

Original article

Systematic review and meta-analysis of randomized and nonrandomized studies on fractional flow reserve-guided revascularization

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ABSTRACT

Introduction and objectives: Several studies have investigated the effectiveness of fractional flow reserve (FFR) guidance in improving clinical outcomes after myocardial revascularization, yielding conflicting results. The aim of this study was to compare clinical outcomes in patients with coronary artery disease following FFR-guided or angiography-guided revascularization.**Methods:** Both randomized controlled trials (RCTs) and nonrandomized intervention studies were included. Coprimary endpoints were all-cause death, myocardial infarction, and major adverse cardiovascular events (MACE). The study is registered with PROSPERO (CRD42022344765).**Results:** A total of 30 studies enrolling 393 588 patients were included. FFR-guided revascularization was associated with significantly lower rates of all-cause death (OR, 0.63; 95%CI, 0.53–0.73), myocardial infarction (OR, 0.70; 95%CI, 0.59–0.84), and MACE (OR, 0.77; 95%CI, 0.70–0.85). When only RCTs were considered, no significant difference between the 2 strategies was observed for any endpoints. However, the use of FFR was associated with reduced rates of revascularizations and treated lesions. Metaregression suggested that the higher the rate of revascularized patients the lower the benefit of FFR guidance on MACE reduction compared with angiography guidance ($P = .012$). Similarly, higher rates of patients with acute coronary syndromes were associated with a lower benefit of FFR-guided revascularization ($P = .039$).**Conclusions:** FFR-guided revascularization was associated with lower rates of all-cause death, myocardial infarction and MACE compared with angiographic guidance, with RCTs and nonrandomized intervention studies yielding conflicting data. The benefits of FFR-guidance seem to be less evident in studies with high revascularization rates and with a high prevalence of patients with acute coronary syndrome.

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Revisión sistemática y metanálisis de estudios aleatorizados y no aleatorizados sobre revascularización guiada por reserva fraccional de flujo

RESUMEN

Introducción y objetivos: Varios estudios han investigado la eficacia de guiarse por la reserva fraccional de flujo (RFF) para mejorar los resultados clínicos tras la revascularización miocárdica, con resultados contradictorios. El objetivo es comparar los resultados clínicos en pacientes con enfermedad coronaria tras una revascularización guiada por RFF o por angiografía.**Métodos:** Se incluyeron estudios de intervención, tanto ensayos clínicos aleatorizados (ECA) como estudios no aleatorizados. Los objetivos coprimarios fueron la muerte por cualquier causa, el infarto de miocardio y los eventos adversos cardiovasculares mayores (MACE). El estudio está registrado en PROSPERO (CRD42022344765).**Resultados:** Se incluyeron en total 30 estudios con 393.588 pacientes. La revascularización guiada por RFF se asoció con tasas significativamente inferiores de muerte por cualquier causa (OR = 0,63; IC95%, 0,53–0,73), infarto de miocardio (OR = 0,70; IC95%, 0,59–0,84) y MACE (OR = 0,77; IC95%, 0,70–0,85). Cuando solo se tuvieron en cuenta los ECA, no se observaron diferencias significativas entre las 2 estrategias en ningún criterio de valoración. Sin embargo, el uso de la RFF se asoció con tasas reducidas de revascularización y de lesiones tratadas. El análisis de metarregresión indicó que, cuanto mayor es la

Palabras clave:

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tasa de pacientes revascularizados, menor es el beneficio de utilizar la RFF en la reducción de los MACE, en comparación con la revascularización guiada por angiografía ($p = 0,012$). Asimismo altas tasas de pacientes con síndrome coronario agudo se asociaron con menor beneficio de la revascularización guiada por RFF ($p = 0,039$).

Conclusiones: La revascularización guiada por RFF se asoció con menores tasas de muerte por todas las causas, infarto de miocardio y MACE en comparación con la revascularización guiada por angiografía, con datos contradictorios procedentes de ECA y estudios no aleatorizados. Los beneficios de la revascularización guiada por RFF parecen ser menos evidentes en los estudios con altas tasas de revascularización y con alta prevalencia de pacientes con síndrome coronario agudo.

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Abbreviations

FFR: fractional flow reserve
 MACE: major adverse cardiovascular events
 MI: myocardial infarction
 NRSI: nonrandomized study of intervention
 OR: odds ratio
 RCT: randomized clinical trial

INTRODUCTION

Fractional flow reserve (FFR) is an intracoronary pressure-derived index that quantifies the hemodynamic significance of coronary stenoses. The use of FFR to guide coronary revascularization is recommended by guidelines¹ following the publication of several landmark clinical randomized controlled trials (RCTs) such as the “Fractional Flow Reserve Versus Angiography for Multivessel Evaluation” (FAME)² and the “Fractional Flow Reserve guided PCI vs Medical Therapy in Stable Coronary Disease” (FAME 2).³ Following these seminal studies, the benefit of the FFR-guided revascularization strategy has been confirmed in several nonrandomized studies. However, FFR has been challenged in some clinical settings (eg, in patients with acute coronary syndromes or severe multivessel disease),^{4,5} raising doubts about its overall usefulness in clinical practice. This meta-analysis provides an updated assessment of the available literature to define which strategy is preferable when comparing FFR-guided vs angiography-guided revascularization according to the study type and different patient subsets.

METHODS

Selection criteria and search strategy

The present analysis was conducted according to the recommendations of the Cochrane Collaboration⁶ and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements.⁷ Studies were considered eligible if they provided comparison between clinical endpoints following FFR-guided or angiography-guided revascularization. Both RCTs and nonrandomized intervention studies (NRSI) were included; studies with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as revascularization strategies were considered. If an NRSI provided both propensity score matched and unmatched cohorts, only matched cohorts were included. From inception through April 2023, PubMed/MEDLINE and Cochrane/CENTRAL databases were systematically searched for studies matching the inclusion criteria. A detailed search algorithm can be found in the supplementary data. A minority of articles was

selected through citation searching and from authors' contributions. Two authors (F. Mangiacapra and L. Paolucci) independently selected eligible works at the title/abstract level and disagreements were resolved by a senior author (E. Barbato). Eligible articles were evaluated at the full-text level. Risk of bias was estimated using the Cochrane RoB 2 tool for RCTs⁸ and the ROBINS-I tool for NRSI.⁹

Clinical endpoints

Coprimary endpoints were all-cause death, myocardial infarction (MI) and major adverse cardiovascular events (MACE) at longest available follow-up. Among the 25 studies reporting MACE, 7 reported major adverse cerebral and cardiovascular events.^{10–16} To ensure that the analysis was sufficiently powered, we decided to merge these outcomes and refer to them simply as “MACE”. The various MACE definitions used are summarized in [table 1 of the supplementary data](#). Secondary endpoints were any revascularization, a combination of target vessel failure/target lesion failure and the occurrence of periprocedural MI.

