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β -thromboglobulin and Incident Cardiovascular Disease Risk: the Atherosclerosis Risk in Communities Study

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Abstract

Introduction—Although it has been suggested that increased concentrations of activated platelet biomarkers are associated with increased risk of incident cardiovascular disease (CVD) in the general population, evidence for this association is still controversial. Thus, we tested the hypothesis that activated platelets, measured by higher concentrations of β -thromboglobulin, are associated with increased risk of incident CVD (coronary heart disease, heart failure ischemic stroke, and atrial fibrillation).

Materials and Methods—We prospectively followed a cohort random sample of the Atherosclerosis Risk in Communities (ARIC) cohort, aged 45–64 years, and free of CVD at baseline who had previous measurements of plasma β -thromboglobulin. We identified incident CVD from 1987 through 2013, and used a weighted Cox proportional hazard models to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs).

Results—During the 14,387 person-years of follow-up for the 746 participants, we identified 140 coronary heart diseases, 123 heart failures, 54 ischemic strokes, and 126 atrial fibrillations. The age-, sex-, and race-adjusted model showed no association between plasma β -thromboglobulin and CVD, regardless of subtypes. After further adjustment for other CVD risk factors, including antiplatelet agent use, β -thromboglobulin remained unassociated with CVD risk.

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Conflict of Interest

None.

Ethics approval

The institutional review boards of the collaborating institutions approved the study.

Conclusions—In the prospective population-based ARIC cohort, β -thromboglobulin was not associated with CVD risk. Our results do not support the hypothesis that a blood marker of higher platelet activity reflects increased future risk of CVD in the general population.

Keywords

platelet activity; cardiovascular disease; general population; prospective study

INTRODUCTION

Platelets are a key contributor to atherothrombosis and thromboembolic events (1, 2). Platelets may be activated by impaired endothelial antithrombotic properties, reactive oxygen species deriving from cardiovascular risk factors such as smoking and diabetes, or upstream prothrombotic and pro-inflammatory proteins (3). Activated platelets adhere to the arterial wall, accelerate the inflammatory process by releasing their granules, contributing to atherosclerosis, and also play a key role in thrombus formation upon erosion or rupture of an atherosclerotic plaque (3). Abundant previous reports have suggested that increased levels of activated platelets are associated with increased risk of cardiovascular morbidity and mortality among patients with cardiovascular disease (CVD) (4–7).

However, there is limited evidence on the association between basal platelet activity and CVD risk in populations without clinical CVD (7). Some studies have reported that P-selectin and CD40 ligand—considered to be markers for activated platelets—are associated positively with incident CVD in the general population (8–10); other population studies found no association between these markers and CVD (11, 12). Other platelet function tests such as aggregometry, mean platelet volume, platelet count, bleeding time and thromboxane appear to have no associations with incident CVD risk in the general population (7). Thus, further investigations are necessary to confirm the association.

In ARIC, β -thromboglobulin, which is a well-established marker for activated platelets, was measured previously on blood stored from ARIC clinic examinations in nested case-cohort studies done during early follow-up. ARIC reported no association of β -thromboglobulin with early coronary heart disease or stroke (13). ARIC now has long-term follow-up on multiple CVD events, including heart failure and atrial fibrillation (AF) as well as coronary heart disease and stroke. Thus, we used these long-term follow-up data to test the hypothesis that activated platelets, measured by higher concentrations of β -thromboglobulin, are associated with increased risk of incident CVD (coronary heart disease, heart failure and ischemic stroke). In addition, because of growing evidence on the association between atherosclerosis and AF (14), we also investigated the association between β -thromboglobulin and AF risk.

METHODS

Study Design, Setting, and Population

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing population-based prospective study of cardiovascular diseases (15). In 1987–1989, the ARIC Study recruited

and examined 15,792 mostly Caucasian or African American men and women aged 45–64 from 4 U.S. communities [Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); and suburbs of Minneapolis, Minnesota]. The baseline home interview and clinic examination measured various demographic characteristics, health behaviors, and cardiovascular conditions. The participants were re-examined in 1990–1992 (visit 2, 93% return), in 1993–1995 (visit 3, 86% return), 1996–1998 (visit 4, 80% return) and 2009–2011 (visit 5, 41% return). The cohort was followed to the present for cardiovascular events.

ARIC previously measured plasma β -thromboglobulin, using stored samples, in the nested case-cohort study of incident coronary heart disease cases from ARIC visit 1 to December 31, 1991. The reference group was a stratified random sample of participants free of baseline coronary heart disease in the ARIC cohort. For the reference cohort random sample, which is the focus of this analysis, ARIC had oversampled participants with thin average carotid intima-media thickness measurements at baseline (<30th percentile) and used different sampling fractions by age sex, and race (16).

