Prognostic Significance of Elevated Baseline Troponin in Patients With Acute Coronary Syndromes and Chronic Kidney Disease Treated With Different Antithrombotic Regimens
A Substudy From the ACUITY Trial

Subasit Acharji, MD; Usman Baber, MD; Roxana Mehran, MD; Martin Fahy, MSc; Ajay J. Kirtane, MD, SM; Alexandra J. Lansky, MD; Gregg W. Stone, MD

Background—Elevation of baseline cardiac troponin in patients presenting with acute coronary syndromes (ACS) confers an adverse prognosis. The prognostic value of troponin elevation in patients with chronic kidney disease (CKD) and ACS is less certain.

Methods and Results—In the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial, 13 819 patients with moderate and high-risk ACS were assigned randomly to receive heparin plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin monotherapy. Among 2179 patients with CKD (creatinine clearance <60 mL/min), baseline troponin elevation was present in 1291 patients (59.2%). Major bleeding and major adverse cardiac events (MACE), including death, myocardial infarction (MI), or unplanned revascularization, were examined according to baseline troponin status and randomization arm. Patients with CKD in whom the baseline troponin level was elevated had significantly higher rates of death, MI, and MACE at 30 days and 1 year compared with CKD patients without elevated baseline troponin. By multivariable analysis, baseline troponin elevation in patients with CKD was an independent predictor of composite death or MI at 30 days (hazard ratio [95% CI] = 2.05 [1.48, 2.83], P < 0.0001) and 1 year (1.72 [1.36, 2.17], P < 0.0001). In CKD patients with baseline troponin elevation, bivalirudin monotherapy compared with heparin plus a GPI significantly reduced the 30-day rates of major bleeding with nonsignificantly different rates of MACE at 30 days and 1 year.

Conclusions—In patients with ACS and CKD, baseline troponin elevation is associated with significantly worse short- and long-term clinical outcomes. Bivalirudin monotherapy safely reduces major bleeding in ACS patients with CKD and baseline troponin elevation.

Key Words: acute coronary syndromes ▪ chronic kidney disease ▪ troponin ▪ outcomes

Previous studies have demonstrated the value of baseline cardiac troponins in predicting adverse events and in guiding therapy in acute coronary syndromes (ACS). However, many large-scale trials demonstrating the use of troponins have excluded patients with renal failure, in whom troponin excretion is prolonged and peak levels may be exaggerated compared with patients with normal kidney function. We recently reported from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial that chronic kidney disease (CKD) is associated with adverse outcomes in patients with ACS after an early invasive strategy, including reduced survival and an increased incidence of bleeding complications. Little is known, however, about the impact of baseline troponin elevation on outcomes in moderate- and high-risk ACS patients with CKD undergoing early management. Moreover, given their high propensity toward both ischemic and hemorrhagic complications, the best adjunctive antithrombotic regimen to optimize outcomes in high-risk ACS patients with CKD is still debated. We therefore sought to evaluate the impact of baseline troponin elevation on clinical outcomes in patients with moderate- and high-risk ACS and CKD, and to examine the safety and efficacy of contemporary antithrombotic regimens in this population.

Methods

Study Population and Design

The design and the results of the ACUITY trial have been published previously. Briefly, 13 819 patients with moderate- and high-risk non-ST-segment elevation ACS were randomized in an open-label fashion equally to 1 of 3 antithrombotic regimens: heparin (unfractionated or enoxaparin at site discretion) plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin monotherapy. Among 2179 patients with CKD (creatinine clearance <60 mL/min), baseline troponin elevation was present in 1291 patients (59.2%). Major bleeding and major adverse cardiac events (MACE), including death, myocardial infarction (MI), or unplanned revascularization, were examined according to baseline troponin status and randomization arm. Patients with CKD in whom the baseline troponin level was elevated had significantly higher rates of death, MI, and MACE at 30 days and 1 year compared with CKD patients without elevated baseline troponin. By multivariable analysis, baseline troponin elevation in patients with CKD was an independent predictor of composite death or MI at 30 days (hazard ratio [95% CI] = 2.05 [1.48, 2.83], P < 0.0001) and 1 year (1.72 [1.36, 2.17], P < 0.0001). In CKD patients with baseline troponin elevation, bivalirudin monotherapy compared with heparin plus a GPI significantly reduced the 30-day rates of major bleeding with nonsignificantly different rates of MACE at 30 days and 1 year.

