

# Late percutaneous coronary intervention for an occluded infarct-related artery in patients with preserved infarct zone viability: A pooled analysis of cardiovascular magnetic resonance studies

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## Abstract

**Background:** *The results of clinical trials assessing the effect of late opening of infarct-related artery (IRA) on left ventricular ejection fraction (LVEF) and size in stable patients are equivocal, which may be related to the fact that the presence of viability was not a requirement for randomization in these trials. The aim of the study was to assess the influence of late percutaneous coronary intervention (PCI) with optimal medical therapy (OMT) vs. OMT alone on cardiac function and remodeling in patients presenting infarct zone with preserved viability on cardiovascular magnetic resonance (CMR).*

**Methods:** *The analysis included pooled data of 43 patients from 3 randomized studies. All patients underwent CMR before randomization, but only in 1 previously unpublished study was preserved viability required for randomization to treatment. Follow-up CMR was performed after 6–12 months.*

**Results:** *Late PCI with OMT led to improved LVEF ( $+5 \pm 7\%$  vs.  $-1 \pm 6\%$ ,  $p = 0.005$ ), decreased left ventricular end-systolic volume ( $-11 \pm 19$  mL vs.  $12 \pm 40$  mL,  $p = 0.02$ ) and a trend towards a decrease in end-diastolic volume ( $-7 \pm 27$  mL vs.  $15 \pm 47$  mL,  $p = 0.07$ ) in comparison to OMT alone. Increased LVEF and decreased left ventricular volumes were observed after the analysis was restricted to patients with left anterior descending artery (LAD) occlusion.*

**Conclusions:** *In patients with the presence of infarct zone viability, OMT with late PCI for an occluded IRA (particularly LAD) is associated with improvement of left ventricular systolic function and size over OMT alone. (Cardiol J 2013; 20, 5: 552–559)*

**Key words:** myocardial infarction, occluded artery, infarct-related artery, viability, percutaneous coronary intervention, optimal medical treatment

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## Introduction

Restoration of blood flow to an infarct-related artery (IRA) in the first 12 h of evolution is a cornerstone of contemporary treatment of acute myocardial infarction (MI) [1, 2]. It decreases the infarct size, preventing the expansion of myocardial necrosis and its consequences [1, 2]. However, due to their late presentation, up to one third of patients do not receive reperfusion therapy [3].

Randomized clinical trials assessing the benefits of late percutaneous coronary intervention (PCI) on top of optimal medical therapy (OMT) of a totally occluded IRA, in comparison to OMT alone, showed equivocal results [4–8], with most of them failing to demonstrate any significant improvement in cardiac systolic function and/or remodeling with PCI [4, 5, 8]. Lack of significant benefit of the invasive approach on left ventricular (LV) performance in this group of patients could have been responsible for a similar or even higher rate of clinical end-points observed in this group during follow-up in comparison to OMT alone [4, 6, 9]. These results might have been impacted by the fact that the presence of infarct zone viability was not required for randomization in these trials, and therefore late PCI was performed in patients both with and without viability [10, 11].

This hypothesis is supported by the results of a meta-analysis on patients with chronic ischemia, which showed that only patients with myocardial viability [assessed with echocardiography or single-photon emission computed tomography (SPECT)] benefited from revascularization [12]. Also studies with the use of cardiovascular magnetic resonance (CMR) performed in the setting of chronic ischemia demonstrated that patients with LV systolic dysfunction and preserved myocardial viability (defined by means of low dose dobutamine test or delayed enhancement) benefited from revascularization in terms of cardiac function and remodeling, and/or improved survival [13–16].

The aim of this study was to determine whether late opening of an occluded IRA in patients with the presence of infarct zone viability on CMR improved cardiac function and volume over OMT alone.

## Methods

### Study group

Initially the study was planned as a single center randomized clinical trial: Cardiovascular Magnetic Resonance for the Occluded Infarct-Related Artery Treatment (COAT; Clinical Trials.

gov NCT00968383). It included patients who met the Occluded Artery Trial (OAT) inclusion criteria but did not meet the OAT exclusion criteria as reported previously [17], and additionally had preserved infarct zone viability. Preserved infarct zone viability was defined as delayed enhancement (DE) not exceeding 50% of transmural thickness in at least half of the segments of the infarct zone on initial CMR examination. Infarct zone included all LV segments with signal intensity > 2 standard deviations of the mean signal intensity of the remote myocardium on dark-blood T2-weighted short-tau inversion-recovery fast-spin echo sequences indicating myocardial edema [18, 19]. Eligible patients were randomized (1:1 ratio) to PCI + OMT or to OMT alone and followed-up for 6 months until a second CMR examination. All CMR studies were performed with a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany).

