

# Optimal Cutoff Levels of More Sensitive Cardiac Troponin Assays for the Early Diagnosis of Myocardial Infarction in Patients With Renal Dysfunction

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**Background**—It is unknown whether more sensitive cardiac troponin (cTn) assays maintain their clinical utility in patients with renal dysfunction. Moreover, their optimal cutoff levels in this vulnerable patient population have not previously been defined.

**Methods and Results**—In this multicenter study, we examined the clinical utility of 7 more sensitive cTn assays (3 sensitive and 4 high-sensitivity cTn assays) in patients presenting with symptoms suggestive of acute myocardial infarction. Among 2813 unselected patients, 447 (16%) had renal dysfunction (defined as Modification of Diet in Renal Disease–estimated glomerular filtration rate  $<60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ ). The final diagnosis was centrally adjudicated by 2 independent cardiologists using all available information, including coronary angiography and serial levels of high-sensitivity cTnT. Acute myocardial infarction was the final diagnosis in 36% of all patients with renal dysfunction. Among patients with renal dysfunction and elevated baseline cTn levels ( $\geq 99$ th percentile), acute myocardial infarction was the most common diagnosis for all assays (range, 45%–80%). In patients with renal dysfunction, diagnostic accuracy at presentation, quantified by the area under the receiver-operator characteristic curve, was 0.87 to 0.89 with no significant differences between the 7 more sensitive cTn assays and further increased to 0.91 to 0.95 at 3 hours. Overall, the area under the receiver-operator characteristic curve in patients with renal dysfunction was only slightly lower than in patients with normal renal function. The optimal receiver-operator characteristic curve–derived cTn cutoff levels in patients with renal dysfunction were significantly higher compared with those in patients with normal renal function (factor, 1.9–3.4).

**Conclusions**—More sensitive cTn assays maintain high diagnostic accuracy in patients with renal dysfunction. To ensure the best possible clinical use, assay-specific optimal cutoff levels, which are higher in patients with renal dysfunction, should be considered.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00470587. (*Circulation*. 2015;131:2041-2050. DOI: 10.1161/CIRCULATIONAHA.114.014245.)

**Key Words:** high-sensitivity ■ kidney ■ myocardial infarction ■ renal insufficiency ■ troponin

Acute myocardial infarction (AMI) is a major cause of death and disability in Europe and the United States.<sup>1</sup> Its rapid and accurate diagnosis is critical for effective evidence-based medical management and treatment<sup>2-4</sup> but is still an unmet clinical need. Delays in diagnosing disease

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**Clinical Perspective on p 2050**

(“rule in”) hold back prompt use of evidence-based therapies.<sup>5,6</sup> Delays in excluding AMI (“rule out”) interfere with

Received November 11, 2014; accepted March 27, 2015.

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The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.014245/-/DC1>.

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.114.014245

evaluation of alternative diagnoses and contribute to medical errors and costs associated with crowding in the emergency department (ED).<sup>7-9</sup>

For several reasons, patients with renal dysfunction merit particular attention. First, the incidence of AMI is increased in this vulnerable subgroup.<sup>10,11</sup> Second, atypical clinical presentation of AMI may be more frequent.<sup>12,13</sup> Third, left ventricular hypertrophy is common and often results in ECG changes that may mimic or obscure AMI. Fourth, patients with renal dysfunction are more prone to adverse events related to cardiovascular medication, for example, anticoagulation, as well as to cardiovascular procedures, including coronary angiography and coronary intervention.<sup>12</sup>

More sensitive cardiac troponin (cTn) assays with a limit of detection below the 99th percentile of a healthy reference population and improved precision have recently become available in clinical practice.<sup>14-16</sup> While sensitive (s) assays allow the detection of cTn in 20% to 50% of healthy individuals, high-sensitivity (hs) assays allow the detection of cTn in even 50% to 90% of healthy individuals.<sup>17</sup> These assays improved the early diagnosis of AMI in unselected patients with suspected AMI.<sup>18,19</sup> However, their clinical utility in patients with renal dysfunction has recently been questioned.<sup>20-22</sup> For example, elevated cTn levels above the 99th percentile were observed in up to 40% of patients with renal dysfunction and diagnoses other than AMI, potentially reducing the specificity for AMI.<sup>20-22</sup> Although the 99th percentile is the undisputed reference value to diagnose AMI according to the universal definition of AMI, optimal clinical decision levels or cutoff levels at presentation to the ED may well differ from the 99th percentile.<sup>4</sup>

We therefore aimed to examine the diagnostic performance and to identify the optimal cutoff levels of 7 more sensitive cTn assays for the early diagnosis of AMI in patients with renal dysfunction.

## Methods

### Study Design and Population

The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective, international, multicenter study designed and coordinated by the University Hospital Basel (Basel, Switzerland).<sup>19,23,24</sup> From April 2006 to June 2013, 3030 consecutive patients >18 years of age presenting to the ED with symptoms suggestive of AMI with an onset or peak within the last 12 hours were recruited after providing written informed consent. Although enrollment was completely independent of renal function, allowing the inclusion of a large number of patients with various degrees of renal dysfunction, patients with terminal kidney failure requiring regular long-term dialysis were excluded. For this analysis, patients were also excluded if no creatinine value at presentation to the ED was available (n=18), if none of the 7 investigational cTn assays were available at baseline (n=107), or if the final diagnosis remained unclear after adjudication (n=92; for details, see the online-only Data Supplement). Because some patients had missing data for some of the 7 investigational cTn assays, 7 assay-specific subcohorts with a large overlap but numerically not identical sizes were derived from the main cohort.