Conclusions—In patients with ACS and CKD, baseline troponin elevation is associated with significantly worse short- and long-term clinical outcomes. Bivalirudin monotherapy safely reduces major bleeding in ACS patients with CKD and baseline troponin elevation. (Circ Cardiovasc Interv. 2012;5:00-00.)

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WHAT IS KNOWN

- Patients with chronic kidney disease (CKD) may have elevated troponin levels and decreased troponin clearance.
- The relationship between baseline troponin elevation and outcomes in patients with CKD and acute coronary syndromes (ACS) has not been established.

WHAT THE STUDY ADDS

- Patients with CKD and ACS in whom the baseline troponin levels were elevated (compared with normal baseline troponin levels) had greatly increased rates of death and myocardial infarction at 30 days and 1 year, although the magnitude of troponin elevation did not further improve discrimination for death or myocardial infarction beyond any elevation above normal.
- In these patients, procedural anticoagulation with bivalirudin monotherapy resulted in significant reductions in major bleeding at 30 days while effectively suppressing adverse ischemic events, compared with either eptifibatide or bivalirudin plus a glycoprotein IIb/IIIa inhibitor.
- These findings demonstrate that baseline troponin elevation is an important prognostic marker in moderate and high-risk patients with ACS and CKD treated with an early invasive strategy.

The study was approved by the institutional review board or ethics committee at each participating center, and all patients signed written informed consent.

Angiographic Analysis
As part of a formal substudy, quantitative coronary angiography of the baseline and final angiograms from 6921 consecutive patients from United States centers was performed by an angiographic core laboratory at the Cardiovascular Research Foundation, New York, NY, blinded to treatment assignment. To quantify the extent and burden of coronary artery disease (CAD), angiographic analysis included the number of diseased vessels (those in which any lesion with a diameter stenosis of >30% was present), the extent of CAD burden (the total length in millimeters of all lesions with a >30% diameter stenosis in all major epicardial vessels and branches), the Duke jeopardy score,11 baseline thrombolysis in myocardial infarction (TIMI) flow,12 and detailed qualitative and quantitative analysis of all PCI lesions.

Clinical End Points and Definitions
The principal end points of the ACUITY trial and the present analysis were (1) composite major adverse cardiac events ([MACE], composed of death from any cause, myocardial infarction [MI], or unplanned revascularization for ischemia), (2) major bleeding according to the ACUITY scale, and (3) net adverse clinical events (consisting of MACE or major bleeding). The component definitions of these end points have been reported previously,4 and were adjudicated by a Clinical Events Committee blinded to the treatment assignment. CKD was defined as a CrCl <60 mL/min using the Cockcroft-Gault equation.13 Anemia was defined as hematocrit <39% (or hemoglobin <13 g/dL) for men and <36% (or hemoglobin <12 g/dL) for women, according to the World Health Organization criteria.14

Statistical Analysis
In the present study we compared the baseline characteristics and outcomes among patients with CKD with versus without baseline troponin elevation (either I or T) greater than the upper limits of the local laboratory normal. Categorical values were compared by Chi-square or Fisher Exact test. Continuous variables are presented as medians with interquartile ranges, and were compared using Kruskal-Wallis test. Thirty-day and 1-year follow up outcomes were analyzed using time-to-event methodology, presented as Kaplan-Meier estimates and compared with the log-rank test. Cox proportional hazards regression analysis was performed to evaluate the impact of troponin elevation on the 30-day and 1-year rates of composite death or MI. The specific variables entered into the models were baseline troponin elevation (yes/no), randomized treatment group, age, sex, diabetes, insulin-treated diabetes, hypertension, hyperlipidemia, current smoking, previous MI, previous PCI, previous CABG, ST-segment deviation, creatinine clearance, hemoglobin level, and baseline white blood cell count. The probability values, hazard ratios, and corresponding 2-sided 95% CI for predictors are presented. All statistical analysis was performed by SAS V8.2 (SAS Institute Inc.).