The study was prematurely stopped due to low enrollment. However we decided to pool individual data from the COAT trial with individual data extracted from previously published randomized studies on late opening of a totally occluded IRA with the use of CMR, but without the viability criterion used for randomization. The criteria for inclusion into the pooled analysis were: (a) total occlusion of an IRA (TIMI flow 0–1) within the first month after MI, (b) stable clinical condition of patients (lack of symptoms of heart failure or ischemia at rest), (c) randomization to PCI + OMT or OMT alone, (d) at baseline, presence of infarct zone viability by CMR, (e) CMR data on LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) at baseline and at follow-up. Two studies met such inclusion criteria [7, 20].

In brief, one by Bellenger et al. [20] (the TOAT trial substudy) included stable patients with occluded left anterior descending artery (LAD) between 3 and 28 days after MI and non-significant disease in other coronary arteries [5]. PCI was performed at the time of angiography or within 2 weeks of angiography. Practical considerations therefore precluded baseline CMR of all patients before angiography. In these cases it was done shortly after PCI. In all other cases CMR was performed before PCI. All CMR studies were done with the use of a 1.5 T scanner (Picker Edge, Picker, Cleveland, OH, USA) and repeated after 1 year post-MI. Myocardial viability was defined at baseline by means of low dose dobutamine test (up to 10  $\mu\text{g}/\text{kg}/\text{min}$ ). Infarct zone viability in individual patients was not analyzed in that study. Therefore, for the purpose of the current analysis, infarct zone viability

was defined as a wall motion improvement by at least one full grade (where 1: normal wall motion, 2: hypokinetic, 3: akinetic and 4: dyskinetic) in at least 2 LV dysfunctional segments.

The other by Silva et al. [7] included patients with anterior MI admitted between 12 h and 14 days after MI. All patients underwent CMR with a 1.5 T scanner (SIGNA, CV/I, General Medical Electric Systems, Waukesha, MN, USA) and DE technique before PCI or shortly after the procedure. Neither for this study was infarct zone viability analyzed with CMR previously reported. Therefore for the purpose of the current analysis, infarct zone viability was defined as DE not exceeding < 50% of transmuralty in at least half of the segments supplied by the LAD. A second CMR examination was performed after 6 months of follow-up.

Both of the studies published previously included only patients with LAD occlusion, while the COAT trial included also patients with right coronary artery (RCA) occlusion. Therefore, to limit the inclusion bias, we decided to perform an additional analysis restricted only to patients with LAD occlusion. The scheme of pooled data analysis is presented in Figure 1.

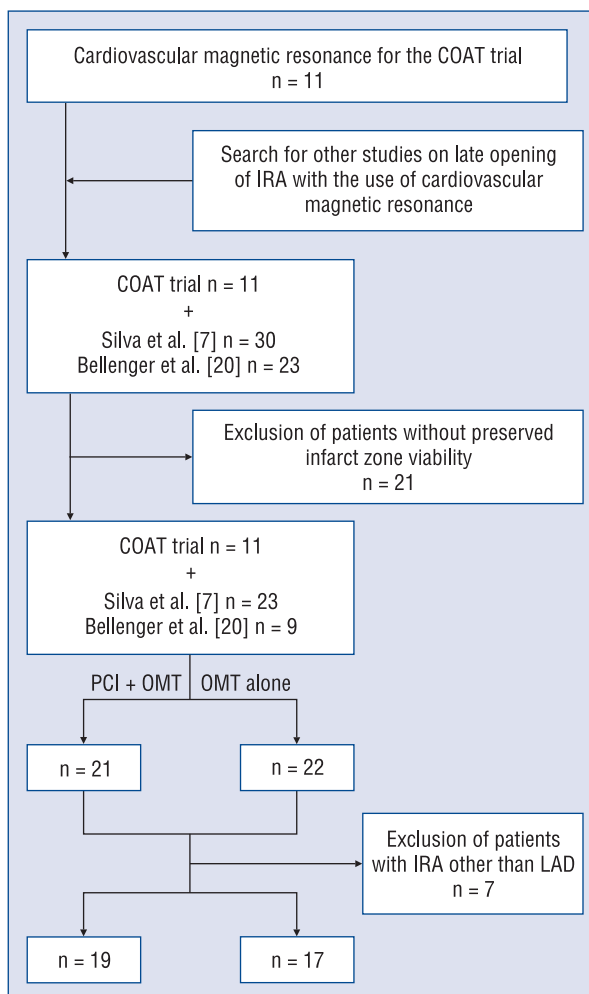
Institutional review boards approved the study protocols, and each patient provided a written informed consent.

