One-year clinical outcome of angiography, fractional flow reserve and instantaneous wave-free ratio guided percutaneous coronary intervention: A PRISMA-compliant meta-analysis

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Abstract. The present study aimed to compare the clinical outcome of patients with coronary artery disease (CAD) who underwent a revascularization using conventional coronary angiography or a physiologically guided revascularization with Fractional Flow Reserve (FFR). Furthermore, outcomes in FFR guided percutaneous coronary intervention (PCI) and instantaneous wave-free ratio (iFR) guided PCI were compared. The analysis was performed for reported outcomes at a 1-year follow-up. After searching PubMed, EMBASE, and Web of Science for suitable publications, a total of 15,880 subjects were included. Comparing angiography guided and FFR guided PCI showed no significant difference in major adverse cardiac events [odds ratio (OR), 0.78; 95% confidence interval (CI), 0.59-1.04; P=0.09; I^2=73%], death from any cause (OR, 0.74; 95% CI, 0.46-1.18; P=0.20; I^2=74%), myocardial infarction (OR, 0.93; 95% CI, 0.81-1.07; P=0.31; I^2=0%) or unplanned revascularization (OR, 0.71; 95% CI, 0.41-1.23; P=0.22; I^2=79%). In addition, no significant difference could be found between iFR and FFR guided PCI for major adverse cardiac events (OR, 0.97; 95% CI; 0.76-1.23; P=0.81; I^2=0%), death from any cause (OR, 0.66; 95% CI, 0.40-1.11; P=0.12; I^2=0%), myocardial infarction (OR, 0.83; 95% CI, 0.56-1.24; P=0.37) or unplanned revascularization (OR, 1.16; 95% CI, 0.85-1.58; P=0.34; I^2=16%). Overall, there was a tendency towards better outcomes of FFR in all four clinical endpoints compared with angiography guiding of PCI, and furthermore iFR showed no significant inferiority when compared to FFR in said clinical endpoints. When conducting a network meta-analysis, the results confirmed a non-inferiority of iFR compared to angiography guided revascularization.

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Abbreviations: CAD, coronary artery disease; CABG, coronary artery bypass graft; DES, drug eluting stents; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiac event; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized clinical trial

Key words: atherosclerosis, coronary artery disease, coronary angiography, fractional flow reserve, instantaneous wave-free ratio, percutaneous coronary intervention, meta-analysis

Introduction

Finding the best course of treatment for coronary artery disease (CAD) is a recurring challenge in everyday clinical practice. Coronary revascularization is only justified for hemodynamically relevant stenosis (1,2). While coronary angiography can identify a coronary stenosis by conventional visual assessment, defining the functional hemodynamic significance of an intermediate stenosis can be difficult.

During cardiac catherization, the functional flow reserve (FFR) can be measured as the maximum available blood flow in a stenosed coronary segment. FFR is the current gold standard for deciding if revascularization is required in angiographically ambiguous coronary artery stenosis and is recommended by the 2014 ESC/EACTS guidelines on myocardial revascularization and the 2011 ACCF/AHA/SCAI guidelines for percutaneous coronary intervention (PCI) (3,4).

Despite this recommendation and the alleged benefits, the use of FFR is still limited. The administration of vasodilators such as adenosine, which is required to induce maximal hyperaemia when measuring FFR, can cause side effects (i.e. chest pain, dyspnoea, AV-blockage) during the procedure. Those side effects, cost and increased procedural time are preventing FFR from becoming a standard procedure in day-to-day clinical setting.

A rather new method used to determine the severity of a coronary stenosis is the instantaneous wave-free ratio (iFR). By identifying a period of naturally occurring constant peripheral resistance during diastole, there is no need for vasodilators (5).

Several studies have shown similar diagnostic accuracy for FFR and iFR in the same coronary artery (5-7).

Following the described comparable accuracy of FFR and iFR, the goal of this meta-analysis was to compare the clinical outcome of patients with CAD in which the stenosis was either evaluated visually by coronary angiography alone, or by hemodynamic assessment using FFR or iFR.

Materials and methods

Study design. This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and is based on the review of previously published articles (8-16). No ethical approval and patient consent were necessary.

Literature search. In July 2017 PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), were searched for studies evaluating the clinical outcomes of FFR and iFR. The keywords were 'fractional flow reserve' and 'myocardial' or 'fractional flow reserve' or 'wave-free ratio' or 'iFR and coronary' or 'FFR and coronary' with no other filter. No language restrictions were applied. We selected studies, which used a comparative analysis to identify a culprit coronary lesion.

Patient population with inclusion and exclusion criteria. The following inclusion criteria were applied. The design was either a randomized clinical trial (RCT) or an observational study comparing either angiography and FFR guided or iFR and FFR guided PCI. Participants were adult (18 years and older) patients with indication for PCI. All data of one-year clinical outcomes (major adverse cardiac event (MACE), death from any cause, myocardial infarction (MI) or unplanned revascularization) could be retrieved from the published full text.

We applied the following exclusion criteria. The studies were not conducted on humans (studies on animals or *in vitro* systems). The literature presented results from a sub-study, was a duplicate or did not report clinical outcomes of angiography or FFR and iFR. All literature, that contained only diagnostic studies, surveys, reviews, case reports, comments, or meta-analysis. Three investigators (SB, ACS and VB) selected studies independently, and disagreements were resolved by discussion among all authors.

The following data of eligible studies were documented (Table I): Name of the study, first author, year of publication, and details of the study design, characteristics of patients, data of clinical outcomes, and the studies were sorted by analyzed type of culprit assessment.

Statistical analysis. In case the extracted data was appropriate for pooled analysis, a meta-analysis was performed. Dichotomous data was analyzed using the Mantel-Haenszel model and reported as an odds ratio (OR). Forest plots were used for visualization of the results.

