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Temporal biomarker concentration patterns during the early course of acute coronary syndrome

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Abstract

Objectives: Biomarker concentrations and their changes during acute coronary syndrome (ACS) provide clinically useful information on pathophysiological processes, e.g. myocardial necrosis, hemodynamic stress and inflammation. However, current evidence on temporal biomarker patterns early during ACS is limited, and studies investigating multiple biomarkers are lacking.

Methods: We measured concentrations of high-sensitivity cardiac troponin T (hs-cTnT) and I (hs-cTnI), NT-terminal pro-B-type natriuretic peptide, C-reactive protein, and growth-differentiation factor-15 (GDF-15) in plasma samples obtained at randomization in ACS patients from the PLATelet inhibition and patient Outcomes (PLATO) trial. Linear regressions with interaction analyses were used to investigate the associations of biomarker concentrations with the time from symptom onset and to model temporal biomarker concentration patterns.

Results: The study population consisted of 16,944 patients (median age 62 years; 71.3 % males) with 6,853 (40.3 %) having ST-elevation myocardial infarction (STEMI) and 10,141 (59.7 %) having non-ST-elevation ACS (NSTE-ACS). Concentrations of all biomarkers were associated with time from symptom onset ($p_{interaction}$<0.001), apart for GDF-15 ($p_{interaction}$=0.092). Concentration increases were more pronounced in STEMI compared to NSTE-ACS. Temporal biomarker patterns for hs-cTnT and hs-cTnI were different depending on sex whereas biomarker patterns for the other biomarkers were similar in cohorts defined by age and sex.

Conclusions: Temporal concentration patterns differ for various biomarkers early during ACS, reflecting the variability in the activation and duration of different pathophysiological processes, and the amount of injured myocardium. Our data emphasize that the time elapsed from symptom onset should be considered for the interpretation of biomarker results in ACS.

Keywords: acute coronary syndrome; biomarkers; temporal concentration pattern

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Introduction

Early blood sampling for measurement of circulating biomarkers is a cornerstone in the triage, diagnosis and management of patients with acute coronary syndrome (ACS). Biomarker concentrations and their changes convey information on the timing and type of pathophysiological processes that may not be readily captured by other diagnostic methods. Information on the consistency and variability of the temporal patterns of biomarker concentrations early during ACS is however, sparse and often derived from limited cohorts of selected patients [1–9].

There are several levels of complexity to this topic. Temporal patterns may be different for biomarkers reflecting

different processes evolving during ACS. The type of ACS, i.e. ST-elevation myocardial infarction (STEMI) or non-ST-elevation ACS (NSTE-ACS), is known to contribute to differences in biomarker patterns given differences in the completeness and duration of coronary flow reduction and the extent of myocardial injury. There may also be differences in relation to patient characteristics, e.g. age and sex.

We have therefore investigated temporal patterns of biomarker concentrations early during ACS. Notably, this phase of the disease course is important for patient assessment and decision-making. Samples for biomarker analyses had been obtained from a very large cohort prior to invasive procedures. Specifically, we studied biomarkers of cardiomyocyte necrosis (high-sensitivity cardiac troponin T [hs-cTnT] and I [hs-cTnI]), hemodynamic stress (NT-terminal pro-B-type natriuretic peptide [NT-proBNP]), inflammation (C-reactive protein [CRP]) and growth-differentiation factor-15 (GDF-15) which integrates information on oxidative stress, inflammation and biological ageing. We explored the concentrations of these biomarkers in relation to the time elapsed from symptom onset and hypothesized that there might be differences in temporal dynamics between the different types of ACS and between specific patient subsets, reflecting the variability in the activation and duration of different pathophysiological processes.

Materials and methods

Study population

This is an observational post-hoc study of patients included in the PLATelet inhibition and patient Outcomes (PLATO) trial (ClinicalTrials.gov identifier: NCT00391872). PLATO was an international, multicenter, double-blind, randomized control trial comparing ticagrelor and clopidogrel in addition to aspirin for the prevention of cardiovascular events in 18,624 patients with ACS [10]. Patients were included in the PLATO trial if they were hospitalized for STEMI or NSTE-ACS with symptom onset during the previous 24 h and lasting ≥10 min while at rest. For NSTE-ACS, at least two of three criteria were required: ST-segment depression or transient elevation ≥1 mm in two or more contiguous leads, a positive biomarker result indicating myocardial necrosis, or one additional risk factor (age >60 years, prior myocardial infarction or coronary artery bypass grafting, carotid artery disease, previous ischemic stroke, transient ischemic attack, carotid stenosis or cerebral revascularization, diabetes mellitus, peripheral artery disease, or chronic kidney disease). For STEMI, study inclusion also required a planned primary percutaneous coronary intervention. Among exclusion criteria, the most important included fibrinolytic therapy within 24 h, need for oral anticoagulation therapy, need for dialysis, and clinically important anemia or thrombocytopenia [10].

