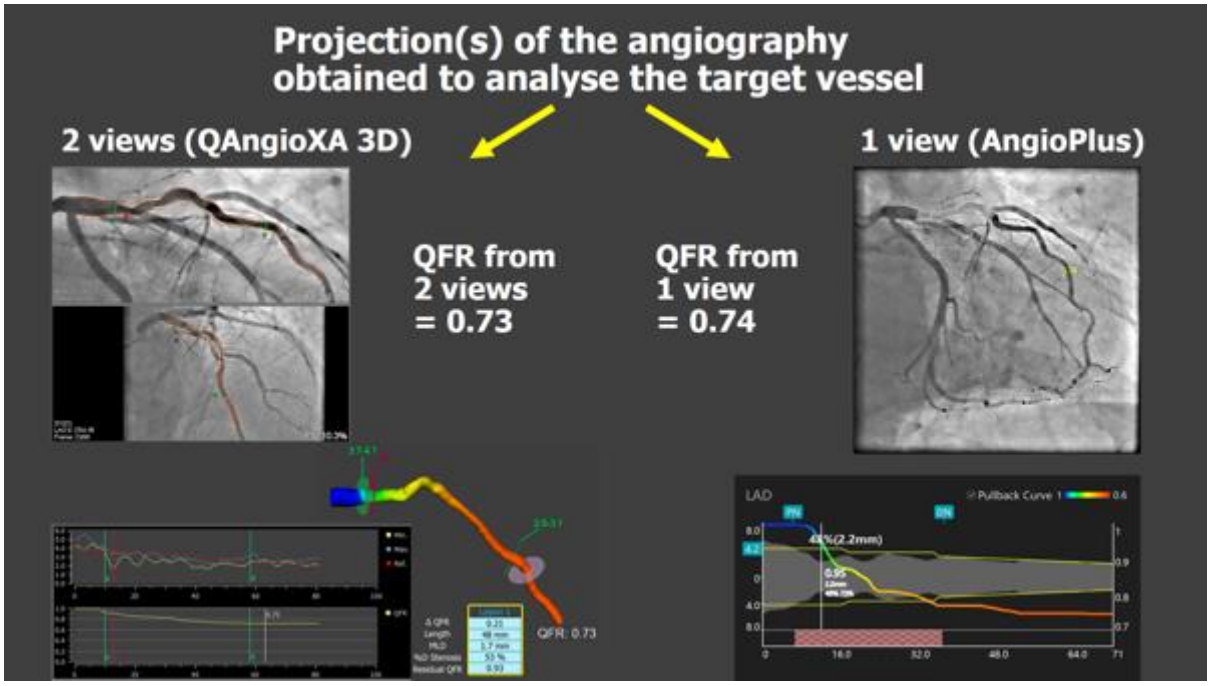
	Multivessel TALENT	***SYNTAX II***		
	N=1674	N=771	95% CI of the difference	P value
Lesion location				
RCA	436 (26.1%)	176 (22.8%)	-0.4% to 6.9%	0.066
LAD	716 (42.8%)	352 (45.7%)	-7.0% to 1.5%	0.199
LCX	519 (31.0%)	243 (31.5%)	-4.4% to 3.5%	0.828
Bifurcation	552 (37.1%)	257 (33.3%)	-4.3% to 3.7%	0.892
Total occlusion	77 (5.0%)	81 (10.5%)	-8.3% to -3.5%	<0.001
Lesion length >20mm	877 (59.2%)	323 (41.9%)	13.0% to 21.6%	<0.001
Heavy calc.	186 (12.6%)	115 (14.9%)	-5.3% to 0.7%	0.135
Diffuse disease	119 (10.7%)	66 (8.6%)	-0.6% to 4.8%	0.127
Intravascular imaging	1270 (85.8%)	615 (79.8%)	2.7% to 9.4%	<0.001
IVUS use	908 (61.3%)	615 (79.8%)	-22.2% to -14.7%	<0.001
OCT use	368 (24.8%)	NA		NA
Average stent number per vessel	1.6 ± 0.8	1.7 ± 0.9	-0.17 to -0.03	0.006
Average stent diameter (mm)	2.98 ± 1.14	NA		NA
Total stent length per vessel (mm)	39.3 ± 22.7	42.6 ± 24.2	-5.3 to -1.3	0.001
Pre-PCI QFR	0.60 ± 0.22	0.67 ± 0.18	-0.09 to -0.05	<0.001
Post-PCI QFR	0.93 ± 0.09	0.91 ± 0.07	0.01 to 0.03	<0.001
In-stent QFR	0.02 ± 0.04	0.02 ± 0.03	-0.003 to 0.003	1

Abbreviations: QFR, quantitative flow ratio; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumferential artery; LMT, left main trunk; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Supplementary Table 3. Paired pre- and post-PCI QFR is subdivided by the main branch.