### Study end-points

The study end-points included change in LVEF, LVEDV and LVESV at follow-up in patients treated with late PCI + OMT in comparison to those treated with OMT alone.

### Statistical analysis

Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables. For continuous variables means and standard deviations or medians and interquartile ranges were utilized, taking into account the assessment of normality of distribution by means of the Shapiro-Wilk test. Categorical variables were compared by either Fisher's exact or  $\chi^2$  test and continuous variables by the Student *t* test or the Mann-Whitney test for unpaired samples, where appropriate. Changes in cardiac function and size with intervention (PCI + OMT or OMT alone) were analyzed with a paired samples Student *t* test. All tests were 2-sided with the significance level of  $p < 0.05$ . Statistical analyses were performed with the use of the SAS 9.3.1 software (SAS Institute Inc., Cary, NC, USA) [21].



**Figure 1.** The scheme of pooled data analysis; COAT — Cardiovascular magnetic resonance for the Occluded infarct-related Artery Treatment; LAD — left anterior descending artery; PCI — percutaneous coronary intervention; OMT — optimal medical therapy; IRA — infarct-related artery.

## Results

The characteristics of the analyzed clinical trials are presented in Table 1. All patients received aspirin and angiotensin converting enzyme inhibitor (ACE-I) and most of them were treated with beta-blockers and statins. Clopidogrel was administered to all patients in the COAT trial and to patients who received stents in the other 2 studies. Only few patients received diuretics.

Pooling of data revealed 21 patients treated with late PCI + OMT and 22 patients treated with OMT alone. There were no differences in baseline characteristics of the population in both treatment arms, except a more frequent use of clopidogrel in patients treated invasively, as described above

**Table 1.** Characteristics of the analyzed clinical trials.

	COAT trial	Silva et al. [7]	Bellenger et al. [20]
Years of the study	2009–2011	1999–2001	1997–1999
Infarct-related artery	LAD: 36%, RCA: 64%	LAD: 100%	LAD: 100%
Method of viability assessment	Delayed enhancement	Delayed enhancement	Low-dose dobutamine
No. of randomized patients with preserved infarct zone viability	11 (100%)	23/30 (76%)	9/23 (39%)
Treatment:			
PCI + OMT	5 (45%)	12 (53%)	4 (44%)
OMT alone	6 (55%)	11 (47%)	5 (56%)
Follow-up [months]	6	12	6
Time between MI and randomization	3–28 days	12 h–14 days	3–28 days
Time between MI and CMR [days]	13 ± 5	11 ± 4	54 ± 18
Male sex	9 (82%)	15 (65%)	9 (100%)
Age [years]	58 ± 13	54 ± 9	57 ± 11
Risk factors:			
Diabetes	0 (0%)	3 (13%)	3 (33%)
Hypertension	9 (82%)	10 (44%)	3 (33%)
Dyslipidaemia	7 (64%)	6 (26%)	3 (33%)
Current smoker	2 (18%)	10 (44%)	5 (55%)
TIMI flow:			
0	8 (73%)	14 (61%)	6 (66%)
1	3 (27%)	9 (39%)	3 (33%)
Multivessel disease	1 (9%)	15 (65%)	0 (0%)
Medications on discharge:			
Aspirin	11 (100%)	23 (100%)	9 (100%)
Clopidogrel*	11 (100%)	12 (52%)	4 (44%)
Statin	11 (100%)	8 (35%)	9 (100%)
Beta-blocker	11 (100%)	21 (91%)	8 (89%)
ACE-I	11 (100%)	23 (100%)	9 (100%)
Diuretic	1 (9%)	5 (22%)	0 (0%)
LVEF at baseline [%]	59 ± 9	45 ± 9	50 ± 14
LVEDV at baseline [mL]	172 ± 43	149 ± 37	180 ± 46
LVESV at baseline [mL]	73 ± 26	82 ± 28	95 ± 45

