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Impact of core laboratory assessment on treatment decisions and clinical outcomes using combined fractional flow reserve and coronary flow reserve measurements – DEFINE-FLOW core laboratory sub-study

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ABSTRACT

Objective: The role of combined FFR/CFR measurements in decision-making on coronary revascularization remains unclear. DEFINE-FLOW prospectively assessed the relationship of FFR/CFR agreement with 2-year major adverse cardiac event (MACE) and target vessel failure (TVF) rates, and uniquely included core-laboratory analysis of all pressure and flow tracings. We aimed to document the impact of core-laboratory analysis on lesion classification, and the relationship between core-laboratory fractional flow reserve (FFR) and coronary flow reserve (CFR) values with clinical outcomes and angina burden during follow-up.

Methods: In 398 vessels (348 patients) considered for intervention, ≥1 coronary pressure/flow tracing was approved by the core-laboratory. Revascularization was performed only when both FFR(≤0.80) and CFR(<2.0) were abnormal, all others were treated medically.

Results: MACE was lowest for concordant normal FFR/CFR, but was not significantly different compared with either discordant group (low FFR/normal CFR: HR:1.63; 95%CI:0.61–4.40; $P = 0.33$; normal FFR/low CFR: HR:1.81; 95%CI:0.66–4.98; $P = 0.25$). Moreover, MACE did not differ between discordant groups treated medically and the concordant abnormal group undergoing revascularization (normal FFR/low CFR: HR:0.63; 95%CI:0.23–1.73;$P = 0.37$; normal FFR/low CFR: HR:0.70; 95%CI:0.22–2.21;$P = 0.54$). Similar findings applied to TVF.

Conclusions: Patients with concordantly normal FFR/CFR have very low 2-year MACE and TVF rates. Throughout follow-up, there were no differences in event rates between patients in whom revascularization was deferred due to preserved CFR despite reduced FFR, and those in whom PCI was performed due to concordantly low FFR and

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CFR. These findings question the need for routine revascularization in vessels showing low FFR but preserved CFR.
Clinical trial registration: http://ClinicalTrials.gov NCT02328820

1. Introduction

Both fractional flow reserve (FFR) and coronary flow reserve (CFR) can be used to estimate the reduction in myocardial blood flow caused by coronary stenoses. CFR uses measurements of coronary flow, performed at resting and hyperemic conditions, to assess if the vasodilatory capacity of the coronary microcirculation is trimmed by upstream stenosis [1]. Conversely, FFR uses the hyperemic translesional pressure ratio as an estimate of blood flow in the presence of the stenosis as a fraction of the expected blood flow in the absence of the stenosis [2]. Both FFR and CFR were validated against non-invasive stress testing modalities, providing cut-off values for the presence of inducible myocardial ischemia [3,4]. In clinical practice, FFR is more frequently used to guide revascularization, while CFR is predominantly used to evaluate the microcirculation. Yet, combining both indices provides a richer picture of coronary hemodynamics by comprehensive assessment of both epicardial and microvascular coronary domains [5–7]. Discordance between FFR and CFR in stenosis classification, occurring in 30–40% of stenoses, denotes a more granular characterization of coronary hemodynamics which may convey useful information for clinical purposes [5,6].

DEFINE FLOW prospectively evaluated the prognostic value of combined FFR and CFR measurements [8], and suggested that the natural history of vessels with abnormal FFR and preserved CFR is not non-inferior to that of vessels with both normal FFR and CFR [9]. However, event rates in vessels with abnormal FFR and preserved CFR treated medically were not different from those in vessels that underwent revascularization, and exploratory analyses demonstrated that the use of core laboratory approved FFR and CFR data was associated with consistently lower event rates in vessels where revascularization was deferred, suggesting an important impact of data quality on the relationship of coronary hemodynamics with clinical outcomes.

This core laboratory sub-study of DEFINE FLOW details the impact of core laboratory assessment on stenosis classification, its relation to angina burden, and its impact on clinical outcomes across all quadrants defined by contemporary FFR and CFR thresholds.

2. Methods

2.1. Study oversight

DEFINE FLOW was a prospective, nonblinded, nonrandomized, multicenter trial comparing the natural history of coronary artery disease in relation to FFR and CFR values. DEFINE FLOW was registered at http://clinicaltrials.gov (NCT02328820). The overall study results have been reported elsewhere [9].

2.2. Recruited subjects

Patients undergoing assessment of an intermediate coronary stenosis were eligible for enrolment. Subjects were excluded for left ventricular ejection fraction <30%, severe hypertrophy, or ST-segment elevation myocardial infarction (MI) within the previous 3 weeks, left main location, prior CABG, (chronic) total occlusion, culprit vessels of an acute coronary syndrome or those supplying blood to previously infarcted myocardial territory. Operators could exclude any vessel felt too tortuous, calcified, or high-grade for safe instrumentation with the pressure/flow wire. All subjects provided written informed consent prior to enrolment.

