Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction

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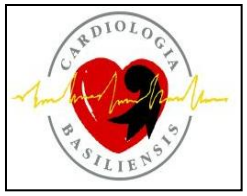

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- Roche,
- Siemens.

The current universal definition of AMI requires a rise and/or fall in biomakers (cardiac troponin), with at least one value above the 99th percentile reference value, in patients with evidence of myocardial ischemia.

Recent work

- **20%**
  - Macrae AR, et al. Assessing the requirement for the 6-hour interval between specimens in the American Heart Association Classification of Myocardial Infarction in Epidemiology and Clinical Research Studies. *Clin Chem. 2006;52:812– 818.*
- **30%**
  - Apple FS, 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;55:930 –937
- **117 % - 243%**
  - Giannitsis E, et al. High sensitivity cardiac troponin T for early prediction of evolving non-Stsegment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clin Chem. 2010;56:642– 650.*
- **235%.**
  - Kavsak PA, Ko DT, Wang X, Macrae AR, Jaffe AS. 2007 Universal myocardial infarction definition change criteria for risk stratification by use of a high-sensitivity cardiac troponin I assay. *Clin Chem. 2010;56:* 487–489.

Purpose

- To determine the diagnostic accuracy of early absolute (Δ) and relative (Δ%) changes in sensitive cTn within the first hour and the first 2 hours for the diagnosis of AMI in a non-selected heterogeneous population of patients presenting with acute chest pain to Emergency Department.

Methods

- The Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study is an ongoing prospective, international, multicenter study designed and coordinated by the University Hospital Basel, Switzerland.
- From April 2006 to June 2009, consecutive patients who presented to the ED with symptoms suggestive of AMI such as chest pain and angina pectoris with onset or peak of symptoms within the last 12 hours were recruited.
- Patients <18 years or with terminal kidney failure requiring dialysis were excluded
- Patients with ST-elevation myocardial infarction (STEMI, n=50) were removed from this analysis.