Renal function was quantified by estimating glomerular filtration rate (eGFR) with the use of the abbreviated Modification of Diet in Renal Disease Study equation based on plasma creatinine level, age, and sex, as described in detail elsewhere.<sup>25-27</sup> For this analysis, renal dysfunction was defined as an eGFR of <60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>.<sup>26</sup> All creatinine measurements were performed on a Roche Modular P1 analyzer with the enzymatic Creatinine-PAP method for quantification (Roche Diagnostics, Switzerland). Serum creatinine can be

converted from micromoles per liter to milligrams per deciliter by dividing by 88.4.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the paper, and made the decision to submit it for publication. The assays were donated by the manufacturers, which had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit for publication.

### Routine Clinical Assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography. Levels of cTn were measured at presentation and serially thereafter as long as clinically indicated. Timing and treatment of patients were left to discretion of the attending physician.

### Adjudicated Final Diagnosis

Adjudication of the final diagnosis was performed centrally in a core laboratory (University Hospital Basel) and included levels of Roche hs-cTnT to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn assays (which allows the additional detection of small AMIs that were missed by the adjudication based on conventional cTn assays).<sup>20,21</sup> Two independent cardiologists reviewed all available medical records—patient history, physical examination, results of laboratory testing (including hs-cTnT levels), radiological testing, ECG, echocardiography, cardiac exercise stress test, lesion severity, and morphology in coronary angiography—pertaining to the patient from the time of ED presentation to the 90-day follow up. Specifically, the patients' description of pain (typical, atypical, nonspecific), time since onset and peak of symptoms, and new ECG findings were taken into account for the adjudication of the final diagnosis. Furthermore, in patients with renal dysfunction, cTn levels of prior admissions were considered to assess whether the cTn levels were elevated previously. If the patient was taken to the catheterization laboratory, the presence of an acute occlusion, an acute culprit lesion with less than Thrombolysis in Myocardial Infarction grade 3 flow, and new wall motion abnormalities were considered evidence of AMI if observed in combination with an acute rise or fall in hs-cTnT. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

AMI was defined and cTn levels were interpreted as recommended in current guidelines.<sup>1,2,28</sup> In brief, AMI was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least 1 cTn value above the 99th percentile of healthy individuals, together with a significant rise or fall.<sup>14,28,29</sup> The criteria used to define rise or fall are described in detail in the Methods section in the online-only Data Supplement.

### Investigational cTn Analysis

Details on the 7 cTn assays used in this analysis are given in the Methods section in the online-only Data Supplement. All 7 more sensitive cTn assays were centrally measured in a core laboratory. As for all cTn assays, the 7 more sensitive cTn assays are not biologically equivalent.

### Follow-Up and Clinical End Points

After hospital discharge, patients were contacted after 3, 12, and 24 months by telephone calls or in written form. Information on death was furthermore obtained from the national registry on mortality, the diagnosis registry of the hospitals, and the family physicians' records. The primary prognostic end point was survival within 2 years.

### Statistical Analysis

Details on statistical analysis can be found in the online-only Data Supplement.

## Results

### Patient Characteristics

Among the 2813 unselected patients in the total cohort, 447 (16%) had renal dysfunction (Table 1). Among the

7 assay-specific subcohorts, baseline characteristics and final diagnoses were comparable (Table I in the online-only Data Supplement). Patients with renal dysfunction differed from patients with normal renal function in multiple baseline characteristics, including higher prevalence

