Review Article

Angiographic quantitative flow ratio in acute coronary syndrome: beyond a tool to define ischemia-causing stenosis—a literature review

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Background and Objective: Numerous studies have demonstrated the safety and effectiveness of physiology-guided coronary revascularization in chronic coronary syndrome, resulting in a high level of guideline recommendation for these patients. However, the application of coronary physiology in acute coronary syndrome (ACS), especially in the acute phase of myocardial infarction, remains challenging. Over the last decade, the number of novel physiological indices derived from the computation of angiography have been developed as alternatives to pressure wire-based fractional flow reserve. Among these angiography-based indices, the quantitative flow ratio (QFR) is undoubtedly the one with the largest amount of data cumulated so far. In this article, we aim to review the related studies that describe efforts to investigate the diagnostic role of QFR and discuss perspectives for its current and future applications in the setting of the ACS.

Methods: A literature search was performed on the electronic databases, including PubMed, Google Scholar and Web of Science covering publications in English up to May 2022.

Key Content and Findings: An emerging body of evidence has validated the diagnostic accuracy of angiography-derived QFR for the assessment of functional severity of coronary stenosis in both acute and chronic coronary syndromes. In parallel, multiple technologies, i.e., QFR-based pullback pressure gradient index, angiography-derived index of microcirculatory resistance and intravascular imaging-based morphofunctional evaluation methods, have been proposed, allowing operators to easily obtained physiological data of micro and macro-circulation, together with atherosclerotic lesion characteristics in catheterization laboratories. More recently, promising results supporting the clinical value of QFR in guiding revascularization and predicting outcomes for ACS patients have been published.

Conclusions: Angiography-based QFR bears the potential of a wider adoption of coronary physiology assessment in the ACS setting due to its quicker and less-invasive nature. However, the current evidence mainly derived from retrospective studies or post-hoc analyses of prospective trials. Future studies are needed to further explore the benefits of QFR-guided revascularization on outcomes in ACS.

Keywords: Coronary physiology; quantitative flow ratio; percutaneous coronary intervention; acute coronary syndrome; narrative review

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Introduction

Given improving clinical outcomes with physiology-guided percutaneous coronary intervention (PCI), international guidelines recommend the use of fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) for identifying ischemia-causing stenoses requiring revascularization (1,2). However, despite a large body of supporting evidence, the adoption of the conventional physiological assessment is limited in daily practice due to a series of concerns, including increased procedural time and cost, the need for invasive pressure wire advancement and the need to induce hyperemia with adenosine injection (3,4). To overcome these limitations, different physiology techniques derived from the computation of coronary angiography have been developed by multiple groups (5-8), potentially providing new opportunities for wide adoption in the catheterization laboratory. Among these angiography-based simulators to wire-based FFR, quantitative flow ratio (QFR) is currently the one with the largest amount of supporting clinical evidence (6,9-11).

Nevertheless, the well-established coronary physiological approaches of assessing lesion severity and for guiding revascularization in patients with chronic coronary syndrome (CCS) have not been extrapolated to the context of acute coronary syndrome (ACS) (2,12,13). An early PCI of the culprit vessel to restore myocardial perfusion is the current standard of care for patients presenting with ST-segment elevation myocardial infarction (STEMI) (13), or for those with high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (14). Under these circumstances, it appears unnecessary for the functional assessment of the culprit lesion before interventional treatment, along with the evidence showing that hemodynamic severity of the infarcted-related artery (IRA) evaluated by FFR or QFR at the acute phase of myocardial infarction (MI) may be underestimated due to the presence of microvascular dysfunction (15,16). However, for culprit vessels after stent implantation in ACS, recent studies have revealed the prognostic value of QFR in predicting long-term adverse cardiac outcomes (16,17). In addition, around half of acute myocardial infarction (AMI) patients have multivessel disease (MVD), with angiographically significant stenoses located in non-culprit vessels (18). Multiple clinical trials robustly demonstrated that complete revascularization with PCI of non-culprit lesions (NCLs) under the guidance of coronary angiography or physiology improves outcomes in patients with STEMI and MVD (19-21). Therefore, further application of coronary physiology in ACS patients has been attempted, and angiography-derived QFR, due to its less-invasive nature, may extend the benefits of physiological assessment for this high-risk subset of CAD patients.

ACS represents a broad spectrum of CAD, including patients with STEMI as well as non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina. As more sensitive cardiac-specific troponin measurements have been widely used, the detection of MI appeared to increase, while the diagnosis of unstable angina showed a reciprocal decrease (14,22). Hence, this review article will summarize the available data of angiographic QFR in different clinical scenarios of ACS, mainly focusing on the acute phase of MI, providing insights toward diagnostic accuracy of QFR for the functional assessment of non-culprit vessels and clinical implications of QFR-derived physiological parameters. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-334/rc).

Methods

A literature search was performed on the electronic databases, including PubMed, Google Scholar and Web of Science covering publications up to May 2022. The relevant guidelines and original articles published in English language were included. We present the detail of our search strategy in *Table 1*.