2.3. Coronary physiology and treatment protocol

The study design has been published in detail [8]. After coronary angiography, a 0.014″ pressure and Doppler velocity sensor-equipped guidewire (ComboWire XT, Philips-Volcano, San Diego, California) was equalized at the tip of the guiding catheter and placed distal to the lesion. Pressure and flow measurements at baseline and after an intracoronary bolus of adenosine (100 μg for left and right coronary artery, reduced to 60 μg in the event of atrioventricular block) were performed at least twice. Based on the intracoronary assessments, lesions with FFR $\leq$ 0.8 and CFR < 2.0 as the average of duplicate measurements underwent immediate PCI. The protocol called for initial medical therapy for all other lesions. Ad-hoc treatment decisions were based on the operator-derived average FFR and CFR, since core laboratory review occurred after completion of the index procedure. Optionally, the operator could make additional measurements using intravenous adenosine or adenosine triphosphate at 140 μg/kg/min, or could repeat physiologic assessment after PCI. Operators could perform PCI of lesions not enrolled in the study without physiologic assessment for culprit lesions for an acute presentation, sufficient non-invasive testing to justify revascularization or marked angiographic severity.

2.4. Core laboratory analysis

Physiologic tracings were anonymized and sent to a central core laboratory for blinded review, without knowledge of enrolling site, clinical background, angiographic images, or operator-reported FFR and CFR values. Each tracing received a binary judgment (accept or reject), and accepted tracings were analysed independently for FFR and CFR values.

2.5. Clinical outcomes

Subjects were followed every 6 months until the final 2-year visit. At each assessment, symptoms, anti-anginal medications, and clinical events were recorded. Anginal status was measured using the Canadian Cardiovascular Society (CCS) classification. Tracked clinical events included death (judged as cardiovascular or not), cerebrovascular accident (CVA), MI (target vessel related or not), and revascularization (including target lesion, target vessel, and non-target vessel related).

2.6. Study endpoints

The primary endpoint of 2-year MACE-rate was a composite of all-cause death, MI, and any revascularization. The secondary endpoint was 2-year TVF-rate, which was a composite of cardiac death, target vessel MI, and target lesion or target vessel revascularization. An independent clinical events committee adjudicated events using standard definitions. Additional endpoints focused on reasons for core laboratory exclusion of hemodynamic traces, impact of core laboratory trace analysis on FFR and CFR values, and angina burden.

2.7. Statistical methods

Patients with at least one core laboratory accepted measurement were analysed. Per-protocol analysis was performed according to the core laboratory-defined FFR and CFR values, excluding cases where ad-hoc treatment decisions retrospectively did not match the core laboratory-defined FFR/CFR group. For these analyses, measurement with the highest core laboratory defined CFR and its accompanying FFR

was used to stratify vessels and patients according to normal/abnormal FFR and CFR for survival and angina analyses.

Follow-up was censored at 2 years, or at the last known event-free time point, whichever came first. Kaplan Meier curves were constructed, and (marginal) Cox regression analysis with adjustments for clustering of vessels within patients was used to calculate hazard ratios and 95% confidence intervals. Relative risks for angina were estimated using Poisson regression with robust error variance, adjusted for clustering of vessels within patients. As a sensitivity analysis, patients were hierarchically attributed the FFR/CFR group with the worst physiological profile (concordant low, low FFR/normal CFR, normal FFR/low CFR, concordant normal) and Cox regression analysis for MACE and Poisson regression for angina burden were repeated in the hierarchically defined FFR/CFR groups.

Descriptive data was analysed on per-patient basis for clinical characteristics, and on per-vessel basis for the rest of the calculations. For patient-based analyses, linear and logistic regression models with Huber-White robust standard errors were used to adjust for clustering of vessels from the same subject. From these analyses, adjusted means and prevalences with 95% confidence intervals are presented.

The STATA 13.1 (StataCorp, College Station, Texas) software package was used for all calculations. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Core laboratory findings and impact on FFR and CFR values

Between October 2014 and November 2017, we enrolled 455 subjects with 669 lesions, of which 1724 measurements in 564 vessels were evaluated by the core laboratory. Supplemental Table 1 summarizes the reasons for unsuccessful or absent measurements for 105 vessels. A total of 1193 measurements (69.2%) from 456 vessels were accepted by the core laboratory. The most frequent reasons for measurement exclusion by the core laboratory were issues with the coronary pressure tracing in 46.4% (pressure drift, incorrect normalization, unexplained sudden changes in aortic or distal pressure tracings), and issues with the coronary flow tracing in 38.4% (noise spikes, signal loss, or absence of accurate baseline flow) of excluded cases. Other issues, such as highly irregular heart rate due to frequent ectopic beats or atrial fibrillation, absent ECG tracings, or missing data, occurred in 11.6% of excluded cases.

In 438 vessels considered for percutaneous intervention (excluding vessels identified as reference vessels and post-PCI measurements), at least one core-laboratory accepted measurement was available. In these lesions, median core-laboratory defined average FFR was 0.83 (Q1-Q3: 0.76–0.89), and median site-defined average FFR was 0.83 (Q1-Q3: 0.75–0.89). Median core-laboratory defined average CFR was 2.2 (Q1-Q3: 1.8–2.6), and median site-defined average CFR was 2.2 (Q1-Q3: 1.7–2.6). Lesion stratification according to binary FFR and CFR thresholds led to a change in lesion classification in 11.4% of lesions (50 out of 438) between site and core-laboratory analyses. When the core laboratory-defined maximum CFR value and accompanying FFR value were used, median FFR was 0.84 (Q1-Q3: 0.76–0.89), and median CFR was 2.3 (Q1-Q3: 1.9–2.8). Using these FFR and CFR values led to a change in lesion classification in 15.3% (67 out of 438) of lesions compared with site-defined analyses.

