Systemic Cardiac Troponin T is Associated with Incident Atrial Fibrillation among Patients with Suspected Stable Angina Pectoris

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The research is funded by the Department of Heart Disease, Haukeland University Hospital.

Disclosures: Dr. Aakre reports personal fees from Roche Diagnostics and Siemens. The other authors report no relationship that could be construed as a conflict of interest.

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Abstract

Higher concentrations of cardiac troponin T are associated with coronary artery disease (CAD) and adverse cardiovascular prognosis. The relation with incident atrial fibrillation (AF) is less explored. We studied this association among 3568 patients evaluated with coronary angiography for stable angina pectoris without previous history of AF. The prospective association between high-sensitivity cardiac troponin T (hs-cTnT) categories (≤3 ng/L; n=1694, 4-9; n=1085, 10-19; n=614 and 20-30; n=175) and incident AF and interactions with the extent of CAD were studied by Kaplan Meier plots and Cox regression. Risk prediction improvements were assessed by receiver operating characteristic area under the curve (ROC-AUC) analyses. During median (25-75 percentile) 7.3 (6.3-8.6) years of follow-up 412 (11.5%) were diagnosed with AF. In a Cox model adjusted for age, sex, body mass index, hypertension, diabetes mellitus, smoking, estimated glomerular filtration rate, and left ventricular ejection fraction, hazard ratios (HRs) (95% confidence intervals [CIs]) were 1.53 (1.16 – 2.03), 2.03 (1.49 – 2.78) and 2.15 (1.40 – 3.31) when comparing the 2^{nd}, 3^{rd} and 4^{th} to the 1^{st} hs-cTnT group, respectively (P for trend < 0.000001). The strongest association between hs-cTnT levels and incident AF was found among patients without obstructive CAD (P_{int} = 0.024) and adding hs-cTnT to established AF risk factors improved risk classification slightly (ΔROC 0.006, P=0.044). In conclusion, in patients with suspected stable angina higher levels of hs-cTnT predicted increased risk of incident AF. This was most pronounced in patients without obstructive CAD suggesting an association not mediated by coronary disease.

Keywords: Cardiac troponin T; atrial fibrillation; stable angina

Introduction

Atrial fibrillation (AF) is prevalent and associated with increased morbidity and mortality [1]. Troponins are specific forms of regulatory proteins vital for muscle contraction and a candidate AF risk predictor [2]. Acute myocardial injury is characterized by acute elevations in systemic concentrations of cardiac troponins [3] [4]. Earlier studies have shown correlation between stable elevated troponin concentrations and future heart failure and mortality [5] [6]. In patients with stable coronary artery disease (CAD) increased serum troponin concentrations are related to future acute cardiovascular (CV) events [6] [7]. Patients with CAD have increased risk of AF [8] [9], and the co-occurrence of AF signals a worse outcome in patients with established CAD [10] [11]. CAD and AF share several risk factors [12], and studies have shown an association between systemic troponin concentration and incident AF [13] [14] [15]. Mechanisms and pathophysiological pathways for this remain elusive. Any incremental risk prediction of AF by cardiac troponins has not been confirmed [13]. The aim of this study was to assess whether serum high-sensitive cardiac troponin T (hs-cTnT) was associated with incident AF in a population with presumed stable coronary artery disease and investigate if this association was modified by the extent of obstructive CAD as evaluated by coronary angiography.

Methods

The WEstern Norway Coronary Angiography Cohort (WECAC) study population has been described previously [16]. In short it consists of 4166 patients who underwent planned coronary angiography for suspected stable angina pectoris (SAP) at either Haukeland (Bergen, Norway) or Stavanger (Stavanger, Norway) university hospitals during 2000 – 2004. About 2/3 were enrolled in the Western Norway B vitamin Intervention Trial (WENBIT), and randomized to receive B-vitamin treatment or placebo for secondary CVD prevention [17].

Patients with previous AF or AF at baseline (n=318) were excluded. Additionally, we excluded patients with baseline serum troponin of ≥30 ng/L to minimize the risk of including patients with possible acute coronary syndrome. This left 3568 participants available for the final analyses. The patients were categorized according to concentrations of hs-cTnT; non-detectable (≤3 ng/L), low (4-9 ng/L), moderately elevated (10-19 ng/L) and strongly elevated (20-30 ng/L).

All patients provided written, informed consent. The study was approved by the regional ethics committee and was carried out according to the Declaration of Helsinki. Information on patients' lifestyle and medical history was obtained from self-administered questionnaires and verified by comparing to hospital records and has previously been described [16]. Coronary catheterization and angiography was performed by invasive cardiologists. The extent of CAD was scored (0-3) by aggregating the number of significantly stenosed arteries, defined as a >50% luminal narrowing of any epicardial coronary artery or main branch.