\*COAT — for 12 months in all patients, Silva et al. [7] — for 30 days after PCI only, Bellenger et al. [20] — for 2 weeks after PCI only; ACE-I — angiotensin converting enzyme; CMR — cardiovascular magnetic resonance; LAD — left anterior descending artery; LVEF — left ventricular ejection fraction; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; MI — myocardial infarction; OMT — optimal medical therapy; PCI — percutaneous coronary; RCA — right coronary artery; TIMI — thrombolysis in myocardial infarction

(Table 2). Importantly, there were no differences in baseline LVEF, LVEDV and LVESV. Successful PCI was performed in 97% of cases (in 1 patient it was impossible to cross the occlusion site with a guidewire).

Late PCI with OMT led to an increase in LVEF (+5 ± 7% vs. -1 ± 6%, p = 0.005), decrease in LVESV (-11 ± 19 mL vs. 12 ± 40 mL, p = 0.02) and a trend towards a decrease in LVEDV (-7 ± 27 mL vs. 15 ± 47 mL, p = 0.07) in comparison to OMT alone, as shown in Figures 2A–C.

An additional analysis was performed for patients with LAD occlusion only. It excluded 7 patients with RCA occlusion from the COAT. The LAD only subgroup consisted of 19 patients treated with late PCI + OMT and 17 patients who received OMT alone (Fig. 1).

A comparison of patients with LAD occlusion treated with PCI + OMT vs. OMT alone did not demonstrate significant differences in baseline characteristics except a more frequent use of clopidogrel in patients treated invasively as described

**Table 2.** Baseline characteristics of patients treated with PCI + OMT or with OMT alone — pooled data from the 3 studies.

	PCI + OMT (n = 21)	OMT alone (n = 22)	P
Male sex	16 (76%)	18 (82%)	0.72
Age [years]	58 ± 11	54 ± 10	0.24
Risk factors:			
Diabetes	2 (10%)	4 (18%)	0.66
Hypertension	10 (48%)	12 (54%)	0.88
Dyslipidaemia	9 (43%)	7 (32%)	0.66
Current smoker	6 (29%)	11 (50%)	0.26
TIMI flow:			0.72
0	10/17 (59%)	12/17 (71%)	
1	7/17 (41%)	5/17 (29%)	
Multivessel disease	8 (38%)	8 (36%)	1.00
Medications on discharge:			
Aspirin	21 (100%)	22 (100%)	1.00
Clopidogrel*	21 (100%)	6 (27%)	0.0001
Statin	14 (67%)	14 (64%)	1.00
Beta-blocker	21 (100%)	19 (86%)	0.23
ACE-I	21 (100%)	22 (100%)	1.00
Diuretic	2 (10%)	4 (18%)	0.66
Mean LVEF at baseline [%]	49 ± 11	50 (12)	0.77
Mean LVEDV at baseline [mL]	162 ± 40	161 (45)	0.95
Mean LVESV at baseline [mL]	84 ± 30	81 (34)	0.82

Abbreviations as in Table 1

previously. Importantly, there were no differences in baseline cardiac function and size between patients treated invasively and conservatively (LVEF 48 ± 10% vs. 48 ± 12%, p = 0.97; LVEDV 162 ± 42 mL vs. 152 ± 45 mL, p = 0.51; LVESV 85 ± 29 mL vs. 81 ± 38 mL, p = 0.72).

In the LAD occlusion subgroup, late PCI with OMT led to an increase in LVEF (+4 ± 6% vs. -2 ± 7%, p = 0.004) and a decrease in LVEDV (-7 ± 28 mL vs. 23 ± 48 mL, p = 0.03) and LVESV (-11 ± 19 mL vs. 18 ± 43 mL, p = 0.01) in comparison to OMT alone as shown in Figures 2D–F.

During follow-up there was only one important clinical event in the OMT group (non-fatal MI) and no events in the PCI group.

