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Review Article

Prognostic differences between physiology-guided percutaneous coronary intervention and optimal medical therapy in coronary artery disease: A systematic review and meta-analysis

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ABSTRACT

Background: Intracoronary physiology, particularly fractional flow reserve (FFR), has been used as a guide for revascularization for patients with coronary artery disease (CAD). The optimal treatment in the physiological grey-zone area has been unclear and remains subject to ongoing debate.

Methods: We conducted a systematic review of randomized controlled trials and observational studies comparing the prognostic effect of percutaneous coronary revascularization (PCI) and optimal medical therapy (OMT) in patients with CAD. Studies were identified by medical literature databases. The outcomes of interest were major adverse cardiac events (MACE) and its components, death, myocardial infarction (MI), and repeat revascularization.

Results: A total of 16 studies with 27,451 patients were included. The pooled analysis demonstrated that PCI was associated with a prognostic advantage over OMT in patients with FFR value ≤0.80 (RR: 0.64, 95 % CI: 0.45–0.90, $p < 0.01$). Patients with an FFR value >0.80 were shown to benefit more from OMT (RR 1.38, 95 % CI 1.24–1.53, $p < 0.01$). The analysis also showed that there was no significant difference in MACE in the grey-zone area (FFR 0.75–0.80) (RR 0.64, 95 % CI: 0.35–1.16, $p = 0.14$), but a significant reduction in repeat revascularization (RR 0.54, 95 % CI, 0.31–0.91, $p < 0.01$) when patients were treated with PCI.

Conclusions: Among patients with CAD and FFR values >0.80, OMT was associated with favorable outcomes over PCI in reducing the risk of MACE. However, among patients with FFR values ≤0.80, revascularization was superior in terms of reducing MACE. The available evidence supports the guideline-recommended use of an FFR cut-off of ≤0.80.

1. Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality worldwide [1]. Chronic CAD is routinely treated with revascularization including percutaneous coronary intervention (PCI) when adequate and has been shown to improve outcomes and quality of life among these patients [3].

Coronary angiography (CAG) is the pivotal tool to guide revascularization, but it is limited by uncertainty in determining the clinical significance of intermediary lesions. Intracoronary physiology, *i.e.* either non-hyperemic pressure indices or fractional flow reserve (FFR) are operator independent and standardized indices used to guide revascularization and thus serve as the gold standard for assessment of physiological stenosis severity [4].

FFR is defined as the ratio between the maximal coronary flow in the presence of stenosis and the maximal theoretical flow in a hypothetical normal vessel. The DEFER – Trial was the first randomized controlled trial (RCT) to demonstrate the safety of deferring stable lesions with an

Abbreviations: ACS, Acute coronary syndrome; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; CAG, Coronary angiography; CI, Confidence interval; DM, Diabetes mellitus; FFR, Fractional flow reserve; HR, Hazard ratio; MACE, Major adverse cardiac events; MESH, Medical subject heading; MI, Myocardial infarction; OMT, Optimal medical therapy; PCI, Percutaneous coronary intervention; PPG, Pullback pressure gradient; RCT, Randomized controlled trial; RR, Risk ratio.

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FFR value >0.75 [5]. In addition, the FAME trial showed that FFR-guided PCI was superior to angiography guidance in terms of reducing the risk of death, myocardial infarction (MI), and repeat revascularization [6]. Later, FAME-2 showed that with a FFR cut-off of ≤0.80 major adverse cardiovascular events (MACE) occurred less frequent with PCI compared with optimal medical therapy (OMT) in patients with stable CAD [7]. Thus, a FFR of 0.75–0.80 is considered a grey-zone and has thus been subject to debate in terms of optimal treatment (revascularization *versus* medical treatment).

The aim of this systematic review is to evaluate the prognostic effect of physiology-guided PCI *versus* OMT in terms of the effectiveness of the treatment strategies on MACE.

2. Methods

This study was conducted in compliance with the PRISMA 2020 Checklist (Table 1 in the Supplementary material). The systematic review was not registered, and a review protocol was not prepared beforehand.

2.1. Search strategy

PubMed, EMBASE (OVID), and Cochrane databases were used to find studies comparing physiology-guided revascularization to OMT. Search terms included: "Percutaneous coronary intervention", "PCI", "revascularization", "fractional flow reserve", "FFR", "optimal medical therapy", "OMT", "medical therapy", "medical treatment", "conservative Therapy", "conservative treatment", and "defer*". The search filter was set for Title/abstract, and additionally, "percutaneous coronary intervention" and "fractional flow reserve" were also searched as medical subject heading (MESH) terms in PubMed and the Cochrane Library. In Embase the "explode" function was used as it does not feature the "MESH term filter".

Clinical outcomes of interest were MACE including its components all-cause mortality, MI, and repeated revascularization. Residual angina and cardiac death were a secondary outcome. All studies included had a minimum follow-up of one year.

2.2. Selection criteria

To be included, studies had to meet the following requirements: (1) The study population had either acute coronary syndrome (ACS),

Table 1
Baseline characteristics.