To compare the extent of revascularization deferral (ie, number of performed PCIs and treated lesions) between FFR- and angiography-guidance, an exploratory analysis was conducted using RCTs with only PCI as the revascularization strategy.

Data analysis

The number of events for each endpoint and the cohort size were extracted by careful evaluation of articles. If there were zero events in both groups for a certain outcome, a continuity factor of 1 was used. Heterogeneity was assessed using I^2 statistics.¹⁷ Odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated using a random-effects model according to the Der Simonian and Leird method.¹⁸ A fixed-effects model according to the Mantel-Haenszel method was used to assess OR heterogeneity (complete absence indicated by I^2 statistic values near 0%).¹⁸ The absolute number of performed PCIs and treated lesions in the RCTs subgroup were compared using a Pearson chi-square test between the 2 groups. The rates of acute coronary syndromes (ACS) and revascularization deferral in the FFR arms of RCT and NRSI were compared in a similar fashion. Two separate analyses were conducted for the coprimary endpoints. In the primary analysis, both RCT and NRSI were included using a cross study design modelling within a Bayesian framework. With this method, studies with a suspected low level of evidence (ie, NRSI) are progressively undersized by inflating their mean effects variances by a w_j factor (minimum relative weight: $w_j \sim 0$; maximum relative weight: $w_j = 1$). No prior distributions of bias vectors were assumed.¹⁹ The results of the Bayesian adjustment are reported as logOR and 95%CI.

In the secondary analysis, only RCT and propensity score matching adjusted/prospective NRSI were included.^{20,21} Publica-

Table 1
Main characteristics of the included studies

Study and year	Type	Country	Patients (FFR vs angio)	FFR threshold	Clinical setting	Revascularization strategy	Angiographic inclusion of stenoses	Clinical endpoints	Follow-up, mo
<i>Nonrandomized studies</i>									
Wrongpraparut <i>et al.</i> 2005 ²³	Prospective non-RCT	USA	57 vs 80	0.75	MVD CCS (100%)	PCI	Intermediate stenoses	MACE, death, MI, TLR, any revascularization	30
Koo <i>et al.</i> , 2008 ²⁴	Prospective non-RCT	South Korea	110 vs 110	N/A	Bifurcation lesions ACS (57.3%) CCS (42.7%)	PCI	> 50%	MACE, cardiac death, MI, TVR	9
Puymirat <i>et al.</i> , 2012 ²⁵	Retrospective	Belgium	222 vs 476	0.80	Small coronary vessels disease UA (17.5%) CCS (82.5%)	PCI	Intermediate stenoses	MACE, death, MI, TVR	60 (median: 34)
Di Serafino <i>et al.</i> , 2013 ²⁶	Retrospective	Belgium	65 vs 158	0.80	Bypass graft lesions UA (23.7%) CCS (76.3%)	PCI	> 40% and < 70%	MACCE, death, MI, TVR	48
Li <i>et al.</i> , 2013 ²⁷	Retrospective	USA	1090 vs 6268	0.75	All-comers ACS (11.7%) CCS (88.3)	PCI	Intermediate stenoses	MACE, death, MI, any revascularization	84 (median: 44.9)
Toth <i>et al.</i> 2013 ²⁸	Retrospective	Belgium	198 vs 429	0.80	CABG CCS (100%)	CABG	> 50% and < 70%	MACE, death, MI, TVR	36
Fröhlich <i>et al.</i> , 2014 ²⁹	Retrospective-PSWM	UK	919 vs 919	N/A	All-comers CCS (59.6%) NSTEMI (40.4%)	PCI	N/A	death	16 (median)
Di Gioia <i>et al.</i> , 2016 ³⁵	Retrospective-PSWM	Belgium, Italy, Austria	106 vs 212	0.80	AS CCS (91.9%) ACS (8.1%)	PCI and CABG	> 50% and < 70%	MACE, death, MI, any revascularization	60
De Backer <i>et al.</i> , 2016 ³⁶	Retrospective-PSWM	Denmark	695 vs 695	0.80	All-comers CCS (100%)	PCI	> 50% and < 90%	MACE, death, MI, TLR, any revascularization	48 (median in the FFR group: 21.3)
Sawant <i>et al.</i> , 2018 ¹³	Retrospective-PSWM	USA	190 vs 190	0.80	All-comers CCS (100%)	PCI	N/A	MACE, death, MI, any revascularization	60 (median: 41)
Fournier <i>et al.</i> , 2018 ³⁷	Retrospective-PSWM	Belgium, Austria, Italy	198 vs 198	0.80	CABG CCS (100%)	CABG	> 50% and < 70%	MACE, death, MI, TVR	104 (median: 85)
Lunardi <i>et al.</i> , 2019 ¹¹	Retrospective	Italy	94 vs 122	0.80	TAVR CCS (100%)	PCI	> 30%	MACCE, death, MI, new elective PCI	48
Di Gioia <i>et al.</i> , 2020 ¹⁴	Retrospective-PSWM	Belgium, Italy	433 vs 866	0.80	HF CCS (100%)	PCI and CABG	> 50% and < 70%	MACCE, death, MI, any revascularization	60
Parikh <i>et al.</i> , 2020 ³⁸	Retrospective	USA	2967 vs 15022	N/A	All-comers CCS (100%)	PCI and CABG	> 40% and < 70%	MACE, death, MI, any revascularization	12
Völz <i>et al.</i> , 2020 ³⁹	Retrospective-PSWM	Sweden	3367 vs 20493	N/A	All-comers CCS (100%)	PCI	> 50%	Death	4.7 y (median)
Omran <i>et al.</i> , 2020 ⁴²	Retrospective	USA	7832 vs 296716	N/A	ACS STEMI (25.4%) NSTEMI (48.8) UA (25.8%)	PCI	N/A	In-hospital death, bleedings, coronary dissections, AKI	1
Wong <i>et al.</i> , 2021 ⁴⁰	Retrospective	Australia	542 vs 9762	N/A	All-comers CCS (51%) ACS (49%)	PCI	N/A	Death, MI	12

Table 1 (Continued)