3.2. Core-laboratory based analyses of DEFINE FLOW

In 398 out of 438 stenosed vessels from 348 subjects, measurements were available that retrospectively adhered to the treatment protocol using the core laboratory FFR and CFR values. This formed the study population. Supplemental Table 2 summarizes the 40 excluded lesions that would have undergone different treatment according to the core laboratory FFR and CFR values as compared with the treatment decision made by the operator. Supplemental Table 3 details individual site-defined mean FFR and CFR values and core laboratory-defined maximal FFR and CFR for these vessels.

Fig. 1 details how the study population divided into 4 groups based on the.

FFR $\leq$ 0.8 and CFR $<$ 2.0 thresholds. Table 1 summarizes key baseline characteristics for the entire cohort, and across FFR/CFR groups. Overall median FFR was 0.85 (Q1-Q3: 0.77–0.90) and CFR was 2.3 (Q1-Q3: 1.9, 2.8). Fig. 2 depicts the relationship between FFR and CFR. The majority of lesions (68.8%) displayed concordance, 207 lesions (52.0%) had normal FFR and CFR, whereas 67 lesions (16.8%) low FFR and CFR. Disagreement between FFR and CFR occurred in 124 lesions (31.2%), where 54 lesions (13.6%) had normal FFR with low CFR, and 70 (17.6%) lesions had low FFR and normal CFR.

3.3. Clinical outcomes across groups defined by FFR and CFR agreement

Fig. 3 displays time-to-event curves for MACE (Panel A) and TVF (Panel B) across the groups defined by FFR and CFR. The event rates across groups and between-group comparisons are summarized in Table 2.

The risk for MACE was numerically higher but not significantly different for patients with discordant low FFR with normal CFR compared to patients with concordant normal FFR and CFR (HR 1.63; 95% CI: 0.61 to 4.40; $P = 0.33$). There was no difference in the risk for MACE between patients with discordant low FFR with normal CFR compared with patients with concordant low FFR and CFR whom underwent revascularization (HR 0.63; 95% CI: 0.23 to 1.73; $P = 0.37$). Similarly, the risk for MACE was numerically higher but not significantly different for patients with discordant normal FFR with low CFR compared with patients with concordant normal FFR and CFR (HR 1.81; 95% CI: 0.66 to 4.99; $P = 0.25$). Moreover, the risk for MACE was similar between patients with discordant low FFR with normal CFR and patients with concordant low FFR and CFR whom underwent revascularization (HR 0.70; 95% CI: 0.22 to 2.21; $P = 0.54$). Sensitivity analysis using a hierarchical attribution of patients to a single FFR/CFR group led to similar results and conclusion (Supplemental Table 4).

Similar to the findings for MACE, the risk for TVF was numerically higher but not significantly different for vessels with discordant low FFR with normal CFR compared with vessels with concordant normal FFR and CFR (HR 2.51; 95% CI: 0.77 to 8.24; $P = 0.13$). Again, there was no difference in TVF risk for vessels with discordant low FFR and normal CFR, nor for vessels with discordant normal FFR and low CFR when compared with vessels with concordant low FFR and CFR which underwent revascularization (HR for low FFR/normal CFR: 1.21; 95% CI: 0.32 to 4.51); $P = 0.78$; HR for normal FFR/ low CFR: 1.27; 95% CI: 0.32 to 5.08; $P = 0.73$).

3.4. Relationship between invasive physiology findings and angina

Information regarding angina status was available in 338 patients (97.1%). Overall, 44.5% of these subjects reported CCS class II-IV angina at baseline. There was a significant reduction in reported angina at 6-month follow-up, when 9.7% of subjects reported CCS class II-IV angina, and which persisted throughout follow-up (9.7% at 12-month follow-up, 8.9% at 18-month follow-up, and 8.2% at 24-month follow-up). Throughout follow-up, there were no relevant differences across groups in the number of anti-anginal medications used (Supplemental Table 5). There was no significant difference in the occurrence of CCS class II-IV angina at baseline or during follow-up across the groups (Fig. 4). Sensitivity analysis using a hierarchical attribution of patients to a single FFR/CFR group led to similar results and conclusion (Supplemental Fig. 1).

A total of 42 patients (12.1%) in the study population underwent concomitant revascularization of a lesion deemed the culprit for anginal symptoms without physiological assessment due to severe angiographic