Diagnostic performance of QFR: from CCS to ACS

The concept and validation of QFR in CCS

The three key steps in computational estimation of coronary physiology are reconstruction of geometric models from coronary images, applying hemodynamic boundary conditions and selecting fluid dynamics solutions (23). QFR is a well-established approach enabling rapid computation of FFR based on coronary angiography. For QFR computation, geometric model of coronary tree is reconstructed in 3-dimensional (3D) from paired two angiographic projections at least 25° apart. The coronary flow is estimated by frame count-based flow velocity and the pressure drop is calculated based on fluid dynamic equations (6,9). The FAVOR (Functional Assessment by Various Flow Reconstructions) pilot study (6) was the first to show the feasibility and diagnostic accuracy of QFR in identifying flow-limiting

Table 1 Summary of the literature search strategy

Items	Description
Date of search	June 2022
Databases searched	PubMed, Google Scholar and Web of Science
Search terms used (including MeSH and free text search terms and filters)	fractional flow reserve, FFR, quantitative flow ratio, acute coronary syndrome, ACS, acute myocardial infarction, STEMI, myocardial infarction, index of microcirculatory resistance, pullback pressure gradient index, intravascular ultrasound, optical coherence tomography
Timeframe	Up to May 2022
Inclusion and exclusion criteria	All relevant reviews and original articles with focus on the QFR in the setting of ACS and all articles had to be published in English language
Selection process	The search was conducted independently by JC, HL and DY; data selection is the intersection of the search of these three authors

FFR, fractional flow reserve; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; QFR, quantitative flow ratio.

stenosis in core-lab setting. Notably, QFR was calculated using 3 flow models based on the different hyperemic flow velocities in this study. Fixed-flow QFR (fQFR) is calculated based on the population-averaged fixed empiric hyperemic flow velocity of 0.35 m/s. Adenosine-flow QFR (aQFR) and contrast-flowed QFR (cQFR) are acquired using TIMI frame count on coronary angiography during the setting with and without drug-induced hyperemia, respectively. All three QFR approaches showed good diagnostic accuracy in identifying functionally significant lesions. Importantly, cQFR, which was computed without pharmacologically induced hyperemia, showed no significant difference in predicting FFR compared with aQFR, resulting in a wide adoption of the cQFR model in subsequent validation studies and current practice.

Similar results were observed in three major prospective validations (9-11), as summarized in *Table 2* (6,9-11,24,25). Overall, in all three trials, QFR has a high area under of the curve (AUC) for predicting an FFR ≤0.80, ranging from 0.85 for WIFI II (Wire-Free Functional Imaging II) trial (11), to 0.92 and 0.96 for FAVOR II Europe-Japan (10) and FAVOR II China study (9), respectively. Furthermore, the measurement time of online QFR was significantly shorter than FFR [5.0 minutes (3.5–6.1) *vs.* 7.0 minutes (5.0–10.0)] (10). An individual patient-level meta-analysis, which included 819 patients with 969 analyzable vessels from the aforementioned four prospective trials, revealed that the diagnostic performance of QFR was 84% sensitivity, 88% specificity, a positive predictive value of 80%, and a negative predictive value of 95% (24) (*Table 2*). Notably, these early validation studies mainly focused on selected patients with stable clinical scenarios and intermediate lesions, and those who presented with MI at the acute phase were ineligible for inclusion (9-11). Although FAVOR II China and FAVOR II Europe-Japan studies included patients scheduled for secondary evaluation of NCLs after 72 hours of primary PCI, only 14 of the 308 patients and 6 of the 272 patients, respectively, presenting with AMI entered the final analysis, limiting its validity in ACS setting (9,10).

Validation studies of QFR in ACS

As mentioned previously, the use of invasive FFR in the acute setting of MI is inconvenient due to several inherent limitations. From a practical standpoint, angiography-derived QFR, which can be easily obtained during or after primary PCI with no requirement for additional invasive procedures or administration of coronary vasodilators that carry side effects, may offer an attractive alternative for this unmet clinical need. Furthermore, QFR, as a research tool, can be computed both offline and online, allowing clinicians to wildly review available angiograms from a functional perspective. With these advantages, accumulating studies have investigated the diagnostic value of QFR for the functional assessment of NCL in ACS (*Table 3*) (26-35).

Spitaleri *et al.* (26), for the first time, validated the role of QFR in identifying flow-limiting NCL in patients with STEMI and MVD. The researchers found, based on two independent cohorts consisting of 34 and 49 NCLs, that QFR values showed excellent reproducibility between the timing of index and staged procedures, and had a good diagnostic accuracy with FFR measurement as standard reference. This was further supported by multiple

Table 2 Diagnostic performance of QFR in patients from prospective studies

Trial	FAVOR Pilot (6)	FAVOR II China (9)	FAVOR II E-J (10)	WIFI II (11)	Meta-analysis (24)	μQFR study (25)
Year	2016	2017	2018	2018	2019	2021
No. of patients	73	308	272	172	819	306
No. of vessels	84	332	317	255	969	330
Population					Patients from FAVOR Piolt/II China/E-J and WIFI II	Patients from FAVOR II China
Stable CAD	100%	22.4%	98%	100%		
UA		66.5%	NA			
AMI		4.5%	2%			
Diameter stenosis	46.1±8.9%	46.5±11.3%	45±10%	50±12%	44.8±12.6%	NA
Simulators	cQFR	cQFR	cQFR	cQFR	cQFR	μQFR
Company	Medis Medical	Pulse Medical	Medis Medical	Medis Medical	Medis & Pulse	Pulse Medical
Analysis time (min)	NA	4.36±2.55	5.0 (3.5–6.1)	NA	NA	1.1±0.4
Mean FFR	0.84±0.08	0.82±0.12	0.83±0.09	0.82±0.11	0.83±0.10	0.82±0.12
FFR ≤0.80	32%	34%	33%	36%	35%	36%
AUC	0.92 (0.85–0.97)	0.96 (0.94–0.98)	0.92 (0.89–0.96)	0.86 (0.81–0.91)	0.92 (0.90–0.95)	0.97 (0.95–0.99)
Accuracy, %	86 [78–93]	93 [89–95]	87 [NA]	83 [NA]	87 [85–89]	93 [90–96]
Sensitivity, %	74 [54–89]	95 [89–98]	87 [78–92]	77 [66–85]	84 [77–90]	88 [80–93]
Specificity, %	91 [81–97]	92 [87–95]	87 [82–91]	86 [79–91]	88 [84–91]	96 [93–98]
PPV, %	80 [59–93]	86 [78–91]	76 [68–84]	75 [65–84]	80 [76–85]	93 [87–97]
NPV, %	88 [77–95]	97 [94–99]	93 [89–96]	87 [80–92]	95 [93–96]	93 [89–96]

