White paper

# Clinical evidence for Caas vFFR – the FAST study series

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# List of abbreviations

| | |
|---|---|
| **AUC** | area under the curve |
| **CI** | confidence interval |
| **ECRI** | European Cardiovascular Research Institute |
| **FAST** | Fast Assessment of STenosis severity |
| **FFR** | fractional flow reserve |
| **IVUS** | intravascular ultrasound |
| **iwFR** | instantaneous wave-free ratio |
| **LMCA** | left main coronary artery |
| **MLA** | minimal lumen area |
| **NPV** | negative predictive value |
| **PCI** | percutaneous coronary intervention |
| **PPV** | positive predictive value |
| **QCA** | quantitative coronary analysis |
| **TVF** | target vessel failure |
| **vFFR** | vessel fractional flow reserve |

# Introduction

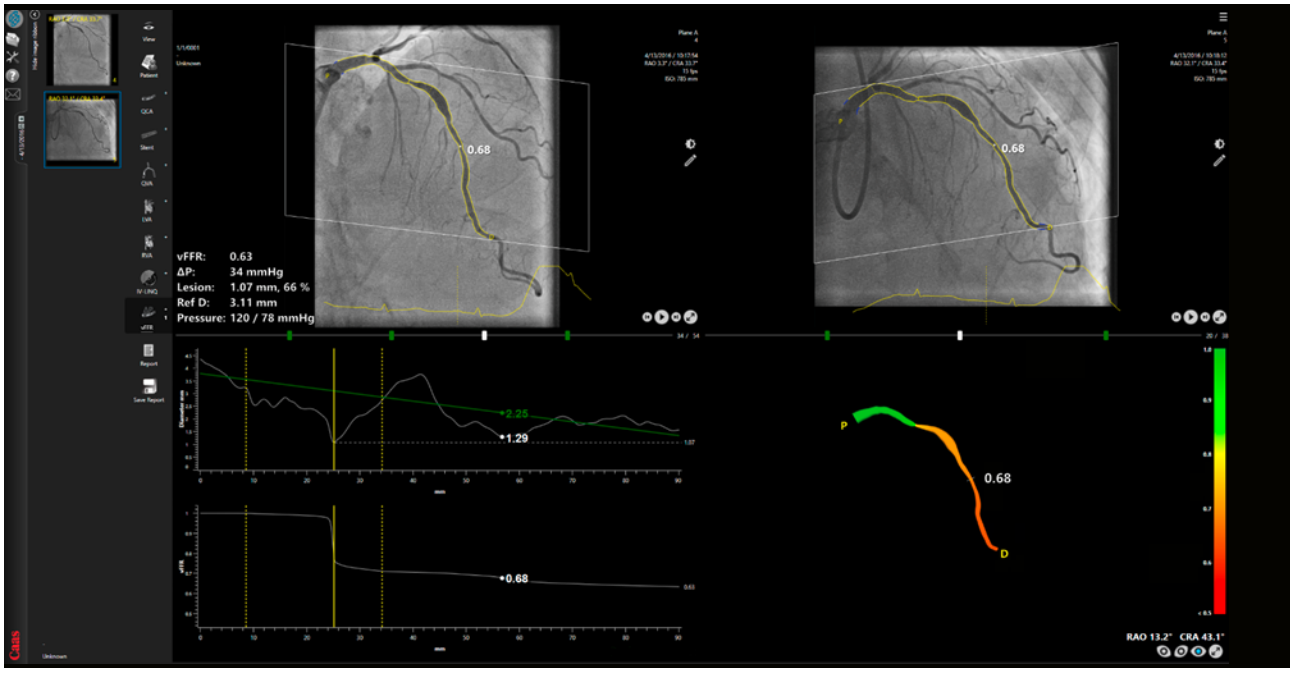
The superiority of physiology-guided revascularization over angiography-guided percutaneous coronary intervention (PCI) in intermediate coronary lesions is supported by a growing body of evidence. [1] Although functional assessment of a coronary stenosis using either pressure wire-based fractional flow reserve (FFR) or instantaneous wave-free ratio (iwFR) is recommended in the absence of a positive non-invasive ischemia test according to current guidelines, it is still underutilized in clinical practice. The limited clinical adoption might be the result of longer procedure and fluoroscopy times and additional costs associated with wire-based physiological lesion assessment, the invasive nature of the latter, or the administration of hyperemic agents with known side effects to the patients.

