Data Article

# Details on high frequency blood collection, data analysis, available material and patient characteristics in BIOMArCS

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## ARTICLE INFO

## ABSTRACT

The Biomarker Study to Identify the Acute Risk of a Coronary Syndrome (BIOMArCS) is a prospective, observational study that has been designed to study the evolution of blood biomarkers in post-acute coronary syndrome (ACS) patients. In our recently published study "Temporal evolution of Myeloperoxidase and Galectin 3 during 1 year after acute coronary syndrome admission" [1] in the *American Heart Journal*, we demonstrated that repeatedly measuring MPO and Galectin-3 does not aid to differentiate

between patients with and without adverse cardiac events during 1-year follow-up.

In this Data-In-Brief article, we present further details on data collections and data analysis. In addition, a detailed description of baseline characteristics and the distribution of blood sampling moments is provided. The BIOMArCS dataset contains clinical information and follow-up data on all enrolled 844 patients. These patients underwent a median of 17 (25th −75th percentile 12−20) repeated blood samples in the first year after the index ACS. Blood samples were stored at −80 °C within a median of 82 (25th-75th percentile 58−117) minutes after withdrawal. We collected whole blood, citrate plasma, EDTA plasma, serum and DNA.

The dataset used for the analysis in the accompanying research paper has been made available online. We welcome collaborations for further use of our data, whether or not in combination with other biobanks.

## Specifications Table

| | |
|---|---|
| Subject area | *Medicine* |
| More specific subject area | *Cardiovascular, biomarkers, acute coronary syndromes* |
| Type of data | *Tables, figures* |
| How data was acquired | *Data were required by frequent blood sampling in ACS patients, and batch wise biomarker measurements in a central laboratory. R statistical software (version 2.15.0, available at: www.r-project.org) was used for advanced data analyses, in particular the package JMbayes.* |
| Data format | *Both raw material, and filtered and analyzed material* |
| Experimental factors | *Median 17 (25th-75th percentile 12−20) repeated blood sampling moments during the first year after ACS admission* |
| Experimental features | *Prospective, multicenter, observational cohort study* |
| Data source location | *Data were collected in 18 hospitals in The Netherlands, latitude 50.46-53.32, longitude 3.22-7.12* |
| Data accessibility | *Data is with this article and available in a public repository https://data.mendeley.com/datasets/yt6gxhrgvm/1* |
| Related research article | *M.M. Vroegindewey, V.J. van den Berg, E. Bouwens, K.M. Akkerhuis, R.M. Oemrawsingh, F.W. Asselbergs, F. Lenderink, P. van der Harst, E. Ronner, V.A. Umans, I. Kardys, E. Boersma, Temporal evolution of Myeloperoxidase and Galectin 3 during 1 year after acute coronary syndrome admission, Am. Heart. J. (2019).* [1] |

**Value of the Data**
- High-frequency sampling is to overcome spurious relations due to regression to the mean
- Data can be used to study biomarker normalization patterns early after ACS admission
- Data can be used to study biomarker evolution patterns during the first year after ACS admission
- Data can be used to relate biomarker evolution patterns in individuals with the incidence of adverse cardiac events during 1 year follow-up after ACS admission
- The investigators welcome collaborations for further use of their data to gain insight in biomarker patterns in patients with coronary artery disease, whether or not in combination with other biobanks

## 1. Data

The data shared is generated from a dataset containing 844 patients enrolled in BIOMArCS (Biomarker Study to Identify the Acute Risk of a Coronary Syndrome) between 2008 and 2015 in 18 hospitals in The Netherlands (https://data.mendeley.com/datasets/yt6gxhrgvm/1). This data has been collected to investigate the correlations between high frequency measured biomarker levels and clinical outcomes in the first year after hospital admission for ACS. In this Data-In-Brief article, we provide details on data collection and data analysis, and we provide a detailed description of baseline characteristics and the distribution of sampling moments.

