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Association of sST2 and hs-CRP levels with new-onset atrial fibrillation in coronary artery disease☆

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ABSTRACT

Background: The data on biomarkers as predictors of atrial fibrillation (AF) in patients with coronary artery disease (CAD) are limited.
Methods: A total of 1946 patients with CAD were recruited to the ARTEMIS study. At baseline, the study patients underwent clinical and echocardiographic examinations and had laboratory tests. The patients ($n = 1710$) with the information about the occurrence of new-onset AF during the follow-up were included in the present analysis.
Results: During 5.7 ± 1.5 years of follow-up, 143 (8.4%) patients developed a new-onset AF. Higher values of soluble ST2 (sST2) (20.2 ± 10.8 vs. 17.5 ± 7.2 ng/mL, $p = 0.005$), high-sensitivity troponin T (hs-TnT) (11.9 ± 10.2 vs. 10.3 ± 8.3 ng/L, $p = 0.005$), high-sensitivity C-reactive protein (hs-CRP) (3.3 ± 5.9 vs. 2.0 ± 4.4 mg/L, $p < 0.001$) and brain natriuretic peptide (BNP) (85.6 ± 77.5 vs. 64.9 ± 73.5 ng/L, $p < 0.001$) had significant associations with the occurrence of new-onset AF. In the Cox clinical hazards model, higher age ($p = 0.004$), greater weight ($p = 0.045$), larger left atrial diameter ($p = 0.001$), use of asthma/chronic obstructive pulmonary disease medication ($p = 0.001$) and lack of cholesterol lowering medication ($p = 0.008$) had a significant association with the increased risk of AF. When the biomarkers were tested in the Cox clinical hazards model, sST2 (HR = 1.025, 95% CI = 1.007–1.043, $p = 0.006$) and hs-CRP (HR = 1.027, 95% CI = 1.008–1.047, $p = 0.006$) retained their significant power in predicting AF.
Conclusion: A biomarker of fibrosis, sST2, and a biomarker of inflammation, hs-CRP, predict the risk of occurrence of new-onset AF in patients with CAD. These biomarkers contributed to the discrimination of the AF risk model, but did not improve it markedly.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia confronted in clinical practice [1]. Several factors, such as higher age [2,3], male sex [2,3], hypertension [2,4], diabetes (DM) [2,5], congestive heart failure [2,6] and history of myocardial infarction [2,7], predispose to the risk of development of AF. Atrial fibrosis has been suggested to induce structural remodeling and create a substrate for AF [8–10]. However, data on the markers of fibrosis, such as soluble ST2 (sST2), in relation to the risk for occurrence of AF are scanty [11]. There have been contradictory results about the independent value of galectin-3, another marker of fibrosis, in predicting AF [12,13]. Furthermore, high-sensitivity troponin T (hs-TnT), a marker of myocardial damage, has been shown to be associated with incident AF in an elderly general population [14]. Inflammation has been suggested to precede the progression of fibrosis [15], and it also has a role in pathophysiology of AF [16]. Inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), have been shown to be risk indicators of AF in various populations [17,18]. Furthermore, increased concentrations of brain natriuretic peptide (BNP) induced by myocardial strain have also been observed to predict AF [19,20]. Nevertheless, the data on the value of biomarkers, particularly of those describing fibrosis or inflammation, in predicting new-onset AF in patients with coronary artery disease (CAD) are sparse. Therefore, we assessed the value of sST2, hs-TnT, galectin-3, hs-CRP and BNP in predicting new-onset AF in 1710 patients with CAD during, on average, >5 years of follow-up.

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2. Methods

2.1. Study population and design

The Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection (ARTEMIS) study was carried out in the Division of Cardiology of the Oulu University Hospital and was registered at ClinicalTrials.gov (NCT01426685). The study enlisted 1946 patients who had angiographically documented CAD defined as at least 50% stenosis in one or more major coronary vessels between August 2007 and November 2011. The risk assessments were done from 3 to 6 months after the coronary angiography. Of the patients, 1850 had sinus rhythm at baseline. Those who had atrial fibrillation ($n = 86$), atrial flutter ($n = 5$) or non-sinus rhythm ($n = 2$) at baseline were excluded from the present analysis. The patients were contacted by telephone and/or mail. A total of 140 patients were lost from the follow-up because of no contact by telephone or by mail and no information about the cardiac events in hospital records at the time of analysis of this data. The patients ($n = 1710$) who had a confirmation of whether or not they had had new-onset AF during the follow-up were included in the present analysis. The selection protocol of the patients from the ARTEMIS database to the present analysis is shown in Fig. 1. Of these 1710 patients, 689 had DM. The presence of DM was determined by a fasting capillary plasma glucose level ≥ 7.0 mmol/L on two occasions, a 2-hour value >12.2 mmol/L on the oral glucose tolerance test, or the use of antihyperglycemic medication and a prior diagnosis of DM. In ARTEMIS, patients with DM were matched to patients without DM, according to age, gender, prior MI, and revascularization (percutaneous coronary intervention, bypass graft surgery, or medical treatment). Exclusion criteria were age < 18 years or >85 years, significant valvular disease, permanent pacemaker/implantable cardioverter defibrillator implantation, New York Heart Association (NYHA) or Canadian Cardiovascular Society class IV, and end-stage renal failure requiring dialysis. Patients who had life expectancy <1 year or who were psychologically or physically unable to participate in the study were also excluded. One of the main aims of the ARTEMIS study is to assess risk markers for cardiac events and the influence of treatments on reducing cardiovascular complications in patients who have angiographically documented CAD with or without diabetes. The study was conducted according to the Declaration of Helsinki. The local ethics committee of the Northern Ostrobothnia Hospital District approved the protocol. A written informed consent was collected from each participant.