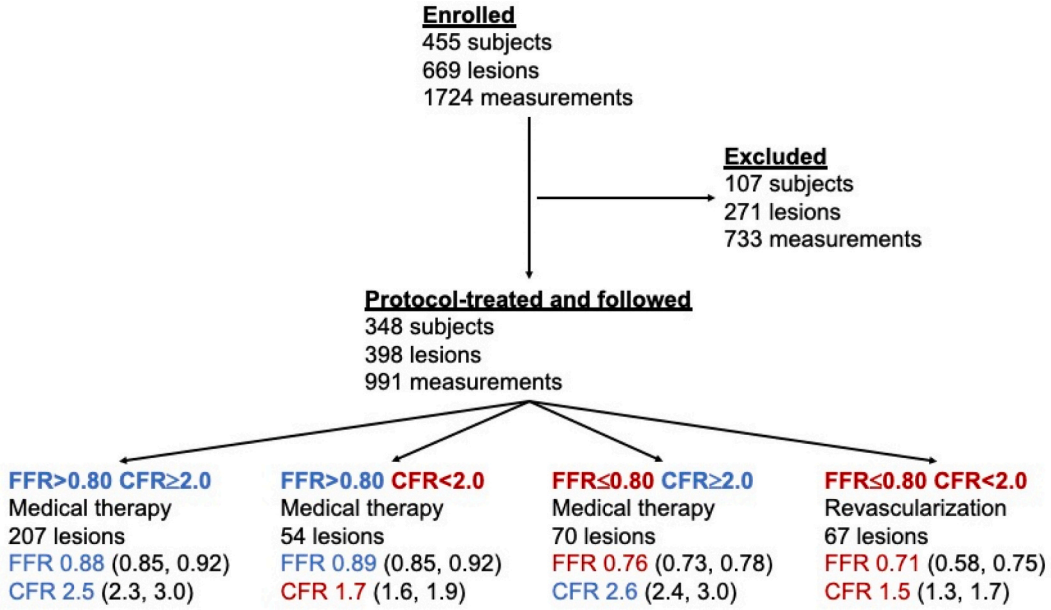

Fig. 1. Study flow diagram.

severity, abnormal non-invasive stress testing results attributable to the perfusion territory of the stenosed vessel, or acute coronary syndrome culprit stenosis. A separate analysis excluding these patients revealed no significant difference in the occurrence of CCS class II-IV angina at baseline or during follow-up across the groups (Supplemental Fig. 2).

4. Discussion

This core-laboratory sub-study of DEFINE FLOW provides unique insight into the relationship of coronary hemodynamics across all quadrants of the FFR/CFR relationship and the natural history of coronary artery disease. Importantly, although mean FFR and CFR values were not statistically different between site and core-laboratory analyses, the use of core-laboratory data led to a change in lesion classification according to binary FFR/CFR thresholds in 11.4% of cases, illustrating the relevance of core-laboratory analysis in hypothesis-generating studies like DEFINE-FLOW. Using core-laboratory data, we observed that combined normal FFR and CFR was associated with an excellent long-term result. Compared with this group, discordant FFR and CFR values had numerically higher but not significantly different rates of MACE and TVF. Importantly, deferral of revascularization in vessels with preserved CFR values despite abnormal FFR was associated with similar event rates as those observed in vessels that underwent revascularization on the basis of concordantly abnormal FFR and CFR values. Moreover, DEFINE FLOW confirms that abnormal CFR in the presence of normal FFR is associated with increased event rates during follow-up. Interestingly, there was no difference in the reduction of angina severity during follow-up across all 4 groups despite no relevant differences in anti-anginal medication use.

4.1. Clinical impact of combined FFR and CFR measurements

FFR-guided coronary intervention is supported by clinical studies documenting a reduction in revascularization procedures versus angiographic guidance, while maintaining equivalent outcomes up to 5-year follow-up [10]. Nonetheless, in vessels associated with abnormal FFR values which are initially managed with optimal medical therapy alone, only 50% undergo coronary revascularization for clinical indications over a 5-year follow-up period and less suffer from MACE [11]. Hence, additional diagnostic strategies may refine the risk stratification provided by FFR to identify those patients that should undergo coronary revascularization to prevent future events.

The value of combining CFR and FFR measurements to obtain a more accurate picture of coronary hemodynamics [5], and to optimize risk stratification has been previously described in detail [6,12]. The four subgroup classification generated by normal or abnormal FFR and CFR values informs on specific pathophysiology of the coronary circulation. Concordant normal FFR and CFR denotes that both coronary conductance and microvascular dynamicity are preserved, and this fact explains the very favourable clinical outcomes of such patients documented in this core laboratory analysis of DEFINE FLOW. In total, 80% of all patients with normal FFR belong to this classification. At the other end of the spectrum, the occurrence of concordantly abnormal FFR and CFR values reflect severely disturbed coronary hemodynamics caused by epicardial vessel narrowing that is flow-limiting and has exhausted microvascular vasodilatory reserve. These patients, which constitute 49% of all patients with abnormal FFR values, underwent protocol-mandated revascularization in DEFINE FLOW. Of note, despite receiving revascularization these patients show higher long-term event rates than those with normal FFR and CFR.

The prognostic implications of the two discordant subgroups have remained ambiguous. Preserved CFR in vessels in which FFR is abnormal indicates that the vasodilator reserve capacity of the coronary circulation is not exhausted. Thus, despite a pressure gradient generated by the stenosis, flow limitation has not reached the ischemia-generating threshold. The median value of CFR in these vessels in DEFINE FLOW was 2.6 (Q1-Q3: 2.4, 3.0), which is far beyond the ischemic CFR threshold of 2.0. The incidence of MACE and TVF for such patients/vessels with abnormal FFR and normal CFR in DEFINE FLOW was not different from patients/vessels whom underwent revascularization, and, moreover, events were dominated by delayed revascularization. Importantly, the event rates in vessels with abnormal FFR and normal CFR treated medically, as well as in vessels that underwent revascularization were similar to previous studies including FAME II [11]. These results suggests that deferral of revascularization in lesions with preserved CFR is not associated with an increase in MACE or TVF rates compared with routine revascularization, where it is important to note that endpoints were driven by delayed revascularization of the target lesion without an increase in the occurrence of death or MI.