Main characteristics of the included studies

Study and year	Type	Country	Patients (FFR vs angio)	FFR threshold	Clinical setting	Revascularization strategy	Angiographic inclusion of stenoses	Clinical endpoints	Follow-up, mo
Adjedj et al., 2022 ⁴¹	Retrospective	France	1259 vs 13125	N/A	All-comers CCS (30.7%) ACS (69.3%)	PCI	< 90%	MACE, death, CV death, MI, any revascularization, TLR, stroke, BARC 3-5 bleedings	12
Gerhardt et al., 2023 ⁴⁴	Retrospective	Germany	629 vs 629	0.80	All-comers ACS (100%)	PCI and CABG	N/A	MACE, death, MI, any revascularization	36
<i>Randomized studies</i>									
Layland et al., 2015 (FAMOUS-NSTEMI) ³⁰	RCT	Scotland	176 vs 174	0.80	All-comers NSTEMI (100%)	PCI and CABG	> 30%	MACE, death, MI,	12
Chen et al., 2015 (DK-CRUSH VI) ³¹	RCT	China	160 vs 160	0.80	Bifurcation lesions CCS (10.8%) UA (70.3%) NSTEMI (11.8%) STEMI (7.1%)	PCI	> 50%	MACE, death, MI, TVR	12
Park et al., 2015 (DEFER-DES) ³²	RCT	South Korea	114 vs 115	0.75	All-comers CCS (50.7%) ACS (49.3%)	PCI	> 40% and < 70%	MACE, death, MI, TLR, any revascularization	60
Van Nunen et al., 2015 (FAME) ³³	RCT	Netherlands, Belgium	509 vs 496	0.80	MVD CCS (67.3%) ACS (32.7%)	PCI	> 50%	MACE, death, MI, any revascularization	60
Zhang et al., 2016 ⁴⁵	RCT	China	110 vs 110	0.80	Elders NSTEMI (100%)	PCI	> 30%	MACE, death, MI	12
Theusen et al., 2018 (FARGO) ¹²	RCT	Denmark	49 vs 48	0.80	CABG CCS (77.5%) UA (6.1%) NSTEMI/STEMI (16.4%)	CABG	> 50%	MACCE, death, MI, any revascularization	6
Toth et al., 2019 (GRAFFITI) ¹⁰	RCT	International	88 vs 84	0.80	CABG CCS (89%) NSTEMI (11%)	CABG	> 30% and < 90%	MACCE, death, MI, TVR	12
Puymirat et al., 2021 (FLOWER-MI) ⁵	RCT	France	586 vs 577	0.80	MVD STEMI (100%)	PCI	> 50%	MACE, death, MI, TLR, any revascularization	12
Rioufol et al., 2021 (FUTURE) ¹⁵	RCT	France	460 vs 467	0.80	MVD CCS (53.8%) ACS (46.2%)	PCI and CABG	> 50%	MACCE, death, MI, stroke, unplanned revascularization	12
Stables et al., 2022 (RIPCORDER-2) ¹⁶	RCT	UK	552 vs 548	0.80	All-comers CCS (48.4%) NSTEMI (51.6%)	PCI and CABG	Routine FFR evaluation in all vessels	MACCE, death, MI, unplanned revascularization	12
Lee et al., 2022 (FRAME-AMI) ⁴³	RCT	Korea	284 vs 278	0.80	MVD and ACS NSTEMI (52.8%) STEMI (47.2%)	PCI	> 50%	All-cause death, MI, MACE, any revascularization	44

AKI, acute kidney injury; ACS, acute coronary syndrome; AS, aortic stenosis; BARC, bleedings academic research consortium; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; FFR, fractional flow reserve; HF, heart failure; MACCE, major adverse cardiovascular and cerebral events; MACE, major adverse cardiovascular events; MI, myocardial infarction; MVD, multivessel disease; N/A, not available; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; PSWM, propensity score weighted matching; RCT, randomized clinical trial; STEMI, ST elevation myocardial infarction; TAVR, transcatheter aortic valve replacement; TLR, target lesion failure; TVR, target vessel failure; UA, unstable angina.

tion bias was estimated by Egger's test. Prespecified sensitivity analyses were performed by removing 1 study at a time across the groups and by using fixed-effect models for outcomes previously evaluated with random-effects models and showing low-to-moderate levels of heterogeneity. Subgroup analysis was performed between RCTs and non-RCT studies and formally evaluated with chi-square and I^2 tests.²²

Random-effects meta-regression analysis was performed to study the influence of revascularization rates and clinical presentation (acute vs chronic) on the coprimary endpoints. The percentage of patients undergoing revascularization and the percentage of patients with ACS enrolled in the FFR arm of each study were used as covariates. For the latter analysis, ACS was defined by the sum of patients with unstable angina (UA), non-ST-segment elevation MI, and ST-segment elevation MI.

Statistical analysis was performed with RevMan version 5.4.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and STATA 16 (Stata Corp, College Station, United States). The study is registered with PROSPERO (CRD42022344765).

RESULTS

Features of the included studies and extent of revascularization deferral in RCTs

The systematic search led to 4520 records considered for title/abstract level evaluation and 43 articles for full-text review, of which 21 were considered eligible for inclusion. Another 8 studies were added from other sources, eventually leading to the inclusion of 30 studies.^{5,10–16,23–44} The PRISMA diagram summarizing the research strategy is reported in [figure 1 of the supplementary data](#). The final analysis included 11 RCTs,^{5,10,12,15,16,30–33,43,45} 2 prospective nonrandomized studies,^{23,24} 8 retrospective propensity score-adjusted studies,^{13,14,29,35–37,39,44} and 9 retrospective unadjusted studies.^{11,25–28,38,40–42} Risk of bias is shown in [figures 2 and 3 of the supplementary data](#). The analysis involved 393 588 patients: 369 527 underwent angiographic guidance and 24 061 underwent FFR-guidance. The main characteristics of the 30 studies are shown in [table 1](#).

The baseline characteristics of the populations enrolled are summarized in [table 2 of the supplementary data](#). High clinical heterogeneity was observed among the studies, which enrolled patients in different clinical settings including ACS, chronic coronary syndromes (CCS), bypass graft lesions, aortic stenosis, and bifurcation lesions.

The extent of revascularization deferral was reported in 9 PCI RCTs^{5,15,16,30–33,43,45}: 2447 of 2947 (83.0%) patients in the FFR-guided group and 2586 of 2929 (88.2%) patients in angiography-guided group underwent PCI ($P < .001$). Data on the number of treated lesions were available in 4 studies.^{5,31–33} Overall, 1485 of 2632 (56.4%) lesions in the FFR-guided group and 2206 of 2606 (86.7%) lesions in the angiography-guided group were treated with PCI ($P < .001$). Results are shown in [table 2](#). Data on the extent of coronary revascularization in the PCI and CABG studies according to different variables are summarized in [tables 3 and 4 of the supplementary data](#), while periprocedural MI event rates in each study are reported in [table 5 of the supplementary data](#).

