Editorial

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

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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? It makes good sense to do this. We know that patients with renal dysfunction are at high risk, 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 System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDHEART).5 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. 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, folic acid,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
most recent controversy has been from the Swedish registry
on stenting; the first report suggested increased mortality with
drug-eluting stents,12 but randomized trials reported no excess
mortality,13 and then 2 years later, from the same registry, the
authors reported no excess.14 The same is true for use of
drug-eluting stents in patients with STEMI, in regard to
and NSTEMI as subgroup analyses. Januzzi et al17 analyzed
them with caution and remind ourselves that they raise a
ningen 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 al17 analyzed
our Treat Angina with Aggrastat and Determine Cost of
Therapy With an Invasive or Conservative Strategy—Throm-
bolysis in Myocardial Infarction 18 (TACTICS-TIMI 18)
data and examined 4 categories of patients with differing
degrees of renal dysfunction gauged by the calculated creat-
ine 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 Dis-
ease (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.18 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.19 This study found
that trends toward reduction in death, MI, and the combina-
tion 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 consen-
sative 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.20
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 observa-
tional 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 prog-
nosis in non-randomized studies."20

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 interven-
tions from randomized trials show that interventions such as
statins21 or low-molecular-weight heparin do not provide the
benefit expected in patients with severe renal dysfunction.2
Patients with renal failure would be at higher risk of compli-
cations 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 provoca-
tive 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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