Author	Design	Treatment groups	FFR	Follow up time,	n.	Age	ACS %	DM %	HT %	HLD %
Hennigan et al. [10]	RCT	PCI	0.75–0.80	1	48	61	0	19.2	84.6	59.6
		OMT		1	52	60	0	19.2	59.6	73.1
Zimmerman et al. [11]	RCT	PCI	> 0.75	15	90	61 ± 9	NA	9	34	48
		OMT		15	91	61 ± 11	NA	15	36	43
Xaplanteris et al. [12]	RCT	PCI	< 0.80	5	441	63.52	0	27.5	77.6	73.8
		OMT		5	447	63,9	0	26.5	77.8	78.9
Ahn et al. [13]	Prospective	PCI	< 1	1.9[a]	2165	64 ± 9.9	30.1	33.7	64.5	64.9
	Registry	OMT		1.9[a]	6468	64 ± 9.7	21.4	30.9	62.2	55.6
		PCI	0.75–0.80	1.9[a]	405	64 ± 9.8	NA	32.6	65.2	75.0
		OMT		1.9[a]	596	64 ± 9.7	NA	33.1	65.4	56.9
Du et al. [14]	Prospective	PCI + CABG	< 0.80	1.75[a]	362	58,7	44.2	43.9	68.5	49.4
	Registry	OMT		1.75[a]	190	59	35,8	38.9	69.5	45.3
Kang et al. [15].	Prospective	PCI + CABG	0.75–0.80	2.9[a]	651	63.8	25	31.2	64.2	55.8
	registry	OMT		2.9[a]	683	64.2	18.3	32.2	64.6	56.8
Lavi et al. [16]	Prospective	PCI	0.75–0.90	1.4	116	65	40	26	73	79
	registry	OMT	0.75–0.90	1.6	165	65	21	26	60	76
Tanaka et al. [17]	Prospective	PCI	> 0.80	1	230	NA	NA	NA	NA	NA
	Registry	OMT		1	1992	NA	NA	NA	NA	NA
		PCI	< 0.80	1	1129	NA	NA	NA	NA	NA
		OMT		1	506	NA	NA	NA	NA	NA
Baptista et al. [18]	Prospective	PCI + CABG	< 0.80	1	454	63.8 ± 10	27.1	36.1	79.5	75.3
	Registry	OMT		1	66	64.9 ± 9.4	13.6	48.5	71.2	80.3
Adjedj et al. [19]	Retrospective	PCI + CABG	0.81–0.85	2.1[a]	62	64 ± 11	26	19	42	48
	cohort	OMT		2.1[a]	691	66 ± 10	24	23	49	58
		PCI + CABG	0.76–0.80	2.1[a]	187	64 ± 10	26	26	53	54
		OMT		2.1[a]	266	64 ± 11	24	24	54	57
		PCI + CABG	0.70–0.75	2.1[a]	200	66 ± 11	24	24	49	56
		OMT		2.1[a]	63	66 ± 11	23	17	46	51
Agarwal et al. [20]	Retrospective	PCI	0.75–0.80	2.5	190	64 ± 8.6	28	44	94	94
	Cohort	OMT		2.5	48	64	25	50	98	93
Bhatt et al. [21]	Retrospective	PCI	0.80–0.85	1.75	101	66	NA	46.5	90.1	91.1
	Cohort	OMT		2.1	95	66	NA	45.3	95.8	82.1
Courtis et al. [22]	Retrospective	PCI	0.75–0.80	1	63	63	51	78	58	78
	Cohort	OMT		1	44	64	45	70	50	70
Kubo et al. [23]	Retrospective	PCI + CABG	0.75–0.80	3.0[a]	78	71 ± 9	NA	45	82	76
	cohort	OMT		3.9[a]	185	69 ± 9	NA	46	79	80
Lindstaedt et al. [24]	Retrospective	PCI	< 0.80	2	39	63.9 ± 11.8	0	25.6	66.6	97.4
	Cohort	OMT		2	48	64.9 ± 10.8	0	20.8	64.6	95.8
Sud et al. [25]	Retrospective	PCI	> 0.80	5	817	66.4	33.5	36.3	80.1	76.3
	Cohort	OMT		5	5604	65.9	35.7	35.7	78.9	74.9
		PCI	< 0.80	5	2022	64.9	35.6	38.6	79.8	76.0
		OMT		5	674	65.7	36.8	38.2	79.4	75.5

Abbreviations: n: number of patients, RCT: Randomized controlled trial, FFR: Fractional flow reserve,PCI: Percutaneous coronary interventions, OMT: Optimal Medical therapy, CABG: Coronary artery bypass grafting, ACS: Acute coronary syndrome, DM: Diabetes Mellitus, HT: Hypertension, HLD: Hyperlipidemia.
[a] Median.

chronic coronary syndrome (CCS), or both, (2) Patients had FFR measured before treatment initiation, (3) OMT and PCI were compared (4) the studies included at least one of the outcomes: death, cardiac death, MACE, MI, any type of repeat revascularization, and/or residual angina (5) the study design was either a controlled clinical trial or an observational study.

Exclusion criteria included: (1) Patients had chronic total occlusions, (2) Studies did not report and compare the treatment strategies, (3) No valid physiological-measurements were performed prior to initiation of both treatment strategies, (4) No valid outcomes were reported, and (5) The study was published in other languages than English. Duplicate studies were removed during article screening.

2.3. Sensitivity analysis and risk of bias assessment

When studies were found to have moderate or high heterogeneity, a sensitivity analysis was performed by excluding studies one by one, thereby examining whether there was a change in the pooled analysis.

Cochrane risk bias rating scale was used to assess the quality of the RCT [8], whereas Robins-I was used to assess the quality of the non-randomized controlled clinical trials [9].

2.4. Data synthesis

Three authors independently reviewed and excluded studies by title, abstract, and full-text review. Screening conflicts were resolved by vote. Data were extracted for baseline characteristics (see Table 1). Lesion characteristics such as multivessel disease and stenosis severity were included and added to Table 4 in the Supplementary material.

2.5. Statistical analysis

The meta-analysis was performed using the generic inverse variant method. The difference in outcomes between PCI and OMT in different intervals of the FFR spectrum were compared. Clinical outcomes were extracted and were used to calculate a risk ratio with 95 % confidence.

Heterogeneity across studies was assessed with the I^2 test. For this review, an I^2 value of 0.25 to 0.50 was regarded as low, 0.50 to 0.75 as moderate, and a value over 0.75 as high heterogeneity.

In this meta-analysis, the included studies were categorized based on the initial FFR value used to determine the treatment strategy. The studies were classified into four categories: 1) Studies in which both the OMT and PCI groups had an FFR value of 0.81 or above, 2) Studies in which both groups had an FFR value $\leq$0.80, 3) Studies in which the FFR value ranged from 0.75 to 0.80, and 4) Studies in which the FFR value