Study Population
The ACUITY trial enrolled a total of 13 819 patients with ACS, and baseline CrCl data were present in 12 939 patients (93.2%). Among these patients, 2469 had baseline CKD, 2179 (88.3%) of whom had measurement of baseline troponin levels, representing the study population. Among these 2179 CKD patients, baseline troponin elevation was present in 1291 patients (59.2%). Baseline characteristics and treatment strategies in CKD patients according to baseline troponin elevation are detailed in Table 1. Compared with patients
Baseline Angiographic Characteristics
A total of 977 CKD patients were entered into the formal angiographic substudy (Table 2). Baseline troponin positive patients had significantly lower left ventricular ejection fraction and more extensive atherosclerosis, including more 3-vessel disease, a greater number of diseased lesions and higher jeopardy score, and a greater incidence of high-risk vessel and lesion characteristics, including baseline TIMI flow grade 0/1 and thrombus.

without baseline troponin elevation, CKD patients with troponin elevation were slightly older and were more likely to be current smokers, have ST-segment deviation, higher TIMI risk scores, and higher red and white blood cell counts. Patients without baseline troponin elevation were more likely to have a history of hypertension, hyperlipidemia, MI, and a history of prior PCI or CAGB.

Study Drug and Procedural Characteristics
Patients with CKD who were baseline troponin positive compared with negative were more likely to be triaged to CABG or PCI rather than medical therapy (Table 3). Anti-thrombotic and antiplatelet therapy was prescribed at similar rates between the 2 groups. Among patients undergoing PCI, TIMI-3 flow was restored in a similar percentage of CKD patients with and without baseline troponin elevation (96.0%)

Table 1. Baseline Clinical and Laboratory Characteristics of Patients With Chronic Kidney Disease According to Baseline Troponin Elevation

Table 2. Baseline Angiographic Characteristics of Patients With Chronic Kidney Disease According to Baseline Troponin Elevation

Table 3. Treatment Strategy and Medications
Table 4. Clinical Outcomes at 30 Days and 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Troponin Positive (N=1291)</th>
<th>Troponin Negative (N=888)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 30 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net adverse clinical events</td>
<td>20.6% (265)</td>
<td>14.8% (131)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Composite ischemia</td>
<td>13.6% (175)</td>
<td>7.9% (70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>4.7% (60)</td>
<td>1.0% (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4.0% (51)</td>
<td>0.7% (6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>0.3% (4)</td>
<td>0.1% (1)</td>
<td>0.33</td>
</tr>
<tr>
<td>MI</td>
<td>8.3% (106)</td>
<td>5.0% (44)</td>
<td>0.003</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>1.7% (22)</td>
<td>0.9% (8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>6.6% (84)</td>
<td>4.3% (38)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death or MI</td>
<td>11.9% (153)</td>
<td>5.6% (50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>3.6% (45)</td>
<td>2.8% (25)</td>
<td>0.33</td>
</tr>
<tr>
<td>Non-CABG major bleeding</td>
<td>10.3% (132)</td>
<td>8.6% (76)</td>
<td>0.16</td>
</tr>
<tr>
<td>At 1 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite ischemia</td>
<td>25.2% (310)</td>
<td>20.6% (166)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death</td>
<td>10.7% (127)</td>
<td>6.8% (51)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cardiac</td>
<td>6.8% (79)</td>
<td>2.7% (23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>2.7% (32)</td>
<td>2.1% (18)</td>
<td>0.42</td>
</tr>
<tr>
<td>MI</td>
<td>13.3% (165)</td>
<td>7.3% (63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>2.3% (29)</td>
<td>1.1% (10)</td>
<td>0.046</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>11.0% (135)</td>
<td>6.5% (56)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Death or MI</td>
<td>20.9% (259)</td>
<td>13.1% (106)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>10.0% (137)</td>
<td>12.2% (89)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Rates are expressed as Kaplan-Meier estimates (no. of events). MI indicates myocardial infarction; CABG, coronary artery bypass grafting.

versus 97.6%, respectively, P=0.45). Troponin positive patients had greater use of β-blockers and angiotensin-converting enzyme inhibitors after discharge, whereas other medications were used at a similar rate in both groups.

