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MICROCIRCULATION FUNCTION ASSESSMENT IN ACUTE MYOCARDIAL INFARCTION: A SYSTEMATIC REVIEW OF MICROCIRCULATORY RESISTANCE INDICES

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Microcirculation Function Assessment In Acute Myocardial Infarction: A Systematic Review of Microcirculatory Resistance Indices

Running Title: Coronary Microvascular Function in Acute Myocardial Infarction

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Abstract

Background: Up to 50% of acute myocardial infarction (MI) patients present with microvascular dysfunction, after a well succeeded percutaneous coronary intervention (PCI), which determines worse clinical outcomes. The main purpose of this study is to provide a critical appraisal of the emerging role of invasive microvascular resistance indices in the MI setting, using the index of microcirculatory resistance (IMR), hyperemic microvascular resistance (HMR) and zero-flow pressure (Pzf).

Methods: We systematically explored relevant studies in the context of MI that correlated microcirculation resistance indices with microvascular dysfunction on cardiac magnetic resonance (CMR) and positron emission tomography (PET), as a guide tool for adjunctive therapeutic interventions and as a prognostic biomarker. We also examined microvascular dysfunction occurring in infarct related arteries (IRA) and non-IRA, and in the case of MI with no obstructive coronary arteries (MINOCA).

Results: The microcirculation resistance indices correlated with microvascular obstruction (MVO) and infarct size (IS) on CMR plus with myocardial viability and reperfusion on PET. Although HMR and Pzf seems to have better diagnostic accuracy for MVO and IS, IMR has more validation data and was the only biomarker used to measure the treatment effect of adjunctive therapies for microvascular dysfunction in acute MI. Both IMR and HMR were predictors of adverse cardiovascular events.

Conclusions: IMR, HMR and Pzf are valuable means to accurately evaluate microcirculation function. Microvascular dysfunction relates to the extent of myocardial damage after an MI, as measured by CMR and PET. Published data does not allow to conclude which one of the indices is superior at evaluating microcirculation function.

Keywords:

Myocardial Infarction (MI), Percutaneous Coronary Intervention (PCI), Microvascular Dysfunction, Index of Microvascular Resistance (IMR), Hyperemic Microvascular Resistance (HMR), Zero-flow Pressure (Pzf).

Abbreviations

ACS Acute coronary syndrome; **APV** Average peak velocity; **AUC** Area under the curve; **CFR** Coronary flow reserve; **CMR** Cardiovascular magnetic resonance; **FDG** Fluorodeoxyglucose; **HF** Heart failure; **HMR** Hyperemic microvascular resistance; **IMH** Intramyocardial hemorrhage; **IMR** Index of microvascular resistance; **IQR** Interquartile range; **IRA** Infarct-related artery; **IS** Infarct size; **LV** Left ventricle; **LVEF** Left ventricular ejection fraction; **MACE** Major adverse cardiovascular events; **MI** Myocardial infarction; **MINOCA** Myocardial infarction with no obstructive coronary arteries; **MVO** Microvascular obstruction; **NSTEMI** Non-ST-segment elevation myocardial infarction; **OR** Odds ratio; **PCI** Percutaneous coronary intervention; **Pd** Mean distal coronary pressure; **PET** Positron emission tomography; **Pzf** Zero-flow pressure; **RCT** Randomized controlled trial; **STEMI** ST-segment elevation myocardial infarction; **WMSI** Wall motion score index.

Introduction

Many patients following an acute myocardial infarction (MI) have adverse clinical outcomes despite a well succeed percutaneous coronary intervention (PCI) (1). The solely treatment of an epicardial coronary obstruction, may not suffice to improve microcirculation in acute coronary syndromes (ACS), and persistent microvascular dysfunction determines worse clinical outcomes (2). Microcirculatory function can be assessed noninvasively using cardiovascular magnetic resonance (CMR) or positron emission tomography (PET), however, this is not achievable at the time of an early invasive reperfusion treatment, to identify those cases with failed reperfusion of microcirculation and with extensive myocardium injury.

Several vascular resistance indices have been proposed to evaluate microcirculation function invasively, that have the advantage of being immediately available in the catheterization laboratory to delineate the specific contribution of microcirculation to myocardial ischemia. The index of microvascular resistance (IMR) is a thermodilution technique that allows the quantitative assessment of the minimum microcirculatory resistance in a coronary artery territory. The hyperemic microvascular resistance index (HMR) represents the ratio of mean distal coronary pressure (Pd) and doppler flow average peak velocity (APV) during hyperemia. Lastly, zero-flow pressure (Pzf) that is extrapolated from pressure-velocity plots, represents Pd at which the coronary blood flow would cease. As opposed to coronary flow reserve (CFR), vascular resistance indices are specific for the microcirculation, independent of hemodynamic variations and are greatly reproducible (3).

The main purpose of this study is to provide a critical appraisal of the emerging role of microvascular resistance indices in the MI setting, and its relation to specific cardiac imaging findings on CMR and PET, therapeutic interventions and clinical outcomes.

Methods & Materials

Protocol and registration

This systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standard and is registered in PROSPERO database (CRD42021228432).

Information sources

A systematic search was performed on PubMed, Embase and Cochrane Controlled Register of Trials (CENTRAL) on November 17, 2020. The search terms are presented in the **Supplementary Table 1**. Interventional and observational original studies were included, and there was no date restriction. Only Portuguese, Spanish, English and French articles were included. **Figure 1** shows PRISMA flow diagram related to our search strategy.

Eligibility criteria

The eligible randomized and nonrandomized studies reported associations between microvascular resistance indices (IMR, HMR and Pzf) - measured invasively in a cardiac catheterization laboratory - and CMR, PET findings of microcirculation dysfunction, myocardial injury and viability in patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI), at the index event. Furthermore, the selected studies included data on microcirculation therapy interventions, culprit/non-culprit coronary lesions, MI with nonobstructive coronary arteries (MINOCA) and clinical outcomes.

Data collection process

One author (M. Silva) systematically screened the titles and abstracts of publications retrieved using the search strategy mentioned above to verify inclusion criteria. The full texts of the selected studies were, again, independently reviewed for eligibility by two co-authors.

Quality Assessment

Two investigators (M. Silva and L. Paiva) assessed the risk of bias of the included studies, following the Cochrane Collaboration's risk of bias tool for randomized clinical trials (RCT) and the Newcastle-Ottawa Scale for observational studies. In RCT, only three had a blinding strategy that included participants, care providers and outcomes assessors which raised some concerns about assignment to intervention and measurement of the outcomes in the remaining

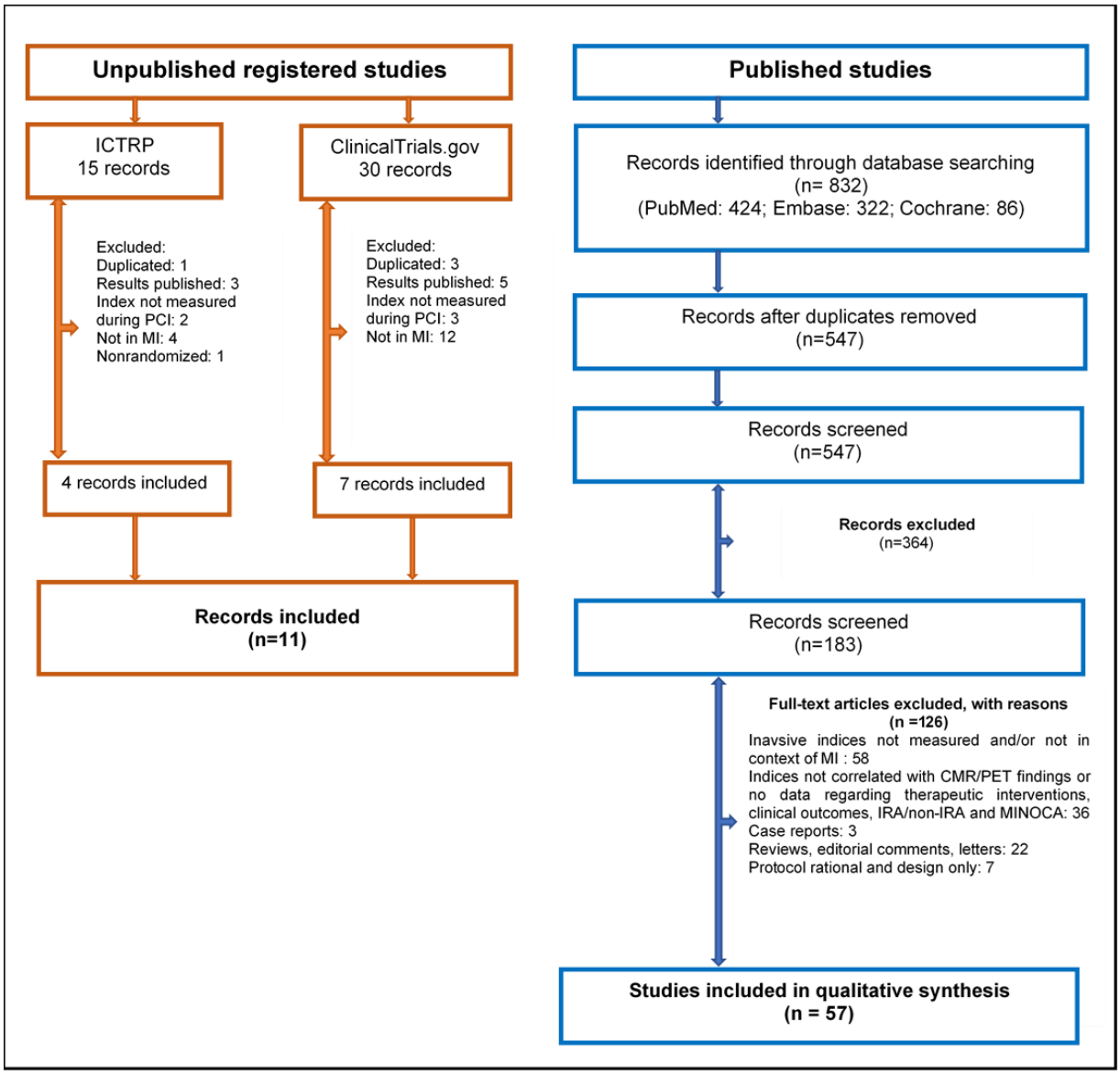

Figure 1 - Flow Diagram of the Search Strategy. **ICTRP** International Clinical Trials Registry Platform; **CMR** Cardiovascular magnetic resonance; **IRA** Infarct-related artery; **MI** Myocardial infarction; **MINOCA** Myocardial Infarction with nonobstructive coronary arteries; **PCI** Percutaneous coronary intervention; **PET** Positron emission tomography

