Timing of Invasive Strategy in Non-ST Elevation Acute Coronary Syndrome: Risk and Reward?

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The optimal timing of an invasive strategy (IS) in non-ST elevation acute coronary syndrome (NSTE-ACS) remains uncertain. Consecutive randomised controlled trials (RCTs) and aggregate meta-analyses deliver a consistent message – no differences in hard clinical outcomes are demonstrated between early and delayed IS in unselected NSTE-ACS patients.[1] However, baseline risk for future ischaemic events and death may correlate with improved clinical outcomes following early IS and subsequent revascularisation. Despite the potential benefit of risk scores to direct therapeutic management, use of stratification criteria such as the Global Registry of Acute Coronary Events (GRACE) score are not commonly used in clinical practice and given a class IIa, level of evidence B recommendation in European Society of Cardiology (ESC) guidelines.[2] We read with interest comments by Aladin *et al* that highlight important and unresolved issues in this space.

While the authors correctly identify the limitations of our meta-analysis published in the *European Heart Journal*,[1] heterogeneity in timing of IS, patient risk profile, pharmacotherapy and devices were acknowledged in the original article. It is necessary to accept such deficiencies in a meta-analysis encompassing twenty years of RCT data. However, we agree that these limitations support the need for a contemporary RCT that tests modern care and therapeutics.

The concern expressed for those patients lost to follow-up when using relative risks (RR) in our statistical model is noteworthy. We conducted subgroup analyses stratified by length of follow-up which did not show any meaningful difference to the estimated effect size nor alter statistical significance of the results for the primary outcome of all-cause mortality:

- short term (30 days) including three RCTs, RR: 1.17 (95% CI: 0.25–5.48)

- medium term (>30 days to 12 months) including 11 RCTs, RR: 0.85 (95% CI: 0.68–1.06)
- long term (>12 months) including 5 RCTs, RR: 0.93 (95% CI: 0.77–1.13)

Furthermore, the RCTs included in our meta-analysis reported differing statistics (i.e., hazard ratio (HR), odds ratio), therefore the calculation and use of RR afforded appropriate pooling of data. Estimates for HR are only valid under the assumption of proportionality, which was not assessed in all included RCTs.

In our opinion, the current class I (level of evidence A) ESC NSTE-ACS guideline recommendation that high-risk NSTE-ACS patients should undergo an early IS within 24 hours is flawed. Level of evidence A recommendations should be derived from multiple RCTs or meta-analyses. Yet, the only data to inform such an approach are hypothesis generating subgroup analyses (GRACE >140) of the TIMACS and VERDICT studies.[3, 4] We agree with Aladin *et al* that more robust data for specific risk-stratified NSTE-ACS patients are required. The RapidNSTEMI trial (NCT03707314), a pragmatic multicentre RCT of very early "STEMI-like" IS versus delayed "standard of care" IS in GRACE 2.0 score stratified NSTE-ACS patients is due to report later this year.[5] Although terminated early due to the impact of COVID-19 pandemic following enrolment of 425 patients, it will inform future discussions and provide a significant contribution to future patient-level meta-analyses of this higher-risk NSTE-ACS population.

497 words

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