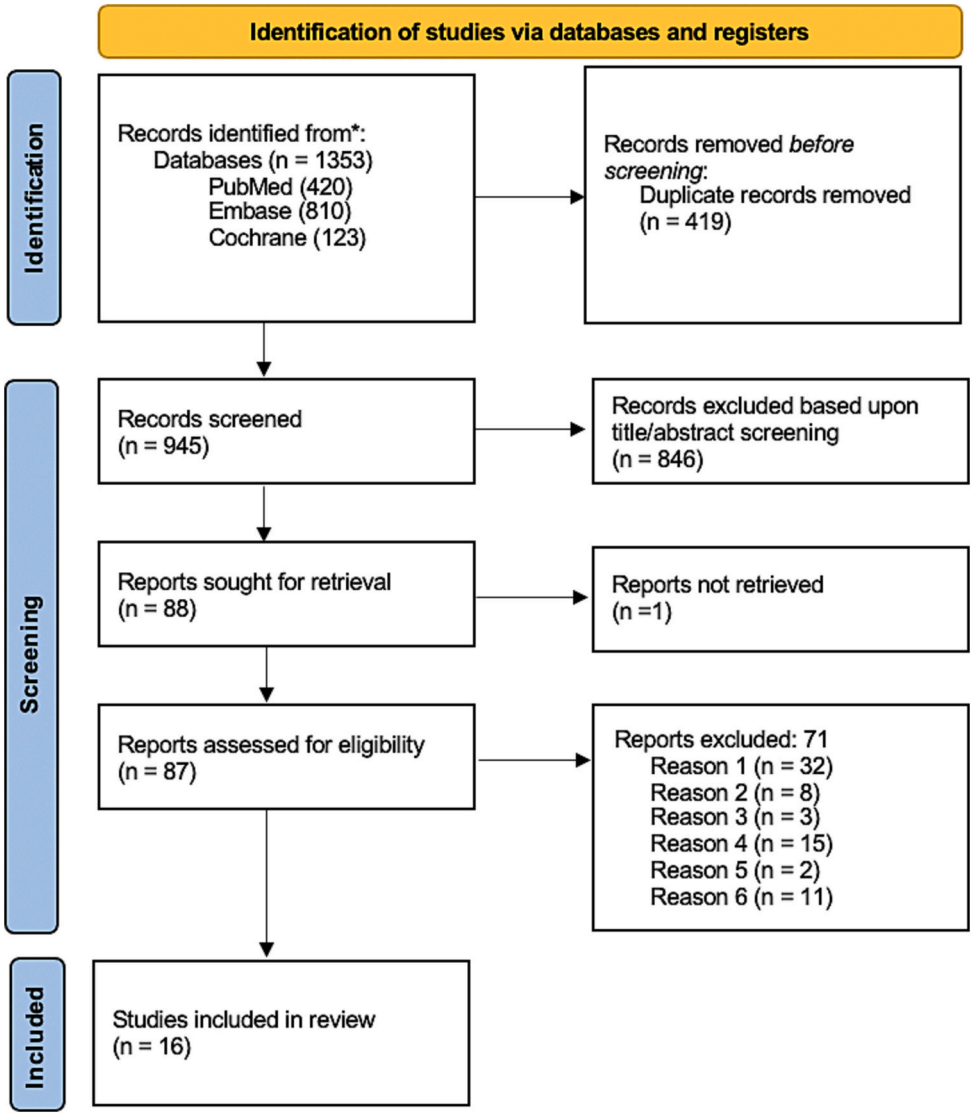

Fig. 1. Flow diagram of study selection.

was ≤0.75. An additional group with a different FFR value, but without its corresponding group, was excluded.

Studies with missing outcome data were not included in the forest plot figures.

All statistical analyses were performed in R (4.1.1) and RStudio (2021.09.0). *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Study selection

The initial research yielded 1353 articles, which were published between 1993 and 2023. We excluded 419 duplicates, leaving 945 articles which were screened for title/abstract of which 88 were assessed for eligibility. One of those 88 was not possible to retrieve.

After assessing the full text, 16 studies were included (see flowchart, Fig. 1, supplementary Table 2).

3.2. Study characteristics

Characteristics of the included studies are summarized in Table 3 in the Supplementary. The list includes type of CAD (chronic and acute disease) that has been investigated, inclusion-, exclusion criteria, primary-, and secondary endpoints.

3.3. Baseline characteristics

Baseline data are listed in Table 1. In total, there were 3 RCT, 6 prospective studies, and 7 retrospective studies.

A total of 27,451 patients were pooled for this review: 9734 in the PCI group and 17,717 in the OMT group. Mean age was 64 years ±2.7 when including patients in both OMT and PCI groups. Mean follow-up time across the studies was 2.4 years. The mean percentage of patients with DM in PCI group was 33.8 % ± 14.6 and for OMT group was 33.7 % ± 13.9 ($p = 0.98$). Mean HT was 68.7 % ± 16.1 for PCI group, whereas mean HT was 66.4 % ± 16.1 ($p = 0.64$). HLD was 69.9 % ± 15.4 for PCI and 68.6 % ± 15.3 for OMT ($p = 0.80$). Mean ACS was 32.5 % ± 8.6 and 27.0 ± 9.2 for PCI group and OMT group respectively ($p = 0.13$). Lesion characteristics are listed in Supplementary Table 4.

3.4. Outcomes in lesions with FFR > 0.80

Two observational prospective and three retrospective studies investigated the prognostic effect of revascularization by PCI compared to OMT in lesions with FFR >0.80. The conclusions of these studies are summarized in Table 2. Data of primary outcomes are listed in Table 5 in the Supplementary.

According to the pooled analysis (Fig. 2), OMT had a prognostic advantage in terms of MACE (RR 1.38, 95 % CI 1.24–1.53, $p < 0.01$), MI (RR 1.67, 95 % CI 1.30–2.14, $p < 0.01$), and repeat revascularization (RR 1.72, 95 % CI 1.35–2.19, p < 0.01).

Table 2
Study conclusions of FFR above 0.80.

Reference	Follow–up time, years	Conclusion
Adjedj et al. [26]	2.1	Stenosis with an FFR > 0,80 were better treated with MT
Ahn et al. [13]	1.9	There was an increase in risk of cardiac death and MI in revascularized group compared to patients treated with MT with an FFR between 0,80–0,85
Sud et al. [25]	5	Higher rates of MACE were found in lesions FFR > 0,80 treated with PCI when compared to deferral.
Tanaka et al. [17]	1	Vessel-related events were less frequent in MT group than in PCI group.

The I^2 was 0 and the *p*-value >0.05 for all three endpoints (MACE: $p = 0.89$; MI: $p = 0.79$, Repeat.Rev.: $p = 0.39$) which indicated no heterogeneity among the studies in this category.

3.5. Outcomes in lesions with FFR ≤ 0.80

A total of five studies were selected: one RCT, two prospective, and two retrospective studies. All studies observed a lower event-rate in the PCI-treated groups compared with OMT alone (Table 3).

