

Transient ST-segment myocardial infarction: a new category of high risk acute coronary syndrome?

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Online publish-ahead-of-print 15 November 2018

This editorial refers to ‘Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial’[†], by J. S. Lemkes et al., on page 283.

Timely reperfusion is the foundational management principle for ST-segment myocardial infarction (STEMI), due to a rapid decline in salvageable myocardium in the first 4–6 h after symptom onset.¹ Primary percutaneous coronary intervention (PCI) is the preferred therapy when performed within 90–120 min of diagnosis.² In the absence of ST elevation, an early invasive strategy is recommended for higher-risk non-ST elevation acute coronary syndromes (NSTEMI-ACS), with the dominant benefit seen in reducing recurrent or refractory ischaemia.^{3–6}

But what is the appropriate strategy for STEMI patients with spontaneous resolution of symptoms and ST segment elevation prior to reperfusion therapy, referred to as transient STEMI? There are very few data concerning this group. Even the scope of this issue is fairly undefined. In a single-centre observational study, 63 of 1244 (5%) patients presenting with STEMI over 6 years had transient STEMI.⁷ In a randomized trial of NSTEMI-ACS patients in Europe, nearly one-quarter of patients had transient ST elevations.⁸ If these estimates are correct, with more than 600 000 myocardial infarctions (MIs) per year in the US,⁹ the incidence could range from 30 000–150 000 per year.

Data concerning management for this group of patients are even more sparse. One might reasonably consider whether these now-asymptomatic patients with resolved ST elevations can be safely treated as patients with NSTEMI-ACS. In a *post hoc* analysis from the ELISA-3 (Early or Late Intervention in High-Risk Non-ST-elevation Acute Coronary Syndromes-3) trial of early vs. delayed angiography in patients with high-risk NSTEMI-ACS, there was no significant benefit seen with early angiography in the subset of patients with transient STEMI for the primary endpoint of death, reinfarction, or recurrent ischaemia.⁸ There are also hypothesis-generating observational data

that raise the possibility that delaying intervention may reduce thrombus burden, and the likelihood of no-reflow and other procedure-related complications in patients with TIMI III flow at the time of angiography.¹⁰

In this context, in this issue of the *European Heart Journal*, Lemkes and colleagues present results of the Timing of revascularization in patients with transient ST-segment elevation myocardial infarction (TRANSIENT) trial, the first randomized, controlled trial of an immediate vs. delayed invasive strategy in patients with transient STEMI.¹¹ Adult patients (N=142) with an initial STEMI presentation, followed by complete resolution of symptoms and ST elevation, were randomized to an immediate angiography strategy vs. a guideline-recommended strategy for NSTEMI-ACS with angiography within 24 h for patients with an elevated Global Registry of Acute Coronary Events (GRACE) score (> 140) or within 72 h for lower-risk patients. The primary endpoint for this comparison was the size of myocardial infarction as a percentage of the left ventricular mass as measured by cardiac magnetic resonance (cMR) imaging on day four. The authors hypothesized that delaying intervention would reduce infarct size, and the analysis was designed to test the superiority of this strategy.

So how did these two groups of patients do? First, with respect to the primary endpoint, the infarct size was 1.3% [interquartile range (IQR) 0.0–3.5%] of left ventricular mass in the immediate angiography group vs. 1.5% (IQR 0.0–4.1%; *P*=0.48) in the delayed group. Critically, this turned out to be a much smaller infarct size than anticipated (a mean infarct size of 10% in the immediate angiography group was assumed). The first implication is that the study was therefore under-powered for the primary endpoint and needs to be interpreted in that context.

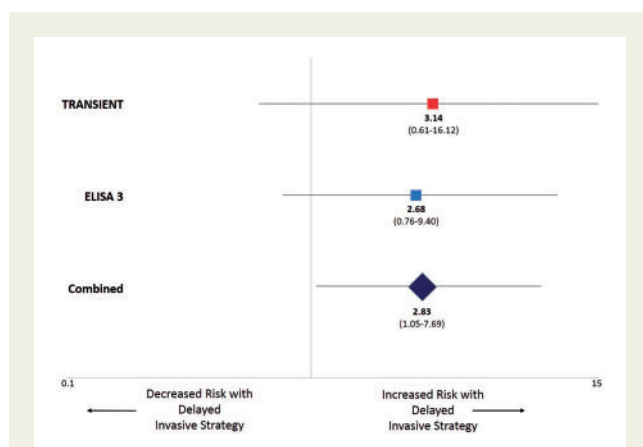
The second important observation from the primary endpoint is that these patients with transient STEMI and Killip class I have small infarcts. cMR is the gold standard for the quantification of infarct size and the timepoint of 4 days from presentation is in line with published data, so we can have confidence in this observation.¹² Further, cMR

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

[†] doi:10.1093/eurheartj/ehy651.