Methods

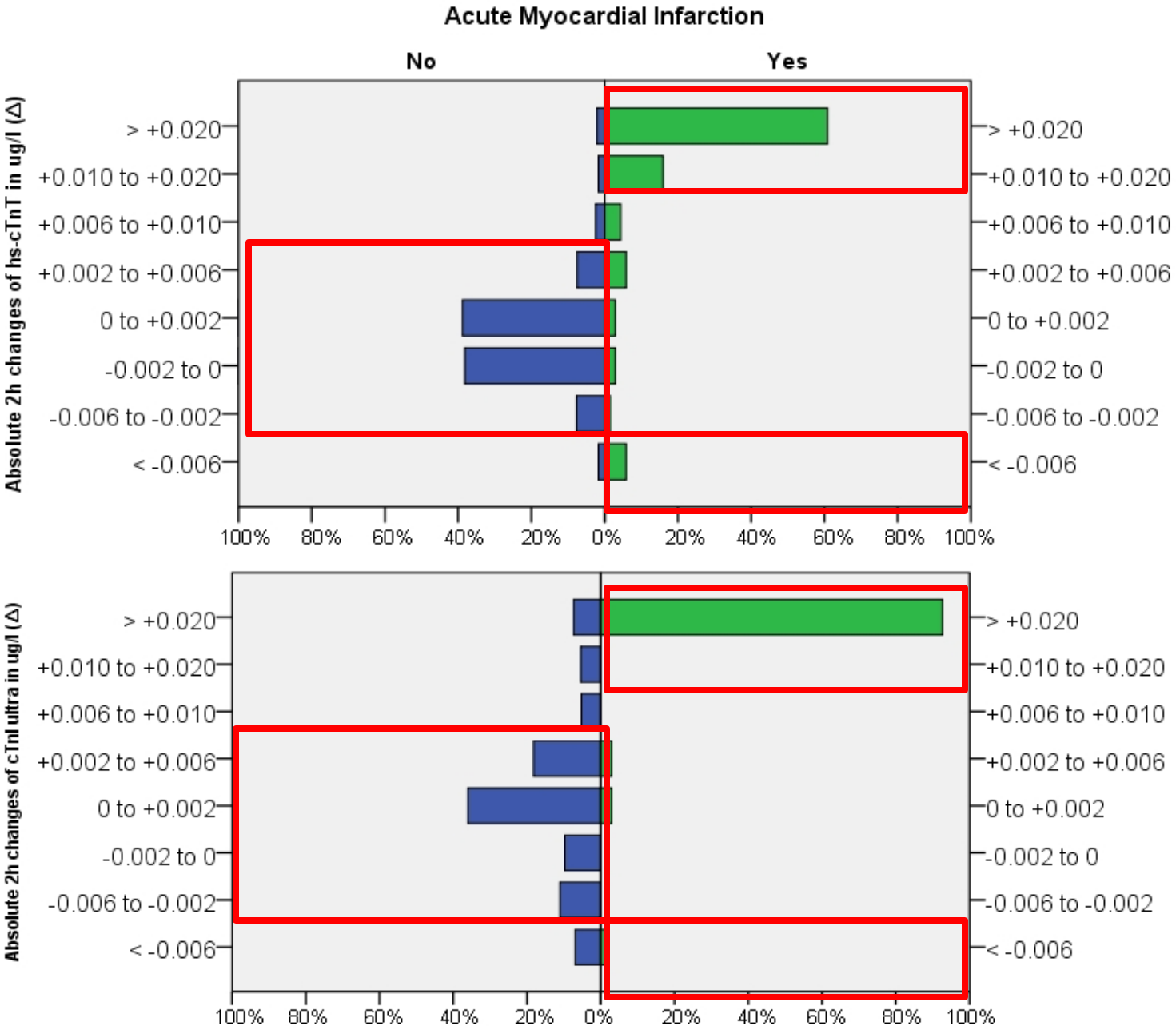
- To determine the final diagnosis for each patient, two independent cardiologists, blinded to measurements of hs-cTnT and cTnI-ultra, reviewed all available medical records pertaining to the patient from the time of ED presentation to 60-day follow-up.
  - Reichlin T, et al.: Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009; 361(9): 858-67.

Assay	LoD (µg/l)	10% CV (µg/l)	99th-percentile (µg/l)
hs-cTnT	0.003	0.013	0.014
cTnI-ultra	0.006	0.030	0.04