All-cause death

All-cause death was reported in 27 studies enrolling a total of 392 242 patients. An FFR-guided strategy was associated with a reduced risk of all-cause death (OR, 0.63; 95%CI, 0.53–0.73;

Table 2

Absolute number of performed PCI and treated lesions in the RCTs subgroup

Study and year RCTs	Performed PCI FFR	Performed PCI angio	P
Layland 2015 ³⁰	136/176 (77.2%)	151/174 (85.8%)	.020
Park 2015 ³²	41/114 (35.9%)	115/115 (100%)	<.001
Chen 2015 ³¹	160/160 (100%)	160/160 (100%)	.999
Van Nunen 2015 ³³	509/509 (100%)	496/496 (100%)	.999
Zhang 2016 ⁴⁵	95/110 (86.3%)	104/110 (94.5%)	.040
Puymirat 2021 ⁵	586/586 (100%)	577/577 (100%)	.999
Rioufol 2021 ¹⁵	328/460 (71.3%)	369/467 (79.0%)	.006
Stables 2022 ¹⁶	308/548 (56.2%)	336/552 (60.9%)	.200
Lee 2022 ⁴³	284/284	278/278	.999
Total	2447/2947 (83.0%)	2586/2929 (88.2%)	<.001
Study and year RCTs	Treated lesions FFR	Treated lesions angio	P
Park 2015 ³²	29/114 (25.4%)	115/115 (100%)	<.001
Chen 2015 ³³	91/160 (56.8%)	102/160 (63.7%)	.250
Van Nunen 2015 ³¹	819/1378 (59.4%)	1237/1350 (91.6%)	<.001
Puymirat 2021 ⁵	546/980 (55.7%)	806/981 (82.1%)	<.001
Total	1485/2632 (56.4%)	2260/2606 (86.7%)	<.001

FFR, fractional flow reserve; PCI, percutaneous coronary intervention; RCT, randomized clinical trial.

$I^2 = 64%$). A funnel plot is reported in [figure 4 of the supplementary data](#). A sensitivity analysis performed by leaving out one study at a time showed no meaningful differences, and the fixed-effects model demonstrated comparable results (OR, 0.55; 95%CI, 0.51–0.59). In subgroup analysis, only NRSI FFR-guidance showed an association with reduced all-cause death (RCTs: OR, 0.99; 95%CI, 0.68–1.44, $I^2 = 31%$; NRSI: OR, 0.56; 95%CI, 0.48–0.65; $I^2 = 64%$), with a significant difference between the study design subgroups ($P = .009$). Mean effect variances adjustment of NRSI confirmed these findings up to a w_j value of 0.2. The results of the primary analysis are shown in [figure 1](#).

Myocardial infarction

The analysis was performed in 25 studies involving 62 212 patients. FFR-guidance was associated with a reduced risk of MI (OR, 0.70; 95%CI, 0.59–0.84; $I^2 = 43%$). A funnel plot can be found in [figure 5 of the supplementary data](#). Sensitivity analysis performed by removing 1 study at a time showed no significant differences and a fixed-effects model supported the results (OR, 0.70; 95%CI, 0.62–0.79). In subgroup analysis, only NRSI FFR-guidance showed an association with reduced MI (RCTs: OR, 0.84; 95%CI, 0.64–1.10; $I^2 = 20%$; NRSI: OR, 0.63; 95%CI, 0.50–0.80; $I^2 = 49%$), with no difference between study design subgroups ($P = .120$). These findings were consistent after adjustment of NRSI mean effect variances up to a w_j value of 0.2. The results are shown in [figure 2](#).

Major adverse cardiovascular events

A total of 25 studies with 52 137 patients were included. FFR-guidance was associated with a reduced risk of MACE (OR, 0.77; 95%CI, 0.70–0.85; $I^2 = 41%$). A funnel plot is shown in [figure 6 of the supplementary data](#). A fixed-effects model supported this finding (OR, 0.76; 95%CI, 0.72–0.82) and sensitivity analysis did not impact the result. In subgroup analysis, only NRSI FFR-guidance showed an association with reduced MACE (RCTs: OR, 0.91; 95%CI, 0.77–1.08; $I^2 = 9%$; NRSI: OR, 0.72; 95%CI, 0.64–0.81; $I^2 = 44%$) and a