The PLATO trial and the current investigation were conducted in adherence to the Declaration of Helsinki and had been approved by Ethical Review Boards. All patients provided written informed consent to participate and received routine medical care with the exception of randomized treatment (ticagrelor or clopidogrel).

Biomarker analysis

Ethylenediaminetetraacetic acid (EDTA) plasma samples were collected at randomization which always took place before invasive procedures. After acquisition, samples were stored in aliquots at −70 °C until analysis which was performed centrally at the Uppsala Clinical Research Center (UCR) Laboratory (Uppsala University, Uppsala, Sweden). Concentrations of hs-cTnT, NT-proBNP and GDF-15 were measured on Cobas Analytics Immunoanalyzers (Roche Diagnostics, Basel, Switzerland). Hs-cTnI and CRP concentrations were measured using the Architect platform (Abbott Diagnostics, Abbott Park, IL, USA).

Statistical analysis

Categorical variables are reported as frequencies and percentages, and continuous variables as medians with interquartile ranges.

Linear regression models were fitted to study the association of each biomarker with the time interval from symptom onset to blood sampling. Symptom onset had been defined in PLATO as the date and time of the onset of the most recent cardiac ischemic symptoms. Biomarker concentrations were log-transformed before inclusion as outcome in the models. To capture non-linear associations, time since symptom onset was included as a restricted cubic spline with five knots, placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the sample distribution of time. The models also included sex, type of ACS (STEMI or NSTE-ACS), and age as a continuous linear term, as well as the interaction of each of these variables with time. To save degrees of freedom, only the linear part of the spline representation of time was included in the interactions. Accordingly, the linear regression models can heuristically be represented as: log(biomarker) ~ rcs(time) + sex + age + acstype + time × sex + time × age + time × acstype. The associations between biomarker concentrations and time elapsed from symptom onset are presented graphically by plotting predictions from these models for combinations of sex, type of ACS and three arbitrarily chosen ages (50, 60 and 70 years). The overall test of any interaction with time was assessed by testing the simultaneous null hypothesis of all three interaction terms in the respective models being zero. The interactions of time with the type of ACS, age or sex, respectively, on biomarker concentrations were also tested. As a sensitivity analysis, models were fitted by adding body mass index, smoking status, hypertension, dyslipidemia, diabetes, chronic renal disease, previous myocardial infarction, previous ischemic stroke, previous heart failure, and peripheral vascular disease as covariates.

The software package R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analyses.

Results

The study population consisted of all patients included in PLATO who had available results for all five biomarkers (n=16,944).

The median age was 62 (25th, 75th percentiles 54–71) years and 12,117 (71.3 %) patients were male. STEMI occurred

Table 1: Clinical characteristics and biomarker results in relation to the type of acute coronary syndrome.

	Total (n=16,994)	STEMI (n=6,853)	NSTE-ACS (n=10,141)	Missing values
Demographics				
Age, years	62 (54–71)	59 (52–68)	64 (56–72)	1 (0.0 %)
Men	12,117 (71.3 %)	5,206 (76.0 %)	6,911 (68.1 %)	–
BMI, kg/m^2	27.5 (24.8–30.5)	27.4 (24.7–30.3)	27.5 (24.8–30.6)	60 (0.4 %)
Risk factors				
Current smoking	6,047 (35.6 %)	3,079 (44.9 %)	2,968 (29.3 %)	–
Hypertension	11,139 (65.5 %)	4,037 (58.9 %)	7,102 (70.0 %)	–
Diabetes	4,256 (25.0 %)	1,389 (20.3 %)	2,867 (28.3 %)	–
Hyperlipidemia	8,014 (47.2 %)	2,723 (39.7 %)	5,291 (52.2 %)	–
Medical history				
Previous MI	3,512 (20.7 %)	918 (13.4 %)	2,594 (25.6 %)	–
Previous PCI	2,261 (13.3 %)	577 (8.4 %)	1,684 (16.6 %)	–
Previous CABG	999 (5.9 %)	176 (2.6 %)	823 (8.1 %)	–
Heart failure	985 (5.8 %)	203 (3.0 %)	77 (7.7 %)	–
Previous TIA	462 (2.7 %)	112 (1.6 %)	350 (3.5 %)	–
Previous stroke	644 (3.8 %)	196 (2.9 %)	448 (4.4 %)	1 (0.0 %)
PAD	1,050 (6.2 %)	308 (4.5 %)	742 (7.3 %)	–
Chronic renal disease	716 (4.2 %)	210 (3.1 %)	506 (5.0 %)	–
Biomarker results				
Hs-cTnT, ng/L	191 (45–654)	172 (44–699)	203 (47–628)	287 (1.7 %)
Hs-cTnI, ng/L	950 (120–4,800)	770 (120–5,200)	1,100 (120–4,700)	592 (3.5 %)
NT-proBNP, ng/L	460 (149–1,300)	284 (82–1,064)	570 (221–1,437)	264 (1.6)%
CRP, mg/L	3.7 (1.6–9.5)	3.4 (1.5–8.7)	4.0 (1.7–10.0)	595 (3.5)%
GDF-15, ng/L	1,549 (1,145–2,219)	1,526 (1,130–2,178)	1,571 (1,155–2,245)	119 (0.7)%