The heterogeneity of studies was calculated using the I^2 index. An I^2 value of 0-25% represents insignificant heterogeneity; >25-50% low heterogeneity; >50-75% moderate heterogeneity; and >75% high heterogeneity (17). All results were calculated using a random-effects model. If concerns for high heterogeneity existed, a sensitivity analysis was performed. Funnel plots were used to visualize publication bias. For other bias, a risk of bias assessment figure was used (Fig. 1). The comparison between angiography and iFR was performed with a network meta-analysis. For meta-analysis calculations, the Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and for network meta-analysis the SAS system release version 9.3 (SAS Institute Inc., Cary, NC, USA) was used. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 756 studies were screened, and nine studies were identified that fulfilled the previously determined inclusion criteria. A flow chart shows the selection process and the reasons for exclusion (Fig. 2). A total of 694 articles were eliminated, since their titles or abstracts did not fit our inclusion criteria.

The full-texts of 62 articles were assessed and 53 were not included in the quantitative and qualitative analysis since they did not contain a one-year follow-up or only analyzed a single method of coronary artery lesion evaluation. In total, the remaining studies included 15,880 patients with a one-year follow-up for MACE-after PCI. Five studies and 8,403 patients were used for the analysis of angiography guided PCI, seven studies with 5,223 patients were used to analyze the FFR guided PCI and two studies with 2,254 patients were used for analysis of the iFR guided PCI. The exact number of patients for each study can be seen in Table I.

Overall, the nine studies did not have significant differences regarding patient baseline characteristics, which can be seen in Table II. Table III shows the rates for MACE one year after the intervention as well as the individual components of MACE, death from any cause, MI-and unplanned revascularization.

Analysis of one-year rates associated with angiography guided vs. FFR guided PCI. All the included studies reported on the outcomes of MACE. After one year the results were OR: 0.78 [95% CI: 0.59-1.04]; P=0.09, I^2=73% and were supportive of better outcomes using FFR guided PCI. As for the single components of MACE, data for death from any cause was available in six of the seven studies and found a slight tendency towards FFR guided PCI with OR: 0.74 [95% CI: 0.46-1.18]; P=0.20, I^2=74%. Five studies published outcomes for MI and when comparing both methods, the results were OR: 0.93 [95% CI: 0.81-1.07]; P=0.31, I^2=0%, but showed no significant difference. Unplanned revascularization was reported in four of the included studies, and they also leaned in favour of FFR guided PCI with an OR: 0.71 [95% CI: 0.41-1.23]; P=0.22, I^2=79%. Forest plots for all primary outcomes can be seen in Fig. 3.

When excluding the three retrospective studies (9,10,14) the preference for FFR remained, but the homogeneity changed to OR: 0.77 [95% CI: 0.59-1.00]; P=0.05, I^2=0% regarding MACE. When comparing outcomes for MI and excluding the retrospective studies, three studies remained, and the results stayed within the same range with an OR: 0.70 [95% CI:

Table I. Characteristics of the included studies.

A, Studies comparing FFR guided PCI and angiography guided PCI

Author, year	Design	Centers (Countries)	Number of enrolled patients for each method[a]	Indication for PCI	Exclusion criteria	Outcomes reported	Maximum Follow-up period (months)	(Refs.)
Tonino *et al* 2009	Prospective RCT	20 (N.A.)	509 (FFR) 496 (Angio)	Multivessel CAD (50% of the vessel diameter in at least two major epicardial coronary arteries)	Recent STEMI (<5 days); NSTEMI with peak creatinine kinase >1,000 U/l; significant left main CAD; previous CABG; cardiogenic shock; extremely tortuous or calcified coronary arteries; life expectancy <2 years; contraindication for drug-eluding stents; pregnancy	Primary endpoint: MACE Secondary endpoints: Procedure time; amount of contrast agent; functional CCS class (after 1 year); HRQoL; number of antianginal medication; individual components of MACE; MACE at 30 days and 6 months; cost-effectiveness	12	(8)
Puymirat *et al* 2012	Retrospective, nonrandomized	1 (1)	222 (FFR) 495 (Angio)	Stable or unstable Angina in small coronary vessel (<3 mm diameter)	Patients with PCI treatment in vessels ≥3 mm; bypass graft stenting; STEMI or non-STEMI; PCI without stenting	Primary endpoint: MACE Secondary endpoints: Stent thrombosis; periprocedural MI; bleeding complications (major thrombolysis in MI); use of transfusion during hospital stay	60	(9)
Li *et al* 2013	Retrospective, nonrandomized	1 (1)	1,090 (FFR) 6,268 (Angio)	Patients referred for revascularization	STEMI; cardiogenic shock; referred for CABG	Primary endpoint: MACE Secondary endpoint: death; MI; repeated revascularization	84	(10)
Chen *et al* 2015	Prospective RCT	8 (1)	160 (FFR) 160 (Angio)	Silent ischemia, Stable or unstable Angina with a single true coronary bifurcation lesion (diameter of stenosis ≤50% in both the main vessel and the side branch, each with a reference diameter of ≥2.5 to ≤4.5 mm)	MI within one month; left ventricular ejection <30%; previous CABG; a distal left main coronary artery trifurcation lesion with a no canalized right coronary artery chronic total occlusion; calcification requiring rotational atherectomy; planned surgery necessitating antiplatelet therapy interrupting within 6 months post-PCI; study drug contraindication or intolerance; estimated glomerular filtration rate <40 ml/min/1.73 m^2: platelet count <10x10^9/l; liver dysfunction;	Primary endpoint: 1 year rate of MACE Secondary endpoints: individual MACE (cardiac death, MI or TVR); stent thrombosis; restenosis	12	(11)

Table I. Continued.

