High-Frequency Biomarker Measurements of Troponin, NT-proBNP, and C-Reactive Protein for Prediction of New Coronary Events After Acute Coronary Syndrome BIOMArCS Study

BIOMArCS Investigators

Published in:
Circulation

DOI:
10.1161/CIRCULATIONAHA.118.036349

Publication date:
2019

Circulation

RESEARCH LETTER

High-Frequency Biomarker Measurements of Troponin, NT-proBNP, and C-Reactive Protein for Prediction of New Coronary Events After Acute Coronary Syndrome

BIOMArCS Study

Rohit M. Oemrawsingh, MD, MSc et al

The BIOMArCS study (Biomarker Study to Identify the Acute Risk of a Coronary Syndrome) was designed to study the relation between temporal changes in cardiovascular biomarkers and ischemic cardiovascular events in patients discharged after acute coronary syndrome admission (The Netherlands Trial Register NTR1698).[1] Eight hundred forty-four patients with acute coronary syndrome were enrolled in 18 hospitals in the Netherlands. Venipuncture was scheduled at 19 regular intervals during a year. Forty-five patients (cases) reached the study end point, defined as the first event of the composite of cardiac death (n=8), myocardial infarction (n=24), or unstable angina requiring urgent coronary revascularization (n=8) within 1 year. BIOMArCS was approved by the institutional review committees of the participating hospitals. All patients gave informed consent.

We used a case-cohort approach for biomarker determination and analysis.[2] The case-cohort study comprises a random subcohort from the full cohort, together with all cases. The main advantage of the case-cohort design over a cohort study is that full covariate data (in our situation, biomarker data) are needed only for the cases and subcohort individuals, not all the original cohort.[3] Thus, the advantages of a cohort study are combined with the efficiency of a nested case-control study.[3] We randomly selected a subcohort of 150 individuals (18%), including 8 cases. Our case-cohort therefore consisted of (all) 45 cases and 142 noncases.

Four established cardiovascular biomarkers were then measured (in 1478 blood samples), reflecting different components of cardiovascular pathophysiology: troponin, which was assessed with high-sensitivity cardiac troponin I and T assays (hs-cTnI [Abbott] and hs-cTnT [Roche]); NT-proBNP (N-terminal pro-B-type natriuretic peptide, validated in-house sandwich ELISA); and high-sensitivity C-reactive protein (hs-CRP [Beckman Coulter]).[1] Biomarker measurements were performed in a single batch; personnel were blinded to any patient data.

Patient-specific longitudinal biomarker trajectories were analyzed by linear mixed-effect models, with adjustment for GRACE (Global Registry of Acute Coronary Events) risk score (including age), sex, clinical risk factors (recorded at inclusion), and creatinine value (recorded at each sampling time point). The relationships between biomarker levels (based on the linear mixed-effect models) and the end point were analyzed by Cox proportional hazard models. Unadjusted hazard ratio estimates for each biomarker were obtained, as well as estimates adjusted for GRACE risk score and multiple biomarkers. We applied bayesian semiparametric joint modeling, enabling simultaneous estimation of the linear mixed-effect and Cox model parameters.[4]

Median age was 62.5 years; 77.9% were male; and 51.7% presented with ST-segment elevation. Measured biomarkers were elevated during the index acute coronary syndrome but subsequently decreased and stabilized within 30 days. Canadian Cardiac Society angina class was ≤1 at 95.5% of the post 30-day visits,

The full author list is available on page 136.

Key Words: acute coronary syndrome ■ biomarkers ■ risk assessment

https://www.ahajournals.org/journal/circ

reflecting clinical stability. Renal function was preserved and stable; median estimated glomerular filtration rate was 90 (interquartile range, 73–114) mL·min^{-1}·1.73 m^{-2} at the final visit. Antiplatelet agents and statins were used at 98.7% and 95.9% of the visits, respectively.