Data given as numbers (with percentages) or medians (with 25th, 75th percentiles). STEMI, ST-elevation myocardial infarction; NSTE-ACSMI, non ST-elevation acute coronary syndrome; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PAD, peripheral artery disease; hs-cTnT, high-sensitivity cardiac troponin T; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, NT-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein; GDF-15, growth-differentiation factor-15.

in 6,853 (40.3 %) patients and 10,141 (59.7 %) patients had NSTE-ACS. The median time from symptom onset to biomarker sampling was 10.5 (4.3–18.7) hours for the total cohort, 5.0 (2.8–10.8) hours in patients with STEMI and 14.9 (7.9–20.7) hours in patients with NSTE-ACS. Table 1 and Supplementary Table S1 provide further information on clinical characteristics and biomarker concentrations.

Figure 1A–E depict the concentrations of hs-cTnT, hs-cTnI, NT-proBNP, CRP and GDF-15 in relation to the time from symptom onset. The concentrations of most biomarkers were higher across longer delay times ($p_{interaction}$<0.001). The only exception was GDF-15 for which concentrations remained stable in relation to the time to sampling ($p_{interaction}$=0.092).

Compared to NSTE-ACS patients, those with STEMI had in general higher biomarker concentrations. Concentrations in STEMI tended either to be higher when sampling was performed at later time points (e.g. NT-proBNP, CRP), or appeared to reach a plateau (e.g. hs-cTnT, hs-cTnI). In NSTE-ACS, highest concentrations for hs-cTnT, hs-cTnI and NT-proBNP were noted in patients undergoing sampling with a delay of 12–14 h. Hs-cTnT reached higher concentrations compared to hs-cTnI. CRP concentrations continued to increase along with longer delay time.

The concentrations of NT-proBNP and GDF-15 were higher in patients with advanced age but the slope of the spline curves indicated no age-dependent association with time. This is supported by the lack of interactions of age and time. Even for hs-cTnT, hs-cTnI and CRP, no such interactions existed (Table 2). Men had overall higher concentrations for both hs-cTnT and hs-cTnI compared to women with diverging spline curves over time ($p_{interaction}$<0.001). Women had higher concentrations for NT-proBNP. However, the slopes of the spline curves indicated no sex-dependent association between NT-proBNP concentrations and time ($p_{interaction}$=0.325). There was also an interaction of sex and time on CRP concentrations ($p_{interaction}$=0.004) but not on concentrations of GDF-15 ($p_{interaction}$=0.963). These findings remained unchanged in the sensitivity applying the extended adjustment set (Table 2; Supplementary Figures S1A–E).

Discussion

This is the largest investigation of temporal biomarker concentration patterns during the early course of ACS. We