Three of the studies reported MACE as a clinical outcome. *Xaplantaris* et al. [12] showed in the FAME – 2 Trial that MACE was lower in the revascularization group (RR 0.51, 95 % CI: 0,39–0.68, $p < 0.01$). Furthermore, the random effect model favored the revascularization strategy regarding MACE (RR: 0.64, 95 % CI: 0.45–0.90, p < 0.01) (see Fig. 3).

The risk of cardiac death was not significantly different between the two groups (RR 0.90, 95 % CI: 0.28–2.89, $p = 0.86$).

In terms of MI, there was a prognostic advantage in the revascularization group (RR 0.75, 95 % CI 0.61–0.93, $p < 0.01$).

The rate of repeat revascularization was significantly reduced in the PCI group compared to OMT group (RR 0.55, 95 % CI: 0.31–0.97, p < 0.01).

Only two studies reported residual angina. Both *Sud* et al. [25] and *Xaplanteris* et al. [12] reported a greater reduction in the frequency of angina in the revascularization group compared with the medical group in the first three years (supplementary Table 7) [12].

3.5.1. Sensitivity analysis

Sensitivity analyses can be viewed in Table 8 in supplementary. In the pooled analysis, heterogeneity with regards to risk of MACE was $I^2 = 79$ %, $p < 0.01$, and repeat revascularization was $I^2 = 86$ %, $p < 0.01$. In terms of MACE, I^2 was reduced to 0 and the RR was at its lowest, (RR 0.52, 95 % CI 0.40–0.67, p < 0.01), when the study by *Sud et al* [25] was excluded.

I^2 for cardiac death was 0 % when the study by *Du et al* [14] was excluded. OMT was shown to have a superior benefit compared to revascularization, however, the difference was not statistically significant (RR 1.45, 95 % CI 0.62–3.39, $p = 0.40$).

Regarding repeat revascularization, the pooled analysis remained stable when studies were excluded one at a time. However, I^2 was the lowest at 72 %, and the risk ratio indicated the most favorable outcome towards revascularization, (RR 0.43, 95 % CI: 0.28–0.67, $p < 0.01$) when the study by *Tanaka* et al. [17] was excluded.

3.6. Outcomes in lesions with FFR in Grey zone (FFR 0.75–0.80)

Two RCT, two prospective, and five retrospective studies were found that investigated whether PCI treatment was associated with more favorable outcomes than medical treatment alone.

Table 4 shows that all studies – apart from *Kang* et al., *Lindstaedt* et al., and *Zimmerman* et al. – concluded that revascularization had a greater effect in reducing event-rates. Data of the primary outcomes can be found in Table 9 in supplementary.

The 15 years follow-up study of the DEFER-Trial demonstrated that a deferral strategy has superior prognosis compared with a revascularization strategy. However, the study population was not limited only to the grey-zone area as the mean FFR was 0.86 ± 0.06 and 0.87 ± 0.07 for the deferred arm and PCI arm respectively [11].

Random effect model indicated that revascularization treatment was associated with a reduction in the rate of MACE compared to OMT (RR 0.64, 95 % CI: 0.35–1.16, $p = 0.14$). *Kang* et al. [15] was the largest study and had the greatest weight in this analysis, and it showed that there was no difference in the MACE rate between the revascularization group and deferral group (RR 1.05, 95 % CI: 0.73–1.50, $p = 0.79$) (Fig. 4).