- Fig. 1. Details on patient enrolment and blood sampling
- Fig. 2. BIOMArCS study flow chart
- Fig. 3. Distribution of blood sampling over time of the case-cohort
- Table 1 shows in detail the BIOMArCS in- and exclusion criteria
- Table 2 describes the baseline characteristics of the complete BIOMArCS cohort and the random sample that was used to construct the case-cohort (see Fig. 2)
- Table 3: presents the baseline characteristics of the endpoint cases and endpoint-free patients who compose the case-cohort
- In a public repository, we made available a dataset containing baseline characteristics, the time-to-event data and the high frequency measured MPO and Galectin 3 measurements of the BIOMArCS patients included in the case-cohort
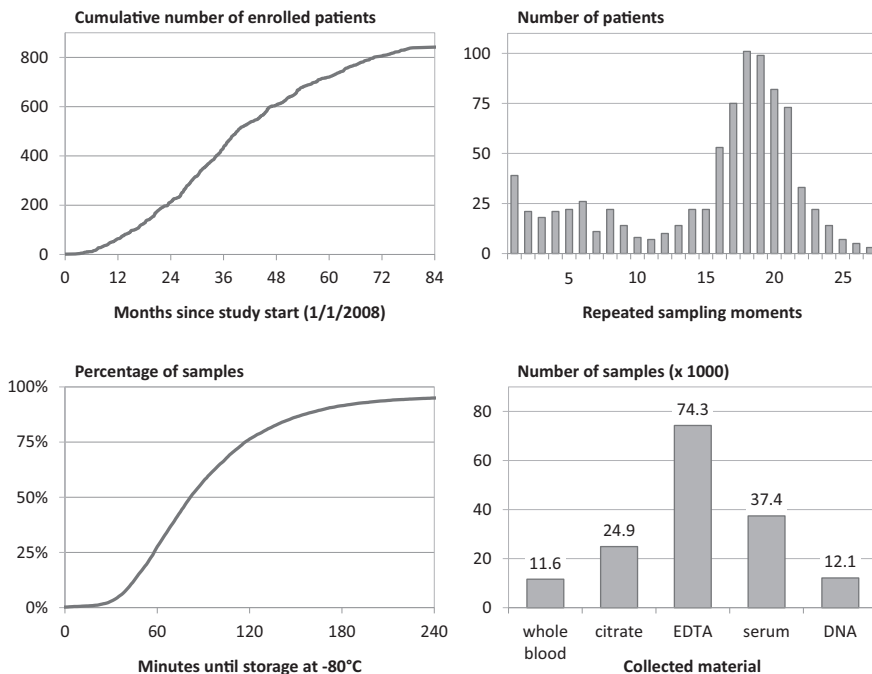


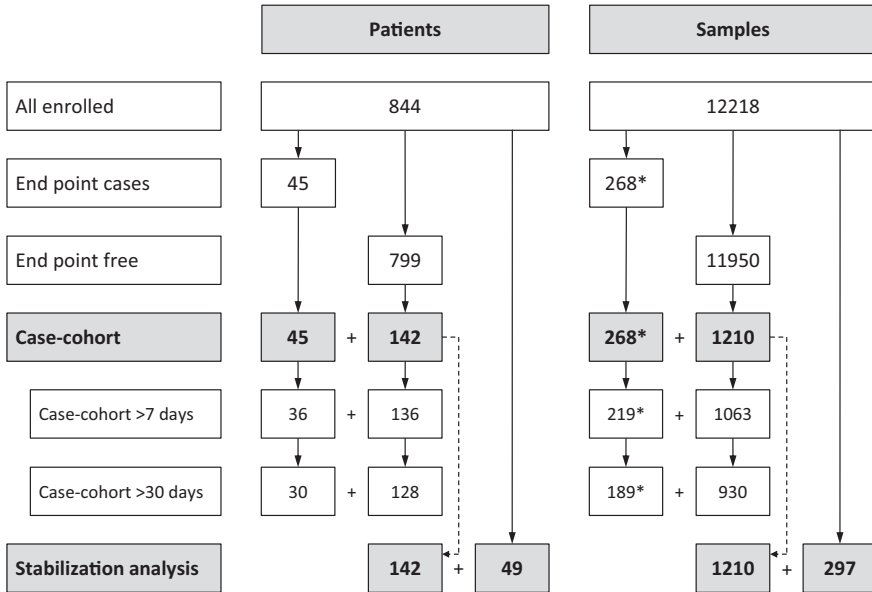**Fig. 1.** Details on patient enrolment and blood sampling.