**Table 1. Baseline Patient Characteristics**

	All Patients (n=2813)	Normal Renal Function (n=2366)	Renal Dysfunction* (n=447)	P Value†	Patients With Renal Dysfunction		
					AMI		P Value†
					Yes (n=160)	No (n=287)	
Male sex, n (%)	1907 (68)	1656 (70)	251 (56)	<0.001	95 (59)	156 (54)	0.305
Age, median (Q1, Q3), y	62 (49, 74)	58 (48, 70)	77 (70, 83)	<0.001	79 (73, 85)	77 (70, 82)	0.004
Cardiovascular risk factors, n (%)							
Diabetes mellitus	488 (17)	363 (15)	125 (28)	<0.001	49 (31)	76 (26)	0.039
Current smoking	720 (26)	675 (29)	45 (10)	<0.001	22 (14)	23 (8)	0.083
History of smoking	1013 (36)	823 (35)	190 (43)	<0.001	58 (37)	132 (46)	0.089
Hypercholesterolemia	1407 (50)	1099 (46)	308 (69)	<0.001	119 (74)	189 (66)	0.062
Hypertension	1741 (62)	1342 (57)	399 (89)	<0.001	148 (93)	251 (88)	0.099
History, n (%)							
Known coronary artery disease	965 (34)	714 (30)	251 (56)	<0.001	96 (60)	155 (54)	0.221
Previous myocardial infarction	653 (23)	475 (20)	178 (40)	<0.001	70 (44)	108 (38)	0.205
Previous revascularization	768 (27)	590 (25)	178 (40)	<0.001	65 (41)	113 (39)	0.795
Peripheral artery disease	171 (6)	112 (5)	59 (13)	<0.001	27 (17)	32 (11)	0.086
Previous stroke	154 (6)	106 (5)	48 (11)	<0.001	22 (14)	26 (9)	0.125
Vital status, median (Q1, Q3)							
Heart rate, bpm	76 (66, 89)	76 (66, 89)	74 (63, 91)	0.162	79 (63, 96)	73 (63, 88)	0.033
Systolic blood pressure, mm Hg	141 (127, 159)	142 (128, 159)	138 (120, 157)	0.001	137 (119, 159)	139 (120, 159)	0.213
Diastolic blood pressure, mm Hg	82 (72, 92)	83 (74, 92)	75 (65, 86)	<0.001	74 (65, 84)	76 (65, 87)	0.157
Body mass index, kg/m <sup>2</sup>	26 (24, 30)	26 (24, 30)	27 (24, 30)	0.414	25 (23, 28)	27 (25, 31)	<0.001
ECG, n (%)							
ST-segment elevation	134 (5)	110 (5)	24 (6)	0.010	23 (15)	1 (0.4)	<0.001
ST-segment depression	322 (11)	228 (10)	94 (21)	<0.001	61 (38)	33 (11)	<0.001
T-wave inversion	375 (13)	287 (12)	88 (20)	<0.001	46 (29)	42 (15)	<0.001
Left bundle-branch block	81 (3)	52 (2)	29 (7)	<0.001	16 (10)	13 (5)	0.024
Diagnostic examinations and interventions, ‡ n (%)							
Stress testing	711 (25)	626 (27)	85 (19)	0.001	20 (13)	65 (23)	0.009
Coronary angiographies	739 (26)	590 (25)	149 (33)	<0.001	94 (59)	55 (19)	<0.001
Coronary interventions	443 (16)	357 (15)	86 (19)	0.027	64 (40)	22 (8)	<0.001
CABG	64 (2)	52 (2)	12 (3)	0.527	10 (6)	2 (1)	<0.001
Renal function, median (Q1, Q3)							
Creatinine, μmol/L	76 (65, 90)	72 (63, 83)	116 (99, 139)	<0.001	120 (106, 147)	115 (96, 135)	0.038
MDRD eGFR, mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	85 (69, 101)	90 (77, 104)	49 (39, 55)	<0.001	47 (37, 55)	49 (41, 55)	0.089
Stages of renal dysfunction, n (%)							
eGFR 30–59 mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	403 (14)	...	403 (90)		141 (88)	262 (91)	0.491
eGFR 15–29 mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	34 (1)	...	34 (8)	NA	14 (9)	20 (7)	
eGFR <15 mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	10 (0.4)	...	10 (2)		5 (3)	5 (2)	

AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; Q1, quartile 1; and Q3, quartile 3.

\*Renal dysfunction was diagnosed if the MDRD eGFR was <60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> at presentation.

†The  $\chi^2$  test was used for comparison of proportions.

‡Performed during or directly after the index visit (within 1 month).

of cardiovascular risk factors, previous myocardial infarction, stroke, and ECG abnormalities. In patients with renal dysfunction, the total rate of additional cardiac testing related to AMI diagnosis (in addition to detailed history, ECG, cTn, chest x-ray), including coronary angiography or cardiac stress testing with or without imaging, was similar to that of patients with normal renal function (52% in both groups;  $P=NS$ ). Coronary angiography was performed more frequently in patients with renal dysfunction (33%) compared with patients with normal renal function (25%;  $P<0.001$ ).

AMI was the adjudicated final diagnosis in 36% of patients with renal dysfunction compared with 18% in patients with normal renal function ( $P<0.001$ ). Both type I AMI and type II AMI were more frequent in patients with renal dysfunction. Among patients with non-ST-segment-elevation myocardial infarction, type II AMI was seen in 23% of patients with renal dysfunction compared with 10% in patients with normal renal function ( $P<0.001$ ; Table II in the online-only Data Supplement). Disagreement between the 2 independent cardiologists adjudicating the final diagnosis was more common in patients with renal dysfunction compared with patients with normal renal function (8.7% versus 5.9%;  $P=0.023$ ) and tended to be more common in patients presenting with elevated levels of hs-cTnT compared with patients presenting with normal levels of hs-cTnT (7.4% versus 5.7%;  $P=0.063$ ).