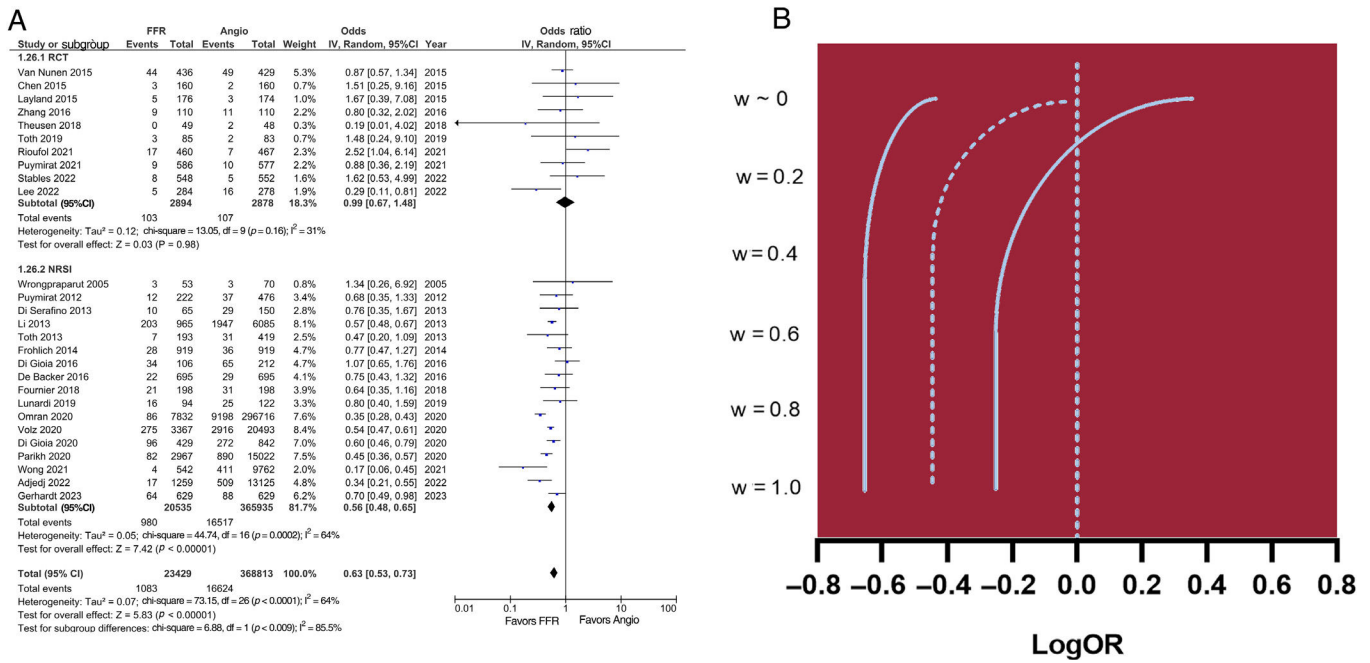


Figure 1. Primary analysis for all-cause death. A: forest plot. B: mean effect variance adjustment of NRSI. 95%CI, 95% confidence intervals; FFR, fractional flow reserve; NRSI, nonrandomized intervention studies; RCT, randomized clinical trials. The bibliographic references mentioned in this figure correspond to: Puymirat et al.,⁵ Toth et al.,¹⁰ Lunardi et al.,¹¹ Thuesen et al.,¹² Di Gioia et al.,¹⁴ Rioufol et al.,¹⁵ Stables et al.,¹⁶ Wongpraparut et al.,²³ Puymirat et al.,²⁵ Di Serafino et al.,²⁶ Li J et al.,²⁷ Toth et al.,²⁸ Fröhlich et al.,²⁹ Layland et al.,³⁰ Chen et al.,³¹ Van Nunen et al.,³³ Di Gioia et al.,³⁵ De Backer et al.,³⁶ Fournier et al.,³⁷ Parikh et al.,³⁸ Völz et al.,³⁹ Wong et al.,⁴⁰ Adjedj et al.,⁴¹ Omran et al.,⁴² Lee et al.,⁴³ Gerhardt et al.,⁴⁴ Zhang et al.⁴⁵

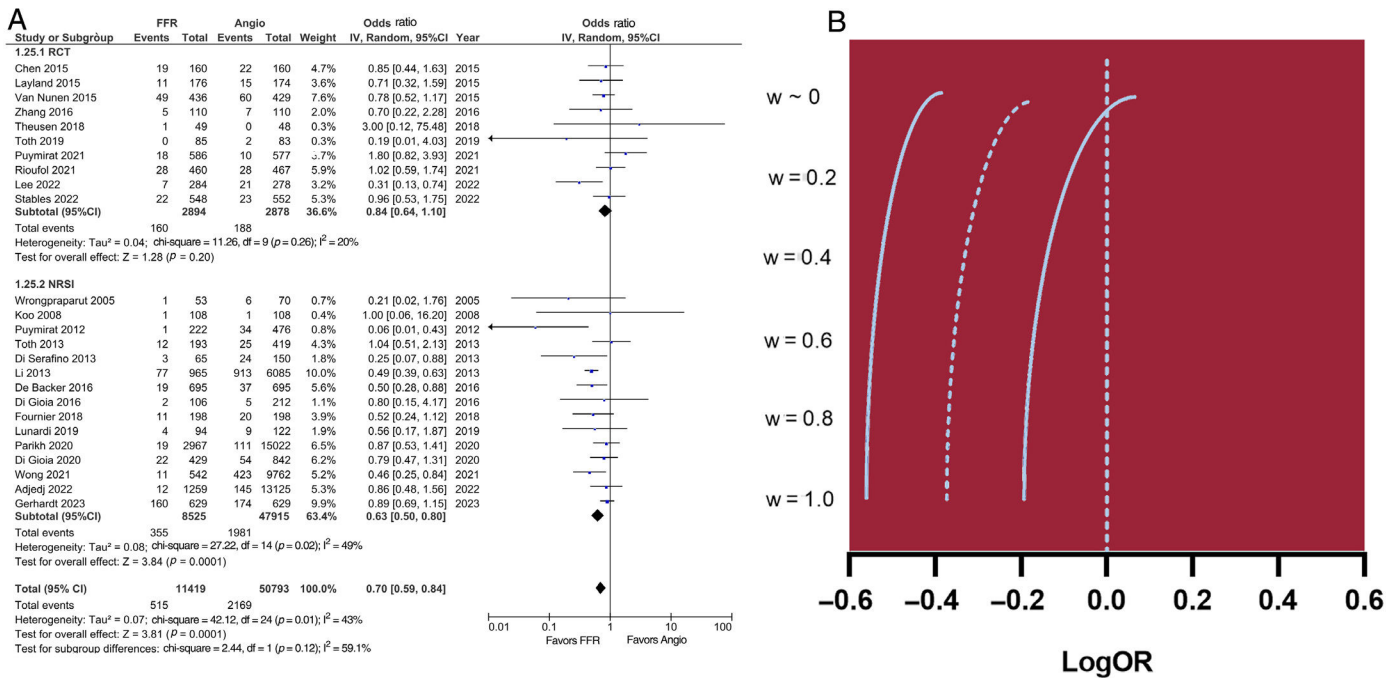


Figure 2. Primary analysis for MI. A: forest plot. B: mean effect variance adjustment of NRSI. 95%CI, 95% confidence intervals; FFR, fractional flow reserve; MI, myocardial infarction; NRSI, nonrandomized intervention studies; RCT, randomized clinical trials. The bibliographic references mentioned in this figure correspond to: Puymirat et al.,⁵ Toth et al.,¹⁰ Lunardi et al.,¹¹ Thuesen et al.,¹² Di Gioia et al.,¹⁴ Rioufol et al.,¹⁵ Stables et al.,¹⁶ Wongpraparut et al.,²³ Koo et al.,²⁴ Puymirat et al.,²⁵ Di Serafino et al.,²⁶ Toth et al.,²⁸ Layland et al.,³⁰ Chen et al.,³¹ Van Nunen et al.,³³ Di Gioia et al.,³⁵ De Backer et al.,³⁶ Fournier et al.,³⁷ Parikh et al.,³⁸ Wong et al.,⁴⁰ Adjedj et al.,⁴¹ Omran et al.,⁴² Lee et al.,⁴³ Gerhardt et al.⁴⁴

