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Utility of 14 novel biomarkers in patients with acute chest pain and undetectable levels of conventional cardiac troponin ☆,☆☆

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ABSTRACT

Background: Patients with acute chest pain having serial undetectable cardiac troponin (cTn) levels, as measured with conventional assays, are considered at very low risk. The aim of this multicenter study was to determine the accuracy of multiple biomarkers in these patients.
Methods: We enrolled 1247 consecutive patients with suspected AMI. Of these, 325 had undetectable levels of cTnT (Roche, 4th generation assay) at presentation and at 6 h. Fourteen novel markers quantifying cardiomyocyte damage, inflammation and/or plaque rupture, and neurohormonal activation were measured at presentation. The occurrence of death or acute myocardial infarction (AMI) (primary end point) and unplanned coronary revascularization (secondary endpoint) were recorded during long-term follow-up.
Results: During a mean follow-up of 668 ± 241 days, death/AMI occurred in 23 patients (7%), unplanned revascularization in 46 (14%). Among all biomarkers, high-sensitive cTnT (hs-cTnT), Midregional pro-adrenomedullin (MR-proADM) and growth differentiation factor-15 (GDF-15) were independently associated with future death/AMI; hs-cTnT was 0.013 (0.008–0.017) μg/l versus 0.006 (0.003–0.010) μg/l, MR-proADM was 0.78 (0.66–1.09) nmol/l versus 0.60 (0.18–0.80) nmol/l and GDF-15 was 1800 (1600–2200) ng/l versus 1100 (800–1700) ng/l in patients with versus without death/AMI during follow-up ($p<0.001$ each). The area under the receiver-operating characteristics curve to predict death/AMI was 0.73 (95%CI 0.63–0.83) for hs-cTnT, 0.71 (95% CI 0.62–0.81) for MR-proADM and 0.78 (95%CI 0.71–0.86) for GDF-15.
Conclusion: Patients with serial undetectable levels of cTnT using the contemporary 4th generation assay are at low but not negligible risk of future cardiac events. Hs-cTnT, MR-proADM and/or GDF-15 might help to further improve risk-stratification in this group.

1. Introduction

Chest pain accounts for up to 5–10% of the consultations in emergency departments (ED) [1]. To date, clinical assessment, electrocardiogram (ECG) and measurement of markers quantifying cardiac necrosis such as cardiac troponins (cTn) form the cornerstones of the diagnosis of acute myocardial infarction (AMI) [2,3]. High-sensitive assays of cTn (hs-cTn) have been developed recently; compared to conventional cTn assays, hs-cTn assays seem to allow an earlier detection of AMI, however at the cost of reduced specificity [4–6]. For multiple reasons, many institutions continue to use conventional cTn assays for the routine management of patients.

Despite the lower sensitivity of these conventional assays, patients who remain "troponin-negative" during serial measurements are at low risk of death or future cardiac events. Recent studies have highlighted that the group of "troponin-negative" acute chest pain patients is very heterogeneous and includes many patients with known or unknown cardiac disease such as unstable angina [7–9]. The best suited clinical tools to appropriately manage and risk stratify this large group of patients, comprising more than two-thirds of all acute chest pain patients [5], remain poorly defined. Finding a new biomarker with the ability to identify patients at greater risk of future cardiac events in this population is an unmet need.

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Recent advances in our understanding of the pathophysiology of AMI as well as the availability of new technologies have led to the discovery of the prognostic significance of multiple biomarkers detectable in peripheral blood, such as markers quantifying cardiomyocyte damage, inflammation and/or plaque rupture, and neurohormonal activation [4,10,11].

The aim of this study was to investigate the prognostic utility of multiple novel biomarkers, representing distinct pathophysiological pathways in AMI, in the prediction of future cardiac events in "troponin-negative" acute chest pain patients.