Lavi et al. illustrated that a PCI treatment led to a lower HR in terms

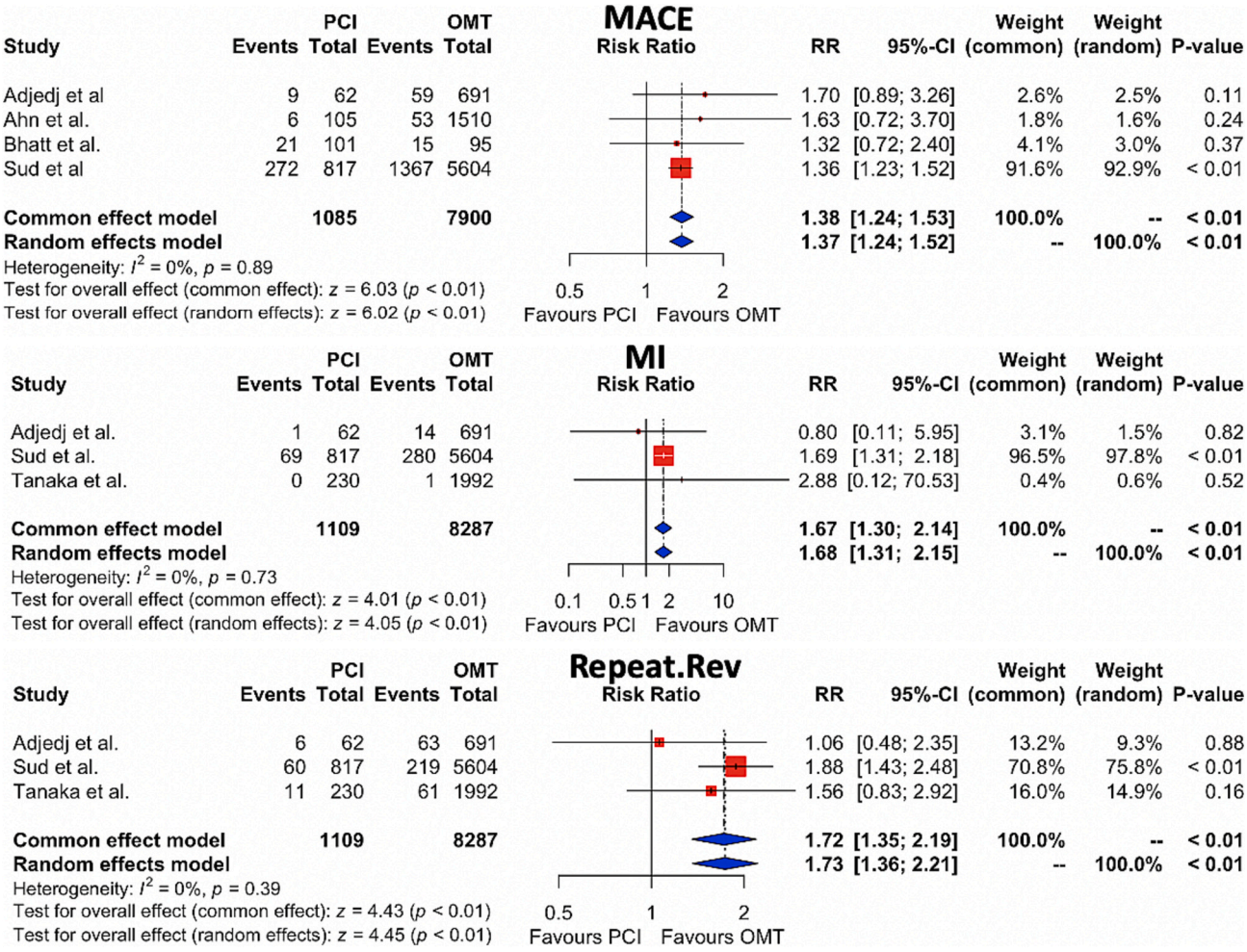

Fig. 2. Pooled analysis: Comparison between revascularization and medical treatment in patients with FFR above 0.80. MACE (Major adverse cardiac events), MI (Myocardial Infarction), and Repeat.Rev. (Repeat revascularization), PCI (Percutaneous coronary intervention), OMT (Optimal medical therapy), RR (Risk ratio), CI (Confidence interval).

Table 3
Study conclusions of FFR below 0.80.

Author	Follow – up, years	Study Conclusion:
Baptista et al. [18]	1	MACE rate was more frequent in patients with an FFR < 0.80 and were deferred.
Du et al. [14]	1.75	Deferral with an FFR < 0.80 was associated with a higher risk of subsequent revascularization
Sud et al. [25]	5	PCI treated group had lower rates of MACE in ischemic lesions (FFR < 0.80)
Tanaka et al. [17]	1	Vessel-related events were more frequent in MT group than in PCI group.
Xaplanteris et al. [12]	5	Initial FFR – guided PCI strategy resulted in a sustained clinical benefit as compared to MT alone.

of MACE than a deferral strategy in the grey-zone [16].

When the random effect model was applied to compare MI, it showed that there was no difference in the rate of this endpoint between the revascularization group and the OMT group (RR 1.05, 95 % CI: 0.31–3.6, $p = 0.94$). *Kang* et al. (RR 4.41, 95 % CI: 1.67–11.62, $p < 0.01$) and *Lindstaedt* et al. (RR 11.06, 95 % CI: 0.61–199.11, $p = 0.10$) showed a favorable outcome in the OMT group.

The analysis demonstrated that revascularization significantly reduced the incidence of repeat revascularization and cardiac death. The random effect model indicated that there was a much greater benefit in revascularization compared to OMT (RR 0.54, 95 % CI, 0.31–0.91, $p <$ 0.01) for repeat revascularization and (RR 0.48, 95 % CI 0.27–0.87, $p =$ 0.02) for cardiac death.

In terms of improvement of angina symptoms, 3 studies reported residual angina: *Courtis* et al. [22], *Lindstaedt* et al. [24], and *Hennigan* et al. [10]. *Courtis* et al. and *Hennigan* et al. reported that revascularization treatment was associated with an improvement in angina symptoms. *Lindstaedt* et al. reported a lower symptom burden in the OMT group. However, it should be noted that the latter study had the lowest weight in the pooled analysis.

3.6.1. *Sensitivity analysis*

As illustrated in Fig. 4, the statistical heterogeneity was between 67 % to 79 % indicating that there was moderate to high heterogeneity among the studies in terms of MACE, MI, and repeat revascularization. Sensitivity analysis can be viewed in Table 11 in supplementary. When excluding studies sequentially in the MACE analysis, the result of treatment changed significantly. Heterogeneity became lowest (71 %) when *Lindstaedt* et al. [24] was excluded. Furthermore, the analysis showed a significant improvement in PCI treatment after the exclusion of the study (RR 0.53, 95 % CI: 0.32–0.88, $p < 0.01$).

The analysis of cardiac death showed no heterogeneity among the studies when *Lindstaedt* et al. was excluded, and the common effect model showed a significant improvement in the revascularization group compared to OMT (RR 0.41, 95 % CI, p < 0.01).