Data are expressed as mean ± SD, median (25th, 75th percentiles), or n%. CAD, coronary artery disease; UA, unstable angina; AMI, acute myocardial infarction; AUC, area under of the curve; PPV, positive predictive value; NPV, negative predictive value; FFR, fractional flow reserve; QFR, quantitative flow ratio; cQFR, contrast-flow QFR; μQFR, Murray law-based QFR; NA, no acquired.

prospective trials (27,28) or retrospective observational studies (29,30). An iSTEMI substudy (27) compared the diagnostic performance of acute QFR in 70 NCLs with staged (median 13 days after primary PCI) QFR, iFR and FFR, and reported a moderate to excellent classification agreement, varying from 74% [95% confidence interval (CI): 65–83%] for staged iFR, 84% (95% CI: 76–90%) for staged FFR to 93% (95% CI: 87–99%) for staged QFR. In patients with NSTEMI undergoing primary PCI, QFR also displayed an excellent diagnostic correlation with FFR [AUC 0.964 (95% CI: 0.903–0.974)], which is equivalent to the accuracy of non-hyperemic pressure ratios (28). Recently, two large observational studies (29,30) with the inclusion of both STEMI and NSTE-ACS patients, further proved the feasibility and effectiveness of QFR analysis derived from acute angiograms to assess the hemodynamic relevance of NCLs, as judged by staged QFR (29) or planned standard ischemia testing (30) including invasive FFR, non-invasive stress cardiac magnetic resonance imaging (CMR) and single-photon emission computed tomography. Moreover, Dettori *et al.* (36) recently revealed that QFR in NCLs of patients with previous MI exhibited a good diagnostic value for determining not only the presence, but also the extent and severity of myocardial ischemia assessed by staged CMR.

Interestingly, the diagnostic accuracy and AUC of QFR derived in ACS patients from the studies above were numerically similar to those reported in studies focusing on stable patients (9,11). In order to directly compare the QFR diagnostic value in different clinical scenarios, Lauri *et al.* (31) retrospectively investigated 82 patients (91 NCLs) with STEMI and a propensity matched group of 69 stable angina patients (91 target vessels). It was shown that QFR applied to NCL during primary PCI had a comparable

Table 3 Diagnostic performance of QFR for functional assessment of non-culprit lesions in ACS

First author, year	Population	No. of patients [vessels]	Reference	Staged time*	AUC	Accuracy %	Sensitivity %	Specificity %	PPV %	NPV %
Acute coronary syndrome										
Spitaleri 2018 (26)	STEMI	45 [49]	Index FFR	–	0.96	94	88	97	94	94
Sejr-Hansen 2019 (27)	STEMI	NA [70]	Staged QFR	13 days	NA	93	92	94	94	94
			Staged FFR	13 days	0.89	84	83	84	81	96
			Staged iFR	13 days	0.81	74	73	74	69	78
Tebaldi 2020 (28)	NSTEMI	116 [184]	Index FFR	–	0.96	88	72	94	81	90
Erbay 2021 (29)	ACS	321 [513]	Staged QFR	49 days	NA	94	95	94	91	97
Milzi 2021 (30)	AMI	220 [280]	Staged FFR, stress CMR or SPECT	Within 6 months	0.89	NA	84	86	NA	NA
All-comers										
Lauri 2019 (31)	STEMI	82 [91]	Staged FFR	8 days	0.91	84	80	86	78	87
	SA	69 [91]	FFR	–	0.94	89	87	90	90	90
Choi 2020 (32)	All-comers	452 [559]	FFR	–	0.95	91	92	87	87	95
	ACS	117 [153]	Index FFR	–	0.95	91	90	85	85	94
	Stable CAD	335 [446]	FFR	–	0.96	92	96	89	89	96
Kirigaya 2021 (33)	STEMI	50 [65]	Staged QFR	14 days	0.97	92	89	95	92	92
	Stable CAD	77 [95]	FFR	–	0.88	85	80	91	91	80
Lee 2021 (34)	All-comers	915 [1,077]	FFR	–	0.98	96	94	96	94	96
	AMI	103 [132]	FFR	NA	0.97	92	93	92	93	92
	Angina	812 [945]	FFR	–	0.98	96	94	97	94	97
Hwang 2019 (35)	AMI	82 [105]	FFR	NA	0.97	93	96	91	91	96
	Stable CAD	182 [253]	FFR	–	0.95	90	90	90	83	94

*, staged time indicated the time between secondary procedures in nonculprit arteries and index procedures in culprit lesions. AUC, area under of the curve; PPV, positive predictive value; NPV, negative predictive value; STEMI, ST-segment elevation myocardial infarction; SA, stable angina; NSTEMI, non-ST-segment elevation myocardial infarction; CAD, coronary artery disease; ACS, acute coronary syndrome; AMI, acute myocardial infarction; FFR, fractional flow reserve; QFR, quantitative flow ratio; iFR, instantaneous wave-free ratio; CMR, cardiac magnetic resonance; SPECT, single-photon emission computed tomography; NA, no acquired.

diagnostic performance compared with the stable CAD group [AUC 0.91 (0.85–0.97) *vs.* 0.94 (0.89–0.99), P=0.499], using staged FFR as the reference standard. Similar results were reported in several real-world studies among all-comer patients with CAD (32-34), showing that high diagnostic accuracy and agreement of QFR to predict FFR regardless of various clinical settings including acute STEMI (32-34), NSTE-ACS (32,34) or prior MI (32,37). In another study by Hwang *et al.* (35), QFR showed an excellent correlation (r=0.863 with FFR *vs.* 0.740 with iFR) and discrimination (AUC =0.953 with FFR *vs.* 0.880 with iFR) with respect to both FFR and iFR in patients with SCAD or AMI. However, the diagnostic performance of QFR was better when using FFR as the reference standard, probably because the simulated coronary flow model of QFR was originally proposed to mimic FFR.