The present manuscript further documents the clinical relevance of vessels with normal FFR but abnormal CFR. This discordant group is attributed to microvascular disease or diffuse epicardial atherosclerosis,

Table 1
Baseline characteristics across groups defined by FFR and CFR.

	FFR normal CFR normal	FFR normal CFR low	FFR low CFR normal	FFR low CFR low	Entire cohort
Evaluated patients*	173	44	67	64	348
Age, years	67 (66–68)	69 (66–72)	65 (63–68)	68 (66–71)	67 ± 10
Male	74 (68–80)	80 (67–88)	79 (67–87)	76 (64–85)	262 (75)
Hypertension	67 (59–73)	74 (59–85)	60 (48–70)	65 (52–76)	229 (66)
Dyslipidemia	88 (82–92)	89 (75–95)	91 (82–96)	91 (79–96)	307 (88)
Family history	36 (29–43)	40 (27–55)	42 (30–54)	32 (21–45)	122 (35)
Active smoker	21 (15–27)	9 (4–20)	29 (19–40)	19 (12−31)	71 (20)
Diabetes	25 (19–32)	22 (13–36)	24 (16–36)	42 (30–54)	95 (27)
Renal dysfunction	9 (5–14)	13 (6–25)	10 (5–20)	7 (3–17)	30 (9)
Prior MI	23 (17–30)	26 (15–40)	34 (24–46)	27 (17–39)	87 (25)
Prior PCI	36 (29–43)	43 (30–58)	46 (34–57)	40 (29–53)	132 (38)
Peripheral vascular disease	4 (2–9)	7 (2−22)	4 (1−12)	10 (5–20)	20 (6)
Cerebrovascular disease	9 (6–14)	7 (2–22)	6 (2–14)	7 (3–17)	30 (9)
Clinical presentation stable angina	81 (75–86)	85 (71–93)	86 (75–92)	75 (63–84)	282 (81)
Medications					
Aspirin	86 (80–91)	83 (71–91)	90 (80–95)	89 (78–95)	305 (88)
Second antiplatelet**	62 (54–68)	69 (54–80)	68 (56–78)	85 (73–92)	232 (67)
Beta blocker	60 (53–67)	54 (40–67)	61 (50–72)	62 (49–73)	209 (60)
Calcium antagonist	33 (27–40)	48 (35–62)	31 (22–43)	45 (34–58)	126 (36)
Nitrates	48 (41–55)	50 (36–64)	49 (37–60)	38 (27–50)	161 (46)
Statin	78 (72–84)	83 (70–92)	83 (72–90)	85 (73–92)	276 (79)
RAAS antagonist	52 (45–59)	63 (49–75)	60 (48–71)	53 (41–65)	192 (55)
Diuretic	18 (13–24)	13 (6–25)	31 (22–43)	8 (3–17)	60 (17)
Evaluated vessels	207	54	70	67	398
Coronary artery					
LAD	133 (64)	29 (54)	55 (79)	47 (70)	264 (66)
LCx	41 (20)	19 (35)	5 (7)	10 (15)	75 (19)
RCA	33 (16)	6 (11)	10 (14)	10 (15)	59 (15)
Lesion location					
Proximal	73 (35)	17 (31)	23 (33)	29 (43)	142 (36)
Middle	98 (47)	24 (44)	36 (51)	26 (39)	184 (46)
Distal	36 (17)	13 (24)	11 (16)	12 (18)	72 (18)
Diameter stenosis, %	58 ± 11	62 ± 14	62 ± 10	77 ± 11	62 ± 13
Fractional flow reserve	0.88 (0.85, 0.92)	0.89 (0.85, 0.92)	0.76 (0.73, 0.78)	0.71 (0.58, 0.75)	0.85 (0.77, 0.90)
Coronary flow reserve	2.5 (2.3, 3.0)	1.7 (1.6, 1.9)	2.6 (2.4, 3.0)	1.5 (1.3, 1.7)	2.3 (1.9, 2.8)

Data presented as adjusted means and prevalences with 95% confidence intervals for patient-based analyses, and n(%), mean ± standard deviation, or median (Q1-Q3) for vessel-based analyses. MI: myocardial infarction, PCI: percutaneous coronary intervention, RAAS: renin angiotensin aldosteron system, LAD: left anterior descending coronary artery, LCx: left circumflex coronary artery, RCA: right coronary artery.