A, Studies comparing FFR guided PCI and angiography guided PCI

Author, year	Design	Centers (Countries)	Number of enrolled patients for each method[a]	Indication for PCI	Exclusion criteria	Outcomes reported	Maximum Follow-up period (months)	(Refs.)
					pregnancy; expected life span <1 year			
Layland *et al* 2015	Prospective RCT	6 (1)	176 (FFR) 174 (Angio)	NSTEMI and at least one risk factor for CAD with invasive management planned or history of recurrent ischemic symptoms within 5 days	Presence of ischemic symptoms without medical therapy; hemodynamic instability; MI with persistent ST elevation; anti-platelet intolerance; planned non-coronary surgery; history of CABG; coronary disease; life expectancy <1 year	Primary endpoint: Difference in patient numbers allocated to medical treatment between the PCI and the FFR guided group Secondary endpoint: Feasibility and safety of routine FFR; relationship between FFR and stenosis severity as assessed by angiography; MACE; hospital resources; HRQoL	12	(12)
Park *et al* 2015	Prospective RCT	6 (1)	114 (FFR) 115 (Angio)	Intermediate coronary stenosis in a native coronary artery with a reference diameter of <2.5 mm	Angiographically significant left main disease; cardiogenic shock; chronic kidney disease; a life expectancy <2 years; conductions disturbance more than first degree AV-block; contraindication to adenosine	Primary endpoint: MACE (after 2 and 5 years)	60	(13)
De Backer *et al* 2016	Retrospektive, nonrandomized	1 (1)	695 (FFR) 695 (Angio)	Stable Angina	Coronary stenosis <50% or >89%	Primary endpoint: MACE Secondary endpoints: Death; MI; repeated revascularization; combined endpoint of death and MI	48	(14)

B, Studies comparing FFR guided PCI and instantaneous wave-free ratio (iFR®) guided PCI

Davies *et al* 2017	Prospective RCT	49 (19)	1,250 (FFR) 1,242 (iFR)	Intermediate coronary stenosis	Tandem stenosis, previous CABG, significant left main artery stenosis, total coronary occlusion, restenosis, hemodynamic instability, contraindication to adenosine	Primary endpoint: MACE	12	(15)

Table I. Continued.

B, Studies comparing FFR guided PCI and instantaneous wave-free ratio (iFR®) guided PCI

Author, year	Design	Centers (Countries)	Number of enrolled patients[b]	Indication for PCI	Exclusion criteria	Outcomes reported	Maximum Follow-up period (months)	(Refs.)
					administration or PCI or drug eluting stent, heavily calcified or tortuous vessels, significant hepatic or lung disease or malignant disease with unfavorable prognosis, pregnancy, severe valvular heart disease, recent STEMI, more than one target vessel			
Götberg *et al* 2017	Prospective RCT	15 (3)	1,007 (FFR) 1,012 (iFR)	Stable or unstable Angina, NSTEMI	Previous CABG; life expectancy <1 year; unstable hemodynamics	Primary endpoint: MACE Secondary endpoints: MI; death; unplanned revascularization; chest discomfort during the procedure; TVR; stent thrombosis; restenosis	12	(16)

[a]Total: 2,966 (FFR) and 8,387 (Angio); [b]Total: 2,257 (FFR) and 2,254 (iFR). Angio, angiography; CAD, coronary artery disease; CABG, coronary artery bypass graft; CCS, canadian cardiovascular society; FFR, fractional flow reserve; HRGoL, health-related quality of Life; iFR, instantaneous wave-free ratio; MACE, major adverse coronary event; MI, myocardial infarction, NSTEMI; non ST elevation myocardial infarction; OS, observational study; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

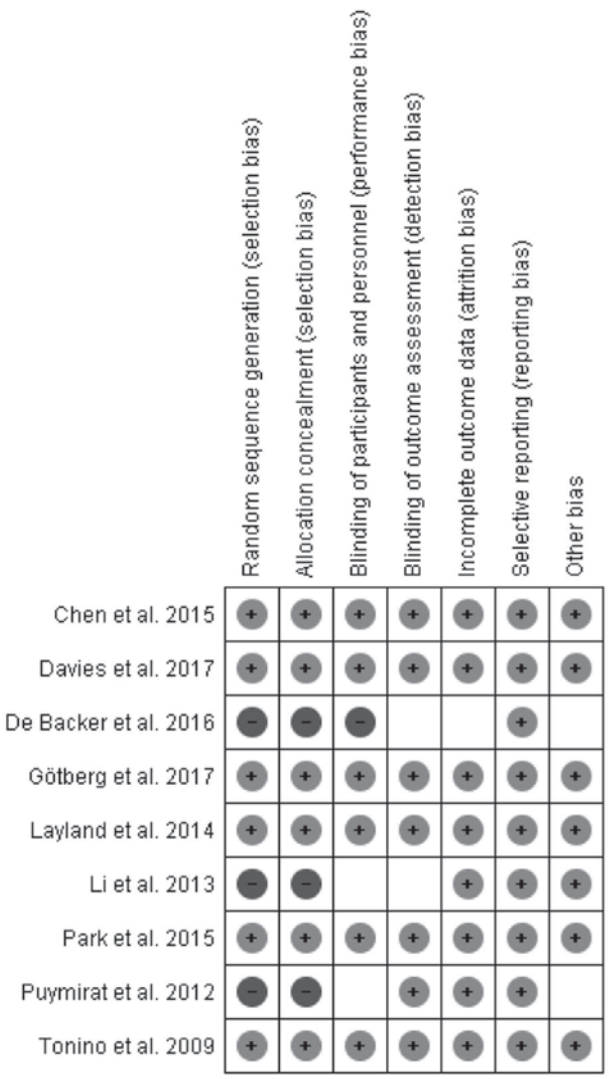

Figure 1. Table assessing risk of bias.

0.50-1.00]; P=0.05, I^2=0%. The assessment for any risk of bias, which is visualized in Fig. 1, only showed a high risk for selection and performance bias in those three retrospective studies.