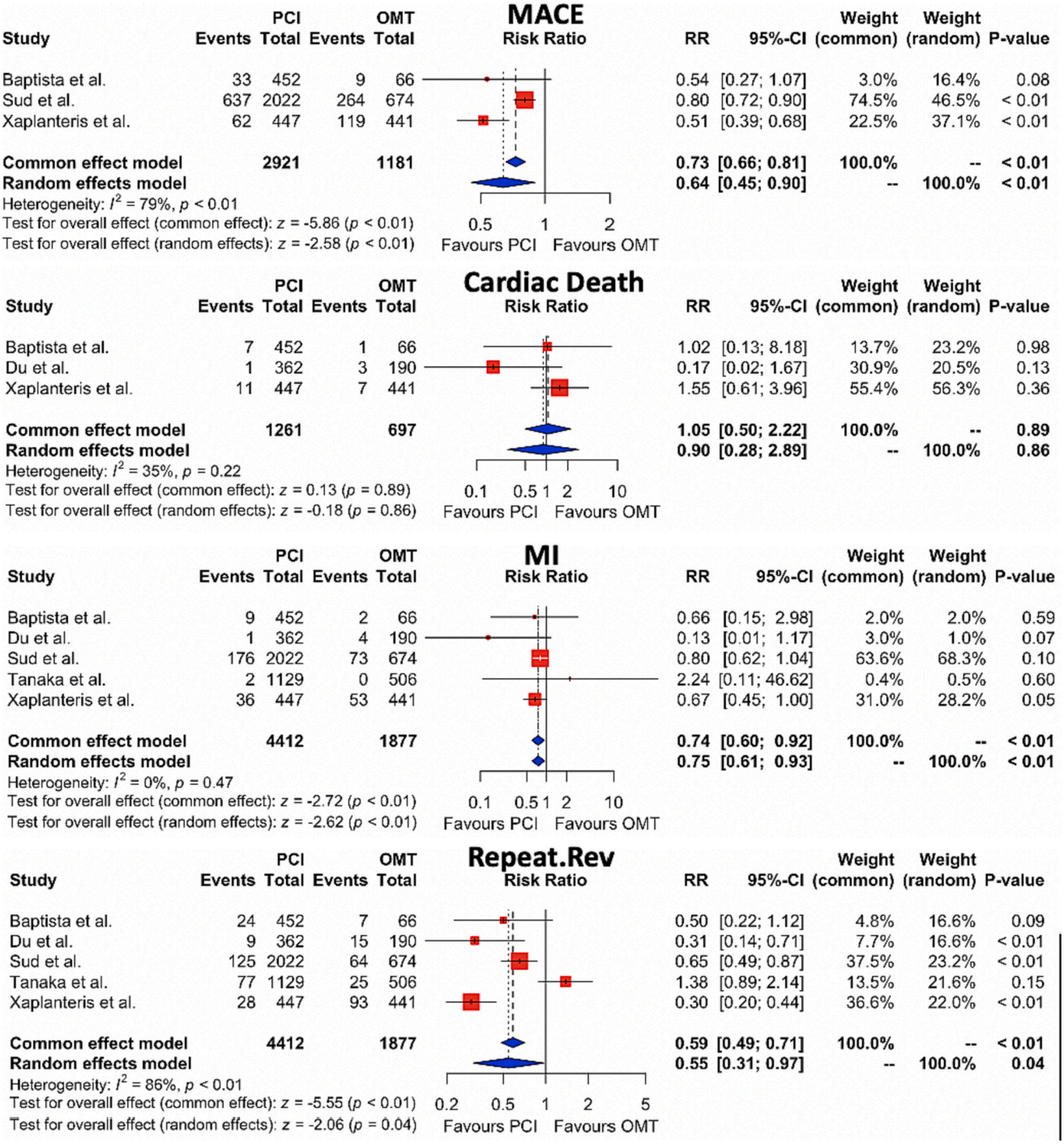

Fig. 3. Pooled analysis: Comparison between revascularization and medical treatment in patients with FFR below 0.80. MACE (Major adverse cardiac events), Cardiac death, MI (Myocardial Infarction), and Repeat.Rev. (Repeat revascularization),: PCI (Percutaneous coronary intervention), OMT (Optimal medical therapy), RR (Risk ratio), CI (Confidence interval).

In terms of MI, the lowest I^2 value was achieved when *Kang* et al. [15] was excluded. The analysis showed a moderate level (I^2 = 48 %), however, there was no statistically significant difference between OMT and PCI (RR 0.65, 95 % CI 0.21–2.04, p = 0.46).

I^2 was reduced to 58 % for repeat revascularization. The random effect model showed a significant improvement in revascularization treatment (RR 0.48, 95 % CI 0.30–0.77, p < 0.01).

3.7. Outcomes in lesions with an FFR < 0.75

Three studies discovered a prognostic benefit of revascularization compared with OMT in terms of MACE rate in patients with FFR <0.75. The conclusion of each study can be viewed in Table 5 and outcome data can be viewed in Table 12 in supplementary.

Additionally, heterogeneity was found to be 0 %, and therefore, a common effect model was applied that favored revascularization in terms of MACE and target lesion failure (TLF), (RR: 0.60, 95 % CI: 0.41–0.88, p < 0.01) (Fig. 5).

Table 4
Study conclusions of FFR in grey zone (0.75–0.80).

Author	Follow – up, years	Study Conclusion:
Adjedj et al. [26]	2.1	More favorable outcomes are found in the revascularization group than the deferred below an FFR value of 0.80
Agarwal et al. [20]	2.5	In CAD patients with grey-zone FFR, PCI was associated with lower incidence of MACE.
Courtis et al. [22]	5	PCI treated group had lower rates of MACE in ischemic lesions (FFR < 0,80)
Kang et al. [15]	2.9	Revascularization was not associated with better outcomes for stenosis with grey-zone FFR.
Kubo et al. [23]	5	In grey-zone FFR, PCI decreased frequency of TVF
Lindstaedt et al. [24]	2	Medical therapy should be the first line of treatment strategy in grey – zone.
Zimmerman et al. [11]	15	Patients with stable CAD have an excellent outcome in lesions with FFR > 0.75 when treated medically.

3.8. Quality assessment

Quality assessments of included studies are shown in Supplementary Table 14.

Three randomized controlled trials were generally considered low risk. Hennigan et al., the DEFER-Trial and FAME 2-Trial explained their randomization method. However, the treatment strategy was not blinded, which increases allocation bias. Other factors such as detection bias, incomplete outcome data, and selective reporting were judged as low risk of bias. All the nonrandomized studies were evaluated to have an overall moderate risk of bias. Therefore, we included all the studies in this analysis. Compared to the RCT, the nonrandomized studies often had a serious risk of bias in selecting its participants and a serious risk of bias in confounding.

4. Discussions

This systematic review differs from previous reviews as it not only includes studies focusing exclusively on grey zone FFR but also incorporates trials that investigate other FFR intervals as well. This approach will provide a solid overview of the optimal treatment over the FFR spectrum and highlight the importance of considering the incorporation of this index for future RCT that will further investigate revascularization treatment for patients with CAD.

By gathering all available evidence, this review attempted to make a more solid case for the choice of using either a cut-off value of 0.75 as proposed in DEFER trial, or a value of 0.80 as proposed in the FAME trial.

4.1. FFR > 0.80

The findings of this review indicate that an OMT strategy was associated with a lower risk of MACE in patients with FFR values above 0.80 compared to patients treated with PCI. It is widely accepted that PCI treatment should be refrained from in lesions with an FFR above 0.80, as this value excludes ischemia in 90 % of cases [27]. Factors that can explain this are that performing PCI in functionally insignificant stenosis may lead to either a complication related directly to the PCI or to an event due to long-term failure of the stent. MI and repeat revascularization varied mostly in favor of OMT group. Thus, the implantation of an unnecessary stent may lead to restenosis with the need for repeat revascularization or stent-thrombosis with MI, and these events are obviously circumvented with OMT.

4.2. FFR ≤ 0.80

Current guidelines recommend PCI in patients with an FFR of 0.80 or below. PCI was associated with a reduction in MACE compared to patients treated with OMT as well as its individual components: MI, and especially repeat revascularization. However, the analysis did not demonstrate a significant reduction in terms of cardiac death. It is important to highlight that among studies with a follow-up period between 1 and 2 years, no significant differences were observed in MACE components except for repeat revascularization. This observation is in line with the findings of the FAME-2 trial, as PCI was generally associated with a better prognosis, but only urgent revascularization was revealed to have a statistically significant improvement over the short run. However, a significant improvement in MI was observed in the 5-year follow-up [7,12]. Also, in the 5-year follow-up of *Sud* et al. the point estimates for the risk difference generally favored the PCI group [25]. Therefore, this review suggests that PCI offers more benefits in the long term, and, that it is plausible that a more pronounced difference in favor of PCI may have been detected if the studies had a longer follow-up duration. This finding supports the current guidelines [4].