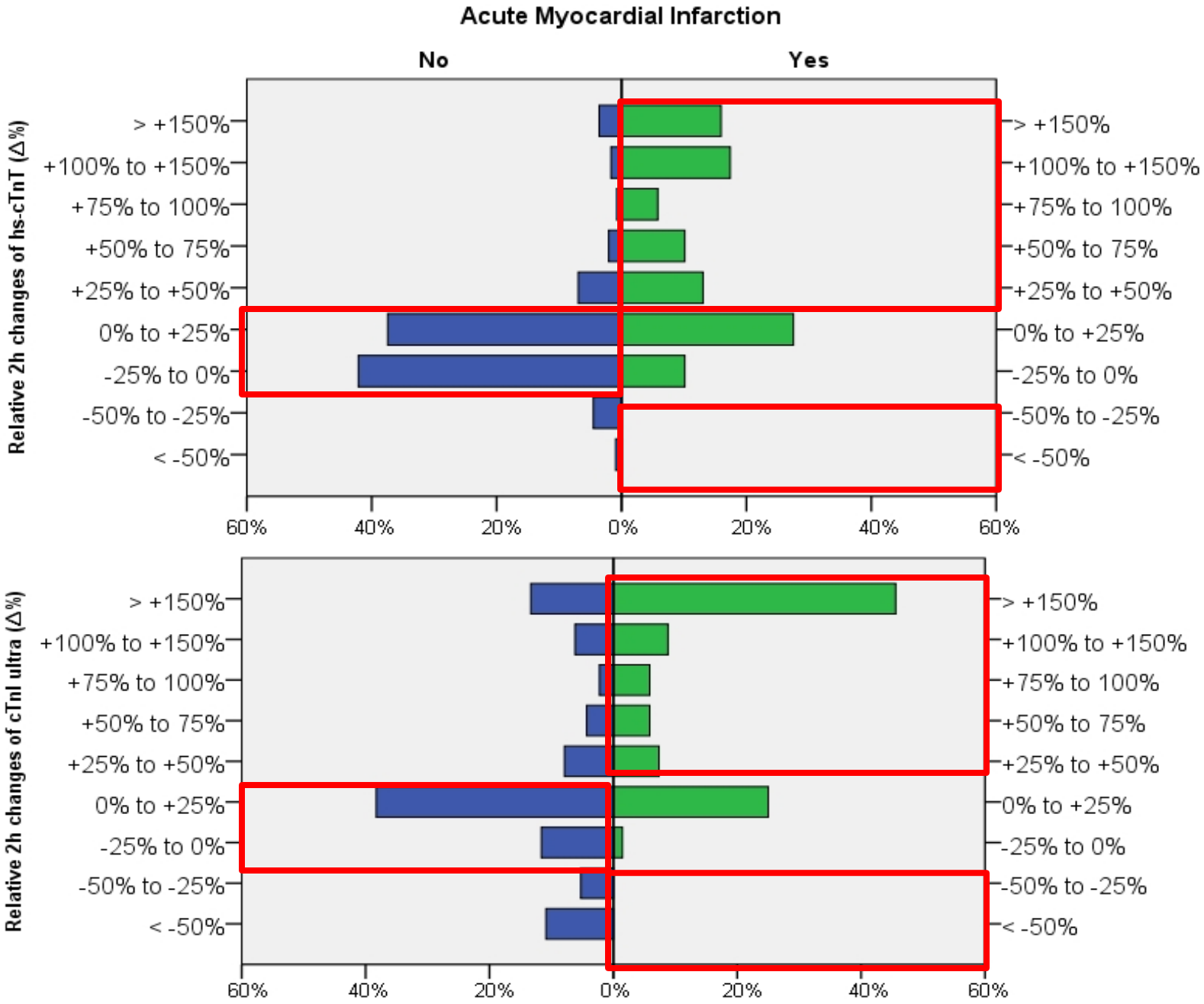
- Among the 1197 patients, samples at presentation as well as after 1 hour for measurement of both high-sensitive cardiac troponin T (hs-cTnT) and cardiac troponin I ultra (cTnI-ultra) were available in 836 patients. Of these, additional samples after 2 hours were available in 590 patients.

Table 1	Baseline characteristics of the patients			
	All patients n=836	AMI n=108	No AMI n=728	p-Value
Male gender – no. (%)	563 (67)	73 (68)	490 (67)	0.95
Age – yr	64 [51 - 76]	74 [63 - 82]	63 [50 - 74]	<0.001
Body mass index (kg/m^2)	27 [24 - 30]	26 [24 - 29]	27 [24 - 30]	0.19
Medical history – no. (%)				
Coronary Artery Disease	308 (37)	49 (45)	259 (36)	0.05
Previous Myocardial Infarction	212 (25)	36 (33)	176 (24)	0.04
Arterial Hypertension	536 (64)	81 (75)	455 (63)	0.01
Hypercholesterolemia	390 (47)	55 (51)	335 (46)	0.34
Previous Stroke	51 (6)	17 (16)	34 (5)	<0.001
Peripheral Artery Disease	58 (7)	13 (12)	45 (6)	0.03
Diabetes	173 (22)	26 (24)	146 (21)	0.24
Smoker (current and past)	499 (60)	75 (62)	430(60)	0.75
eGFR – (ml/min/m^2)	89 [70 - 106]	75 [59 - 100]	91 [73 - 107]	<0.001
Medications – no. (%)				
Platelet inhibitors	357 (43)	52 (48)	305 (42)	0.22
Beta-Blocker	324 (39)	45 (42)	279 (38)	0.51
ACE-Inhibitor / Angiotensin Receptor Blocker	346 (41)	50 (46)	296 (41)	0.27
Calcium antagonist	144 (17)	22 (20)	122 (17)	0.35
Statin	306 (37)	40 (37)	266 (37)	0.92
BNP ≥ 400 pg/ml	93 (13)	34 (35)	59 (9)	<0.001