The biosampling and biochemical analyses have been described in detail in earlier reports [16] [18]. Serum and plasma for study-specific analyses were immediately prepared and stored in 2 mL Vacutainer® tubes (Becton, Dickinson and Company, United States) at -80°, before later being thawed and analyzed by laboratory staff blinded to clinical outcomes. Hs-cTnT was analyzed with a high sensitive cardiac troponin T assay on Modular E170 from Roche diagnostics with a limit of blank of 3 ng/L and an upper 99th percentile of 14 ng/L.

The endpoint was incident AF, defined according to the International Classification on Diseases (ICD) 10th edition; I48.XX or being registered with AF as the cause of death. Information on endpoints was obtained from the Cardiovascular Disease in Norway (CVDNOR; https://cvdnor.b.uib.no/) project [19], which provided information on discharge diagnoses from Norwegian hospitals, and from the Norwegian Cause of Death Registry

(www.ssb.no) during 1994-2009, and linked to each patient's unique 11-digit national identification number.

Continuous and categorical variables are reported as medians (25^{th} -75^{th} percentiles) and percentages, respectively, with trends across hs-cTnT/CAD categories assessed with logistic and linear median regression. Event-free survival across hs-cTnT categories was studied by Kaplan-Meier plots and differences assessed by the log-rank test. We applied generalized additive regression model (GAM) plot, to visualize a potential non-linear relationship between hs-cTnT as a continuous parameter and incident AF. Cox regression was used to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) for incident AF according to hs-cTnT categories, using the lower category as reference. Risk associations were assessed unadjusted and after adjustment for age, sex, body mass index (BMI), hypertension, diabetes mellitus, smoking, CRP, the number of significantly stenosed epicardial arteries at angiography (CAD 0-3), left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), medications (aspirin, calcium channel blockers, beta blockers, loop diuretics, angiotensin converting enzyme (ACE) inhibitors and statins) at discharge, peripheral artery disease, and previous coronary revascularization. Risk associations between extent of CAD at baseline and incident AF were assessed in similar models.

The potential hs-cTnT relationship was further explored in subgroups according to the extent of CAD), gender, median age, smoking, hypertension and eGFR. Effect modifications were evaluated by adding interaction product terms into the multivariate Cox models. We compared model fit using the Akaikes information criterion (AIC) and explored model discrimination by calculating areas under receiving operator characteristics curves (ROC-AUC). By determining the continuous net reclassification improvement (NRI > 0) and the

integrated discrimination improvement (IDI), we evaluated whether adding hs-cTnT to the multivariate model improved risk classification for incident AF.

A 2-sided P value of less than 0.05 was considered statistically significant. The statistical analyses were carried out in R version 3.0.2 (the R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study population are described in Table 1. According to hs-cTnT categories, 47.5%, 30.4%, 17.2% and 4.9% had non-detectable (<3 ng/L), low (4-9 ng/L), moderately (10-19 ng/L) or strongly (20-30 ng/L) elevated hs-cTnT concentrations, respectively. Higher hs-cTnT was associated with male sex and higher age, as well as with lower eGFR and LVEF. There was also a positive relationship with hypertension, diabetes and previous MI, mirrored by more use of ACE-inhibitors and loop diuretics. There was no significant association between hs-cTnT and BMI whereas an inverse relationship was observed between hs-cTnT and current smoking.

Baseline characteristics according to the extent of CAD are reported in Supplemental Table 1. In short, an increasing number of stenosed coronary arteries was associated with male gender and with higher age and higher levels of hs-cTnT. There was a positive relationship with prior atherosclerotic vascular disease, coronary revascularization and diabetes mellitus. There were no differences according to BMI, systolic or diastolic blood pressure.

During median (25^{th} – 75^{th} percentile) follow-up of 7.3 (6.3-8.6) years, 412 (11.5%) patients were diagnosed with incident AF. The Kaplan-Meier plot in Figure 1 shows increasing risk of AF according to higher levels of hs-cTnT (P for log-rank test < 0.000001). Accordingly, in Cox models we observed a positive association between hs-cTnT and incident AF, which remained after adjusting for potential confounders, putting patients in the

3rd and 4th hs-cTnT groups at approximately doubled risk of AF as compared to patients with undetectable hs-cTnT concentrations (Table 2). Moreover, as shown in Supplemental Figure 1 the risk relationship seemed to reach a plateau at hs-cTnT concentrations of approximately 15 ng/L.

Increasing extent of CAD at baseline was associated with incident AF in a univariate model but not after multivariate adjustment. There was, however, a significant interaction between the extent of CAD at baseline and the risk association between hs-cTnT and AF (Figure 2). Notably, the strongest association was found amongst patients without obstructive CAD at angiography (P for interaction = 0.024). We found no significant effect modifications in the other evaluated subgroups (P for interaction ≥ 0.082, Figure 2).