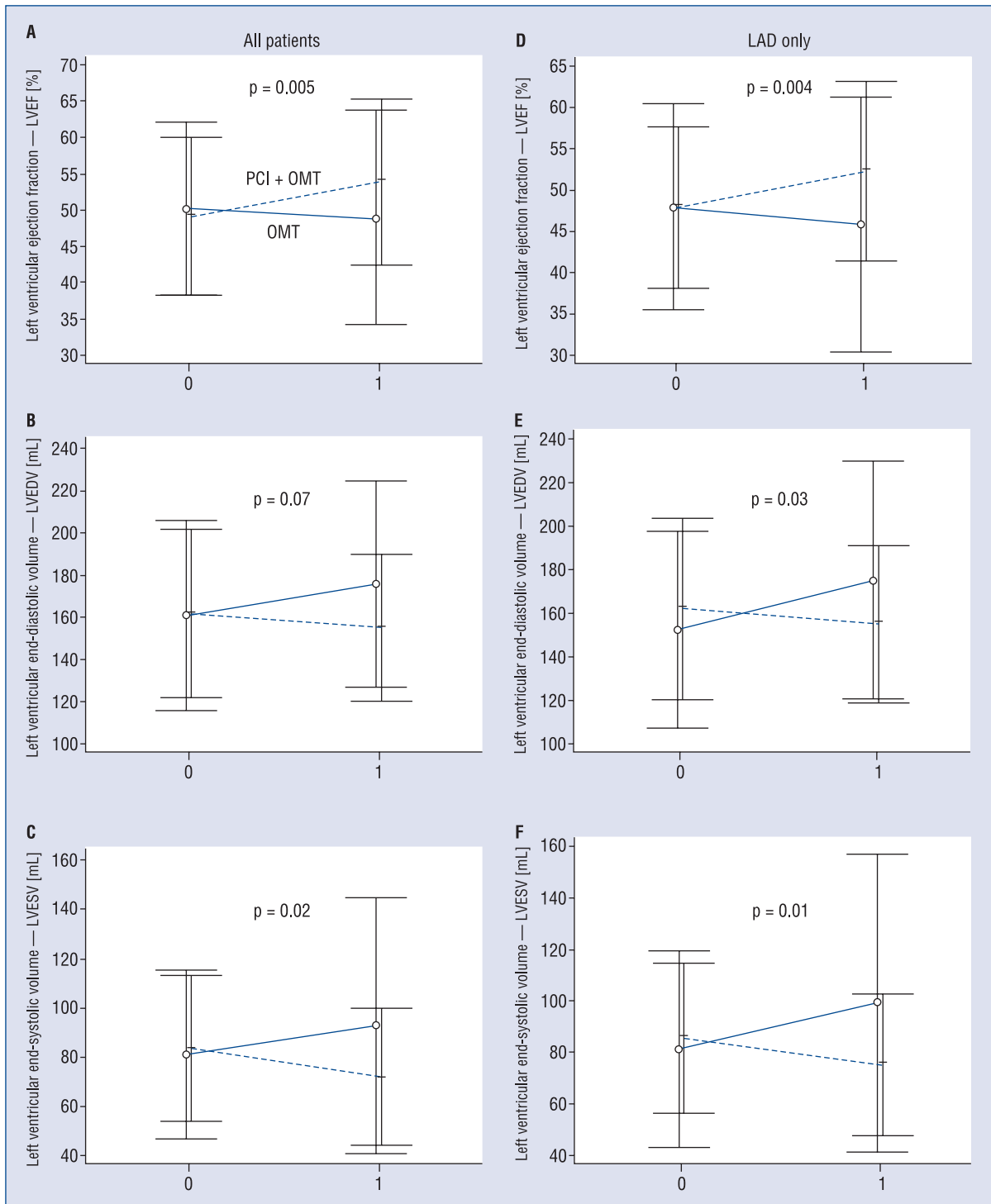
### Discussion

Previous studies assessing cardiac function and remodeling after late PCI for a totally occluded IRA with OMT vs. OMT alone showed conflicting results [4–8]. In most of the studies, there was no difference in LVEF at follow-up for the 2 strategies [4, 5, 8]. Only few trials demonstrated an improvement in cardiac systolic function after late PCI, but changes in LV size were either not analyzed

in these studies [6] or no significant influence of the invasive strategy on cardiac remodeling was observed [7]. Equivocal results were also observed for the influence of late PCI on LV remodeling. Horie et al. [4] demonstrated an improvement in LVEDV and LVESV with late opening of an IRA, while other studies showed no differences in these parameters [7, 8] or even adverse effects of late PCI on LV size [5]. Lack of influence of late PCI on cardiac function and remodeling may explain the lack of benefits of late PCI in terms of reduction of negative outcomes observed in most trials [4, 6, 9].

