International Journal of Cardiology 171 (2014) 44–48

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Atrial natriuretic peptide as a predictor of atrial fibrillation in a male population study. The Study of Men Born in 1913 and 1923

Zacharias Mandalenakis [a,*], Henry Eriksson [a], Lennart Welin [a,b], Kenneth Caidahl [a,c], Mikael Dellborg [a], Annika Rosengren [a], Georgios Lappas [a], Jan Hedner [a], Saga Johansson [a,d], Kurt Svärdsudd [e], Per-Olof Hansson [a]

[a] Institute of Medicine, Department of Molecular and Clinical Medicine/Cardiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[b] Department of Medicine, Lidköping Hospital, Lidköping, Sweden
[c] Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden
[d] Department of Epidemiology, AstraZeneca R&D, Mölndal, Sweden
[e] Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Article history:
Received 7 June 2013
Received in revised form 16 September 2013
Accepted 17 November 2013
Available online 23 November 2013

Keywords:
Atrial fibrillation
Atrial natriuretic peptide
Population study

ABSTRACT

Background: Atrial fibrillation is one of the most common arrhythmias in clinical practice and it is often diagnosed after a complication occurs. The study aimed to evaluate the predictive value of atrial natriuretic peptide (ANP) for atrial fibrillation in a male population-based study.

Methods and results: This study is a part of the "Study of Men Born in 1913 and 1923", a longitudinal prospective cohort study of men, living in the city of Gothenburg in Sweden. A population-based sample of 528 men was investigated in 1988 when they were aged 65 years ($n = 134$) and 75 years ($n = 394$), and they were followed up for 16 years. Blood samples were collected from all 528 men at baseline and plasma ANP levels were analyzed by radioimmunoassay. Hazard ratios were estimated by competing-risk regression analysis.

One hundred five participants were excluded because of a prior diagnosis of atrial fibrillation, congestive heart failure, severe hypertension, or severe chronic renal insufficiency. Of the remaining 423 participants, 90 men were diagnosed with atrial fibrillation over the 16-year follow-up. In multivariable analysis, men in the two highest quartiles of ANP levels had a significantly higher risk for atrial fibrillation compared with men in the lowest ANP quartile. The adjusted ratio was 3.14 (95% CI 1.59–6.20) for the third ANP quartile and 3.36 (95% CI 1.72–6.54) for the highest quartile of ANP level.

Conclusions: In this population-based longitudinal study, we found that elevated ANP levels at baseline predicted atrial fibrillation during a follow-up time of 16 years.

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice and its prevalence in the general population of most Western countries is 0.5% to 2.5%.[1,2] The clinical manifestation of AF varies from asymptomatic to severe congestive heart failure symptoms. The diagnosis is confirmed by electrocardiogram (ECG), but a large proportion of patients have paroxysmal AF, and it may also be undetected or "silent" [3]. AF is associated with an approximate 5-fold risk of stroke [4] and the risk is equally elevated in sustained and paroxysmal AF [5]. Paroxysmal AF is also an important cause of apparent cryptogenic stroke [6]. Early detection and treatment of AF may reduce or even prevent the risk of complications, such as thromboembolic stroke [7]. A biomarker with high sensitivity for detecting AF would improve the ability of early paroxysmal AF detection, and enable the clinician to take preventive action against ischemic stroke.

Henry et al. suggested that stretch receptors from the left atrium were responsible for an increase of urine flow after causing obstruction of the mitral orifice with a balloon in a dog experiment [8]. Atrial natriuretic peptide (ANP), or atrial natriuretic factor, was first described by de Bold in the early 1980s as a polypeptide hormone secreted mainly by cardiac atrial muscle cells in rats [9]. Several prior reports found increased levels of ANP in patients with congestive heart failure, chronic renal failure, and severe hypertension due to inhibition of renin–angiotensin–aldosterone hormones, and direct vasodilator and renal effects [10–18]).

Furthermore, recent studies have shown an elevation of B-type natriuretic peptides to be predictive of AF [19,20]). A previous study analyzed pro-ANP as a predictor for AF in a community-based population sample [20]. However, there is still limited knowledge concerning ANP

* Corresponding author at: Department of Medicine/Cardiology, Sahlgrenska University Hospital/Östra, Diagnosvägen 11, SE-416 50 Gothenburg, Sweden. Tel.: +46 31 3436633, +46 76 7676966; fax: +46 31 191416.
E-mail address: zacharias.mandalenakis@gu.se (Z. Mandalenakis).

0167-5273/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2013.11.042

levels in the general population and the extension of elevated ANP levels as a risk factor for developing AF or other cardiovascular events.

The present study aimed to evaluate the predictive properties of ANP for the development of AF in a general population-based sample during 16 years of follow-up.

2. Methods

2.1. Study population

The "Study of Men Born in 1913 and 1923" is a longitudinal, prospective population-based study of men born in 1913 and 1923, living in the city of Gothenburg in Western Sweden. A random sample of one third of men born in 1913, all 50-year old men and living in the city of Gothenburg, were invited to repeated health examinations in 1963, 1967, 1973, 1980, 1988, and 1993. In addition, another random sample of one tenth of 50-year old men born in 1923 were invited to screening in 1973, 1980, 1988, and 1993. The study populations and sampling procedures have been described previously [21–26]). The Gothenburg Regional Research Ethics Board approved the present study.

The baseline data in the present study are derived from the screening in 1988. A total of 528 men, 394 at the age of 75 years and 134 at the age of 65 years, participated in these examinations, and blood samples were collected for plasma ANP analyses. Twenty-three participants with AF were excluded, either because of a medical history suggesting AF or because of ECG signs at baseline or at prior investigations. Moreover, to reduce potential confounding of ANP levels, 8 men were excluded because of congestive heart failure, 7 men were excluded because of severe chronic renal insufficiency (defined as creatinine clearance <30 ml/min), and another 67 men were excluded because of severe hypertension at baseline (defined as defined as systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg). After exclusion, 423 participants were eligible for study analysis.

