Journal of the American Heart Association

EDITORIAL

Non–ST-Segment–Elevation Myocardial Infarction: When Is Rapid Revascularization Critical?

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Acute myocardial infarction (AMI) remains a devastating event in patients with cardiovascular disease worldwide.[1] Among patients suffering an AMI, non–ST-segment–elevation MI (NSTEMI) is approximately twice as common as ST-segment–elevation myocardial infarction (STEMI).[2] The efficacy of immediate reperfusion in the setting of STEMI is well established, consistent with the pathophysiology of atherosclerotic plaque rupture/erosion and thrombosis.[3] In patients with NSTEMI, the efficacy of an invasive strategy with revascularization in appropriate patients is also well established.[4] However, in contrast to STEMI, the optimal timing of invasive coronary angiography and revascularization in NSTEMI is controversial, with some evidence that high-risk patients benefit from an early invasive strategy.[5–11] Thus, current guidelines recommend an early invasive strategy within 24 hours of hospital admission in patients with NSTEMI and a high-risk profile, in particular a GRACE (Global Registry of Acute Coronary Events) risk score >140.[12,13] However, the recent 2020 European Society of Cardiology guidelines acknowledge that there is a gap in evidence of NSTEMI care concerning the optimal timing of angiography and revascularization and further research is needed.[12]

See Article by Butt et al.

The original VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) trial,[14] which was a multicenter, open-label, parallel-group, randomized controlled trial, evaluated the optimal timing of invasive coronary angiography in patients with non–ST-segment–elevation acute coronary syndromes (n=2147). The majority, but not all, of the patients in VERDICT would qualify as having an NSTEMI. The principal finding was a very early strategy (<12 hours), as compared with standard invasive strategy (48–72 hours), did not reduce the risk of the composite end point of all-cause mortality, nonfatal AMI, or hospital admission for refractory myocardial ischemia or heart failure, except for those with a GRACE risk score >140. In the present study in this issue of the *Journal of the American Heart Association (JAHA)*, Butt et al sought to perform a predefined subgroup analysis of the VERDICT trial to determine the efficacy of early invasive therapy compared with a standard care and its impact on all-cause mortality according to the GRACE risk score overall and according to its components.[15]

In the current study, 2092 patients with GRACE scores were evaluated, with a median 4.1 years follow-up. There was a significant interaction between treatment assignment and GRACE score for risk of death; there was a trend toward decreased all-cause mortality with the early invasive strategy in patients with a GRACE score >140 (hazard ratio [HR], 0.83; 95% CI,

Key Words: Editorials ■ acute coronary syndrome ■ GRACE score ■ heart failure ■ invasive coronary angiography ■ mortality

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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0.63–1.10). It was more concerning, however, that the risk of all-cause mortality with an early invasive strategy was increased in patients with a GRACE score ≤140 (HR, 2.04; 95% CI, 1.16–3.59; *P* for interaction, 0.006), with the proportion of deaths attributed to a cardiovascular cause. In addition, the early invasive strategy reduced heart failure hospitalization risk for a GRACE score >140 but not with a GRACE score ≤140 (*P* for interaction, 0.02). The authors concluded that large-scale randomized clinical trials, preferably with long-term follow-up, are warranted to establish whether an early invasive strategy is beneficial in high-risk patients with NSTEMI but also whether an early invasive strategy can be harmful among those with a low risk.

The investigators should be praised for this contribution providing a spotlight on the optimal timing for an invasive angiography and revascularization for patients with NSTEMI. They were able to evaluate a large number of patients from the well-constructed VERDICT trial and highlight the optimal timing for high-risk and low-risk patients. Among the limitations outlined by the investigators, the most important is that this is a subgroup analysis and the GRACE score was done post hoc and was not powered to determine potential difference in outcome due to the early invasive strategy according to the GRACE score. Further, it is difficult to draw conclusions when the overall VERDICT trial was negative in regard to its primary end point. The investigators findings are hypothesis generating and future large, randomized clinical trials are needed.

One challenge of drawing conclusions from this study is that these patients represent a heterogenous patient population in terms of etiology and patient presentation. The underlying etiology for the NSTEMI such as plaque rupture, plaque erosion, spontaneous coronary artery dissection, myocardial infarction with nonobstructive arteries or demand ischemia can vary drastically. Furthermore, the presentation may range from clinically stable to cardiogenic shock. Diagnostically, the lack of ST-segment–elevation is not a reliable noninvasive diagnostic sign for occlusion. Indeed, patients with a lateral or posterior MI may not demonstrate ST changes, despite total artery occlusion, and delay in treatment may be detrimental. In addition, some patients with NSTEMI may have partially patent artery but insufficient flow to vulnerable subendocardium leading to myocardial ischemia and necrosis. Finally, even with adequate blood flow, the plaque may be unstable with overlying thrombus and be subject to occluding once again, causing reinfarction.

This patient population in VERDICT was indeed heterogenous, where not every patient was truly a NSTEMI. Roughly 70% of patients with a GRACE score ≤140 and about 87% with a GRACE score >140 had troponin elevation. Acute coronary syndromes without troponin elevation can be ambiguous and there is no evidence that urgent angiography improves outcomes. Thus, in fact, GRACE score >140 and evidence of an AMI may have even greater benefit with an early intervention. This discrepancy in the clinical presentation of patients included in the VERDICT trial emphasize further the need for larger clinical trials looking specifically at rapid NSTEMI revascularization.