2. Methods

2.1. Study design and population

This study is a subgroup analysis of patients from the ongoing "*A*dvantageous *P*redictors of *A*cute *C*oronary Syndromes *E*valuation" (APACE) cohort study, who had *c*TnT concentrations measured at presentation and repeated after 6 h below the limit of detection (*c*TnT<0.01 μg/l at presentation and after 6 h, as measured with the 4th generation cTnT, using an Elecsys 2010 analyser, Roche Diagnostics, Mannheim, Germany).

The design and first results of the APACE cohort have been previously reported [5,6,12,13]; briefly, the cohort included consecutive patients with chest pain within the last 12 h suggestive of AMI (see Appendix A for more details).

All patients provided written informed consent. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee at each participating centers.

Our objective was to examine the possible merit of investigational biomarkers in the prediction of future cardiac events during prolonged follow-up.

2.2. Clinical assessment

At presentation to the hospital, all patients underwent a detailed clinical evaluation, ECG, standard blood tests and chest X-ray (see Appendix A). The necessity of additional investigations, medical treatment, as well as the decision to discharge or hospitalize the patients was left at the discretion of the attending physician.

The diagnosis at initial hospital attendance was retrospectively adjudicated at 60 days by at least two experimented cardiologists (see Appendix A for more details).

2.3. Investigational assays of the biomarkers

For the measurements of cardiac biomarkers, blood samples were collected at presentation, were centrifuged and were frozen at 80 °C until they were assayed in a blinded fashion in two batches in a dedicated core laboratory.

The following biomarkers were measured and their prognostic significance assessed:

B-type natriuretic peptide (BNP) [14], NTproBNP, Copeptin [15,16], myeloperoxydase (MPO) [17], mid-regional pro A-type natriuretic peptide (MR-proANP) [18], mid-regional pro-adrenomedullin (MR-proADM) [19], c-terminal-pro-Endothelin-1 (CT-proET-1) [20], c-reactive protein (CRP), myeloid-related Protein 8/14 (MRP8/14) [21], pregnancy-associated plasma protein A (PAPP-A), growth differentiation factor 15 (GDF-15) [22] and hs-cTnT [5] (see Appendix A for more details).

2.4. Follow-up and clinical endpoints

After hospital discharge patients were followed after at regular intervals by telephone calls or in written form. Any reported clinical event – in particular cardiovascular events – since presentation to the ED, were reviewed by asking the patient or a close relative and traced by establishing contact with the respective family physician and treating institution. If unsuccessful, the primary care physicians were contacted and both the medical records of the hospitals and the death certificates were consulted.

The primary endpoint was the occurrence of death or AMI during prolonged follow-up. The secondary endpoint was the occurrence of unplanned revascularization. Death included all-cause mortality. AMI was defined as myocardial necrosis in the setting of clinical signs of myocardial ischemia, according to current guidelines [2]. Unplanned revascularization was defined as any coronary revascularization that was not planned during the initial hospitalization.

2.5. Statistical analysis

The data are expressed as means ± standard deviation (SD), median (interquartile range) numbers (percentage) as appropriate. The association between biomarkers and the endpoints were analyzed first using Mann Whitey *U* test. In order to assess the possible independent diagnostic information offered by these markers, a Cox model analysis was then performed including all biomarkers that emerged from univariate analysis. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity throughout the concentrations of the most pertinent biomarkers according to logistic regression [23]. The rate of death/AMI over time was reported graphically using the Kaplan–Meier method; the log-rank test was applied for the time to death. All hypothesis testing was two-tailed and a *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using STATA Version 10.1 (StataCorp LP, College Station, TX).

3. Results

Out of 1247 consecutive patients enrolled, 325 patients had undetectable cTnT levels at presentation and after 6 h (*c*TnT<0.01 μg/l). Their baseline characteristics are reported in Table 1.

The median age was 63 years, 67% patients were male; 123 (38%) patients had known cardiovascular disease, and 198 (61%) had at least 2 atherosclerosis risk factors. ST-deviation on ECG was recorded in 40 patients (12%).