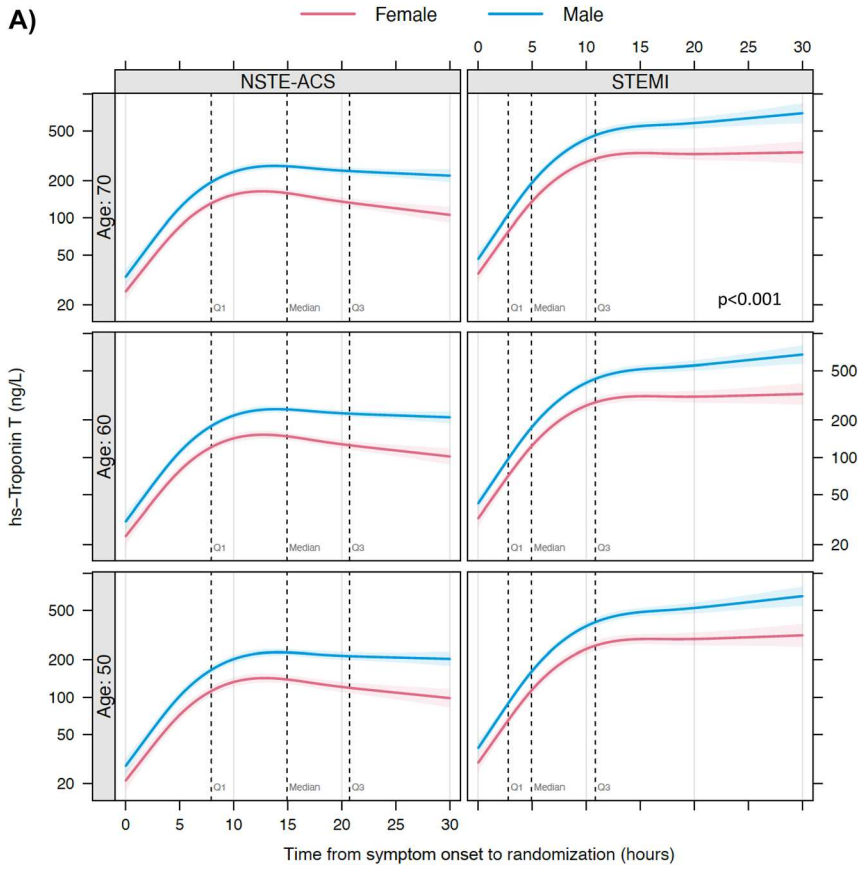


Figure 1: Biomarker concentrations in relation to the time interval from symptom onset. (A) hs-cTnT; (B) hs-cTnI; (C) NT-proBNP; (D) CRP; and (E) GDF-15. Restricted cubic splines including sex, age, type of acute coronary syndrome (STEMI or NSTE-ACS) and the interaction of each of these variables with time from symptom onset to blood sampling. The time interval was limited to 30 h from symptom onset in the graphs since there was a considerable decrease in the number of patients randomized at later timepoints. p-Values refer to the overall test of any interaction with time. hs-Troponin T, high-sensitivity cardiac troponin T; hs-Troponin I, high-sensitivity cardiac troponin I; NT-proBNP, NT-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein; GDF-15, growth-differentiation factor-15; STEMI, ST-elevation myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome.

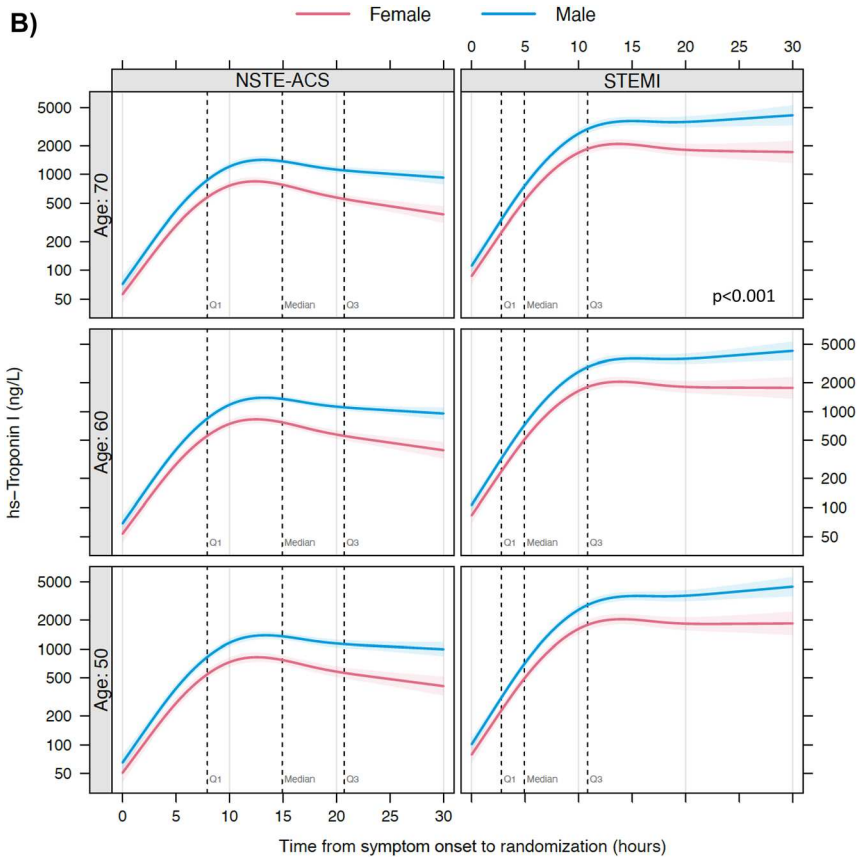
noted considerable variations. This emphasizes the importance of the acuteness of pathophysiological reactions to the ischemic event and the amount of injured myocardium. Our data also emphasize that the time elapsed from symptom onset should be considered for the interpretation of biomarker results in ACS.

