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 (NSTE-ACSs). 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 NSTE-ACS patients, which appears to be driven predominantly by a significant reduction in nonfatal myocardial infarction (MI) and maintained over long-term follow-up (5-year period).

It is in this context that the study by Mahmoud et al6 in the March issue of JAMA should be viewed. The investigators examined in-hospital survival among 363,500 diabetic patients presenting with NSTE-ACS between 2012 and 2013. 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 followed by revascularization within 48 hours of presentation) was associated with lower unadjusted inhospital 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. In addition, early invasive strategy was associated with a shorter length of hospital stay (by 1 day), but with significantly higher total hospital charges.

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 NSTE-ACS patients. 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. 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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DOI: 10.1161/JAHA.117.005773

Invasive strategy was associated with a significant reduction in recurrent or refractory ischemia. Moreover, a reduction in refractory ischemia at 6 months, which was driven by a 70% reduction in refractory ischemia. The reduction in recurrent ischemia with an early invasive strategy was subsequently confirmed by additional meta-analyses and was associated with a significant reduction in the length of stay (by 28% in 1 report) and costs (even when 50% of NSTE-ACS patients underwent percutaneous coronary intervention during weekends). Notably, an early invasive strategy carries no safety issues, even when implemented very early—within <6 hours—or as an immediate strategy. Although considered a soft end point, reducing recurrent or refractory ischemia post-NSTE-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. The ACUITY investigators demonstrated that a delayed percutaneous coronary intervention approach (>24 hours) post-NSTE-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. Therefore, the American College of Cardiology/American Heart Association guidelines recommended an early invasive strategy for NSTE-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 NSTE-ACS can receive a delayed approach (within 25–72 hours), including those with diabetes mellitus. 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. It is unfortunate that the investigators did not examine the merits of a true invasive strategy (within <24 hours) in their current report, 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. A meta-analysis by O’Donoghue et al 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 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. 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. 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.

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

Another noteworthy finding from the current study is the alarming low rate (63%) of invasive strategy among diabetic patients with NSTE-ACS, of whom >95% had non-ST-elevation MI. Although this might be influenced by the lack of standardized definitions in the National Inpatient Sample administrative database (and the consequent risks of miscoding 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, nearly 79% of ACS patients were risk stratified as moderate or high risk and thus qualify to undergo an invasive strategy per current guidelines. In the multinational PLATO (Platelet Inhibition and Patient Outcomes) trial,
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DOI: 10.1161/JAHA.117.005773

Journal of the American Heart Association

References

None.

Disclosures

None.


**Key Words:** Editorials • angiography • coronary • early invasive strategy • infarction • mortality • revascularization
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J Am Heart Assoc. 2017;6:e005773; originally published May 20, 2017;
doi: 10.1161/JAHA.117.005773
The Journal of the American Heart Association is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

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http://jaha.ahajournals.org/content/6/5/e005773