Risk stratification in patients with unstable angina using absolute serial changes of 3 high-sensitive troponin assays

Tobias Reichlin, MD, [a,b,c] **Raphael Twerenbold, MD,** [b] **Claudia Maushart, MD,** [b] **Miriam Reiter, MD,** [b] **Berit Moehring, MD,** [a,b] **Nora Schaub, MD,** [b] **Cathrin Balmelli, MD,** [b] **Maria Rubini Gimenez, MD,** [a] **Rebeca Hoeller, MD,** [a] **Konstantin Sakarikos, MD,** [a] **Beatrice Drexler, MD,** [b] **Philip Haaf, MD,** [b] **Stefan Osswald, MD,** [a] **and Christian Mueller, MD, FESC** [a,b] ***Basel, Switzerland; and Boston, MA***

Background It is unknown whether unstable angina (UA) results in previously nondetectable low-level myocardial necrosis. We compared the pattern of myocardial necrosis between patients with UA, acute myocardial infarction (AMI), and noncardiac chest pain (NCCP) using 3 high-sensitive cardiac troponin (hs-cTn) assays.

Methods In a multicenter study, we enrolled 842 unselected patients with acute chest pain in the emergency department. Roche hs-cTnT, Beckman Coulter hs-cTnI, and Siemens hs-cTnI were determined in a blinded fashion at presentation and after 1, 2, 3, and 6 hours. The final diagnosis was adjudicated by 2 independent cardiologists.

Results A change in hs-cTn of ≥2 ng/L within the first hour after presentation as assessed with Roche hs-cTnT, Beckman Coulter hs-cTnI, and Siemens hs-cTnI was observed in 26%, 31%, and 32% of patients with UA (n = 115) compared with 91%, 92%, and 96% in patients with AMI (n = 120) and 12%, 23%, and 16% in patients with NCCP (n = 415; $P < .001$ for all comparisons between UA and AMI, $P > .05$ for all comparisons between UA and NCCP). In patients with UA, such a 1-hour change in hs-cTn of ≥2 ng/L was associated with an increased risk of death or AMI during the 30-day follow-up ($P = .003$, .03, .03) and 2-year follow-up ($P < .001$, .002, and .006).

Conclusions In marked contrast to patients with AMI, most patients with UA do not exhibit relevant hs-cTn changes. The minority of UA with hs-cTn changes, however, has a significantly worse short- and long-term outcome. (Am Heart J 2013;165:371-378.e3.)

The acute coronary syndrome (ACS) is a major cause of death and disability worldwide. It comprises 2 entities: acute myocardial infarction (AMI) and unstable angina (UA). Although the diagnosis and treatment of AMI have advanced considerably throughout the last decades,[1-3] progress has been limited for UA. The electrocardiogram (ECG) and contemporary biomarkers both have poor sensitivity and specificity.[1,2] In addition, the benefit associated with more aggressive treatment including early revascularization and antithrombotic therapy is very small, if present at all.[4-6] Lack of progress in UA may, at least in part, be caused by our limited ability to assess different patterns of myocardial injury within the group of traditionally diagnosed patients with UA. Accordingly, it is unknown whether some of these patients actually had small areas of myocardial necrosis that were below the limit of detection (LoD) of standard cardiac troponin (cTn) assays.[7]

The high-sensitive cTn (hs-cTn) assays provide a new window to the myocardium by enabling the measurement of cTn concentrations undetectable with prior generations of tests. It has therefore become possible to measure cTn in healthy subjects with high precision.[8-10] This feature makes hs-cTn measurement a clinically available tool to assess myocardial necrosis in patients with UA. Assessment of absolute changes in hs-cTn levels during serial testing allows us to differentiate acute myocardial injury from potentially underlying more chronic myocardial disease.

The primary aim of this analysis was to assess the amount and dynamic of myocardial necrosis in patients with UA in comparison with patients with AMI and noncardiac chest pain (NCCP) using 3 hs-cTn assays. The

From the [a]Department of Cardiology, University Hospital Basel, Basel, Switzerland, [b]Department of Internal Medicine, University Hospital Basel, Basel, Switzerland, and [c]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.

ClinicalTrials.gov no. NCT00470587.

Submitted July 7, 2012; accepted November 11, 2012.

Reprint requests: Christian Mueller, MD, FESC, Division of Cardiology, Department of Internal Medicine, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail: chmueller@uhbs.ch

0002-8703/$ - see front matter

http://dx.doi.org/10.1016/j.ahj.2012.11.010

secondary aim was to assess the prognostic relevance of hs-cTn levels and changes in patients with UA for short- and long-term follow-up.

Methods

Study design and population

*A*dvantageous *P*redictors of *A*cute *C*oronary Syndrome *E*valuation (APACE) is an ongoing prospective international multicenter study designed and coordinated by the University Hospital Basel.[11,12] From April 2006 to June 2009, a total of 1,247 consecutive patients presenting to the emergency department (ED) with acute chest pain symptoms suggestive of AMI such as acute chest pain and angina pectoris with an onset or peak within the last 12 hours were recruited. Patients with terminal kidney failure requiring dialysis were excluded. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. All patients underwent an initial clinical assessment that included clinical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood tests, and chest radiography. Timing and treatment for patients were left at the discretion of the attending physician.

Adjudicated final diagnosis

Adjudication of final diagnoses was performed centrally in the core laboratory (University Hospital Basel) for all patients, as described previously.[11,12] In brief, 2 independent cardiologists blinded to hs-cTn measurement reviewed all available medical records (including patient history, physical examination, results of laboratory testing including local cTn values, radiologic testing, ECG, echocardiography, cardiac exercise test, and coronary angiography) pertaining to the patient from the time of ED presentation to 60-day follow-up. In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist.