Limitations and pitfalls of QFR measurement in ACS

Although accumulating favorable data have been released on the feasibility and effectiveness of QFR when applied to an ACS setting, several potential limitations and pitfalls

should be noted in practice. First, the current evidence from the validation studies might not extrapolated to the overall group of ACS patients, i.e., the patients with hemodynamic instability requiring vasopressors or assist devices. In addition, not all the vessels were interrogated for the enrolled patients. QFR was not assessed in IRA because primary PCI of such vessels guided by angiography was still the standard treatment (13,14). As there is general agreement that coronary physiology should be applied to intermediate lesions with diameter stenosis (DS) of 30% to 90%, studies regarding QFR adoption in ACS applied similar criteria of lesion selection (27,35). Technically, the feasibility and diagnostic accuracy of QFR, as an angiography-derived method, depends on the quality of images. Despite using optimal images and projections, severe vessel overlapping, tortuosity or ostial disease in main vessels remains challenging for the QFR computations. Encouragingly, Murray law-based QFR (μQFR) (25), the next generation of QFR, was developed to calculate FFR from a single angiographic view, and showed a comparable diagnostic performance with the existing QFR required two angiographic projections (*Table 1*). This would, to some extent, optimize the process of QFR computation and enable wider accessibility of physiological assessment in some circumstances.

As the high incidence of severe coronary microvascular dysfunction (CMD) in the acute phase of MI, there has been concern about the utility of functional assessment in this clinical situation (38). Mejía-Rentería *et al.* (39) found that QFR showed lower diagnostic performance in patients with CMD, as assessed by index of microcirculatory resistance (IMR). In this study, the proportion of ACS was 30%, and NCLs were investigated. In the context of STEMI after PCI of culprit and non-culprit lesions, Tang *et al.* (16) found that post-PCI QFR value at index procedure was significantly decreased at the staged PCI in CMD group (0.940±0.088 *vs.* 0.928±0.094, P<0.001), while no statistical difference was found in patients without CMD (0.916±0.107 *vs.* 0.918±0.099, P=0.64). Future prospective trials are needed to explore the effect of microvascular circulation on the behavior of QFR accuracy using integrated physiological modalities, such as coronary flow reserve and CMR. Lastly, the diagnostic accuracy of NCL using QFR during ACS decreased close to the FFR cutoff of 0.80 (31), in line with the results observed in stable CAD patients (11). To maximize the accuracy of QFR, some researchers proposed a hybrid QFR-FFR approach, in which invasive FFR testing is only performed for lesions with QFR value within the "grey zone" (between 0.75 and 0.85) (29,31,40). Although the boundaries of QFR "grey zone" are not well defined, this hybrid strategy may provide useful information for clinical decision making with a substantial impact on patient's comfort and cost-effectiveness.

Prognostic implications of QFR in ACS

The majority of the related evidence regarding the clinical significance of coronary physiology in ACS is derived from population presented with STEMI and MVD. A number of randomized controlled trials (RCTs) (19,41-43) and meta-analyses (44,45) have shown a reduction in major adverse cardiovascular events (MACE) with complete revascularization compared with the strategy of IRA-only PCI for STEMI patients. Accordingly, the latest American College of Cardiology and the American Heart Association guidelines on myocardial revascularization listed a class IA recommendation for PCI of NCLs, either guided by FFR or angiography, among STEMI patients with hemodynamically stable condition (2). Moreover, Strong evidence favoring the use of FFR in comparison to angiography revascularization has been gained from stable CAD (46,47). Of importance, intermediate stenoses, which may benefit from functional assessment, account for around 70% of coronary lesions located in non-culprit vessels in ACS (18,48). For these reasons, completeness of revascularization guided by coronary physiology in ACS patients has been attempted. However, the recent FLOWER-MI (Flow Evaluation to Guide Revascularization in Multi-Vessel ST-Elevation Myocardial Infarction) trial showed that FFR-guided PCI was not superior on both clinical and economic endpoints compared to angiography-guided PCI in STEMI, although the statistical power was inadequate and follow-up limited to a 1-year duration (21,49). Whether benefits can be achieved using physiological approaches among ACS patients remains controversial. In this section, we will discuss the clinical implications of QFR assessment before and after the procedure in ACS.

