EuroIntervention

Chronic total coronary occlusions and the Occluded Artery Trial. A critical appraisal.

Gerald S. Werner[1]*, MD, FACC, FESC; Carlo Di Mario[2], MD, FACC, FRCP, FESC; Alfredo R. Galassi[3], MD, FACC, FESC; Anthony Gershlick[4], MD, FRCP, FESC; Bernhard Reimers[5], MD, FESC; George Sianos[6], MD, PhD, FESC; Horst Sievert[7], MD, PhD, FESC; Thierry Lefevre[8], MD, FESC; Nicolaus Reifart[9], MD, PhD, FESC for the EuroCTO Club

1. Klinikum Darmstadt, Darmstadt, Germany; 2. Royal Brompton Hospital & Imperial College, London, United Kingdom; 3. Ospedale Ferrarotto, Univ. of Catania, Catania, Italy; 4. Univ. of Leicester, Leicester, United Kingdom; 5. Ospedale di Mirano, Venice, Italy; 6. Thoraxcentre, Erasmus University, Rotterdam, The Netherlands; 7. Katharinenhospital Frankfurt, Frankfurt, Germany; 8. Institut Cardiovasculaire Paris Sud, Massy, Paris, France; 9. Main-Taunus-Klinik Bad Soden, Germany

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One of the highlights of the recent AHA 2006 was the long-awaited presentation of the Occluded Artery Trial (OAT)[1], a commendable effort of a large group of investigators headed by Dr. Judith Hochman to address the open artery hypothesis[2] in a large-scale randomised trial. Within only few months, several editorials and comments in various journals took up the presented data and drew often far-reaching conclusions on the futility of treating occluded coronary arteries in general[3,4]. This included also chronically occluded arteries (CTOs), which are by definition arteries occluded for more than three months and supplied by collateral arteries[5]. But these lesions were not included in OAT, a study dealing with recent occlusions post-MI[6].

The open artery hypothesis was a widely accepted concept despite the absence of confirmation from randomised controlled trials[7]. The question now arises whether the new data presented by the OAT trial indeed replace and forfeit the open artery concept. The present comment and discussion of the OAT trial will address these issues on the basis of a critical analysis of the published data, and discuss strength but also pitfalls and shortcomings of these data. We will also try to better define the patient population for whom the conclusions drawn by the authors and commentators are applicable.

The OAT results

In OAT patients with a recent myocardial infarction (MI) of 3-28 days with angiographically confirmed diagnosis of an occluded infarct-related artery, were randomised to medical treatment or to an interventional attempt to open the occluded infarct-related artery. During a mean follow-up of approximately three years there was no advantage of the interventional approach in terms of survival and there were more recurrent MIs than with the conservative approach[1]. These data were further corroborated by a substudy conducted in Canada, the TOSCA-2 trial, which looked at changes of left ventricular function during follow-up, and observed a slight improvement of LV function over time but no difference between the treatment arms[8].

The validity and integrity of these data are not questioned, but there are considerable issues with their generalisation to daily clinical practice. There is no doubt that primary PCI for acute MI is lifesaving in the short and long-run, proven by several randomised trials with different time windows after symptom onset[9,10]. Also, in patients with no access to primary PCI within 90 min and therefore treated with thrombolysis, there is concordant evidence from the randomised studies[11-14] that the transfer to angioplasty in the first 24 hours is clinically beneficial. There are clear indications to primary PCI or early angiography and angioplasty after thrombolysis

* *Corresponding author: Medizinische Klinik I, Klinikum Darmstadt, Grafenstrasse 9, D-64283 Darmstadt, Germany*
E-mail: gerald.werner@klinikum-darmstadt.de

in the current guidelines. If the guidelines are properly applied, only a minority of AMI patients are likely to still have an occluded artery after three or more days from the acute episode and then meet the eligibility criteria for OAT.

OAT and subacutely occluded arteries after MI

A total of 2,166 patients finally enrolled during five years in 217 centres which was lower than originally planned, yet still ranks this study among the largest interventional studies. Yet, those randomised represent a small highly selected group of the population actually treated in the participating centres. This important information is essential; studies like the recent COURAGE trial, when less than 6% of patients screened were actually enrolled, are unlikely to have general application for a population of patients with chronic angina[15]. The OAT publication lacks important information – that is the number of patients screened and potentially eligible and why they were not enrolled – especially when only one patient per year and centre was enrolled in the US. The low inclusion number per centre in a population which is probably more common in clinical practice suggests that the patients finally randomised were highly selected patients, and that the screening process before randomisation was subjective and not transparent to the reader of the paper. The inclusion criteria should guarantee a high-risk study population, but one of the two major risk criteria, a moderately impaired ejection fraction <50%, was present in only about half of all patients, and a more severely reduced ejection fraction of below 40, was present in just 20%. The overall mortality was 9% within four years, which is surprisingly low and atypical for a post MI patient group. This suggests, that the study group was in fact not a high-risk subset.