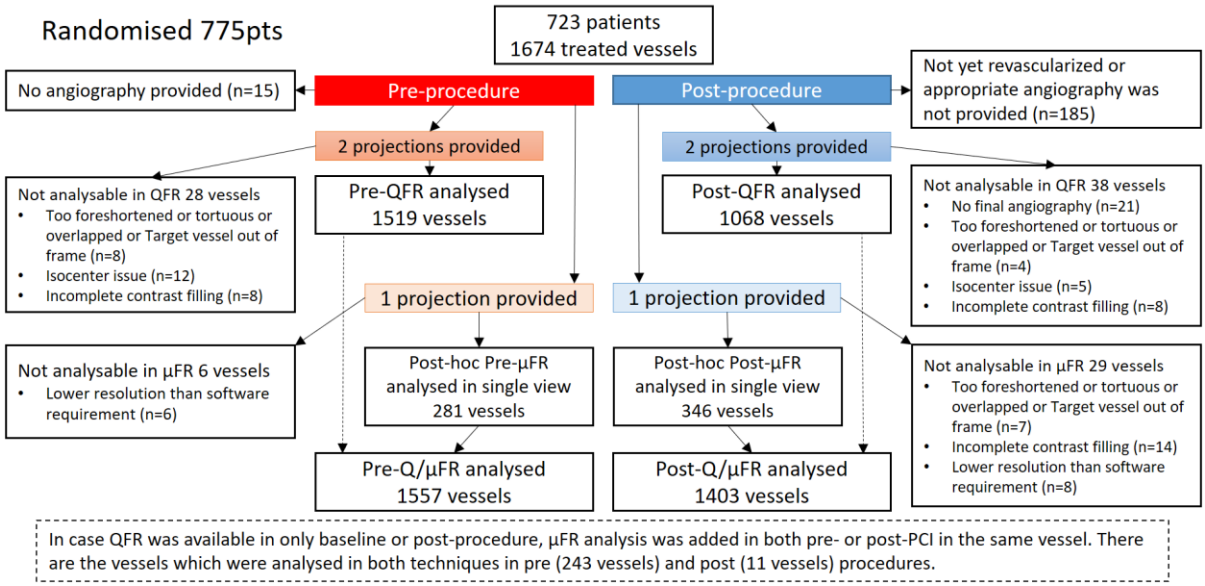
Lesion				
	RCA	LAD	LCX	P value
Number	345	591	436	
Pre QFR	0.58 ± 0.25	0.58 ± 0.22	0.66 ± 0.19	<0.001
Post QFR	0.94 ± 0.10	0.91 ± 0.09	0.95 ± 0.08	<0.001
Post QFR ≥ 0.91	281 (81.4%)	390 (66.0%)	379 (86.9%)	<0.001
Δ QFR	0.02 ± 0.11	0.02 ± 0.07	0.01 ± 0.02	0.131

Delta QFR is defined as post-QFR minus pre-QFR in the same vessel. For calculating delta QFR, 1372 vessels which could obtain paired pre- and post-QFR were presented in this table.
Abbreviations: RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumferential artery; QFR, quantitative flow ratio.



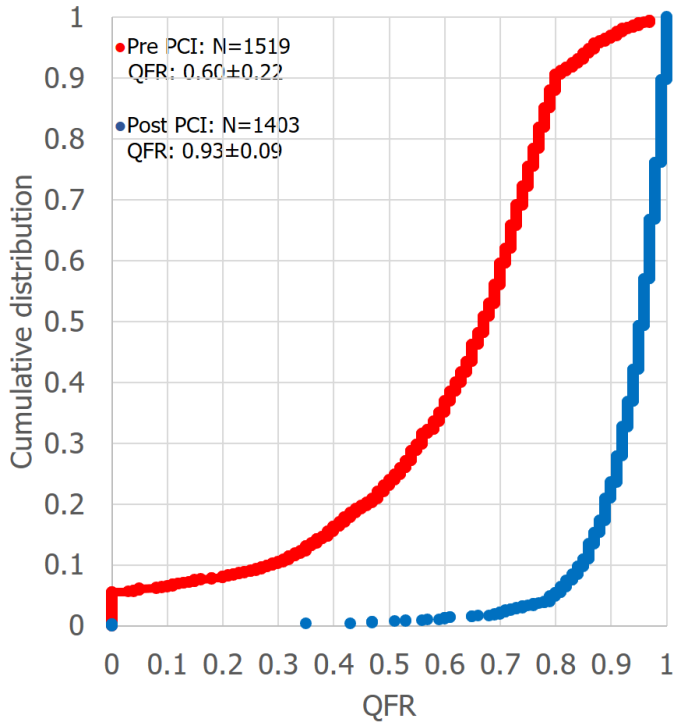
Supplementary Figure 1. QFR measurement.