Adding hs-cTnT to the multivariate logistic regression model improved the model fit as assessed by the AIC (AIC in model without hs-cTnT 2184 versus AIC in model with hs-cTnT 2174, P = 0.001). ROC-AUC was slightly improved (delta ROC AUC 0.006, P = 0.044) as was the integrated discrimination improvement (IDI 0.004, P = 0.008) (Supplemental Table 2). However, the net reclassification of patients was not significantly improved (NRI 0.057, P = 0.293).

Discussion

In this large and well defined cohort of patients evaluated for stable angina pectoris, we observed a strong association between hs-cTnT and incident AF also after extensive multivariate adjustment. The strongest risk relation between hs-cTnT and incident AF was found in the subgroup of patients without obstructive CAD at baseline.

Both hs-cTnT and high sensitive cardiac troponin I (hs-cTnI) have previously been studied with regards to AF. A large prospective cohort from the Cardiovascular Health Study found a significant and independent association between hs-cTnT and incident AF [14]. In the Atherosclerosis Risk In Communities (ARIC) study [13], patients with hs-cTnT

concentrations above 14 ng/L had increased risk of AF. A higher risk of incident AF has also been found with increasing hs-cTnI in the Framingham cohort [15]. Our study suggested that the strongest dose-relationship was present among patients with hs-cTnT in the interval from <4 - 15 ng/L, whereas the association tapered off at higher concentrations. Also, neither the ARIC [13] nor the Framingham study found any improvement in predictive ability for cardiac troponins beyond traditional risk factors. In contrast, we observed a significant improvement in model discrimination by adding hs-cTnT, albeit no significant improvement in reclassification. A large heterogeneity in CVD patients' phenotypes could explain this inconsistency as our study population consisted of patients with presumed stable angina pectoris, whereas the ARIC and Framingham cohorts drew samples of the general population without angiographic data.

Reports have suggested an association between an underlying burden of coronary arteriosclerosis and increasing troponin levels among patients without ACS, as serum troponin concentrations are higher in patients with greater severity of CAD [20]. This could be due to small-vessel disease causing low-grade necrosis or ischemic strain [21] [22]. It has also been suggested that coronary artery stenosis, even non-obstructive stenosis (<50%), might induce defects in cardiomyocyte cell membranes leading to leakage of troponins from cell cytosol [21] [22] due to a mismatch between oxygen demand and supply.

However, as shown in our study, the hs-cTnT-AF relationship was not confounded by the extent of CAD, hypertension, or kidney disease as measured by eGFR. Notably, the association between hs-cTnT and incident AF was strongest in patients without obstructive CAD during baseline angiography. This challenges the mechanistic perspective on chronic cardiac troponin release [23] and strengthens the hypothesis that chronically elevated hs-cTnT in stable patients represent cellular and subcellular metabolic changes leading to

myocardial apoptosis or catabolism of the troponin complex. These potential changes might also be related to structural diseases of the myocardium such as heart failure.

There are no current established biomarkers for such metabolic processes, but interestingly, we previously showed a strong positive relationship between hs-cTnT and plasma dimethylglycine [16], a metabolite in the choline oxidation pathway. Notably, this pathway is closely related to suggested regulators of cellular life cycles, such as mitochondrial function [24] and the production of nucleotides [25], indicating a potential role of hs-cTnT to reflect cardiomyocytes' regenerative abilities.

The major strength of the current study is the large size of a well-described cohort, a long follow-up time and the inclusion of patients limited to lower levels of hs-cTnT, making it less likely that patients with active high risk CVD were included. The baseline angiography data in all patients is also a major strength. The hs-cTnT-atrial fibrillation association was strongest among patients without obstructive CAD and no other significant effect modifications were observed, including subgroup analyses for eGFR and hypertension. Unfortunately, echocardiographic measures other than LVEF were not collected and we were not able to evaluate whether the risk association differed according to left ventricular mass. Blood samples from patients recruited at Stavanger University Hospital (n=751) were drawn immediately after coronary angiography, while samples at Haukeland University Hospital were drawn at baseline, usually 1-3 days before coronary angiography. It is, however, unlikely that this would introduce bias according to the prognostic performance of hs-cTnT among patients with stable CHD [26]. The current cohort consisted of predominantly older Caucasian men, and the results might therefore not be applicable to people differing according to age, ethnicity or gender.

In conclusion, in patients with presumed stable angina pectoris we observed a strong dose-response relation between systemic hs-cTnT concentrations and long-term risk for atrial

fibrillation. The association was particularly strong in the subgroup without obstructive CAD at baseline, suggesting that the association is not mediated by chronic myocardial ischemia.

Acknowledgements

We thank all the recruiting study personnel, as well as the staff performing the laboratory analyses at Bevital AS, Bergen, Norway (www.bevital.no). We are also grateful to Tomislav Dimoski at the Norwegian Knowledge Centre for the Health Services, Oslo, Norway, for his contribution by developing the software necessary for obtaining data from Norwegian public hospitals, conducting the data collection and quality assurance of data in this project.

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