### cTn Levels at Presentation

In patients with renal dysfunction and in patients with normal renal function, cTn levels at presentation, as assessed by all 7 more sensitive cTn assays, were significantly higher in patients whose final diagnosis was AMI compared with those with other diagnoses ( $P<0.001$  for comparisons). Among the patients whose final diagnosis was not AMI, patients with renal dysfunction had significantly higher baseline levels of all 7 more sensitive cTn assays compared

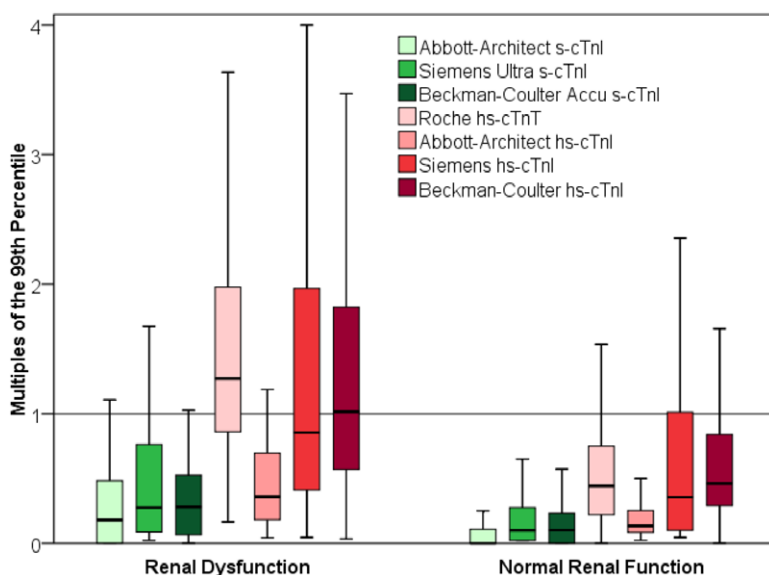
with patients with normal renal function ( $P<0.001$  for all comparisons with patients with normal renal function). Overall, 12% of patients with renal dysfunction and a final diagnosis other than AMI had elevated baseline levels above the 99th percentile with Abbott-Architect s-cTnI, 20% with Siemens-Ultra s-cTnI, 12% with Beckman-Coulter Accu s-cTnI, 71% with Roche hs-cTnT, 17% with Abbott hs-cTnI, 46% with Siemens hs-cTnI, and 54% with Beckman-Coulter hs-cTnI. Among patients with normal renal function, the percentages were significantly lower (7%, 7%, 7%, 15%, 6%, 23%, and 21%, respectively;  $P<0.001$  for all comparisons; Figure 1). Among patients with renal dysfunction and elevated ( $\geq 99$ th percentile) baseline cTn levels, AMI was the most common diagnosis for all assays (range, 45%–80%; Figure 2). Among patients with renal dysfunction and normal baseline cTn levels, noncardiac cause of chest pain is the most common diagnosis (Figure I in the online-only Data Supplement). Details on median absolute changes of hs-cTnT during serial sampling are shown in Table IIIA and IIIB in the online-only Data Supplement.

### Correlations Between cTn levels and eGFR

Among patients with final diagnoses other than AMI, all 7 more sensitive cTn assays correlated significantly and inversely with renal function as quantified with the Modification of Diet in Renal Disease eGFR formula (correlation coefficient,  $r$ , ranging from  $-0.448$  to  $-0.222$ ;  $P<0.001$  for all correlations). The correlation between eGFR and hs-cTnT was stronger compared with the correlation between eGFR and hs-cTnI as measured with all assays (Figure II in the online-only Data Supplement).

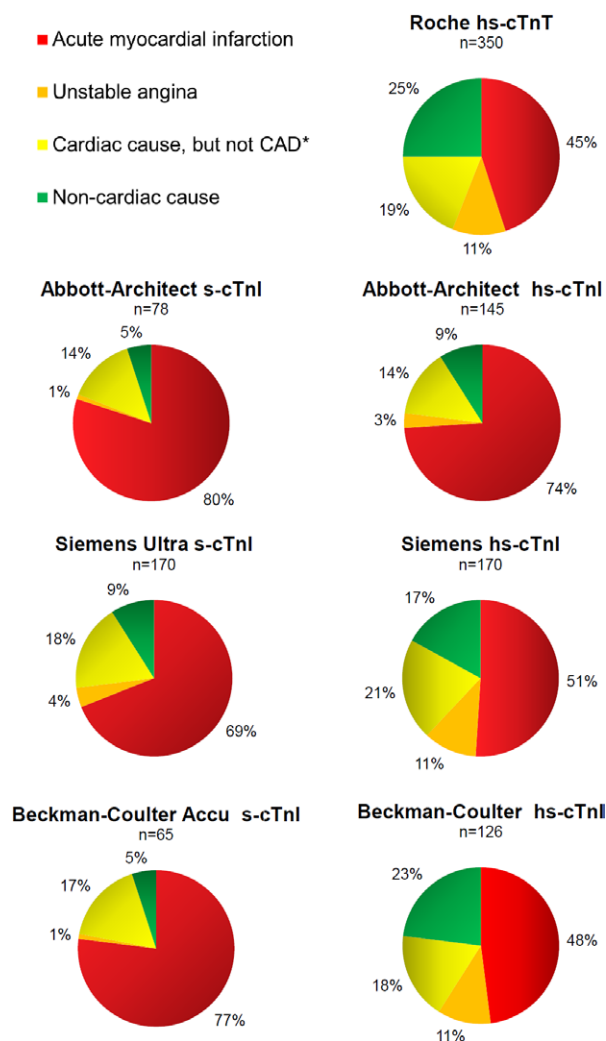
### Diagnostic Accuracy of More Sensitive cTn

In patients with renal dysfunction, the diagnostic accuracy for measurements obtained at presentation, as quantified by the area under the receiver-operating characteristic curve (AUC), overall was high (AUC, 0.87–0.89) for all 7 more



**Figure 1.** Baseline levels of more sensitive cardiac troponin (cTn) assays at presentation in patients with final diagnosis other than acute myocardial infarction. cTn levels are displayed as multiples of the 99th percentile. Boxes represent interquartile ranges; whiskers display ranges (without outliers further than 1.5 interquartile ranges). **Left,** In patients with renal dysfunction. **Right,** In patients with normal renal function. hs indicates high-sensitivity; and s, sensitive.