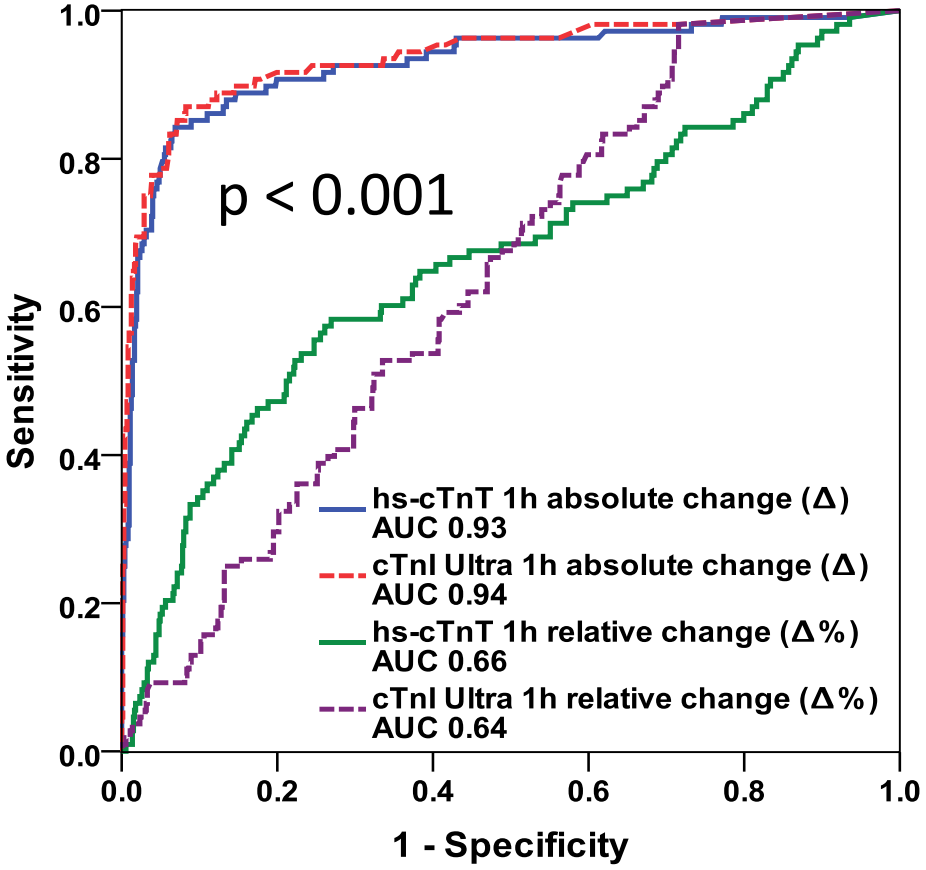
Absolute 2 hour changes (Δ)



