Fractional flow reserve versus angiography-guided revascularization in coronary artery disease. Systematic review and meta-analysis

Mikołaj Błaziak[1], Szymon Urban[1], Maksym Jura[1], Weronika Wietrzyk[1], Bartłomiej Stańczykiewicz[3], Michał Jarocki[1], Kamila Florek[2], Aleksandra Jędrasek[1], Oskar Szymański[1], Magdalena Grzesiak[1], Wiktor Kuliczkowski[1]

[1]Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland
[2]Institute of Heart Diseases, Students' Scientific Group of Invasive Cardiology, Wroclaw Medical University, Wrocław, Poland
[3]Department of Psychiatry, Division of Consultation Psychiatry and Neuroscience, Wroclaw Medical University, Wrocław, Poland

Editorial
by Böhm et al.

Correspondence to:
Szymon Urban, MD,
Institute of Heart Diseases,
Wroclaw Medical University,
Borowska 213, 50–556 Wrocław,
Poland.
phone: + 48 71 733 11 12
e-mail:
szymon.urban.wro@gmail.com

DOI: 10.33963/v.phj.102941

Received:
July 17, 2024

Accepted:
October 1, 2024

Early publication date:
October 9, 2024

ABSTRACT

Background: Randomized controlled trials (RCTs) comparing the clinical outcomes of fractional flow reserve (FFR)-guided and angiography-guided revascularization in patients with coronary artery disease yielded inconsistent results.

Aims: This study aimed to assess whether FFR-guided revascularization reduces the rates of hard clinical endpoints in comparison with the angiography-guided approach alone.

Methods: This systematic review was conducted in June 2024 using Embase, Clinicaltrials.gov, Cochrane Library, and EBSCO databases. Only RCTs that evaluated stable and unstable coronary artery disease and acute myocardial infarction (MI) were included. Eight RCTs involving 4713 patients were included in the meta-analysis.

Results: FFR guidance was associated with a reduction in MI (risk ratio [RR], 0.75 [95% confidence interval [CI], 0.58–0.96]; $P = 0.02$) and a lower rate of revascularization (standardized mean difference — 0.12 [95% CI, –0.14 to 0.09]; P <00001). There were no differences between FFR-guided and angio-guided revascularization in major adverse cardiovascular events (RR, 0.84 [95% CI, 0.69–1.02]; $P = 0.08$), all-cause mortality (RR, 1.00 [95% CI, 0.58–1.74]; $P = 0.99$), and unplanned revascularization (RR, 0.89 [95% CI, 0.72–1.10]; $P = 0.28$).

Conclusions: FFR-driven revascularization was associated with a significantly lower rate of MI for the entire population and also the acute coronary syndrome subset. These results were achieved with substantially fewer revascularization procedures compared with angiographic guidance alone.

Key words: angiography, coronary artery disease, fractional flow reserve, percutaneous coronary intervention

INTRODUCTION

Over the past decade, landmark clinical randomized trials have demonstrated the superiority of fractional flow reserve (FFR)-guided revascularization in the reduction of hard endpoints in comparison with angiography alone [1, 2]. Consequently, functional evaluation with the use of FFR received the highest-level recommendation in the American Heart Association and European Society of Cardiology (ESC) guidelines for revascularization, class IA [3–5]. Recent ESC guidelines covering all types of acute coronary syndrome (ACS) lowered recommendations for FFR use in the ST-segment elevation myocardial infarction (STEMI) to class III [6]. Additionally, subsequent randomized controlled trials (RCTs) evaluating the clinical utility of FFR in various settings

WHAT'S NEW?

This is the first meta-analysis of randomized controlled trials comparing fractional flow reserve (FFR) and angiography-driven revascularization head-to-head in obstructive coronary artery disease, which showed the superiority of FFR guidance. The main finding of the present analysis was that functional assessment significantly reduced the rate of myocardial infarction. Moreover, this effect was achieved with a diminished frequency of revascularization in the FFR arm.

have shown inconsistent results, challenging previous reports [7, 8].

Hence, we decided to conduct a meta-analysis of RCTs comparing these two techniques head-to-head, focusing on endpoints such as death, nonfatal myocardial infarction (MI), repeat revascularization, and a composite of their components in patients with obstructive coronary artery disease (CAD).

METHODS

We conducted a literature review with meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. The study design was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42023402326. The review did not include clinical studies or patient data.

Data sources and search strategy

Two independent reviewers (MB and SU) searched the following online databases: EBSCO (including Academic Search Ultimate, ERIC, Health Source Nursing/Academic Edition, and MEDLINE), Embase, Clinicaltrials.gov, and Cochrane Library (trials) for articles published before 15 June 2024. We considered records with no restrictions on the publication date. We used the following key words separately and in combination to identify relevant records: (fractional flow reserve) OR (fraction flow reserve) OR (FFR) OR (physiology guide*) OR (physiology assess*) OR (physiology revasc*) OR (physiology test*) OR (functional guide*) OR (functional assess*) OR (functional revasc*) OR (functional test*) OR (invasiv* assess*) OR (invasiv* guide*) OR (invasiv* test*) OR (pressure wire) OR (hyperemic pressure ratio*) AND coronary OR (coronary artery disease) OR CAD OR angiography OR (percutaneous coronary intervention*) OR PCI OR angioplasty OR stent* OR (percutaneous transluminal coronary angioplasty) OR PTCA OR revascularisation* OR (myocardial reperfusion) OR bypass OR CABG OR (coronary artery bypass surgery) OR (coronary bypass surgery) OR (surgical revasc) OR (myocardial bridg*) OR STEMI OR (ST segment elevation) OR NSTEMI OR (non-ST segment elevation) OR (myocardial infarction) OR ACS OR (acute coronary syndrom*) OR multivessel OR multi-vessel OR three-vessel OR (triple vessel) and NOT comput* OR tomogra* OR CT. Only articles that were completed, terminated, or with results were considered. Disagreements between the two investigators during the screening process were resolved through discussion with a third reviewer (WK). For completeness, further screening by two reviewers (KF and AJ) of the references of the included records and studies that cited them was performed to identify other relevant publications.