Analysis of one-year rates associated with FFR guided vs. *iFR guided PCI*. When analyzing the two available studies, there was no significant difference between FFR and iFR regarding MACE with OR: 0.97 [95% CI: 0.76-1.23]; P=0.81. Both studies also reported on the individual components of MACE, and when comparing the two methods in terms of death from any cause (OR: 0.66 [95% CI: 0.40-1.11]; P=0.12, I^2=0%), MI OR: 0.83 [95% CI: 0.56-1.24]; P=0.37, I^2=0%, and unplanned revascularization (OR: 1.16 [95% CI: 0.85-1.58]; P=0.34, I^2=16%), neither reached the level of significance but showed a tendency towards iFR guided revascularization. The forest plots for all primary outcomes are presented in Fig. 4.

Network-analysis of one-year rates associated with angiography guided vs. *iFR guided PCI*. When conducting a network-analysis to compare angiography and iFR guided revascularization after one-year, the result for MACE was OR: 0.80 [95% CI: 0.55-1.17]; P=0.25. Death from any cause had an OR of: 1.12 [95% CI: 0.56-2.25]; P=0.75 and MI an OR: 1.12 [95% CI: 0.74-1.71]; P=0.60. The results for unplanned revascularization were OR: 0.61 [95% CI: 0.33-1.15]; P=0.13.

Discussion

This meta-analysis was conducted to analyze the clinical outcomes as described above of studies containing angiography and FFR guided PCI or iFR compared to FFR guided PCI. When comparing FFR and iFR with angiography outcomes, the main finding was a tendency towards FFR/iFR in all 4 clinical endpoints.

With the analysis of MACE having factored in all seven included studies, one could interpret these results to be the most convincing. When looking at the Odds Ratio, a tendency towards FFR becomes clear, and this is supported by the results of the individual components of MACE. Although the I^2 of MACE, death from any cause and unplanned revascularization were >50%, we decided not to exclude further studies in order to uphold a larger number of included patients.

FFR was first tested on its usefulness to determine the need for revascularization in intermediate coronary stenosis two decades ago (18), and thereafter several studies have been carried out to show the safety of FFR and its superiority over angiography guided PCI. Such studies include FAME (Fractional Flow Reserve vs. Angiography for Guiding Percutaneous Coronary Intervention) (8) and DEFER (Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis) (1). The later published FAME 2 study (Fractional Flow Reserve-Guided PCI vs. Medical Therapy in Stable Coronary Disease) further showed significantly better outcomes for FFR guided PCI combined with best medical treatment in comparison to best medical treatment alone (2) and was stopped prematurely due to the efficacy of the combined therapy. For additional information on the clinical outcomes of FFR guided PCI, the FAME 3 study is looking to compare this method with CABG surgery in patients with multivessel CAD (19).

In contrast to our findings, a meta-analysis by Enezate *et al* (20) showed preference towards FFR and found a significant difference regarding MACE and MI at not exactly 1 year but >9 months follow-up (OR: 0.51 [95% CI: 0.37-0.70]; P<0.0001, I^2=21% and OR: 0.54 [95% CI: 0.39-0.75]; P=0.0003, I^2=17%, respectively) and also for in-hospital events (OR: 0.63 [95% CI: 0.47-0.86]; P=0.004, I^2=75% and OR: 0.53 [95% CI: 0.40-0.70]; P<0.00001, I^2=19%, respectively). Another finding of this study was the lower rate of PCI performed compared to the total number of lesions when using FFR, showing that not every visually identified lesion results in a reduction of blood flow and necessarily needs a PCI.

Furthermore, a meta-analysis by Zhang *et al*, which included studies with follow-ups from 9 up to 50.9 months, supports the superiority of FFR guided PCI (21). They analyzed the combined incidents of MACE and major adverse cardiac and cerebrovascular events and found a decreased event rate in FFR guided PCI (OR: 1.71 [95% CI: 1.31-2.23; P<0.001, I^2=55%). This preference for FFR remained when retrospective studies (OR: 1.41 [95% CI: 1.06-1.88; P=0.02, I^2=48%) were excluded. Since this meta-analysis was carried

