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Revascularization of the Infarct-related Artery: Never Too Late?

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ABSTRACT

During the early phase of an acute myocardial infarction (MI), current consensus is that reperfusion of the infarct-related artery (IRA) should be implemented as soon as possible, more effectively accomplished via percutaneous coronary intervention (PCI). The clinical approach to the occluded IRA late after MI remains controversial, but current practice shows a strong trend in favor of PCI, which is based on the late open artery hypothesis. However, late PCI on IRAs also has the potential for harm from procedure-related complications. An attempt is made herein to critically overview the current data on this important topic, mainly based on recent meta-analyses with somewhat diverging results, indicating that clinical judgment and an individualized approach still remains a valid guide.

KEY WORDS: *myocardial infarction; percutaneous coronary intervention; infarct-related coronary artery; recanalization; reperfusion; revascularization*

During the early phase of an acute myocardial infarction (MI), current consensus is that reperfusion of the infarct-related artery (IRA) should be implemented as soon as possible. According to the current ACC/AHA/SCAI and ESC guidelines primary percutaneous coronary intervention (PCI) is the treatment of choice when delivered rapidly (no longer than 90 minutes from patient's first medical contact), by experienced teams in high-volume centers, specifically when the time from the onset of symptoms is shorter than 12 hours.[1,2] In this early phase the main goal is myocardial salvage, which is critically time-dependent. Prompt restoration of blood flow reduces infarct size, preserves global left ventricular function, and thus improves patient survival.

Unfortunately, the number of patients treated within 12 hours of the onset of symptoms is still disappointing, since 8.5% to 40% of patients present beyond 12 hours.[3] The clinical approach to the occluded IRA late after MI remains variable and controversial, but current practice shows a strong trend in favor of PCI, which is based on the late open artery hypothesis.[4,5] According to this theory late patency of an IRA is associated with reduction in adverse post-infarction remodeling, increased electrical stability, and provision of collateral vessels to other coronary beds for protection against future events.[6] It was initially conceived during the fibrinolytic era when several studies suggested that the effects of IRA reperfusion on left ventricular function and survival might, to some extent, be independent of one another.[7,8] Further support was provided by nonrandomized, retrospective studies of patients with a first MI, where long-term survival was found to be substantially better among those with anterograde flow in the infarct-related artery than among those whose infarct-related artery was persistently occluded.[9,10] Other studies showed that patients with a persistently occluded IRA after MI were more likely than those with a patent artery to have late potentials on

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signal-averaged electrocardiography and inducible ventricular tachyarrhythmias during invasive programmed electrical stimulation.[11,12] The late open artery hypothesis thus forms a solid theoretical basis in favor of late intervention in order to reperfuse occluded IRAs. However, late PCI on IRAs also has the potential for harm from procedure-related complications, distal embolization of atherothrombotic debris resulting in myocardial injury, and loss of recruitable collateral flow to other coronary territories.[13-15]

RANDOMIZED TRIALS TESTING THE LATE OPEN ARTERY HYPOTHESIS

Several randomized trials of small or modest sample sizes compared PCI versus medical therapy for total IRA occlusion late after MI. Although their results were not definitive, potential improvements in left ventricular function and probably even clinical events suggested that late opening of occluded arteries after MI should be seriously considered.[16-20] These studies were followed by the publication of OAT (Occluded Artery Trial) in 2006, which was the first large, randomized trial to test the late open artery hypothesis.[21] This trial tested the hypothesis that routine PCI for total occlusion 3 to 28 days after MI would reduce the composite endpoint of death, reinfarction, or class IV heart failure. Stable patients (n =2166) with an occluded infarct artery after MI (of whom almost 20% received fibrinolytic therapy for the index event) were randomized to optimal medical therapy and PCI with stenting or optimal medical therapy alone. Inclusion criteria included total occlusion of the infarct-related artery with TIMI grade 0 or 1 antegrade flow and left ventricular (LV) ejection fraction (LVEF) less than 50% or proximal occlusion of a major epicardial artery with large myocardial region at risk. Exclusion criteria included NYHA class III or IV heart failure, serum creatinine greater than 2.5 mg/dL, left main or 3-vessel disease, clinical instability, or severe inducible ischemia on stress testing if the infarct zone was not akinetic or dyskinetic. The 4-year combined end point was 17.2% in the PCI group and 15.6% in the medical therapy group (HR 1.16, 95% CI 0.92 to 1.45, p = 0.2). Re-infarction rates tended to be higher in the PCI group, which may have attenuated any benefit in LV remodeling. There was no interaction between treatment effect and any subgroup variable. It should be noted that even in the absence of significant effects on hard end points, the OAT study showed that patients treated with PCI were significantly less likely to have angina at 4, 12, and 24 months, while that difference disappeared at the third year of follow up.