studies. Other three studies revealed relevant missing outcome data, mostly due to withdrawal of patients during follow-up. Only one study showed concerns about the timing of recruitment of participants because the allocation of the patients to the intervention group was made during PCI and according to operator's decision. Regarding non-randomized studies, none of them demonstrated that the outcome of interest was not present at start of study. This was expected because PCI is an invasive procedure with risks that is not performed by routine. PCI is performed accordingly to international guidelines criteria, and it is not recommended to be done in asymptomatic patients. So, PCI is mainly performed at the index event of ischemic

acute events with no baseline data. Furthermore, most studies did not have control group, which reduced their comparative capacity and underpowered the conclusions reached. Despite this, the assessment of outcomes, follow-up time and adequacy were very accurate in most studies. The quality assessment of RCT is presented in the risk of bias summary **(Supplementary Table 2)** and observational studies as Newcastle-Ottawa Scale summary **(Supplementary Table 3)**.

Results

Search results

Lastly 57 studies met the including criteria (**Figure 1**): 38 were observational studies and 19 were RCT. Subdividing articles by topics: 17 non-randomized studies related to CMR and PET findings; 4 observational articles showed data about correlations between resistance indices; 8 non-randomized and all 19 RCT measured therapeutic interventions on microcirculation function; 8 non-randomized studies reported clinical outcomes, 8 observational papers described culprit and non-culprit artery microvascular findings after MI and only 1 non-randomized was related to MINOCA.

Myocardial ischemia consequences assessed by invasive indices and cardiac imaging

Myocardial ischemia occurs by a complex interplay between obstructive coronary artery disease and microcirculatory disfunction. Within <1 hour of ischemia, oedema develops in the territory of the infarct related artery (IRA). While endothelial cells are more resilient to ischemia than cardiomyocytes (cell death after 3 hours), prolonged ischemia eventually results in endothelial dysfunction and subsequent capillary permeability, release of vasoconstrictors and inflammatory cytokines and impaired vasomotion. This results in microvascular obstruction (MVO) and intramyocardial haemorrhage (IMH), which reflects a more irreversible degree of myocardial damage (4,5). Microvascular resistance indices parallel microvascular perfusion, correlating with MVO, myocardial haemorrhage, infarct size/viability and left ventricular function (4). The key characteristics of the invasive measures of microvascular resistance, using IMR, HMR and Pzf are summarized in the **Figure 2 - Central Illustration.**

CMR and PET imaging findings and Microcirculation Resistance Indices

Several articles studied the association between MVO and infarct size (IS), quantified on CMR, and coronary invasive resistance indices, mainly using IMR measurements (**Table 1**). IMR is

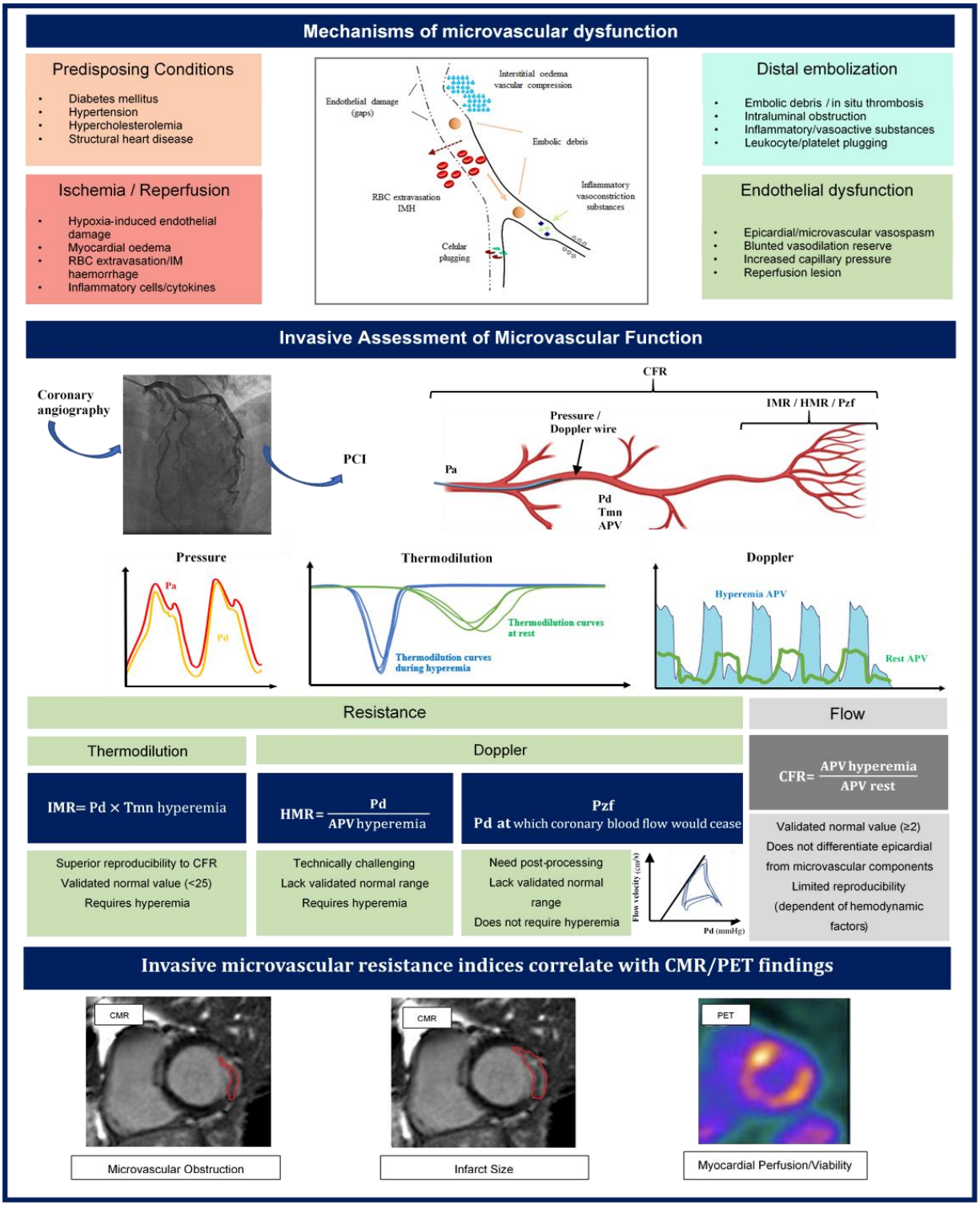

Figure 2 (Central Illustration) - Mechanisms and invasive assessment of microvascular dysfunction and correlation between invasive microvascular resistance indexes with CMR/PET images in the context of Acute Coronary Syndromes. **APV** Average peak velocity; **CFR** Coronary flow reserve; **CMR** Cardiovascular magnetic resonance; **IMH** Intramyocardial hemorrhage; **IMR** Index of microvascular resistance; **HMR** Hyperemic microvascular resistance; **Pa** Aortic pressure; **Pd** Mean distal coronary pressure; **PET** Positron emission tomography; **Pzf** Zero-flow pressure; **RBC** Red Blood Cells; **TMN** Mean transit time. Images kindly provided by Instituto de Ciências Nucleares Aplicadas à Saúde (ICNAS)

a functional measure of the microvascular viability continuum within the distribution of a coronary artery. Patients without microvascular disease usually present IMR values <25, while IMR ≥25 correlate with impaired myocardium perfusion, similar to ischemic myocardium in the presence of obstructive coronary artery disease (6). Although a binary cut-off value is useful for medical decision-making, microvascular resistance is often weakly correlated with anatomic damage and/or interstitial changes reflected by MVO and IS on CMR (**Figure 3**).