Cardiac troponin T and I

The concentrations of hs-cTnT and hs-cTnI exhibited strong associations with time from symptom onset. Highest concentrations in NSTE-ACS patients were noted if sampling was performed after 12–14 h. In STEMI in contrast, hs-cTn concentrations did not differ considerably when sampling was performed after 15 h. Accordingly, hs-cTn concentrations seem to reach a plateau phase at this time point, likely explained by ongoing cTn release from the infarcted myocardium due to early remodeling [11].

Hs-cTnI concentrations were higher compared to hs-cTnT regardless of the type of ACS. This finding corresponds with data from smaller cohorts demonstrating earlier increases and higher peak concentrations for hs-cTnI compared to hs-cTnT [1–3]. This difference appears to be caused by a faster proteolytic degradation of cTnI in necrotic myocardial tissue which results in a quicker release of measurable cTnI fragments into the circulation [12]. cTnT in contrast, remains mostly bound to cardiac myofibrils where it to a greater extent, is degraded by phagocytes [12]. Consequently, only a smaller proportion of cTnT reaches the circulation and at a later stage compared to cTnI.

Hs-cTn concentrations did not differ by age. However, men were found to have higher hs-cTn concentrations than women, potentially owing to a greater proportion of women with unstable angina included in PLATO [13]. The sex-discrepancy in hs-cTn concentrations increased over time in both STEMI and NSTE-ACS, as illustrated by the diverging spline curves. The cause of this intriguing finding is not clear. No similar patterns emerged for the other investigated biomarkers. As such, the observed sex-difference for hs-cTn appears not to reflect variations in hemodynamic stress or inflammation. Differences in cardiovascular risk factors or comorbidities do not appear to matter either, as suggested by the results of our sensitivity analysis. Greater cardiac muscle mass in men [14] with potentially more releasable cTn may be one contributing factor for the findings reported here.



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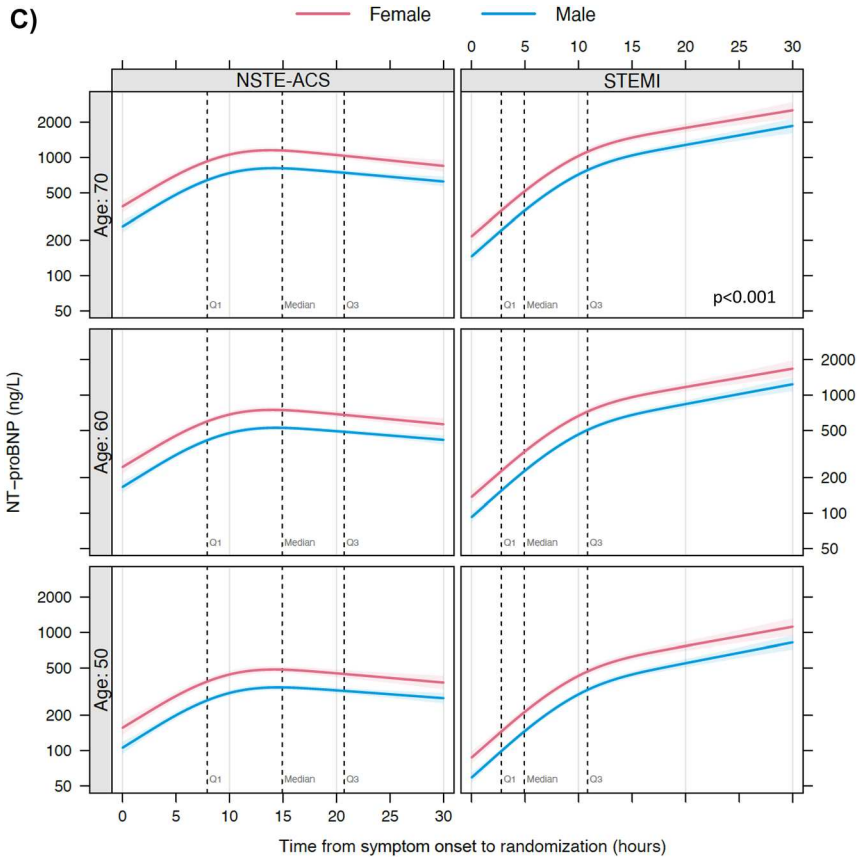
However, final infarct size, as assessed by magnetic resonance imaging, has been shown to be similar in men and women [15, 16]. Further research on sex-differences in hs-cTn release during ACS and the underlying explanations is clearly needed.