Despite the absence of anginal symptoms in the post 30-day period, cases had sustained and significantly higher hs-cTnI than noncases (Figure). The mean values of the patient-specific means were 13.0 pg/mL and 6.7 pg/mL (P<0.001). Cases also had higher hs-cTnT (15.7 pg/mL versus 8.6 pg/mL; P<0.001) and NT-proBNP (99.8 pmol/L versus 47.1 pmol/L; P=0.001) but not hs-CRP (2.7 mg/L versus 2.1 mg/L; P=0.138). Hazard ratios for the end point per 1-SD increase were 1.87 (95% CI, 1.27–2.72) for hs-cTnI, 1.87 (95% CI, 1.27–2.75) for hs-cTnT, 2.38 (95% CI, 1.41–4.33) for NT-proBNP, and 1.46 (95% CI, 0.82–2.62) for hs-CRP. The significant associations remained after adjustment for GRACE risk score. Cardiac troponins and NT-proBNP were correlated (Spearman r=0.54 and 0.46 for hs-cTnI and hs-cTnT, respectively), resulting in attenuated associations with the end point in multimarker models (Figure).

During the asymptomatic post 30-day period, biomarkers tended to remain stable in the individual patient. We did not observe a (steady or more sudden) rise in the studied biomarkers before the end point. Nevertheless, 20.4% of patients had isolated peak values of hs-cTnI above the reference change value[5] of 10 pg/mL. In a post hoc analysis, there were no temporal associations between these peaks and the end point. Still, the hazard ratio for the end point for an incident hs-cTnI peak above the reference change value was 2.90 (95% CI, 1.04–7.27;