Regarding MVO, de Maria et al. (6) showed discordance between IMR>40 and MVO in more than one-third (37%) of STEMI cases. Nonetheless, the majority of the discordant cases with MVO had IMR values between 25 and 40, and patients presenting both MVO and IMR>40 had no regression in myocardium scar at 6 months. In a previous study, MICRO-AMI, IMR presented a stronger relationship to MVO (r=0.70, p<0.001) after MI, especially in those with IMR>40 (7). The microvascular resistance indices using doppler flow velocity (HMR and Pzf), showed a significant correlation with MVO although this methodology lacks validated normal range values. In patients with acute MI, Williams et al. (1) reported that HMR and IMR measurements correlated with MVO volume on CMR (HMR: r=0.46, p=0.001; IMR: r=0.36, p=0.01). Furthermore, HMR had significant superior diagnostic accuracy over IMR at predicting microvascular dysfunction (HMR_{AUC} 0.82 vs. IMR_{AUC} 0.58; p<0.001). In the OxAMI study (2), Pzf correlated significantly with MVO (r=0.49, p=0.02), and was a significantly better predictor of infarct extension than HMR or IMR. The modest effect size of the correlation, frequently seen between microcirculation resistance indices and MVO, seem to indicate that microvascular dysfunction and MVO are distinct clinical findings that often occur concurrently after MI. Furthermore, MVO and invasive microcirculatory measurements are typically obtained at different time points following an acute MI and use different techniques to evaluate the microvascular compartment. Taking that into consideration and despite IMR, as a continuous variable, showed inferior correlation factors comparing with other indices, in subgroup analysis, a cut-off of IMR>40 appears to be the only one with a strong correlation factor and thus the best predictor of MVO.

Concerning IS measured on CMR, IMR showed no or weak correlation in the early days after STEMI (<4 days) (6,7). However, IMR presented a stronger relationship of strength to IS (r=0.78; p<0.001) in delayed CMR, several days after MI (> 10 days) (8). Similar results were seen with other microvascular resistance indices: Teunissen et al. reported a low to moderate correlation with IS (HMR: r=0.41, p<0.001) if CMR measures were obtained 4-6 days after STEMI (9), and a stronger correlation was found (Pzf: r=0.72, p<0.001) if CMR measures were attained more than 10 days after MI (8). At 6 months follow-up, despite other articles revealed a significant but weak correlation between IMR and IS (6,10), the OxAMI study reported no relation between those two variables and even showed a significant and strong correlation

between IS and HMR (r=0.54, p=0.009) and Pzf (r=0.77, p<0.001) (2). These results seem to indicate that the invasive indices correlate better with IS more than 10 days after MI. This occurs because, following MI, the infarcted tissue experiences several changes such as oedema and IMH (5) that can falsely enlarge the real size of infarction. Some studies already showed the reduction of IS over time (6), so the measurement of it is more reliable several days after the acute event. At this point, Pzf seems to have stronger correlation with IS, however, the variability and lack of data does not allow us to state this conclusion with certainty.

Few microcirculation studies reported PET findings. One study used fluorodeoxyglucose (FDG) uptake to quantified regional myocardial viability after MI and reported that IMR was strongly related to myocardial viability (r=-0.74; p<0.001) and was a predictor of left ventricle (LV) function recovery (AUC 0.89, p<0.001) (11). In a previous study, Pzf (r= -0.70; p<0.001) also correlated strongly with myocardial viability (12). Furthermore, Teunissen et al. (9) used H2(15)O to quantified myocardial perfusion and reported HMR as an independent predictor of microvascular injury and decreased myocardial blood flow after MI (p=0.02). These findings suggest that microcirculation integrity, as assessed by vascular resistance indices, are a reliable early on-site determinant of myocardial viability.

Differences in diagnostic accuracy between microvascular resistance indexes

Currently, there is no true reference standard for invasive measurements of microvascular function. The vast majority of data regarding vascular resistance indices derives from IMR and, importantly, HMR and Pzf lack a well-validated normal range. Discrepancies in microcirculation measurements between vascular resistance indices may occur due to differences in the estimation of flow or the amount of myocardium subtended and flow-limiting stenosis (3). Although, several studies showed that resistance indices had no significant differences in their diagnostic accuracy, they often show a modest effect size correlation between them: IMR vs. HMR (r=0.39; p<0.001), IMR vs. Pzf (r=0.75, p<0.001) and HMR vs. Pzf (r=0.55, p=0.002) (1,8,9). Consequently IMR, HMR and Pzf should not be considered equivalent measures of microvascular function (**Figure 3**) or predictors of myocardial damage in the MI setting.

Microvascular resistance indexes and clinical outcomes

Microvascular dysfunction is increasingly being recognized as an important marker of adverse clinical events in MI patients. It can be encountered in up to 50% of STEMI patients, even after angiographically successful revascularization (13). Thus, microcirculation assessment can potentially add prognostic value to the findings of coronary angiography and functional assessment of an epicardial lesion (e.g., fractional flow reserve), as a surrogate of IS, MVO

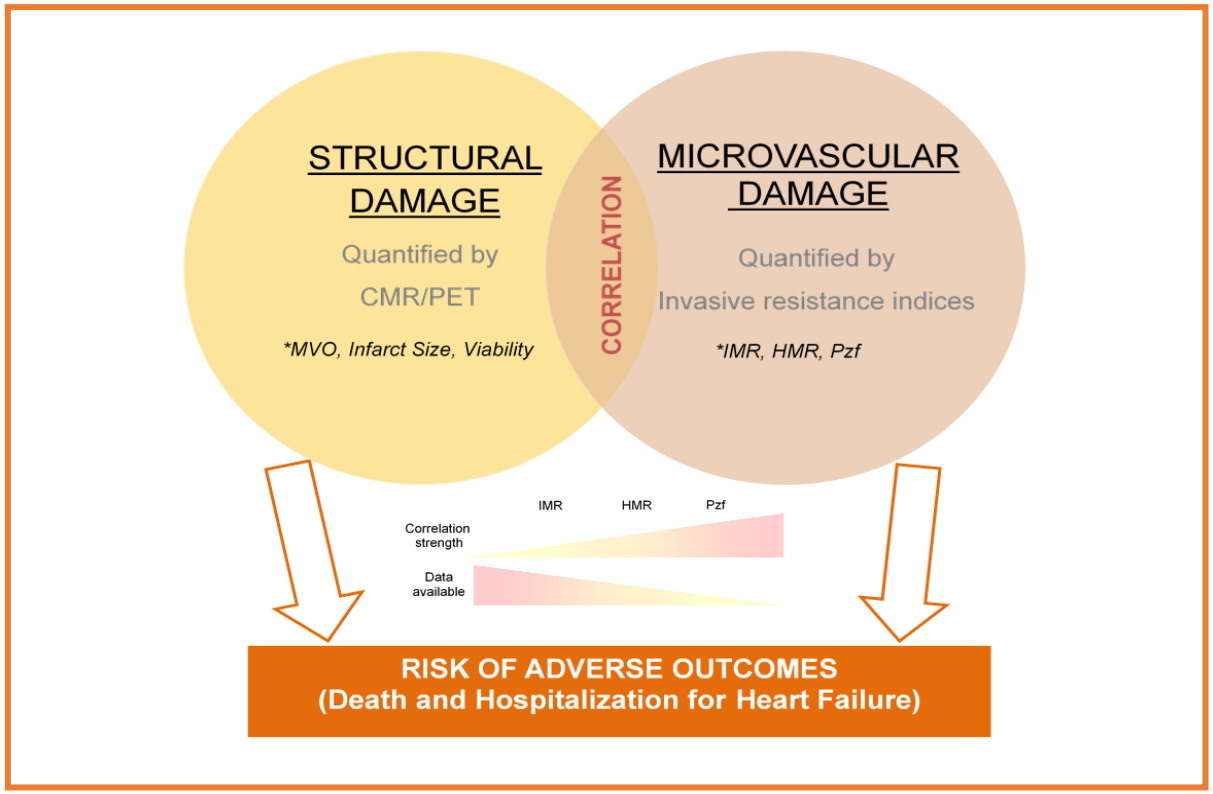

Figure 3 - Distinct Domains of Myocardial Damage After Myocardial Infarction**. CMR** Cardiovascular magnetic resonance; **IMR** Index of microvascular resistance; **HMR** Hyperemic microvascular resistance; **MVO** Microvascular obstruction; **PET** Positron emission tomography; **Pzf** Zero-flow pressure.

and, potentially, myocardial viability of the IRA (**Table 1**).

In a subset of patients of T-TIME trial (14), consisting in 144 STEMI randomized to intracoronary infusion of either placebo or alteplase, IMR > 40 was associated with heart failure (HF) hospitalization (OR 5.34; p = 0.002) and all-cause death/HF hospitalization (OR 4.08, p = 0.005), predicting higher risk of major adverse cardiovascular events (MACE) at one-year of clinical follow up. Fearon et al. (15) enrolled 253 patients in a multicentric study to evaluate clinical outcomes in primary PCI cases. During an approximately 3-year follow up, they reported that patients with IMR > 40 had a 2 times higher relative risk of hospitalization for HF (p = 0.034) and 4 times greater risk of all-cause death (p = 0.028), and IMR >40 was the only independent predictor of death. Furthermore, Carrick et al. (16) studied 283 STEMI patients and categorized accordingly to IMR (≤40 or >40) and coronary flow reserve (CFR) (≤2.0 or >2.0), measured at the end of PCI. They concluded that IMR had superior prognostic value for risk stratification of death or HF, then other traditional markers of myocardial reperfusion, such as symptom-to-reperfusion time, angiographic blush grade or CFR.

A recent study by de Waard et al. (17) using HMR to measure microvascular dysfunction after MI, reported that HMR can be used to detect patients at risk of adverse clinical outcomes. A

cut-off value of 3.0 $mmHgcm^{-1}$, was a significant predictor of death and hospitalization for HF, superior to CFR predictive value. These findings were corroborated by Jin et al. (18), showing HMR as an independent predictor of future cardiovascular events.

