Atherosclerosis 243 (2015) 192–197

Contents lists available at ScienceDirect

Atherosclerosis

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

Inflammation and hemostasis in atrial fibrillation and coronary heart disease: The REasons for Geographic And Racial Differences in Stroke study

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ARTICLE INFO

Article history:
Received 18 June 2015
Received in revised form
14 August 2015
Accepted 4 September 2015
Available online 8 September 2015

Keywords:
Atrial fibrillation
Coronary disease
Biological markers

ABSTRACT

Background: Recent studies suggest atrial fibrillation (AF) is an independent risk factor for coronary heart disease (CHD).
Aims: To determine if alterations in hemostasis or inflammation explain the association between AF and CHD.
Methods: C-reactive protein (CRP), D-dimer, factor VIII, and fibrinogen were measured in incident CHD cases (n = 647) and a stratified cohort random sample (CRS, n = 1104) between 2003 and 2007 from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Using a case-cohort approach, Cox models examined whether inflammation or hemostasis biomarkers explained the association between AF and CHD.
Results: In participants free of CHD at baseline, 12.2% of CHD cases and 7.1% of the CRS had AF. Over a median follow-up of 4.4 years, all biomarkers were associated with an increased risk of CHD in those with and those without AF after adjusting for CHD risk factors. The association of D-dimer with CHD was greater in those with AF (HR 2.52, 95% CI = 1.49, 4.26) than those without AF (HR 1.34, 95% CI = 1.12, 1.61) (p-interaction = 0.02). Similar interactions were not observed for the other biomarkers.
Conclusions: Our results suggest that alterations in D-dimer, a marker of hemostasis, explain the association between AF and CHD. Potentially, D-dimer is a useful biomarker to assess CHD risk in persons with AF.

1. Introduction

Atrial fibrillation (AF) affects approximately 3 million Americans and the prevalence is projected to increase to ~5.6 million over the next 30 years [1,2]. For unknown reasons, AF recently has been implicated as an independent risk factor for cardiovascular mortality and fatal and non-fatal coronary heart disease (CHD) [3–7].

Increased levels of inflammation and hemostasis biomarkers are associated with AF and CHD [8–12]. Persons with AF who have increased fibrin-fragment D-dimer (D-dimer) levels have a higher risk of stroke and CHD events [8–10]. Similarly, increased levels of circulating C-reactive protein (CRP) are associated with an increased risk of stroke, vascular events, and mortality in persons with AF [11,12]. Potentially, alterations in inflammation or hemostasis explain the increased CHD risk in those with AF.

Using data from the REasons for Geographic And Racial

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.09.009
0021-9150/

Differences in Stroke (REGARDS) study, we examined whether CRP, D-dimer, factor VIII, or fibrinogen were associated with CHD in individuals with AF and whether these biomarkers modified the association between AF and CHD. We hypothesized that the CHD risk in persons with AF would either be modified or dependent on elevated biomarkers of inflammation or hemostasis. For this analysis, we assumed that D-dimer and factor VIII were representative biomarkers of hemostasis, and that CRP and fibrinogen were markers of inflammation [13]. By understanding what drives the increased CHD risk in AF, future investigators will be able to develop strategies to assess CHD risk and reduce the burden of CHD in persons with AF.

2. Methods

2.1. Study population

REGARDS is a prospective cohort study designed to identify causes of regional and racial disparities in stroke mortality in the contiguous United States. Between January 2003 and October 2007, a total of 30,239 participants were recruited by over-sampling blacks and residents of the southeastern stroke belt region (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). Demographic information, medical history, and oral informed consent were obtained using a computer-assisted telephone interview followed by an in-home visit for written informed consent, physical examination, and fasting phlebotomy 3–4 weeks after the telephone interview. The study received institutional review board approval from all participating institutions. Details of the study design have been published previously [14].

We examined whether inflammatory or hemostasis biomarkers were associated with CHD in individuals with AF and whether these biomarkers modified the association between AF and CHD. Participants with AF were identified at baseline and followed for subsequent CHD events. CRP, D-dimer, factor VIII, and fibrinogen were measured using a stratified case-cohort design [15]. This analysis included all CHD cases ($n = 647$) occurring between 2003 and 2009 (December 31, 2009). These participants were followed at 6 month intervals by telephone for the detection of incident CHD events. In addition, a cohort random sample (CRS; $n = 1104$) was selected and stratified to ensure representation across age, race, and sex [16]. Of these, 224 individuals with prevalent CHD at baseline were excluded and 883 participants remained in the CRS.