Prognostic value of QFR measurement in ACS

The recently published studies focusing on the prognostic value of QFR in patients with ACS are presented in *Table 4* (16,17,32,50-57). A study by Choi *et al.* (32) enrolling 452 all-comer patients with CAD (25.9% with ACS) demonstrated that vessels with QFR ≤0.80 showed a significantly higher risk of vessel-related adverse events

Table 4 Prognostic implications of QFR in patients with ACS

First author, year	Population	Primary endpoint	Comparison	No. of patients [vessels]	Result
Pre-interventional QFR					
Erbay 2021 (17)	Patients with ACS after primary PCI	2-yr POCE (death, nonfatal MI, IDR)	Nonculprit vessels with QFR ≤0.85 *vs.* >0.85	792 [1,231]	23.0% *vs.* 2.2%, P<0.001
Choi 2021 (32)	All-comer patients with ≥1 intermediate stenoses (25.9% with ACS)	2-yr VOCE (vessel-related cardiac death, MI, ischemia-driven TLR)	Vessels with QFR ≤0.80 *vs.* QFR >0.80	452 [599]	4.2% *vs.* 0.9%, P=0.022
Zhang 2021 (50)	All-comer patients underwent angiography-guided PCI (82.7% with ACS)	2-yr POCE (death, any MI, IDR)	QFR-consistent *vs.* QFR-inconsistent treatment group	1391 [2,543]	8.4% *vs.* 14.7%, P<0.001
Bär 2021 (51)	Patients with STEMI ≥1 untreated non-target vessel after angiography-guided CR	5-yr POCE (cardiac death, spontaneous non-TV-MI, non-TVR)	Patients with QFR ≤0.80 *vs.* QFR >0.80	617 [946]	62.9% *vs.* 12.5%, P<0.001
Zhang 2021 (52)	Patients with STEMI and multivessel disease	1-yr POCE (death, nonfatal MI, IDR)	QFR-guided functional CR *vs.* IRA-only group	229 [NA]	9.6% *vs.* 20.1, P=0.025
Post-interventional QFR					
Tang 2021 (16)	Patients with STEMI and multivessel disease	2-yr VOCE (vessel-related cardiac death, MI, TVR)	Vessels with post-PCI QFR ≤0.91 *vs.* >0.91	186 [415]	20.8% *vs.* 5.7%, P<0.001
Erbay 2021 (17)	Patients with ACS after primary PCI	2-yr POCE (death, nonfatal MI, IDR)	Post-PCI culprit vessels with QFR ≤0.89 *vs.* >0.89	792 [792]	25.6% *vs.* 4.8%, P<0.001
Kogame 2019 (53)	Stable CAD Patients with 3 vessel disease	2-yr VOCE (vessel-related cardiac death, MI, TVR)	Vessels with post-PCI QFR <0.91 *vs.* ≥0.91	393 [771]	12.0% *vs.* 3.7%, P<0.001
Biscaglia 2019 (54)	Patients with stable CAD or NSTE-ACS	2-yr VOCE (vessel-related cardiac death, MI, IDR)	Vessels with post-PCI QFR ≤0.89 *vs.* >0.89	602 [751]	25% *vs.* 3.5%, P<0.001
QFR-derived functional SYNTAX score					
Spitaleri 2018 (26)	Patients with STEMI with ≥1 untreated non-culprit lesion	5-yr POCE (death, any MI, any revascularization)	Functional IR *vs.* functional CR guided by QFR-derived residual FSS	110 [NA]	46% *vs.* 24%, P=0.01
Asano 2019 (55)	All-comer patients with de novo 3 vessel disease (excluded left main disease)	2-yr POCE (death, any MI, any revascularization)	low-risk *vs.* intermediate-risk *vs.* high-risk group classified by QFR-derived FSS	386 [836 lesions]	3.7% *vs.* 11.0% *vs.* 19.0%, P=0.05
Zhang 2020 (56)	Patients with left main or multivessel disease (56.6% with UA and 28.3% with AMI)	2-yr POCE (death, any MI, IDR)	low-risk *vs.* intermediate-risk *vs.* high-risk group classified by QFR-derived FSS	607 [NA]	9.1% *vs.* 13.5% *vs.* 22.3%, P=0.0004
Tang 2020 (57)	Patients with STEMI with ≥1 non-culprit lesion after successful PCI of culprit lesion	2-yr POCE (death, any MI, IDR)	Functional IR *vs.* functional CR guided by QFR-derived residual FSS	354 [NA]	22.0% *vs.* 7.4%, P<0.001

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; POCE, patient-oriented composite endpoints; ACS, acute coronary syndrome; VOCE, vessel-oriented composite endpoints; MI, myocardial infarction; TLR, target lesion revascularization; IDR, ischemia-driven revascularization; STEMI, ST-segment elevation myocardial infarction; CR, complete revascularization; TVR, target vessel revascularization; IRA, infarcted-related artery; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; CAD, coronary artery disease; AMI, acute myocardial infarction; UA, unstable angina; IR, incomplete revascularization; FSS, functional SYNTAX score; NA, no acquired.

compared to those with QFR >0.80 at 2-year [hazard ratio (HR) 4.650, 95% CI: 1.254–17.240, P=0.022]. Similarly, a patient-level sub-analysis of randomized PANDA III (Comparison of BuMA eG Based BioDegradable Polymer Stent With EXCEL Biodegradable Polymer Sirolimus-eluting Stent in "Real-World" Practice) trial (50), evaluating QFR in 1,391 patients (82.7% with ACS) undergoing angiography-guided PCI, documented that patients receiving physiology-consistent PCI based on baseline QFR had a lower risk of 2-year MACE than patients with QFR-inconsistent treatment (8.4% *vs.* 14.7%, P<0.001). Notably, approximately 41% of patients were treated with PCI under the guidance of angiography, however, not in accordance with QFR-recommended revascularization (vessels with baseline QFR ≤0.80 were treated with PCI and vessels with baseline QFR >0.80 were deferred). In an acute STEMI setting, Bär *et al.* (51) conducted QFR analyses in 946 untreated nontarget vessels among 617 patients undergoing primary PCI and angiography-guided complete revascularization. The results showed QFR ≤0.80 in non-target vessel was associated with a higher risk of MACE at 5-year follow-up (HR 7.33, 95% CI: 4.54–11.83, P<0.001). Differences were mainly driven by spontaneous nontarget vessel MI and nontarget vessel revascularization. Of note, QFR was calculated for all eligible nontarget vessels regardless of the degree of DS, which leads to a relatively low proportion (3.8%) of vessels with QFR ≤0.80. Overall, these findings suggest the incremental prognostic value of QFR over angiography alone in NCL assessment in ACS patients.