Acute myocardial infarction was defined and cTn levels were interpreted as recommended in the current guidelines.[1,13-15] Assays used in the participating sites were Abbott (Baar, Switzerland) Axsym cTnI ADV, Beckman Coulter (Nyon, Switzerland) Accu cTnI, and Roche (Rotkreuz, Switzerland) cTnT fourth generation, all of which are well-validated current standard cTn assays with comparable performance in the diagnosis of AMI (see the online Appendix for details on use of each of the local cTn assays for final diagnosis adjudication).[14,15] Unstable angina was diagnosed in patients with normal local cTn levels and typical angina at rest, a deterioration of a previously stable angina (clinical diagnosis without further tests, n = 13), in cases of positive cardiac exercise testing (n = 21) or cardiac catheterization with coronary arteries found to have a stenosis of 70% or greater (n = 80), and in 1 ambiguous case in which follow-up information revealed AMI within 60 days. Further predefined diagnostic categories included cardiac but not coronary symptoms (eg, perimyocarditis and tachyarrhythmias), NCCP, and symptoms of unknown origin.

Investigational hs-cTn analysis

Blood samples were collected at presentation to the ED in serum tubes for determination of Roche hs-cTnT and in heparin plasma tubes for determination of Beckman Coulter hs-cTnI and Siemens hs-cTnI. Additional samples were collected at 1, 2, 3, and 6 hours. The most common reasons for missing values during serial sampling (especially at later time points) were early transfer to the catheterization laboratory, diagnostic procedures around the sampling time points, and transfer to the coronary care unit or the regular floors if the patients were admitted. After centrifugation, samples were frozen at −80 °C until assayed in a blinded fashion in a dedicated core laboratory. Measurements were performed from samples never thawed before for Roche hs-cTnT in the first 800 patients and from samples with 1 previous thawing cycle for Roche hs-cTnT in the remaining patients and for the 2 hs-cTnI assays in all patients. The variability in troponin measurement attributable to long-term −80 °C storage and to 1 freeze-thaw cycle has been assessed in previous studies and was found to be of only a small magnitude.[16,17] Samples for measurement of all 3 hs-cTn assays at presentation and after 1 hour were available in 842 patients.

Roche hs-cTnT was measured on the Elecsys 2010. Limit of blank and LoD have been determined to be 3 and 5 ng/L, an imprecision corresponding to 10% coefficient of variation (CV) was reported at 13 ng/L, and the 99th percentile of a healthy reference population was reported at 14 ng/L.[8] Beckman Coulter hs-cTnI was measured on the Access 2 analyzer using an investigational prototype assay. According to the manufacturer, LoD is 2 ng/L, and the 99th percentile of a healthy reference population is 9 ng/L, with a 10% CV lower than the 99th percentile. For Siemens, a recently refined research prototype hs-cTnI assay was used. As reported by the manufacturer, LoD is 0.5 ng/L, the imprecision level corresponding to 10% CV is found at 3 ng/L, and the 99th percentile of a healthy reference population is 9 ng/L for this assay. Glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula.[18]

Follow-up and prognostic end point

Patients were contacted by telephone interview performed by trained researchers blinded to the results of laboratory testing after 3 and 12 months of follow-up and yearly thereafter. In case of recurrent acute chest pain events, review of all available medical records was performed to adjudicate nonfatal AMIs during follow-up. In case of uncertainties about vital status, referring physicians and administrative databases of the respective hometowns were contacted.

For this analysis, the prognostic end points used were a composite of all-cause mortality and nonfatal AMI up to 30 days and up to 2 years of follow-up.

Statistical analysis

Continuous variables are presented as means ± SD or medians with interquartile range (IQR), and categorical variables are presented as numbers and percentages. Continuous variables were compared using the Mann-Whitney *U* test, and categorical variables were compared using the Pearson χ^2 test. Kaplan-Meier analysis was performed for the combined end point of death or AMI, and log-rank testing was used to assess statistical significance of absolute changes within 1 hour. Based on previous findings, 3 categories for 1-hour absolute changes were defined as >4, 2 to 4, and <2 ng/L.[12] We used Cox proportional hazard models to compute hazard ratios (HRs) and 95% CIs of

Table. Baseline characteristics of the patients

	All patients (n = 842)	UA (n = 115)	AMI (n = 120)	Noncardiac (n = 415)	Others (n = 192)	*P*
Age (y)	64 (51-75)	69 (58-76)	74 (61-82)	58 (47-72)	66 (54-78)	<.001
Male gender, no. (%)	568 (68)	94 (82)	81 (68)	274 (66)	119 (62)	.003
Risk factors, no. (%)						
Hypertension	539 (64)	97 (84)	87 (73)	221 (53)	134 (70)	<.001
Hypercholesterolemia	290 (46)	84 (73)	57 (48)	164 (40)	85 (44)	<.001
Diabetes	169 (20)	34 (30)	30 (25)	62 (15)	43 (22)	.001
Current smoking	190 (23)	16 (14)	30 (25)	108 (26)	36 (19)	.02
History of smoking	307 (37)	61 (53)	43 (36)	137 (33)	66 (34)	.001
History, no. (%)						
Coronary artery disease	299 (36)	84 (73)	51 (43)	107 (26)	57 (30)	<.001
Previous myocardial infarction	207 (25)	59 (51)	36 (30)	76 (18)	36 (19)	<.001
Previous revascularization	224 (27)	69 (60)	31 (26)	81 (20)	43 (22)	<.001
Peripheral artery disease	51 (6)	13 (11)	12 (10)	15 (4)	11 (6)	.004
Previous stroke	52 (6)	4 (4)	19 (16)	18 (4)	11 (6)	.001
Creatinine clearance (mL min^{-1} m^{-2})	89 (71-106)	84 (67-104)	75 (59-100)	95 (77-111)	85 (66-100)	<.001
ECG findings, no. (%)						
Left bundle-branch block	34 (4)	4 (4)	13 (11)	9 (2)	8 (4)	<.001
ST-segment elevation	21 (3)	4 (4)	10 (8)	1 (0.2)	6 (3)	<.001
ST-segment depression	88 (11)	11 (10)	36 (30)	9 (2)	32 (17)	<.001
T-wave inversion	60 (7)	14 (12)	13 (11)	21 (5)	12 (6)	.02
No significant ECG abnormalities	639 (76)	82 (71)	48 (40)	375 (90)	134 (70)	<.001