The adjudicated final diagnosis was as follows; AMI in none, unstable angina in 60 (18.5%) patients, cardiac but non-coronary cause in 52 (16.0%) patients, non cardiac cause in 170 (52.3%) patients and unknown in 43 (13.2%) patients. A coronary angiography was performed in 38 patients, including 21 patients (all having a gold standard diagnosis of unstable angina) who had percutaneous coronary intervention. Most of these patients remained event free during follow-up.

Mean follow-up duration was 668 ± 241 days and 90% of the cohort had complete follow-up of more than 360 days.

3.1. Death and/or AMI during follow-up

Death or AMI occurred in 23 patients (7.1%), including 12 patients (3.7%) who deceased. The rates of 1-y mortality and 1-y mortality/AMI were 1.9% and 3.7% respectively. The adjudicated final diagnosis in these patients who deceased or had AMI during follow-up was unstable angina in 11, cardiac but non-coronary cause in 2, non cardiac in 9 and unknown in a single patient. When compared to patients free of death/AMI during follow-up, these patients were older, had more past MI or cardiovascular diseases, and as a consequence, were more often treated with cardioactive drugs (Table 1).

Among the 14 biomarkers that we measured, the following were increased in patients who died or had AMI when compared to patients free of events during follow-up: myoglobin, hs-cTnT, GDF-15, MR-proANP, BNP and NT-proBNP, MR-proADM and CT-pro-ET-1

Table 1
Patient baseline characteristics (*n* = 325).

	Total	Death/AMI	No death/AMI	*p*
	(*n* = 325)	(*n* = 23)	(*n* = 302)	
Age, years	63 (51–74)	76 (65–82)	61 (51–73)	<0.001
Male sex	218 (67.1)	19 (82.6)	103 (34.1)	0.112
Hypertension	197 (60.6)	17 (73.9)	180 (59.6)	0.176
Hypercholesterolemia	157 (48.3)	16 (69.6)	141 (46.7)	0.034
Diabetes	72 (22.2)	8 (34.8)	64 (21.2)	0.130
Body Mass Index (kg/m^2)	27.3 ± 4.6	27.0 ± 5.4	27.3 ± 4.5	0.577
Smoking	78 (24.1)	7 (30.4)	71 (23.6)	0.459
Past myocardial infarction	86 (26.5)	15 (65.2)	71 (23.5)	<0.001
Past coronary artery disease	123 (37.9)	18 (78.3)	105 (34.8)	<0.001
Known renal failure[a]	25 (7.7)	4 (17.4)	21 (7.0)	0.088
Aspirin	130 (40.0)	14 (60.9)	116 (38.4)	0.034
Clopidogrel	45 (13.9)	6 (26.1)	39 (12.9)	0.078
Beta-adrenergic blocker	139 (42.8)	19 (82.6)	120 (39.7)	<0.001
ACE inhibitor/ARB	137 (42.2)	14 (60.9)	123 (40.7)	0.059
Statin	126 (38.8)	14 (60.9)	112 (37.1)	0.024
Duration of chest pain, hours	3.8 ± 3.4	4.2 ± 3.5	3.8 ± 3.4	0.316
Heart rate, bpm	78 ± 19	82 ± 18	77 ± 19	0.202
Systolic BP, mmHg	147 ± 27	150 ± 32	147 ± 27	0.567
Diastolic BP, mmHg	85 ± 15	89 ± 17	85 ± 14	0.143
ST segment deviation	40 (12.3)	5 (21.7)	35 (11.6)	0.153
Creatinine, μmol/l	78 ± 21	89 ± 28	77 ± 20	0.101
GFR, ml/min/1.73 m^2	91 ± 25	82 ± 25	92 ± 25	0.062
Hemoglobin, g/dl	143 ± 14	139 ± 14	139 ± 14	0.096
Coronary angiography	38 (11.7)	3 (13.0)	35 (11.6)	0.741
Coronary revascularization	21 (6.5)	3 (13.0)	18 (6.0)	0.183

[a] Patients with terminal renal failure were not included in the study.