4.3. FFR grey zone (FFR 0.75–0.80)

Based on the DEFER–Trial, patients with stable disease can be deferred safely if FFR is above 0.75. However, it should be taken into consideration that the mean FFR was 0.86 ± 0.06 and 0.87 ± 0.07 in the deferred arm and PCI arm respectively. Furthermore, it has been suggested that a defer strategy is preferred even among patients with higher cardiac risks including ACS and multivessel diseases. On the other hand, in the FAME-2 trial the mean FFR was 0.68 ± 0.10 for OMT group and 0.68 ± 0.15 for PCI group. Only a low proportion of patients with grey zone FFR were included in the available RCT. Therefore, for this study, a separate category has been formed which focuses exclusively on patients with FFR within the grey zone.

The pooled analysis revealed that a PCI treatment for patients within the FFR grey zone had a reduction in MACE. This effect was mainly driven by a reduction in repeat revascularization; however, cardiac death was also significantly favored by PCI. Therefore, any risk associated with the PCI procedure is overcome by the prevention of complications that may follow revascularization. According to a substudy from the EXCEL trial, it was demonstrated that repeat revascularization, including target vessel revascularization and target lesion revascularization, was associated with a higher risk of all-cause mortality and cardiovascular mortality [28], and thus led to a worse prognosis. Furthermore, a larger proportion of the collected studies also revealed a greater symptomatic benefit in terms of a reduction in angina burden in the PCI group.

It should be noted that the analysis of studies investigating grey zone consists only of nonrandomized trials which are more susceptible to bias (see Table 14 in supplementary), and the current available RCTs do not represent lesions within the grey zone area. The COMFORTABLE study will be the first RCT to investigate the prognosis of PCI *vs.* OMT in patients with stable CAD and FFR in the grey zone [29].

4.4. FFR < 0.75

The analysis showed that revascularization had a prognostic advantage over OMT in patients with an FFR value <0.75. FFR values below 0.75 indicate a more severe narrowing of the coronary arteries, which can lead to a more pronounced reduction in blood flow to the heart muscle and an increased risk of MACE. The analysis suggests that OMT may not be as effective as PCI in reducing ischemia. Therefore, this review supports a revascularization strategy in lesions with an FFR below 0.75.

Based on the data analysis in this study, an FFR – value of ≤0.80 appears to be the ideal cut-off, as all analyzed studies found that OMT

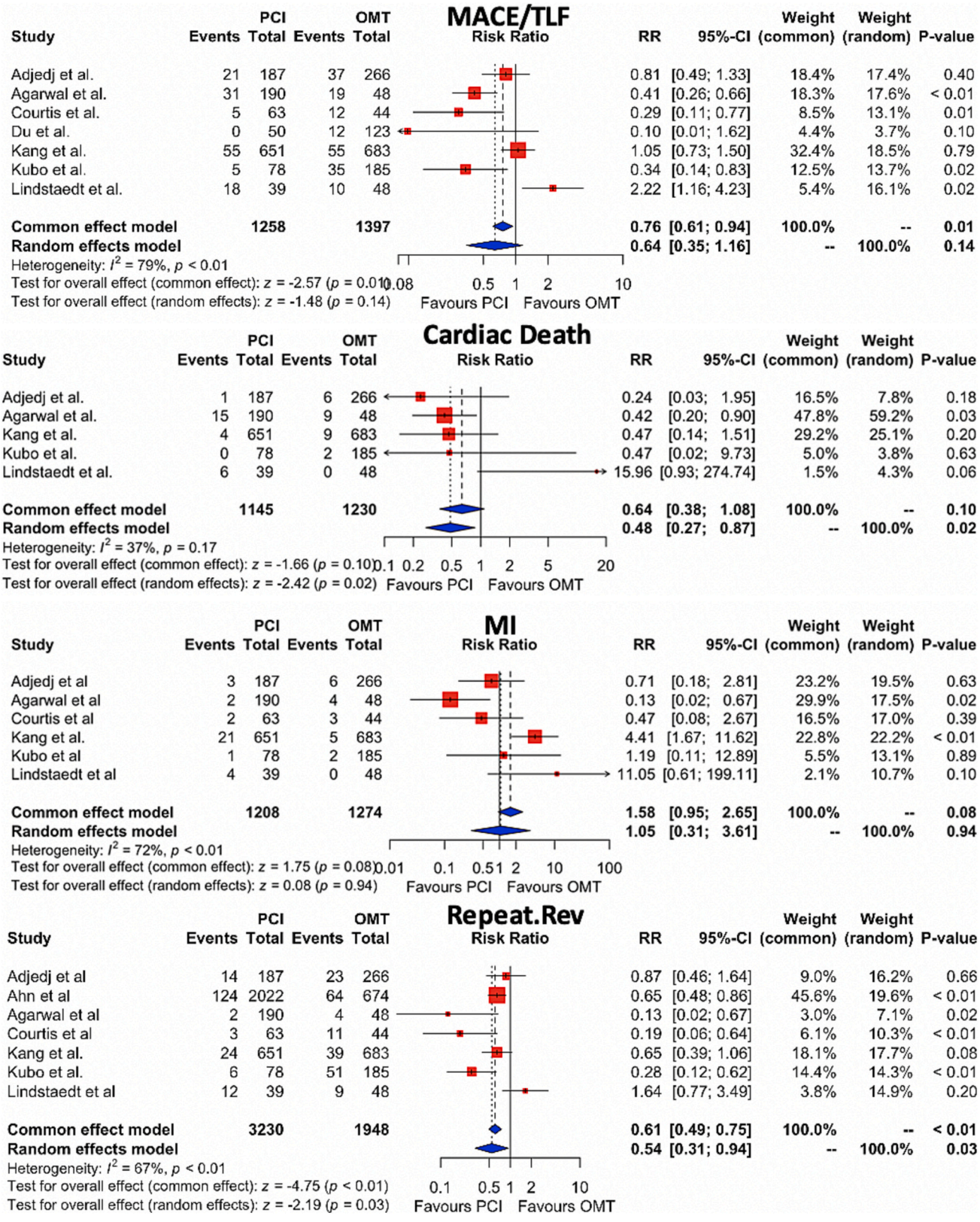

Fig. 4. Pooled analysis: Comparison between revascularization and medical treatment in patients with FFR grey zone. MACE (Major adverse cardiac events), Cardiac death, MI (Myocardial Infarction), and Repeat.Rev. (Repeat revascularization), PCI (Percutaneous coronary intervention), OMT (Optimal medical therapy), RR: (Risk ratio), CI (Confidence interval).