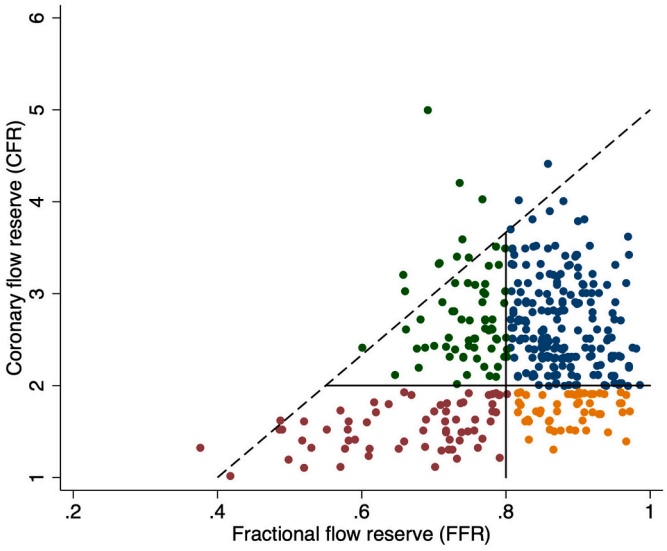

Fig. 2. Scatterplot of combined FFR and CFR. Distribution of FFR and CFR values across the study population.

and its management remains debated. Current clinical practice guidelines recommend measuring CFR or microcirculatory resistance in patients with angina and non-ischemic FFR values to rule out a microvascular cause of symptoms [13]. In DEFINE FLOW, vessels with normal FFR and abnormal CFR exhibited increased event rates compared with vessels with normal coronary hemodynamics, with event rates as high as in vessels that underwent revascularization. Hence, these results suggest that also these lesions do not benefit from routine revascularization in terms of the occurrence of adverse events. Future research will reveal if the prognosis of these patients can be improved by addressing microvascular dysfunction through specific treatments.

The data from the current report are similar to those recently reported in the large retrospective ILIAS (Inclusive physiological assessment in angina syndromes) Registry involving 2725 coronary arteries, where discordant FFR/CFR measurements were associated with increased TVF rates over a 5-year follow-up period compared with concordant normal FFR/CFR values, and no difference was documented in the 5-year TVF rate for vessels with FFR/CFR discordance compared with vessels that underwent revascularization [14]. Our data support these findings in the prospective non-randomized DEFINE FLOW study.

In combination, the findings from the present study point towards a clinical relevance of high-quality coronary pressure and flow measurements for decision-making in clinical practice. However, since these could represent spurious findings in a small hypothesis-generating study like DEFINE FLOW, particularly after exclusion of measurements by the core laboratory, further assessment of these findings in larger clinical cohorts is warranted.

4.2. Impact of FFR/CFR discordance on angina burden

Throughout follow-up, no differences were documented in the incidence of CCS class II-IV angina across FFR/CFR groups, despite no difference in the number of anti-anginal medications used. The reduction of CCS class II-IV from 40% at baseline to 10% in all 4 groups is important as it may explain the low event rate in the DEFINE FLOW. These results were unaltered when excluding patients whom underwent PCI of a concomitant lesion that did not undergo physiological assessment at the operator's discretion. Moreover, vessels with discordance

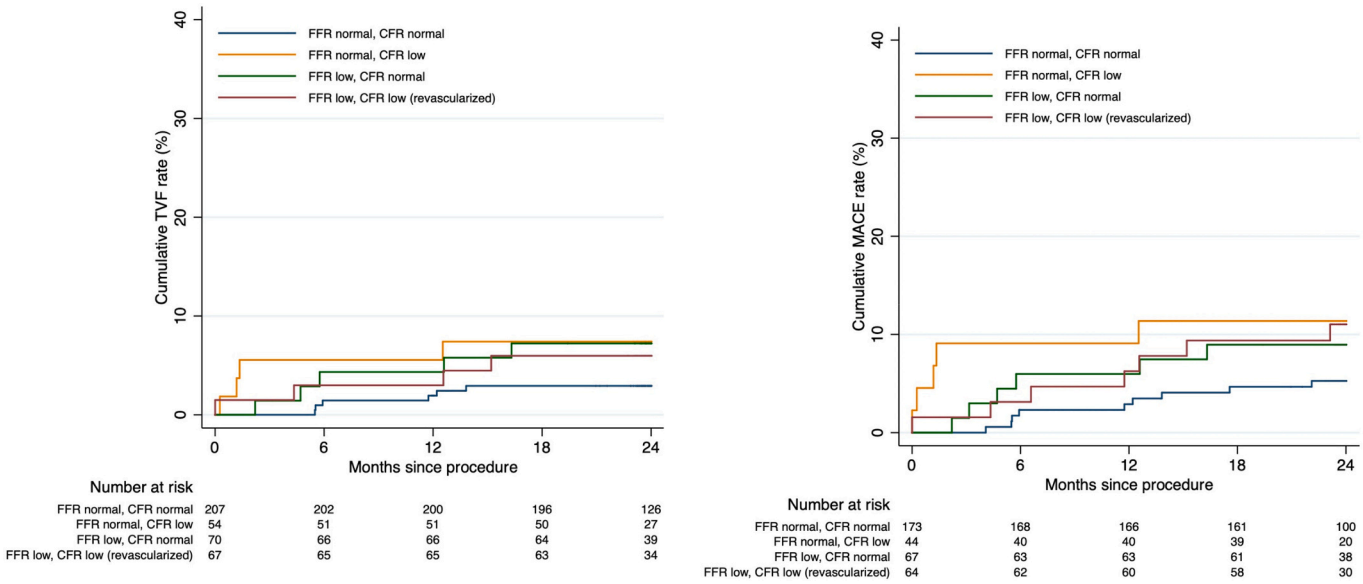

Fig. 3. Kaplan Meier time-to-event curves for *A. major* adverse cardiac events (MACE), and B. target vessel failure (TVF) during 2-year follow-up. The Kaplan Meier curve for MACE was based on hierarchical attribution of patients to FFR/CFR groups.