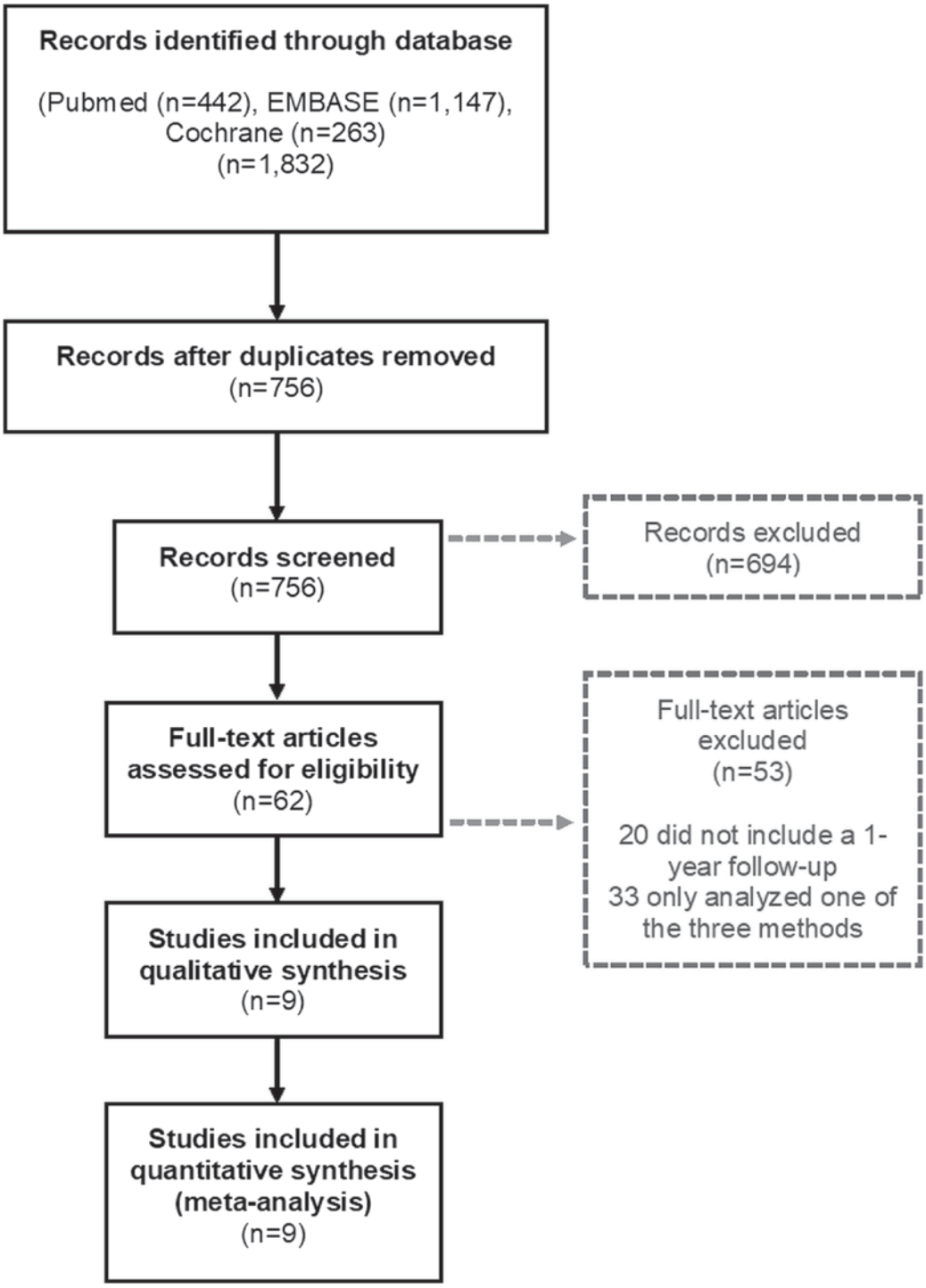

Figure 2. Flow chart representing the study selection process.

out in 2015, only one randomized study could be included, and the incorporation of the latest randomized trials may alter the results.

In addition, not all studies support the findings of the FAME study. The DEFER-DES study, which compared the 5-year outcomes of angiography and FFR guided PCI using drug eluting stents (DES), did not find any superiority for FFR guided DES implantation or routine DES implantation regarding the rate of MACE (11.6±3.0 and 14.2±3.3%, respectively (P=0.55) (13). A meta-analysis including only prospective studies from 2016 also found no significant difference for MACE (OR: 0.82 [95% CI: 0.64-1.06]; P=0.13, I^2=0%), mortality or repeat revascularization (22). Only the comparison regarding MI reached a significant level showing a preference for FFR (OR: 0.67 [95% CI: 0.47-0.96]; P=0.03, I^2=0%). Several sensitivity analyses were conducted, where only the exclusion of the FAME study generated a change in MI results [OR: 0.81 (95% CI: 0.46-1.43); P=0.47, I^2=0%] and the difference between the two methods did not remain. Differing from our study, that meta-analysis did not have the focus on one-year outcomes but included studies with reported outcomes from 3 months up to 5 years, which might lead to

Table II. Patient characteristics of the included studies.

A, Studies comparing FFR guided PCI and angiography guided PCI

Author, year	Method used for PCI	Patients	Age ± SD	BMI ± SD (kg/m^2)	Male (%)	HTN (%)	Diabetes (%)	HC (%)	Current smoking (%)	Family history of CAD (%)	Prior MI (%)	MVD (%)	(Refs.)
Tonino	FFR	509	64.6±10.3	N.A.	384 (75.4)	312 (61.3)	123 (24.2)	366 (71.9)	138 (27.1)	205 (40.3)	187 (36.7)	509 (100)	(8)
et al 2009	Angiography	496	64.2±10.2	N.A.	360 (72.6)	327 (65.9)	125 (25.2)	362 (73.0)	156 (31.5)	190 (38.3)	180 (36.3)	496 (100)	
Puymirat	FFR	222	71.6±9.8	26.6±4.3	129 (58)	130 (59)	58 (26)	137 (62)	86 (39)	77 (35)	N.A.	38 (17)	(9)
et al 2012	Angiography	495	71.7±10.6	27.0±4.4	336 (68)	323 (65)	163 (33)	333 (67)	226 (46)	143 (29)	N.A.	46 (9)	
Li	FFR	1,090	65.7±11.3	30.4±5.8	683 (62.7)	864 (79.2)	306 (28.0)	608 (55.7)	140 (12.8)	N.A.	270 (25)	73 (19.8)	(10)
et al 2013	Angiography	6,268	67.9±11.6	30.2±5.9	4,416 (70.4)	4,897 (78.1)	1,862 (29.7)	5,119 (81.6)	836 (13.3)	N.A.	1,882 (31.0)	2186 (19)	
Chen	FFR	160	65.2±9.6	N.A.	121 (75.6)	116 (72.5)	48 (30.0)	27 (16.9)	66 (41.3)	N.A.	12 (7.5)	112 (69.8)	(11)
et al 2015	Angiography	160	65.4±9.2	N.A.	116 (72.5)	106 (68.3)	43 (26.9)	32 (20.0)	64 (40.0)	N.A.	19 (11.9)	110 (68.8)	
Layland	FFR	176	62.3±11.0	N.A.	133 (75.6)	78 (44.3)	26 (14.8)	71 (40.3)	72 (40.9)	N.A.	22 (12.5)	51 (29.0)	(12)
et al 2015	Angiography	174	61.6±11.1	N.A.	127 (73.0)	81 (46.6)	26 (14.9)	56 (32.2)	71 (40.8)	N.A.	24 (13.8)	55 (31.6)	
Park	FFR	114	62±10	N.A.	83 (72.8)	73 (64)	30 (26)	80 (70)	30 (26)	N.A.	22 (19)	72 (63)	(13)
et al 2015	Angiography	115	63±10	N.A.	87 (75.7)	65 (57)	39 (34)	78 (68)	38 (33)	N.A.	20 (17)	66 (57)	
De Backer	FFR	695	64.6±10.5	28.3±10.6	511 (73.5)	465 (66.9)	179 (25.8)	511 (73.5)	173 (24.9)	343 (49.4)	238 (34.2)	199 (28.7)	(14)
et al 2016	Angiography	695	64.7±10.3	27.7±7.9	507 (72.9)	477 (68.6)	164 (23.6)	514 (74.0)	180 (25.9)	328 (47.2)	237 (34.1)	202 (29.1)	