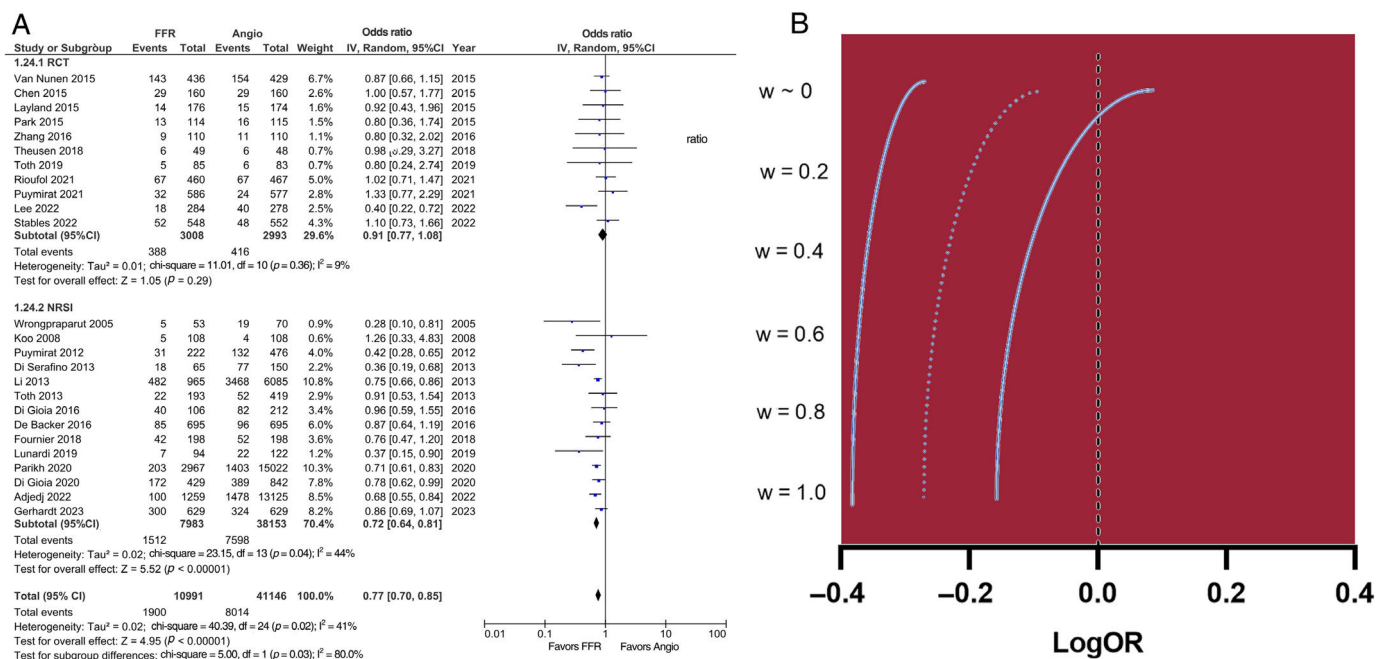


Figure 3. Primary analysis for MACE. A: forest plot. B: mean effect variance adjustment of NRSI. 95%CI, 95% confidence intervals; FFR; fractional flow reserve; MACE, major adverse cardiovascular events; NRSI, nonrandomized intervention studies; RCT, randomized clinical trials. The bibliographic references mentioned in this figure correspond to: Puymirat et al.,⁵ Toth et al.,¹⁰ Lunardi et al.,¹¹ Thuesen et al.,¹² Di Gioia et al.,¹⁴ Rioufol et al.,¹⁵ Stables et al.,¹⁶ Wongpraparut et al.,²³ Koo et al.,²⁴ Puymirat et al.,²⁵ Di Serafino et al.,²⁶ Li J et al.,²⁷ Toth et al.,²⁸ Layland et al.,³⁰ Chen et al.,³¹ Park et al.,³² Van Nunen et al.,³³ Di Gioia et al.,³⁵ De Backer et al.,³⁶ Fournier et al.,³⁷ Parikh et al.,³⁸ Adjedj et al.,⁴¹ Lee et al.,⁴³ Zhang et al.⁴⁵

significant difference between study design subgroups was evident ($P = .030$). These findings were confirmed even for high values of NRSI mean effect variances ($w_j = 0.2$). These results are reported in figure 3.

Influence of revascularization deferral and ACS rates on clinical outcomes

The rates of PCI or CABG deferral in NRSI and RCTs were 63.0% and 12.9%, respectively ($P < .001$) (figure 4). The association between FFR-guided revascularization and reduced MACE was blunted with increasing numbers of patients treated with PCI or CABG. The MACE logOR increased by 0.032 for every 10% increase of the covariate (95%CI, 0.006-0.075; $P = .057$). A similar association was evident with all-cause death [logOR, 0.064; 95%CI, 0.027-0.102; $P = .001$], but not with MI ($P = .167$).

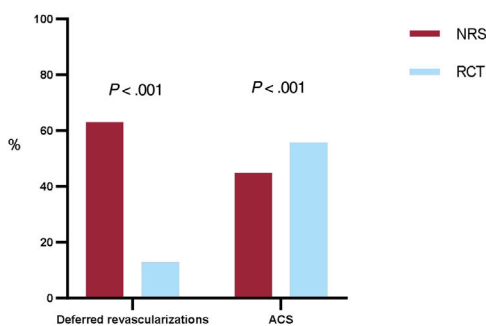


Figure 4. Rates of coronary revascularization deferral and ACS in NRSI and RCTs. ACS, acute coronary syndromes; NRSI, nonrandomized intervention studies; RCT, randomized clinical trials.

The rate of ACS was lower in the NRSI compared with RCTs (respectively: 44.9% vs 55.7%; $P < .001$, figure 4). Meta-regression analysis suggested an inverse relationship between the percentage of patients with ACS and the association between FFR-guided revascularization and reduced MACE: logOR for MACE increased by 0.020 for every 10% increase of the covariate (95%CI, 0.001-0.039; $P = .039$). A tendency toward significance was found for the MI outcome ($P = .050$), while no association was found for all-cause death ($P = .754$).

Secondary analyses of the coprimary endpoints

Secondary analyses were performed including only RCTs and adjusted/prospective NRSI. The results of the primary analyses were confirmed for all coprimary endpoints (all-cause death: OR, 0.77; 95%CI, 0.63-0.93; $I^2 = 50%$; MI: OR, 0.79; 95%CI, 0.67-0.94; $I^2 = 9%$; MACE: OR, 0.86; 95%CI, 0.78-0.95; $I^2 = 2%$). Notably, no difference was found between RCTs and adjusted/prospective NRSI for these outcomes. These results are reported in figure 5. Forest plot analyses are reported in figures 7, 8 and 9 of the supplementary data.

Secondary endpoints

The risk of further revascularizations (OR, 0.93; 95%CI, 0.83-1.04; $I^2 = 29%$) or target vessel failure/target lesion failure (OR, 0.75; 95%CI, 0.55-1.01; $I^2 = 29%$) was not increased by FFR. An exploratory analysis using a fixed-effects model showed significant benefit in the FFR-guided group for this latter outcome (OR, 0.75; 95%CI, 0.57-1; $I^2 = 29%$). The risk of periprocedural MI was reduced in the FFR-guided group (OR, 0.60; 95%CI, 0.39-0.95; $I^2 = 41%$). Forest plot analyses are reported in figures 10, 11 and 12 of the supplementary data.