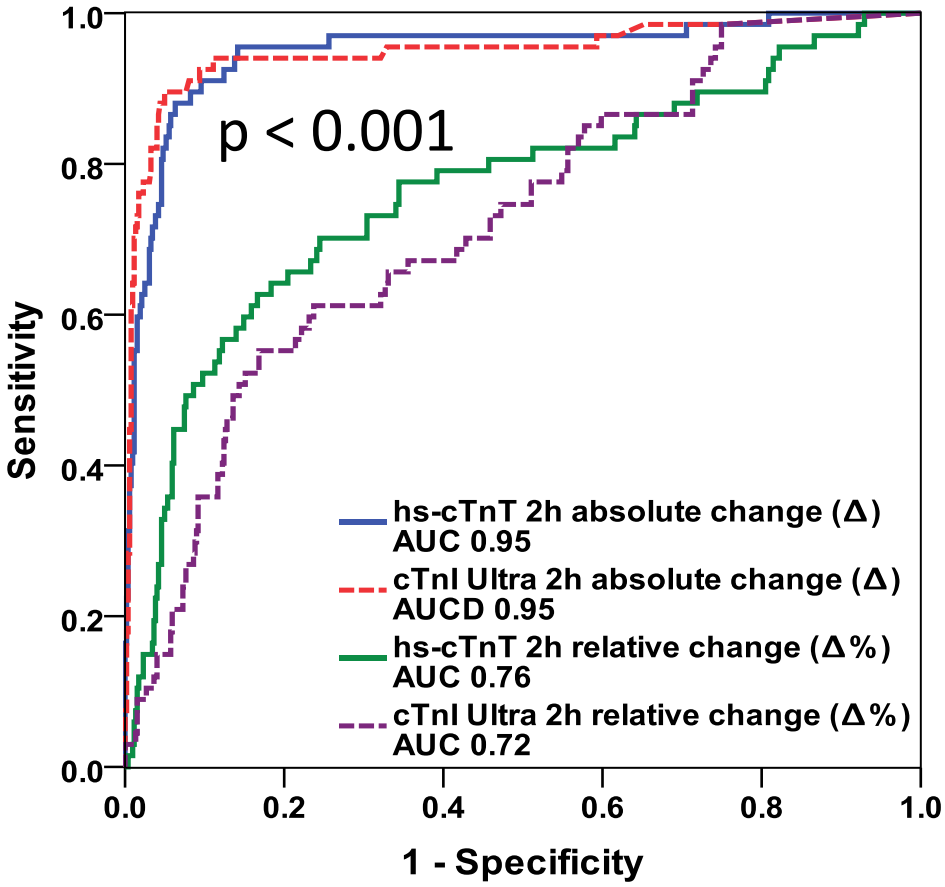
Relative 2 hour changes (Δ%)



1 hour changes



2 hour changes



AUC indicates area under the curve.

Table 2	Area under the receiver operator characteristic curves for the diagnosis of AMI for absolute (Δ) and relative (Δ%) changes in cTn after 1 and 2 hours from presentation.							
	AUC (95 % CI)	p-Value	ROC cut off	Patients above cut-off	Sensitivity	Specificity	PPV	NPV
hs-cTnT								
1 hour (n=836, 108 with AMI)								
Absolute change (Δ)	0.93 (0.90 - 0.96)	<0.001	0.004	17 %	84	93	66	97
Relative change (Δ%)	0.66 (0.60 - 0.72)		17	30 %	57	74	27	91
2 hours (n=590, 67 with AMI)								
Absolute change (Δ)	0.95 (0.92 - 0.98)	<0.001	0.007	16 %	89	93	64	98
Relative change (Δ%)	0.76 (0.70 - 0.83)		30	21 %	64	84	35	94
cTnI-ultra								
1 hour (n=836, 108 with AMI)								
Absolute change (Δ)	0.94 (0.91 - 0.97)	<0.001	0.016	19 %	86	92	64	98
Relative change (Δ%)	0.64 (0.59 - 0.69)		43	35 %	53	66	19	91
2 hours (n=590, 67 with AMI)								
Absolute change (Δ)	0.95 (0.91 - 0.99)	<0.001	0.020	19 %	93	91	58	99
Relative change (Δ%)	0.72 (0.66 - 0.79)		117	21 %	57	83	32	93

AUC denotes area under the receiver operator characteristic (ROC) curve; CI denotes confidence interval; PPV denotes positive predictive value; NPV denotes negative predictive value.

Table 3 The area under the receiver operator characteristic curves for the diagnosis of AMI for absolute (Δ) and relative (Δ%) changes in cTn after 1 and 2 hours from presentation according to baseline cTn levels.