**Figure 2.** Distribution of final diagnoses in patients with renal dysfunction and cardiac troponin (cTn) levels above the 99th percentile at presentation. hs Indicates high-sensitivity; and s, sensitive. \*Coronary artery disease.

sensitive-cTn assays (Table 2 and Figure 3). Diagnostic accuracy further increased to 0.91 to 0.95 for samples obtained at 3 hours (Table IV in the online-only Data Supplement) and for combinations of the baseline level with early absolute changes (eg, at 1 hour: AUC, 0.90–0.93; Table V in the online-only Data Supplement). No significant differences among the 7 more sensitive cTn assays were observed ( $P=NS$  for all comparisons). Overall, the AUCs in patients with renal dysfunction were only slightly lower than in patients with normal renal function. The AUC for levels obtained at presentation in patients with normal renal function was 0.91 to 0.94 ( $P<0.05$  for the 4 assays with the largest sample size/comparisons with patients with renal dysfunction).

Among patients with different stages of renal dysfunction, AUCs for all more sensitive cTn assays were lower in the lowest tertile of renal function ( $eGFR \leq 42$  mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>) compared with the intermediate tertile ( $eGFR, 42–53$  mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>). This difference was statistically significant for the 3 assays with the largest sample

size. In contrast, the AUCs were comparable for all assays in patients in the highest tertile ( $eGFR >53$  mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>) and the intermediate tertile (Table VI in the online-only Data Supplement).

### Diagnostic Performance in the Early Diagnosis of AMI at the 99th Percentile

Overall, at the 99th percentile, all 7 more sensitive cTn assays showed higher sensitivity (77%–98%) in patients with renal dysfunction compared with patients with normal renal function. This increase in sensitivity, however, was associated with a decrease in specificity (32%–89%;  $P<0.001$ ; Table VIIA and VIIB in the online-only Data Supplement). Sensitivity and specificity at the 99th percentile differed markedly between the more sensitive cTn assays. For 3 of the 4 hs-cTn assays, the specificity and positive predictive value at the 99th percentile were <60% and 55%, respectively.

### Optimal Cutoff Levels for cTn in the Early Diagnosis of AMI

The optimal cutoff levels to separate AMI from other conditions underlying acute chest pain in the ED determined by the receiver-operator characteristic curve analysis in patients with renal dysfunction were close to the 99th percentile for the 3 s-cTn assays (1.0 times the 99th percentile for Abbott-Architect s-cTnI, 1.2 times the 99th percentile for Siemens Ultra s-cTnI, and 0.9 times the 99th percentile for Beckman-Coulter Accu s-cTnI) and substantially higher for most hs-cTn assays (2.1 times the 99th percentile for Roche hs-cTnT, 1.1 times the 99th percentile for Abbott-Architect hs-cTnI, 3.6 times the 99th percentile for Siemens hs-cTnI, and 2.8 times the 99th percentile for Beckman-Coulter hs-cTnI).

Overall, all cutoff levels fulfilling a predefined criteria (derived by receiver-operator characteristic curve, optimized for sensitivity, optimized for specificity) were higher in patients with renal dysfunction compared with patients with normal renal function. The optimal receiver-operator characteristic curve–derived cutoff levels in patients with renal dysfunction were 1.9 to 3.4 times the levels in patients with normal renal function.

### Prognostic Performance of More Sensitive cTn in Renal Dysfunction

Median follow-up was 759 days (first quartile, 455 days; third quartile, 895 days). Overall, 182 patients (6%) died during follow-up. Cumulative survival at 2 years was 79% in patients with renal dysfunction versus 96% in patients with normal renal function (log-rank  $P<0.001$ ; Figure III in the online-only Data Supplement). Survival was 67% among patients with renal dysfunction and AMI versus 85% in patients with renal dysfunction and diagnoses other than AMI (log-rank  $P<0.001$ ). Levels of cTn as measured with all 7 more sensitive cTn assays were higher in deceased patients compared with survivors and accordingly predicted long-term survival (Table VIII and Figure IV in the online-only Data Supplement).

