

## TROPONIN T LEVELS IN PATIENTS WITH ACUTE CORONARY SYNDROMES, WITH OR WITHOUT RENAL DYSFUNCTION

RONNIER J. AVILES, M.D., ARMAN T. ASKARI, M.D., BERTIL LINDAHL, M.D., PH.D., LARS WALLENTIN, M.D., PH.D., GANG JIA, M.S., E. MAGNUS OHMAN, M.D., KENNETH W. MAHAFFEY, M.D., L. KRISTIN NEWBY, M.D., ROBERT M. CALIFF, M.D., MAARTEN L. SIMOONS, M.D., ERIC J. TOPOL, M.D., AND MICHAEL S. LAUER, M.D.

### ABSTRACT

**Background** Among patients with suspected acute coronary syndromes, cardiac troponin T levels have prognostic value. However, there is concern that renal dysfunction may impair the prognostic value, because cardiac troponin T may be cleared by the kidney.

**Methods** We analyzed the outcomes in 7033 patients enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries IV trial who had complete base-line data on troponin T levels and creatinine clearance rates. The troponin T level was considered abnormal if it was 0.1 ng per milliliter or higher, and creatinine clearance was assessed in quartiles. The primary end point was a composite of death or myocardial infarction within 30 days.

**Results** Death or myocardial infarction occurred in 581 patients. Among patients with a creatinine clearance above the 25th percentile value of 58.4 ml per minute, an abnormally elevated troponin T level was predictive of an increased risk of myocardial infarction or death (7 percent vs. 5 percent; adjusted odds ratio, 1.7; 95 percent confidence interval, 1.3 to 2.2;  $P < 0.001$ ). Among patients with a creatinine clearance in the lowest quartile, an elevated troponin T level was similarly predictive of increased risk (20 percent vs. 9 percent; adjusted odds ratio, 2.5; 95 percent confidence interval, 1.8 to 3.3;  $P < 0.001$ ). When the creatinine clearance rate was considered as a continuous variable and age, sex, ST-segment depression, heart failure, previous revascularization, diabetes mellitus, and other confounders had been accounted for, elevation of the troponin T level was independently predictive of risk across the entire spectrum of renal function.

**Conclusions** Cardiac troponin T levels predict short-term prognosis in patients with acute coronary syndromes regardless of their level of creatinine clearance. (N Engl J Med 2002;346:2047-52.)

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**C**ARDIAC troponins are useful in establishing a diagnosis and prognosis in patients who present with suspected acute coronary syndromes.<sup>1-4</sup> Renal dysfunction may interfere with the prognostic value of troponins because their clearance may be decreased.<sup>5-12</sup> We conducted a study to determine the prognostic value of base-line cardiac troponin T levels in relation to re-

nal function in a large population of patients who presented with suspected acute coronary syndromes.

### METHODS

The Global Use of Strategies to Open Occluded Coronary Arteries IV in Acute Coronary Syndromes study was a randomized, double-blind, placebo-controlled trial evaluating the effect of an infusion of abciximab, given for either 24 or 48 hours, on the composite end point of death or myocardial infarction in patients with high-risk acute coronary syndromes who were not undergoing early revascularization. The study was conducted between July 17, 1998, and April 21, 2000. Details of the design and primary results of the trial have been published elsewhere.<sup>13</sup> The investigators had full access to all data and conducted all analyses; the sponsors had no control over the decision to publish.

### Study Population

The participants were recruited from 458 hospitals in 24 countries.<sup>13</sup> Patients were eligible if they had either or both of the following sets of findings: one or more episodes of angina while at rest that lasted at least five minutes and new ST-segment depression of at least 0.5 mm; or an abnormal result on a cardiac troponin T or troponin I strip test or a quantitative cardiac troponin T or troponin I level above the upper limit of normal on the assay used locally. Patients with renal disease were not excluded. The protocol was approved by each hospital's institutional review board or ethics committee, and all participants gave written informed consent.