Outcomes

The primary endpoints of the study were major adverse cardiovascular events (MACE) and individual components of the composite endpoint, including all-cause mortality, nonfatal MI, and unplanned revascularization.

Eligibility criteria

The inclusion criteria were as follows: 1) RCTs comparing clinical outcomes with FFR-guided and angiography-guided myocardial revascularization, 2) populations with obstructive CAD presenting with either ACS, stable CAD, or unstable angina, 3) reporting of at least one of the endpoints of interest: MACE, a composite of all-cause or cardiovascular mortality, MI, repeat revascularization, and the single components of the aforementioned endpoints, 4) hyperemic FFR as an assessment method, 5) age of patients >18, and 6) full-text articles published in English. The following publications were excluded: 1) studies evaluating FFR-guided PCI with optimal medical treatment, 2) studies comparing FFR-guided revascularization of non-culprit lesions with PCI of culprit lesions exclusively in ACS, 3) studies using physiological assessments different from FFR, 4) studies in which PCI was performed using only bare-metal stents, 5) non-randomized studies of interventions, 6) animal model studies, 7) case reports, 8) non-original studies (e.g. reviews, editorials, and commentaries), and 9) conference abstracts.

Data collection and analysis

The extracted data included: 1) year of publication, 2) size of the FFR and angiography groups, 3) enrolment criteria, 4) MACE definition, 5) length of follow-up, 6) baseline and demographic characteristics, 7) number of performed treatment strategies of PCI/coronary artery bypass graft (CABG)/ optimal medical treatment, 8) proportion of used drug-eluting stents, 9) used FFR cut-off, 10) angiography percentage stenosis threshold for revascularization, and 11) number of events for each endpoint.

Statistical analysis

Analyses were performed using random-effects models with the Mantel-Haenszel method. The risk ratios and 95% confidence intervals (CI) were calculated for each outcome. The I^2 statistic was used to measure heterogeneity. Heterogeneity was considered moderate when I^2 ranged

between 50% and 75% and high when I^2 was more than 75% [10]. For statistical analysis, we used Review Manager version 5.4.1 (the Cochrane Collaboration, 11–13 Cavendish Square, London, W1G 0AN, UK). The results were considered statistically significant when the *P*-value was less than 0.05.

Subgroup and sensitivity analysis

The differences in outcomes between the assessed approaches were tested by subgroup analysis. This analysis was conducted for both the ACS and stable CAD subgroups. Data were sourced from clinical trials that either exclusively enrolled ACS or stable CAD patients or had heterogeneous cohorts following appropriate stratification. A leave-one-out sensitivity analysis was performed to assess whether a single trial accounted for the heterogeneity.

Risk of bias assessment

The risk of bias (ROB) was assessed using the Cochrane-designed tool ROB 2, dedicated to randomized clinical trials [11]. Two independent reviewers (MG and OS) carried out quality evaluation, and all discrepancies were resolved through discussion.

Grading the quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the overall quality of the acquired evidence [12]. GradePRO GDT (McMaster University and Evidence Prime Inc.) was used to build a certainty of evidence table and summary of findings.

RESULTS

The initial online screening identified 11 571 records, eight of which met the inclusion criteria. The trial selection process is illustrated in Figure 1. Altogether, these studies presented data from 4713 patients, 2361 in the FFR group and 2352 in the angiography group. In the meta-analysis, we decided to incorporate the FAME trial with a 2-year follow-up because of the presence of a sub-analysis related to the ACS setting [2]. The predominant revascularization