2.2. Coronary heart disease events

CHD was defined as the composite of definite and probable myocardial infarction (MI) and definite and probable acute cardiac death. Events were adjudicated by an expert panel and details of the CHD adjudication process in REGARDS have been described [17]. Cases were assigned to 2 independent adjudicators and disagreements were adjudicated by committee review. The test for agreement between adjudicators yielded a κ level >0.80 for the presence of definite or probable MI and definite or probable acute cardiac death.

Guided by current expert opinion, medical records for suspected cases of MI were obtained and reviewed for the presence of the following: presence of signs or symptoms suggestive of ischemia; a rising and/or falling pattern in cardiac enzyme levels (troponin or CK-MB) over 6 or more hours with a peak level $\geq$2 times the upper limit of normal; and electrocardiogram changes consistent with ischemia or MI, guided by the Minnesota code and classified as evolving diagnostic, positive, nonspecific, or not consistent with ischemia [18,19]. Definite cases of MI included those with diagnostic enzymes or electrocardiogram. Probable MI included cases with elevated but not diagnostic enzymes with a positive but non-diagnostic electrocardiogram, or a positive electrocardiogram in the presence of ischemic signs or symptoms if cardiac enzyme data were missing.

Acute cardiac death was ascertained using the following sources of data: interviews with proxies or next of kin about circumstances immediately prior to death, autopsy reports, hospital records, death certificates, or National Death Index data. For hospitalized events, the underlying cause was definite or probable if the death occurred within 28 days of hospital admission in definite or probable MI cases; postmortem findings were consistent with MI within 28 days; or the death occurred within 6 hours of hospital admission with symptoms and/or signs consistent with cardiac etiology and other confirmatory data (e.g., cardiac enzymes or electrocardiographic data). For non-hospitalized events, the cause of death was definite or probable acute CHD if the death included one of the following: sudden cardiac death; documented definite or probable MI within 28 days of death and no evidence of a non-coronary etiology; autopsy evidence of recent coronary occlusion or MI within 28 days of death; history of CHD and/or documented cardiac pain within 72 hours preceding death and no evidence of a non-coronary etiology; or autopsy evidence of chronic CHD (e.g., coronary atherosclerosis and myocardial scarring).

2.3. Laboratory

Blood was collected during the in-home examination after an 8- to 10-hour fast and sample processing and validation of the laboratory data have been reported [20]. Fasting morning blood samples were obtained and after centrifugation, serum, plasma, and the cell layer were shipped overnight with 2 frozen gel ice packs to the University of Vermont Laboratory for Clinical Biochemistry Research. Upon receipt, samples were cataloged and re-centrifuged at 4 °C for 30,000 g-minutes, then stored at −80 °C. The following analytes were used in this analysis: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting glucose, CRP, D-dimer, factor VIII, fibrinogen, serum creatinine, and urinary albumin and creatinine from a spot urine specimen [20,21].

2.4. Covariates

Age, sex, race (black or white), smoking status, and region of residence were self-reported. Smoking was defined as current, never, or former. Diabetes was classified as present if the fasting glucose level was $\geq$126 mg/dL (or non-fasting glucose $\geq$200 mg/dL in those failing to fast) or if participants reported the use of insulin or oral hypoglycemic medications. The current use of aspirin, statins, warfarin, and antihypertensive and lipid-lowering medications was self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. After each participant rested for 5 min in a seated position, blood pressure was measured using a sphygmomanometer. Two values were obtained following a standardized protocol and averaged. Baseline renal disease was assessed by serum creatinine measurements and estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. eGFR was dichotomized at 60 mL/min per 1.73 m^2. Additionally, urine albumin-to-creatinine ratio (ACR) was calculated. Baseline cardiovascular disease was confirmed by self-reported history of stroke or peripheral arterial disease. AF was identified at baseline by the study-scheduled electrocardiogram recorded during the in-home visit and also