### Study Protocol

All patients were treated with aspirin. Patients were randomly assigned to one of three groups: abciximab for 24 hours and placebo for 24 hours, abciximab for 48 hours, or placebo for 48 hours. Abciximab (ReoPro, Centocor) was administered as a bolus of 0.25 mg per kilogram of body weight, followed by an infusion of 0.125  $\mu$ g per kilogram per minute, up to a maximum of 10 mg per kilogram per minute. All patients received an infusion of unfractionated heparin, except those participating in the substudy of low-molecular-weight heparin. Treatment with cardiac medications was left to the discretion of the treating physician. The use of glycoprotein IIb/IIIa inhibitors in patients who later underwent percutaneous coronary intervention was also left to the discretion of the treating physician. Electrocardiography was performed at base line, 48 hours, and 30 days.

From the Department of Cardiology, the Cleveland Clinic Foundation, Cleveland (R.J.A., A.T.A., G.J., E.J.T., M.S.L.); the Department of Cardiology, University of Uppsala, Uppsala, Sweden (B.L., L.W.); the University of North Carolina, Chapel Hill (E.M.O.); the Duke Clinical Research Institute, Durham, N.C. (K.W.M., L.K.N., R.M.C.); and the Department of Cardiology, University Hospital Rotterdam, Rotterdam, the Netherlands (M.L.S.). Address reprint requests to Dr. Lauer at the Department of Cardiology, Desk F25, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44951, or at [lauer@ccf.org](mailto:lauer@ccf.org).

Peter Berger, M.D., Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minn., was also an author.

### Troponin T Analysis

Base-line blood samples for measurement of troponin T were obtained before randomization, centrifuged, frozen in aliquots at  $-20^{\circ}\text{C}$ , and then shipped to a central core laboratory in Uppsala, Sweden, where they were stored at  $-70^{\circ}\text{C}$  before being thawed and analyzed. Personnel who were unaware of the clinical data performed all measurements of troponin T.

Troponin T levels were determined by means of a third-generation troponin T assay (Elecsys, Roche Diagnostics) that uses recombinant human cardiac troponin T as standard material.<sup>8,10</sup> The 99th percentile of the troponin T level in a reference population is below the lower limit of detection of 0.01 ng per milliliter. However, on the basis of experience with the second-generation assay, the cutoff point for the prognostic evaluation was prespecified as 0.1 ng per milliliter. The interassay coefficient of variation at a discriminator value of 0.1 ng per milliliter was below 10 percent.

### Renal Function

Base-line creatinine concentrations (in milligrams per deciliter) were routinely measured and recorded for all patients. Age and weight in kilograms were also available for all patients. The creatinine clearance rate was calculated with the equation of Cockcroft and Gault, with adjustment for sex:  $[(140 - \text{age}) \times (\text{weight in kilograms})] \div [72 \times \text{serum creatinine concentration in milligrams per deciliter}]$ .<sup>14</sup>

### End Points

The primary end point was a composite of death and myocardial infarction within 30 days. A secondary end point was death within 30 days. The definition of myocardial infarction used in the trial has been published previously.<sup>13</sup> A blinded clinical events committee classified all end points.

### Statistical Analysis

Analyses included all patients who had complete core-laboratory data on troponin T levels and creatinine clearance and 30-day follow-up data on death and myocardial infarction. All analyses were prespecified. Base-line characteristics were analyzed in each quartile of creatinine clearance and in groups defined according to the troponin T level, creatinine clearance rate, or both; these analyses were performed with the use of frequency distributions and chi-square tests. Age was dichotomized into 65 years or younger and older than 65 years, and weight was dichotomized into 90 kg or less and more than 90 kg. An abnormal troponin T level was defined as a value of at least 0.1 ng per milliliter, and a cutoff point of 0.03 ng per milliliter was used in secondary analyses. The troponin T level was not treated as a continuous variable because the distribution of the data was highly skewed and all values of less than 0.01 ng per milliliter — the lower limit of discrimination of the assay — were recorded as 0.01 ng per milliliter. An abnormal creatinine clearance rate was defined as a value in the lowest quartile (less than 58.4 ml per minute).