predictors of 24-month mortality. All hypothesis testings were 2 tailed, and a *P* value of less than .05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows 15.0 (SPSS Inc, Chicago, IL) and MedCalc 9.6.4.0 (MedCalc Software, Ostend, Belgium).

Funding: This study was supported by research grants from the Swiss National Science Foundation (PP00B-102853), the Swiss Heart Foundation, Abbott, Roche, Siemens, and the Department of Internal Medicine, University Hospital Basel. Biomarker testing was conducted by Roche, Siemens, and Beckmann Coulter. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Characteristics of patients

Among the 842 patients presenting to the ED with acute chest pain, the adjudicated final diagnosis was UA in 115 (14%), AMI in 120 (14%), cardiac symptoms of origin other than coronary artery disease in 120 (14%), NCCP in 415 (49%), and symptoms of unknown origin in 72 (9%). Baseline characteristics of all patients and of patients with AMI, UA, and NCCP are shown in Table.

Absolute changes of hs-cTn according to final diagnosis

Changes in levels of the 3 hs-cTn assays in serial sampling according to final diagnosis are shown in Figure 1A-C and in Supplementary Table I of the online Appendix. In summary, a change in hs-cTn of ≥2 ng/L within the first hour after presentation as assessed with Roche hs-cTnT, Beckman Coulter hs-cTnI, and Siemens hs-cTnI was observed in 26%, 31%, and 32% of patients with UA compared with 91%, 92%, and 96% in patients with AMI and 12%, 23%, and 16% in patients with NCCP ($P < .001$ for all comparisons between UA and AMI, $P > .05$ for all comparisons between UA and NCCP).

The same pattern was observed for median changes after 2 hours. No association was observed between time since onset of symptoms and amount of changes in patients with UA (data not shown).

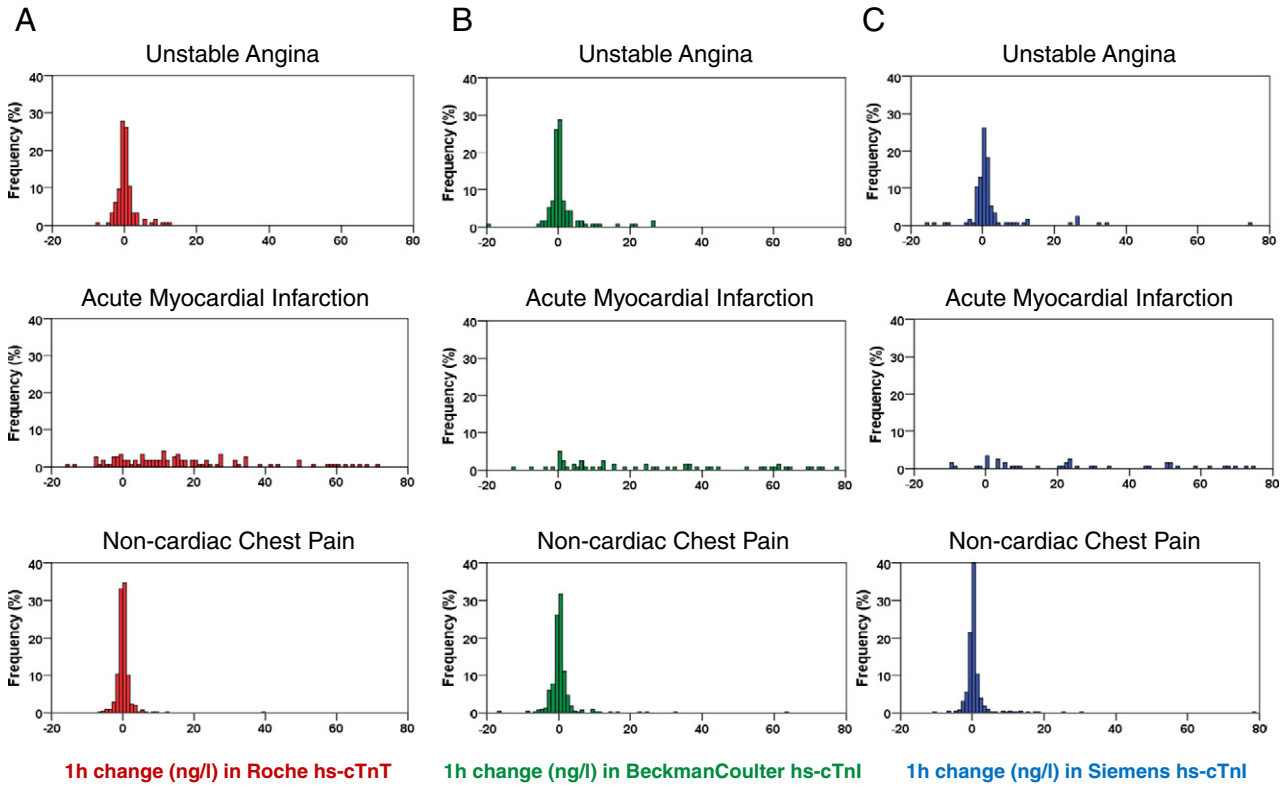
Levels of hs-cTn at presentation according to final diagnosis