B, Studies comparing FFR guided PCI and Instantaneous Wave-free Ratio (iFR®) guided PCI

Author, year	Method used for PCI	Patients	Age ± SD	BMI (kg/m^2)	Male (%)	HTN (%)	Diabetes (%)	HC (%)	Current Smoking (%)	Family history of CAD (%)	Prior MI (%)	MVD (%)	(Refs.)
Davies	FFR	1,250	65.2±10.6	N.A.	929 (74.3)	884 (70.7)	376 (30.1)	792 (63.4)	262 (21.0)	N.A.	376 (30.1)	519 (41.5)	(15)
et al 2017	iFR	1,242	65.5±10.8	N.A.	962 (77.5)	873 (70.3)	382 (30.8)	794 (63.9)	243 (19.6)	N.A.	358 (28.8)	505 (40.7)	
Götberg	FFR	1,007	67.4±9.2	27.6 ±4.3	766 (75.2)	710 (69.7)	213 (20.9)	704 (69.2)	167 (16.3)	N.A.	335 (32.9)	368 (36.1)	(16)
et al 2017	iFR	1,012	67.6±9.6	27.6 ±4.3	756 (74.2)	730 (71.6)	232 (22.8)	733 (71.9)	159 (15.6)	N.A.	337 (33.1)	364 (35.7)	

BMI, Body-mass index; CAD, coronary artery disease; FFR, fractional flow-reserve; HC, hypercholesterolemia; HTN, hypertension; iFR®, Instantaneous Wave-free Ratio; MI, myocardial infarction; MVD, multi-vessel-disease; N.A., not available; PCI, percutaneous coronary intervention; SD, standard deviation.

Table III. Primary endpoints at 12 months of the included studies.

A, Studies comparing FFR guided PCI and angiography guided PCI

Author, year	Method used for PCI	Patients	Death from any cause (%)	Myocardial infarction (%)	Unplanned revascularization (%)	MACE (%)	(Refs.)
Tonino *et al* 2009	FFR	509	9 (1.8)	29 (5.7)	33 (6.5)	67 (13.2)	(8)
	Angiography	496	15 (3.0)	43 (8.7)	47 (9.5)	91 (18.3)	
Puymirat *et al* 2012	FFR	222	3 (1.4)	N.A.	10 (4.5)	13 (5.9)	(9)
	Angiography	479	13 (2.7)	N.A.	59 (12.3)	90 (18.8)	
Li *et al* 2013	FFR	1,090	120 (11.0)	135 (18.2)	N.A.	206 (18.9)	(10)
	Angiography	6,268	690 (11.0)	826 (13.2)	N.A.	1,292 (20.6)	
Chen *et al* 2015	FFR	160	3 (1.9)	19 (11.9)	9 (5.6)	29 (18.1)	(11)
	Angiography	160	2 (1.3)	22 (13.8)	11 (6.9)	29 (18.1)	
Layland *et al* 2015	FFR	176	5 (2.8)	11 (6.2)	N.A.	14 (8.0)	(12)
	Angiography		174	3 (1.7)	15 (8.6)	N.A.	
Park *et al* 2015	FFR	114	N.A.	N.A.	N.A.	5 (4.4)	(13)
	Angiography		115	N.A.	N.A.	N.A.	
De Backer *et al* 2016	FFR	695	110 (15.8)	217 (31.2)	254 (36.5)	255 (36.7)	(14)
	Angiography	695	191 (27.5)	210 (30.2)	231 (33.2)	236 (34.0)	

B, Studies comparing FFR guided PCI and Instantaneous Wave-free Ratio (iFR®) guided PCI

Author, year	Method used for PCI	Patients	Death from any cause (%)	Myocardial Infarction (%)	Unplanned Revascularization (%)	MACE (%)	(Refs.)
Davies *et al* 2017	FFR	1,182	13 (1.1)	28 (2.4)	63 (5.3)	83 (7.0)	(15)
	iFR	1,148	22 (1.9)	31 (2.7)	46 (4.0)	78 (6.8)	
Götberg *et al* 2017	FFR	1,007	12 (1.2)	17 (1.7)	46 (4.6)	61 (6.1)	(16)
	iFR	1,012	15 (1.5)	22 (2.2)	47 (4.6)	68 (6.7)	

FFR, fractional flow-reserve; iFR®, instantaneous wave-free ratio; MACE, major adverse cardiac events; N.A., not available; PCI, percutaneous coronary intervention.