Some of the limitations can be addressed by angiography-derived technologies. In the past decade, several indices have been developed by different vendors and clinically validated. Vessel fractional flow reserve (vFFR) is one of these indices, available with Caas Workstation developed by Pie Medical Imaging (Maastricht, the Netherlands).

Caas vFFR software allows for calculation of the vFFR value from two angiographic views with at least 30 degrees difference in angulation to generate a 3D QCA, using the routinely invasively measured aortic root pressure as an input boundary condition.

Siemens Healthineers and Pie Medical Imaging have established a strong collaboration to address customers' unique preferences by providing flexibility concerning the utilization of vFFR in combination with angiography systems from Siemens Healthineers: On the one hand, Caas Workstation with vFFR, a software product that is fully compatible with all ARTIS systems, on the other, an integrated version of vFFR available with the QuantWeb application package on ARTIS icono (QuantWeb vFFR)*. This white paper summarizes the available literature substantiating the safety and effectiveness of vFFR for functional assessment of coronary stenoses. It also discusses ongoing trials that will help to further strengthen the body of evidence on the use of vFFR in the pursuit of a quicker and less stressful diagnosis, and lower-cost of diagnostic evaluation.

**Figure 1:** Commercially available software for angiography-based FFR: vFFR *with permission from Pie Medical Imaging B.V.*




* *syngo* Application Software required

# The FAST (Fast Assessment of STenosis severity) study series

The FAST study series is the body of evidence supporting the diagnostic performance of Caas vFFR led by the interventional team from Erasmus MC Rotterdam (Rotterdam, the Netherlands) headed by Dr. Joost Daemen. Their work started in 2018 to validate Caas vFFR and they have now covered various pre- and post-PCI physiology assessment scenarios in multiple retrospective and prospective studies.

## Pre-PCI scenarios

vFFR was first validated in the single-center **FAST I** study. In this retrospective analysis of a series of 100 patients presenting with stable angina or non-ST elevation myocardial infarction, in which FFR had been measured for intermediate coronary artery lesions with a pressure wire, the corresponding angiograms of these patients were used to calculate vFFR and to investigate the diagnostic performance of the software compared with pressure wire-based FFR. In the FAST I study, vFFR showed a strong linear correlation with FFR ($r = 0.89$, $p < .001$) and a high diagnostic accuracy (area under the curve (AUC) 0.93; 95% confidence interval (CI) 0.88 – 0.97) to detect a FFR ≤ 0.80. Also, a low interobserver variability was detected ($r = 0.95$, $p <. 001$). [2]

The **FAST EXTEND** study built on the results of FAST I, analyzing 294 patients. The study confirmed the findings of FAST I in a larger cohort of patients with a more severe and diverse lesion complexity. Specifically, vFFR showed excellent accuracy in predicting FFR ≤ 0.80 (AUC: 0.94; 95% CI 0.92 – 0.97) and a strong correlation with FFR in the overall cohort ($r = 0.89$), consistent in specific lesion subsets and in specific coronary arteries. [3]

The positive results from FAST I and FAST EXTEND were subsequently confirmed in the prospective observational multicenter **FAST II** study, covering a total of 334 patients at 6 sites in Italy, Germany, the U.S., Japan, the Netherlands, and France. FAST II demonstrated a good correlation between vFFR, as computed by either a blinded core lab or local site personnel, and pressure wire-based FFR ($r = 0.76$ and $r = 0.74$; $P < .001$, respectively). The study also showed excellent diagnostic accuracy of vFFR in identifying lesions with an invasive wire-based FFR ≤ 0.80 (AUC 0.93; 95% CI: 0.90 – 0.96; $p <. 001$), even in more complex lesions. This included bifurcations, tortuous and calcified lesions, and patients presenting with non-ST-elevation acute coronary syndrome. Positive predicted value (PPV), negative predicted value (NPV), and diagnostic accuracy were all 90%. Sensitivity and specificity were 81% and 95%, respectively. [4]