Patients were grouped according to the quartile of creatinine clearance. Simple logistic regression was used to estimate the odds ratios for the quartiles of creatinine clearance and the groups defined according to troponin T status. Multivariable logistic-regression analyses were performed to adjust for potential confounders.<sup>15,16</sup>

When considering the creatinine clearance rate as a continuous variable, we used a generalized additive model with logit-link and spline methods to determine the univariable relation between renal function and death or myocardial infarction within 30 days, according to troponin T status.<sup>16</sup> On the basis of the univariable analysis, we developed a multivariable logistic-regression model with linear and quadratic terms for creatinine clearance. Interactions between troponin T status and both linear and quadratic terms for creatinine clearance were included in the model to analyze the re-

lation among troponin T status, creatinine clearance, and death or myocardial infarction within 30 days. We used a stepwise method to introduce significant covariates into the model. Beta coefficients of the linear and quadratic terms for creatinine clearance, troponin T status, their interactions, and the covariance matrix of the estimates were used to calculate the adjusted odds ratios (and 95 percent confidence intervals) for abnormal troponin T levels in relation to the rate of creatinine clearance. Reported P values are two-sided. All statistical analyses were performed with SAS software, version 6.12 (SAS Institute).

## RESULTS

### Study Patients

Of 7800 patients enrolled, 7033 (90.2 percent) had complete clinical, troponin T, and creatinine clearance data. Data on troponin T levels were missing for 673 patients (8.6 percent), creatinine clearance data were missing for 82 patients (1.1 percent), and data for both variables were missing for 12 patients (0.2 percent). Thirty-day follow-up was complete for all 7033 patients.

Base-line characteristics according to troponin T status and creatinine clearance status are presented in Table 1. Patients with both abnormal troponin T levels and creatinine clearance rates in the lowest quartile were older and more likely to have diabetes and to have a history of myocardial infarction. The quartile groups were similar in terms of treatment with abciximab or placebo.

### Troponin T and Creatinine Clearance

Only 11 patients had severe renal impairment, with a creatinine clearance of less than 10 ml per minute. The median creatinine clearance rate was 76 ml per minute, and the 25th and 75th percentile values were 58 and 99 ml per minute, respectively. The distribution of troponin T levels was highly skewed. The median troponin T level was 0.12 ng per milliliter (25th and 75th percentile values, 0.01 and 0.47 ng per milliliter, respectively). Troponin T was abnormally elevated to 0.1 ng per milliliter or higher in 3645 patients (52 percent), and to 0.03 ng per milliliter or higher in 4512 patients (64 percent).

### Troponin T, Creatinine Clearance, and Outcomes

To evaluate whether the troponin T status was predictive of the outcome in patients with abnormal creatinine clearance and in those with normal creatinine clearance, we analyzed both troponin T status and creatinine clearance as categorical variables. The troponin T level was considered to be abnormal at the prespecified cutoff point of 0.1 ng per milliliter as well as at a lower cutoff point of 0.03 ng per milliliter.

The results of the univariable and multivariable analyses are shown in Table 2. Death or myocardial infarction occurred in 581 patients. Of these patients, 305 had a nonfatal myocardial infarction, 71 had a fatal myocardial infarction, and 205 died with-

**TABLE 1. BASE-LINE CHARACTERISTICS ACCORDING TO GROUPS DEFINED BY CREATININE CLEARANCE AND TROPONIN T STATUS.\***

CHARACTERISTIC	CREATININE CLEARANCE AND TROPONIN T LEVEL				P VALUE†
	BOTH NORMAL (N=2605)	ABNORMAL TROPONIN T LEVEL ONLY (N=2695)	ABNORMAL CREATININE CLEARANCE ONLY (N=783)	BOTH ABNORMAL (N=950)	
	no. (%)				
Age >65 yr	1037 (40)	1104 (41)	689 (88)	877 (92)	<0.001
Female sex	1073 (41)	669 (25)	463 (59)	468 (49)	<0.001
Weight >90 kg	447 (17)	587 (22)	23 (3)	36 (4)	<0.001
Smoker	657 (25)	970 (36)	89 (11)	134 (14)	<0.001
Medical condition					
Hypercholesterolemia	883 (34)	730 (27)	217 (28)	237 (25)	<0.001
Hypertension	1394 (54)	1154 (43)	524 (67)	573 (60)	<0.001
Diabetes mellitus	500 (19)	521 (19)	198 (25)	260 (27)	<0.001
ST-segment depression	2364 (91)	1829 (68)	735 (94)	765 (81)	<0.001
Medical history					
Myocardial infarction	740 (28)	713 (26)	304 (39)	399 (42)	<0.001
Chronic stable angina	1422 (55)	872 (32)	532 (68)	487 (51)	<0.001
Bypass surgery	217 (8)	219 (8)	90 (11)	90 (9)	0.02
Angioplasty	256 (10)	233 (9)	93 (12)	75 (8)	0.02
Heart failure	170 (7)	99 (4)	110 (14)	144 (15)	<0.001
Stroke	44 (2)	55 (2)	24 (3)	45 (5)	<0.001
Abciximab treatment	1734 (67)	1826 (68)	526 (67)	616 (65)	0.41

\*Abnormal creatinine clearance was defined as a measurement in the lowest quartile (<58.4 ml per minute), and an abnormal troponin T level was defined as a level of 0.1 ng per milliliter or higher.