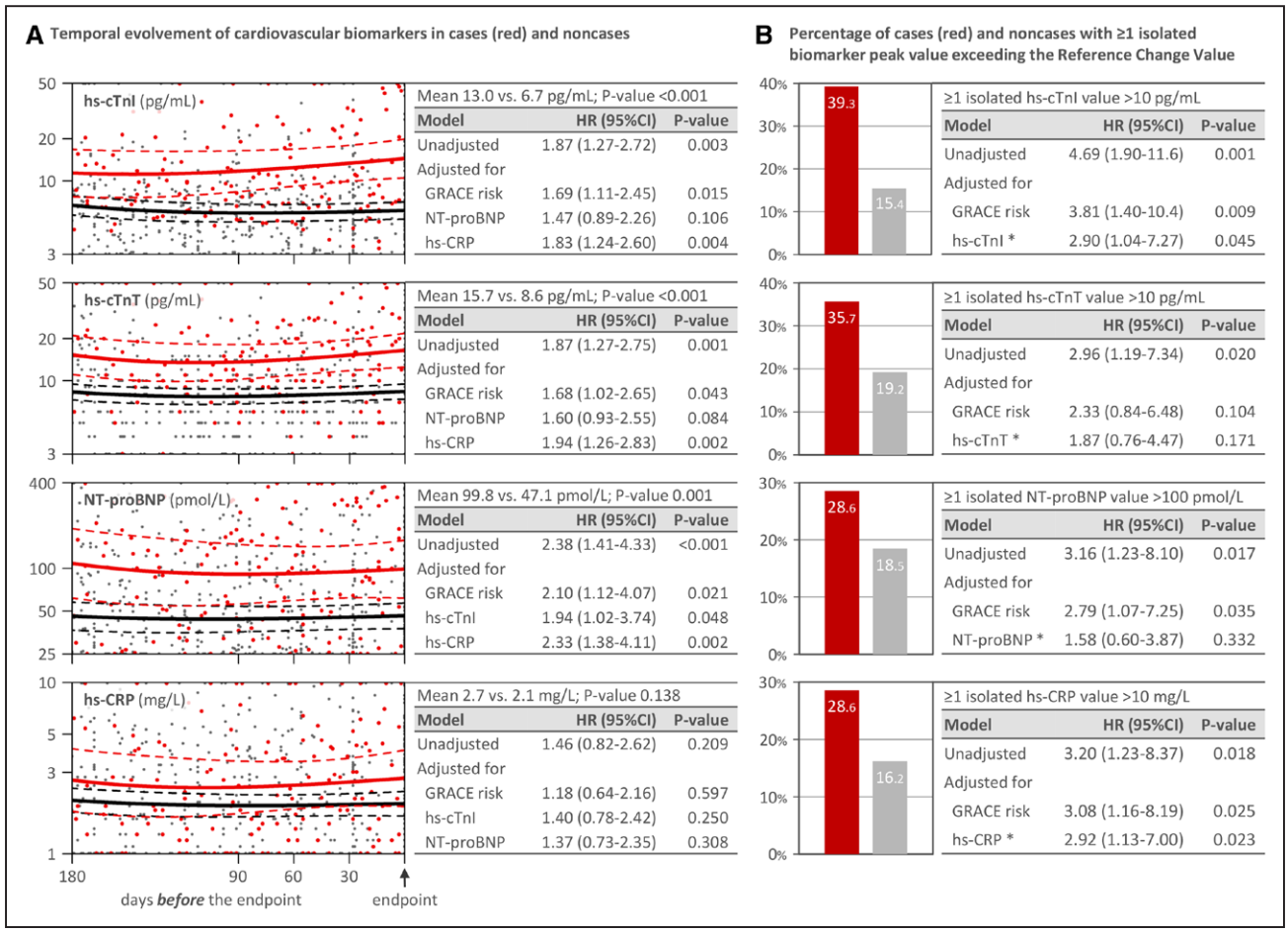

Figure. Temporal evolution of established cardiovascular biomarkers and biomarker peak values in cases who reached the study end point (red dots and lines) and noncases.

Data represent all measurements that were obtained in the 30-day period after the index acute coronary syndrome. A total of 30 patients reached the study end point in this period (15 end-point cases occurred in the first 30 days). **A**, Temporal evolution of biomarkers until the study end point (t=0 in cases) or until the last blood sample was obtained (t=0 in noncases). Dots represent measurements in individual cases (red) and noncases. Solid bold lines represent group mean values; dashed lines represent the corresponding 95% CIs based on linear mixed-effect models. Hazard ratios (HRs) for the study end point are calculated for a 1-SD increase in the biomarker (on the log scale) at any time point and are based on joint models for longitudinal and survival data. We present unadjusted HRs and HRs adjusted for GRACE (Global Registry of Acute Coronary Events) risk and multiple biomarkers. **B**, Percentage of cases (red) and noncases with ≥1 isolated biomarker peak values exceeding the reference change value. HRs for the study end point are calculated for a biomarker peak value above the reference change value,[5] which was 10 pg/mL for high-sensitivity cardiac troponin I (hs-cTnI), 10 pg/mL for high-sensitivity cardiac troponin T (hs-cTnT), 100 pmol/L for NT-proBNP (N-terminal pro-B-type natriuretic peptide), and 10 mg/L for high-sensitivity C-reactive protein (hs-CRP). HRs are based on joint models for longitudinal and survival data, with peak modeled as a time-dependent covariate. We present unadjusted HRs and HRs adjusted for GRACE risk and patient-specific longitudinal level of the corresponding biomarker. *Patient-specific longitudinal biomarker level.

P=0.045), adjusted for the patient-specific longitudinal stable hs-cTnI level (Figure). Incident hs-CRP peaks above the reference change value (10 mg/L) also contained independent predictive information, but hs-cTnT (10 pg/mL) and NT-proBNP (100 pmol/L) peaks did not.

Two limitations of our work need particular attention. First, differences in biomarker levels between cases and noncases might be explained by unmeasured factors, including the severity of coronary disease and left ventricular remodeling; cardiac imaging was lacking. Second, despite the large number of measurements, the small number of events precluded full multivariable adjustment for the relation between biomarkers and the study end point.

BIOMArCS demonstrated that longitudinal hs-cTn and NT-proBNP elevations and incident hs-cTnI and hs-CRP peaks were associated with coronary events in clinically stable patients after acute coronary syndrome. Because the studied biomarkers did not rise before the event, longitudinal monitoring with these markers, within this particular sampling protocol, may not identify a high-risk period in individuals.

ARTICLE INFORMATION

Data sharing: The data, analytical methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure (contact the corresponding author).