The Total Occlusion Study of Canada 2 (TOSCA-2) was a substudy of OAT which included 332 patients who were submitted to repeated coronary and LV angiography one year after randomization.[22] Patients in the PCI group had the IRA patent in 83% of cases while this was true for only 25% of the medically treated patients. Despite this difference no significant benefit of the PCI strategy was found concerning LV function, in concert with the OAT results.

These results have challenged the late open artery hypothesis and its clinical implications. Because of the findings of the OAT trial a new recommendation was included in the latest 2007 focused update[23] of the ACC/AHA/SCAI 2005 PCI guidelines: PCI of a totally occluded infarct artery greater than 24 hours after STEMI is not recommended (Class III) in asymptomatic patients with 1- or 2-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia. (Level of Evidence: B).

TWO RECENT META-ANALYSES TESTING THE STRATEGY OF LATE PCI TO RECANALIZE AN IRA

The first meta-analysis by Ioannidis and Katritsis[24] included data from the small and medium sized studies published before OAT (Table 1), as well as data from OAT trial and its sub-study TOSCA-2. The 2617 patients included were examined for clinical outcomes including death, MI, death or MI and congestive heart failure (CHF), while for 653 of them a change in LVEF could be determined. There were no statistically significant differences for any clinical outcome, with trends for an increase in MI (risk ratio 1.26, P = 0.19) and decrease in CHF (risk ratio 0.67, P = 0.19) in the PCI arm. The PCI arm showed a slight superiority in LVEF. The authors concluded that the open artery hypothesis does not seem to translate to clinically meaningful advantages and that benefits of late reperfusion do not justify the costs and high radiation times for both patients and physicians encountered with interventions for recanalization of totally occluded IRAs.

In the second and most recent meta-analysis by Abbate et al[25] studies were included if they compared PCI with medical management and randomized clinically stable patients >12 h and up to 60 days after acute MI. Studies included were finally the same as in the meta-analysis of Ioannidis and Katritsis, with the inclusion of four additional studies TOPS,[26] ALKK,[27] BRAVE-2[3] and SWISSI II[28] (Table 2). The analysis comprised 3560 patients yielding significantly improved survival in the PCI group (OR: 0.49, 95% CI: 0.26 to 0.94, p = 0.030). These benefits were associated with similarly favourable effects on cardiac remodeling, such as improved LVEF in the PCI group.

The results of these two meta-analyses initially seem contradictory, however one can find an explanation when the four additional trials included in the second meta-analysis are closely examined. Their inclusion criteria were not adapted to strictly test the late open artery hypothesis. The *BRAVE- 2 study*, which comprised 365 patients, examined whether routine PCI of MI latecomers, in the time window of 12-48 hrs

TABLE 1. Randomized studies published before the Open Artery Trial (OAT)[21] testing the late open infarct artery hypothesis.

Study (year)	Patients number (PCI/MED)	Inclusion criteria	LAD as IRA	Days from MI to PCI	Totally occluded IRA (TIMI 0-1)	Stent	Follow up (months)	End-points	Findings
TOMIIS [16] (1994)	44 (25/19)	STEMI ≤6 weeks old	PCI: 40%, MED: 47%	11±9 (all ≤6 weeks)	100%	0%	4	**Primary:** LVEF	By intention to treat no significant improvement with PCI. Improved LVEF when IRA patent (+9.4 ±6.2%), versus when non patent (1.6±8.8%).
								Secondary: Patency status of the IRA	By intention to treat: PCI: 40%, MED: 19% (p=0.231) When PCI successful: PCI: 60%, MED: 19% (p=0.047).
Horie et al [17] (1998)	83 (44/39)	Q wave antero-septal MI, admission >24 hours from symptom onset	100%	8±10 (1-21)	100%	0%	60	**Primary:** Death, non fatal MI, CHF	Significant reduction of total cardiac events and single parameters of the composite end-point.
								Secondary: At 6 months: LVEF, LV regional wall motion, LVEDV index and LVESV index	At 6 months: similar LVEF and LV regional wall motion. Reduced LVEDV index and LVESV index with PCI.
TOAT [18] (2002)	66 (32/34)	Anterior MI, LAD proximal occlusion at coronary angiography, clinical stability	100%	26±18 (3-42)	100%	100%	12	**Primary:** LV ESV, LV EDV, LV function	LV ESV, LV EDV: significantly increased in the PCI group. LVEF: no difference
								Secondary: Death, non fatal MI, CHF, stroke, revascularization. QoL measures	42% increased adverse events with PCI. Improvement of QoL measures with PCI
DECOPI [19] (2004)	212 (109/103)	Q-wave MI >48 hours old, clinically stable, no spontaneous or low level recurrent ischemia	PCI: 27% MED: 29%	2 -15	100%	80.4%	34	**Primary:** Cardiac death, non fatal MI or VT/VF	No difference (PCI-7.3%, MED-8.7%, p=0.68)
								Secondary: Cardiac death, non fatal MI, VT/VF or hospitalization for CHF. LVEF at 6 months.	No difference for the composite (PCI-10.1%, MED-12.6%, p=0.56). Higher (5%) LVEF with PCI. Costs higher with PCI. Post - hoc analysis after angiography at 6 months: significantly lower all cause and cardiovascular mortality when IRA was found patent.
Silva et al [20] (2005)	30 (18/12)	Anterior MIs admitted 0.5-14 days after symptoms, IRA occluded, no moderate or severe ischemia/viability at the IRA territory	100%	8±3	100%	100%	6	**Primary:** LV EF and volumes	Improvement in LV EF with PCI, deterioration with MED. LV volumes without significant change.
								Secondary: Adverse cardiac events	No statistically significant difference