Moreover, as left main coronary artery (LMCA) lesions were underrepresented in the first validation studies, the feasibility of Caas vFFR was evaluated separately for this use case in the **FAST Left Main** study. FAST Left Main was designed as an observational single-center cohort study with a total of 256 patients, screened for eligibility to correlate vFFR values with intravascular ultrasound (IVUS) measurements of LMCA minimal lumen area (MLA), as recommended in the guidelines for LMCA assessment. The analysis showed a good correlation between vFFR and LMCA MLA ($r = 0.792$; $p < .001$) and good diagnostic accuracy of vFFR ≤ 0.8 in identifying lesions with MLA < 6.0 $mm^2$, considered the diagnostic equivalence to invasive FFR < 0.80 (sensitivity 98%, specificity 71.4%, AUC 0.95, 95% CI: 0.89 –1.00, $p = .001$). Compared with the IVUS MLA threshold of 6.0 $mm^2$ as a reference, a vFFR value of ≤ 0.83 had the highest sensitivity and specificity (91.8% and 85.7%, respectively). [5]

## Post-PCI scenarios

A growing body of evidence also supports the prognostic value of post-PCI physiological assessment after stent implantation and, therefore, the use of FFR to assess procedural success in terms of how well stent implantation restored blood flow in the respective target lesion. [6]

The observational, retrospective, single-center **FAST POST** cohort study included 100 FFR SEARCH registry patients with stable or non-ST-elevation myocardial infarction who underwent post-PCI FFR assessment. It further evaluated the diagnostic accuracy of vFFR to detect invasive FFR < 0.90 after stent implantation. Study results demonstrated a good linear correlation between post-PCI FFR and vFFR (r = 0.88; p<. 001), along with a low interobserver variability (r = 0.95; p<. 001). Moreover, vFFR had a higher accuracy in the identification of patients with FFR values < 0.90 (AUC 0.98, 95% CI: 0.96 – 1.00) as compared with 3D-QCA (AUC 0.62, 95% CI: 0.94 – 0.74). Sensitivity, specificity, PPV, and NPV were 80%, 97%, 94%, and 88%, respectively. [7]

In 2022, the five-year follow-up data for the **FAST Outcome** study investigating the prognostic value of vFFR on long-term vessel-related events was published. vFFR was carried out post-stenting in 748 patients (832 vessels) and related to the clinical outcome of these patients. Although, based on the present FAST Outcome data, it did not prove possible to extract a meaningful binary cut-off value of post-PCI vFFR to predict target vessel failure (TVF), the study demonstrated that lower post-PCI vFFR values are associated with a significantly increased risk of TVF and target vessel revascularization at five-year follow-up. [8]

# Outlook

The aforementioned studies demonstrated the feasibility and accuracy of vFFR in assessing the physiological impact of a coronary stenosis, both in pre-PCI use cases for diagnostic decision support and in a post-PCI context. However, dedicated prospective outcome data comparing vFFR to routine guideline recommended PCI including physiology assessment is needed to further drive the clinical adoption.

As such, the ongoing international, multicenter, randomized controlled **FAST III** trial (cinicaltrials.gov identifier: NCT04931771) aims to demonstrate the non-inferiority of a vFFR-guided revascularization strategy as compared with an FFR-guided PCI, both in terms of clinical outcomes and cost effectiveness. FAST III will include 2,228 patients at up to 40 sites in 7 European countries. The investigator-initiated trial is led by Dr. Joost Daemen from Erasmus MC Rotterdam, the Netherlands, and supported by the European Cardiovascular Research Institute (ECRI) as sponsor. Pie Medical Imaging and Siemens Healthineers are jointly funding this study to further strengthen the body of evidence for vFFR. [9]

In addition to the aforementioned studies, the **LIPSIA STRATEGY** trial (clinicaltrials.gov identifier: NCT03497637) is an ongoing German multicenter prospective trial at 7 sites enrolling 2,000 patients. Like FAST III, the trial aims to investigate a vFFR- vs FFR-guided revascularization strategy. The study is led by Prof. Holger Thiele from Leipzig Heart Centre, Germany.