Another important clinical scenario to perform physiological assessment is in the catheterization laboratory after the index procedure. Multiple studies have used FFR to ascertain the prognostic relevance of post-PCI functional assessment in patients with stable CAD and ACS (58-60). Accordingly, investigators attempted to explore the clinical value of post-procedural QFR in various clinical settings. Two post-hoc analyses of multicenter prospective studies—SYNTAX II and HAWKEYE (Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation)—confirmed that post-PCI QFR was feasible and could offer prognostic information with procedural results and clinical outcomes (*Table 4*) (53,54). However, these studies mainly involved CCS patients, excluding patients in the acute phase of MI. Recently, Tang *et al.* (16) analysed QFR after stent implantation in 415 vessels included both culprit and nonculprit lesions from 186 STEMI patients, and found that post-PCI QFR <0.91 was associated with subsequent vessel-oriented cardiovascular events. Furthermore, Erbay *et al.* (17) evaluated the prognostic implication of pancoronary QFR assessment in a large cohort of 792 ACS patients and first reported post-PCI QFR ≤0.89 for culprit vessels as a best cut-off value to predict MACE at 2 years. Although the optimal post-PCI physiological thresholds of culprit and nonculprit vessels need to be further validated in future studies, QFR may provide a valuable tool for evaluating and optimizing PCI results, as the index can be easily obtained from routine coronary angiograms after PCI.

QFR-derived functional SYNTAX score and functional complete revascularization

The SYNTAX score (SS), which can objectively grade the anatomic complexity of CAD, was prospectively derived from the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial and remains the most widely used and validated risk score to guide revascularization strategy in patients with MVD (61,62). Besides, it was reported that the functional SS (FSS), which was calculated by counting only flow-limiting stenosis with FFR ≤0.8, had a better discriminant ability in predicting clinical outcomes compared with anatomic SS (63). Building on this concept, the hypothesis that QFR-based FSS may improve risk classification and subsequently influence the treatment decision for patients with MVD was proved in subanalyses of the SYNTAX II and PANDA III trials (55,56) (*Table 4*). Due to the retrospective manner, many angiographic images were not suitable for QFR analysis in all 3 vessels, resulting in QFR-based FSS was acquired in only 28.2% and 53.7% of the entire population, respectively. Nevertheless, these studies both demonstrated the applicability of calculating a QFR-based FSS and validated its potential for predicting future cardiovascular events. Spitaleri *et al.* (26) further introduced, on the basis of a small cohort of 110 STEMI patients following successful primary PCI, a residual FSS guided by QFR (only NCL with QFR ≤0.80 and left untreated was taken into account in the SS calculation) to define functional complete revascularization (QFR-based residual FSS =0). The results revealed that, at 5-year follow-up, the risk of MACE (a combined incidence of death, MI or any revascularization) was significantly reduced in patients with functional complete revascularization (HR 2.3, 95% CI: 1.2–4.5, P=0.01). By applying this scoring system, Tang *et al.* (57) consistently confirmed, in a single-center study of 354 STEMI patients, the 2-year benefits in MACE

of QFR-guided functional complete over incomplete revascularization (7.4% *vs.* 22.0%, P<0.001). Therefore, the improved scoring system combining anatomic and QFR-based physiological assessment might be a fast and feasible tool for risk stratification and PCI guidance in ACS patients with MVD.

Randomized clinical trial data

At present, neither of novel angiography-derived physiological technologies are recommended for routine use in clinical practice guidelines due to the absence of robust clinical trial evidence. More recently, the results of the FAVOR III China trial comparing outcomes of patients undergoing QFR-guided and angiography-guided PCI were reported, allowing QFR become the first angiographic flow measurement for PCI guidance with RCT data (64). A total of 3,825 patients with stable CAD or ACS [2,428 (63.5%) patients with ACS, including 207 patients with post-MI within 30 days] were randomly assigned to the QFR-guided or the angiography-guided group. At 1-year follow-up, the QFR-guided strategy was associated with a reduction in the primary endpoint MACE, a composite of death from any cause, MI, or ischemia-driven revascularization (IDR), compared with angiography-guidance alone (5.5% *vs.* 8.8%, HR 0.65, 95% CI: 0.51–0.83, P=0.004). The difference was driven by a substantial reduction in MI and IDR. Of importance, QFR assessment changed the treatment plan for 445 (23.3%) of 1,913 patients, mainly due to the treatment deferral of angiographically severe obstructive lesions originally intended for PCI, and thus reduce the number of stents implanted. In another prospective study, which randomized 229 patients with STEMI and MVD to QFR-guided complete revascularization *vs.* IRA-only treatment, showed QFR guidance was associated with a reduction in MACE at 1 year (9.6% *vs.* 20.1%, P=0.025) (52). These studies provide evidence that QFR may serve as a valuable tool for decision-making in the catheterization laboratory in addition to wire-based FFR and iFR.