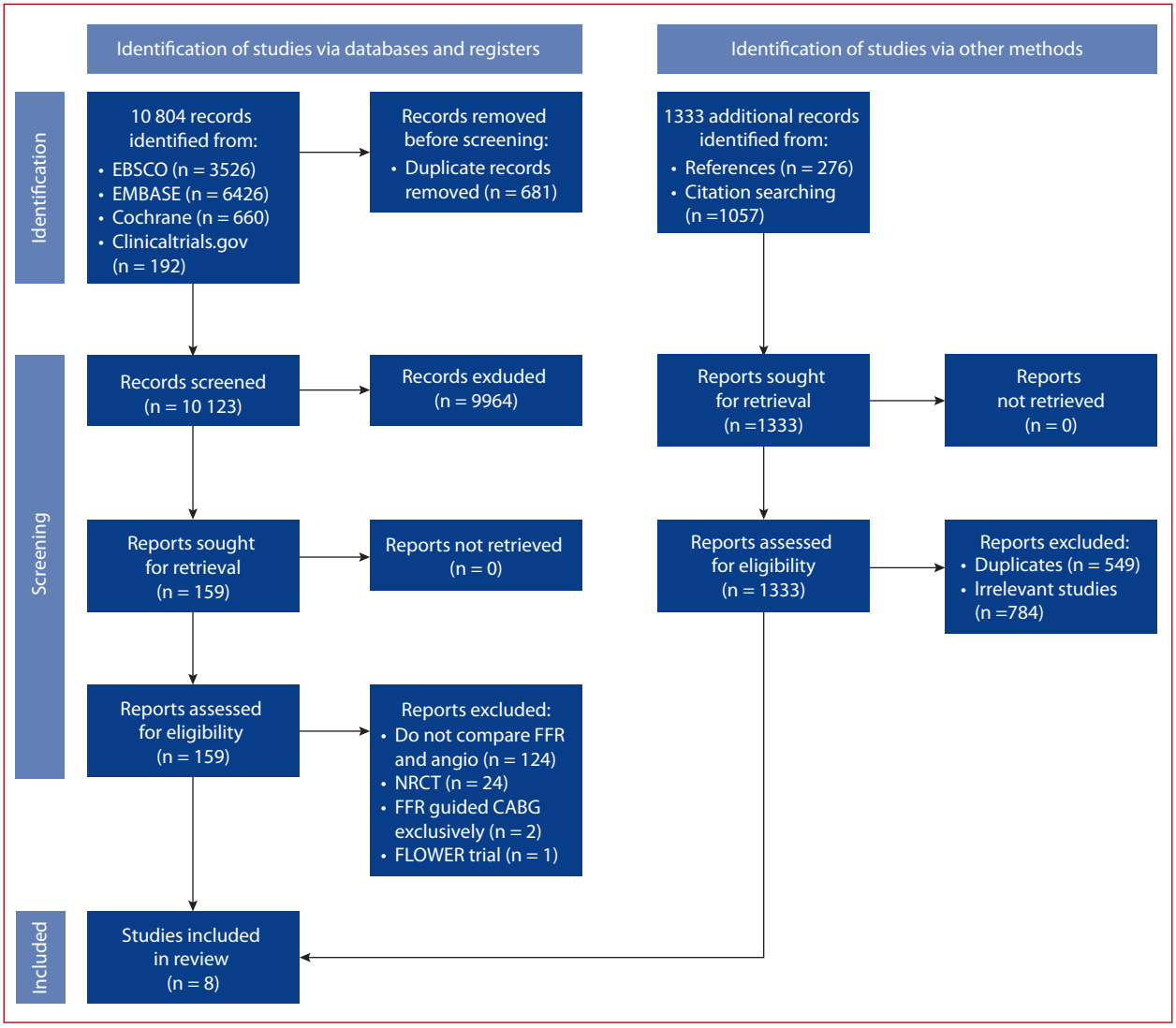


Figure 1 Flowchart of the systematic review process

Table 1. Characteristics of included RCTs

Study	Year	Angio group	FFR group	Enrolment criteria	MACE definition	Follow-up	Main findings
RIPCORD 2	2022	552	548	Stable angina or NSTEMI	All-cause mortality, stroke, MI and unplanned revascularization	1 year	No difference in MACE between the FFR group and the angio group (9.5% vs. 8.7%; $P = 0.064$).
FRAME-AMI	2022	278	284	STEMI or NSTEMI	Death, MI, or unplanned revascularisation	3.5 years	Lower composite rates of MACE were observed in the FFR group compared to the angio group (7.4% vs. 19.7%; $P = 0.003$).
FUTURE	2021	467	460	ACS or stable angina or silent ischemia or atypical chest pain	Death from any cause, nonfatal MI, stroke, unplanned revascularization	1 year	No difference in MACE between FFR group and angio group (14.6% vs. 14.4%; $P = 0.85$).
Zhang et al.	2016	110	110	NSTEMI	Cardiovascular death, nonfatal MI, or unplanned hospitalization for heart failure	1 year	No difference in MACE and MACCE between the FFR-guided group and the angiography-guided group — MACE (8.2% vs. 10%; $P = 0.639$), MACCE (9.1% vs. 11.8%; $P = 0.509$)
DKCRU-SH-VI	2015	160	160	Stable or unstable angina	Cardiac death, MI, or ischemia-driven target vessel revascularization	1 year	No differences between the FFR group and and the angio group according to: MACE (18.1% in both groups; $P = 1.00$)
DEFER-DES	2015	115	114	Stable angina and ACS	Cardiac death, MI, and target lesion revascularization	5 year	No difference in MACE rates between the FFR group and the angio group (11.6 ± 3.0% vs. 14.2 ± 3.3%; $P = 0.55$)
FAMOUS–NSTEMI	2015	174	176	NSTEMI	Cardiac death, hospitalization for MI or heart failure	1 year	No difference in MACE between the FFR and angio groups (8% vs. 8.6%; $P = 0.89$)
FAME	2009	496	509	Stable, unstable angina and NSTEMI	Death, myocardial infarction, and repeat revascularization	2 year	No difference in MACE between the FFR and angio groups (22.4% in the angio group and 17.9% in the FFR group, $P = 0.08$)

Abbreviations: ACS, acute coronary syndrome; angio, angiography; CABG, coronary-artery bypass grafting; FFR, fractional flow reserve; MACCE, major adverse cardiac and cerebral event; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

strategy was treatment with PCI exclusively in five studies and both PCI and CABG in three studies. The dominant definitions of the composite endpoints were all-cause death, myocardial revascularization, and unplanned revascularization. The differences in the MACE components are described in Table 1. The mean follow-up period was 13.3 months. In seven trials, an FFR cut-off ≤0.80 was used to detect the hemodynamic significance of the lesions, except in one study, where a cut-off ≤0.75 was applied [13]. To perform the subgroup analysis, we asked the corresponding authors to share data on the proportion of ACS and stable CAD in the investigated cohorts. The general characteristics of the included trials are listed in Table 2.

MACE

The composite endpoints were reported in 308 participants (13%) in the FFR group and 368 participants (15.6%) in the angiography group. There was no difference in the trial-defined MACE (RR, 0.84; 95% CI, 0.69–1.02; $P = 0.08$) (Figure 2). The sensitivity analysis excluding the RIPCORD 2 trial showed a reduction in MACE for FFR-guided revascularization (RR 0.80; 95% CI, 0.65–0.98; $P = 0.04$) (Supplementary material, *Figure S3*). In the subgroup analysis, the effects remained neutral for the stable CAD population (RR, 1.17; 95% CI, 0.46–2.98; $P = 0.74$) (Supplementary material, *Figure S3*), but a reduction was found in the FFR arm in the ACS subset (RR, 0.71; 95% CI, 0.55–0.92; $P = 0.01$) (Supplementary material, *Figures S1* and *S2*). The sensitivity analysis excluding the FUTURE trial demonstrated a difference in favor of the FFR arm in the ACS group (RR 0.68; 95% CI, 0.50–0.92; $P = 0.01$).

All-cause mortality

Deaths occurred in 60 (2.6%) patients in the FFR group and 63 (2.8%) in the angiography group. There was no difference in all-cause mortality between FFR-guided and angiography-guided revascularization (RR, 1.00; 95% CI, 0.58–1.74; $P = 0.99$). The effects remained neutral for the stable CAD subgroup (RR, 0.72; 95% CI, 0.30–1.73; $P = 0.47$) and for the ACS subgroup (RR, 0.64; 95% CI, 0.37–1.08; $P = 0.10$).

Myocardial infarction

MI occurrence was observed in 123 participants (5.4%) in the FFR-driven group and 165 participants (7.4%) in the angiography-driven group. There was a reduction in MI for FFR-guided revascularization (RR, 0.75; 95% CI, 0.58–0.96; $P = 0.02$). The effects remained for the ACS subgroup (RR, 0.57; 95% CI, 0.41–0.81; $P = 0.002$ but were insignificant for the stable CAD subgroup (RR, 1.04; 95% CI, 0.35–3.11; $P = 0.94$).