†P values are for the four-way comparison among groups.

out a documented myocardial infarction. Thus, 276 patients died. Among patients with a creatinine clearance above the 25th percentile value of 58.4 ml per minute, an abnormally elevated troponin T level was predictive of an increased risk of myocardial infarction or death (7 percent vs. 5 percent; unadjusted odds ratio, 1.6; 95 percent confidence interval, 1.2 to 2.0;  $P<0.001$ ) in analyses using a cutoff point for the troponin T level of 0.1 ng per milliliter. Similarly, among patients in the lowest quartile of creatinine clearance, an abnormal troponin T level was associated with an increased risk of myocardial infarction or death (20 percent vs. 9 percent; unadjusted odds ratio, 2.5; 95 percent confidence interval, 1.9 to 3.3;  $P<0.001$ ;  $P$  for interaction = 0.01). When we used the lower cutoff point for the troponin T level of 0.03 ng per milliliter, an abnormal troponin T level also conferred an increased risk among patients in the lowest quartile of creatinine clearance (odds ratio, 2.7; 95 percent confidence interval, 1.9 to 3.8;  $P<0.001$ ).

In multivariable analyses, after adjustment for potential confounders — including sex and the presence or absence of an age of more than 65 years, ST-

segment depression, and a history of angina, myocardial infarction, heart failure, stroke, diabetes mellitus, bypass surgery, and angioplasty — an abnormally elevated troponin T level (0.1 ng per milliliter or higher) was predictive of an increased risk of myocardial infarction or death among patients with a creatinine clearance rate above the 25th percentile (adjusted odds ratio, 1.7; 95 percent confidence interval, 1.3 to 2.2;  $P<0.001$ ). Similarly, an abnormal troponin T level among patients in the lowest quartile of creatinine clearance was associated with an increased risk (adjusted odds ratio, 2.5; 95 percent confidence interval, 1.8 to 3.3;  $P<0.001$ ;  $P$  for interaction = 0.06). The adjusted risk was also significantly increased among patients in the lowest quartile of creatinine clearance when a cutoff point of 0.03 ng of troponin T per milliliter was used (adjusted odds ratio, 2.7; 95 percent confidence interval, 1.9 to 3.8;  $P<0.001$ ).

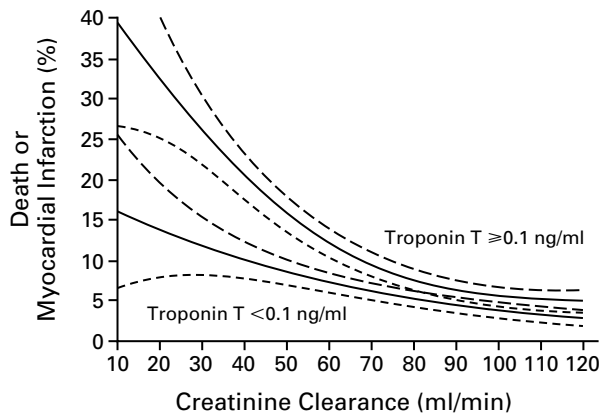
The unadjusted predicted rates of events (and their 95 percent confidence intervals) according to the troponin T status (normal vs. abnormal) in relation to creatinine clearance considered as a continuous variable are shown in Figure 1 (with a cutoff point

**TABLE 2.** UNADJUSTED AND ADJUSTED ODDS RATIOS FOR DEATH OR MYOCARDIAL INFARCTION WITHIN 30 DAYS ACCORDING TO TROPONIN T STATUS AND QUARTILE OF CREATININE CLEARANCE.\*