**Table 2. Diagnostic Performance of cTn at Presentation in Patients With Renal Dysfunction and in Patients With Normal Renal Function**

Assay	Normal Renal Function		Renal Dysfunction		P Value*
	n	ROC AUC (95% CI)	n	ROC AUC (95% CI)	
s-cTn assays					
Abbott-Architect s-cTnI	1095	0.91 (0.89–0.94)	219	0.89 (0.85–0.94)	0.449
Siemens Ultra s-cTnI	2247	0.92 (0.91–0.94)	416	0.87 (0.84–0.91)	0.013
Beckman-Coulter Accu s-cTnI	964	0.92 (0.89–0.94)	190	0.89 (0.84–0.94)	0.576
hs-cTn assays					
Roche hs-cTnT	2366	0.94 (0.93–0.95)	447	0.87 (0.84–0.91)	<0.001
Abbott-Architect hs-cTnI	1921	0.94 (0.93–0.95)	366	0.87 (0.83–0.91)	<0.001
Siemens hs-cTnI	1591	0.94 (0.92–0.95)	283	0.89 (0.84–0.93)	0.034
Beckman-Coulter hs-cTnI	964	0.93 (0.90–0.95)	190	0.89 (0.84–0.94)	0.217

CI indicates confidence interval; cTn, cardiac troponin; hs, high-sensitivity; ROC AUC, area under the receiver-operating characteristic curve; and s, sensitive.

\*Comparisons of the ROC AUC of patients with renal dysfunction and normal renal function.

## Discussion

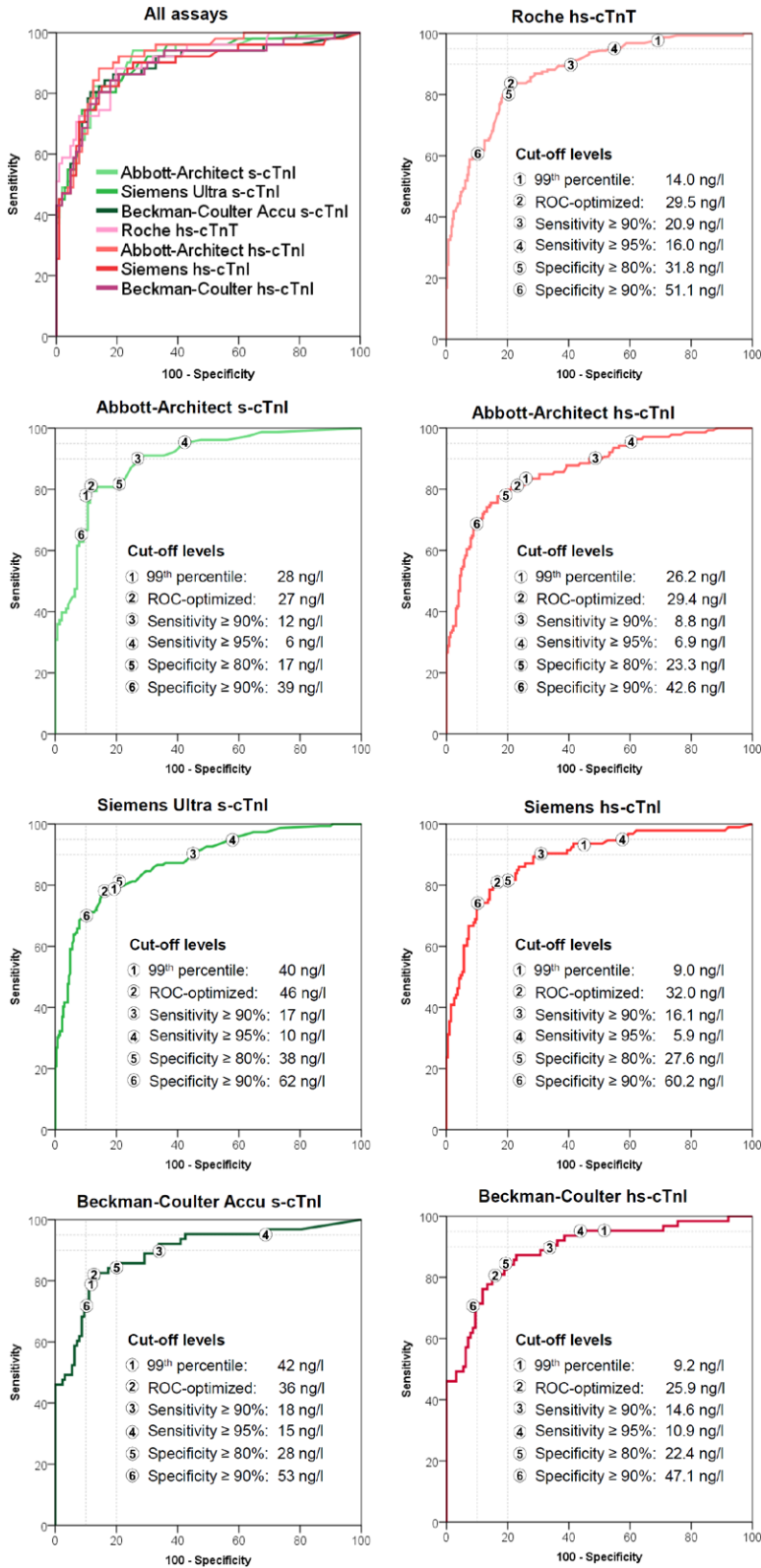
In this multicenter study, we examined the diagnostic performance and identified the optimal cutoff levels of 7 more sensitive cTn assays for the early diagnosis of AMI in patients with renal dysfunction. We report 7 novel findings that have important clinical implications for the early diagnosis of AMI in that they clearly highlight that more sensitive cTn assays maintain high diagnostic utility in patients with renal dysfunction as long as optimized cutoff levels are used.