Unplanned revascularization

Unplanned revascularization occurred in 155 participants (7.4%) in the FFR group and 173 participants (8.3%) in the angiography group. There was also no difference between the FFR group and the angiography group in the rates of unplanned revascularization procedures (RR, 0.89 [95% CI,

Table 2. Patient and procedural characteristics from included RCTs

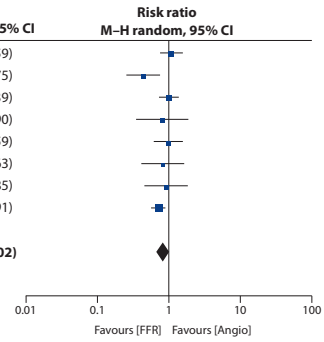
Study	Strategy	Age, mean ± SD, or median (IQR)	Male, %	Diabetes mellitus, %	Tabacco user, %	LVEF,mean ± SD	ACS, %	Left main disease, %	Three vessel disease, %	Heart failure, %	Proportion of PCI, %	Proportion of CABG, %	Second generation DES, %	FFR cut-off	Angiography stenosis thresholds for PCI/CABG
RIPCORD 2	Angio group	64.3 ± 10.2	77.2	17.6	65.0	N/A	53.1	8.7	6.5	23.4	60.9	9.2	N/A	≤0.8	≥30
	FFR group	64.3 ± 10.0	73.5	20.6	58.5	N/A	50.4	7.8	11.3	21.4	56.2	11.9	N/A		
FRAME –AMI	Angio group	62.7 ± 11.5	84.2	30.9	37.8	53.6 ± 10.2	100	N/A	32.4	N/A	100	0	94.8	≤0.8	≥50
	FFR group	63.9 ± 11.4	84.5	34.2	32.0	53.2 ± 9.8	100	N/A	44.7	N/A	100	0	97.3		
FUTURE	Angio group	66 ± 11	82.0	32.0	26.0	56 ± 11	45.61	11	50	N/A	79	12	94	≤0.80	≥50
	FFR group	65 ± 10	85.0	31.0	24.0	55 ± 12	46.96	13	54	N/A	71	12	95		
Zhang et al.	Angio group	70 ± 3.4	70.9	32.7	28.2	N/A	100	N/A	N/A	1.0	100	0	N/A	≤0.8	≥70 (≥50 for left main)
	FFR group	70 ± 3.7	68.2	36.4	26.4	N/A	100	N/A	N/A	2.0	100	0	N/A		
DKCRUSH-VI	Angio group	65.4 ± 9.2	72.5	26.9	40.0	60.6 ± 8.7	77.5	8.8	36.3	N/A	100	0	100	≤0.8	≥70
	FFR group	65.2 ± 9.6	75.6	30.0	41.3	61.3 ± 7.4	79.4	9.4	39.6	N/A	100	0	100		
DEFER-DES	Angio group	63 ± 10	75.0	34.0	33.0	61 ± 9	48	0	23	N/A	100	0	100	≤0.75	40–70
	FFR group	62 ± 10	73.0	26.0	26.0	62 ± 9	51	0	20	N/A	100	0	100		
FAMOUS–NSTEMI	Angio group	61.6 ± 11.1	73.0	14.9	40.8	N/A	100	3.4	7.5	N/A	79.9	6.9	N/A	≤0.8	≥30
	FFR group	62.3 ± 11	75.6	14.8	40.9	N/A	100	1.1	6.8	N/A	71	6.2	N/A		
FAME	Angio group	64.2 ± 10.2	72.6	25.2	31.5	57.1 ± 12.0	35.89	0	N/A	N/A	100	0	100	≤0.8	≥50
	FFR group	64.6 ± 10.3	75.4	24.2	27.1	57.2 ± 11.0	29.47	0	N/A	N/A	100	0	100		

Abbreviations: DES, drug-eluting stent; LVEF, left ventricular ejection fraction; N/A, not applicable; other — see Table 1

A

Study of subgroup	FFR Events	FFR Total	Angio Events	Angio Total	Weight	Risk ratio M–H random, 95% CI
RIPCORD 2	52	548	48	552	15.8%	1.09 (0.75–1.59)
FRAME AMI	18	284	40	278	10.0%	0.44 (0.26–0.75)
FUTURE	67	460	67	467	19.0%	1.02 (0.74–1.39)
Zhang et al.	9	110	11	110	4.8%	0.82 (0.35–1.90)
DKCRUSH-VI	29	160	29	160	12.0%	1.00 (0.63–1.59)
DEFER-DES	13	114	16	115	6.7%	0.82 (0.41–1.63)
FAMOUS-NSTEMI	14	176	15	174	6.5%	0.92 (0.46–1.85)
FAME	106	176	142	496	25.2%	0.73 (0.58–0.91)
Total (95% CI)		**2361**		**2352**	**100.0%**	**0.84 (0.69–1.02)**
Total events	308		368			

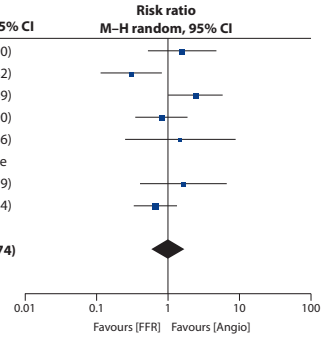
Heterogeneity: Tau² = 0.03; χ^2 = 11.21, df = 7 (*P* = 0.13); I² = 38%
Test for overall effect: Z = 1.73 (*P* = 0.08)



B

Study of subgroup	FFR Events	FFR Total	Angio Events	Angio Total	Weight	Risk ratio M–H random, 95% CI
RIPCORD 2	8	548	5	552	13.4%	1.61 (0.53–4.90)
FRAME AMI	5	284	16	278	15.1%	0.31 (0.11–0.82)
FUTURE	17	460	7	467	16.9%	2.47 (1.03–5.89)
Zhang et al.	9	110	11	110	17.4%	0.82 (0.35–1.90)
DKCRUSH-VI	3	160	2	160	7.3%	1.50 (0.25–8.86)
DEFER-DES	0	114	0	115		Not estimable
FAMOUS-NSTEMI	5	176	3	174	10.0%	1.65 (0.40–6.79)
FAME	13	509	19	496	19.9%	0.67 (0.33–1.34)
Total (95% CI)		**2247**		**2237**	**100.0%**	**1.00 (0.58–1.74)**
Total events	60		63			