QFR was mainly performed by QAngioXA 3D if the target vessel has 2 optimal views both in the baseline and just after procedure. In case only 1 view is available either baseline or procedure or both, QFR was analysed by AngioPlus. The cartoon shows the mock case to analyse the same vessel to show that 2 technologies should have the approximately same value, as we confirmed in the internal analysis of the Core lab.
Abbreviation: QFR, quantitative flow ratio.



Supplementary Figure 2. Flowchart of pre- and post-PCI QFR analysis.

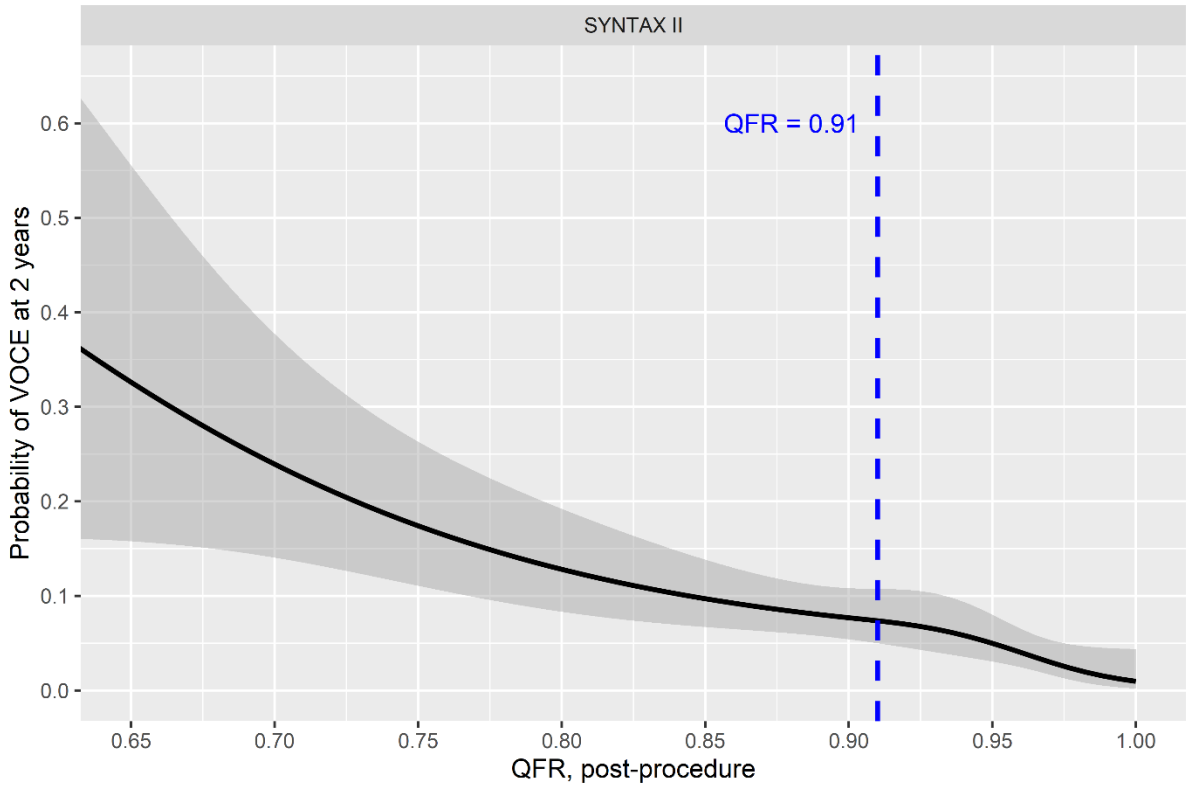
Abbreviation: QFR, quantitative flow ratio.