It should be noted that none of the randomized clinical trials on late PCI for an occluded IRA included the infarct zone viability criterion as a requirement for randomization to treatment, which could have influenced the results. It is likely that changes in LV function and size after MI in patients with infarct zone necrosis were similar irrespective of the treatment strategy as long as OMT was introduced. On the other hand, restoration of blood flow and oxygen supply to the dysfunctional, but viable (hibernating) segments of the LV should improve their systolic function and prevent LV remodeling [22].

This issue has been also raised by commentators of the OAT trial — the largest clinical trial



**Figure 2A–F.** Change in cardiac function and size for the two treatment strategies. Repeated measures analysis of variance for all patients (A–C) and for patients with left anterior descending artery (LAD) as the infarct-related artery (IRA) only (D–F). Percutaneous coronary intervention (PCI) + optimal medical therapy (OMT) group (dashed line), OMT alone group (solid line). Means and standard deviations (SD) are presented.

on late PCI so far [9–11]. These concerns were addressed in the ancillary study to OAT trial — the OAT-NUC study dedicated to the analysis of infarct zone viability. It was based on SPECT and

showed that 31% of patients did not have a preserved viability (severely reduced viability group) defined as at least 40% of the marker uptake [23]. The study demonstrated that the presence of in-

infarct zone viability (moderately retained viability group) predicted an improvement in LVEF in the whole group, but no differences in the improvement in LV systolic function or volumes in relation to the treatment strategy (PCI + OMT vs. OMT) in patients with preserved viability were observed. However, the OAT-NUC study was limited by reproducibility and accuracy of the SPECT used for the viability assessment. This method was shown to underestimate the size of necrosis in comparison to CMR due to its lower spatial resolution, and therefore the percentage of patients with moderately retained viability might have been overestimated [24]. It has been demonstrated that CMR should be currently considered as the gold standard of accuracy and reproducibility for assessing volumes, mass, and wall motion [25].

In spite of all of the considerations above, we decided to perform a single center randomized clinical trial assessing the results of late PCI with OMT vs. OMT alone, but only in patients with preserved infarct zone viability established by means of CMR. Because of the difficulties in recruiting patients to obtain the predefined sample size we proposed to the authors of other published studies on late PCI for the totally occluded IRA performed with the use of CMR, to develop a collaborative publication. None of these studies took into account the role of preserved infarct zone viability in individual patients. With this approach, we were able to demonstrate that late PCI with OMT in the subgroup of patients with viable myocardium after MI is associated with improvement of both cardiac systolic function and size, over OMT alone. The opening of IRA seemed particularly efficacious in patients with LAD occlusion, which may suggest that the group of patients with the largest area of myocardium at risk may benefit most from revascularization.

Our findings are supported by the results of PCI in the group of stable patients with silent ischemia on stress imaging (a marker of a viable myocardium), which showed marked differences in LVEF, LVESV and LVEDV favoring late PCI [26]. It should be noted however that, contrary to the current analysis, total occlusion of an IRA was not required for randomization into treatment.

### Limitations of the study

Our study is not free from limitations of an explorative, pooled data analysis. However, we have attempted to lower the existing inclusion bias by limiting the analysis to patients with LAD occlusion. It can be observed that the frequency of the use of

some medications, which was considered optimal at the time when 2 of the analyzed studies were conducted, is no longer satisfactory [7, 20]. However, it is similar to the OAT trial, which is used as an evidence for current guidelines of management in acute MI [1]. Besides the use of ACE-I considered as main drugs preventing LV remodeling was higher in the current analysis than in the OAT trial, which further supports the results. Furthermore, with this sample size we were unable to analyze clinical end-points. However, recently published results of the VIAMI-trial, which included stable patients with acute MI not treated with primary or rescue PCI and with viability by dobutamine echocardiography, demonstrated that PCI after at least 48 h improved outcomes in comparison to conservative strategy [27]. Our findings suggest that the improved event-free survival observed with late PCI of an IRA in the VIAMI-trial may be the consequence of an improved LV systolic performance and size.

### Conclusions

In patients with preserved infarct zone viability, OMT with late PCI for an occluded IRA (particularly LAD) is associated with improvement of LV systolic function and size over OMT alone. This study should be considered as introduction to a discussion on a routine use of late PCI of the occluded IRA in patients with preserved infarct zone viability.

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**Conflict of interest:** none declared

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