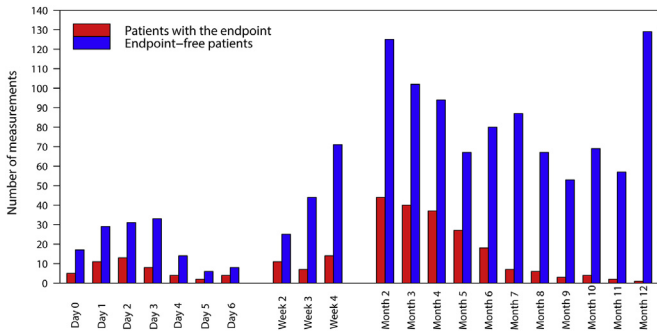Fig. 2. BIOMArCS study flow chart. * Available blood samples prior to the moment of the study endpoint.



Fig. 3. Distribution of blood sampling over time of the case-cohort.

## 2. Experimental design, materials, and methods

### 2.1. Prospective data collection

Our dataset contains the detailed patient and biomarker data from BIOMArCS (Biomarker Study to Identify the Acute Risk of a Coronary Syndrome). BIOMArCS is a prospective, observational study that has been designed to evaluate the evolution of blood biomarkers in relation to the occurrence of repeat cardiac events in post-acute coronary syndrome (ACS) patients [2]. BIOMArCS was conducted during 2008−2015 in 18 hospitals in The Netherlands.

Detailed information on the in- and exclusion criteria and study procedures are provided in Table 1. Briefly, patients aged ≥40 years who were admitted with an ACS and had ≥1 cardiovascular risk factor were eligible. Preferably, patients were enrolled during hospital admission, but inclusion at the first outpatient visit post-discharge (usually 4−6 weeks later) was allowed. Venipuncture was performed at

**Table 1**
Inclusion and exclusion criteria.

A patient must meet all the following inclusion criteria
1   Age $\geq$40 years
2   Complaints of typical ischemic chest pain, lasting 10 minutes or more within the preceding 24 hours prior to presentation
3a  ECG: (non)persistent ST segment elevation >1·0 mm in two or more contiguous leads, or dynamic ST segment depression >1·0 mm in two or more contiguous leads, OR
3b  Biochemical evidence of myocardial injury: CK-MB or (high-sensitivity) Troponin I or (high-sensitivity) Troponin T elevation according to the applicable ESC guidelines of non ST-elevation acute coronary syndromes
4   Presence of at least 1 of the following risk factors: age $\geq$75 years, diabetes, prior cardiovascular disease, prior cerebrovascular disease and prior peripheral arterial disease.
    In addition, the following characteristics counted as half a risk factor (i.e. two of these are required for inclusion): age $\geq$65 years in men, age $\geq$70 years in women, hypertension, hypercholesterolemia, current smoking, microalbuminuria, positive family history of coronary artery disease
5   Written informed consent
A patient cannot be included in case of any of the following exclusion criteria
1   Myocardial ischemia precipitated by a condition other than atherosclerotic coronary artery disease
2   Left ventricular ejection fraction <30%, or end-stage congestive heart failure (NYHA class III or IV)
3   Renal dialysis, or severe chronic kidney disease with measured or calculated GFR (Cockroft-Gault or MDRD4 formula) of <30 ml/min/1·73 m$^2$
4   Co-existent condition with life-expectancy <1 year or otherwise not expected to complete follow-up

admission, discharge, and subsequently every 2 weeks during the first half-year and monthly thereafter. Follow-up blood sampling was terminated permanently after coronary artery bypass grafting (CABG), hospital admission for heart failure, or a deterioration of renal function leading to an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m$^2$, since circulating biomarker concentrations may be significantly influenced by these conditions. It was optional to terminate blood sampling after the study endpoint was reached.