Troponin Elevation and Outcomes

Adverse events at 30 days and 1 year in CKD patients with versus without baseline troponin elevation are presented in Table 4. Patients with baseline troponin elevation had significantly higher rates of 30-day mortality and non-Q-wave MI, resulting in increased rates of MACE and net adverse clinical

Table 5. Independent Predictors of Composite Death or Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>HR [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-d death or MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin elevation</td>
<td>2.05 [1.48, 2.83]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (per 10 y increment)</td>
<td>1.26 [1.05, 1.50]</td>
<td>0.01</td>
</tr>
<tr>
<td>Insulin-treated diabetes</td>
<td>1.58 [1.08, 2.33]</td>
<td>0.02</td>
</tr>
<tr>
<td>ST-segment deviation ≥1 mm</td>
<td>1.58 [1.19, 2.09]</td>
<td>0.001</td>
</tr>
<tr>
<td>1-y death or MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin elevation</td>
<td>1.72 [1.36, 2.17]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (per 10 y increment)</td>
<td>1.31 [1.14, 1.50]</td>
<td>0.0002</td>
</tr>
<tr>
<td>Male</td>
<td>1.35 [1.08, 1.69]</td>
<td>0.007</td>
</tr>
<tr>
<td>Insulin-treated diabetes</td>
<td>1.58 [1.17, 2.13]</td>
<td>0.003</td>
</tr>
<tr>
<td>ST-segment deviation ≥1 mm</td>
<td>1.42 [1.15, 1.75]</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline Hgb (per unit increase)</td>
<td>0.90 [0.84, 0.96]</td>
<td>0.002</td>
</tr>
</tbody>
</table>

HR [95% CI] indicates hazard ratio with 95% confidence interval; MI, myocardial infarction; Hgb, hemoglobin.

reactions, with nonsignificantly different rates of unplanned repeat revascularization and major bleeding. At 1 year the rates of mortality, MI (both Q-wave and non-Q-wave), and MACE remained higher in CKD patients with versus without baseline troponin elevation. Death or MI also was more frequent in patients with CKD in whom more extensive CAD was present, regardless of baseline troponin status (Figure 1). Among patients with no significant coronary disease, the death or MI rate remained higher in those with versus without baseline troponin elevation (14.7% versus 2.5%, P=0.06).

After adjusting for differences in baseline clinical, ECG, and laboratory findings (Table 5), baseline troponin elevation in patients with CKD was an independent predictor of composite death or MI at 30 days (hazard ratio [95% CI]=2.05 [1.48, 2.83], P<0.0001) and at 1 year (1.72 [1.36, 2.17], P<0.0001). Whereas the rates of composite death or MI were increased in CKD patients with versus without baseline troponin elevation, the magnitude of troponin elevation beyond normal was not related to subsequent events (Figure 2).

One-year rates of death or MI stratified by presence or absence of CKD and baseline troponin elevation are presented in Figure 3. Compared with patients without CKD or baseline troponin elevation (n=3922), death or MI rates were highest

Figure 1. One-year rates of composite death or myocardial infarction according to troponin status and number of diseased vessels as determined by the angiographic core laboratory. P_trend=0.046 for troponin positive patients and 0.14 for troponin negative patients.
among those with both CKD and baseline troponin elevation (n=1291), while similar rates of death or MI were observed among those with either CKD or baseline troponin elevation alone.

**Impact of the Degree of Renal Failure**
A total of 176 out of 2179 patients (8.1%) had a baseline CrCl of <30 mL/min. As shown in Table 6, baseline troponin elevation was associated with a significantly higher incidence of most adverse events at both 30 days and 1 year among those with CrCl between 30 to 60 mL/min. In contrast, there were no significant differences in the incidence of the analogous adverse events between those with and without baseline troponin elevation and CrCl <30 mL/min. Interaction tests between CKD severity and baseline troponin elevation were significant for the occurrence of MI and non-Q-wave MI at both 30 days and 1 year, and for death or MI at 30 days.

**Impact of Antithrombotic Regimen**
The 1291 CKD patients with baseline troponin elevation were randomized to 1 of 3 antithrombotic regimens: heparin plus a GPI (n=422), bivalirudin plus a GPI (n=429), or bivalirudin alone (n=440). CKD patients with baseline troponin elevation treated with bivalirudin monotherapy rather than heparin, plus a GPI or bivalirudin, plus a GPI, had significantly lower 30-day rates of major bleeding, with nonsignificantly different rates of death, MI, and MACE at 30 days and 1 year (Figure 4).