Levels of Roche hs-cTnT, Beckman Coulter hs-cTnI, and Siemens hs-cTnI at presentation were 11 ng/L (IQR 6-19 ng/L), 8 (4-14 ng/L), and 7 (4-15 ng/L) in patients with UA compared with 108 (48-194 ng/L), 251 (58-1093 ng/L), and 359 (103-1820 ng/L) in patients with AMI and 6 (3-11 ng/L), 4 (3-7 ng/L), and 3 (1-7 ng/L) in patients with NCCP (all *P* values <.001 for comparison with UA). Elevations in admission levels above the 99th percentiles were observed in 40%, 45% and, 43% of patients with UA, in 93%, 97%, and 98% of patients with AMI, and in 15%, 17%, and 19% of patients with NCCP.

Outcome in UA by changes of hs-cTn

In the group of patients with UA, follow-up information was available at 30 days in 100% of the patients and at 2 years in 94%. There were 9 deaths and 27 AMIs during a median length of follow-up of 777 days, resulting in a total

Figure 1



Changes of hs-cTn within the first hour according to adjudicated final diagnosis. Frequency histograms of changes within the first hour in nanograms per liter for Roche hs-cTn T (**A**), Beckman Coulter hs-cTnI (**B**), and Siemens hs-cTnI (**C**) according to the adjudicated final diagnosis.

of 31 composite end points of death or nonfatal AMI. To assess the prognostic impact of absolute changes within the first hour, patients were divided into 3 groups according to absolute 1-hour changes of <2, 2 to 4, and >4 ng/L. As shown in Figure 2A-C, a lower proportion of patients with UA in the lowest group reached the combined end point both at 30 days of follow-up (2%, 4%, 4%) compared with patients in the second (26%, 16%, 14%) and third groups (18%, 16%, 17%) and 2 years of follow-up (14%, 14%, and 15% vs 47%, 44%, and 36% vs 36%, 33%, and 35%). Although all comparisons between the lowest group and the medium/highest group were significant (all *P* values ≤.05), no significant differences were found between the medium and the highest groups (all *P* values >.5).

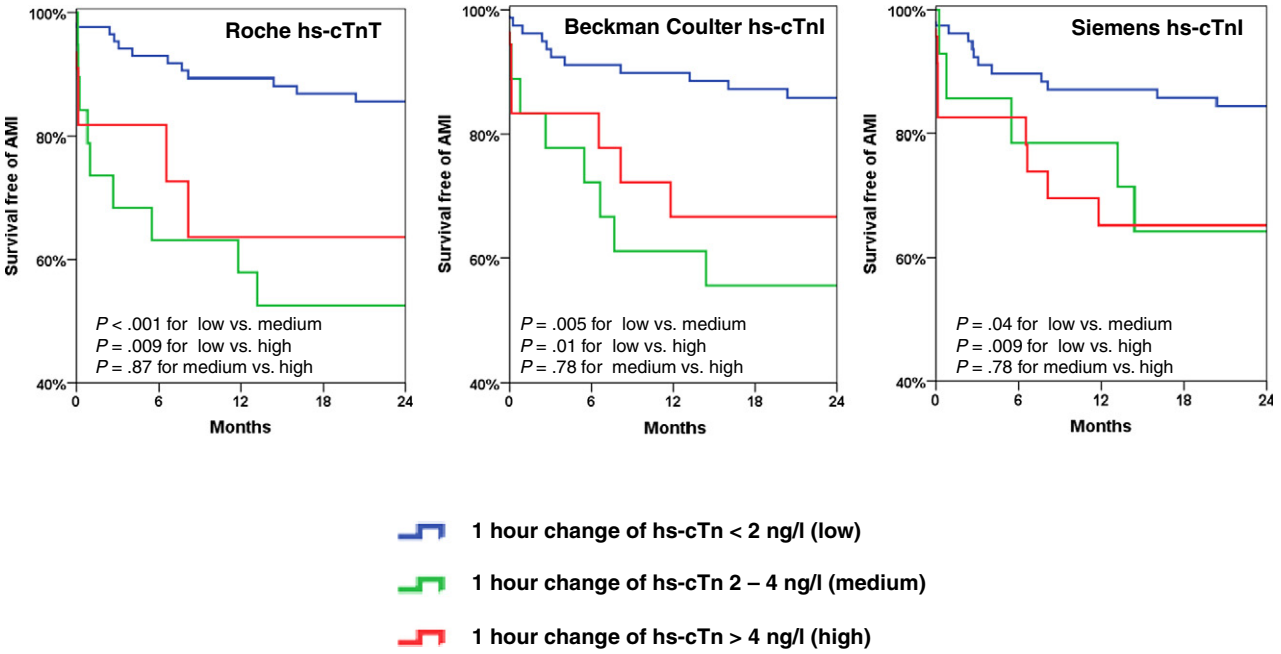
Taken together, a 1-hour change in hs-cTn of ≥2 ng/L in patients with UA had an HR for the combined end point of death or AMI during follow-up at 30 days of 10.6 (95% CI 2.2-51.0, *P* = .003) and at 2 years of 3.7 (1.8-7.5, *P* < .001) if assessed with Roche hs-cTnT, of 4.7 (1.2-18.8, *P* = .03) and 3.1 (1.5-6.3, *P* = .002) with Beckman Coulter hs-cTnI, and of 4.4 (1.1-17.7, *P* = .03) and 2.7 (1.3-5.5, *P* = .006) with Siemens hs-cTnI.

