Data Article

Data on the power of high betatrophin to predict cardiovascular deaths in coronary patients

Andreas Leiherer a, b, c, *, Janine Ebner a, c, Axel Muendlein a, b, Eva M. Brandtner a, Christina Zach a, c, Kathrin Geiger a, Peter Fraunberger b, c, Heinz Drexel a, b, d, e

a Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria
b Private University of the Principality of Liechtenstein, Triesen, Liechtenstein
c Medical Central Laboratories, Feldkirch, Austria
d Drexel University College of Medicine, Philadelphia, PA, USA
e Division of Angiology, Swiss Cardiovascular Center, University Hospital of Bern, Switzerland

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ABSTRACT

Betatrophin is a protein which is produced by the liver and by adipose tissue. There are no clear data about serum betatrophin’s cardiovascular role and it is unknown, whether betatrophin is associated with the risk of cardiovascular death. This article provides additional data on the association of betatrophin with its power to predict cardiovascular death in coronary patients. In addition, this data article demonstrates the performance of betatrophin as a biomarker using c-statistics. Analyzed data was derived from 553 coronary patients. Betatrophin was measured in serum samples and cardiovascular deaths were recorded for a median of 7.1 years. This data article is related to a research article titled “High betatrophin in coronary patients protects from cardiovascular events” [1].

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1. Data

It has been mentioned in the main article [1] that there is a significant association between high betatrophin in serum of 553 coronary patients and a low risk for cardiovascular events. Here, further data on the association between betatrophin and cardiovascular death are provided. In total 64 patients succumbed to cardiovascular death. Table 1 gives an overview about the frequency of different types of cardiovascular deaths. There were no significant differences between different groups \( (p = 0.768) \) nor between vascular-related (vascular death + fatal insult) and cardiac-related (fatal myocardial infarction, sudden cardiac death, terminal heart failure, and other cardiac death) deaths \( (p = 0.692) \). Fig. 1 demonstrates that high betatrophin protects from cardiovascular death during follow up time. The data summarized in Table 2 shows the comparison of different prediction models for cardiovascular death. The prediction of cardiovascular deaths is significantly higher applying an enhanced prediction model comprising betatrophin compared to a basic model lacking betatrophin.

2. Experimental design, materials and methods

2.1. Design and analyses

Characterization and basic laboratory measurement of patients was done as described in the main article [1]. In short, all 553 coronary patients were recruited between 2005 and 2008. Only patients who were referred to elective coronary angiography for the evaluation of established or suspected stable CAD were enrolled. Patients undergoing coronary angiography for other reasons and patients with acute coronary syndromes were excluded. Serum betatrophin levels were determined with a commercial uromodulin enzyme-linked immunosorbent assay (ELISA) kit (BioVendor, Brno, Czech Republic; catalog no. RD191347200R), which was specific for human betatrophin. The inter- and intra-assay coefficient of variation was \( \leq 3.9\% \) and 7.4\% respectively. Serum betatrophin was 10.4 \( \pm \) 12.9 ng/ml...
Table 1
Causes of cardiovascular deaths.

| Cause                        | n  | Betatrophin, mean ± SD (ng/ml) |
|------------------------------|----|--------------------------------|
| Vascular death               | 5  | 8.2 ± 2.9                      |
| Fatal insult                 | 8  | 6.8 ± 1.9                      |
| Fatal myocardial infarction  | 5  | 6.6 ± 1.5                      |
| Sudden cardiac death         | 3  | 4.9 ± 0.9                      |
| Terminal heart failure       | 21 | 8.4 ± 7.2                      |
| Other/unknown cardiac death  | 22 | 15.7 ± 28.8                    |
| total                        | 64 | 10.4 ± 17.6                    |

| Model 1                      | HR=0.39 [0.21-0.75] p=0.005 |
| Model 2                      | HR=0.41 [0.21-0.79] p=0.008 |
| Model 3                      | HR=0.39 [0.20-0.76] p=0.006 |
| Model 4                      | HR=0.45 [0.28-0.91] p=0.026 |
| Model 5                      | HR=0.48 [0.24-0.95] p=0.036 |
| Model 6                      | HR=0.47 [0.23-0.94] p=0.032 |

Fig. 1. Betatrophin as predictor of cardiovascular death. The Forest plot represents the hazard ratios (HR) with 95% confidence interval (CI) for the association between high betatrophin (status) in serum and cardiovascular death risk in the study population. Model 1 represents a univariate analysis. Model 2 includes the covariates age, gender, and body mass index (BMI). Model 3 includes the parameters included in model 2 and in addition the concentration of triglycerides, of high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and the type 2 diabetes (T2DM), hypertension, current smoking and significant coronary artery disease (CAD) status. Model 4 includes the parameters included in model 3 and in addition the Vitamin D concentration. Model 5 includes the parameters included in model 4 and in addition the estimated glomerular filtration rate (eGFR) and the concentration of brain natriuretic peptide (BNP), C-reactive protein (CRP), and troponin I. Model 6 includes the parameters included in model 5 and in addition the treatment status with respect to acetylsalicylic acid (ASA), beta blocker, angiotensin converting enzyme (ACE) inhibitors, angiotensin (AT)-2 receptor antagonists, and statins.

Sixty-four cardiovascular deaths were recorded during follow up. Betatrophin concentration is given as mean ± standard deviation (SD).

(mean ± SD) on average and its median was 7.5 ng/ml with an IQR of 5.4–10.6 ng/ml and minimum (min) and maximum (max) of 1.2 ng/ml and 136.4 ng/ml respectively.

The median follow up time of the study, described in the main article, was 7.1 years with an interquartile range (IQR) of 5.9–7.5 years. No patients were lost during follow up, resulting in a 100% follow-up rate. The endpoint “cardiovascular death” was a composite of fatal insult, vascular death, fatal myocardial infarction, sudden cardiac death, terminal heart failure, and other cardiac death.

2.2. Statistical analysis

Statistical analyses are described in detail in the main article [1]. In particular, to determine the incidence of the respective endpoint, we used Cox proportional hazards models. In the case continuous data showed a skewed distribution (skewness >1 or < -1), these data were log transformed and z-
transformed before analysis. In order to examine the value of uromodulin as a biomarker [2] several cox regression models were fitted with the respective study endpoint as the dependent variable and c-statistics were applied. The respective models were compared according to their linear predictor score using calculation of area under the curve (AUC), Harrell’s C and Somers’ D, as well as integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices. All missing values were missing completely at random (MCAR), according to Little’s MCAR test. All data were analyzed according to complete case analysis. All statistical analyses as described in this data article were performed with SPSS 26.0 for Windows (SPSS, Inc., Chicago, IL) and R statistical software v. 3.6.1 (http://www.r-project.org) including specific software packages (survIDINRI [3,4]).

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**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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