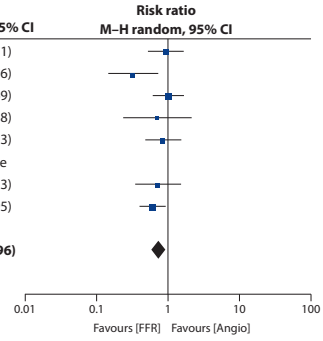
Heterogeneity: Tau² = 0.28; χ^2 = 12.46, df = 6 (*P* = 0.05); I² = 52%
Test for overall effect: Z = 0.01 (*P* = 0.99)



C

Study of subgroup	FFR Events	FFR Total	Angio Events	Angio Total	Weight	Risk ratio M–H random, 95% CI
RIPCORD 2	22	548	23	552	16.1%	0.96 (0.54–1.71)
FRAME AMI	7	284	21	278	8.1%	0.33 (0.14–0.76)
FUTURE	28	460	28	467	19.6%	1.02 (0.61–1.69)
Zhang et al.	5	110	7	110	4.8%	0.71 (0.23–2.18)
DKCRUSH-VI	19	160	22	160	16.0%	0.86 (0.49–1.53)
DEFER-DES	0	114	0	115		Not estimable
FAMOUS-NSTEMI	11	176	15	174	10.0%	0.72 (0.34–1.53)
FAME	31	509	49	496	25.3%	0.62 (0.40–0.95)
Total (95% CI)		**2247**		**2237**	**100.0%**	**0.75 (0.58–0.96)**
Total events	123		165			

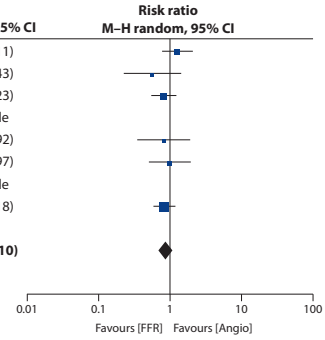
Heterogeneity: Tau² = 0.02; χ^2 = 6.93, df = 6 (*P* = 0.3); I² = 13%
Test for overall effect: Z = 2.27 (*P* = 0.02)



D

Study of subgroup	FFR Events	FFR Total	Angio Events	Angio Total	Weight	Risk ratio M–H random, 95% CI
RIPCORD 2	33	548	26	552	17.2%	1.28 (0.78–2.11)
FRAME AMI	7	284	12	278	5.1%	0.57 (0.23–1.43)
FUTURE	37	460	46	467	25.2%	0.82 (0.54–1.23)
Zhang et al.	0	110	0	110		Not estimable
DKCRUSH-VI	9	160	11	160	5.9%	0.82 (0.35–1.92)
DEFER-DES	15	114	15	115	9.7%	1.01 (0.52–1.97)
FAMOUS-NSTEMI	0	176	0	174		Not estimable
FAME	54	509	63	496	36.9%	0.84 (0.59–1.18)
Total (95% CI)		**2075**		**2068**	**100.0%**	**0.89 (0.72–1.10)**
Total events	155					

Heterogeneity: Tau² = 0.00; χ^2 = 3.39, df = 5 (*P* = 0.64); I² = 0%
Test for overall effect: Z = 1.08 (*P* = 0.28)



E

Study of subgroup	FFR Events	FFR Total	Angio Events	Angio Total	Weight	Risk ratio M–H random, 95% CI
RIPCORD 2	373	548	387	552	29.7%	–0.02 (–0.08 to 0.03)
FRAME AMI	182	284	270	278	15.2%	–0.33 (–0.39 to –0.27)
FUTURE	382	460	424	467	25.0%	–0.08 (–0.12 to –0.03)
Zhang et al.	95	110	104	110	5.9%	–0.08 (–0.16 to 0.00)
DKCRUSH-VI	22	160	51	160	8.6%	–0.18 (–0.27 to –0.09)
DEFER-DES	24	114	44	115	6.2%	–0.17 (–0.29 to –0.06)
FAMOUS-NSTEMI	136	176	151	174	9.4%	–0.10 (–0.17 to –0.02)
FAME	0	509	0	496		Not estimable
Total (95% CI)		**1852**		**1856**	**100.0%**	**–0.12 (–0.14 to –0.09)**
Total events	1214		1431			

Heterogeneity: χ^2 = 69.26, df = 6 (*P* <0.00001); I² = 91%
Test for overall effect: Z = 8.90 (*P* <0.00001)

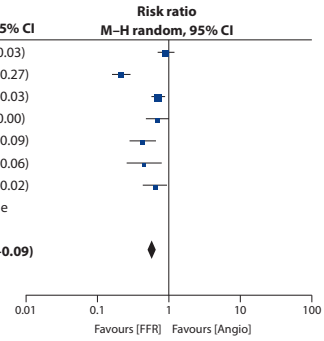


Figure 2 Forest plots of **A.** MACE. **B.** All-cause mortality. **C.** MI. **D.** Unplanned revascularization. **E.** Planned revascularization during index procedure (PCI + CABG). Forrest plots of the subgroup analysis and sensitivity analysis are available in the Supplementary material

