underestimate can be created. Using estimates from a long-term trial creates a downward bias in the event rates and potentially affects the results and interpretation of a meta-analysis. Furthermore, potential imbalances in the pattern of events and censoring will change the relative rates between the 2 groups.

A meta-analysis of all open artery hypothesis trials is certainly reasonable, although the OAT and TOSCA-2 studies will dominate such analyses of clinical outcomes and function respectively because of their large numbers. A recently published meta-analysis of the 6 trials that included only studies of patients with total occlusions showed no effect of the study intervention on death, MI, heart failure, or their composite (10). The Abbate et al. (1) meta-analysis, with its selective inclusion and exclusion of studies, methodological limitations of aggregate, nonpatient level data, and the marked and statistically significant heterogeneity of populations, duration of follow-up and of treatment effect, contributes little to inform medical practice.

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Reply

We welcome the letter of Dr. Džavík and colleagues and other OAT (Occluded Artery Trial) study investigators in reference to our recently published report (1) as it presents an occasion to discuss, in a scholarly manner, the benefits of late revascularization of the infarct-related artery (IRA) in patients with acute myocardial infarction (AMI).

While Dr. Džavík and colleagues state that our meta-analysis "misses the mark," we conversely believe that they may have missed the point of our analysis. This meta-analysis is not meant to be an alternative to the OAT study but rather an integration of available information to medical practice with a diverse assessment of the question of whether revascularization of the IRA should be attempted in patients presenting >12 h after AMI. This study is not meant specifically to investigate whether there is a clinical correlate to the "open artery hypothesis" (2), although in some ways its findings support such hypotheses.

The OAT study (3) was designed to clinically test the "open artery hypothesis" but failed to show any benefit or harm from late revascularization. Enrollment, however, was stopped early, events were fewer than anticipated, median follow-up was <3 years, and the cardiology community expressed concerns regarding the applicability of the results to real-life scenarios. No detailed registry of the screened patients has been taken in order to appraise the external validity of the trial and compare outcomes of randomized versus nonrandomized patients. It is unclear whether many occlusions that were deemed feasible and functionally important were immediately attempted (thus excluding them from randomization), with potentially less ideal candidates available for randomization.

Approximately 1 year after publication of the OAT study, the SWISSI II (Swiss Interventional Study on Silent Ischemia Type II) study (4) showed a survival benefit for patients with inducible ischemia after AMI randomized to late revascularization of the IRA. Therefore, we attempted to put these disparate results into perspective using the meta-analytic technique with the belief that inclusion of multiple trials in the meta-analysis may reduce the enrollment bias by including more investigators and different patient pools, including patients with different degrees of IRA stenosis.

We agree that our analysis is characterized by heterogeneity among studies but we see this not as a flaw in the design but rather an opportunity to detect differences in study designs, study population, and, ultimately, results. We included in the analysis 10 studies randomizing patients to late revascularization of the IRA or

medical therapy only. Four studies including 910 patients did not require angiographic determination of total occlusion before randomization resulting in the inclusion of some patients with subtotal occlusion. Nevertheless, 84% of patients in the meta-analysis had total occlusion, making it unlikely that the mortality benefit was driven exclusively by the 16% of patients with subtotal occlusion. Dr. Džavík and colleagues criticize this approach as they think the analysis should have been limited to the 6 studies with total occlusion. The criticism of mixing apples with oranges is not uncommon but fails to appreciate the value of the meta-analytic technique. While the presence of heterogeneity in a meta-analysis requires more conservative tests to be performed (random effects vs. fixed effects), it does not jeopardize the results of the analysis while providing an opportunity for meta-regression looking for covariables that may explain why different studies provided different results (5–10). Using a metaphor, we argue that patients are apples and oranges with many individual characteristics. Thus, a study on only apples may not be useful when dealing with oranges, whereas a study on fruit in general may be equally applicable and appropriate for making inferences on apples as well as oranges. We felt that it was better to include all studies and all patients, and then perform a meta-regression to identify potential cofactors. If we had not included the 4 studies we would have missed an opportunity to analyze outcomes of 910 patients the majority of which did have total IRA occlusion. The results of our analysis suggest that, although a benefit exists in the entire cohort of patients, those studies with more liberal angiographic inclusion criteria were more likely to be positive than those with more strict criteria, and, therefore, we learned not only that late revascularization was associated with improved survival but also that patients with subtotal occlusion may benefit the most. These findings are consistent with the results of 2 individual studies, the ALKK (Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte) study (11) and the SWISSI II study (4), which enrolled patients late after AMI independent of IRA status and showed a survival benefit for late percutaneous coronary intervention. Furthermore, we are not sure that total and subtotal occlusions are 2 different disease processes as we believe that they are 2 presentations of the same process and that significant functional and clinical overlap exists between the 2 conditions.

Dr. Džavík and colleagues challenged our choice of studies to be included stating that "thousands of additional patients in post-MI revascularization studies" could have been included. They fail to quote such studies. Perhaps they refer to the numerous studies addressing the value of an early invasive versus early conservative strategy for patients with acute coronary syndromes (12). If this were the case, we would point out that such studies did not randomize patients to late revascularization of the IRA after AMI but rather on early and elective angiography versus delayed and selective angiography in such patients, therefore not addressing the question of whether revascularization of the IRA should be attempted >12 h after AMI.