### 2.2. Endpoint definition and adjudication

The endpoint in our dataset was defined as the first event of the composite of cardiac death, myocardial infarction, or unstable angina requiring urgent coronary revascularization within 1 year. Event adjudication was performed by a Clinical Event Committee (CEC) consisting of two experts. In case of disagreement, a third expert was consulted and consensus was sought. It is important to realize that study patients were extensively seen by research personnel during follow-up, not only for venipuncture, but every time also for an interview regarding anginal complaints, intercurrent hospitalizations, and changes in medication etc. Hence, data on most follow-up events could be derived in the medical dossier at the participating site. Otherwise, discharge letters, ECGs, clinical lab and cathlab reports were retrieved from the site of treatment. CEC members were given full access to all clinical data. The CEC members were blinded for all biomarker data collected for the purpose of the BIOMArCS study.

### 2.3. Blood sampling and analysis

Details on blood sampling are presented in Fig. 1. We obtained a median of 17 (25th-75th percentile 12−20) repeated blood samples per patient. Blood samples were first handled on-site and then stored at −80 °C within a median of 82 (25th-75th percentile 58−117) minutes after withdrawal. We collected whole blood, citrate plasma, EDTA plasma, serum and DNA. Series of samples were subsequently transported under controlled conditions to the Erasmus MC, Rotterdam, for long-term storage.

Biomarkers were analyzed batch wise in a central laboratory and in a blinded fashion, after data collection was completed and study endpoints had been adjudicated. Thus, any influence of biomarker values on patient management and endpoint adjudication (and vice-versa) can be excluded, while batch-to-batch variations are avoided.

The MPO and Galectin-3 measurements that have been made available in the accompanying dataset, were measured in serum samples. MPO was measured with a 384-ELISA plate (Nunc, Thermo

**Table 2**

Baseline characteristics of complete cohort and random sample.

|  | Complete cohort | Random sample | Patients with daily sampling on day 1–4 |
|---|---|---|---|
| Number of patients | 844 | 150 | 68 |
| Age, year | 62.5 (54.3–70.2) | 62.7 (55.0–71.0) | 62.4 (54.9–70.8) |
| Man | 657/843 (77.9) | 118 (78.7) | 53 (77.9) |
| Cardiovascular risk factors |  |  |  |
| Diabetes Mellitus | 196/834 (23.5) | 26 (17.3) | 14 (20.6) |
| Hypertension | 463/834 (55.5) | 79 (52.7) | 35 (51.5) |
| Hypercholesterolemia | 411/834 (49.3) | 75 (50.0) | 26 (38.2) |
| Current smoker | 337/833 (40.5) | 64 (42.7) | 25 (36.8) |
| Body mass index | 28.0 (5.9) | 27.6 (3.8) | 27.4 (3.8) |
| History of cardiovascular disease |  |  |  |
| Myocardial infarction | 224/833 (26.9) | 45 (30.0) | 11 (16.2) |
| CABG | 83/834 (10.0) | 13 (8.7) | 4 (5.9) |
| PCI | 218/833 (26.2) | 41 (27.5) | 8 (11.8) |
| Stroke | 75/834 (9.0) | 19 (12.7) | 5 (7.4) |
| Peripheral vessel disease | 74/834 (8.9) | 10 (6.7) | 7 (10.3) |
| Presentation on admission |  |  |  |
| GRACE risk score | 96 (78–119) | 110 (88–130) | 112 (94–132) |
| Heart rate | (N = 833) 75 (19) | 73 (17) | 79 (18) |
| SBP, mmHg | (N = 831) 140 (27) | 137 (27) | 134 (25) |
| Diagnosis |  |  |  |
| STEMI | 430/832 (51.7) | 69 (46.0) | 36 (52.9) |
| NSTEMI | 314/832 (37.7) | 58 (38.7) | 27 (39.7) |
| Unstable angina pectoris | 88/832 (10.6) | 23 (15.3) | 5 (7.4) |
| PCI performed | 676/783 (86.3) | 116/139 (83.5) | 52/63 (82.5) |
| Medication recorded at first assignation 7 days post discharge |  |  |  |
| Aspirin | 758/797 (95.1) | 136/144 (94.4) | 56/61 (91.8) |
| P2Y12 inhibitor | 758/797 (95.1) | 132/144 (91.7) | 56/61 (91.8) |
| Vitamin K antagonist | 55/797 (6.9) | 10/144 (6.9) | 5/61 (8.2) |
| Statin | 768/797 (96.4) | 138/144 (95.8) | 58/61 (95.1) |
| Beta-blocker | 718/797 (90.1) | 123/144 (85.4) | 58/61 (95.1) |
| Ace inhibitor or ARB | 662/797 (83.1) | 121 (84.0) | 59/61 (98.7) |

