

Merits of Invasive Strategy in Diabetic Patients With Non-ST Elevation Acute Coronary Syndrome

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An invasive strategy (coronary angiography with intent to perform revascularization) and an ischemia-guided strategy are 2 commonly used approaches to treat patients with non-ST elevation acute coronary syndromes (NSTEMIs). These strategies are not mutually exclusive. Patients treated upfront with an ischemia-guided strategy (previously called a conservative or selectively invasive strategy) may cross over to an invasive strategy because of a variety of clinical scenarios, including recurrent ischemic symptoms, objective evidence of ischemia on noninvasive stress testing, and new clinical indicators of increased risk. Conceptually, there are myriad advantages of an invasive strategy. These include a definitive and accurate diagnosis and prognostication, prompt revascularization—sometimes in the same setting through ad-hoc percutaneous coronary intervention—and likely earlier discharge. On the other hand, given its invasive nature, angiography can be associated with increased complications (eg, vascular bleeding, contrast-induced acute kidney injury) and possibly higher upfront costs. Overall, clinical trials have demonstrated that a routine invasive strategy reduces the incidence of major cardiac events among NSTEMI patients,^{1–3} which appears to be driven predominantly by a significant reduction in nonfatal myocardial infarction (MI)^{1,2,4} and maintained over long-term follow-up (5-year period).⁵

It is in this context that the study by Mahmoud et al⁶ in the March issue of *JAHA* should be viewed. The investigators examined in-hospital survival among 363 500 diabetic patients presenting with NSTEMI between 2012 and

2013.⁶ They queried the National Inpatient Sample database for all hospitalized patients with primary diagnoses of non-ST-elevation MI and unstable angina and compared outcomes of patients undergoing an invasive versus an initial conservative strategy. After propensity score matching, their analyses yielded well-balanced groups (21 681 diabetic patients in each group, representing nearly 12% of the initial population) with comparable patient and hospital characteristics. Of the overall study population, 45.3% underwent an early invasive strategy. Compared with an initial conservative approach, early invasive strategy (defined in the current study as coronary angiography±revascularization within 48 hours of presentation) was associated with lower unadjusted in-hospital mortality in the overall cohort, a finding that was also evident in the propensity-matched cohort of patients and across most analyzed subgroups, except those with unstable angina.⁶ In addition, early invasive strategy was associated with a shorter length of hospital stay (by 1 day), but with significantly higher total hospital charges.⁶

The authors are to be congratulated on their laudable efforts. Their study is the largest report in the literature examining the merits of early invasive strategy in diabetic NSTEMI patients.⁶ It is relatively contemporary and reflects real-world practices. The observed mortality reduction with early invasive strategy in this high-risk population is remarkable and was maintained after propensity score matching and following additional sensitivity analyses in which patients with length of stay <48 hours were excluded to account for the immortal time bias. The study findings were also corroborated by secondary propensity score analyses using a modified adjustment model and a tighter match tolerance.

On the other hand, the study has many limitations, many of which are explicitly outlined by the authors.⁶ These include the lack of long-term outcomes, lack of data on pharmacotherapies and imaging and laboratory data, as well as the inherent shortcomings of the source of the study population. The National Inpatient Sample database is an administrative database and lacks the scientific rigor of a clinical database with well-defined diagnoses and adjudicated outcomes. In addition, there were no data on noninvasive stress testing, and it is unclear whether the conservative group in this study

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constitutes a true ischemia-guided strategy. Moreover, >30% of patients in the conservative group received revascularization, which might have underestimated the benefits of the invasive strategy.⁶

One of the major shortcomings of the study is that the investigators examined an outdated definition of early invasive strategy. According to both the American and European NSTEMI-ACS guidelines,^{7,8} an early invasive strategy is currently defined as a strategy implemented within 24 hours of presentation whereas a delayed invasive strategy is implemented within 25 to 72 hours. This artificial delineation is meant to help clinicians triage patients and streamline their flow into the cardiac catheterization laboratory, but is also driven by evidence from clinical trials. The TIMACS (Timing of Intervention in Acute Coronary Syndromes) study was the largest trial (N=3031 patients) comparing a *true* invasive (≤ 24 hours) versus a delayed invasive strategy (≥ 36 hours).⁹ Although the primary study end point was not met, an early invasive strategy was associated with a significant reduction in the composite secondary end point of death, MI, or refractory ischemia at 6 months, which was driven by a 70% reduction in refractory ischemia.⁹ The reduction in recurrent ischemia with an early invasive strategy was subsequently confirmed by additional meta-analyses¹⁰ and was associated with a significant reduction in the length of stay (by 28% in 1 report¹⁰) and costs (even when 50% of NSTEMI-ACS patients underwent percutaneous coronary intervention during weekends).¹¹ Notably, an early invasive strategy carries no safety issues, even when implemented very early—within <6 hours¹²—or as an immediate strategy.¹³ Although considered a soft end point, reducing recurrent or refractory ischemia post-NSTEMI-ACS is clinically important and is supported by evidence from the literature. In the TIMACS trial, refractory ischemia was associated with more than a 4-fold increase in subsequent MI.⁹ The ACUITY investigators demonstrated that a delayed percutaneous coronary intervention approach (>24 hours) post-NSTEMI-ACS was associated with worse 30-day composite of death or MI and was an independent predictor of short-term and 1-year major cardiac adverse events.¹⁴ Therefore, the American College of Cardiology/American Heart Association guidelines^{7,15} recommended an early invasive strategy for NSTEMI-ACS patients who are at high risk, such as those with a Global Registry of Acute Coronary Events risk score >140, new or presumably new ST depression, or significant temporal changes in troponin levels. Moderate-risk patients with NSTEMI-ACS can receive a delayed approach (within 25–72 hours), including those with diabetes mellitus.⁷ Notably, a small proportion of patients will need an urgent or immediate invasive approach, such as those with refractory angina and hemodynamic or electrical instability.⁷ It is unfortunate that the investigators did not examine the merits of a *true* invasive strategy (within