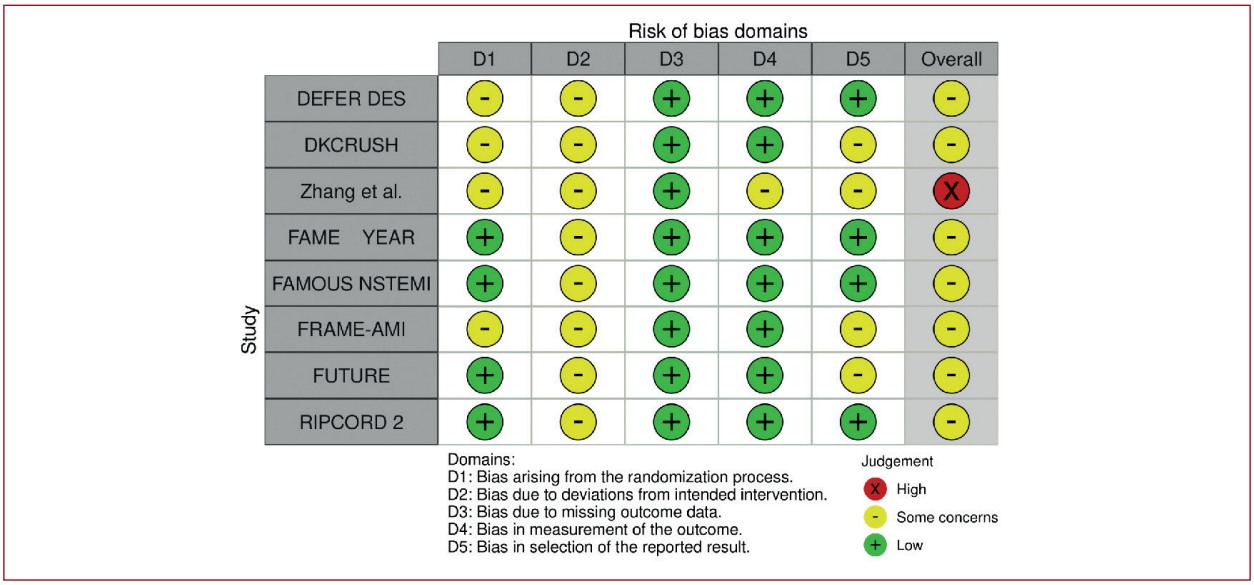


Figure 3 Risk of bias (ROB) of the included studies

0.72–1.10; $P = 0.28$). The effects remained neutral for the ACS subgroup (RR, 0.76; 95% CI, 0.55–1.05; $P = 0.01$) and the stable CAD subgroup (RR, 0.81; 95% CI, 0.53–1.25; $P = 0.34$). In the ACS subset, sensitivity analyses demonstrated that the reduction of unplanned revascularization in the FFR arm reached statistical significance after removing the DK-CRUSH VI trial (RR, 0.76; 95% CI, 0.59–0.98; $P = 0.04$).

Planned revascularization during the index procedure

The number of performed index revascularization procedures was 1214 (65.5%) in the FFR group and 1431 (77.1%) in the angiography group, resulting in a lower rate of revascularization in the FFR arm (standardized mean difference — 0.12; 95% CI, –0.14 to –0.09; $P < 0.0001$). The effects almost achieved statistical significance in the ACS subgroup analysis (standardized mean difference, –0.17; 95% CI, –0.34 to 0.00; $P = 0.05$).

ROB and certainty of the evidence

The results of the ROB assessment are shown in Figure 3. The quality of evidence in RCTs was low for three endpoints and moderate for two endpoints (Supplementary material, *Table S1*).

DISCUSSION

To our knowledge, this is the first meta-analysis of RCTs that compared FFR- and angiography-driven revascularization head-to-head in obstructive CAD and showed the superiority of FFR guidance. The main finding of our analysis was that functional assessment significantly reduced MI rates. Moreover, this effect was achieved with a diminished frequency of revascularization in the FFR arm. In comparison with other meta-analysis trials, selection was performed according to the latest ESC guidelines, which do not recommend the application of physiological evaluation in multivessel disease (MVD) in STEMI [6, 14, 15]. The current guidelines recommend complete revascularization for non-infarct-related arteries based on angiographic severity in this setting. In line with this recommendation, we decided to exclude the FLOWER MI trial, where functional measurements were conducted exclusively among STEMI patients, from our meta-analysis [16].

A novel finding of our meta-analysis is that functional guidance can significantly reduce the number of MI episodes in the entire population and also the ACS subset. This outcome can likely be attributed to the capability of physiological evaluation to accurately detect the lesions, which are responsible for reversible ischemia, thereby enabling more informed decisions about initiating invasive treatments. Notably, a lower PCI rate in the FFR arm contributed to the reduced risk of potential complications such as stent thrombosis, in-stent restenosis, and PCI-related MI, as convincingly shown by the results from the FRAME-AMI trial [8]. In that study, the FFR arm recorded three PCI-related MI incidents and 11 in the angiography arm (HR 0.26; CI, 0.07–0.94; $P = 0.04$). It is worth noting that complete PCI in ACS at the time of MI may lead to an underestimation of PCI-related MI due to the overlapping release of troponin from the culprit lesion and PCI-related myocardial damage. Furthermore, a sub-analysis of the FRAME-AMI trial demonstrated that FFR-driven PCI would be more cost-effective compared to the angiography-guided approach [17].

The main uncertainty related to FFR use at the time of MI is that functional assessments in areas of infarction or ischemia can be unreliable due to the impossibility of achieving sufficient hyperemia. One potential mechanism is microvascular dysfunction, which can lead to false-negative FFR values. What is more, microvascular contraction can also occur in the territory of non-culprit lesions [18]. Previously, several studies showed that complete revascularization based on angiography guidance

in STEMI improves the outcomes in comparison with culprit-vessel-only PCI [19–20]. Further trials demonstrated the superiority of FFR-guided complete revascularization in ACS patients with MVD [21, 22]. However, a subsequent meta-analysis demonstrated that complete revascularization in patients with STEMI and MVD is superior to culprit-vessel-only PCI when the decision to perform PCI is based solely on angiographic severity rather than on FFR assessment [23]. In consequence, the current ESC guidelines provide robust recommendations for PCI in STEMI with MVD, advocating complete revascularization based on angiographic assessment in class IB. Conversely, recommendations for NSTEMI patients are less robust. The debatable issue remains the optimal timing for complete PCI in MVD as well as the choice of the best guidance tool for intermediate lesions [24]. The results from observational data suggest that complete revascularization in NSTEMI and MVD can also be superior to culprit-vessel-only PCI [25]. In the FAMOUS-NSTEMI trial, a greater proportion of patients in the FFR arm had deferred PCI compared to the angiography group, and this results achieved almost statistical significance (71.0% in the FFR group and 79.9% in the angiography group; $P = 0.057$). We hypothesize that delaying physiological assessments in NSTEMI until the staged procedure would result in fewer PCIs without the risk of false-negative FFR results while achieving equivalent or even superior clinical outcomes. Further studies are required to assess the period necessary for recovery of the vasodilatory capacity of the coronary circulation to conduct a reliable physiological evaluation.