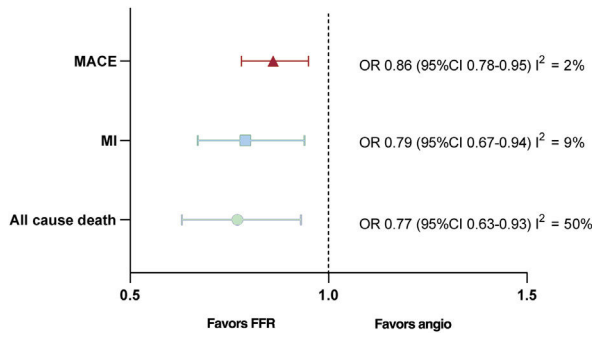


Figure 5. Main results of the secondary analysis for the 3 coprimary outcomes. 95%CI, 95% confidence intervals; FFR, fractional flow reserve; MACE, major adverse cardiovascular events; MI, myocardial infarction; OR, odds ratio.

DISCUSSION

Our meta-analysis comparing FFR-guided vs angiography-guided revascularization strategies demonstrated that: a) FFR-guided revascularization were associated with overall improved clinical outcomes, as in both primary (including all studies) and secondary analyses (including RCTs and adjusted NRSI), the rates of MI and MACE were reduced in the FFR-guided group; b) although these findings were mainly driven by data from NRSI, their relative influence can be largely undersized without compromising the final results; c) the percentage of coronary revascularization deferral and ACS was higher in NRSI than in RCTs, d) the benefits of FFR-guided revascularization in reducing MACE and all-cause

death seemed to be less pronounced in studies with higher revascularization rates and a high prevalence of ACS; e) when only RCTs were analysed, an FFR-guided strategy was associated with significant deferral of lesions without compromising patient safety. The results of the present analysis are briefly synthesized in figure 6. Our findings confirm the results of previous studies investigating this topic in RCTs^{46,47} and identify the possible influence of data from NRSI in evaluation of the benefit of an FFR-guided strategy. Moreover, this is the first analysis investigating the role of revascularization deferral and type of coronary syndrome in determining the association between FFR and clinical outcomes at a meta-analytic level.

Clinical outcomes of FFR-guided revascularization

Compared with angiography, the adoption of physiology has the advantage of distinguishing epicardial coronary stenoses associated with myocardial ischemia,⁴⁸ for which revascularization might be warranted, from those where revascularization could be deferred.⁴⁹ The association between reduced FFR and adverse events has been widely described.⁵⁰ Studies investigating the natural history of coronary lesions have shown that there is a strong relationship between lesion severity (evaluated with FFR) and rates of MACE and MI.^{51,52} These data are supported by evidence showing a high grade of inflammatory stress in FFR-positive lesions⁵³ that could increase plaque instability. Consequently, the reduced rates of MI after revascularizing FFR-positive lesions could be associated with reduced mortality and MACE rates during follow-up. Compared with angiography, the addition of FFR maintains the benefits in terms of spontaneous MI reduction. At the same time, by deferring functionally insignificant lesions, FFR

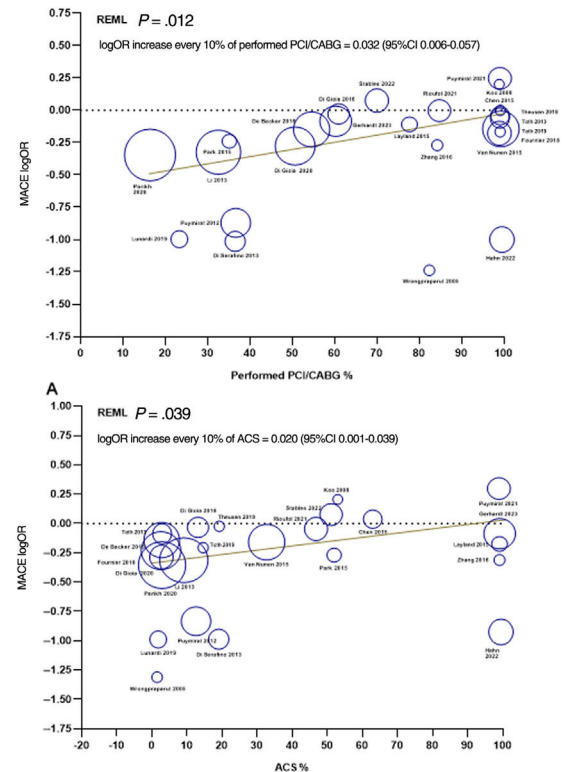
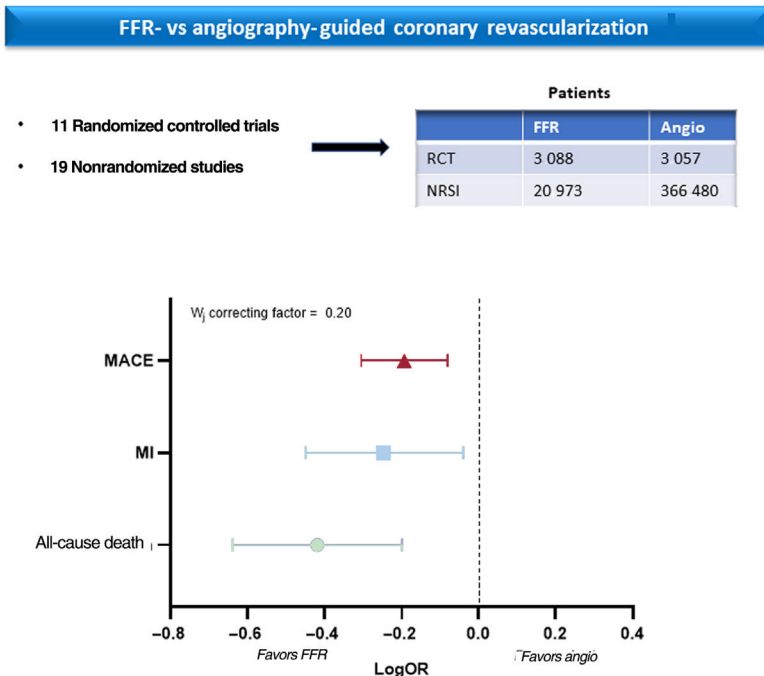


Figure 6. Central illustration. FFR- vs angiography-guided coronary revascularization. 95%CI, confidence intervals; ACS, acute coronary syndromes; CABG, coronary artery bypass grafting; FFR, fractional flow reserve; MACE, major adverse cardiovascular events; MI, myocardial infarction; NRSI, nonrandomized intervention studies; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized clinical trials; REML, restricted maximum likelihood.

decreases the risks associated with procedural myocardial injury,⁵⁴ which is related to impaired outcomes.^{55,56} Accordingly, our findings support that FFR-guided revascularization is consistently associated with a lower risk of MI and MACE. Moreover, when considering RCTs of patients treated with PCI, FFR adoption was associated with a lower number of interventions, confirming that deferring PCI in nonfunctionally significant lesions is safe.