QFR-based physiological assessment of CAD pattern

The mechanisms underlying suboptimal functional results after PCI are different, mainly due to the unsatisfactory stent deployment and the presence of residual diffuse disease (65). In recent years, there have been increasing efforts to characterize functional patterns of coronary atherosclerotic disease by using FFR or iFR pullback (66-68). A proof-of-concept study by Nijjer *et al.* (66) demonstrated that visual assessment of the iFR pullback tracing can physiologically map the entire coronary artery and can predict functional result after PCI in serial or diffuse lesions. Recently, Collet *et al.* (68) proposed the pullback pressure gradient (PPG) index derived from the motorized FFR pullback as a quantitative parameter to objectively discriminate between focal and diffuse disease. The PPG index is a continuous metric with higher values close to 1 indicate physiologically focal disease, whereas lower values close to 0 represent physiologically diffuse disease. As QFR software provides the virtual pullback curve by depicting pressure drop in each vessel segment, it is possible to calculate QFR-based PPG index without pressure wire. This concept has been recently validated by Biscaglia *et al.* (69) and Shin *et al.* (70), showing that the PPG index derived from QFR is feasible and reproducible in the discrimination of CAD patterns, and can predict post-PCI FFR or QFR results. Although preliminary and limited to a subset of CCS patients, these results, if further validated in various clinical settings, indicated that QFR-derived index of functional atherosclerotic pattern might be applicable for predicting PCI results and assisting lesions-specific treatment decision.

QFR-based physiological assessment of microcirculatory resistance

Coronary angiography as well as FFR and its simulators are tools to detect ischemic heart disease and myocardial ischemia attributed solely to epicardial stenoses. There is now greater recognition that CMD is emerging as another potential cause of angina (71). Therefore, various methods have been developed for microcirculatory assessment in the catheterization laboratory, and one of the most widely used indices is the IMR (72). However, similar to FFR, the adoption of IMR is extremely low in clinical practice because of the additional need for pressure-temperature sensor wire and hyperemic agents. With the recent development of functional coronary angiography techniques, researchers have proposed numerous wire-free parameters to estimate IMR using different methodologies (73-75). The series of subanalyses of the OxAMI (Oxford Acute Myocardial Infarction) study demonstrated the feasibility of calculating microcirculatory resistance based on the QFR system (labelled as IMR_{angio}) and validated its diagnostic performance by comparison with wire-based IMR across patients with STEMI, NSTE-ACS and

stable CAD (73,76). A later study from the same group, in 262 STEMI patients with primary PCI, found that non-hyperemic IMR_{angio} of IRA with a cutoff value of 43U, independently predicted the long-term outcomes (77). These findings were further confirmed by Choi *et al.* (78) in a larger cohort with 10-year clinical follow-up data using another angiography-based method to derive IMR. Even if these data are preliminary, it seems that integrating angiography-derived QFR and IMR might be helpful for differentiating epicardial and microvascular disease, enabling us to acquire important information in a variety of scenarios, especially for the setting of MI with non-obstructive coronary artery disease.

QFR and intravascular imaging-defined plaque vulnerability

Intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), are well-established methods for the assessment of coronary plaque vulnerability that can increase the risk of future cardiovascular events (79-81). Several studies have revealed the clinical association between vulnerable plaque features and coronary physiological parameters, including wire-based FFR and angiographic QFR (82-84). Kanno *et al.* (84) found that QFR severity was associated with a higher prevalence of OCT-defined thin-cap fibroatheroma (TCFA) in stable patients. Similar findings were reported by Dan *et al.* (85) and Zuo *et al.* (86), showing that lower QFR value was related to IVUS or OCT-defined vulnerable plaque features (i.e., minimal lumen area, plaque burden and TCFA) in both stable angina and NSTEMI patients. However, in a recent study of 87 patients with CCS, QFR was not associated with features of plaque vulnerability such as fibrous cap thickness, although significant correlations were found between QFR and OCT-derived intraluminal stenosis parameters (87). Indeed, the complex interactions exist between coronary physiology and morphological plaque characteristics, which may differ in hyperemic, non-hyperemic or computational physiological indices (88). More recently, Zeng *et al.* (89) demonstrated that high lipid burden was associated with a numerical higher FFR value compared with OCT-derived computational FFR in assessing functional severity of coronary stenosis, which might be caused by larger luminal deformation of lipid-rich plaque.

Notably, the vulnerable plaque features were more commonly detected in the non-culprit vessels of ACS patients than the target vessels of patients with stable CAD, which partly led to a worse outcome for ACS patients after deferral of NCLs based on functional assessment (90,91). On the other hand, a post hoc analysis of the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) and IBIS-4 (Intergraded Biomarkers Imaging Study 4) studies revealed that QFR could provide additional prognostic information in predicting 5-year MACE beyond virtual histology IVUS-based plaque characteristics (92). These findings suggest coronary physiology and plaque morphology have independent significances on clinical outcomes, and thus integrative evaluation of these 2 aspects of coronary plaque may provide a better understanding of the pathology of ACS. Recent advances in technology have enabled the fast computation of FFR from IVUS [denoted as ultrasonic flow ratio (UFR)] or OCT [denoted as optical flow ratio (OFR)], allowing assessment of both plaque morphology and coronary physiology without pressure wire and induced hyperemia. The accuracy of UFR and QFR were 92% and 90%, respectively, in the prediction of FFR ≤0.80 in the retrospective validation studies (93,94). The angiography-based QFR and intracoronary imaging-derived physiological indices are both computational approaches to determine the functional severity of the coronary stenosis. The fundamental difference between them is in the geometric reconstruction and the estimated hyperemic flow. A fixed hyperemic flow velocity was used for UFR/OFR computation because information on coronary flow can not be acquired from intracoronary images. However, IVUS or OCT images with high resolution provide more accurate lumen geometry than angiographic images. A recent study by Huang *et al.* (95) demonstrated that OFR was superior to QFR in the identification of flow-limiting coronary stenosis. Moreover, in the subset of patients with prior MI, the diagnostic performance of OFR was not influenced and significantly better than QFR. The recent published outcome study enrolling 604 patients with ACS showed that the presence of OFR ≤0.84 and lipid-to-cap ratio (a new morphologic parameter to define vulnerable plaque) >0.33 were both associated with an increased risk of nonculprit vessel-related MACE at 2 years. Importantly, the combination of lipid-to-cap ratio and OFR in NCLs significantly improved the prognostic performance in predicting future cardiovascular events (96). This indicates comprehensive morphofunctional profiling of coronary plaques may provide valuable information for clinician to aid decisions on revascularization in the catheterization laboratory.