There was a trend toward a decreased rate of MACE in the FFR group compared to the angiography group (308 vs. 368 events, respectively), and this analysis almost reached statistical significance ($P = 0.08$). The sensitivity analysis demonstrated that after the exclusion of the RIPCORD 2 trial, FFR guidance decreased the incidence of MACE (RR, 0.80; 95% CI, 0.65–0.98; $P = 0.04$) [7]. That study aimed to assess whether systematic FFR measurement can improve outcomes. Functional assessments were conducted in all vessels suitable for revascularization with at least 1 stenosis of ≥30% in visual assessment. In consequence, this manner of administering FFR can be a bias in the interpretation of the findings. Moreover, this result underscores another issue in RCTs evaluating FFR utility – population heterogeneity. This includes different types of ACS alongside stable CAD and applying FFR in various contexts, which leads to challenges in interpreting the results. We demonstrated this effect in the subgroup analysis that focused exclusively on ACS patients. In that cohort, the FFR group exhibited a reduction in MACE (RR, 0.71 [95% CI, 0.55–0.92]; $P = 0.01$). The results of the subgroup analysis for stable CAD are questionable due to the limited available data; our findings are based mainly on the outcomes from the FAME trial.

Although data support FFR utilization for guiding revascularization, the adoption of this technique in clinical practice remains relatively low [26]. This can be attributed to several factors, including longer procedural time, additional costs, and reimbursement problems. A recent study showed that FFR adoption slowly rose between 2009 and 2017 from 14.8% to 18.5% in CAD with intermediate lesions and from 44% to 75% in patients who underwent PCI [27]. In the context of ACS, physiological assessments can be particularly valuable in NSTEMI patients to identify the culprit lesion, especially when coronary angiography images are inconclusive or ambiguous. Alternatively, a novel angiography-derived index calculating FFR values without the need for pressure wires and hyperemic agents could overcome these barriers. However, its diagnostic accuracy still requires improvements [28–31].

Limitations

This meta-analysis has several limitations. First, the definition of MACE differed in the studies. Most RCTs used composite endpoints consisting of all-cause death, MI, and unplanned revascularization; however, the inclusion of stroke varied. Second, there were differences in the duration of follow-up and clinical heterogeneity of the study participants across the RCTs. Third, this was not a patient-level meta-analysis, and we were unable to extract cohorts treated with a uniform method (either PCI or CABG). However, since most trials utilized PCI exclusively for revascularization, we decided to exclude the FARGO and GRAFFITI trials, where CABG was employed exclusively [32, 33]. For similar reasons, we were unable to exclude patients with STEMI in the FRAME-AMI trial. Nevertheless, the majority of the study population, exceeding 50%, involved NSTEMI patients, and sensitivity analysis indicated that this trial did not impact the outcomes.

CONCLUSIONS

The adoption of FFR in myocardial revascularization in CAD patients has been associated with a significant reduction of MI across the entire study population and also in the ACS subset. Moreover, these results were achieved with a significantly lower rate of revascularization compared with using only angiographic guidance. Functional assessment can accurately identify epicardial stenosis that is hemodynamically significant and requires revascularization. These results are likely attributable to the occurrence of PCI-related events and necessary stenting in the angiography arm. We believe that the results of our meta-analysis, which shows the potential for outcome improvement, will encourage interventional cardiologists to integrate functional assessments in catheterization laboratories routinely. Further RCTs are necessary to elucidate the best timing and assessment tool to perform multivessel PCI in the NSTEMI setting.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Conflict of interest: None declared.

Funding: This work was supported by the subsidy no. SUBZ. A460.24.040 for the Institute of Heart Diseases, Wroclaw Medical University, Poland.