Categorical variables are presented as number (percentage). Continuous variables with normal distribution are presented as mean (SD) and as median (25th-75th percentile) otherwise.
ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; CAD: coronary artery disease; DBP: diastolic blood pressure; GRACE risk score: Global Registry of Acute Coronary Events risk score; NSTEMI: non-STEMI; PCI: Percutaneous coronary intervention; SBP: systolic blood pressure; STEMI: ST-elevation myocardial infarction.

#460372), with a lower limit of detection of 609 pg/ml. The corresponding 10% coefficient of variation was 5.7%. GAL-3 was measured with a custom built Luminex immune-assay validated in the University Medical Centre Utrecht, the Netherlands. The corresponding lower limit of quantification was 0.06 pg/ml, the upper limit of quantification was 1000 pg/ml and the reference sample value was 158.43 pg/ml. The inter-assay coefficient of variation of the used GAL-3 custom build assay was 13.9% and the intra-assay coefficient of variation was 14.45%.

## 2.4. Case cohort approach to analyze the long-term temporal evolution of biomarkers

BIOMArCS enrolled a total of 844 patients of whom 45 reached the study endpoint. Consequently, the ratio of patients who reached the study endpoint to those who did not was 1:17.8, which, from statistical point of view, implies an overly large number of endpoint-free patients. For cost-efficacy reasons, we preferred to limit the amount of biomarker tests in endpoint-free patients, while maintaining all available information in study endpoint cases. Furthermore, we required to leave open the possibility of creating multiple-biomarker models describing absolute risks. Based on these considerations, we chose a case-cohort analysis. In order to maintain the statistical power of the full cohort, we chose a sampling proportion of at least 10% [3], and an endpoint to non-endpoint ratio of at least 1:3.

**Table 3**
Baseline characteristics of endpoint cases and endpoint-free patients.

|  | Endpoint cases | Endpoint-free patients | p-value |
|---|---|---|---|
| Number of patients | 45 | 142 |  |
| Age, year | 67.4 (57.1−76.5) | 62.6 (55.0−70.9) | 0.075 |
| Man | 36 (80.0) | 111 (78.2) | 0.79 |
| Cardiovascular risk factors |  |  |  |
| Diabetes Mellitus | 17 (37.8) | 24 (16.9) | 0.003 |
| Hypertension | 22 (48.9) | 77 (54.2) | 0.53 |
| Hypercholesterolemia | 20 (44.4) | 72 (50.7) | 0.46 |
| Current smoker | 17 (37.8) | 60 (42.2) | 0.52 |
| Body mass index | 27.2 (3.7) | 27.8 (3.8) | 0.36 |
| History of cardiovasvular disease |  |  |  |
| Myocardial infarction | 14 (31.1) | 43 (30.3) | 0.92 |
| CABG | 11 (24.4) | 12 (8.5) | 0.004 |
| PCI | 14 (31.1) | 38 (27.0) | 0.59 |
| Stroke | 9 (20.0) | 16 (11.3) | 0.13 |
| Peripheral vessel disease | 10 (22.2) | 9 (6.3) | 0.004 |
| Presentation on admission |  |  |  |
| GRACE risk score | 121 (98−141) | 109 (88−130) | 0.022 |
| Heart rate | 75 (16) | 73 (17) | 0.59 |
| SBP, mmHg | 145 (24) | 138 (27) | 0.095 |
| DBP, mmHg | 72 (3) | 81 (17) | 0.48 |
| Diagnosis |  |  | 0.46 |
| 　STEMI | 16 (35.6) | 65 (45.8) |  |
| 　NSTEMI | 22 (48.9) | 56 (39.4) |  |
| 　Unstable angina pectoris | 7 (15.6) | 21 (14.8) |  |
| PCI performed | 34 (87.2) | 109 (82.6) | 0.50 |
| Medication recorded at first assignation 7 days post discharge |  |  |  |
| Aspirin | 45 (100) | 132 (93.0) | 0.20 |
| P2Y12 inhibitor | 44 (96.8) | 128 (90.4) | 0.37 |
| Vitamin K antagonist | 5 (9.7) | 11 (7.9) | 0.57 |
| Statin | 44 (96.8) | 136 (95.6) | 0.46 |
| Beta-blocker | 42 (93.5) | 121 (85.1) | 0.72 |
| Ace inhibitor or ARB | 41 (90.3) | 120 (84.2) | 1.00 |