Authors

Rohit M. Oemrawsingh, MD, MSc; K. Martijn Akkerhuis, MD,PhD; Maarten de Mulder, MD, PhD; Victor A. Umans, MD, PhD; Bas Kietselaer, MD, PhD; Carl Schotborgh, MD; Eelko Ronner, MD, PhD; Timo Lenderink, MD, PhD; Anho Liem, MD, PhD; David Haitsma, MD, PhD; Pim van der Harst, MD, PhD; Folkert W. Asselbergs, MD, PhD; Arthur Maas, MD; Anton J. Oude Ophuis, MD, PhD; Ben Ilmer, MD; Rene Dijkgraaf, MD; Robbert J. de Winter, MD, PhD; S. Hong Kie The, MD, PhD; Alexander J. Wardeh, MD, PhD; Walter Hermans, MD, PhD; Etienne Cramer, MD, PhD; Ron H. van Schaik, PhD; Imo E. Hoefer, MD, PhD; Pieter A. Doevendans, MD, PhD; Maarten L. Simoons, MD, PhD; Eric Boersma, PhD; For the BIOMArCS Investigators

Correspondence

Eric Boersma, PhD, Erasmus MC, Department of Cardiology, Room Na317, PO Box 2040, 3000 CA Rotterdam, Netherlands. Email h.boersma@erasmusmc.nl

Affiliations

Erasmus MC, University Medical Center Rotterdam, the Netherlands (R.M.O., K.M.A., M.d.M., R.H.v.S., M.L.S., E.B.). Medical Center Alkmaar, the Netherlands (V.A.U.). Maastricht University Medical Center, the Netherlands (B.K.). HagaZiekenhuis, Den Haag, the Netherlands (C.S.). Reinier de Graaf Hospital, Delft, the Netherlands (E.R.). Zuyderland Hospital, Heerlen, the Netherlands (T.L.). Sint Franciscus Gasthuis, Rotterdam, the Netherlands (A.L.). Admiraal de Ruyter Hospital, Goes, the Netherlands (D.H.). University Medical Center Groningen, the Netherlands (P.v.d.H.). University Medical Center Utrecht, the Netherlands (F.W.A., I.E.H., P.A.D.). Gelre Hospital, Zutphen, the Netherlands (A.M.). Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands (A.J.O.O.). Working Group on Cardiovascular Research Netherlands, Utrecht, the Netherlands (A.J.O.O.). Havenziekenhuis, Rotterdam, the Netherlands (B.I.). St. Jansdal Hospital, Harderwijk, the Netherlands (R.D.). Academic Medical Center, Amsterdam, the Netherlands (R.J.d.W.). Treant Zorggroep, location Bethesda, Hoogeveen, the Netherlands (S.H.K.T.). Medisch Centrum Haaglanden location Westeinde, Den Haag, the Netherlands (A.J.W.). Elizabeth-Tweesteden Hospital, Tilburg, the Netherlands (W.H.). Radboud University Medical Center Nijmegen, the Netherlands (E.C.). Netherlands Heart Institute, Utrecht (P.A.D.).

Sources of Funding

BIOMArCS was funded by the Netherlands Heart Foundation (grant 2007B012), the Netherlands Heart Institute, the Working Group Cardiovascular Research Netherlands, and Eli Lilly through unrestricted research grants. The funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or decision to submit the manuscript for publication.

Disclosures

None.

REFERENCES

1. Oemrawsingh RM, Akkerhuis KM, Umans VA, Kietselaer B, Schotborgh C, Ronner E, Lenderink T, Liem A, Haitsma D, van der Harst P, Asselbergs FW, Maas A, Oude Ophuis AJ, Ilmer B, Dijkgraaf R, de Winter RJ, The SH, Wardeh AJ, Hermans W, Cramer E, van Schaik RH, Hoefer IE, Doevendans PA, Simoons ML, Boersma E. Cohort profile of BIOMArCS: the BIOMarker study to identify the Acute risk of a Coronary Syndrome: a prospective multicentre biomarker study conducted in the Netherlands. *BMJ Open*. 2016;6:e012929. doi: 10.1136/bmjopen-2016-012929
2. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika*. 1986;73:1–11.
3. Sharp SJ, Poulaliou M, Thompson SG, White IR, Wood AM. A review of published analyses of case-cohort studies and recommendations for future reporting. *PLoS One*. 2014;9:e101176. doi: 10.1371/journal.pone.0101176
4. Rizopoulos D. *Joint Models for Longitudinal and Time-to-Event Data, with Applications*. Boca Raton, FL: Chapman & Hall/CRC; 2012.
5. Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. *Crit Rev Clin Lab Sci*. 1989;27:409–437. doi: 10.3109/10408368909106595