N-terminal pro-B-type natriuretic peptide

The concentrations of NT-proBNP were higher along with longer delay time from symptom onset. Interestingly, NSTE-ACS patients undergoing early blood sampling had higher NT-proBNP concentrations compared to those with STEMI. This likely reflects higher prevalence of pre-existing conditions associated with elevated NT-proBNP in these patients, e.g. congestive heart failure and hypertension [17]. The highest NT-proBNP concentrations were noted in patients undergoing sampling at 12–14 h from symptom onset. This indicates that a peak is reached at this time point. Previous data on early NT-proBNP changes during NSTE-ACS are somewhat ambiguous since timing referred to study inclusion which occurred at least one day after the ischemic event [4, 5]. Our study thus, provides clarifying evidence in this regard.

In STEMI, NT-proBNP concentrations continued to increase across patients with longer delay time to blood sampling, and concentrations reached higher levels compared to NSTE-ACS. This reflects the association of this biomarker with greater hemodynamic stress and infarct size in these patients [6]. Our data are consistent with other studies that have studied NT-proBNP kinetics using serial samples and demonstrating peak concentrations at 24–48 h in STEMI [5, 6]. A second peak may occur on day 2–5 indicating the event of adverse remodeling [5, 6].

NT-proBNP concentrations were associated with higher age in both STEMI and NSTE-ACS. Women had higher concentrations of NT-proBNP. Regardless of age and sex however, NT-proBNP concentrations followed similar temporal patterns as indicated by paralleling spline curves. The differences observed here appear thus, not to reflect intrinsic age- or sex-related variations in the pathophysiology of ACS but rather the well-known associations between NT-proBNP, age and female sex [18, 19]. Underlying explanations include age-related changes affecting the heart, renal function, and natriuretic peptide metabolism, greater prevalence of diastolic dysfunction in women and the effect of sex hormones [18, 19]. Taken together, our data emphasize that neither age



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nor sex need to be considered in ACS for management decisions based on the magnitude of early NT-proBNP concentration changes.

C-reactive protein

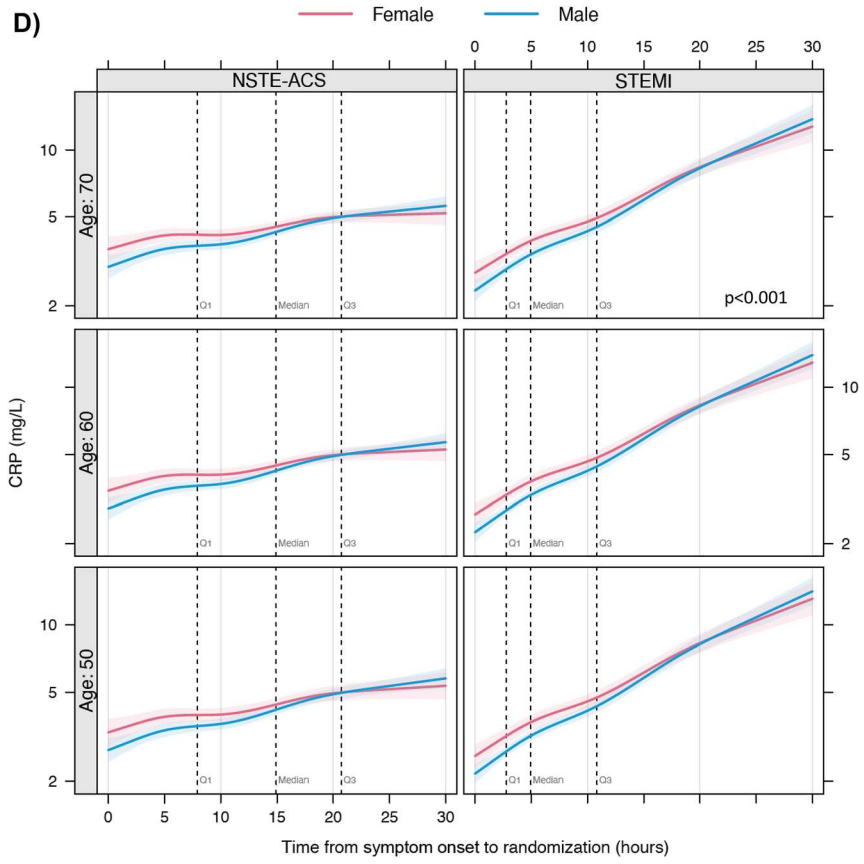
The concentrations of CRP increased with longer time from symptom onset, regardless of age and sex. These data correspond with previous findings reporting peak CRP concentrations at 40–54 h in NSTE-ACS and 48–72 h in STEMI [7–9], i.e. at timepoints beyond our observation period.