These results proved that both IMR and HMR are accurate predictors of MACE, hospitalization due to HF and all-cause of death. Therefore, they can be an important tool to stratify and follow patients with higher microvascular disfunction in order to prevent these adverse clinical outcomes. There is no data related to Pzf, so its prognostic ability should be evaluated in future studies.

Microcirculation in culprit and non-culprit infarct related arteries

More than 50% of STEMI patients present with multivessel coronary disease and PCI of non-culprit vessels among these patients is associated with improved clinical outcomes compared to culprit vessel–only PCI (19,20). The decision to perform PCI of the non-culprit vessel is usually based on the angiographic appearance, often obviating a comprehensive evaluation of epicardial and microvascular function and their potential prognostic significances.

Data on non-culprit IRA using microvascular resistance indices is limited and based in non-randomized trials with small sample sizes (**Table 1**). Choi et al. (21) enrolled 100 MI cases that underwent a comprehensive coronary physiologic assessment after primary PCI and compared to 203 patients with stable ischemic heart disease. Microcirculation function was evaluated in culprit and non-culprit IRA of both acute MI and stable ischemic heart disease patients. The authors reported that IMR was significantly higher in the culprit IRA rather than in the non-culprit arteries (33.0±21.0 vs. 17.9±10.5; $p < 0.001$). However, IMR was not different between non-culprit vessel of acute MI and ischemic stable heart disease patients (18.5±11.4) (**Figure 4**). These results indicating that microvascular damage is predominantly localized in the culprit IRA in STEMI patients, were later corroborated by Mejía-Rentería et al. (22), also using IMR, and Teunissen et al. (9) through HMR results. Despite that, some studies (19, 20) found that IMR in the non-culprit arteries after MI was abnormally high (IMR > 25) in 21-28% of the acute MI patients and previous trials (23,24,25) reported that patients with MI had a depressed myocardial stress perfusion, particularly in the infarcted region but also in noninfarcted regions. These higher IMR values in non-IRA might be explained by MI size, since it is plausible that after a large MI with extensive microvascular damage there is more coronary hemodynamic disturbance than in smaller ischemic injuries. Furthermore, the remodelling of remote myocardium due to increased overload and the higher stimulus of neuronal sympathetic axis promote structural changes in coronary vessels, reducing arterial lumen and causing higher vascular resistances (24). However, regarding myocardial perfusion studies

(23,24,25) as there is no baseline data or a control group for comparison of the myocardium perfusion, it is not possible to determine whether the perfusion deficit was already present before the MI (due to, e.g., generalized atherosclerotic process (20), which may be a factor in common with stable angina) or if it occurred after the ischemic event. Moreover, these abnormal IMR results did not correlate with macrovascular injury or adverse cardiovascular events related to non-culprit IRA at 6 months of follow (19) which raises some concerns about its clinical significance.

The REDUCE-MVI substudy (26) randomized 98 patients with STEMI, who had an angiographic intermediate stenosis in at least one non-culprit IRA and performed a microvascular function assessment at the primary PCI and 1 month later. Median IMR was 18.0 (IQR 13.5-27.0) at the index event and decreased to 14.5 (IQR 11.0-21.0, p = 0.06) at follow-up. Both IMR in the acute setting and IMR temporal change were correlated significantly with myocardial salvage index on CMR. Moreover, the authors found a blunted vasodilatory response of the microcirculation to adenosine at the acute event, which was most pronounced in patients with large IS, low left ventricular ejection fraction (LVEF) and with microvascular injury. These findings suggest that coronary hemodynamics are altered in the acute MI setting in the non-culprit IRA. Although the reduced hyperemic flow in the IRA territory is primarily explained by the microvascular injury, the blunted flow response to adenosine is still poorly understood in the non-culprit territory. Possibly related to reduced sensitivity of adenosine receptors in the remote myocardium (27), and the interplay of local vasoconstrictors/inflammation and extravascular compression secondary to myocardial oedema. Moreover, Bax et al. (28) reported that HMR values in non-IRA normalized earlier than IRA, supporting that consequences of MI are more easily reversed in the non-culprit territory. These results indicate that, although there is a variation of IMR values in non-IRA during follow-up time after MI, it is not as significant and it seems to reverse more easily than in IRA. Besides, the association between these changes in non-IRA and clinical outcomes is not yet well evaluated.

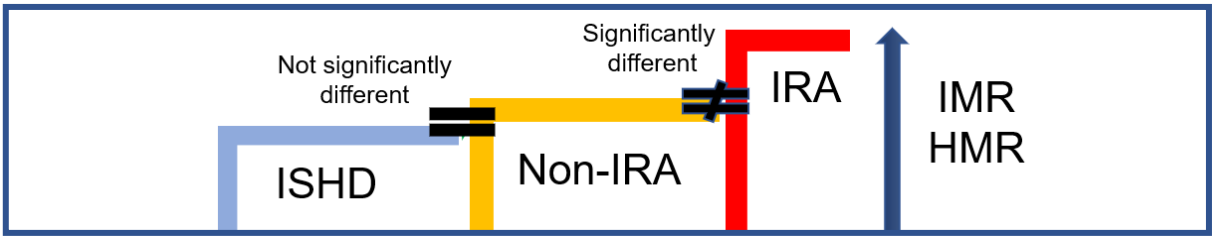

Figure 4 Microvascular resistance indices variation in ischemic stable heart disease patients, non-infarct and infarct related arteries in myocardial infarction patients. **HMR** Hyperemic microvascular resistance; **IMR** Index of microvascular resistance; **IRA** Infarct-related artery; **ISHD** Ischemic stable heart disease

Table 1 Non-randomized controlled trials of microvascular resistance indices in acute coronary syndromes

First author/ study	Sample size	Index	Intervention	IRA/ Non-IRA	Cardiac imaging associations with microcirculation measures / IRA and non-IRA microcirculation measures	Follow-up time / Association between clinical outcomes and invasive indexes
Williams et al. (1)	**44** ACS	**IMR, HMR** after PPCI	No	Only IRA	CMR 1 day after MI; HMR (r=0.46; p=0.001) and IMR (r=0.36; p=0.01) correlated with MVO; HMR was not significantly superior over IMR to predict MVO (AUC 0.75 vs. 0.66) IMR correlated with HMR (r=0.39; p=0.0006);	Not measured/not reported
Patel et al. / OXAMI study (2)	**34** STEMI	**IMR, HMR, Pzf** after PPCI	No	Only IRA	CMR 6 months after MI; IMR did not correlate with MVO and IS; HMR correlated to IS (r=0.54, p=0.009); Pzf correlated to MVO mass (r=0.49; p=0.02) and IS (r=0.77; p<0.0001); Predictors of ≥24% of infarction: AUC_{IMR} 0.54 (p=0.77), AUC_{HMR} 0.74 (p=0.04), AUC_{Pzf} 0.94 (p<0.0001); Pzf was a better predictor of IS than HMR (p=0.04) or IMR (p=0.03); Optimal cut-off was 42 mmHg (100% sensitivity,73% specificity)	Not measured/not reported
De Maria et al. (6)	**110** STEMI	**IMR** after PPCI	No	Only IRA	CMR 2 days and 6 months after MI; IMR correlated with MVO (r=0.29, p=0.002) and IS at 48h (r=0.21, p=0.03) and 6 months (r=0.43, p=0.001)	Not measured/not reported
McAlindon et al. / MICRO-AMI study (7)	**50** STEMI	**IMR** after PPCI	No	Only IRA	CMR 2-4 days and 3 months after MI; IMR correlated (r=0.61; p<0.001) and was predictive of MVO (AUC 0.78); Optimal IMR cut-off was 40 (sensitivity 59%, specificity 92%); IMR was not associated with IS	Not measured/not reported
Kitabata et al. (8)	**27** ACS	**IMR, Pzf** after PPCI	No	Only IRA	CMR 13±2 days after MI; IS was significantly correlated to IMR (r=0.78, p<0.0001) and Pzf (r=0.72, p=0.0002). IMR correlated with Pzf (r=0.75, p<0.0001)	Not measured/not reported
Teunissen et al. (9)	**60** STEMI	**HMR, Pzf** after PPCI	No	IRA and non-IRA	CMR and $H_2{}^{15}O$ PET 4-6 days after MI; HMR was associated with MVO (r=0.46; p<0.01), and IS (r=0.41; p<0.01); Predictors of MVO: AUC_{HMR} 0.68 (p=0.03), AUC_{Pzf} 0.75 (p=0.01); a significant correlation between HMR and Pzf (r=0.55; p=0.002); HMR correlated (r=0.56; p<0.001) and was a predictor of MPR (OR 2.50; p=0.02) on PET. HMR in IRA was higher vs. control (2.87±1.45 vs. 2.26±0.83 $mmHgcm^{-1}s$; p=0.02). HMR in non-IRA vs. control no different. A significant increasing HMR trend was found between control<non-IRA<IRA (p<0.01). HMR was higher in patients with vs. without MVO only in IRA (3.33±1.50 vs. 2.41±1.26 $mmHgcm^{-1}s$; p=0.03)	Not measured/not reported
Scarsini et al. / OXAMI study (10)	**45** STEMI	**IMR** after PPCI	No	Only IRA	CMR 48h and 6 months after MI; IMR predicted IS at 48h (AUC=0.71; 95%CI 0.71-0.99) and was significantly correlated to IS at 6 months (r=0.35, p=0.027)	Not measured/not reported
Lim et al. (11)	**38** ACS	**IMR** after PPCI	No	Only IRA	FDG PET 8±1 days after MI; IMR negative correlation to FDG uptake (r= -0.74, p<0.001)	Not measured/not reported
Shimada et al. (12)	**27** ACS	**Pzf** after PPCI	No	Only IRA	FDG PET 3 days after MI; Pzf negative correlation to FDG uptake (r= -0.70, p<0.001)	Not measured/not reported
Maznyczka et al. (14)	**144** STEMI	**IMR** after PPCI	No	Only IRA	CMR 2-7 days and 3 months after MI; IMR was associated (OR 0.01; p=0.001) and correlated to MVO (r=0.20; p=0.016) at 2-7 days of MI; IS was associated with IMR at 3 months (OR 0.12; p<0.001) and with IMR>40U (OR 9.12; p< 0.001)	1-year follow-up / HHF associated with IMR (OR 1.02, p<0.001), IMR>40U (OR 5.34, p=0.002), IMR>44U (OR 6.92,p=0.001); Death/HHF associated with IMR (OR 1.02, p=0.001), IMR>40U (OR 4.08, p=0.005), IMR>44U (OR 5.33, p=0.001)
Fearon et al. (15)	**253** STEMI	**IMR** after PPCI	No	Only IRA	CMR or PET not performed	Median 2.8 years / IMR>40U was a predictor of death (HR 4.30; p=0.02) and death or HHF (HR 2.20; p=0.03)