Supplementary Figure 3. Cumulative distributions of pre- and post-PCI QFR.

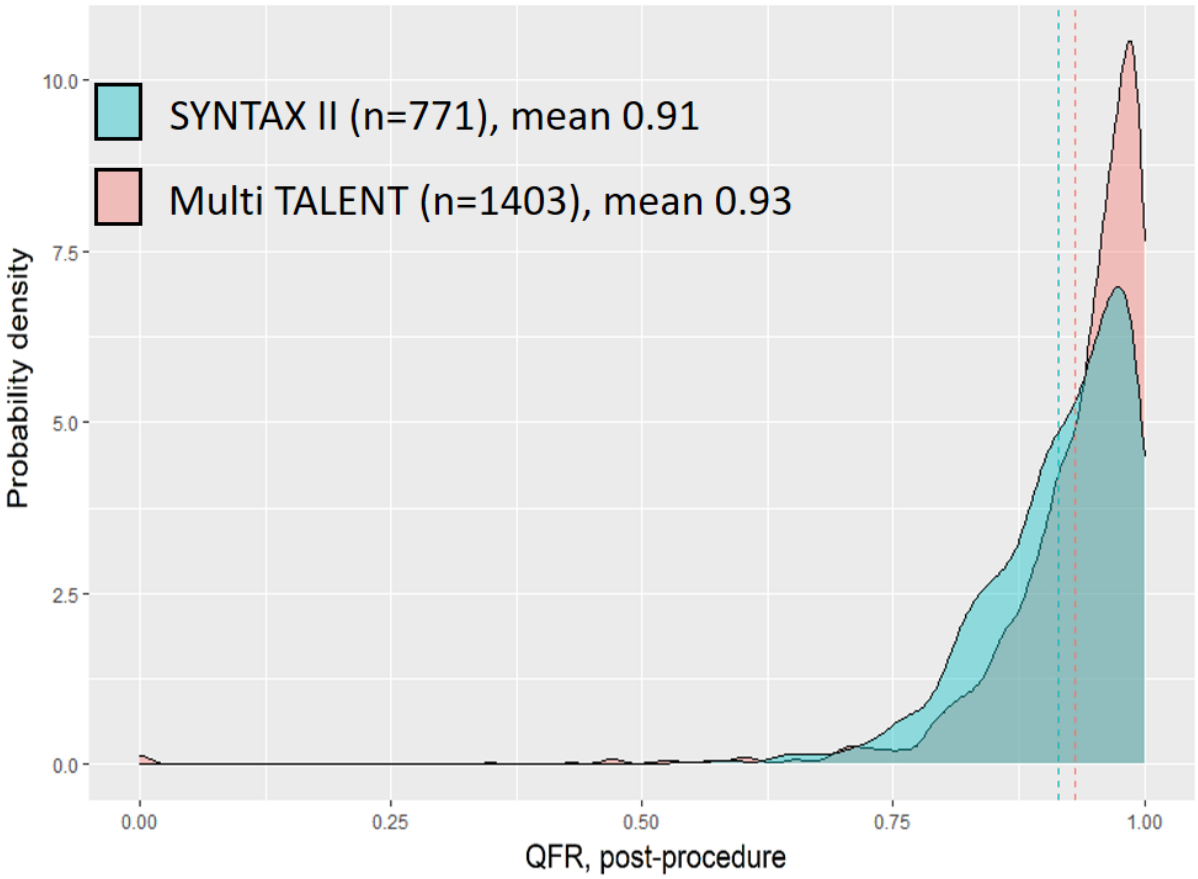
Red line shows pre-PCI QFR and blue line shows post-PCI QFR. Mean ± standard deviation of each value is presented on the left upper side.

Abbreviations: PCI, percutaneous coronary intervention; QFR, quantitative flow ratio.