Initial CRP concentrations were higher in patients with NSTE-ACS compared to those with STEMI. This may be explained by more pronounced vascular inflammation in our NSTE-ACS subset or alternatively, a higher prevalence of comorbidities associated with higher CRP concentrations such as diabetes mellitus [20] or renal dysfunction [21]. However, the association between CRP concentrations and time from symptom onset was stronger in STEMI patients who also had higher concentrations when undergoing sampling at later timepoints. CRP is a marker of the intensity of the inflammation in the infarcted myocardium [22] which explains why CRP elevations were more pronounced and longer-lasting in STEMI [8, 9].

Growth-differentiation factor-15

Concentrations of GDF-15 were higher in patients with more advanced age and those having STEMI. There was no sex-difference. Moreover, we observed no temporal variation in GDF-15 concentrations.

In animal models, GDF-15 is induced in the myocardium in response to pathological stress associated with ischemia-reperfusion injury or inflammation [23]. However, the data presented here provide no convincing evidence that GDF-15 might be involved in the early activation of pathways during ACS in humans. Accordingly, GDF-15 cannot be used for diagnostic purposes in this setting. Given the relative stability of its concentrations over time, GDF-15 is instead well suited as a marker of risk [24, 25] and might be useful as decision support concerning treatment measures. This is supported by recent data from our research group, identifying GDF-15 as the strongest contributor to adverse outcome in the recently published ABC-ACS ischemia score [26].



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The importance of timing of biomarker measurement

Our findings emphasize the importance of timing aspects for the interpretation of biomarker results. This is an important issue when assessing populations with different manifestations of ACS. Many studies apply biomarker results obtained at fixed timepoints, e.g. upon admission or randomization into controlled trials [1, 3, 5, 8, 9]. Such a strategy does however not, take into account the dynamic nature of biomarker changes in ACS, as evidenced by our data. It is thus, essential to consider the delay time since onset of chest pain when interpreting differences in biomarker concentrations between individual patients or in cohorts with different manifestations of ACS. This applies not only to the cardiac troponins but to any biomarker exhibiting early concentration changes following myocardial ischemia, e.g. NT-proBNP and CRP. It should be emphasized that the assessment of true biomarker concentration changes during ACS requires serial sampling. However, current guidelines recommend such an approach only for diagnostic purposes and using cTn [27].

Strengths and limitations

Our investigation has several strengths. We investigated a broad and large international cohort of patients with ACS patients with high-quality data from a pivotal trial. This enabled us to study several sizable subcohorts of clinical relevance. Multiple biomarkers were assessed in parallel which provided the possibility to demonstrate and compare the dynamics of several key pathophysiological processes in ACS. The plasma samples were obtained before invasive procedures which allowed us to model the “natural course” of the disease without interference from interventional attempts to restore coronary blood flow.

There are also some limitations that deserve comment. Our cohort stems from a randomized controlled trial. Accordingly, it probably represents a somewhat selected subset of the general ACS population based on some of the exclusion criteria related to the tested study treatment. The diagnoses of the index events as STEMI and NSTE-ACS were defined by the local PLATO investigators without central adjudication. We focused on established biomarkers and GDF-15 which has an emerging role in cardiovascular