2.2. Laboratory tests

All the laboratory tests were done using standardized methods after 12-hour overnight fast. The diagnosis of DM was based on the criteria of the World Health Organization (WHO 1999). Inflammation markers, cardiac markers and renal function were obtained from the blood and urine samples and analyzed in the hospital laboratory. sST2, galectin-3 and hs-CRP concentrations were determined from the serum samples (BN Prospec System, Siemens Healthcare Diagnostics; Human ST2/IL-1 R4 Quantikine ELISA, R&D Systems Inc., Minneapolis, Minnesota; BG Medicine, Waltham, Massachusetts, respectively) whereas BNP and hs-TnT were determined from the plasma samples (ADVIA Centaur XP, Siemens Healthcare Diagnostics and MODULAR ANALYTICS, Roche Diagnostics, respectively).

2.3. Echocardiographic examinations

Two-dimensional, M-mode and Doppler echocardiography were performed and analyzed according to the American Society of Echocardiography guidelines [21] utilizing General Vivid 7 ultrasound machine with its analysis program by three cardiologists. Left ventricular mass (LVM) was calculated using the following formula $LVM(g) = 0.8 \times \{1.04\,[(\text{left ventricular internal diastolic diameter (LVIDd)} + \text{posterior wall thickness (PWTd)} + \text{septum wall thickness (SWTd)})^3 - \text{LVIDd}^3]\} + 0.6$ [22]. LVM index was obtained by dividing LVM by body surface area.

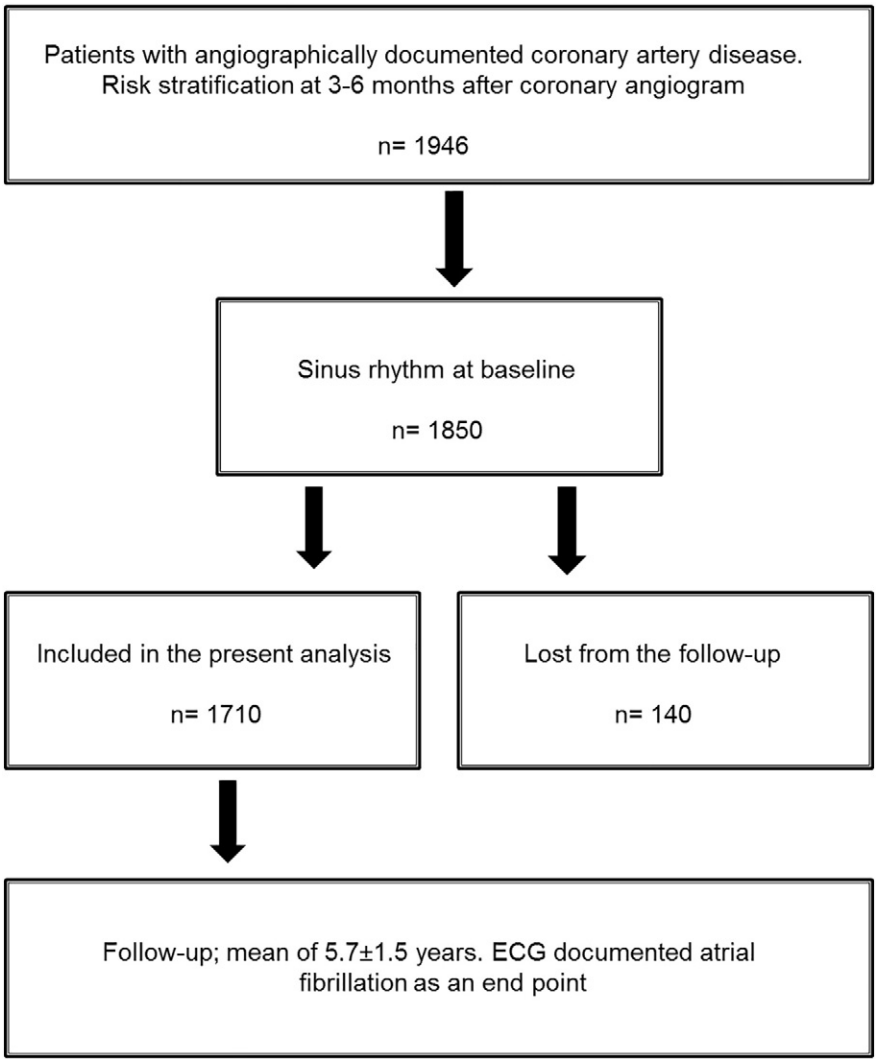

Fig. 1. The flow chart of the present study.