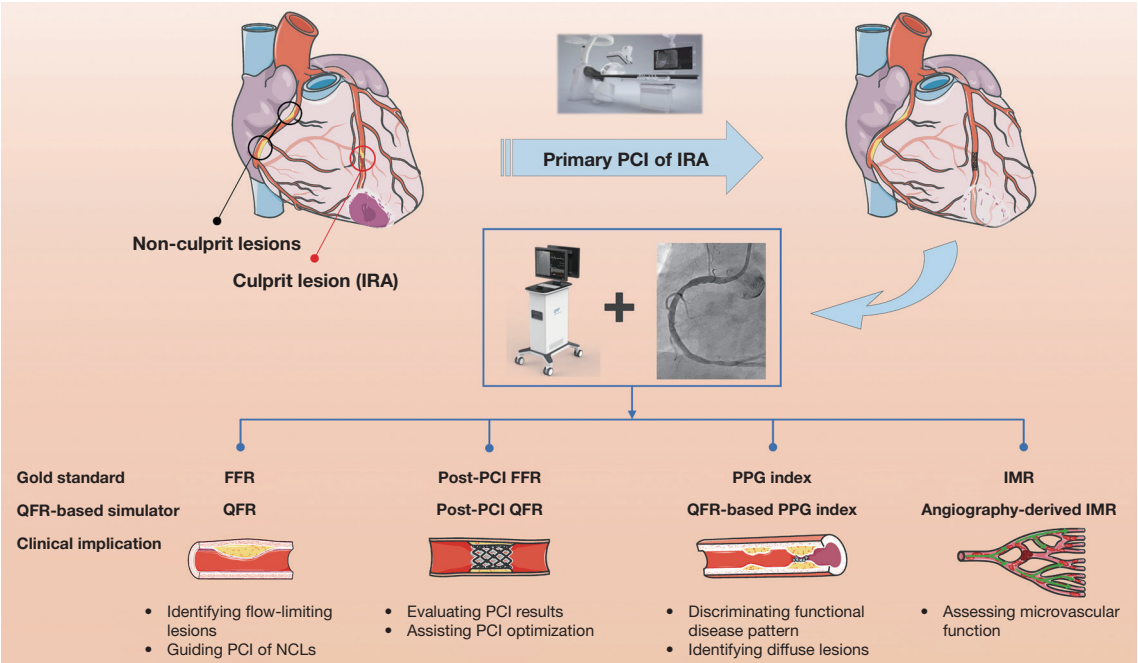

Figure 1 Clinical implications of QFR and QFR-derived physiological indices in ACS. IRA, indicates infarcted-related artery; NCL, non-culprit lesion; PCI, percutaneous coronary intervention; FFR, fractional flow reserve; QFR, quantitative flow ratio; PPG, pullback pressure gradient; IMR, index of microcirculatory resistance.

Future perspectives

Although the diagnostic accuracy of QFR with FFR has been demonstrated in multiple studies, and its clinical value in comparison with angiography was shown in FAVOR III China trial, the clinical outcome data are still insufficient, particularly for high-risk ACS patients. The ongoing FAVOR III European-Japan randomized trial (NCT03729739) will directly compare the outcomes of QFR-guided and FFR-guided revascularization in 2000 patients presenting with both acute and chronic coronary syndromes. The QFR-STEMI (Quantitative Fractional Ratio-guided Revascularization in STEMI Patients With Multi-vessel Disease, NCT04259853) and QUOMODO (QUantitative Flow Ratio Or Angiography for the assessMent of nOn-culprit Lesions, NCT04808310) (97) trials will focus on the management of NCLs in STEMI.

In particular, various techniques derived from QFR have been proposed to comprehensively evaluate coronary circulation and atherosclerotic lesion characteristics, i.e., post-PCI QFR for assessing PCI results, QFR-based PPG index for determining physiological disease pattern and angiography-derived IMR for identifying microcirculatory dysfunction (*Figure 1*). Despite pilot studies showing promising clinical value of these new technologies, more studies are required for further validation. Intracoronary imaging modalities can provide information on the pathobiology of ACS. For this high-risk subset of CAD patients, the novel UFR or OFR, if further confirmed in prospective studies, might be a useful adjunctive tool for operators in the diagnosis and treatment of ACS during cardiac catheterization.

Conclusions

An emerging body of evidence indicates that angiography-derived QFR bears the potential of a wider adoption of coronary physiology assessment due to its nature of being less-invasive, time-saving and economy-friendly. In parallel, multiple technologies, i.e., QFR-based PPG index, angiography-derived IMR and intravascular imaging-based morphofunctional evaluation methods, have been proposed, allowing operators to easily obtained physiological data of micro and macro-circulation, together with atherosclerotic lesion characteristics in catheterization laboratories. Future studies are needed to further explore the benefits of these approaches on outcomes in ACS.

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Footnote

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