			AUC (95 % CI)	p-Value	ROC cut off	Sensitivity	Specificity	PPV	NPV
hs-cTnT	< 0.014 µg/l at presentation	**1 hour (n=540, 7 with AMI)**							
		Absolute change (Δ)	0.85 (0.61 - 1.00)	0.027	0.004	86	95	19	100
		Relative change (Δ%)	0.83 (0.59 - 1.00)		45	86	90	10	99
		2 hours (n=396, 6 with AMI)							
		Absolute change (Δ)	0.98 (0.96 - 1.00)	0.052	0.005	100	95	22	100
		Relative change (Δ%)	0.95 (0.91 - 0.99)		39	100	86	10	100
	≥ 0.014 µg/l at presentation	**1 hour (n=296, 101 with AMI)**							
		Absolute change (Δ)	0.88 (0.83 - 0.93)	<0.001	0.005	84	86	75	91
		Relative change (Δ%)	0.70 (0.64 - 0.77)		17	55	86	67	79
		2 hours (n=194, 61 with AMI)							
		Absolute change (Δ)	0.91 (0.86 - 0.96)	<0.001	0.008	90	87	76	95
		Relative change (Δ%)	0.79 (0.71 - 0.87)		16	75	80	64	88
cTnI-ultra	< 0.040 µg/l at presentation	**1 hour (n=666, 12 with AMI)**							
		Absolute change (Δ)	0.80 (0.67 - 0.94)	0.006	0.002	92	61	4	100
		Relative change (Δ%)	0.70 (0.55 - 0.85)		11	92	43	3	100
		2 hours (n= 485, 9 with AMI)							
		Absolute change (Δ)	0.89 (0.72 - 1.00)	0.027	0.023	89	96	30	100
		Relative change (Δ%)	0.86 (0.69 - 1.00)		150	89	87	11	100
	≥ 0.040 µg/l at presentation	**1 hour (n= 170, 96 with AMI)**							
		Absolute change (Δ)	0.87 (0.81 - 0.92)	<0.001	0.053	76	89	90	74
		Relative change (Δ%)	0.71 (0.63 - 0.79)		40	52	86	83	58
		2 hours (n= 105, 58 with AMI)							
		Absolute change (Δ)	0.86 (0.78 - 0.94)	0.001	0.131	76	89	90	75
		Relative change (Δ%)	0.74 (0.64 - 0.83)		98	50	91	88	60

Limitations

1. We cannot quantify the potential clinical benefit associated with the application of the absolute and/or relative changes in cTn concentrations to diagnose AMI in patients with chest pain.
2. The group of patients with cTn levels additionally available after 6 hours was slightly biased by the fact that patients with AMI often were already transferred to the catheterization laboratory or to the coronary care unit by 6 hours.
3. Patients with terminal kidney failure requiring dialysis were excluded.

Findings

1. **Early absolute cTn changes were superior to relative cTn changes in diagnosing AMI** among unselected patients with symptoms suggestive of AMI.
2. The ability of absolute cTn changes to diagnose AMI was similar for both assays.
3. The diagnostic superiority of absolute over relative cTn changes was **independent of the underlying cTn baseline** value and consistent in important subgroups of patients such as the elderly and patients with impaired renal function.
4. The **combination of baseline levels with absolute**, but not relative changes significantly improved the diagnostic accuracy provided by baseline cTn levels.
5. The optimal cut off values as derived by ROC curve analysis for the 2 hour absolute cTn changes were about **half the 99th percentile value** of their respective assay.

APACE Recruiting centres:

Currently recruiting (red) and planned (orange) APACE study sites

6 hour troponin

- Values of cTn at baseline as well as after 1 hour, 2 hours, and 6 hours were available in a subgroup of 305 patients (36%).
- Diagnostic accuracies for AMI were similar for absolute 1-hour, 2-hour, and 6-hour changes in hs-cTnT (AUCs, 0.91, 0.96, 0.95; *P>0.05 for all comparisons)* and in cTnI-ultra (AUCs, 0.91, 0.94, 0.95; *P>0.05 for* all comparisons).

