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EDITORIAL COMMENT

Invasive Strategy After Non–ST-Segment Elevation Acute Coronary Syndrome

Timing and Controversies*

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An invasive strategy is the preferred modality in the majority of patients presenting with a non-ST-segment-elevation acute coronary syndrome (NSTE-ACS). Its timing has been controversial and the subject of several investigations. In particular, early invasive strategy (EIS), defined as coronary angiography within 24 h after NSTE-ACS with intent to perform revascularization, has generated concerns regarding its safety, benefits, and cost effectiveness.

THE CURRENT META-ANALYSIS

In this issue of *JACC: Cardiovascular Interventions*, Bonello et al. (1) conducted a meta-analysis of 10 randomized controlled clinical trials (RCTs) to compare early versus delayed invasive strategies after NSTE-ACS. Their report, inclusive of 6,397 subjects, demonstrates no differences in mortality, myocardial infarction (MI), or major bleeding. EIS was however associated with a 45% statistically significant reduction in recurrent ischemia or refractory angina, and shorter length of stay (LOS) by a median of 2.3 days.

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STRENGTHS AND LIMITATIONS. The authors are to be congratulated on their excellent work. They did a comprehensive search, adhered to the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols) reporting guidelines (2), and utilized the Cochrane Collaboration guidelines (3) to assess study quality and risk of bias. They also used the robust random effects model uniformly, regardless of statistical heterogeneity, and corroborated their findings by sensitivity analyses.

However, their report has several limitations. It has biases inherent to literature-based aggregate data meta-analyses. The lack of individual patient data precludes more granular analyses. Extensive heterogeneity exists with respect to timing of invasive strategy and other study characteristics. The lower range limit for the time between randomization and angiography was 20.5 h in the delayed invasive group, which likely underestimates the effects of EIS. The included studies had variable recruitment periods (as early as 2000 to 2001), with the earlier ones being currently largely outdated. For instance, the median LOS in the EIS group was 4.7 days (1), while a more contemporary analysis showed a median LOS of 3 days after NSTE-ACS (4). The lack of uniformity in the definitions of MI and bleeding, and the variability in follow-up (1 to 48 months), are also noteworthy.

CONTRIBUTIONS AND IMPLICATIONS. Bonello et al. (1) added 3 RCTs and 1,027 subjects to the meta-analysis by Navarese et al. (5). The findings of both reports remain however largely similar. The current meta-analysis basically reaffirms that EIS is not associated with significant differences in hard outcomes and only a significant reduction in recurrent ischemia, compared to a delayed strategy (1). It added the salubrious finding of shorter LOS with EIS (1).

Bonello et al. (1) added only 48 mortality events to the earlier meta-analysis (a 21% increase in the

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primary endpoint). Their meta-analysis still remains probably underpowered to detect a mortality difference. However, given the reduction in the summary effect size for mortality and narrowing of its confidence interval with the added trials, and given the concordant lack of effect across all studies, it is highly unlikely that a mortality difference truly exists between both strategies. After all, routine invasive strategy after NSTE-ACS has not been shown to reduce mortality when compared to an ischemia-guided strategy (6,7), and it is improbable that an early compared to a delayed invasive strategy will have such an effect (except possibly in very selective patients). A substudy from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial showed that delay to percutaneous coronary intervention >24 h after NSTE-ACS was significantly associated with increased 30-day and 1-year mortality, and was an independent significant predictor of both outcomes (8). These post hoc findings were however fraught with bias and likely driven by unmeasurable differences in risk profiles despite robust multivariable adjustment (8).

The current report (1) demonstrates a reversal in trend (albeit still statistically insignificant, and with notable between-study heterogeneity) toward reduced MI with EIS compared to the earlier meta-analysis (5). Importantly, 3 RCTs demonstrated a significant reduction in MI with EIS, of which 2 were the contemporary SISCA (Invasive Strategy in Acute Coronary Syndrome) and RIDDLE-NSTEMI (Randomized study of Immediate versus Delayed Invasive Intervention in patients with Non ST-segment Elevation Myocardial Infarction) trials (9,10). Whether this indicates a potentially emerging signal of MI reduction remains to be proven in future trials. A reduction in recurrent MI with EIS is certainly plausible: subjects in TIMACS who experienced a refractory ischemia had a significant fourfold increase in subsequent MI (11). The TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial, the largest RCT in the meta-analysis, was itself relatively underpowered (11).

ADVANTAGES OF THE INVASIVE STRATEGY

NSTE-ACS usually occurs following coronary plaque disruption (e.g., rupture, erosion) and superimposed thrombus formation. This results in significant but incomplete obstruction of the coronary artery, acute imbalance in myocardial oxygen demand-supply, and subsequent myocardial ischemia. Optimal medical therapy with antithrombotic and anti-ischemic medications helps stabilize the culprit lesion and mitigate ischemia. However, despite advances in the medical armamentarium, mechanical recanalization of the infarct-related artery with scaffolding of the disrupted plaque (predominantly via percutaneous coronary intervention/stenting) remains the definitive therapy for NSTE-ACS: it ensures restoration of optimal coronary blood flow, prevents reocclusion, and reduces recurrent events. Coronary artery bypass graft, the other revascularization modality, is performed nowadays in ≤10% to 20% of NSTE-ACS patients. Notably, both revascularization modalities require a guiding coronary angiography, which is the defining cornerstone of the invasive strategy.