QUARTILE OF CREATININE CLEARANCE	MYOCARDIAL INFARCTION OR DEATH		UNADJUSTED ODDS RATIO (95% CI)	P VALUE	ADJUSTED ODDS RATIO (95% CI)†	P VALUE
	TROPONIN T ≥0.1 ng/ml	TROPONIN T <0.1 ng/ml				
	no./total no. in quartile (%)					
First	186/950 (20)	70/783 (9)	2.5 (1.9–3.3)	<0.001	2.5 (1.8–3.3)	<0.001
Second	91/886 (10)	60/917 (7)	1.6 (1.2–2.3)	0.004	1.8 (1.3–2.6)	<0.001
Third	61/879 (7)	47/883 (5)	1.3 (0.9–2.0)	0.16	1.4 (0.9–2.1)	0.16
Fourth	46/930 (5)	20/805 (2)	2.0 (1.2–3.5)	0.008	2.3 (1.3–4.1)	0.003
	no./total no. in quartile (%)					
	TROPONIN T ≥0.03 ng/ml		TROPONIN T <0.03 ng/ml			
	no./total no. in quartile (%)					
First	214/1180 (18)	42/553 (8)	2.7 (1.9–3.8)	<0.001	2.7 (1.9–3.8)	<0.001
Second	115/1113 (10)	36/690 (5)	2.1 (1.4–3.1)	<0.001	2.4 (1.6–3.6)	<0.001
Third	86/1102 (8)	22/660 (3)	2.5 (1.5–4.0)	<0.001	2.6 (1.6–4.4)	<0.001
Fourth	58/1117 (5)	8/618 (1)	4.2 (2.0–8.8)	<0.001	4.8 (2.3–10.4)	<0.001

\*The first quartile of creatinine clearance included values below 58.4 ml per minute; the second quartile included values between 58.4 and 76.9 ml per minute; the third quartile included values between 77.0 and 98.6 ml per minute; and the fourth quartile included values greater than 98.6 ml per minute. CI denotes confidence interval.

†The odds ratios were adjusted for the presence or absence of an age greater than 65 years, ST-segment depression, and a history of angina, myocardial infarction, bypass surgery, angioplasty, diabetes mellitus, stroke, and heart failure.



**Figure 1.** Incidence of the Primary End Point of Death or Myocardial Infarction, According to the Base-Line Troponin T Level and Creatinine Clearance Rate.

The curves were derived from generalized additive models with a logit-link function, smoothed with the use of a spline method. The rate of death or myocardial infarction was significantly higher among patients with a base-line troponin T level of 0.1 ng per milliliter or higher across the entire spectrum of creatinine clearance rates, according to an unadjusted analysis. The dashed lines indicate the 95 percent confidence intervals.

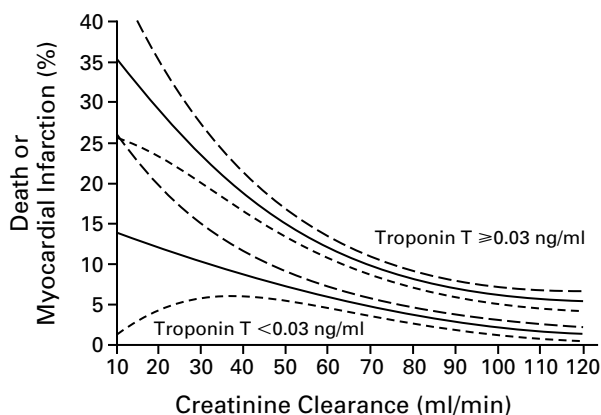
of 0.1 ng per milliliter) and Figure 2 (with a cutoff point of 0.03 ng per milliliter). The curves were derived from generalized additive models with the use of a logit-link function, with the curve for creatinine clearance smoothed by a spline method.

Figure 3 shows the adjusted odds ratios for death or myocardial infarction among patients with abnormal troponin T levels in relation to the creatinine clearance rate considered as a continuous variable. Odds ratios were adjusted for all significant covariates shown in Table 1 and were derived from the multivariable logistic-regression model.

An abnormal troponin T level at base line was associated with an increased risk of death within 30 days among patients in all quartiles of creatinine clearance, including the lowest quartile (adjusted odds ratio, 3.4; 95 percent confidence interval, 2.3 to 5.2;  $P < 0.001$ ;  $P$  for interaction = 0.10).