Factors influencing the benefits of FFR-guidance

Current guidelines recommend the implementation of coronary angiography with physiologic assessment to guide revascularization of intermediate stenoses in patients without prior evidence of myocardial ischemia.¹ However, clinical adoption of FFR has been modest over the years.^{38,57} In addition to several possible logistic reasons limiting FFR penetration, there might also have been conflicting evidence from RCTs following the results of the initial trials.^{16,30–34} A critical appraisal of the literature suggests that major differences in study designs affecting the ratio of performed/deferred interventions should be thoroughly accounted for when estimating the effectiveness of FFR. In the FAME trial, intermediate lesions considered for invasive functional evaluation with FFR were at least 50% diameter stenosis by visual estimation.² In contrast, a 30% diameter stenosis was adopted in other major RCTs.³⁰ The inclusion of lesions with less than 30% diameter stenosis can be expected to dilute the potential clinical benefit associated with functional assessment. In fact, in a hypothetical study randomizing patients to FFR or angiography, the inclusion of mild coronary lesions could be expected to lead to a higher rate of deferred interventions even in patients not treated with physiology guidance. If we assume that the superiority of FFR is related to the proportion of safely deferred nonindicated interventions compared with angiography, this could hinder the detection of a net clinical benefit. Our analysis supports the hypothesis that the benefit of FFR-guidance is more evident when the proportion of revascularization deferral is higher compared with pure angiography-guidance, possibly due to the lower risk of late and acute complications.^{42,58}

We found an association between the rates of patients enrolled with ACS and the benefits of an FFR-guided revascularization strategy. The effectiveness of FFR in detecting significant lesions depends on the achievement of steady-state and maximal coronary hyperemia. In the setting of ACS (especially during ST-segment elevation MI), dynamic changes in the microvascular function of both the jeopardized and nonjeopardized myocardium can lead to increased resting and reduced hyperemic coronary flow. These modifications could hinder the effectiveness of FFR in detecting significant lesions, potentially leading to underestimation.⁵⁹ Currently, conflicting data are available regarding the reliability of FFR evaluation in this setting and no definitive conclusions can be drawn.^{60–62} Additionally, further possible explanations could be proposed to justify our finding. In the acute setting, several conditions can hamper the effectiveness of FFR, including hemodynamic instability, challenges in identifying the real nonculprit lesions,³⁰ the need for multiple interventions,⁵ and the risk of endangering nonculprit vessels during FFR guidewire manipulation.¹⁶ Further studies are needed to address this topic, focusing on the relationship between ACS subtypes and the length of follow-up.

Clinical outcomes according to study type

One interesting point from our analysis is the striking difference in effect size between RCTs and NRSI. Recently published meta-analyses of RCTs have shown that FFR-guided

revascularization was not superior to angiography in improving outcomes.^{46,47} These results highlight the inconsistency currently existing between data from RCT and NRSI.⁶³ One of the main purposes of our study was to explore the nature of these conflicting data and to evaluate the relative contribution of observational studies in determining the benefits of FFR-guided revascularization. In our study, the influence of NRSI could be largely undersized without compromising the final evidence of a clinical benefit derived from the use of FFR. Similar findings have been confirmed including only adjusted NRSI. It is reasonable to assume that in NRSI, residual confounding from selection bias persists, especially in the absence of statistical adjustment. On the other hand, it could be argued that RCTs are highly selective, plagued by the so-called “entry bias”, and their generalizability is often questionable due to their tendency to exclude higher-risk patients.⁶⁴ Among potential confounding factors, the appropriateness of physiological assessment based on clinical presentation and a differential risk profile of included patients may account for the observed divergence.⁶³ Besides these considerations, other factors can influence the conflicting results of RCTs and NRSI, including the higher rate of patients deferred in NRSI and the limits of some RCTs in terms of sample sizes and the low number of observed events.⁶³ Nevertheless, the interpretation of NRSI should be cautious and based on a thorough evaluation of inclusion/exclusion criteria and patient risk profiles.

Limitations

This study has several limitations. First, the lack of patient-level data prevented us from performing prespecified adjustments. This should be particularly considered when evaluating our results on the relationship between clinical outcomes, ACS rates and deferral rates, due to the possibility of significant uncontrolled collinearity between these confounders. Moreover, although we performed several statistical computations to balance the evidence from different study types, we cannot assume that these results are comparable to those from only pooled RCTs in terms of quality. In this regard, propensity score matching is only one of the available methods used to adjust for confounders, and several strategies could have led to slightly different results. Again, when including NRSI in a meta-analytic framework, positive bias related to selective reporting can be difficult to address. Eventually, including a large number of significantly different studies has surely led to a residual unavoidable heterogeneity. Although we showed that there are significant differences between RCTs and NRSI in terms of inclusion criteria (eg, angiographic severity of the lesions), ACS rates, deferral rates and others, we cannot directly assume that our methodological efforts to manage these major sources of heterogeneity have been completely effective. Therefore, we believe that our results can only be considered as hypothesis-generating.

CONCLUSIONS

Our analysis found that FFR-guided revascularization was associated with a significant reduction in all-cause death, MI, and MACE. These findings are driven by data from nonrandomized studies. Regardless of the study type, FFR effectively reduces the rates of non-beneficial revascularization without compromising clinical outcomes. The benefits of FFR-guidance may be lower when the number of patients with ACS and the revascularization rates are higher.

FUNDING

None.

ETHICAL CONSIDERATIONS

Review article not requiring ethical statement.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used to draft the manuscript or perform analyses.

AUTHORS' CONTRIBUTIONS

F. Mangiacapra, L. Paolucci, and E. Barbato conceived the idea. F. Mangiacapra, L. Paolucci, and M.M. Viscusi performed the studies' research. F. Mangiacapra, L. Paolucci, and N.P. Johnson performed the statistical analysis. F. Mangiacapra and L. Paolucci, drafted the paper. All authors critically revised the manuscript.

CONFLICTS OF INTEREST

None.

WHAT IS KNOWN ABOUT THE TOPIC?

- FFR-guided coronary revascularization is associated increased rates of safely deferred interventions, but recent studies have questioned its benefits in terms of clinical outcomes.

WHAT DOES THIS STUDY ADD?

- Data from randomized and nonrandomized studies suggest that FFR can lead to reduced rates of all-cause death, MACE, and MI. These findings are mostly driven by the results of nonrandomized studies. The benefits of FFR-guided revascularization are lower in studies with high rates of nondeferred interventions and ACS patients.

APPENDIX A. APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.rec.2024.02.010>

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