2.2. Follow-up

A flowchart of the follow-up is shown in Fig. 1. Of the 489 men still alive in 1993, 339 attended the re-examination. Of those 150 men who did not participate in the 1993 screening, 29 answered a questionnaire, 67 were interviewed by telephone, and their medical records from the hospital and outpatient clinics were reviewed for the diagnoses of AF.

Follow-up and comorbidity data were collected by the Swedish Hospital Discharge Registry for all participants from 1972 to 2004, and by previous screening examinations in 1963, 1967, 1973, and 1980. Death certificates and autopsy reports were obtained and studied for those who died during follow-up according to the register of the National Cause of Death Register. Systematic 12-lead ECG recordings from 1963, 1980, 1988, and 1993 were read by a physician and examined for AF (including atrial flutter). Medical records from the hospitals and outpatients were collected for all participants and reviewed for AF. Thus, the follow-up rate of clinical diagnoses of atrial fibrillation was 100% according to hospital diagnosis.

2.3. General measurements

The baseline examination in 1988 included a medical history and a physical examination. Information on smoking habits was obtained by questionnaire. Smoking was classified as current smokers or non-smokers. A physical examination was performed and blood pressure was recorded in the right arm in the sitting position, after a 5-min interview. A mercury sphygmomanometer with a cuff size of 12 × 23 cm was used. All blood pressure measurements were recorded by the same observer to the nearest 2 mm Hg. Height was measured to the nearest centimeter. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Standard 12-lead ECGs were recorded at rest with the patients in the supine position. Paper speed was 50 mm/s and calibration was 1 mV:10 mm.

2.4. Blood sampling and analyses

Blood samples for determination of plasma ANP, serum creatinine, cholesterol and triglyceride levels, as well as fasting blood glucose levels, were drawn from the antecubital vein during rest. Samples from ANP analyses were obtained in pre-chilled EDTA tubes, cold centrifuged, and stored at −80 °C pending analysis. While routine clinical techniques were used for other measurements, plasma ANP was analyzed by a specific radioimmunoassay technique [27]. In brief, rabbit anti-human-a-natriuretic peptide (Peninsula Laboratories, California) was used showing complete cross reactivity with the human peptide (ANP 99–126, a-hANP). Plasma ANP was estimated through direct comparison with the a-hANP standard curve. The detection limit was 15.4 pg/ml and the inter-assay variability was less than 5%.

2.5. Definitions

In 1987, there was a change from the eighth to ninth revision of the International Classification of Diseases (ICD), and diagnoses in the present study were re-coded to ICD-9. The Swedish ICD versions were used. AF was defined as AF or atrial flutter detected on the ECG recording at any of the screening examinations or in diagnoses from the Swedish Hospital Discharge Register (ICD9 code 427D or ICD10 code I48). Severe hypertension was defined as systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg. Severe chronic renal insufficiency was defined as chronic kidney disease with creatinine clearance <30 ml/min according to the Cockcroft–Gault equation, or by ICD9 codes 585.4 and 585.5, or ICD10 codes N18.4 and N18.5. Congestive heart failure was defined as pharmacological treatment of heart failure at baseline, or by ICD9 code 428 or ICD10 code I50. Coronary heart disease was defined by the ICD9 codes 410–414 or ICD10 codes I20–I25.

2.6. Statistical analysis

All statistical analyses were performed using the SAS software (version 9.3, SAS Institute, Cary, NC) and the R statistical system (version 2.15.1, R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics are presented for all participants ($n = 423$) within ANP quartiles and different cohorts as a percentage or mean value with standard deviation (SD). Trend analysis for proportions was used with the Cochran–Armitage statistic. The follow-up time

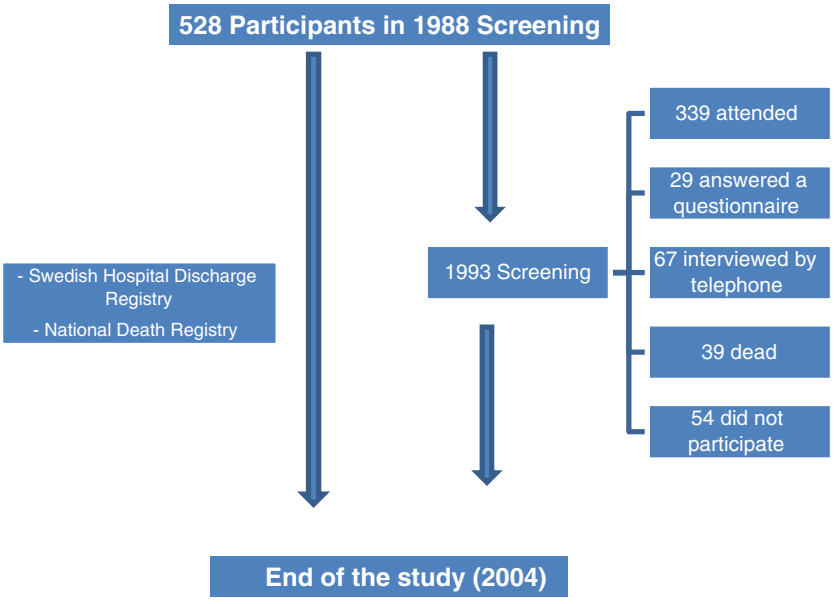

Fig. 1. Follow-up of the study.