Patients with UA showing a 1-hour change in hs-cTn ≥2 ng/L according to the 3 hs-cTn assays studied were slightly older compared with the other patients with UA, but no other consistent differences in baseline characteristics were found (Supplementary Tables II-IV in the online Appendix). In terms of treatment, we found no significant differences in neither medical nor interventional treatment.

Outcome in UA by combination of changes and presentation levels of hs-cTn

Combination of the criteria for 1-hour hs-cTn changes (≥2 ng/L vs <2 ng/L) and hs-cTn levels at presentation (≥99th percentile vs <99th percentile) in patients with UA showed that 50% (Roche), 49% (Beckman Coulter), and 50% (Siemens) of all patients with UA fulfilled neither criterion; 24%, 20%, and 18% had no relevant change but an elevated hs-cTn level at presentation; 10%, 6%, and 8% had a relevant change but no elevation in levels at presentation; and 16%, 25%, and 24% fulfilled both criteria. The event rates of the combined end point of death or AMI after 2 years of follow-up in these 4 groups were 14%, 15%, 50%, and 39% for Roche hs-cTnT (*P* = .001); 16%, 19%, 29%, and 41% for Beckman Coulter hs-

Figure 2



Outcome in patients with UA according to 1-hour changes of hs-cTn. Kaplan-Meyer curves displaying the survival free of AMI during follow-up in patients with UA according to a 1-hour change of <2, 2 to 4, and >4 ng/L in Roche hs-cTn T (**A**), Beckman Coulter hs-cTnI (**B**), and Siemens hs-7cTnI (**C**).

cTnI (P = .008); and 19%, 5%, 21%, and 39% for Siemens hs-cTnI (P = .009; Figure 3A-C).

Discussion

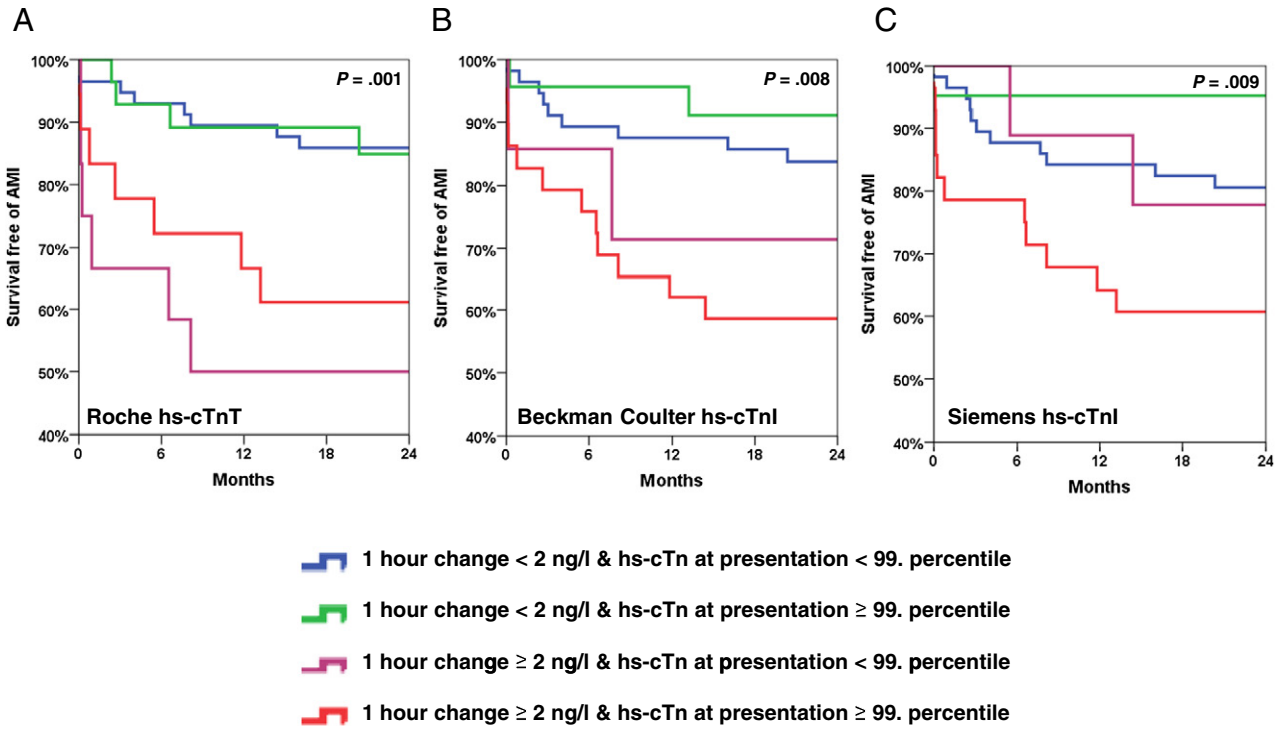
This analysis of data derived from a prospective multicenter study aimed to assess the amount, dynamics and prognostic relevance of myocardial necrosis in patients with UA by using 3 novel hs-cTn assays. We report 3 major findings:

First, most patients with UA did not show changes in hs-cTn and thereby resembled patients with NCCP and were strikingly different from patients with AMI. Second, the minority of patients with UA who had hs-cTn changes was at significantly increased risk for death and AMI during short- and long-term follow-up. Third, all of these findings were consistent between the 3 hs-cTnT and hs-cTnI assays used.