Table 2
Adverse event rates across groups defined by FFR and CFR.

	FFR normal CFR normal	FFR normal CFR low	FFR low CFR normal	FFR low CFR low
Treatment	Medical therapy	Medical therapy	Medical therapy	Revascularization
MACE	5.3% (3.0–9.4)	9.3% (3.9–20.5)	8.6% (3.9–17.8)	13.4% (6.7–25.1)
Hazard ratio versus FFR > 0.8 CFR ≥ 2	–	1.81 (0.66 *to* 4.99)	1.63 (0.61 to 4.40)	2.59 (1.07 to 6.26)*
Hazard ratio versus revascularized	0.39 (0.16 to 0.93)*	0.70 (0.22 to 2.21)	0.63 (0.23 to 1.73)	–
MACE components				
Death	0.5 (0.1–3.3)	–	1.4 (0.2–9.5)	–
Myocardial infarction	1.0 (0.2–3.8)	1.9 (0.3–12.1)	–	1.5 (0.2–9.9)
Revascularization	4.8 (2.6–8.8)	7.4 (2.8–18.2)	7.1 (3.0–16.1)	12.0 (5.6–23.5)
Lesions	207	54	70	67
TVF	6 (2.9)	4 (7.4)	5 (7.1)	4 (6.0)
Hazard ratio versus FFR > 0.8 CFR ≥ 2	–	2.64 (0.75 to 9.36)	2.51 (0.77 to 8.24)	2.08 (0.59 to 7.36)
Hazard ratio versus revascularized	0.48 (0.14 to 1.71)	1.27 (0.32 to 5.08)	1.21 (0.32 to 4.51)	–
TVF components				
CV death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TVMI	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)
TVR	1(0.5%)	1 (1.9%)	1 (1.4%)	1 (1.5%)
TLR	5 (2.4%)	3 (5.6%)	5 (7.1%)	2 (3.0%)

Event rates presented as adjusted means and prevalences with 95% confidence intervals for patient-based analyses, and n(%) for vessel-based analyses. Hazard ratios and 95% confidence intervals derived from (marginal) Cox regression models.
MACE: major adverse cardiac events, MI: myocardial infarction, TVF: target vessel failure, CV: cardiovascular, TVMI: target vessel myocardial infarction, TVR: target vessel revascularization, TLR: target lesion revascularization.

between FFR and CFR managed medically were associated with a similar incidence of delayed revascularization as the incidence of repeat revascularization in vessels that directly underwent revascularization, and were associated with a similar reduction in angina burden throughout follow-up. In the absence of an impact of concomitant PCI, differences in anti-anginal medications, or delayed revascularization of ischemia-inducing lesions that were initially managed medically, the equivalent reduction of angina burden across groups can potentially be explained by the reassuring effect of physiology results not warranting coronary revascularization. This is supported by the fact that the reduction in angina class in this DEFINE FLOW core lab analysis was similar in magnitude as observed in the FAME II trial [15].

4.3. Core laboratory assessment of pressure and flow measurements

In total 30.8% of measurements were excluded after core-laboratory analysis. The reasons for exclusion were equally related to problems identified in pressure and flow traces, which emphasizes the need for improvement of these techniques. Lesion classification was altered in 11.6% of cases when using core laboratory-defined data, which is important because the inclusion of patients or vessels where decision-making is based on measurements that should not qualify for clinical decision-making would pose a risk for misinterpretation of the clinical relevance of combined pressure and flow measurements in a small study like DEFINE FLOW. In this regard, it is important to realize that the flow velocity measurement technology used in DEFINE FLOW is dated and relatively technically challenging, precluding interpretation of the clinical feasibility of combined pressure and flow velocity measurements from these data. Nonetheless, with improvement of invasive flow measurement techniques and their expansion to clinical practice, the technical robustness of such techniques and their clinical feasibility are important aspects that will ultimately define the clinical value of combined CFR and FFR measurements in daily practice, and should be part of future clinical studies.

4.4. Study limitations

This is a small non-randomized study that should be considered hypothesis-generating. This is illustrated by the large confidence intervals obtained with Cox regression analysis. Further adequately powered studies are required to evaluate the safety and cost-