Compared to ischemia-guided strategy (previously called conservative or selectively invasive strategy), routine invasive strategy reduced the composite endpoint of mortality and MI, driven mostly by a significant reduction in MI (6,7). These benefits appear confined to moderate- and high-risk patients (6), whereas their low-risk counterparts can be safely treated with an ischemia-guided strategy (12). Both strategies are not mutually exclusive, and an initial ischemia-guided strategy often crosses over to an invasive strategy (e.g., significant spontaneous or inducible ischemia despite optimal medical therapy). Importantly, accurate and continuous risk stratification after NSTE-ACS (realizing the dynamic risk status early on), preferably with an objective risk score, is essential.

ADVANTAGES OF THE EARLY INVASIVE STRATEGY

The current meta-analysis (1) confirms the safety and incremental benefits (reduction in ischemia and LOS) of early compared to delayed invasive strategy. Previously, a cooling period to passivate the infarct-related artery medically was advocated. This is no longer needed in the current era of enhanced antithrombotic and interventional therapies, when even very early invasive approach appears to be safe (9,13,14). Actually, ~5% to 10% of NSTE-ACS patients (e.g., heart failure, cardiogenic shock) will need immediate invasive strategy (within <2 h). The observed reduction in LOS in the current meta-analysis is noteworthy, and likely has cost implications. A TIMACS trial substudy demonstrated salubrious cost-saving effects of EIS, even in subjects presenting during weekends (15).

CONCLUSIONS AND FUTURE DIRECTIONS

Although it is safe, beneficial, and cost saving, implementation of EIS nonselectively in NSTE-ACS patients remains challenging. Its routine application places

untoward burden on the cardiac catheterization laboratory and its value remains unproven, given especially the lack of evidence for a hard outcome benefit. Pre-specified subgroup analysis from the TIMACS trial (admittedly, a study that did not meet its primary objective) demonstrated that EIS reduced the composite of death, MI, or stroke in high-risk subjects (i.e. those with GRACE (Global Registry of Acute Coronary Events) score >140) (11). Based largely on these findings (11), the 2104 American Heart Association/American College of Cardiology guideline currently advocates EIS as a reasonable approach in preference to a delayed strategy for high-risk NSTE-ACS patients (12). Notably, the TIMACS trial had an accrual period between 2003 and 2008, and predated several interventional and medical advances (e.g., new $P2Y_{12}$ receptor inhibitors). A contemporary RCT is therefore needed to examine the efficacy of EIS after NSTE-ACS. Such a trial should ideally enroll subjects who are at moderate risk or higher, and be adequately powered to detect differences in clinically meaningful endpoints. Until then, EIS cannot be routinely recommended to all patients with NSTE-ACS requiring an invasive approach.

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REFERENCES

1. Bonello L, Laine M, Puymirat E, et al. Timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes and clinical outcomes: an updated meta-analysis. J Am Coll Cardiol Intv 2016;9:2267–76.

2. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

3. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

4. Vavalle JP, Lopes RD, Chen AY, et al. Hospital length of stay in patients with non-ST-segment elevation myocardial infarction. Am J Med 2012;125:1085–94.

5. Navarese EP, Gurbel PA, Andreotti F, et al. Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis. Ann Intern Med 2013;158:261–70.

6. Fox KA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. J Am Coll Cardiol 2010;55:2435–45.

7. Elgendy IY, Kumbhani DJ, Mahmoud AN, et al. Routine invasive versus selective invasive strategies for non-ST-elevation acute coronary syndromes: an updated meta-analysis of randomized trials. Catheter Cardiovasc Interv 2016 Aug 12 [E-pub ahead of print].

8. Sorajja P, Gersh BJ, Cox DA, et al. Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY trial. J Am Coll Cardiol 2010;55:1416–24.

9. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, et al. Immediate versus delayed invasive intervention for non-STEMI patients: the RIDDLE-NSTEMI study. J Am Coll Cardiol Intv 2016;9:541–9.

10. Reuter PG, Rouchy C, Cattan S, et al. Early invasive strategy in high-risk acute coronary syndrome without ST-segment elevation. The Sisca randomized trial. Int J Cardiol 2015;182:414–8.

11. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75.

12. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–228.

13. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. JAMA 2003;290:1593–9.

14. Montalescot G, Cayla G, Collet JP, et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA 2009;302:947–54.

15. Lamy A, Tong WR, Bainey K, et al. Cost implication of an early invasive strategy on weekdays and weekends in patients with acute coronary syndromes. Can J Cardiol 2015;31:314–9.

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