<24 hours) in their current report,⁶ which might have been explored in secondary analyses and which could have influenced clinical practice and guideline recommendations in diabetic patients.

The morality benefit in the current study is intriguing and runs counter to other reports.^{5,16,17} A meta-analysis by O'Donoghue et al¹⁶ demonstrated that the reduction in recurrent nonfatal MI was greater among diabetic patients compared with their nondiabetic counterparts, but no mortality reduction was observed with either patient populations. It is possible that previous reports were underpowered to detect a mortality benefit among diabetics. In TIMACS, diabetics represented only 27% of the overall study population, and in the large, comprehensive meta-analysis by O'Donoghue et al,¹⁶ inclusive of 9 randomized, clinical trials and 9904 patients, only 17% of the overall total population were diabetic. The current report, on the other hand, examined a very large diabetic population and the propensity analyses appeared to be well conducted.⁶ The survival benefit was also confirmed in the propensity-adjusted multivariable logistic regression model, across multiple subgroups, and in sensitivity analyses. Nevertheless, given the retrospective and observational nature of the current report, it is conceivable that unmeasurable confounders, which could not be accounted for, might explain the observed mortality differences between groups.⁶ Notably, diabetic patients in the current study who underwent an early invasive strategy were significantly younger and had fewer comorbidities compared with their counterparts receiving an initial conservative strategy.⁶

Another interesting finding by Mahmoud et al is the lack of benefit with an early invasive strategy among patients with unstable angina.⁶ This is in accord with other trials^{1,2} and a large collaborative meta-analysis showing no benefit in lower-risk patients with negative baseline biomarker levels.⁴ Notably, diabetic patients with unstable angina were appropriately less likely to receive an early invasive strategy in the current study.⁶ These findings support the American College of Cardiology/American Heart Association guidelines recommending an ischemia-guided strategy in low-risk patients.⁷

Another noteworthy finding from the current study is the alarming low rate (63%) of invasive strategy among diabetic patients with NSTEMI-ACS, of whom >95% had non-ST-elevation MI.⁶ Although this might be influenced by the lack of standardized definitions in the National Inpatient Sample administrative database (and the consequent risks of mis-coding and erroneous diagnoses), this low rate may also indicate undertreatment of diabetic patients in the real world. In the original Thrombolysis in Myocardial Infarction risk score derivation work,¹⁸ nearly 79% of ACS patients were risk stratified as moderate or high risk and thus qualify to undergo an invasive strategy per current guidelines.⁷ In the multinational PLATO (Platelet Inhibition and Patient Outcomes) trial,

which predated the current report and included patients outside the United States, the subpopulation of patients with NSTEMI-ACS, of whom at least 93% had Thrombolysis in Myocardial Infarction risk scores 3 to 7 (ie, moderate-/high-risk subjects), had an overall rate of coronary angiography of 81%.¹⁹ In the current report, the lower magnitude of benefit from an early invasive strategy observed during weekends compared to weekdays is also thought provoking.⁶ We previously reported delayed and suboptimal treatments after acute MI in patients presenting during off-hours,²⁰ which can further explain the current study subgroup finding.⁶ Notably, the compared subgroups were not matched, and all comparisons should be considered exploratory and interpreted with caution.⁶

Overall, this is an important study given the current epidemic of diabetes mellitus in the United States and the increase in non-ST-elevation MI diagnoses with the rapid clinical adoption of high-sensitivity troponins. The current report addresses important and unmet needs in this expanding patient population. The lack of benefit from an invasive strategy among diabetic patients with unstable angina has an important clinical implication and lends support to the notion that patients with negative biomarkers can be treated safely with an ischemia-guided strategy. On the other hand, the mortality reduction with an early invasive strategy in diabetic patients with non-ST-elevation MI is very interesting, but remains intriguing. This salutary finding needs to be confirmed in future prospective, randomized, clinical trials using standardized definitions and adjudicated long-term hard outcomes.

Disclosures

None.

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