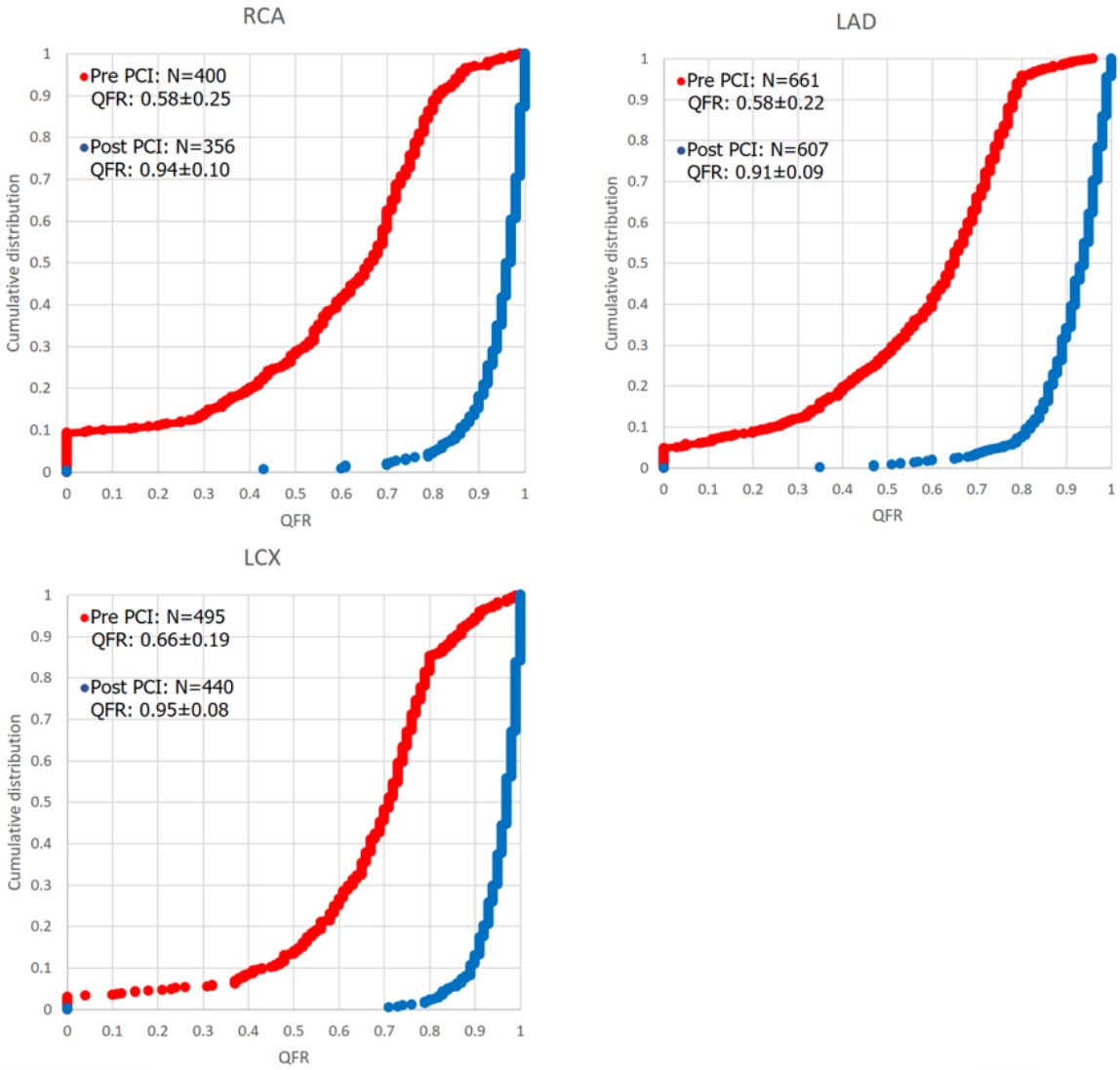
Supplementary Figure 4. Relationship between the probability of 2-year VOCE and post-procedure QFR in the SYNTAX II trial, as estimated using a logistic regression model with a restricted cubic spline.

Abbreviations: VOCE, vessel-oriented composite endpoint; QFR, quantitative flow ratio.



Supplementary Figure 5. Distributions of the available post-procedure QFR measurements in the SYNTAX II trial and Multivessel TALENT trial.

Distributions of the available post-procedure QFR measurements in post-procedure QFR measurements in the SYNTAX II trial (vessel number 771) and the initial half population randomised in Multivessel TALENT (vessel number 1372).
Abbreviation: PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; VOCE, vessel-oriented composite endpoint.



Supplementary Figure 6. Cumulative distributions of pre- and post-PCI QFR are subdivided by the main branch.

Relationship of pre- and post-PCI QFR divided by main vessels was presented. Red line shows pre-PCI QFR and blue line shows post-PCI QFR. Mean ± standard deviation of each value is presented on the left upper side.

Abbreviations: RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumferential artery; QFR, quantitative flow ratio.