**Discussion**
The principal findings from the present study are (1) baseline cardiac troponin elevation in moderate and high-risk patients with ACS and CKD, managed with an early invasive strategy, is associated strongly with subsequent death and MI at 30 days and 1 year, (2) however, among patients with CKD and with baseline troponin elevation, the magnitude of elevation beyond normal was not found to be predictor of composite death or MI, and (3) treatment of high-risk ACS patients with CKD and baseline troponin elevation with bivalirudin monotherapy compared with heparin, plus a GPI, safely reduced bleeding complications while effectively suppressing adverse ischemic events.
Aviles and colleagues demonstrated that the short-term prognosis in patients with ACS is worse in those with baseline troponin elevation, regardless of renal function. Other studies have reported that the prognostic use of baseline cardiac troponins to predict risk for subsequent adverse outcomes is diminished in patients with renal insufficiency in a variety of clinical settings, including patients with ACS. However, not all patients in these studies had ACS, and some had end stage renal disease requiring dialysis. Thus, the prognostic significance of baseline troponin elevation in patients with moderate and high-risk ACS and moderate CKD (CrCl 30–60 mL/min) remains unsettled. The present study demonstrates that baseline troponin measurements are helpful in predicting both short-term and long-term outcomes in patients with ACS managed with an early invasive strategy, despite the possibility of false-positive measurements due to renal clearance impairment.

Among CKD patients with elevated baseline troponins, we were unable to demonstrate that the absolute level of troponin elevation beyond normal carried further prognostic significance. In contrast, a report from the CRUSADE registry did observe an increase in mortality with increasing troponin levels in patients with CKD. There are several possible explanations for these discrepant results. First, the CRUSADE sample size was significantly larger than the present study (n = 13 819), and included many more patients with severe CKD (CrCl <30 mL/min), thereby reducing our power to detect significant differences across troponin strata. Second, neither study used a central core laboratory for troponin measurement, differences across troponin strata. Second, neither study used a central core laboratory for troponin measurement, thereby potentially introducing measurement errors (in both studies). Third, there are differences in the types of patients enrolled and data ascertainment between large-scale registries and randomized trials. Finally, all patients in ACUITY underwent an early invasive management strategy, with provision of all other class I guideline therapies, whereas the treatment approaches in CRUSADE
were not standardized. Further studies are warranted to determine the use of the magnitude of baseline troponin elevations in patients with CKD.

The adverse prognosis of patients with ACS and CKD with baseline troponin elevation is likely in part because of coexistent demographic, laboratory, and angiographic characteristics imparting increased risk. Concordant with previous series, patients with baseline troponin elevation in our series were more likely to have ST-segment deviation on the admission ECG,20 an important adverse prognostic indicator in ACS21–26 (although the ECG can be unreliable in patients with CKD due to frequent ST-segment changes from left ventricular hypertrophy, electrolyte disturbances, conduction system abnormalities, and medications).27 Conversely, patients with CKD and baseline troponin elevation were more likely to be current smokers, a finding paradoxically associated with improved short-term risk in some prior ACS studies.28 ACS patients with CKD and baseline troponin elevation were also less likely to have several classic risk factors for CAD or atherosclerosis, including hypertension, hyperlipidemia, and history of prior MI, PCI, or CABG. Nonetheless, after adjustment for these differences in demographic, ECG, and laboratory variables, baseline troponin elevation remained a powerful independent predictor of 30-day and 1-year composite death or MI in ACS patients with CKD managed with an early invasive strategy.

The formal ACUITY angiographic substudy, the largest such study to date to evaluate the extent of coronary artery disease and lesion characteristics in an independent core laboratory, provided a unique opportunity to further investigate the differences in ACS patients with CKD with versus without baseline troponin elevation. Patients with baseline troponin elevation had more extensive CAD and were more likely to have thrombotic lesions with reduced TIMI flow, as suggested in prior studies without angiographic core laboratory confirmation.20,29–31 As only 977 of the 2179 patients with CKD in the present report were included in the formal angiographic substudy, we did not include the angiographic variables in the multivariable analysis. Nonetheless, the 1-year rates of death or MI were shown to be related both to the extent of CAD and troponin status at baseline, suggesting that consideration of baseline clinical, laboratory, and angiographic data provide the most comprehensive risk stratification in ACS patients with CKD, as we have previously shown for the entire ACUITY study population.32

We also found that the associations between baseline troponin elevation and adverse events were stronger in those with moderate as opposed to severe CKD, with significant interactions present between the severity of CKD and troponin elevation for several end points, including MI and non-Q wave MI at both 30 days and 1 year. Although these stratified analyses are suggestive of effect modification according to CKD severity, the small sample size in the severe CKD group (n=127) precludes drawing definitive conclusions regarding the impact of baseline troponin elevation on adverse events in those with severe CKD. Pending larger studies, these findings should be considered exploratory.