Carrick et al. (16)	**283** STEMI	**IMR** after PPCI	No	Only IRA	CMR 2 days and 6 months after MI; IMR>40U was independently associated with MVO, 2 days after MI (OR 2.82; p<0.001)	Median 845 days / IMR>40U associated with all-cause death or HHF (OR 4.36; p<0.001)
De Waard et al. (17)	**176** ACS	**HMR** after PPCI	No	Only IRA	CMR 24h to 2 weeks after MI; HMR significantly predicted MVO (AUC of 0.76; 95% CI 0.67-0.85) with optimal cut-off of 3.0 mmHgcm^{-1}s	Median 3.2 years / HMR>3.0 mmHgcm^{-1}s was associated with death (HR 6.4, 95%CI: 1.3-32.0) and HHF (HR 7.0; 95%CI: 1.5-33.7)
Jin et al. (18)	**145** STEMI	**HMR** after PPCI	No	Only IRA	CMR or PET not performed	Mean 85±43 months / HMR optimal cut-off of 2.82 mmHgcm^{-1}s (AUC 0.82; p=0.006) predicted cardiac death and HHF; HMR>2.82 mmHgcm^{-1}s was associated with MACE (HR 1.74; p<0.001).
Díez-Delhoyo et al./ FISIOIAM study (19)	**84** STEMI	**IMR** after PPCI	No	Only Non-IRA	CMR or PET not performed; IMR>25U in non-culprit lesions in 28% of cases. Macrovascular and microvascular dysfunction were not correlated with each other	6-months follow-up / No adverse events (mortality, MI, revascularization) related to non-IRA.
Ntalianis et al. (20)	**14** ACS	**IMR** after PPCI and 35 days later	No	IRA and non-IRA	CMR or PET not performed; IMR values on non-IRA lesions were found in normal range (<30U) in 79% of patients. These values did not change during follow-up (4 days to 3 months later)	Not measured/not reported.
Choi et al. (21)	**100** ACS	**IMR** after PPCI	No	IRA and non-IRA	CMR or PET not performed; IMR was higher in IRA than non-IRA (33.0 vs. 17.9U, p<0.001); and control (vs. 18.5U, p<0.001); IMR was not significantly different in non-IRA vs. control.	Not measured/not reported.
Mejía-Rentería et al. (22)	**49** ACS	**IMR** 6 days after MI	No	Only Non-IRA	CMR or PET not performed; IMR in non-IRA vs. control was not significantly different (15.6 non-IRA vs. 16.7U control) in the subacute phase of MI	Not measured/not reported.
Van der Hoeven et al. (26)	**73** STEMI	**IMR** after PPCI and 1 month	No	Only Non-IRA	CMR 2-7 days and 1 month after MI; IMR decreased from index event to 1-month (18.0 vs. 14.5U p=0.06). IMR correlated to myocardial salvage index (r=–0.43; p=0.001)	Not measured/not reported.
Bax et al. (28)	**73** ACS	**HMR** after PPCI	No	IRA and non-IRA	CMR or PET not performed; HMR of IRA was higher vs. non-IRA at the acute event (3.2±1.7 vs. 2.2±1.7 mmHgcm^{-1}s). HMR in IRA showed a significant decreased from acute to 1 week and 6 months follow-up (3.2>2.0>1.8 mmHgcm^{-1}s). In non-IRA, HMR decreased from acute to 1 week, but stabilized at 6 months (2.2>1.7 p<0.0001 and 1.8 mmHgcm^{-1}s, respectively)	Not measured/not reported.
Morimoto et al. (39)	**18** STEMI	**IMR** after PPCI	Intra-coronary sodium nitroprusside	Only IRA	CMR or PET not performed; IMR values lowered after intracoronary sodium nitroprusside (76.0±42.0 vs. 45.0±37.0U; p=0.0006)	Not measured/not reported.
Kostic et al. (40)	**32** STEMI	**IMR** after PPCI	Intra-coronary nicorandil	Only IRA	CMR or PET not performed. Echocardiography 3 months later; IMR values lowered after administration of nicorandil (9.9 ± 3.7 vs. 14.1 ± 5.1U, p < 0.001). WMSI improved from baseline (1.1±0.2 vs. 1.1±0.1, p=0.004)	Not measured/not reported.
Ito et al. (41)	**40** STEMI	**IMR** after PPCI	Intra-coronary nicorandil vs. placebo	Only IRA	CMR or PET not performed; Nicorandil decreased IMR values against placebo (18.7 vs. 27.7U, p<0.001)	Not measured/not reported.
Verna et al. (49)	**47** ACS	**HMR** 3.5±4.7 days after ACS	No	Abnormal WM artery vs. reference territory	CMR or PET not performed; HMR was significantly higher in the territory related to abnormal wall motion (2.64±1.23 vs. 2.05±0.56 mmHgcm^{-1}s; p=0.008)	Not measured/not reported.
Yoo et al. (53)	**34** ACS	**IMR** after PPCI	No	Only IRA	CMR 6 ± 4 days after MI; IMR correlated with MVO (r=0.75; p<0.001)	Not measured/not reported
Ahn et al. (54)	**40** STEMI	**IMR** after PPCI	No	Only IRA	CMR 7 days after MI; IMR associated (OR 1.15, 95% CI 1.05-1.26) and was predictive of MVO (AUC 0.87; p<0.001); optimal cut-off value was 27U (74% sensitivity, 88% specificity)	Not measured/not reported
Scarsini et al. (55)	**165** STEMI	**IMR** after PPCI	No	Only IRA	CMR 48h and 6 months after MI; IMR predicted MVO at 48h (OR 1.02; p=0.008) and IS at 48h (OR 1.01; p=0.022) and 6 months (OR 1.02; p= 0.017)	Not measured/not reported

Yoon et al. (56)	**50** STEMI	**IMR** after PPCI	No	Only IRA	FDG PET 7 days after MI; IMR negative correlation to FDG uptake (r=-0.39, p=0.006)	Not measured/not reported
Firman et al. (64)	**45** STEMI	**IMR** after PPCI	AT + PCI vs. PCI alone	Only IRA	CMR or PET not performed; There were no significant differences in IMR values between groups	Not measured/not reported.
Yoon et al. (67)	**58** STEMI	**HMR** after PPCI	DPD + PCI vs. PCI alone	Only IRA	CMR or PET not performed; HMR was lower in the DPD group (2.4±1.4 vs. 3.1±1.4 mmHg·cm^{1}·s, p=0.045)	Not measured/not reported.
De Maria et al./ OxAMI-PICSO study (68)	**105** STEMI	**IMR** after PPCI	PICSO + PCI vs. PCI alone	Only IRA	CMR 6 months later; At 24-48h, patients treated with PICSO had lower IMR (24.8 vs. 45.0U, p<0.001). In cases with high pre-stenting IMR, PICSO was significantly associated with lower IMR values (OR 0.10, p=0.009). IS was lower in PICSO group (26 vs. 33%; p=0.006); Cases with pre-stenting IMR>40U treated with PICSO were inversely correlated with IS>24% (OR 0.24; p=0.04)	Not measured/not reported.
Fahrni et al. / Insights OxAMI study (69)	**260** STEMI	**IMR** after PPCI	No	Only IRA	CMR or PET not performed	30 days follow-up / IMR was a predictor of major cardiac events (AUC 0.90; 95% CI 0.85-0.93); IMR≤40U identified all patients free of major cardiac events (100% sensitivity, 62% specificity).
Maznyczka et al. (70)	**271** STEMI	**IMR** after PPCI	No	Only IRA	CMR 2-7 days after MI; IMR showed an AUC of 0.69 (p<0.001) for predicting presence of MVO	5 years follow-up / Death and HHF at 30 days: AUC $_{IMR}$ 0.74 (p<0.001) and 5 years after MI AUC $_{IMR}$ 0.64 (p=0.002); MACE at 30 days: AUC $_{IMR}$ 0.74 (p<0.001) and 5 years after MI AUC $_{IMR}$ 0.66 (p<0.001).
Fukunaga et al. (71)	**88** STEMI	**IMR** after PPCI	No	Only IRA	CMR within 2 weeks after MI; No data associating IMR with CMR was reported	6 months follow-up/ Optimal cut-off of IMR for cardiac death, nonfatal MI and HHF was 37U (AUC 0.68, sensitivity 75%, specificity 61%). IMR was not associated with MACE (HR 0.99; p=0.59).
De Maria et al. (72)	**45** STEMI	**IMR** before and after PPCI	No	IRA and non-IRA	CMR 48h after MI; No data on IMR and CMR was reported. 15 STEMI had non-IRA measures: IMR was higher in IRA vs. non-IRA (31 vs. 19U; p=0.01)	Not measured/not reported.
De Silva et al. (73)	**31** Non-STEMI	**HMR** 2-7 days after MI	No	Only IRA	CMR before and 3 months after MI; HMR of IRA was higher than reference (2.34 vs. 1.90 mmHgcm^{-1}s, p=0.001) and correlated to infarct mass (r=0.48; p=0.03)	Not measured/not reported.
Karamasis et al. (74)	**32** STEMI	**IMR** after PPCI	Stent post-dilatation with NC-balloons	Only IRA	CMR or PET not performed; IMR before and after stent post-dilatation was not significantly different (44.9±25.6 vs. 48.8±34.2U, p=0.26)	Not measured/not reported.
De Maria et al. (75)	**85** STEMI	**IMR** after PPCI	Stent implantation	Only IRA	CMR or PET not performed; IMR after stenting was lower than before intervention (49.7 vs. 29.2U, p<0.001). Patients with pre-stenting IMR>40U, had a greater improvement in IMR (67.7 to 36.7U, p<0.001), despite in 28 patients it remained >40U. In pre-stenting IMR<40U group, stenting did not improve IMR values	Not measured/not reported.

