Should We Manage Patients With Non–ST Segment Elevation Myocardial Infarction With Renal Failure With an Invasive Strategy?

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S ummer and colleagues raise an important question: Should we manage patients presenting with non–ST-segment elevation myocardial infarction (NSTEMI) with an early invasive strategy?1 It makes good sense to do this. We know that patients with renal dysfunction are at high risk,2 and the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines both recommend an early invasive strategy for patients with unstable angina/NSTEMI who are high risk.3,4 Neither guideline, however, specifically notes that renal dysfunction should be a specific indication for an invasive strategy.

The investigators analyzed 23 262 consecutive NSTEMI patients who had been included in a nationwide coronary care unit registry between 2003 and 2006 called the Swedish Web for Enhancement of Development and Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART).1 Patients were divided into medically or invasively treated if revascularized within 14 days of admission. They found that for patients with worse renal function, the rate of performing revascularization was lower. This “risk paradox” has been seen in other registries, in which higher-risk patients are actually managed less intensively.5 They also found that 1-year mortality was substantially higher for those on dialysis or having an estimated glomerular filtration rate (GFR) <15 mL/min (~55%) versus ~40% for those with estimated GFR 15 to 29 mL/min and ~5% for those with normal renal function. Thus, estimated GFR is clearly an important risk marker. They went on to compare mortality between medically managed patients and those who had revascularization and found overall a difference in mortality, with 36% lower adjusted mortality among those who had revascularization. They then split out the group by baseline renal function and found a lower mortality for those who had been revascularized versus not in most groups but not in the 278 patients who were on dialysis or had estimated GFR <15 mL/min. In this small subgroup, comprising 1.2% of their study population, mortality was 44% in those who had undergone revascularization with an invasive strategy versus 53% in those treated medically (thus observed to be 17% lower actually). However, when they adjust these data for differences in baseline characteristics, the adjusted hazard ratio is 1.61, with wide confidence intervals (0.84 to 3.09). They cite these data to state that they find “questionable” the value of an early invasive strategy in patients with renal failure or on dialysis.1

We should, however, consider several limitations of these data before fully adopting the conclusion. First, and most importantly, this is an observational study, and thus many variables confound the relationship being examined. Many clinical characteristics that influence mortality differ between the 2 groups, and these variables (such as age and diabetes mellitus) that are more prevalent in the nonrevascularized group could be the factors that lead to the mortality observations. Multivariate adjustment attempts to correct for this, but we know that this is not perfect. This discrepancy is strikingly seen in that unadjusted mortality is actually numerically 17% lower, and only after adjustment for baseline differences is it suggested to be higher, but nonsignificantly 60% higher. This instability in the data gives one pause regarding the strength of the observation.

Second, this is a small subgroup, and thus changing our clinical approach on the basis of only a limited number of patients could lead to erroneous conclusions. Third, the authors report only mortality but not myocardial infarction (MI) or recurrent acute coronary syndrome, 2 end points that are more strongly affected by an invasive strategy. Thus, here we have only 1 end point, and no data are reported to determine whether there is a consistent finding on other end points. Fourth, no interaction P value is reported for the mortality end point. This is actually the proper way to identify whether a different response is seen in 1 subgroup versus another.

The key issue, though, is that this is an observational study, where results can be confounded and should not be relied on as strong evidence; therefore, we need to be very circumspect when considering them to guide treatment. There is a long (and growing) list of treatments that have been adopted or advocated on the basis of observational studies but that end up failing to show benefit when tested in randomized trials: Hormone replacement therapy,6 folate,7 and vitamin E8 are some key ones. The issue of whether cancer is caused or prevented by statins continues to be raised from case-control observational studies,9 despite >500 000 patient-years of data from randomized trials showing no difference.10,11 The

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most recent controversy has been from the Swedish registry on stenting; the first report suggested increased mortality with drug-eluting stents, but randomized trials reported no excess mortality, and then 2 years later, from the same registry, the authors reported no excess. The same is true for use of drug-eluting stents in patients with STEMI, in regard to which 1 registry has suggested an increased mortality, but randomized trials have found no increase. This long series of discrepancies reminds us that observational studies examining therapies are often confounded, and we need to look at them with caution and remind ourselves that they raise a hypothesis but should not be relied on to guide treatment.