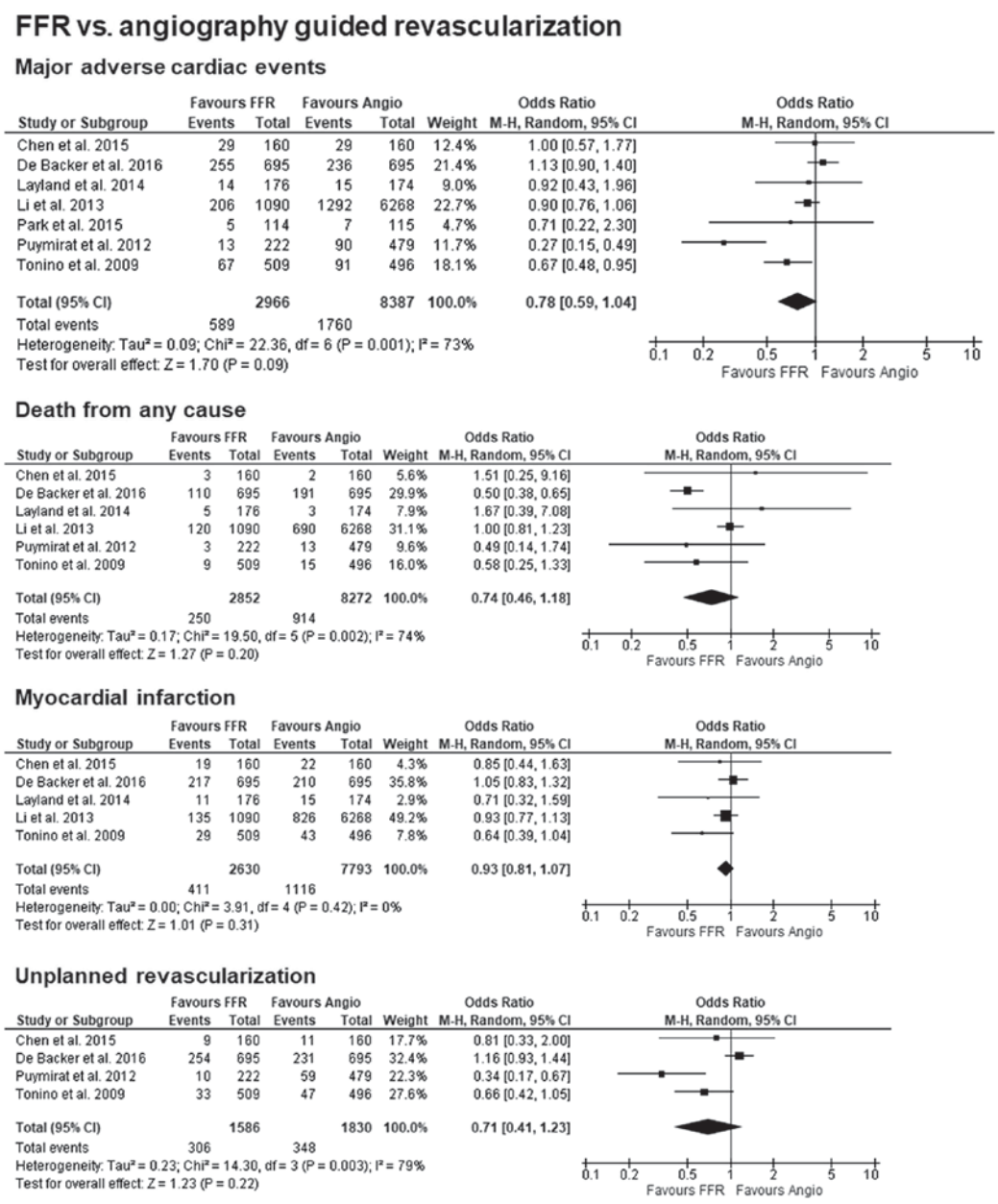

Figure 3. Forest plots showing the statistical results of 1-year clinical outcomes of FFR or angiography guided percutaneous coronary intervention. All four plots show a non-significant tendency towards FFR; Major Adverse Cardiac Events OR: 0.78 [95% CI: 0.59-1.04]. FFR, Fractional Flow Reserve.

a better discrimination for MACE and overall survival. The focus on the exact same follow-up point of time is a new aspect of this meta-analysis and improves the comparability of the included studies and their individual results.

Excluding the retrospective studies from this current analysis prompted a change of results regarding MACE as well. By doing this, the trend moved stronger towards FFR, and the heterogeneity moved from high to low. This may indicate the existence of influencing factors in these three retrospective studies. With more studies being published in the future, in another meta-analysis carried out later one may alter the inclusion criteria and thus reduce the heterogeneity. One way could be to only include prospective RCT's or to exclude any study which had NSTEMI as an indication for PCI such as Layland *et al* (12).

Another aspect of our meta-analysis was the difference between iFR guided and FFR guided PCI, since the absence of inferiority of iFR compared to FFR has been shown in the iFR-SWEDHEART (14), as well as in DEFINE-FLAIR (15). Both studies were published in 2017, after the accuracy of iFR was first compared to FFR in the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) (5) and the CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study) study (6). The statistical analysis had a high homogeneity throughout and showed that iFR was not inferior to FFR in all four entities. This must be seen in the context of iFR-SWEDHEART and DEFINE-FLAIR being the only multicenter, randomized, blinded trials focusing on FFR guided and iFR guided PCI, since iFR is a rather new technique. In addition, both studies reported on the observed discomfort of the patients during the procedure and showed significant lower numbers in chest discomfort (P<0.001) when using iFR. With both included