ACS Acute coronary syndromes; **AT** Aspiration thrombectomy; **AUC** Area under the curve; **CI** Confidence interval; **CMR** Cardiovascular magnetic resonance; **DPD** Distal protection device; **FDG** Fluorodeoxyglucose; **HHF** Hospitalization for heart failure; **HMR** Hyperemic microvascular resistance; **IMR** Index of microvascular resistance; **IRA** Infarct related artery; **IS** Infarct size; **MACE** Major adverse cardiac events; **MI** Myocardial infarction; **MPR** Myocardial perfusion reserve; **MVO** Microvascular obstruction; **PET** Positron emission tomography; **PICSO** Pressure controlled intermittent coronary sinus occlusion; **PPCI** Primary percutaneous coronary intervention; **Pzf** Zero-flow pressure; **STEMI** ST segment elevation myocardial infarction; **WM** Wall motion; **WMSI** Wall motion score index

Therapeutic interventions and microvascular resistance indexes

No published RCT used microvascular dysfunction to guide patient's selection for adjunctive therapy after MI. However, microcirculation assessment may possibly identify disease severity and predict therapy outcomes, which is being assessed in some ongoing trials (**Table 2**).

Table 2 Registered, no published RCT using microvascular resistance indices to select patients or evaluate the efficacy of different therapeutic interventions in acute coronary syndromes

Study / Regist number	Sample size Start date status	Intervention	Blinding	Indices and timing	Purpose of using the indexes	Primary outcome
NCT03581513 (29)	n=880 Start: 2017 Status: completed	Immediate vs. deferred stenting	No blinding	**IMR** after PCI	Select patients for therapy; Cut-off of 40 was used: IMR>40U and IMR≤40U are subgroups randomized to immediate and deferred PCI	Clinical outcomes at 1 year follow-up
RESTORE-MI/ ACTRN 126180007782 80 (30)	n=800 Start: 2018 Status: recruiting	Intracoronary tenecteplase post-stenting vs. placebo	Participants, care provider, investigator, outcomes assessor	**IMR** after drug during PCI	Select patients for therapy; IMR>32U post-PCI were randomized for intervention; patients with IMR≤32U only follow-up was performed	Clinical outcomes at 1 year follow-up
OPTIMAL/ NCT02894138 (31)	n=80 Start: 2016 Status: recruiting	Intracoronary alteplase post-stenting vs. placebo	Participants, outcomes assessor	**IMR** before and after drug during PCI	Select patients for therapy; IMR>30U randomized for intervention; IMR≤30U non-randomized patients will undergo only follow-up	Ratio of infarct size to area at risk on CMR 2-9 days and 3 months after procedure
PATA-STEMI/ NCT01824641 (76)	n=128 Start: 2012 Status: unknown	Aspiration thrombectomy vs. standard PCI	Participants, outcomes assessor	**IMR** after PCI	Measure response to therapy	Comparison of IMR between groups
GUARDIANCO RY/ NCT03087175 (77)	n=52 Start: 2016 Status: unknown	MGuard stent vs. DES/BMS	No blinding	**IMR** after PCI	Measure response to therapy	Comparison of IMR between groups
Intracor/ NCT02105870 (78)	n=40 Start: 2012 Status: unknown	Intracoronary bolus of abciximab vs. placebo	Participants, care provider, investigator, outcomes assessor	**IMR** before and after drug during PCI	Measure response to therapy	Comparison of IMR between groups
RESIST-ACS/ NCT01491256 (79)	n=100 Start: 2010 Status: unknown	High dose vs. low dose atorvastatin before PCI	Participants, care provider, investigator	**IMR** after PCI	Measure response to therapy	Comparison of IMR between groups
FITTER/ NCT04141579 (80)	n=150 Start: 2020 Status: active, not recruiting	Subcutaneous Evolocumab vs. placebo	Participants, care provider, investigator	**IMR** after PCI at baseline and 14 weeks later	Measure response to therapy	FFR change in non-IRA lesions from baseline to 14 weeks follow-up
ENDORA-PCI / ACTRN 126150007095 49 (81)	n=52 Start: 2015 Status: recruiting	Ambrisentan (endothelin receptor antagonist) vs. placebo	Participants, care provider, investigator, outcomes assessor	**IMR** before and after interventio n, during PCI	Measure response to therapy	Peri-procedural change in IMR after drug administration in NSTEMI patients
PORT / NTR4040 (82)	n=72 Start: 2013 Status: recruiting	Intermittent reperfusion + aspiration thrombectomy vs. standard PCI	No blinding	**IMR** after PCI	Measure response to therapy	Difference in IS between groups on CMR 3 months after procedure
ANTMAN / ACTRN 126180016102 24 (83)	n=130 Start: 2018 Status: recruiting	Clopidogrel vs. Ticagrelor	No blinding	**IMR** before and after PCI	Measure response to therapy	Comparison of IMR in NSTEMI between groups

BMS Bare metal stent; **CMR** Cardiovascular magnetic resonance; **DES** Drug eluting stent; **FFR** Fractional flow reserve; **IMR** Index of microvascular resistance; **IRA** Infarct related artery; **IS** Infarct size; **MGuard** Polyethylene Terephthalate Micronet Mesh-Covered Stent; **PCI** Percutaneous coronary intervention

The *Research on STEMI Reperfusion Strategy Based on Microcirculation Function* (NCT03581513) will randomize 880 patients with STEMI accordingly to pre-stenting IMR values, to an immediate or deferred stenting strategy (29). The *Restoring Microcirculatory Perfusion in STEMI* (RESTORE-AMI, ACTRN12618000778280) is an ongoing randomized trial in which patients with IMR>32 will be eligible for adjunctive intracoronary thrombolysis or placebo (30). The *Optimal Coronary Flow After PCI for Myocardial Infarction* trial (OPTIMAL, NCT02894138), is an open-label pilot study that will randomize patients presenting within 12 hours of symptom onset and IMR >30 to intracoronary alteplase or placebo, which includes CMR measurements of IS in the index event and after 3 months (31).

Several studies used microvascular function to measure the efficacy of adjunctive treatments in patients with ACS, mostly using IMR (**Table 3**). Regarding the impact of antiplatelet drugs in the microcirculation, the CV-TIME (*Clopidogrel Versus Ticagrelor on Coronary Microvascular Injury in ST-Segment Elevation Myocardial Infarction*) trial (32) showed that IMR, immediately after primary PCI, was lower in the ticagrelor compared to clopidogrel group (22.2 vs. 34.4; p = 0.005). However, at baseline and 3 months later, wall motion score index (WMSI) and LVEF on echocardiography, were not different between both groups. In a similar study, Park et al. (33) found that IMR was significantly lower in the ticagrelor group 6 months after the index event. The REDUCE-MVI (*Reducing Microvascular Dysfunction in Acute Myocardial Infarction with Ticagrelor*) trial, randomized 110 STEMI patients to investigated whether the increase plasma adenosine values induced by ticagrelor maintenance therapy was associated with less infarct-related microvascular injury compared to prasugrel maintenance treatment. At 1 month, the study reported no differences in plasma adenosine concentrations, IMR, IS or MVO between groups. Importantly, IMH was observed more frequently in patients receiving prasugrel (23% vs. 43%; p = 0.04) (34). In conclusion, despite being associated with lower IMR values, ticagrelor groups did not show higher myocardial viability and function on cardiac imaging compared to other antiplatelet drugs. Furthermore, regarding clinical outcomes only prasugrel seems to be inferior to ticagrelor, presenting a higher hemorrhagic risk.