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Take home figure Odds ratios (95% confidence intervals) for major adverse cardiovascular events at 30 days for the TRANSIENT trial and the Early or Late Intervention in High-Risk Non-ST-elevation Acute Coronary Syndromes-3 (ELISA 3) trial, along with a meta-analysis using a random effects model. ELISA: Early or Late Intervention in High-Risk Non-ST-elevation Acute Coronary Syndromes-3; TRANSIENT: Timing of revascularization in patients with transient ST-segment elevation myocardial infarction.

has been shown to be a reasonable surrogate marker for subsequent clinical events.¹²

These findings support the combination of symptoms and ST segment abnormalities as reliable markers of TIMI flow status in a contemporary cohort of acute MI patients receiving upfront P2Y12 inhibition. This point should not be taken for granted. It is reassuring and quite clinically relevant to see that only one patient in the immediate angiography group, and no patients without recurrent symptoms in the delayed angiography group, had TIMI 0–1 flow.

There are some important additional issues raised by the findings. First, randomization to immediate vs. delayed angiography led to a divergence in medical treatment and revascularization strategy. Patients in the early angiography group were more frequently treated with bivalirudin rather than heparin or fondaparinux, and were more likely to receive PCI than patients in the delayed angiography group. Conversely, patients with delayed angiography received more bypass surgeries than did immediate angiography patients. These differences point to the real clinical implications of a decision to manage a patient as a STEMI with immediate angiography vs. NSTEMI-ACS with delayed angiography. This study was not designed to assess the effects of these differences in non-randomized treatments, but the downstream divergence in care emphasizes the importance of choosing an appropriate upfront treatment strategy.

Finally, it is intriguing that the authors structured the trial to show the superiority, rather than non-inferiority, of a delayed angiography strategy. While the results were neutral overall, there are concerning signals in this under-powered trial. There were trends toward larger infarct size with delayed angiography, both by cMR and integral high-sensitivity troponin concentration, as well as toward higher rate of major adverse cardiovascular events (MACE) (8.5 vs. 2.9%; $P=0.28$) in the delayed group. This latter figure includes the four patients randomized to delayed angiography who underwent urgent revascularization for recurrent ischaemia, and mirrors a trend observed in

the ELISA-3 *post hoc* analysis of transient STEMI patients (*Take home figure*).⁸ As recurrent ischaemia is the principle event reduced by early intervention in NSTEMI-ACS, these are important endpoint events occurring with delayed angiography and there is a consistent signal for harm now from two data sources (*Take home figure*). Just because the analysis for superiority in this trial was neutral does not imply that non-inferiority has been demonstrated in this small group.

In summary, Lemkes and colleagues have added appreciably to the understanding of a perplexing clinical scenario. They have shown that stable patients with transient STEMI are an overall low-risk group with small infarcts, and that the upfront treatment strategy has important downstream implications for medical therapy and revascularization. Further, symptoms and electrocardiogram findings, the bedrock of clinical assessment in acute MI, remain excellent predictors of TIMI flow grade in a contemporary cohort of patients receiving early P2Y12 inhibition. Importantly, however, the safety of a delayed approach to angiography in this cohort remains in question, as there were trends toward larger infarcts and more frequent ischaemic events in this under-powered analysis in which non-inferiority was not tested. Even so, Lemkes and colleagues should be commended for a well-executed trial in a novel population with important clinical ramifications.

Conflict of interest: Dr Bergmark reports personal fees from Janssen Pharmaceuticals, personal fees from Daiichi Sankyo, grants from MedImmune, personal fees from Quark Pharmaceuticals, personal fees from Abbott Vascular, outside the submitted work. Dr Faxon reports other from Boston Scientific, other from Medtronic, other from AKEBIA, other from Baim Institute, outside the submitted work.

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Corrigendum

doi:10.1093/eurheartj/ehy384
Online publish-ahead-of-print 26 June 2018

Corrigendum to: Initiating anticoagulation with the intention of cardioverting: does drug choice matter? [*Eur Heart J* 2018;**39**:2972–2974].

The authors wish to apologize for the following error: in the reporting of embolic and bleeding events, '6 strokes (6 apixaban vs. 0 heparin/VKA)' was stated instead of '6 strokes (6 heparin/VKA vs. 0 apixaban)'. This has now been corrected online and in print.

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