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 All patients underwent CMR before randomization, but only in 1 previously unpublished study was preserved viability required for randomization to treatment.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 ± 7% vs. –1 ± 6%, p = 0.005), decreased left ventricular end-systolic volume (–11 ± 19 mL vs. 12 ± 40 mL, p = 0.02) and a trend towards a decrease in end-diastolic volume (–7 ± 27 mL vs. 15 ± 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
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 endpoints 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 transmurality 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 μg/kg/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 transmurality 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 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].

**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.
Łukasz A. Małek et al., Late recanalization of viable myocardium in STEMI

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
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

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

<table>
<thead>
<tr>
<th></th>
<th>PCI + OMT (n = 21)</th>
<th>OMT alone (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>16 (76%)</td>
<td>18 (82%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Age [years]</td>
<td>58 ± 11</td>
<td>54 ± 10</td>
<td>0.24</td>
</tr>
<tr>
<td>Risk factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (10%)</td>
<td>4 (18%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (48%)</td>
<td>12 (54%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>9 (43%)</td>
<td>7 (32%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6 (29%)</td>
<td>11 (50%)</td>
<td>0.26</td>
</tr>
<tr>
<td>TiMi flow:</td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>0</td>
<td>10/17 (59%)</td>
<td>12/17 (71%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7/17 (41%)</td>
<td>5/17 (29%)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>8 (38%)</td>
<td>8 (36%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Medications on discharge:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>21 (100%)</td>
<td>22 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Clopidogrel*</td>
<td>21 (100%)</td>
<td>6 (27%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Statin</td>
<td>14 (67%)</td>
<td>14 (64%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>21 (100%)</td>
<td>19 (86%)</td>
<td>0.23</td>
</tr>
<tr>
<td>ACE-I</td>
<td>21 (100%)</td>
<td>22 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diuretic</td>
<td>2 (10%)</td>
<td>4 (18%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean LVEF at baseline [%]</td>
<td>49 ± 11</td>
<td>50 (12)</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean LVEDV at baseline [mL]</td>
<td>162 ± 40</td>
<td>161 (45)</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean LVESV at baseline [mL]</td>
<td>84 ± 30</td>
<td>81 (34)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1
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-
It can be observed that the frequency of the use of mitomycin C, when included in the analysis of patients with LAD occlusion, which may 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.

Limitations of the study

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 included in the group of patients with the largest area of myocardium at risk may benefit most from revascularization.

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.

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 an 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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