Categorical variables are presented as number (percentage). Continuous variables with normal distribution are presented as mean (SD) and as median (25th-75th percentile) otherwise.
ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; CAD: coronary artery disease; DBP: diastolic blood pressure; GRACE risk score: Global Registry of Acute Coronary Events risk score; NSTEMI: non-STEMI; PCI: Percutaneous coronary intervention; SBP: systolic blood pressure; STEMI: ST-elevation myocardial infarction.

The case-cohort design was first described by Prentice in 1986 [4], and has since been discussed from various viewpoints, including sampling of the sub cohort, analysis methods and comparison with the nested case-control design [5]. Nowadays, the case-cohort design is accepted as a useful tool in the epidemiological armamentarium to obtain valid effect estimates [6]. Although it is not widely used in the medical literature, it has been applied in several landmark epidemiological studies, such as ARIC, EPIC and MORGAM [5,7,8]. As Sharp et al. state: 'The main advantage of the case-cohort study design over a cohort study is that full covariate data are only needed on the cases and sub cohort individuals, not all the original cohort, potentially saving time and money if measures such as biomarkers or genotypes are required' [9]. When appropriate sampling and analysis methods are applied, the case-cohort provides unbiased estimates of relative (effect) measures - in our case hazard ratios [10]. An advantage over a nested case-control study is that it also enables unbiased estimations of absolute measures, such as risks, hazards, etc. In addition, the same random sub cohort can be used for studying different outcomes with different case definitions, rather than identifying a new set of controls for each separate outcome.

A random sample of 150 patients was selected from the full dataset of 844 patients, which included 8 patients who reached the study endpoint. Hence, the ratio of study endpoint cases to endpoint-free patients was 8:142 (5.3%), which is similar to 45:844 (5.3%) in the full dataset, as expected. In Table 2, the baseline characteristics of the patients included in the random sample (150) can be compared with

the entire cohort (844). Hereafter, the random sample was enriched with the remaining 37 endpoint cases, so that the case-cohort analysis set consists of (all) 45 endpoint cases and 142 endpoint-free patients. Table 3 shows the differences in baseline characteristics between patients in whom the endpoint occurred and those who remained endpoint-free.

As depicted in Fig. 2, we analyzed all 268 blood samples that were collected in the endpoint cases before the moment of the endpoint, which implies a median of 5 (25th-75th percentile 2 to 8) repeated samples per patient. We further analyzed 1210 blood samples in event-free patients, which was a random selection of 60% of all collected blood samples in these subjects, and implies a median of 9 (25th-75th percentile 6 to 11) repeated samples per patient. Fig. 3 depicts the number of available measurements per moment in time for both patients in whom the endpoint occurred and in those who remained endpoint-free.

## 2.5. Data model to analyze the long-term temporal evolution of biomarkers

In order to investigate the associations between the high frequency measured biomarkers and clinical events in our dataset, we had to combine temporal evolvement patterns of the biomarkers with time-to-event data. For this purpose, we combined linear regression with Cox proportional hazard regression. Linear regression is a powerful instrument to model the temporal evolvement of biomarkers, accounting for clustering of data within a patient. Cox proportional hazard (PH) regression is a well-developed instrument to model a time-to-event process in relation with a biomarker, accounting for its time-dependent nature. However, since both processes are correlated, the use of independent models can cause biased estimates [11]. Instead, in order to obtain valid inferences for the relation between the temporal evolution of a biomarker and the incidence of the primary end point, the longitudinal- and event processes should be jointly modelled [12].

We applied Bayesian semiparametric joint models for that purpose [13]. We developed linear mixed-effects (LME) models to describe the underlying patient-specific longitudinal biomarker trajectories B(t). To allow for non-linear trajectories we used cubic splines functions, whereas the number and position of knots were biomarker specific. Age, sex, and variables regarding cardiovascular risk and -history were included as determinants.