TABLE 2. Randomized studies added in the meta-analysis of Abbate et al.[25] compared to the meta-analysis of Ioannidis and Katritsis.[24]

Study (year)	Patients number (PCI/Med)	Inclusion criteria	LAD as IRA	Time from MI to PCI	Totally occluded IRA (TIMI 0-1)	Stent	Follow up (months)	End-points	Findings
TOPS [26] (1992)	87 (42/45)	Thrombolysed STEMI, negative stress test, ≥50% IRA stenosis	PCI:38% MED:33%	4-14	PCI:10% MED:13%	0%	12	**Primary:** LVEF change from rest to exercise assessed by gated blood-pool scintigraphy 5-7 weeks post MI	No difference between PCI and MED.
								Secondary: - At 12 months: comparisons of cardiac event free survival, infarction free survival, angina free survival. - By 5-7 weeks: resting LVEF and peak exercise heart rate	At 12 months worst infarct free survival (88.7% vs 100%), but slightly better angina free survival with PCI. No other differences.
ALKK [27] (2003)	300 (149/151)	STEMI 8-42 days old, occlusion or significant stenosis of the IRA, clinical stability	PCI:35% MED:37%	23	PCI:29% MED:28%	17%	56	**Primary:** At 1 year: Death, re-infarction, revascularisation, angina necessitating hospitalization	Borderline reduction of event free 1 year survival with medical therapy (p=0.066)
								Secondary: Survival, re-infarction and revascularisation long-term (56 months)	At 56 months: significant mortality reduction with PCI (4 vs 11%). Also significant reduction in re-infarction and revascularisation.
BRAVE [23] (2005)	365 (182/183)	STEMI admitted 12-48 hours after symptom onset, no previous thrombolysis, clinical stability.	PCI:37% MED:38%	0.5-2	56.6% (only 27% had both TIMI 0 and Rentrop 0)	87.4%	3	**Primary:** LV infarct size assessed by SPECT with Tc 99m sestamibi 5-10 days post randomization	Significantly smaller infarct size with PCI
								Secondary: Death, MI or stroke at 30 days	No significant difference (arithmetic trend = 33% relative risk reduction in favour of PCI). Unplanned PCI during the 30 day follow up: PCI-1.1%, MED-32.8%.
SWISSI II [28] (2007)	201 (96/105)	STEMI or non STEMI within last three months and silent ischemia documented by stress imaging, 1 or 2 VD suitable for PCI	PCI:60% MED:61%	32	Not mentioned	0%	120	**Primary:** Death, non fatal MI, revascularisation	Significantly reduced events with PCI (hazard ratio 0.33, 95% CI 0.2-0.55, p=0.001)
								Secondary: Exercise induced ischemia, resting LVEF	Less ischemia in PCI patients (11.6% vs 28.9%, p=0.03), LVEF preserved after PCI but decline with medical therapy.