Table 5
Study conclusions of FFR in <0.75.

Author	Follow – up, years	Study Conclusion:
Adjedj et al [26]	2.1	Incident of MACE was most frequent in FFR 0.70–0.75. Revascularization was associated with better outcomes
Ahn et al [13]	1.9	In lesions with an FFR < 0.75, revascularization treatment showed more favorable outcomes.
Du et al [14]	1.75	Higher risk of TLF incidence was observed among patients in medical treatment group

conveyed the best prognosis in lesions with FFR >0.80. However, it should be noted, the event rates are higher in patients with ACS [30], and therefore more studies are needed to precisely assess the safety of deferring revascularization for this particular group, even when FFR is high. In contrast, isolated measurement of FFR does not take into account the anatomical complexity of the CAD, or the complexity of the patient as illustrated by the syntax I and II scores [31,32] Relying solely on isolated FFR measurement is not sufficient to determine the right treatment. For instance, a frail 84-year-old woman with multiple comorbidities such as sarcoidosis and insulin-dependent diabetes will most likely have a different threshold of FFR compared to an otherwise healthy 40-year-old woman. Thus, all decisions of revascularization should be taken on an individual patient-related basis focusing on symptoms, clinical presentation, patients related factors, complexity of the CAD and physiological measurements.

4.5. Clinical implications and future directions

This systematic review establishes the effectiveness of applying FFR as a guiding strategy for revascularization. The 2018 ECT/EACTS guidelines stated that only 35 % of patients with anatomical stenosis of 50–70 % were hemodynamically relevant (defined as an FFR ≤ 0.80), and 20 % of patients with 70–90 % stenosis was not. These data highlight the importance of the poor correlation between angiography and physiology. Recently pullback pressure gradient (PPG) has been used to differentiate focal from diffuse disease and has been shown to better identify which lesions that may benefit from PCI in terms of residual angina [33]. The pullback pressure recording provides useful information about whether a stent will result in effective treatment of ischemia, or if it may turn too difficult to obtain a satisfactory flow in a diffusely diseased artery. However, future research and clinical validation are needed to establish the clinical utility and impact of PPG as a supplement to FFR in the management of CAD patients. Thus, for now, FFR cut-off is quite robust and identifies, overall, who will benefit from OMT only.

4.6. Limitations

Not all included studies were RCTs. This implies some degree of allocation and selection bias.

Secondly, there was heterogeneity of the included studies in terms of study design, size, characteristics of patient, and follow–up duration. This flaw may limit the generalizability of our findings.

It should also be noted, not all studies that were included in this review used PCI exclusively. However, the studies that investigated both PCI and Coronary artery bypass grafting (CABG) were only considered if PCI covered the larger proportion of the intervention strategy. In a real-world scenario, the decision for many patients also includes CABG. While this current analysis may contribute insights to these real-world decisions, it is imperative to recognize that the data presented herein constitute only a fraction of the comprehensive information required to make these nuanced decisions.

5. Conclusion

The available evidence supports the guideline-recommended use of an FFR cut-off of ≤0.80. Revascularization has a prognostic advantage over OMT in terms of MACE and its components, as well as reducing angina symptoms in patients with FFR ≤0.80. Furthermore, in general, patients with an FFR > 0.80 have a better prognosis when treated with OMT compared with PCI and in this view lesions with FFR > 0.80 can safely be deferred. Importantly, FFR is only one factor in deciding whether or not to revascularize, and the ultimate decision must be made by contextualizing the FFR with the overall medical status of the patient and the associated comorbidities present in the patient.

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Ethical statement

The data of this systematic review is based of previously conducted articles. It does not present data nor experiments with new human participants and animals performed by the authors.

CRediT authorship contribution statement

U. Islam: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **M. Sabbah:** Conceptualization, Supervision, Writing – review & editing. **B.T. Özbek:** Investigation, Methodology, Writing – review & editing. **J.M. Madsen:** Investigation, Methodology, Writing – review & editing. **J.T. Lønborg:** Conceptualization, Supervision, Writing – review & editing. **T. Engstrøm:**

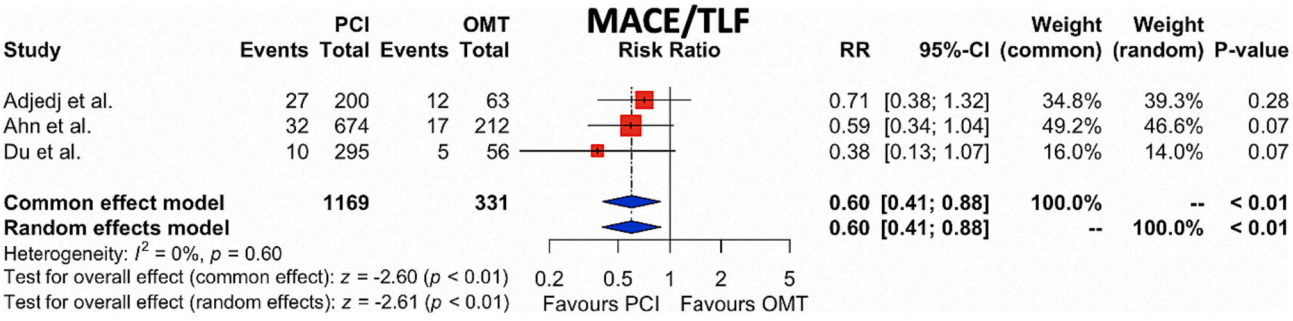

Fig. 5. Pooled analysis: Comparison between revascularization and medical treatment in patients with FFR below 0.75. MACE (Major adverse cardiac events), Cardiac death, MI (Myocardial Infarction), and Repeat.Rev. (Repeat revascularization), PCI (Percutaneous coronary intervention), MT (Optimal medical therapy), RR (Risk ratio), CI (Confidence interval).

Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data used in the meta-analysis were acquired from original articles which are available in the public domain.

Acknowledgment

The authors are solely responsible for the analyses, development, and editing of this review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100362.

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