First, cTn levels at presentation, as assessed by all 7 more sensitive cTn assays, were significantly higher in patients whose final diagnosis was AMI compared with those with other final diagnoses. The prevalence of elevated cTn levels above the 99th percentile in patients with renal dysfunction and a final diagnosis other than AMI differed substantially among the 7 more sensitive cTn assays, ranging from 12% to 71%. Second, despite this, AMI remained the most common final diagnosis among patients with elevated cTn levels for all assays (range, 45%–80%). Third and perhaps most important, for all 7 more sensitive cTn assays, the diagnostic accuracy at presentation was high in patients with renal dysfunction with an AUC ranging from 0.87 to 0.89 and further increased for later sampling points and for combinations of the baseline level with early absolute changes. The diagnostic accuracy of the more sensitive cTn assays at presentation was only slightly lower compared with that in patients with normal renal function. Fourth, diagnostic accuracies were comparable among the 7 more sensitive cTn assays in patients with renal dysfunction with no systematic superiority of hs-cTn assays over sensitive assays. Fifth, at the 99th percentile, all cTn assays showed higher sensitivity but lower specificity in patients with renal dysfunction compared with patients with normal renal function, reflecting the higher baseline levels observed in patients with renal dysfunction even in the absence of AMI. Sixth, the receiver-operator characteristic curve–derived optimal cutoff levels

in patients with renal dysfunction were 2- to 3-times higher in patients with renal dysfunction compared with patients with normal renal function. Seventh, cTn as measured with all 7 more sensitive cTn assays also retained prognostic value and predicted 2-year survival in patients with renal dysfunction. These findings extend the observations made in previous studies investigating the prognostic value of cTn in various other settings.<sup>30–33</sup>

Although the 99th percentile of healthy individuals is the undisputed reference value to diagnose AMI according to the universal definition of AMI,<sup>4</sup> optimal clinical decision levels or cutoff levels at presentation to the ED may well differ from the 99th percentile of healthy individuals. For example, if we aim to rule out AMI at presentation to the ED, the cutoff level achieving high sensitivity and negative predictive value will likely be lower than the 99th percentile to allow for a further increase in cTn during serial sampling. Alternatively, if we aim to rule in AMI at presentation to the ED, the cutoff level achieving high specificity and positive predictive value will likely be higher than the 99th percentile because mild elevations in cTn can often be caused by conditions other than AMI. The fine-tuning of clinical decision levels for specific clinical settings (eg, ED) and patient populations (eg, renal dysfunction) is a key step in the clinical implementation of novel diagnostic tools such as biomarkers and has recently been done successfully for other biomarkers such as B-type natriuretic peptide and procalcitonin.<sup>34–36</sup>

Our findings highlight that these clinical decision levels are assay specific and need to be determined for each assay individually. For example, the clinical decision level for cTn assay A achieving a specificity of 90% in patients with renal dysfunction cannot be reliably extrapolated from observations made with cTn assay B. To some extent, this requirement is explained by biochemical differences among the cTn assays and the challenges to define a healthy reference population to determine the 99th percentile.<sup>4,14</sup> The 99th percentile is currently derived for each assay individually in



**Figure 3.** Diagnostic performance of cardiac troponin (cTn) at presentation in renal dysfunction. Receiver-operating characteristic (ROC) curves are describing the diagnostic performance of the 3 sensitive (s; green) and 4 high-sensitivity (hs; red) cTn assays at presentation for the diagnosis of acute myocardial infarction in patients with renal dysfunction. The figure containing multiple curves (upper left corner) is based on the subset of patients in whom data for all 7 assays are available. The figures for the individual assays are based on all patients with available data for the respective assays to maximize precision for the determination of the respective predefined cutoff levels, which are marked as follows: 1=99th percentile, 2=optimal cutoff derived from the ROC curve, 3=sensitivity  $\geq$ 90%, 4=sensitivity  $\geq$ 95%, 5=specificity  $\geq$ 80%, and 6=specificity  $\geq$ 90%.

unstandardized, healthy cohorts that differ from community-based cohorts.<sup>37</sup> In addition, as shown, for example, by Gore et al,<sup>37</sup> the 99th percentile of community-based cohorts also differs largely and will depend on the cohort's mean age and the prevalence of cardiovascular comorbidities and renal

dysfunction. Some of the differences observed for the performance of the more sensitive cTn assays at the respective 99th percentile of healthy individuals may be associated at least in part with differences between the cohorts of healthy individuals chosen for the determination of the 99th percentile.