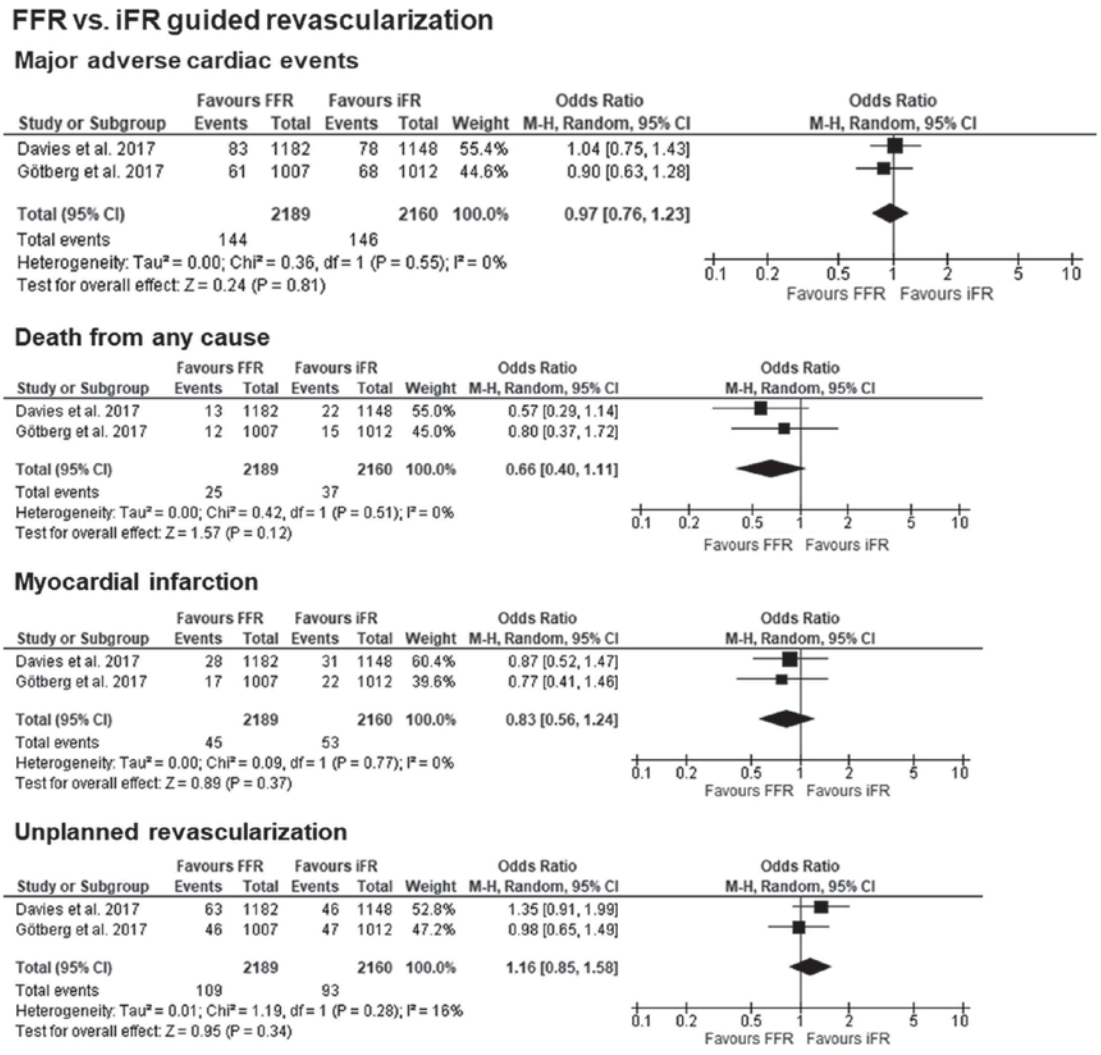

Figure 4. Forest plots showing the statistical results of 1-year clinical outcomes of FFR or iFR guided percutaneous coronary intervention. There is no significant superiority of FFR over iFR; Major adverse cardiac events OR: 0.97 [95% CI: 0.76-1.23]. FFR, Fractional Flow Reserve; iFR, instantaneous wave-free ratio.

studies showing equal diagnostic results it is not surprising for the meta-analysis to confirm the absence of inferiority of iFR. Nevertheless, it is important to validate the results of the individual trials, especially since to our knowledge a meta-analysis of iFR has not been performed at this point.

But, in order to compare angiography and iFR guided revascularization in a more direct way, we also conducted network meta-analysis. Although this network meta-analysis cannot be equated to a direct comparison, one can see that iFR is not inferior to angiography guided revascularization. This result is a very novel aspect of this paper and should be considered when talking about the best procedure when performing PCI.

As described above, iFR achieved similar results in comparison to FFR in similar study conditions. Nevertheless, further investigations should be conducted on iFR by itself in more complex situations, but also in a direct comparison to angiography and other treatment strategies for CAD, such as CABG.

Limitations of this meta-analysis are similar to the limitations of other meta-analyses. This includes the fact that we had no access to primary data, and the accuracy of our analysis depends on the accuracy of the primary sources. This meta-analysis includes prospective randomized controlled trials as well as retrospective non-randomized studies. Furthermore, the threshold for ischemia detection was not defined uniformly between the FFR studies (some studies used 0.75 and others 0.8). Lastly, it should be noted that the sample size of some of the studies was small and the populations for the three interventions all differed in size (angiography guided PCI included 8,403 patients; FFR guided PCI only included 5,223) Furthermore, we could only include two iFR studies in this meta-analysis, since iFR is a relatively new clinical procedure.

Overall, FFR guided PCI showed superiority in MACE during one year of follow up rates when comparing with angiography guided PCI. The high heterogeneity did not remain when excluding three retrospective studies and even reinforced the preference towards FFR. iFR guided PCI also did not show inferiority to FFR guided PCI, and thus one can assume iFR to be superior to solely angiography guided PCI as well. Because low heterogeneity and the small number of available studies limits the validity, further trials should be included in future analyses. A direct comparison of angiography and iFR may

also be advised. When talking about those further studies, not only longer follow-up periods are needed to proof better outcomes for iFR and FFR guided coronary interventions regarding MACE, but also different clinical outcomes have to analyzed.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SB, MB, IA and DL made substantial contributions to the design of the study, the acquisition and interpretation of data, drafting of the manuscript, revision of the manuscript for important intellectual content, and agree to be accountable for all aspects of the work in ensuring that questions associated with the accuracy or integrity of any part of the study are appropriately investigated and resolved. KSEM, SH, FE, ACS and TB made substantial contributions to the acquisition and analysis of data, and drafted the manuscript. All authors gave final approval of the version to be published.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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