In concern to fibrinolytic therapies, a substudy of T-TIME (*Trial of Low-Dose Adjunctive Alteplase During Primary PCI*) trial, randomized 144 STEMI patients to receive alteplase 20 mg, alteplase 10 mg or placebo in the culprit artery. There was no difference in IMR values immediately after primary PCI between the 3 treatment groups. Moreover, there was no difference in MVO presence or IS extent with alteplase versus placebo (35). The lack of an overall treatment effect on microvascular function in the culprit artery contrasts with the findings of a previous study conducted by Sezer et al., using low dose intracoronary streptokinase (36, 37). Kumar et al. (38) performed a recent metanalysis of published RCT studying the effect of

Table 3 Randomized controlled trials of microvascular resistance indexes in acute coronary syndromes

First author / study	Sample size	Intervention	Blinding	Index	Microvascular resistance indices between groups	Imaging tests and timing / Associations with microcirculation measures	Follow-up time / Association between clinical outcomes and invasive indexes
Park et al. / CV-TIME trial (32)	**76** STEMI	Clopidogrel vs. Ticagrelor	No blinding	**IMR** after PPCI	IMR lower in Ticagrelor group (22±2 vs. 34±2U prasugrel, p=0.005)	Echocardiography <1 day and 3 months after MI; WMSI and LVEF were not different between groups.	Not performed / not evaluate
Park et al. (33)	**120** ACS	Clopidogrel vs. Ticagrelor	No blinding	**IMR** after PPCI and 6 months later	IMR values at baseline not different between groups; IMR at 6 months was lower in Ticagrelor group (16±6 vs. 21±8U; p<0.01)	Not performed / not evaluate	6 months follow-up/ No difference in cardiovascular and bleeding events between groups; IMR at baseline and 6 months did not associate with clinical outcomes
Leeuwen et al./ REDUCE-MVI trial (34)	**110** STEMI	Ticagrelor loading dose+ Prasugrel vs. Ticagrelor maintenance dose only	No blinding	**IMR** after PPCI and 1 month later	No difference in IMR values between groups	CMR 1 month after MI; MVO and IS were not different between groups; IMH more frequent in prasugrel group (43 vs. 23% ticagrelor; p=0.04).	1 month follow-up / Prasugrel had more bleeding complications (29 vs. 11%; p=0.02)
Maznyczka et al. (35)	**144** STEMI	Alteplase 20 mg vs. Alteplase 10 mg vs. placebo	Participant staff and researcher blinded	**IMR** after PPCI	IMR values did not differ between the 3 groups	CMR 2-7 days and 3 months after MI; No difference in MVO, IS, IMH, LVEF or LV volumes	3 months follow-up/ No significant differences in MACE
Sezer et al. (36)	**41** STEMI	Intracoronary Streptokinase post-PCI vs. PCI alone	Participant care provider and outcomes assessor blinded	**IMR** 2 days after PPCI	IMR values were lower in the fibrinolytic group (16.3 vs. 32.5U; p<0.001)	SPECT at 6 months; No difference in IS between groups	6 months follow-up/ No significant differences in clinical events between groups
Sezer et al. (37)	**95** STEMI	Intracoronary Streptokinase post-PCI vs. PCI alone	Participant care provider and outcomes assessor blinded	**IMR** 2 days after PPCI	IMR values were lower in the fibrinolytic group (20.2 vs. 34.2U, p<0.001)	SPECT 6 months; Streptokinase group had lower IS (23 vs. 33%; p=0.003) and LVED volumes (96 vs. 118mL; p=0.006). Echocardiography 6 months; Streptokinase group had higher LVEF (57 vs. 52%; p=0.018)	6 months follow-up/ No significant differences in clinical events between groups
Ito et al. (42)	**60** STEMI	Intracoronary nicorandil (first) vs. intracoronary nitroglycerin (first)	Investigator analysing data blinded	**IMR** after PPCI and after every drug administration	Nicorandil decreased IMR significantly more than nitroglycerin (10.8 vs. 2.1U, p=0.0002; 6.0 vs. −1.4U, p<0.0001)	Not performed / not evaluate	Not performed / not evaluate
Xiao et al. (43)	**71** STEMI	Intracoronary pro-urokinase vs. thrombus aspiration	Not reported	**IMR** after PCI	IMR values of pro-urokinase group were lower than aspiration PCI (28.2±7.3 vs. 33.6±8.5U, p=0.005)	SPECT and echocardiography at baseline and 12 months after MI; At 12 months, LVEF was higher (58±6 vs. 55±6%, p=0.043) and IS was lower (18.6±8.6 vs. 22.7±7.7, p=0.046) in pro-urokinase group	12 months follow-up / Incidence of MACE was lower in pro-urokinase group (44.74 vs. 69.70%; p=0.034)
Wang et al. (44)	**50** STEMI	Urokinase, tirofiban and nitroglycerin + thrombus aspiration vs. aspiration alone	Investigator performing echocardiography blinded	**IMR** after PCI	IMR was lower in the combined therapy than aspiration alone group (31.5±13.4 vs. 62.7±22.8U, p= 0.002)	Echocardiography 3 and 12 months after MI; LVEF was higher in the combined therapy group (41.9 vs. 39.8%, p=0.042)	12 months follow-up/ No significant differences regarding MACE; Combined therapy had lower incidence of ventricular aneurysm (4.8 vs. 13.2%, p=0.007)

Ahn et al. (45)	**40** STEMI	Intracoronary bolus Abciximab vs. thrombus aspiration vs. Abciximab + aspiration	No blinding	**IMR** after PCI	IMR values were lower in combined therapy than in the abciximab groups (23.5±7.4 vs. 66.9±48.7U, p=0.001). No differences between combined therapy and aspiration group	CMR 5 days after MI; MVO less frequently in combined therapy than in the abciximab group (18.8 vs. 88.9%, p=0.002). No differences between combined therapy and thrombus or abciximab groups	1 month follow-up/ No significant differences in clinical events between groups
Ubaid et al. (57)	**100** STEMI	Intravenous cangrelor + ticagrelor vs. ticagrelor	No blinding	**IMR** after PPCI	No difference in IMR values between groups.	CMR 12 weeks after MI; No difference in IS between groups.	Not performed / not evaluate
Fu et al. (58)	**41** STEMI	Intracoronary Pro-urokinase +anisodamine vs. aspiration thrombectomy	Imaging investigator blinded to invasive measures	**IMR** after PPCI	Combined therapy group had lower IMR values than aspiration alone (29.3±8.6 vs. 40.5±9.4U, p< 0.001).	SPECT 7 days after MI; Combined therapy group had lower PDA than aspiration alone (14.4±8.5 vs. 19.6±3.3%, p = 0.041).	3 months follow-up/ No significant differences in clinical events between groups.
Wu et al. (59)	**50** STEMI	Intracoronary pro-urokinase vs. placebo	No blinding	**IMR** after PPCI	IMR values were lower in the fibrinolytic group (34.6±7.5 vs. 49.0±9.0U, p<0.001).	Not performed / not evaluate	3 months follow-up/ No differences between groups in MACE, stent thrombosis, HHF and malignant arrhythmia.
Van Geuns et al./ BIVAL study (60)	**78** STEMI	Bivalirudin vs. unfractionated heparin	No blinding	**IMR** after PPCI	IMR was lower in the bivalirudin group (43.5±21.6 vs. 68.7±35.8U, p=0.014).	CMR 5 and 90 days after MI; No significant differences between groups regarding MVO, IS and LVEF.	90 days follow-up/ No significant differences in clinical events between groups.
Kirma et al. (61)	**49** STEMI	Intracoronary bólus of Tirofiban vs. intravenous bólus + infusion of Tirofiban	No blinding	**IMR** measured 4–5 days after PPCI	IMR values were not different between groups.	Echocardiography / SPECT 6 months; No significant differences regarding LVED volume, LVEF and IS between groups.	Not performed / not evaluate
Hoole et al. / IMPACT study (62)	**41** STEMI	Aspiration thrombectomy vs. balloon angioplasty	Investigator analysing data blinded	**IMR** after PPCI	No differences in IMR values between groups, at baseline and post-stenting.	CMR 24h and 3 months after MI; No difference regarding MVO, IS or LV function between groups.	6 months follow-up/ No significant differences in clinical events between groups.
Woo et al. (63)	**63** STEMI	Thrombus aspiration + PCI vs. PCI alone	Not reported	**IMR** after PPCI	IMR was lower in the aspiration group than in PCI alone (23.5±10.2 vs. 34.2±21.7U, p=0.018).	Echocardiography 6 months after MI; Thrombus aspiration had better ΔLVEF (3.3±4.6 vs. 0.7±1.9%, p=0.005) and ΔWMSI (-0.12±0.16 vs. -0.004±0.07, p=0.001).	Not performed / not evaluate
Ito et al. (65)	**36** STEMI	Distal protection device vs. standard PCI	Physicians blinded to treatment group allocation	**IMR** after PCI	IMR was lower in the device group (26.6±25.8 vs. 37.2±23.2U; p=0.032).	Not performed / not evaluate	30 days follow-up/ No significant differences in clinical events between groups.
Tahk et al. (66)	**116** STEMI	Distal protection device vs. standard PCI	Not reported	**HMR** after PCI	HMR was lower in the device group than in standard PCI (2.4±1.4 vs. 3.1±1.3 mmHg cm−1 s, p=0.03).	Echocardiography 1 and 6 months after MI; ΔLVEF and ΔWMSI were similar between groups at baseline and follow up.	6 months follow-up/ There were no differences regarding death, target vessel revascularization and reinfarction between groups.