Our findings confirm and extend findings from a recent single-center study regarding the prognostic implications of relative cTn changes in patients with an ACS.[19] Apple and coworkers[19] found a markedly worse outcome in patients with an increase in cTn I of 30% within the first 6 hours. In our study, acute hs-cTnT and hs-cTnI changes of as little as 2 ng/L within the first hour significantly predicted a worse outcome in patients with UA in terms of death or AMI. The difference in prognosis was most striking within the first months, indicating a significantly increased short-term risk of death or AMI in patients with hs-cTn changes compared with dose without (HRs for death or AMI within 30 days 10.6, 4.7, and 4.4 for Roche hs-cTnT, Beckman Coulter hs-cTnI, and Siemens hs-cTnI in our study).

These observations in UA may have clinical implications for the management of patients with ACS. We used the assessment of absolute changes in hs-cTn levels during a serial testing as a new window with unprecedented sensitivity to differentiate acute myocardial injury from potentially underlying more chronic myocardial disease. It was unknown whether UA results in small areas of acute myocardial necrosis below the LoD of previous cTn assays or whether there is no acute myocardial necrosis and therefore distal embolization at all.[7] In accordance with our findings, the occurrence of hs-cTn elevations above the 99th percentile indicating myocardial necrosis in patients with UA has been reported in 29% and 44% of patients with UA when using sensitive cTn assays in 2 smaller previous studies.[20,21] Those studies, however, lacked information on the dynamics of myocardial necrosis. Our study demonstrates the absence of relevant hs-cTn changes in most patients with UA. In a quarter of patients with UA, however, a pattern of a more chronic rather than acute hs-cTn elevation was observed. The important difference

Figure 3



Outcome according to the combination of 1-hour changes and presentation levels of hs-cTn. Kaplan-Meyer curves displaying survival free of AMI during follow-up in patients with UA according to the combination of 1-hour changes and presentation levels of Roche hs-cTn T (**A**), Beckman Coulter hs-cTnI (**B**), and Siemens hs-cTnI (**C**).

of the presence or absence of hs-cTn changes in patients with AMI and UA underscores the importance of serial blood sampling as well as the rise and fall criterion incorporated into current guidelines when assessing patients with an ACS.[1,22]

These findings may help to explain and possibly also overcome the lack of therapeutic progress seen in recent randomized controlled trials evaluating aggressive treatments including early revascularization, anticoagulation, and triple-antiplatelet therapy in patients with UA.[4-6,23-27] Those short-term treatments are associated with considerable inherent risks. The presence of hs-cTn changes, independent of the hs-cTn level at presentation, identifies a subset of patients with UA who have a significantly worse outcome compared with the other patients with UA. This minority might benefit from aggressive treatment including early invasive strategies that have the potential to favorably modify their markedly increased short-term risk of death and AMI. By contrast, in patients with UA without hs-cTnT changes (most patients), less invasive and more sustained treatment strategies including antiplatelet therapy, high-dose statins, and extensive lifestyle modification may have a better risk-benefit ratio.[5,6,23,26,28-30]

Several limitations of the current study merit consideration. First, the clinical diagnosis of UA is often challenging. Although our final diagnoses were centrally adjudicated by 2 independent experts based on all available medical records pertaining to the patient, including detailed results from coronary angiography including lesion severity and lesion morphology, we cannot exclude that some patients may have been misclassified. Second, owing to transfer to the catheter laboratory or coronary care unit, or early discharge from the ED, not all blood draws for the investigational measurement of hs-cTn at later time points were available in all patients. Third, we cannot comment on the pattern of cardiac necrosis in UA among patients with terminal kidney failure requiring dialysis because such patients were excluded from our study. Forth, we used 3 different hs-cTnT and hs-cTnI assays. We hypothesize that our results can be extrapolated to the use of other hs-cTn assays, but this needs confirmation in further studies.[31]

In conclusion, when assessed with hs-cTnT and hs-cTnI assays, most patients with UA do not exhibit relevant hs-cTn changes, which is in marked contrast to patients with AMI. The minority of patients with UA who have hs-cTn changes, however, have a worse short- and long-term

outcome with an increased risk of death or AMI during follow-up. This improved characterization of patients with UA by use of serial hs-cTn levels in conjunction with all other available information may help to refine treatment and thereby to improve prognosis.

Acknowledgements

We thank the patients who participated in the study, the staff of the ED, the laboratory technicians, and particularly Claudia Stelzig, Michael Freese, Kirsten Hochholzer, Esther Garrido, Irina Klimmeck, Melanie Wieland, Selina Christen, Janine Vögele, Beate Hartmann, and Fausta Chiaverio for their most valuable efforts, and we thank Drs C. Schindler and K. Denhaerynck for expert statistical advice.

Disclosures

Dr Reichlin has received research grants from the Swiss Natinoal 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. Dr Mueller has received research grants from the Swiss National Science Foundation (PP00B-102853) and the Swiss Heart Foundation; research support from Abbott, Biosite, Brahms, Nanosphere, Roche, Siemens, and the Department of Internal Medicine, University Hospital Basel; and speaker honoraria from Abbott, Biosite, Brahms, Roche, and Siemens. All other authors declare that they have no conflict of interest with this study.