Further, all the clinical trials evaluating an early invasive strategy versus standard strategy vary, both in its methods and results. First, the clinical trials vary in terms of the timing of an early invasive strategy versus a standard invasive strategy. A very early invasive strategy in the VERDICT trial was <12 hours; however, this was not consistent across the studies. In some clinical trials the early invasive strategy was as short as 1 hour whereas in others it was up to 24 hours. Second, the timestamp itself varied between studies, meaning the early invasive strategy could have started when the patient arrived in the emergency department whereas in other studies it started after the patient gave consent for the study, potentially delaying the start time overall. Finally, the primary end points and those results have varied between randomized clinical trials.

For example, in the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial,[8] 3031 patients with AMI were randomized to coronary angiography ≤24 (median 14) hours versus ≥36 (median 50) hours. At 6 months, the primary outcome (death, MI, stroke, or refractory ischemia) occurred in 9.6% in the early and 11.3% in the delayed intervention group (HR, 0.85; 95% CI, 0.68–1.06; *P*=0.15). However, in a prespecified subgroup analysis, early intervention improved the primary outcome in the one third of study patients with a GRACE score ≥140 (HR, 0.65; 95% CI, 0.48–0.89) but not in the two thirds with a GRACE score <140 (HR, 1.12; 95% CI, 0.81–1.56; interaction *P*=0.01). As the overall trial was not positive, the benefit for patients with GRACE score ≥140 was considered hypothesis generating.

More recently, there have been clinical trials considering a very early approach for higher risk patients. For example, the RIDDLE-NSTEMI (Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non–ST-Segment–Elevation Myocardial Infarction)[10] trial showed a decrease in the composite of death plus MI at 30 days and 1 year in patients treated with immediate (≤2 [median 1.4] hours) rather than delayed (≤72 [median 61] hours) intervention.[10,16] Alternatively, the LIPSIA-NSTEMI (Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in NSTEMI) trial found no benefit to immediate revascularization (<2 hours versus 10–48 hours) but was underpowered for cardiovascular events.[9] In the Early or Delayed Revascularization for Intermediate and High-Risk Non ST-Elevation Acute Coronary Syndrome trial, 709 patients were randomized to a very early (<2 hours)

or delayed (12–72 hours) invasive strategy. The primary outcome at 30 days of cardiovascular death or recurrent ischemia was 4.4% with the early and 21.3% with the delayed strategy (P<0.001), mostly because of recurrent ischemia. However, the incidence of cardiovascular death was 0.6% and 1.1% (P=0.69) and of MI 1.2% and 0.8% (P=0.72) with the early and delayed strategies, respectively.

There have also been a number of smaller studies. In the ABOARD (Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention) study of 372 patients, there was no advantage to a very early versus delayed revascularization.[7] Conversely, in another small study of 410 patients, ISAR-COOL (Intracoronary Stenting with Antithrombotic Regimen Cooling-Off), there was an advantage to early revascularization.[6] In yet another small study of 220 patients, Early or Late Intervention in unStable Angina, there was a suggestion of benefit to early revascularization.[5] Finally, In the OPTIMA-2 (Optimal Management of Antithrombotic Agents 2) trial of 249 patients there was no difference in infarct size between an early and immediate revascularization.[17]

The authors of the present VERDICT analysis also discussed the results of a recent meta-analysis by Jobs et al[11] including 8 randomized controlled trials[5–10,18,19] (n=5324 patients) comparing early versus delayed invasive strategy in patients the majority of whom had an NSTEMI. The analysis demonstrated that with a median follow-up of 180 days, there was no significant mortality reduction in the early invasive group compared with the delayed invasive group (HR, 0.81; 95% CI, 0.64–1.03; P=0.0879). However, in the prespecified analyses of high-risk patients, the authors found lower mortality with an early invasive strategy in patients with elevated cardiac biomarkers at baseline (HR, 0.761; 95% CI, 0.581 - 0.996), diabetes (HR, 0.67; 95% CI, 0.45–0.99), a GRACE risk score more than 140 (HR, 0.70; 95% CI, 0.52–0.95), and aged 75 years or older (HR, 0.65; 95% CI, 0.46–0.93), although tests for interaction were inconclusive. However; as noted, these trials varied in timing of the different strategies, enrollment, predefined outcomes, and results, making it difficult to draw definitive conclusions.

Finally, a retrospective analysis of the 2016 Nationwide Readmissions Database identified 748 463 NSTEMI hospitalizations in 2016. Of these hospitalizations, 50.3% involved diagnostic angiography, with 34.1% revascularized.[2] Of revascularized patients, 77.6% underwent percutaneous coronary intervention and 22.4% underwent coronary artery bypass grafting. Although percutaneous coronary intervention was frequently performed on the day of admission, the majority occurred over the next several days. The in-hospital mortality rate increased after day 1 (2.1% day 0 to 6.6% day 10) for patients who underwent percutaneous coronary intervention and 30-day in-hospital mortality increased as revascularization was delayed (3.5% day 0 to 9.7% day 6). This study highlights that in the real world, patients undergoing early revascularization differ from those undergoing later revascularization with higher mortality with delayed revascularization. Because of treatment selection bias, observational studies cannot resolve whether early revascularization prevents future events. TIMACS, RIDDLE, LIPSIA-NSTEMI, EARLY, VERDICT, and this retrospective analysis have not resolved the issue, which remains in equipoise.

The VERDICT investigators are to be commended for focusing on the current issue of whether rapid invasive strategy, similar to a patient with STEMI (<90 minutes), would be the ideal treatment strategy for high-risk patients with NSTEMI with a GRACE score >140. A large-scale, multicenter, international randomized clinical trial to study this particular question is under development, the results of which should answer the question and potentially change practice.

ARTICLE INFORMATION

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Disclosures

Weintraub reports research support from Amarin Corporation, National Institutes of Health, Centers for Disease Control and Prevention; consulting Amarin Corporation, AstraZeneca, Janssen, SC Pharma, and The Medicines Company. Case has no disclosures to report.

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