Dr. Džavík and colleagues also quote a recent meta-analysis by Ioannidis et al. (13) recently published in the *American Heart Journal*, which we have commented on in a letter to the Editor (14). While we first disagree with the authors of the meta-analysis regarding the inclusion of the TOAT (The Open Artery Trial) study (15), which had no true baseline cardiac dimension and function assessment, most importantly we disagree with the overly pessimistic interpretation of their results. Despite inclusion of the TOAT study (15), the meta-analysis showed a 2% greater improvement in left ventricular ejection fraction (LVEF) with late revascularization demonstrating, in our opinion, that a benefit indeed exists. Moreover, the relative improvement in ejection fraction goes up to 3% and an approximate 10% reduction in ventricular volumes if the TOAT study is excluded, as we published in a meta-analysis dedicated to assess effects on cardiac remodeling and function in patients with total occlusion published in *Catheterization and Cardiovascular Intervention* (16). Furthermore, neither our meta-analysis (1) nor the one from Ioannidis et al. (13) confirmed the disturbing trend observed in the OAT trial (3) regarding an increase in recurrent myocardial infarction in revascularization patients, which at least supports the safety of a revascularization approach. Regarding the TOAT study (15), we dedicated an entire paragraph in our discussion to the exclusion of this study. What was unexpected in the TOAT study was that while revascularization patients had adverse remodeling they experienced an improvement in functional capacity. After contacting the TOAT investigators, we decided not to include the TOAT data because a potential early recovery in the revascularization arm could have occurred before the "baseline" assessment, thus, biasing the results. Interestingly enough, a substudy of the TOAT study showed that patients with a significant amount of viable myocardium showed more favorable remodeling after revascularization suggesting that a subgroup of patients may indeed benefit from late revascularization (17). The TAMI-6 (Thrombolysis and Angioplasty in Myocardial Infarction-6) study was excluded because randomization occurred 6 to 24 h after AMI (18). Regarding the inclusion of the BRAVE-2 (Beyond 12 Hours Reperfusion Alternative Evaluation) trial (19), we wish to make a simple consideration that only 8 patients received bypass surgery rather than percutaneous coronary intervention (which is unlikely to have changed the 42-day outcome).

The comments regarding the use of statistical methods to compare means rather than individual patient data is a method accepted by most statistical authorities (20,21). We realize that the presence of paired data or individual patient data would have been optimal, but such data were not available even after contacting the principal investigators of the individual studies, including the very same Drs. Džavík, Steg, and Hochman. The bias toward healthier patients in repeated analysis is inevitable but likely equally distributed between the 2 groups or perhaps more prominent in the group with more events. Specifically, all patients in the SWISSI II trial (4) that had an event were censored from the analysis of LVEF. Considering that significantly more patients had an adverse event in the medical group, less patients had available data at follow-up in the medical group (36% vs. 72%). If we assume that only the healthier patients had a repeat LVEF assessment, it is obvious that this may have lead to an overestimation of LVEF in the medical group more so than in the interventional group, thus rendering the analysis even more conservative. The comment on the Kaplan-Meier curve is incomplete if the authors fail to recognize the limitations of the Kaplan-Meier curve, especially when curves are extended beyond median survival (22,23).

In conclusion, our meta-analysis presents an overview of the effect of late revascularization including the largest number of patients to date (3,560 patients). We demonstrate that revascularization of the IRA beyond the 12-h limit is associated with a survival benefit. This observation is not in contrast with the OAT study but rather shows that some patients may benefit more than others. The same OAT study showed (in the online supplement data only) that there was a benefit in terms of angina reduction

with revascularization up to 24 months, and in the TOSCA-2 (Total Occlusion Study of Canada) trial (24), a substudy of the OAT study, there was a trend toward more favorable remodeling.

The results of the OAT study do not prove or disprove the benefits of late revascularization in patients similar to the patients in the OAT study and certainly do not apply to the entirety of post-AMI patients. Unfortunately, despite the efforts of investigators like the OAT Investigators, only 3,560 patients have been randomized to date, and they may not be enough to draw meaningful conclusions and/or identify subgroups of patients with greatest benefit or risk from late revascularization.

We thank Dr. Džavík and colleagues for this opportunity to clarify that our analysis was not designed to prove or disprove the findings of the OAT study, which likely applies to a minority of patients after AMI. Instead, we set out to analyze all available evidence and demonstrated the benefit of late revascularization of the IRA late after AMI.

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Percutaneous Coronary Intervention or Coronary Artery Bypass Graft for Unprotected Left Main Coronary Artery Disease: The Endless Debate

The "state-of-the art" paper written by Taggart et al. (1) calls into question the current evidence in support of percutaneous coronary intervention (PCI) for the treatment of unprotected left main stem disease. In view of the fact that current guidelines still indicate coronary artery bypass grafting (CABG) as the "standard of care," the authors conclude that the use of drug-eluting stents (DES) in "off-label" cases should be discouraged and that good surgical