References

1. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116(22):2634-53.
2. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123(18):e426-579.
3. Kushner FG, Hand M, Smith Jr SC, et al. 2009 Focused updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;120(22):2271-306.
4. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. JAMA 2006;295(13):1531-8.
5. Lindahl B, Venge P, Wallentin L. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. Fragmin in Unstable Coronary Artery Disease Study Group. J Am Coll Cardiol 1997;29(1):43-8.
6. Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non–ST elevation myocardial infarction: results from a randomized trial. JAMA 2001;286(19):2405-12.
7. Wu AH, Jaffe AS. The clinical need for high-sensitivity cardiac troponin assays for acute coronary syndromes and the role for serial testing. Am Heart J 2008;155(2):208-14.
8. Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56(2):254-61.
9. Wu AH, Lu QA, Todd J, et al. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. Clin Chem 2009;55(1):52-8.
10. Venge P, Johnston N, Lindahl B, et al. Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial ischemia. J Am Coll Cardiol 2009;54(13):1165-72.
11. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361(9):858-67.
12. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124(2):136-45.
13. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31(18):2197-204.
14. Apple FS, Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. Am Heart J 2002;144(6):981-6.
15. Apple FS, Jesse RL, Newby LK, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Circulation 2007;115(13):e352-5.
16. Agarwal SK, Avery CL, Ballantyne CM, et al. Sources of variability in measurements of cardiac troponin T in a community-based sample: the atherosclerosis risk in communities study. Clin Chem 2011;57(6):891-7.
17. Basit M, Bakshi N, Hashem M, et al. The effect of freezing and long-term storage on the stability of cardiac troponin T. Am J Clin Pathol 2007;128(1):164-7.
18. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.
19. Apple FS, Pearce LA, Smith SW, et al. Role of monitoring changes in sensitive cardiac troponin I assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events. Clin Chem 2009;55(5):930-7.
20. Wilson SR, Sabatine MS, Braunwald E, et al. Detection of myocardial injury in patients with unstable angina using a novel nanoparticle cardiac troponin I assay: observations from the PROTECT-TIMI 30 Trial. Am Heart J 2009;158(3):386-91.
21. Giannitsis E, Becker M, Kurz K, et al. High-sensitivity cardiac troponin T for early prediction of evolving non–ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. Clin Chem 2010;56(4):642-50.
22. Morrow DA, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines:

clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Circulation 2007;115(13):e356-75.
23. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360(21):2165-75.
24. Low-molecular-weight heparin during instability in coronary artery disease. Fragmin during Instability in Coronary Artery Disease (FRISC) study group. *Lancet* 1996;347(9001):561–8.
25. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344(25):1879-87.
26. James SK, Lindback J, Tilly J, et al. Troponin-T and N-terminal pro–B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. J Am Coll Cardiol 2006;48(6):1146-54.
27. Newby LK, Ohman EM, Christenson RH, et al. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin t-positive status: the paragon-B troponin T substudy. Circulation 2001;103(24):2891-6.
28. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2007;116(7):e148-304.
29. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28(13):1598-660.
30. Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation 2004;109(11):1371-8.
31. Sabatine MS, Morrow DA, de Lemos JA, et al. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J 2009;30(2):162-9.

Appendix

Supplemental methods

Use of local cTn values for adjudication of final diagnoses. Acute myocardial infarction was defined and cTn levels were interpreted as recommended in the current guidelines.[1,13-15] In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia. Cardiac necrosis was diagnosed by at least 1 value of the local standard cTn above the 99th percentile (or above the 10% imprecision value if not fulfilled at the 99th percentile). In the absence of uniformly accepted published guidelines, a significant rise and/or fall was defined as a change of at least 30% of the 99th percentile (or the 10% CV level, respectively) within 6 to 9 hours.[1,13-15]

For the *Roche cTnT fourth-generation assay*, the 10% CV level is 0.035 μg/L. The laboratories of the participating sites reported only 2 decimals; therefore, 0.04 μg/L was used as a cutoff for myocardial necrosis. To fulfil the criteria of a significant change (30% of 99th percentile or 10% CV level), a patient would, for example, need to have a level of <0.01 μg/L at presentation and 0.04 μg/L at 6 hours. A patient would also qualify if the first level is 0.02 μg/L, and the second 0.04 μg/L. A patient would not fulfil the criteria if the first level is 0.03 μg/L and the second is 0.04 μg/L. If the first level is 0.04 μg/L, the second level needs to be at least 0.06 μg/L.

For the *Abbott Axsym cTnI ADV*, the 10% CV level is 0.16 μg/L. A patient having 0.16 μg/L at presentation would meet the criteria for significant change if the second was ≥0.21 μg/L. A patient having <0.12 μg/L at presentation (LoD) would qualify if the second is >0.16 μg/L.

For the *Beckman Coulter Accu cTnI*, the 10% CV level is 0.06 μg/L. A patient having 0.06 μg/L at presentation would qualify if the second is ≥0.08 μg/L. A patient having 0.05 μg/L at presentation would qualify if the second is 0.07 μg/L, but not 0.06 μg/L. A patient having undetectable cTnI (cTnI <0.01 μg/L) at presentation would qualify if the second is ≥0.060 μg/L.

Supplemental Tables

Supplementary Table I. Median changes (IQR) of hs-cTn levels (in ng/L) according to time interval and final diagnosis