Previous studies demonstrated that the beneficial treatment effect of adding a GPI to unfractionated heparin was greater among ACS patients who were troponin positive at baseline than in those who were troponin negative.4 However, there are no specific guidelines regarding adjunctive antithrom-
thrombotic therapy for patients with CKD, ACS, and elevated serum troponins. Concordant with previous series, elevated baseline troponins effectively identify patients with an increased likelihood of intracoronary thrombus and reduced TIMI flow who are most likely to benefit from intravenous GPI therapy.3,20–23 Earlier studies have demonstrated the benefits of an early invasive strategy in ACS patients with CKD.3 In the present study there were no significant differences in death or MI in patients with ACS, CKD, and elevated troponins treated with bivalirudin versus a heparin plus a GPI as part of an early invasive strategy (although a nonsignificant trend toward greater mortality with bivalirudin was present at 30 days that was absent at 1 year). Conversely, bivalirudin significantly reduced major hemorrhagic complications. The anti-ischemic effect of bivalirudin without a GPI in this setting likely relates to its ability to inhibit both thrombin and collagen-dependent platelet activation, as well as thrombin generation.34 Use of bivalirudin monotherapy also avoids unfractionated heparin and GPI overdosing, which may contribute to excessive bleeding, especially in patients with CKD.35,36 although the bivalirudin infusion must also be dose adjusted in patients with moderate renal insufficiency.

Limitations

Several limitations of the present report deserve consideration. First, core laboratory troponin measurement was not used, which might have provided greater accuracy than local laboratory assessment. In asymptomatic patients with renal insufficiency, the elevation of troponin T may predict decreased survival better than troponin I.37 Among patients with elevated baseline troponins in the present report, the proportion with Troponin-T, Troponin-I, and both were 29.8%, 72.2%, and 2.0%, respectively. The event rates in these individual groups are too small to determine whether there are different prognostic implications of the varying troponin types in our study population, although a previous study reported that both troponin T and I were prognostically useful in ACS patients with CKD.20 Second, the extent to which relative overdosing of anti-thrombotic therapy and GPI in patients with CKD contributed to excess bleeding was not determined. Third, approximately 7% of patients in the ACUITY trial did not have baseline CrCl data, and 12% did not have baseline troponin data; these patients were excluded from the present analysis. Fourth, there were too few patients with postprocedural MIs in the present study of CKD patients to specifically examine their prognostic significance as a function of baseline troponin level. Fifth, the present analysis was not prespecified, which can increase the chance of a false-positive result, and should thus be considered hypothesis-generating. Sixth, although all patients presented with symptoms consistent with ACS, we do not have detailed information on the number and pattern (eg, rise and fall) of troponin values assessed prior to catheterization, and thus cannot differentiate myocarditis from chronic persistent troponin elevation in CKD patients. Finally, the ACUITY trial was not powered to detect differences in outcomes among those with CKD and baseline troponin elevation. A larger randomized trial of bivalirudin versus heparin plus a GPI would be required to determine whether there are modest differences in ischemic MACE between these antithrombotic regimens. Further study is required to determine the prognostic use of cardiac biomarkers and the optimal anticoagulant regimen in ACS patients with renal impairment.

Conclusions

Despite concerns of impaired renal clearance, baseline troponin elevation is an important predictor of adverse cardiac outcomes in ACS patients with moderate CKD undergoing an early invasive management strategy, although the absolute magnitude of baseline troponin elevation beyond normal may not provide further prognostic precision. CKD patients with baseline troponin elevation also have more extensive CAD and myocardium at risk, the consideration of after cardiac catheterization that may provide more accurate risk stratification than use of clinical variables alone. Finally, treatment with bivalirudin monotherapy rather than heparin plus a GPI reduces major and minor bleeding complications, while providing comparable long-term anti-ischemic protection in ACS patients with CKD and baseline troponin elevation undergoing an early invasive management strategy.

Sources of Funding

The Medicines Company, Parsippany, NJ.

Disclosures

Dr Mehran has received research grants from BMS/Sanofi and has served as a consultant for Astra Zeneca, Regado Biosciences, Ortho McNeal, and Abbott Vascular. Dr Stone has served as a consultant for Abbott Vascular, Boston Scientific, Medtronic, and The Medicines Company. The other authors report no disclosures.

References


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Circ Cardiovasc Interv. published online February 21, 2012;
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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