ACS Acute coronary syndromes; **CMR** Cardiovascular magnetic resonance; **LVEF** Left ventricular ejection fraction; **HHF** Hospitalization for heart failure; **IMH** Intramyocardial haemorrhage; **IMR** Index of microvascular resistance; **IS** Infarct size; **LV** Left ventricle; **MACE** Major adverse cardiac events; **MI** Myocardial infarction; **MVO** Microvascular obstruction; **OCT** Optical coherence tomography; **PDA** Perfusion descending area; **PPCI** Primary percutaneous coronary intervention; **SPECT** Single-photon emission computed tomography; **STEMI** ST-segment elevation myocardial infarction; **WMSI** Wall motion score index.

intracoronary fibrinolysis, which included 947 MI patients. The authors reported that intracoronary thrombolysis reduced IMR when compared to standard PCI (mean difference: −13.74, p<0.001), however, with no effect of thrombolysis on the occurrence of MACE.

Several non-randomized trials measured the impact of vasodilators in the coronary microcirculation. IMR significantly decreased after intracoronary sodium nitroprusside (39) and nicorandil (40, 41) administration in MI patients. In a crossover study, Ito et al. (42), randomized 60 patients to compare the effects of nicorandil or nitroglycerin on microvascular function. After primary PCI, the first administration of nicorandil decreased IMR significantly more than nitroglycerin (p<0.001). Moreover, after a second intracoronary bolus, nicorandil further decreased IMR, while nitroglycerin did not (p<0.001). Although all these treatments improved IMR, it is important to perform further randomized controlled studies in order to investigate whether this difference has impact on cardiac viability, function and clinical outcomes.

High thrombus burden may induce slow-flow during primary PCI, which is associated with a poor prognosis (43). Wuang et al. (44) investigated 50 patients with anterior STEMI. The combined interventional group received intracoronary urokinase, tirofiban and nitroglycerin plus aspiration thrombectomy, while the control group only had thrombus aspiration alone. The combined therapy group had significantly lower IMR, better LVEF and lower incidence of LV aneurysm compared to aspiration alone. In a similar study, Ahn et al. (45) reported the effects of abciximab versus thrombus aspiration versus both in combination and found that the combination group had significant lower values of IMR and less incidence of MVO on CMR (19% vs. 89%, p=0.002) than the abciximab group. More recently Xiao et al. (43) compared the efficacy of thrombus aspiration versus intracoronary urokinase and reported lower IMR values in the thrombolysis group (28±7 vs. 34±9; p = 0.005). In the 12-month follow-up, the urokinase group showed significantly lower IS (p = 0.043), measured on single-photon emission computed tomography, and higher LVEF on echocardiography (p = 0.046). According to this data, a combined therapy or even a fibrinolytic agent are more effective not only in reducing microvascular resistance but also by improving cardiac outcomes than aspiration thrombectomy alone.

Myocardial Infarction and no obstructive coronary artery disease

Evidence of MI and non-obstructive coronary artery disease has been reported in 5-25% of MI cases, encompassing a wide variety of ethological mechanisms, including epicardial but also microvascular events (46). Although, coronary microvascular dysfunction has largely been described in patients presenting with stable angina and no obstructive coronary artery disease, MINOCA is a distinct clinical entity from ischemia with no obstructive coronary artery disease,

with limited overlap between them (47). Furthermore, clinical outcomes in MINOCA are similar to MI patients with obstructive coronary disease, reporting comparable mortality rates and higher MI recurrence than in a population without significant cardiovascular disease (46). MINOCA clinical heterogeneity (ischemic and nonischemic mechanisms) makes it difficult to identify the true role of microvascular dysfunction in the myocardial injury, whether it is the cause of the acute MI or a consequence of it. Microcirculation data in these patients is scarce, and a limited published studies focus on specific ischemic mechanisms, such as microvascular coronary vasospasm (46), spontaneous coronary artery dissection (48) and Tako-tsubo syndrome (49). Further clinical investigation is needed, to evaluate the role of microvascular angina, microvascular spasm or coronary slow flow phenomenon in MINOCA cases. Presently, the evaluation of microcirculation function is already supported by clinical guidelines (50) and should be consider as part of the diagnostic workup to better characterized the various conditions that result in MINOCA.

Future Perspectives

The potential clinical utility of microvascular resistance indices is under continuous investigation. The possibility of having a microcirculation assessment immediately available in the catheterization laboratory, broadens its applicability and interest in the early reperfusion of MI. Forthcoming studies should clarify the microvascular dysfunction threshold for selecting patients for adjunctive therapies, in the case of failed reperfusion. Therapeutic hypothermia at primary PCI may be an option. The *European Intracoronary Cooling Evaluation in Patients With ST-elevation Myocardial Infarction* (EURO-ICE, NCT03447834) is investigating the safety and efficacy of localized cooling of ischemic myocardium, by cooled saline infusion into IRA (51). Other future investigations should clarify the role of microcirculation function as a surrogate for myocardium viability of the IRA, which may affect stenting strategies (immediate vs. deferred) in ACS. This selective approach to deferred stenting is also being prospectively assessed in *Primary Reperfusion Secondary Stenting* trial (PRIMACY, NCT01542385), which aims to determine whether it reduces no-reflow and salvage myocardium in primary PCI (52). More research is needed to define the clinical importance of non-IRA microcirculation after an acute MI, and better characterize remote myocardium changes occurring in the index event. Furthermore, microcirculation physiology assessment in patients with MINOCA represents an interesting field for future dedicated research. Ongoing and future studies will provide exciting data on the role of microcirculation as the cause or the outcome of myocardial ischemia.

Limitations

The majority of the studies included were observational and showed a significant risk of selection bias, which limited clinical significance of the conclusions reached. Moreover, all the selected RCT focused on therapeutic interventions, reported a small sample size and were mostly single-centre studies. Regarding the amount of invasive microvascular data available, IMR was disproportionately the most published vascular resistance index. IMR cut point > 25 was generally accepted as the marker of microvascular dysfunction. Several studies used IMR>40, which reflected a more severe impairment of myocardial microcirculation, to assess its correlation with MVO, IS and clinical outcomes. HMR and Pzf have no validated cut-off values, and the different thresholds used in the studies, were obtained through ROC curves analysis. The wide range of cut-off values used, the methodological disparities between studies and microcirculation assessment techniques limit the comparison between the different vascular resistance indices.

Conclusions

Microvascular resistance indices are valuable means to accurately evaluate microcirculation function in the acute phase of MI. Microvascular dysfunction relates to the extent of myocardial damage after an MI, as measured by CMR and PET, and with adverse clinical outcomes, however published data does not allow to conclude which one of the indices is superior at evaluating microcirculation function.

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I Supplementary data

Supplementary Table 1 Search strategy

#	**Searches using PubMed, Embase and Cochrane Controlled Register of Trials (CENTRAL) databases**
1	"IMR" OR "Index of microcirculatory resistance" OR "Index of microvascular resistance" OR "Microvascular resistance index" OR "HMR" OR "Hyperemic microvascular resistance" OR "Pzf" OR "Zero-flow pressure"
2	"Acute coronary syndrome" OR "Myocardial infarction" OR "STEMI" OR "ST-elevation myocardial infarction" OR "NSTEMI" OR "Non-ST elevation myocardial infarction"
3	#1 AND #2

Supplementary Table 2 Risk of bias summary

First author / study	Randomization process	Timing of participants identification / recruitment	Assignment to intervention	Adhering to intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Park et al. / CV-TIME trial (32)								
Park et al. (33)								
Leeuwen et al./ REDUCE-MVI trial (34)								
Maznyczka et al. (35)								
Sezer et al. (36)								
Sezer et al. (37)								
Ito et al. (42)								
Xiao et al. (43)								
Wang et al. (44)								
Ahn et al. (45)								
Ubaid et al. (57)								
Fu et al. (58)								
Wu et al. (59)								
Van Geuns et al./ BIVAL study (60)								
Kirma et al. (61)								
Hoole et al. / IMPACT study (62)								
Woo et al. (63)								
Ito et al. (65)								
Tahk et al. (66)								

Supplementary Table 3 Newcastle-Ottawa Scale summary

First author/ study	Selection	Comparability	Outcome
Williams et al. (1)	**	-	**
Patel et al. / OXAMI study (2)	**	-	**
De Maria et al. (6)	**	-	***
McAlindon et al. / MICRO-AMI study (7)	**	-	***
Kitabata et al. (8)	**	-	**
Teunissen et al. (9)	***	*	***
Scarsini et al. / OXAMI study (10)	**	-	***
Lim et al. (11)	**	-	***
Shimada et al. (12)	**	-	**
Maznyczka et al. (14)	**	-	***
Fearon et al. (15)	**	-	***
Carrick et al. (16)	**	-	***
De Waard et al. (17)	***	*	***
Jin et al. (18)	**	-	***
Díez-Delhoyo et al./ FISIOIAM study (19)	**	-	***
Ntalianis et al. (20)	**	-	**
Choi et al. (21)	***	*	***
Mejía-Rentería et al. (22)	***	*	***
Van der Hoeven et al. (26)	**	-	***
Bax et al. (28)	**	-	***
Morimoto et al. (39)	**	-	***
Kostic et al. (40)	**	-	***
Ito et al. (41)	***	*	*
Verna et al. (49)	**	-	***
Yoo et al. (53)	**	-	***
Ahn et al. (54)	**	-	***
Sacrsini et al. (55)	**	-	**
Yoon et al. (56)	**	-	***
Firman et al. (64)	***	*	***
Yoon et al. (67)	***	*	*
De Maria et al. / OxAMI-PICSO study (68)	***	*	***
Fahrni et al. /Insights OxAMI study (69)	**	-	***
Maznyczka et al. (70)	**	-	***
Fukunaga et al. (71)	**	-	***
De Maria et al. (72)	**	-	***
De Silva et al. (73)	**	-	***
Karamasis et al. (74)	**	-	***
De Maria et al. (75)	**	-	***