		UA (n = 115)	AMI (n = 120)	NCCP (n = 415)	*P* value, UA vs AMI	*P* value, UA vs NCCP
1 h	Roche hs-cTnT	0 (–1 to 1)	16 (4 to 58)	0 (–1 to 1)	<.001	.82
	Beckman Coulter hs-cTnI	0 (–1 to 1)	67 (12 to 259)	0 (–1 to 1)	<.001	.57
	Siemens hs-cTnI	1 (–1 to 2)	136 (30 to 523)	0 (0 to 1)	<.001	.26
2 h	No. of patients available (%)	86 (75)	77 (64)	304 (73)		
	Roche hs-cTnT	0 (–1 to 1)	40 (13 to 111)	0 (–1 to 1)	<.001	.93
	Beckman Coulter hs-cTnI	0 (–1 to 2)	144 (42 to 493)	0 (–1 to 1)	<.001	.23
	Siemens hs-cTnI	1 (0 to 3)	328 (87 to 876)	0 (0 to 1)	<.001	.31
3 h	No. of patients available (%)	89 (77)	67 (56)	258 (62)		
	Roche hs-cTnT	0 (–1 to 1)	46 (13 to 182)	1 (0 to 2)	<.001	.82
	Beckman Coulter hs-cTnI	0 (–1 to 2)	235 (46 to 827)	0 (–1 to 1)	<.001	.36
	Siemens hs-cTnI	1 (0 to 3)	414 (70 to 1459)	0 (0 to 1)	<.001	.12
6 h	No. of patients available (%)	57 (50)	41 (34)	155 (37)		
	Roche hs-cTnT	0 (–1 to 1)	52 (13 to 305)	0 (0 to 1)	<.001	.29
	Beckman Coulter hs-cTnI	0 (–1 to 3)	267 (10 to 1700)	0 (–1 to 1)	<.001	.38
	Siemens hs-cTnI	1 (–2 to 3)	423 (49 to 2377)	1 (0 to 2)	<.001	.87

Supplementary Table II. Baseline characteristics of and treatment for patients with UA according to 1-hour changes in Roche hs-cTnT

	Patients with UA with 1-h change ≥2 ng/L (n = 30)	Patients with UA with 1-h change <2 ng/L (n = 85)	*P*
Age (y)	72 (61-82)	69 (58-75)	.07
Male gender, no. (%)	22 (73)	72 (85)	.17
Risk factors, no. (%)			
Hypertension	24 (80)	73 (86)	.45
Hypercholesterolemia	18 (60)	66 (78)	.06
Diabetes	9 (30)	25 (29)	.95
Current smoking	3 (10)	13 (15)	.47
History, no. (%)			
Coronary artery disease	19 (63)	65 (77)	.16
Previous myocardial infarction	13 (43)	46 (54)	.31
Previous revascularization	15 (50)	54 (64)	.19
Creatinine clearance (mL min^{-1} m^{-2})	83 (74-102)	87 (66-105)	.91
Medication at discharge			
Antiplatelet therapy	28 (93)	78 (92)	.78
β-Blockers	24 (80)	70 (82)	.77
Statins	21 (70)	75 (88)	.02
Ca antagonists	9 (30)	38 (45)	.16
Nitrates	14 (47)	28 (33)	.18
Interventional treatment			
Coronary angiography within 30 d	20 (67)	50 (59)	.45
Percutaneous intervention/ coronary artery bypass graft surgery within 30 d	16 (53)	40 (47)	.55

Supplementary Table III. Baseline characteristics of and treatment for patients with UA according to 1-hour changes in Beckman Coulter hs-cTnI

	Patients with UA with 1-h change ≥2 ng/L (n = 36)	Patients with UA with 1-h change <2 ng/L (n = 79)	*P*
Age (y)	73 (59-80)	68 (58-74)	.10
Male gender, no. (%)	27 (75)	67 (85)	.21
Risk factors, no. (%)			
Hypertension	27 (75)	70 (89)	.06
Hypercholesterolemia	28 (78)	56 (71)	.44
Diabetes	11 (31)	23 (29)	.88
Current smoking	2 (6)	14 (18)	.08
History, no. (%)			
Coronary artery disease	27 (75)	57 (72)	.75
Previous myocardial infarction	18 (50)	41 (52)	.85
Previous revascularization	22 (61)	47 (60)	.87
Creatinine clearance (mL min^{-1} m^{-2})	85 (78-100)	83 (66-105)	.81
Medication at discharge			
Antiplatelet therapy	34 (94)	72 (91)	.54
β-Blockers	29 (81)	65 (82)	.82
Statins	30 (83)	66 (84)	.98
Ca antagonists	13 (36)	34 (43)	.48
Nitrates	14 (39)	28 (35)	.72
Interventional treatment			
Coronary angiography within 30 d	24 (67)	46 (58)	.39
Percutaneous intervention/ coronary artery bypass graft surgery within 30 d	21 (58)	35 (44)	.16

Supplementary Table IV. Baseline characteristics of and treatment for patients with UA according to 1-hour changes in Siemens hs-cTnI

	Patients with UA with 1-h change ≥2 ng/L (n = 37)	**Patients with UA with 1-h change <2 ng/L (n = 78)**	***P***
Age (y)	73 (63-79)	67 (57-74)	.02
Male gender, no. (%)	26 (70)	68 (87)	.03
Risk factors, no. (%)			
Hypertension	30 (81)	67 (86)	.51
Hypercholesterolemia	29 (78)	55 (71)	.38
Diabetes	8 (22)	26 (33)	.20
Current smoking	3 (8)	13 (17)	.22
History, no. (%)			
Coronary artery disease	27 (73)	57 (73)	.99
Previous myocardial infarction	21 (57)	38 (49)	.42
Previous revascularization	24 (65)	45 (58)	.46
Creatinine clearance (mL min^{-1} m^{-2})	86 (65-105)	83 (74-100)	.96
Medication at discharge			
Antiplatelet therapy	33 (89)	73 (94)	.41
β-Blockers	32 (87)	62 (80)	.36
Statins	30 (81)	66 (85)	.63
Ca antagonists	14 (38)	33 (42)	.65
Nitrates	16 (43)	26 (33)	.30
Interventional treatment			
Coronary angiography within 30 d	25 (68)	45 (58)	.31
Percutaneous intervention/ coronary artery bypass graft surgery within 30 d	22 (60)	34 (44)	.11