REFERENCES

1. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012; 367(11): 991–1001, doi: 10.1056/NEJMoa1205361, indexed in Pubmed: 22924638.
2. Pijls NHJ, Fearon WF, Tonino PAL, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease. J Am Coll Cardiol. 2010; 56(3): 177–184, doi: 10.1016/j.jacc.2010.04.012, indexed in Pubmed: 20537493.
3. Neumann FJ, Sousa-Uva M. ‚Ten commandments' for the 2018 ESC/EACTS Guidelines on Myocardial Revascularization. Eur Heart J. 2019; 40(2): 79–80, doi: 10.1093/eurheartj/ehy855, indexed in Pubmed: 30615155.
4. Virani S, Newby L, Arnold S, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023; 148(9): e9–e119, doi: 10.1161/cir.0000000000001168, indexed in Pubmed: 37471501.
5. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145(3): e4–e17, doi: 10.1161/CIR.0000000000001039, indexed in Pubmed: 34882436.
6. Byrne R, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023; 44(38): 3720–3826, doi: 10.1093/eurheartj/ehad191, indexed in Pubmed: 37622654.
7. Stables RH, Mullen LJ, Elguindy M, et al. Routine pressure wire assessment versus conventional angiography in the management of patients with coronary artery disease: the RIPCORD 2 trial. Circulation. 2022; 146(9): 687–698, doi: 10.1161/CIRCULATIONAHA.121.057793, indexed in Pubmed: 35946404.
8. Lee JM, Kim HK, Park KH, et al. Fractional flow reserve versus angiography-guided strategy in acute myocardial infarction with multivessel disease: A randomized trial. Eur Heart J. 2023; 44(6): 473–484, doi: 10.1093/eurheartj/ehac763, indexed in Pubmed: 36540034.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021: n71, doi: 10.1136/bmj.n71.
10. Grant J, Hunter A. Measuring inconsistency in knowledgebases. J Intell Inf Sys. 2006; 27(2): 159–184, doi: 10.1007/s10844-006-2974-4.
11. Chapter 8: Assessing risk of bias in a randomized trial. Cochrane Training. https://training.cochrane.org/handbook/current/chapter-08 (July 16, 2024).
12. Ansari MT, Tsertsvadze A, Moher D. Grading quality of evidence and strength of recommendations: A perspective. PLoS Med. 2009; 6(9): e1000151, doi: 10.1371/journal.pmed.1000151, indexed in Pubmed: 19753108.
13. Park SH, Jeon KH, Lee JM, et al. Long-term clinical outcomes of fractional flow reserve-guided versus routine drug-eluting stent implantation in patients with intermediate coronary stenosis: Five-year clinical outcomes of DEFER-DES trial. Circ Cardiovasc Interv. 2015; 8(12): e002442, doi: 10.1161/CIRCINTERVENTIONS.115.002442, indexed in Pubmed: 26643736.
14. Gallone G, Angelini F, Fortuni F, et al. Angiography- vs. physiology-guided complete revascularization in patients with ST-elevation myocardial infarction and multivessel disease: who is the better gatekeeper in this setting? A meta-analysis of randomized controlled trials. Eur Heart J Qual Care Clin Outcomes. 2020; 6(3): 199–200, doi: 10.1093/ehjqcco/qcaa007, indexed in Pubmed: 32011660.
15. Archilletti F, Ricci F, Pelliccia F, et al. Coronary angiography- or fractional flow reserve-guided complete revascularization in multivessel disease STEMI: A Bayesian hierarchical network meta-analysis. Int J Cardiol. 2023; 370: 122–128, doi: 10.1016/j.ijcard.2022.10.170, indexed in Pubmed: 36328114.
16. Puymirat E, Cayla G, Simon T, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. N Engl J Med. 2021; 385(4): 297–308, doi: 10.1056/nejmoa2104650.
17. Hong D, Lee SH, Lee J, et al. Cost-effectiveness of fractional flow reserve-guided treatment for acute myocardial infarction and multivessel disease: a prespecified analysis of the FRAME-AMI randomized clinical trial. JAMA Netw Open. 2024; 7(1): e2352427, doi: 10.1001/jamanetworkopen.2023.52427, indexed in Pubmed: 38270954.
18. Gibson CM, Ryan KA, Murphy SA, et al. Impaired coronary blood flow in nonculprit arteries in the setting of acute myocardial infarction. J Am Coll Cardiol. 1999; 34(4): 974–982, doi: 10.1016/s0735-1097(99)00335-6, indexed in Pubmed: 10520778.
19. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med. 2019; 381(15): 1411–1421, doi: 10.1056/nejmoa1907775, indexed in Pubmed: 31475795.
20. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol. 2015; 65(10): 963–972, doi: 10.1016/j.jacc.2014.12.038, indexed in Pubmed: 25766941.
21. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015; 386(9994): 665–671, doi: 10.1016/s0140-6736(15)60648-1, indexed in Pubmed: 26347918.
22. Smits PC, Laforgia PL, Abdel-Wahab M, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. N Engl J Med. 2017; 376(13): 1234–1244, doi: 10.1056/NEJMoa1701067, indexed in Pubmed: 28317428.
23. Gallone G, Angelini F, Fortuni F, et al. Angiography- vs. physiology-guided complete revascularization in patients with ST-elevation myocardial infarction and multivessel disease: who is the better gatekeeper in this setting? A meta-analysis of randomized controlled trials. Eur Heart J Qual Care Clin Outcomes. 2020; 6(3): 199–200, doi: 10.1093/ehjqcco/qcaa007, indexed in Pubmed: 32011660.
24. Sardella G, Lucisano L, Garbo R, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: the SMILE trial. J Am Coll Cardiol. 2016; 67(3): 264–272, doi: 10.1016/j.jacc.2015.10.082, indexed in Pubmed: 26796390.
25. Rathod KS, Koganti S, Jain AK, et al. Complete versus culprit-only lesion intervention in patients with acute coronary syndromes. J Am Coll Cardiol. 2018; 72(17): 1989–1999, doi: 10.1016/j.jacc.2018.07.089, indexed in Pubmed: 30336821.
26. Kaziród-Wolski K, Sielski J, Gąsior M, et al. Factors affecting short- and long-term survival of patients with acute coronary syndrome treated invasively using intravascular ultrasound and fractional flow reserve: Analysis of data from the Polish Registry of Acute Coronary Syndromes 2017-2020. Kardiol Pol. 2023; 81(3): 265–272, doi: 10.33963/KP.a2022.0261, indexed in Pubmed: 36404732.
27. Parikh RV, Liu G, Plomondon ME, et al. Utilization and outcomes of measuring fractional flow reserve in patients with stable ischemic heart disease. J Am Coll Cardiol. 2020; 75(4): 409–419, doi: 10.1016/j.jacc.2019.10.060, indexed in Pubmed: 32000953.
28. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. J Am Heart Assoc. 2018; 7(14), doi: 10.1161/JAHA.118.009603, indexed in Pubmed: 29980523.

29. Masdjedi K, Tanaka N, Van Belle E, et al. Vessel fractional flow reserve (vFFR) for the assessment of stenosis severity: the FAST II study. EuroIntervention. 2022; 17(18): 1498–1505, doi: 10.4244/EIJ-D-21-00471, indexed in Pubmed: 34647890.
30. Collet C, Onuma Y, Sonck J, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J. 2018; 39(35): 3314–3321, doi: 10.1093/eurheartj/ehy445, indexed in Pubmed: 30137305.
31. Dębski MA, Kruk M, Bujak S, et al. Benefits of the selective invasive strategy guided by CTA and CTA-derived fractional flow reserve in patients with coronary artery disease. Kardiol Pol. 2023; 81(3): 252–258, doi: 10.33963/KP.a2022.0264, indexed in Pubmed: 36446067.
32. Thuesen AL, Riber LP, Veien KT, et al. Health-related quality of life and angina in fractional flow reserve- versus angiography-guided coronary artery bypass grafting: FARGO trial (Fractional flow reserve versus Angiography Randomization for Graft Optimization). Circ Cardiovasc Qual Outcomes. 2021; 14(6): e007302, doi: 10.1161/CIRCOUTCOMES.120.007302, indexed in Pubmed: 34078097.
33. Toth G, Bruyne BDe, Kala P, et al. Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting: the GRAFFITI trial. EuroIntervention. 2019; 15(11): e999–e1005, doi: 10.4244/eij-d-19-00463.