Of note, the 99th percentile of the Roche hs-cTnT, the assay used for the adjudication of the final diagnosis in the present analysis, has rather consistently been reported to be  $\approx 14$  ng/L, whereas the findings for other hs-cTn assays have been more variable.<sup>38</sup>

Our data also confirm previous observations that the diagnostic challenge in patients with renal dysfunction appears to be largely confined to patients presenting without persistent ST-segment elevation and that ST-segment depression or T-wave inversion is much more common in patients with renal dysfunction, even in the absence of AMI.<sup>2-4</sup>

This study is the first analysis that specifically examined diagnostic performance of more sensitive cTn assays in patients presenting to the ED with renal dysfunction and symptoms suggestive of AMI. Our findings may also help to better put into perspective a contradictory conclusion derived from a recent retrospective single-center study analyzing all ED patients with renal dysfunction regardless of symptoms, clinical gestalt, and clinical pretest probability for AMI, which reported lower-than-expected diagnostic accuracy of hs-cTnT for AMI.<sup>22</sup> In that cohort, only 37% of patients had a clinical suspicion of AMI, and trauma, stroke, epileptic seizures, and acute heart failure accounted for the majority of patients. In those patients, the clinical role of measuring cTn is controversial and not at all comparable to the measurement in patients presenting with suspected AMI. In addition, that population of patients provides important methodological challenges for the adjudication of AMI based on the information obtained during routine clinical care, which might have further contributed to those findings. The findings from this prospective multicenter study using a gold standard diagnosis centrally adjudicated by 2 independent cardiologists should help to avoid possible misunderstandings related to the diagnostic utility of more sensitive cTn assays in patients with suspected AMI and renal dysfunctions.

The following limitations of the present study merit consideration. First, we evaluated 7 more sensitive-cTn assays. We hypothesize that our findings can be generalized to other cTn assays with similar sensitivity and precision. However, additional studies need to confirm this hypothesis. Second, in this ongoing prospective study, the subgroup analysis of patients with renal dysfunction was not predefined at the time of the writing of the first protocol but was added as an amendment in 2009, when we were still blinded to the results. Third, we cannot comment on the clinical utility of more sensitive cTn assays in patients undergoing dialysis because such patients were excluded from our study.<sup>39</sup> Fourth, to reflect the clinical information available to the ED physician when interpreting cTn levels, we classified renal dysfunction according to eGFR on the basis of the serum creatinine level obtained in the ED. Accordingly, this classification differs from the definition of chronic kidney disease, which would require renal dysfunction to be present for 3 months.<sup>25-27</sup>

## Conclusions

More sensitive cTn assays maintain high diagnostic accuracy in patients with suspected AMI and renal dysfunction. To ensure the best possible clinical use, assay-specific optimal

cutoff levels, which are higher in patients with renal dysfunction, should be considered.

## Sources of Funding

The study was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Cardiovascular Research Foundation Basel, the University Hospital Basel, Abbott, Roche, Nanosphere, Siemens, 8sense, Bühlmann, and B.R.A.H.M.S.

## Disclosures

Dr Mueller has received research grants from the Swiss National Science Foundation and the Swiss Heart Foundation, the Cardiovascular Research Foundation Basel, 8sense, Abbott, ALERE, Brahms, Critical Diagnostics, Nanosphere, Roche, Siemens, and the University Hospital Basel, as well as speaker honoraria from Abbott, ALERE, Brahms, Novartis, Roche, and Siemens. Dr Reichlin has received research grants from the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the University of Basel, the Professor Max Cloetta Foundation, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria from Brahms and Roche. The other authors report no conflicts. The sponsors had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

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### CLINICAL PERSPECTIVE

In this multicenter study, we examined the diagnostic performance and identified the optimal cutoff levels of 7 more sensitive cardiac troponin (cTn) assays for the early diagnosis of acute myocardial infarction (AMI) in patients with renal dysfunction. We report 7 novel findings that have important clinical implications for the early diagnosis of AMI in that they clearly highlight that more sensitive cTn assays maintain high diagnostic utility in patients with renal dysfunction as long as optimized cutoff levels are used. First, cTn levels at presentations, as assessed by all the more sensitive cTn assays, were significantly higher in patients whose final diagnosis was AMI compared with those with other final diagnoses. The prevalence of elevated cTn levels above the 99th percentile in patients with renal dysfunction and a final diagnosis other than AMI differed substantially among the 7 more sensitive cTn assays, ranging from 12% to 71%. Second, despite this, AMI remained the most common final diagnosis among patients with elevated cTn levels for all assays (range, 45%–80%). Third and perhaps most important, for all 7 more sensitive cTn assays, the diagnostic accuracy at presentation was high in patients with renal dysfunction and further increased for later sampling points. Diagnostic accuracy of the more sensitive cTn assays at presentation was only slightly lower compared with that in patients with normal renal function. Fourth, diagnostic accuracies were comparable among the 7 more sensitive cTn assays in patients with renal dysfunction with no systematic superiority of high-sensitivity cTn assays over sensitive assays. Fifth, at the 99th percentile, all cTn assays showed higher sensitivity but lower specificity in patients with renal dysfunction compared with patients with normal renal function, reflecting the higher baseline levels observed in patients with renal dysfunction even in the absence of AMI. Sixth, the receiver-operating characteristic curve–derived optimal cutoff levels in patients with renal dysfunction were 2- to 3-times higher in patients with renal dysfunction compared with patients with normal renal function. Seventh, cTn as measured with all 7 more sensitive cTn assays also retained prognostic value and predicted 2-year survival in patients with renal dysfunction.