## DISCUSSION

Even though cardiac troponin T may be cleared by the kidney, we found that, among patients presenting with suspected acute coronary syndromes,

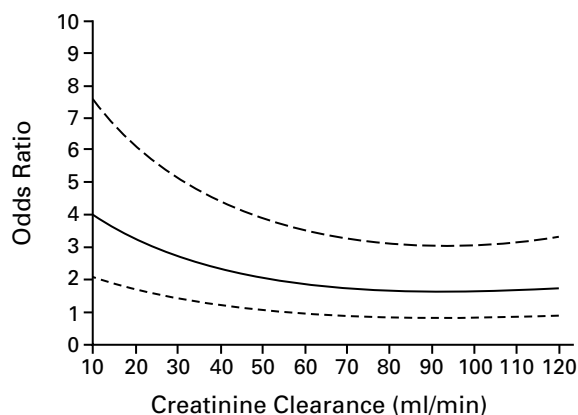


**Figure 2.** Incidence of the Primary End Point of Death or Myocardial Infarction, According to the Base-Line Troponin T Level and Creatinine Clearance Rate.

The curves were derived from generalized additive models with a logit-link function, smoothed with the use of a spline method. The rate of death or myocardial infarction was significantly higher among patients with a base-line troponin T level of 0.03 ng per milliliter or higher across the entire spectrum of creatinine clearance rates, according to an unadjusted analysis. The dashed lines indicate the 95 percent confidence intervals.

base-line measurements of cardiac troponin T were strongly predictive of the risk of death or myocardial infarction, even when impaired renal function was present. Because patients with renal insufficiency were not excluded from our trial, we had the opportunity to evaluate the predictive value of elevations in cardiac troponin T in a large cohort of patients across a wide spectrum of renal function. Until now, the prognostic and diagnostic significance of cardiac troponins among patients with renal dysfunction has been controversial. Whereas some studies have found that the predictive value of elevated levels of troponins was reduced among such patients, others have questioned the prognostic or diagnostic significance of these levels.<sup>5,9,11-13,17-21</sup> Our study supports the value of the test in patients with renal impairment who present with symptoms suggestive of acute coronary syndromes.

Some limitations of our study are noteworthy. We used the equation of Cockcroft and Gault, which uses the serum creatinine concentration, age, weight, and sex to estimate the glomerular filtration rate.<sup>14</sup> Although this equation is used widely in clinical practice, it is only an approximation of the glomerular filtration rate.<sup>22</sup> Nonetheless, the equation not only is practical, but also remains the method of choice for estimating the glomerular filtration rate at the bedside. Given this fact, our analysis is clinically relevant to actual practice situations.



**Figure 3.** Adjusted Odds Ratio for Death or Myocardial Infarction among Patients with Abnormal Troponin T Levels in Relation to Creatinine Clearance Rates.

An abnormal troponin T level was defined as a level of 0.1 ng per milliliter or higher. Odds ratios were derived from the multivariable logistic-regression model and were adjusted for all significant base-line variables. An abnormal troponin T value at base line predicted the risk of death or myocardial infarction within 30 days across the entire spectrum of creatinine clearance rates. The dashed lines indicate the 95 percent confidence intervals.

Our trial differed in some respects from other trials involving patients with acute coronary syndromes.<sup>13</sup> The observed rate of myocardial infarction or death was lower than expected (8 percent vs. 11 percent); a liberal criterion for ST-segment depression (0.5 mm) was used; and the subjects included a high proportion of women (38 percent). It is therefore possible that the trial may have enrolled patients with chest pain syndromes who did not have active unstable coronary disease.

There are two potentially important implications of our findings. First, given that renal dysfunction is common in patients with coronary disease, the ability of cardiac troponin levels to predict the outcome irrespective of the creatinine clearance rate expands their clinical usefulness.<sup>23-25</sup> Second, a number of treatment strategies, such as low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, and aggressive treatment with cardiac catheterization, are emerging as particularly beneficial for patients who present with elevated levels of cardiac troponins.<sup>26-29</sup> Given that levels of cardiac troponins are used to stratify risk and guide therapeutic decisions in patients suspected of having acute coronary syndromes, it is important to define the usefulness of this marker in a growing population of patients with acute coronary syndromes and renal impairment.

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