With respect to the time-to-event process, we assumed that the risk of the primary end point depends on the underlying, actual value of the biomarker at time point t. Consequently, the hazard function was modelled as $h_0(t)*exp(B(t))$. To enable subject-specific survival predictions, the baseline hazard $h_0(t)$ was specified using a B-splines approach.

We developed joint models for each specific biomarker. Log-transformations were applied on biomarker values to assure normal distributions of regression residuals. More specifically, the unit of analysis was the Z-score of the log-biomarker - which was obtained by subtracting the mean value and dividing by the standard deviation on the log-scale - in order to allow a direct comparison of the effect of the separate markers. We present our results as hazard ratios (HR) and corresponding 95% confidence intervals (CI) for a 1 SD difference of the biomarker on the log-scale. Obviously, the risk of the primary end point might be influenced by age and clinical risk factors (Table 3), whereas biomarker levels might be influenced by kidney function. Therefore, all HRs were adjusted for GRACE risk score (for death or myocardial infarction in 6 months after discharge) and creatinine value.

The LME models that we developed did not only provide unbiased estimates B(t) of the level of a biomarker at time point t, but also of its instantaneous rate of change (or: slope) B'(t) at t, which, mathematically, corresponds with the first derivative of B(t). Since we specifically aimed to study change patterns, we not only determined HRs for the biomarker level but also for its instantaneous slope.

R statistical software (version 2.15.0, available at: www.r-project.org) was used for advanced statistical analyses, in particular the package JMbayes. All statistical tests were two-tailed and p-values <0.05 were considered statistically significant.

## 2.6. Patient selection and data model for the analysis of biomarker stabilization

By design, a series of 68 BIOMArCS patients - their characteristics are presented in Table 2 - underwent additional blood sampling at day 1—4, with the aim to study the evolution of biomarker

changes early after ACS admission. Insights into these evolvements allows us to differentiate between 'normal' post-ACS biochemical profiles and a divergent profile potentially caused by (an upcoming) repeat ACS. A total of 49 patients were not included in the case-cohort. For the analysis of 'normal' post-ACS biomarker profiles, we combined their samples with the 142 endpoint-free patients from the case-cohort. Consequently, 191 patients were available, who contributed a median of 8 (IQR 5–10) repeated samples per patient, totaling 1507 measurements (Fig. 2). We chose to exclude study endpoint cases from this analysis to avoid ensuing distortion of biomarker stabilization patterns.

We used LME models to describe the average biomarker stabilization patterns. In these models, time was entered as the independent variable, and the biomarker value as the dependent variable. To allow non-linearity in the association between time and the biomarker value, up to two cubic splines were placed on different time points. For optimal placing of these splines, we used Akaike's information criterion and Bayesian information criteria. Finally, to allow for individual variation, random slopes and random intercepts were included in the models.

For the first 50 days after the index ACS, and based on the fitted LME models, we determined the patient-averaged biomarker value, the number of days on which this value was above the specified population reference, and the time until stabilization. Stabilization (on group level) was defined as a difference in average biomarker level of less than one percent between two consecutive days.

## 2.7. Explanation of variables in dataset

The dataset containing baseline characteristics and the MPO and Galectin-3 measurements of the patients included in the case-cohort has been made available in a public repository. The data is given in a long-format in which each measurement is placed in a new row. Thus in example, for a patient who has had seven sampling moments, there are seven rows.

In the variable names, Hx is short for history. GRACERisk is the GRACE risk score calculated based on the post discharge model as developed by Eagle et al. [14]. For this score the variables age, pulse, systolic blood pressure, initial serum creatinine, positive initial enzymes, ST segment depression, past MI, past congestive heart failure, and in-hospital percutaneous coronary intervention are combined into a single score. DaysOfVenePuncture is the number of days since the index event at which the blood sample was taken. DaysVenePunctureToEvent is the number of days until the event or moment of study discontinuation in patients without event. The remaining variables are self-explanatory.

In a second dataset (baselineBIOMArCS), the baseline characteristics of all patients included in the BIOMArCS are presented.

## Funding

## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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