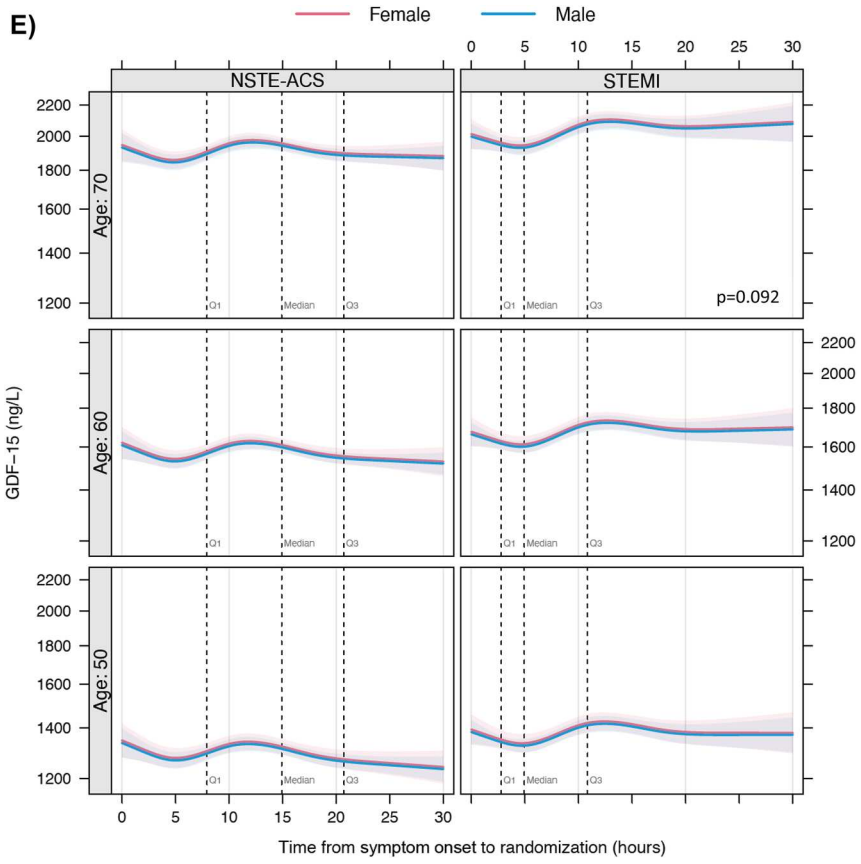

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Table 2: Interactions of the type of acute coronary syndrome, age or sex, and time interval from symptom onset on biomarker concentrations.

Base models			Adjusted models		
Biomarker	**Term**	**p-Value**	**Biomarker**	**Term**	**p-Value**
Hs-cTnT	Type of ACS × time	<0.001	Hs-cTnT	Type of ACS × time	<0.001
	Age × time	0.213		Age × time	0.095
	Sex × time	<0.001		Sex × time	<0.001
	Total interaction	<0.001		Total interaction	<0.001
Hs-cTnI	Type of ACS × time	<0.001	Hs-cTnI	Type of ACS × time	<0.001
	Age × time	0.157		Age × time	0.082
	Sex × time	<0.001		Sex × time	<0.001
	Total interaction	<0.001		Total interaction	<0.001
NT-proBNP	Type of ACS × time	<0.001	NT-proBNP	Type of ACS × time	<0.001
	Age × time	0.191		Age × time	0.067
	Sex × time	0.325		Sex × time	0.314
	Total interaction	<0.001		Total interaction	<0.001
CRP	Type of ACS × time	<0.001	CRP	Type of ACS × time	<0.001
	Age × time	0.121		Age × time	0.224
	Sex × time	0.004		Sex × time	0.002
	Total interaction	<0.001		Total interaction	<0.001
GDF-15	Type of ACS × time	0.046	GDF-15	Type of ACS × time	0.607
	Age × time	0.077		Age × time	0.038
	Sex × time	0.963		Sex × time	0.872
	Total interaction	0.092		Total interaction	0.219

Adjusted models included body mass index, smoking status, hypertension, dyslipidemia, diabetes, chronic renal disease, previous myocardial infarction, previous ischemic stroke, previous heart failure, and peripheral vascular disease as covariates. ACS, acute coronary syndrome.

medicine [24–26]. However, our findings cannot be translated to other biomarkers reflecting similar pathological processes. Temporal biomarker patterns were visualized based on a single blood sample in different patients with different delay times rather than on serial sampling in the same patient. Although our single-sample approach may infer some uncertainty concerning biomarker kinetics patterns, the confidence intervals of the spline curves were rather narrow which is explained by the very large sample size. We cannot exclude the possibility that biomarker concentration patterns might have been affected by early pharmacological treatments. Data on hemodynamics, coronary status and cardiac function had not been documented within the PLATO trial. We are for this reason not able to further explore the associations between temporal biomarker concentration patterns and these entities. Finally, it should be emphasized that the history on onset of symptoms is a rather imprecise estimate of the ischemic event in NSTE-ACS.

Conclusions

Temporal concentration patterns differ for different biomarkers early during ACS. This reflects variations in the activation and duration of pathophysiological processes and differences in the amount of injured myocardium. Temporal biomarker patterns were however, mostly similar in cohorts defined by age and sex and do thus, not indicate major differences in early pathway activation among these groups. Given the dynamic nature of concentration patterns, the use of biomarker results in mixed ACS populations without consideration of timing aspects appears not to be appropriate.

Research ethics: The PLATO trial and the current investigation were conducted in adherence to the Declaration of Helsinki and had been approved by Ethical Review Boards.

Informed consent: All patients particpating in the PLATO trial provided written informed consent to participate and received routine medical care with the exception of randomized treatment (ticagrelor or clopidogrel).

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Data availability: The sponsors of the PLATO trial (AstraZeneca, Cambridge, UK) are committed to responsible sharing of clinical study reports, related clinical documents, and patient level clinical study data. Researchers are invited to submit inquiries online. To submit inquiries, please visit https://astrazenecagrouptrials.pharmacm.com. All data relevant to the study are included in the article or uploaded as supplementary information.

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