This was most probably driven by the tendency of the investigators to include patients rather selectively in the trial. The high prevalence of single-vessel disease (85%) is not typical of an infarct population and demonstrates that patients with advanced disease were not considered for randomisation[16]. The initial power analysis expected a 3-year event rate in the medical group of 25%, the actual rate was only 15.6% after four years, which leaves the study statistically underpowered. And in fact, no conclusion should be drawn from a study which is underpowered.

The patient population was defined to represent occluded arteries after an acute MI within four weeks, but the actual time delay was eight days as median. None, or only mild ischaemia in the territory supplied by the occluded artery was present in 90% of the patients enrolled, and this was tested in only one fourth by an actual stress test. How the presence of ischaemia was determined in the other patients is not explained.

Only 20% of patients had undergone thrombolysis, whereas we should expect the standard of care to be PCI or at least thrombolysis for acute MI, and a population like this – with recent MI – should become the exception rather than the rule in developed countries. For acute MI interventions our accepted goal is to achieve TIMI 3 flow which is achieved in about 95% of patients, and it is not acceptable as standard of care that TIMI 2 flow was considered a successful PCI result in OAT. We learned from the thrombolysis era that TIMI 2 flow does not translate into a good clinical outcome[17]. In fact, in almost 20% of patients even TIMI 2 flow had not been achieved, which represents a low interventional success rate, impacting the intention-to-treat based outcome analysis. Furthermore, the long-term patency achieved with PCI was low as reported in the TOSCA-2 substudy with TIMI 3 in only 75% of patients[8].

One other issue that is not mentioned in the publication, nor in the comments, is the fact that the study reports a 5-year follow-up, but only 45% of the patients had even completed the 3-year follow-up, and just 25% were into the five years of reported follow-up duration. Based on the study hypothesis, a prognostic intervention would require a longer follow-up to show effects if the individual patient risk is as low as in OAT.

OAT and the conclusions from non-significant results

Based on the results achieved in the interventional arm of an obviously low-risk population of asymptomatic post-MI patients, the authors conclude that PCI should not be recommended in this setting. They state that nonfatal MI tended to be increased after PCI (p=0.08) and this was the concluding remark in the abstract, a questionable statement to highlight a trend when a large study of more than 2,000 patients did not yield statistically significant endpoint results, and the prespecified power was not achieved. Furthermore, the PCI success rate, per se, was lower than one would expect in these subacute occlusions, with a considerable number of periprocedural MIs. Both factors would attenuate any possible beneficial effect of PCI in these patients.

The way the results were interpreted, which was not supported by statistical significance, is not acceptable and reveals an underlying bias on the part of the authors. Should we not also accept the fact that, based on OAT, both strategies are equal regarding hard endpoints (death and MI)? Based on the OAT results, the physician can discuss with his patient who had an acute MI on his holiday trip and returned to undergo a diagnostic procedure one week after the event to find a proximally occluded LAD, whether or not to leave this situation as it is, or to reopen it. He should inform his patient that no proven benefit was observed within two to three years of follow-up in a randomised study, but that there is no severe disadvantage to be expected. Furthermore, if we cannot stop atherosclerotic progression in this patient – and who can guarantee this today? – there is the risk of another event in the future with a higher fatality if there is already an occluded artery[16,18].

TOSCA-2 and the open artery hypothesis

One key concept of the open artery hypothesis is the improvement of LV function after late reopening of an infarct-related artery. The benefit of such an intervention was not observed in the TOSCA-2 trial, as a moderate improvement of LV function was observed also in the conservatively treated study arm. However, the interventional success in these subacute MI patients was less than what we would consider optimal for PCI in acute MI. In one of the recent acute MI trials, TIMI 3 was achieved in 95% of lesions[19], in TOSCA-2, this was observed in only 85%. Furthermore, in an era where we achieve a consistent vessel patency even in the more challenging

CTO lesions of 95%[20,21,22,23], TOSCA-2 patients had TIMI 3 flow only in 75% at the time of follow-up angiography. The above-mentioned failure to achieve a contemporary success rate in the TOSCA-2 lesions may impair the actual assessment of the benefit of the open artery hypothesis. In fact, the analysis of LV remodelling in patients with patent versus occluded infarct related lesions at follow-up, irrespective of the treatment arm, showed a highly significant beneficial effect on LV volume after one year with lower end-systolic and end-diastolic volumes[8].