- Relative 6-hour changes were inferior compared with absolute changes (AUC, 0.79 for hs-cTnT and 0.73 for cTnI-ultra; *P0.001 for comparison with 6-hour* absolute changes).

Table 4	The area under the receiver operator characteristic curves for absolute (Δ) and relative (Δ%) change in combination with baseline cTn levels		
		AUC	**p-Value**
hs-cTnT	**Baseline**	0.94	
	1 hour		
	Absolute change (Δ) + Baseline	0.98	<0.001
	Relative change (Δ%) + Baseline	0.94	0.4
	2 hours (n=595)		
	Absolute change (Δ) + Baseline	0.98	<0.001
	Relative change (Δ%) + Baseline	0.94	0.3
cTnI ultra	**Baseline**	0.95	
	1 hour		
	Absolute change (Δ) + Baseline	0.96	0.05
	Relative change (Δ%) + Baseline	0.95	0.5
	2 hours (n=595)		
	Absolute change (Δ) + Baseline	0.97	0.02
	Relative change (Δ%) + Baseline	0.96	0.35

Table 5

Area under the receiver operator characteristic curves for the diagnosis of AMI for absolute (Δ) and relative (Δ%) changes in cTn after 1 and 2 hours from presentation in important patient subgroups

	n	Changes in hs-cTnT				Changes in cTnI-ultra			
		absolute (Δ%)		relative (Δ%)		absolute (Δ%)		relative (Δ%)	
		1h	2h	1h	2h	1h	2h	1h	2h
Male Gender	563	0.92	0.94	0.68	0.80	0.93	0.94	0.64	0.75
Female Gender	273	0.94	0.97	0.63	0.68	0.95	0.98	0.64	0.66
Elderly (age ≥ 70years)	271	0.90	0.94	0.70	0.80	0.95	0.91	0.66	0.73
Impaired renal function (eGFR < 60ml/min/1.73m^2)	125	0.88	0.94	0.62	0.70	0.88	0.92	0.61	0.69
Heart Failure (BNP ≥ 400pg/ml)	93	0.85	0.96	0.65	0.82	0.91	0.92	0.72	0.77
Time since onset of symptoms ≤ 3h	319	0.92	0.97	0.73	0.81	0.93	0.98	0.72	0.85
Time since onset of symptoms 4-10h	282	0.94	0.98	0.74	0.91	0.93	0.94	0.71	0.78
Time since onset of symptoms >10h	235	0.92	0.94	0.52	0.61	0.95	0.92	0.49	0.54

Use of local cardiac troponin assays

- For the **Roche cTnT 4th generation** assay, the 10% CV level is 0.035ug/l. The laboratories of the participating sites reported only two decimals, therefore 0.04ug/l was used as a cut-off for myocardial necrosis. In order to fulfil the criteria of a significant change (30% of 99th percentile or 10% CV level), a patient would e.g. need to have a level of <0.01ug/l at presentation and 0.04ug/l at 6h. A patient would also qualify if the first level is 0.02ug/l and the second 0.04ug/l. A patient would not fulfil the criteria if the first level is 0.03ug/l and the second is 0.04ug/l. If the first level is 0.04ug/l, the second level needs to be at least 0.06ug/l.
- For the **Abbott Axsym cTnI ADV**, the 10% CV level is 0.16ug/l. A patient having 0.16ug/l at presentation would meet the criteria for significant change if the second was ≥0.21ug/l. A patient having <0.12ug/l at presentation (limit of detection) would qualify if the second is >0.16ug/l.
- For the **Beckmann Coulter Accu cTnI**, the 10% CV level is 0.06ug/l. A patient having 0.06ug/l at presentation would qualify if the second is ≥0.08ug/l. A patient having 0.05 at presentation would qualify if the second is 0.07ug/l, but not 0.06ug/l. A patient having undetectable cTnI (cTnI<0.01ug/l) at presentation would qualify if the second is ≥0.06ug/l.