Data from randomized trials have addressed the benefit of an invasive versus conservative strategy in unstable angina and NSTEMI as subgroup analyses. Januzzi et al analyzed our Treat Angina with Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) data and examined 4 categories of patients with differing degrees of renal dysfunction gauged by the calculated creatinine clearance (CrCl). This analysis included 393 patients with CrCl 30 to 60 mL/min but only 28 patients with CrCl <30 mL/min. The overall trial showed a benefit of an early invasive strategy on its primary end point of death, MI, or rehospitalization for acute coronary syndrome, and a similar benefit was seen across the different CrCl groups with no treatment-by-CrCl interaction. Investigators from the Fast Revascularization During Instability in Coronary Artery Disease (FRISC) II trial (including 2 investigators in this analysis) have also reported outcomes of mild to moderate renal dysfunction in a group with CrCl <69 mL/min and found a benefit from an invasive strategy with no treatment-by-CrCl interaction for their primary end point of death or MI or for mortality at 2 years. This subgroup involved 842 patients but did not split out more severe renal dysfunction.

Most recently, a collaborative meta-analysis involving investigators from all of the randomized trials of an invasive versus conservative strategy was published. From the 5 trials that were able to estimate GFR, 1453 patients with chronic kidney disease stage 3 to 5 were enrolled. This study found that trends toward reduction in death, MI, and the combination were seen and a significant reduction in rehospitalization was observed in patients randomized to an early invasive strategy. For mortality, the focus of this article, the relative risk was 0.76 (95% confidence interval, 0.49 to 1.17) favoring an invasive strategy. For the specific subgroup of patients with class 4 or 5 chronic kidney disease (GFR <30 mL/min), the relative risk was 0.41 (95% confidence interval, 0.11 to 1.55). Thus, the randomized data appear to favor an invasive strategy.

We therefore see some differences between the findings from the observational study that compared patients who underwent revascularization with those who did not and the randomized trials that compared an invasive versus a conservative strategy. This difference between observational studies and randomized trials has actually been directly evaluated, in exactly this indication, in the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial. The randomized ICTUS trial, which included very intensive medical therapy in both arms, did not show an advantage of an early invasive strategy in improving outcomes compared with a selective invasive strategy in patients with NSTEMI. However, similar to retrospective analyses from observational studies, actual revascularization was associated with lower mortality and fewer MIs. The authors concluded, “Whether an early invasive strategy leads to a better outcome than a selective invasive strategy cannot be inferred from the observation that revascularized patients have a better prognosis in non-randomized studies.”

So, the question remains: Should we manage patients with NSTEMI with renal failure with an invasive strategy? This article suggests caution, in that the benefit might not be as great as we assume, although randomized trial data in patients with slightly less severe renal dysfunction found benefit. In support of this study’s observations, data on other interventions from randomized trials show that interventions such as statins or low-molecular-weight heparin do not provide the benefit expected in patients with severe renal dysfunction. Patients with renal failure would be at higher risk of complications from angiography, and thus some degree of caution is warranted when a patient is evaluated. Thus, with this study in the back of my mind, when next seeing a patient with NSTEMI and severe renal dysfunction who was not on dialysis, I likely would not rush to the cardiac catheterization laboratory but rather would use intensive medical therapy to stabilize the patient, but I would proceed to angiography if the patient were unstable or had significant ischemia on provocative testing. For NSTEMI patients on dialysis in whom no further harm could occur to renal function, I would (and did for 2 such patients this month) manage them with an invasive strategy.

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Disclosures
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References


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