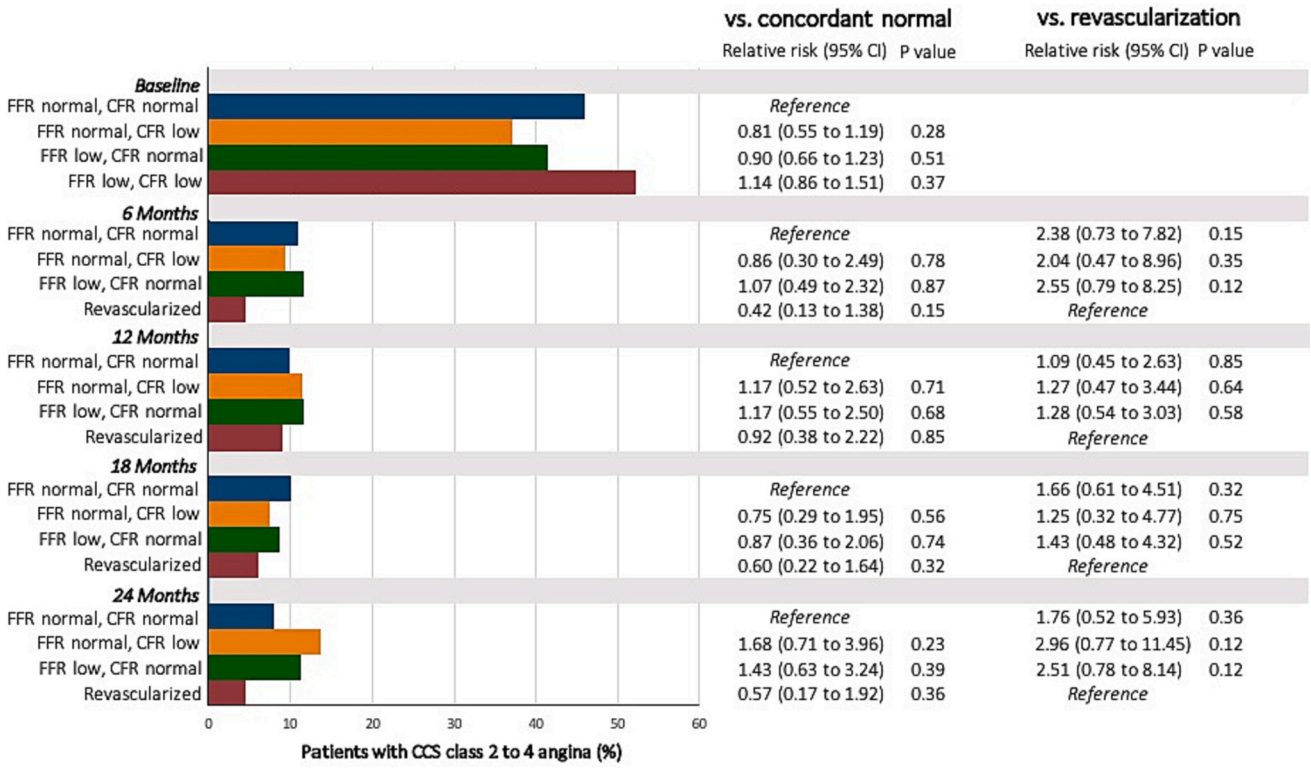

Fig. 4. CCS class II-IV angina across FFR/CFR groups. Throughout follow-up, there were no statistically significant differences in angina burden across groups.

effectiveness of the DEFINE FLOW strategy towards coronary revascularization. Second, the majority of patients had stable angina and physiologically mild lesions limiting extrapolation to other patient cohorts. Patients and operators were un-blinded to the results of the measurements, which may impart bias towards follow-up and additional treatment, and may therefore impact clinical endpoints. Nonetheless, this may lead to an increase in revascularization rates for lesions with abnormal FFR deferred on the basis of normal CFR, which was not observed in DEFINE FLOW.

5. Conclusion

Patients with concordantly normal FFR and CFR have very low 2-year MACE and TVF rates. Throughout follow-up, there were no differences in event rates and angina burden between patients in whom revascularization was deferred due to preserved CFR despite reduced FFR and those in whom PCI was performed due to concordantly low FFR and CFR. Moreover, similarly increased event rates were documented in patients in whom revascularization was deferred with normal FFR but reduced CFR. These findings question the need for routine revascularization in vessels showing low FFR but preserved CFR, and support the clinical relevance of reduced CFR despite normal FFR. These data urge further evaluation of combined FFR/CFR assessment for clinical decision-making.

Disclosures

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CRediT authorship contribution statement

Tim P. van de Hoef: Conceptualization, Investigation, Formal analysis, Visualization, Methodology, Writing – original draft. **Valérie E. Stegehuis:** Investigation, Writing – review & editing. **Maribel I. Madera-Cambero:** Investigation, Writing – review & editing. **Niels van Royen:** Investigation, Writing – review & editing. **Nina W. van der Hoeven:** Investigation, Writing – review & editing. **Guus A. de Waard:** Investigation, Writing – review & editing. **Martijn Meuwissen:** Investigation, Writing – review & editing. **Evald H. Christiansen:** Investigation, Writing – review & editing. **Ashkan Eftekhari:** Investigation, Writing – review & editing. **Giampaolo Niccoli:** Investigation, Writing – review & editing. **Tim Lockie:** Investigation, Writing – review & editing. **Hitoshi Matsuo:** Investigation, Writing – review & editing. **Masafumi Nakayama:** Investigation, Writing – review & editing. **Tsunekazu Kakuta:** Investigation, Writing – review & editing. **Nobuhiro Tanaka:** Investigation, Writing – review & editing. **Lorena Casadonte:** Investigation, Writing – review & editing. **Jos A.E. Spaan:** Investigation, Writing – review & editing. **Maria Siebes:** Investigation, Writing – review & editing. **Jan G.P. Tijssen:** Writing – review & editing. **Javier Escaned:** Investigation, Writing – review & editing. **Jan J. Piek:** Conceptualization, Methodology, Investigation, Writing – review & editing, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.01.009.

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