after symptom onset, could provide benefit over initial medical therapy.[3] It showed that infarct size can be significantly reduced with such a strategy, however only 56.6% of patients submitted to PCI were found with an occluded IRA (defined as having TIMI flow 0 or I) at the time of intervention. A trend towards a reduction of the composite of death, MI or stroke at 30 days was also found (relative risk reduction: 33%). *ALKK study* included 300 clinically stable patients, 8-42 days after MI.[27] The IRA was found occluded in less than one third of patients randomized to PCI or medical therapy, and PCI was related to a significant mortality reduction (4% versus 11% with medical therapy), during long-term follow up (56 months). Re-infarction and the need for revascularization were also reduced significantly. The *SWISSI II study* included 201 patients, who had ST-elevation MI (STEMI) or non-STEMI within the last three months, silent ischemia documented by stress imaging and 1 or 2 vessel disease suitable for PCI.[28] Stents were not used and patients were followed for 10 years. Death, non fatal MI or revascularization were significantly reduced with PCI (HR: 0.33), as was exercise induced ischemia. *TOPS* was a smaller study (87 patients) published in the early 90s.[26] Patients were randomized to PCI or medical therapy if at 4-14 days after thrombolysis they had a negative stress test and an IRA with ≥50% stenosis. Less than 15% of patients had an occluded IRA. Infarct free survival was somehow worse with PCI at 1 year (88.7% vs 100%), but angina-free survival was better. In general, these four studies added to the meta-analysis of Abbate et al[25] a large number of patients (n=953) with clinical scenarios more encouraging towards an interventional strategy. Their addition apparently led to an analysis with results in favor of PCI, in contrast to the study of Ioannidis and Katritsis[24] which included only studies closer to the late open artery hypothesis paradigm.

HOW TO DEAL WITH THE IRA OF A LATECOMER IN CLINICAL PRACTICE

According to the latest focused update of the ACC/AHA/SCAI guidelines[23] PCI is recommended (Class I) after successful fibrinolysis or in patients not undergoing primary reperfusion within the first 12 h, when any of the following is true: objective evidence of recurrent MI (class I, C), presence of moderate or severe spontaneous or induced ischemia after MI (class I, B), cardiogenic shock or hemodynamic instability (class I, B). Furthermore, it is reasonable to perform routine late PCI after an MI (class IIa, C) in patients with LVEF <0.40, heart failure, serious ventricular arrhythmias or even documented CHF only during the acute episode with subsequent EF >0.40. However, PCI of a totally occluded IRA >24 h after an STEMI is not recommended (Class III, B – OAT contribution) in asymptomatic patients with 1- or 2-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia.

These latest guidelines mix two groups of patients: those successfully submitted to fibrinolysis and latecomers who did not benefit from either fibrinolysis or primary PCI. In the first group there has been myocardial salvage and the latest ESC guidelines recommend routine coronary angiography and, if applicable, PCI early after effective thrombolysis (Class I, A) up to 24 h after thrombolysis independent from angina and/or ischemia.[2] The second group, latecomers who did not benefit from an early reperfusion (either thrombolysis or primary PCI), is quite heterogeneous. On the one hand and according to the guidelines, those who are clinically unstable should undoubtedly be treated with late PCI. On the other hand, those who are clinically stable can differ in many aspects: the time from symptom onset to presentation, the number of diseased coronary vessels, whether the IRA is occluded or spontaneously reperfused, the IRA territory, the presence and extent of silent or symptomatic ischemia, the presence of previously infracted myocardium, the LVEF and of course numerous other factors defining their general medical condition and their risk profile.

The OAT results,[21] further supported by the meta-analysis of Ioannidis and Katritsis,[24] are by strict terms the best evidence to date testing the late open artery hypothesis. However, their discouraging results should not be interpreted as an argument against PCI to recanalize IRAs in all MI latecomers. There is some debate on whether OAT patients are representative of real life treatment scenarios. OAT excluded those patients with post-infarction angina and/or moderate to severe ischemia. However, one-third to two-thirds of patients have residual symptomatic or silent ischemia after AMI.[29] Recruitment in the OAT study was indeed difficult and interrupted early; the explanation could be that many cardiologists believed PCI was beneficial for this group, leaving potentially less ideal candidates available for randomization. In addition, length of follow-up was limited, since less than one-half of the patients in OAT had a follow-up that reached 3 years. Of note, despite the lack of benefit concerning death, MI or NYHA class IV heart failure, there was significant relief from angina found with PCI during the first two years of follow up.

The most recent meta-analysis of Abbate et al.[25] gave results in favor of PCI for a mixed population of latecomers after MI, but only after including data from trials not suitable to strictly test the late open artery hypothesis.

The final message is that clinically stable latecomers after MI are a diverse group, and decisions about late PCI on their IRAs should be individualized. The correct approach should not be to routinely recanalize any IRA, but rather to search for correct arguments before doing so, after thoroughly but swiftly analyzing any given patient's clinical situation. For the moment the existing evidence seems still incomplete and current guidelines, although helpful, can not replace the physician's judgment in many clinical scenarios of real practice.

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