OAT and CTOs

While we have clear evidence for the benefit of acute PCI treatment for acute MI, OAT shows that delayed revascularisation of occluded infarct related arteries does not provide a prognostic benefit, at least in a patient subset that fulfils the clinical characteristics of the OAT population. We have to acknowledge that we have no randomised trial for even later intervention in occluded arteries, which are termed chronic total coronary occlusions (CTOs) if the occlusion duration is more than three months[5]. Should – or can – the findings of OAT as the single multicentre, randomised trial in sub-acutely occluded infarct-related arteries be extended to actual chronic occlusions?

The indication to reopen a CTO is a disputed subject in interventional cardiology. In the most recent PCI guidelines, patients with a CTO would represent typically patients with stable angina who would be eligible for a PCI according to the criteria for stable angina lesions. In addition, if the PCI of the CTO is considered to have a low success rate it is not advised to do perform PCI[24,25].

A recent review of the PCI experience at the Mayo Clinic over the past decades reveals that CTOs make up less than 5% of their PCI procedures[26,27]. On the other hand, CTOs are found in a large fraction of patients with stable angina[28,29]. In general, the major reason for this is that the PCI of a CTO is a complex, time and resources consuming procedure with a low procedural success rate, which requires , as well, more than average interventional skills and continuous and on-going personal experience of the operator[30,31]. Randomised trials to show clinical benefit for the recanalisation of long-term occluded arteries are lacking, but the available non-randomised long-term registries totalling more than 4,000 patients unanimously show even a benefit regarding the hard endpoint of survival, but are not unanimously accepted as clinical evidence[32,33]. Still, registry data are accumulating, underscoring what sound clinical reasoning would suggest, e.g. that the presence of a CTO will put a patient at considerably higher risk if he experiences an acute MI in one of the remaining open arteries. Two independent studies showed a three-fold increase in mortality in patients with a CTO and a subsequent acute MI[16,18]. The recently published analysis from the New York State Survey showed that incomplete revascularisation by PCI leaving a CTO untreated led to higher mortality... even during a short follow-up of three years[34].

Are these data invalid now after OAT?

The answer must be... No.

First of all OAT did not include CTOs, and the given angiographic characteristics in OAT and TOSCA-2 are atypical for CTOs. Patients with a CTO entered into studies and registries have a prior STEMI only in about 50% of the cases, less than half have severe LV dysfunction, and the majority have multivessel disease[23,35-37]. One of the reasons why a prior MI is not mandatory for a CTO are well-developed collateral networks, which may have been present already at the time of an acute occlusion and helped to preserve LV function and viability[38]. In OAT, almost all patients had either no visible collaterals or Rentrop grade 1 collaterals, whereas in CTOs 85% of collaterals are of Rentrop grade 3[39]. In general, CTOs with no or very poor collateralisation (Rentrop 0 and 1) are not considered good candidates for a PCI attempt[5].

Summary

The OAT trial and its angiographic substudy TOSCA-2, along with a number of published commentaries, represents examples of over-interpretation of clinical study results. A study that achieved no statistically significant result for any of the study endpoints can only claim to have proven that their null hypothesis cannot be rejected. The lack of power due to a reduction of patient numbers by one third, and an unexpected low event rate, makes it not unlikely that another trial would be able to disprove the null hypothesis. These statistical facts should be accepted by the authors and commentators. Instead, the inconclusive results were interpreted in such a way that they might apply to patient populations which had not been represented in the original trial (like CTOs without prior MI, or with viable myocardium), or for patients who could have been included, such as multivessel high risk patients, but had not been so by the investigators choice. Furthermore, major problems of the study are ignored, such as accepting TIMI 2 flow as a procedural success.

Conclusion

The OAT Trial is a valid addition to the data we have to answer the open artery hypothesis early after an acute MI, but only for those patients within the limits of its inclusion criteria. The study will find its way into future guidelines for interventional therapy, but caution needed not to misinterpret the study results. Interventional therapy needs to be based on evidence based medicine (EBM), which was defined by Dr. Sackett as a conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients[40]. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research. The OAT trial does not add any valuable data in our decision to revascularise a CTO, and the concept of the open artery based on clinical pathophysiology and non-randomised data, as discussed above, still hold true for CTOs and determines good clinical practice.

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