The clinical community is eagerly awaiting the results of these two randomized clinical outcome trials, which will have a major impact on the introduction of angiography-derived FFR in general and vFFR in particular in clinical routine. The FAST III and LIPSIA STRATEGY trials are expected to be completed in 2025 and 2026, respectively.

# References


**[1]** Sanz Sánchez J, Farjat Pasos J, Martinez Solé J, Hussain B, Kumar S, Garg M, et al. Fractional flow reserve use in coronary artery revascularization: A systematic review and meta-analysis. iScience. 2023 Jul 3;26(8):107245. doi: 10.1016/j.isci.2023.107245. eCollection 2023 Aug 18.

**[2]** Masdjedi K, van Zandvoort L, Balbi M, Gijsen F, Ligthart J, Rutten M, et al. Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study. EuroIntervention. 2020 Sep 18;16(7):591-599. doi: 10.4244/EIJ-D-19-00466.

**[3]** Neleman T, Masdjedi K, van Zandvoort L, Tomaniak M, Ligthart J, Witberg K, et al. Extended Validation of Novel 3D Quantitative Coronary Angiography-Based Software to Calculate vFFR: The FAST EXTEND Study. JACC Cardiovasc Imaging. 2021 Feb;14(2):504-506. doi: 10.1016/j.jcmg.2020.08.006. Epub 2020 Sep 30.

**[4]** Masdjedi K, Tanaka N, van Belle E, Porouchani S, Linke A, Woitek F, et al. Vessel fractional flow reserve (vFFR) for the assessment of stenosis severity: the FAST II study. EuroIntervention. 2022 Apr 22; 17(18):1498-1505. doi: 10.4244/EIJ-D-21-00471.

**[5]** Tomaniak M, Masdjedi K, van Zandvoort L, Neleman T, Tovar Forero M, Vermaire A, et al. Correlation between 3D-QCA based FFR and quantitative lumen assessment by IVUS for left main coronary artery stenoses. Catheter Cardiovasc Interv. 2021 Mar;97(4):E495-E501. doi: 10.1002/ccd.29151. Epub 2020 Jul 29.

**[6]** Hwang D, Koo B-K, Zhang J, Park J, Yang S, Kim M, et al. Prognostic Implications of Fractional Flow Reserve After Coronary Stenting: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Sep 1;5(9):e2232842. doi: 10.1001/jamanetworkopen.2022.32842.

**[7]** Masdjedi K, van Zandvoort L, Balbi M, Nuis R-J, Wilschut J, Diletti R, et al. Validation of novel 3-dimensional quantitative coronary angiography based software to calculate fractional flow reserve post stenting. Catheter Cardiovasc Interv. 2021 Oct;98(4):671-677. doi: 10.1002/ccd.29311. Epub 2020 Oct 6.

**[8]** Neleman T, Scoccia A, Masdjedi K, Tomaniak M, Ligthart J, Witberg K, et al. The prognostic value of angiography-based vessel fractional flow reserve after percutaneous coronary intervention: The FAST Outcome study. Int J Cardiol. 2022 Jul 15:359:14-19. doi: 10.1016/j.ijcard.2022.04.021. Epub 2022 Apr 11.

**[9]** Scoccia A, Byrne R, Banning A, Landmesser U, van Belle E, Amat-Santos I, et al. Fractional flow reserve or 3D-quantitative-coronary-angiography based vessel-FFR guided revascularization. Rationale and study design of the prospective randomized FAST III trial. Am Heart J. 2023 Jun:260:1-8. doi: 10.1016/j.ahj.2023.02.003. Epub 2023 Feb 14.

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