The institutional review boards of the collaborating institutions approved the study protocol, and each participant provided written informed consent.

Baseline Measurements

The main exposure of interest was plasma β -thromboglobulin concentration. The laboratory measurements were previously described (13). Plasma β -thromboglobulin was determined by an ELISA assay with kits obtained from Diagnostica Stago (Asnières-sur-Seine, France). The β -thromboglobulin assay has a coefficient of variation of 6.8% and in ARIC, a reliability coefficient was 0.83.

We assessed other potential CVD risk factors, including age, sex, race (white or African American), body mass index (kg/m^2), smoking status (current, former, or never), educational attainment (grade school, high school without graduation, high school with graduation, vocational school, college with or without graduation, and graduate or professional school) (17), alcohol drinking status (current, former, or never), hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or hypertension medication use), diabetes mellitus (a fasting blood glucose ≥ 126 mg/dl, non-fasting blood glucose ≥ 200 mg/dl, a self-reported physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks) (18), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), estimated glomerular filtration rate (eGFR, $\text{mL}/\text{min}/1.73 \text{ m}^2$), electrocardiogram (ECG) based left ventricular hypertrophy, and antiplatelet agent use. Information on antiplatelet agent use was also obtained at visit 2 (1990–1992), 3 (1993–1995), 4 (1996–1998) and 5 (2009–2011). Thus, we used antiplatelet agent use as a time-varying variable.

Confirmation of Incident Cardiovascular Disease

ARIC staff contacted participants annually by telephone to capture all hospitalizations and deaths related to possible CVD (19). They also surveyed lists of discharges from local hospitals and death certificates from state vital statistics offices for potential CVD events. Abstractors reviewed medical records and recorded information to validate CVD outcomes.

Incident coronary heart disease was validated by physician review, and was defined as a definite or probable myocardial infarction, definite coronary death, or coronary revascularization procedure.

Incident heart failure was defined as the first occurrence of either a hospitalization that included an International Classification of Diseases-9th Revision (ICD-9) discharge code of 428 (428.0 to 428.9) among the primary or secondary diagnoses or else a death certificate with an ICD-9 code of 428 or an ICD-10 code of I50 among the listed or underlying causes of death (20). ARIC has shown the validity of ICD-9 Code 428 to be moderately high, with a sensitivity of 93% for identifying acute decompensated heart failure (21).

For patients hospitalized for potential strokes, the abstractors recorded signs and symptoms and photocopied neuroimaging (computed tomography or magnetic resonance imaging) and other diagnostic reports. Using criteria adopted from the National Survey of Stroke, definite or probable strokes were classified by computer algorithm and separate review by a physician, with disagreements resolved by a second physician (22).

ARIC ascertained AF by a 12-lead ECG performed at study visits, by hospitalization discharge summaries, and via death certificates (23–25). AF was defined as the presence of ICD-9 Clinical Modification codes 427.31 or 427.32. AF events associated with open cardiac surgery were not included. The sensitivity and specificity of hospital discharge diagnoses for AF was 84% and 98%, respectively (23).

Statistical Analysis

SAS version 9.3 software (SAS Institute Inc., Cary, NC) was used for statistical analyses. All statistical tests were two-tailed and *P* values < 0.05 were regarded as significant.

Firstly, from 812 participants with β -thromboglobulin in the cohort random sample, we excluded participants who reported or had electrocardiographic evidence of prebaseline coronary heart disease/heart failure/ischemic stroke ($n=22$), and AF ($n=2$) and participants whose data on covariates or outcome status were missing ($n=42$). After exclusions, 746 cohort random sample participants were available for the present analyses.

We computed sampling-weighted mean levels or percentages of CVD risk factors at baseline according to tertiles of β -thromboglobulin. Person-years of follow-up were calculated from the baseline (1987–1989) to the first endpoint: incident first-ever CVD, death, loss to follow-up, or the end of follow-up (December, 2013). Hazard ratios (HRs) of CVD incidence and their 95% confidence intervals (CIs) were calculated after adjustment for CVD risk factors and the stratified sampling weights using a weighted Cox proportional hazard models (PROC SURVEYPHREG) (16). The proportional hazards assumption in the Cox regression was tested using risk factor-by-time interactions and was not violated. Plasma β -thromboglobulin was modeled using tertile cutpoints or using continuous variables, with natural log-transformation because of right-skewness. For coronary heart disease, heart failure and ischemic stroke analyses; Model 1 adjusted for age, sex, and race/ARIC field center (26); and Model 2 adjusted additionally for educational attainment, body mass index, hypertension, diabetes mellitus, HDL cholesterol, LDL cholesterol, smoking status, drinking

status, eGFR, and a time-varying antiplatelet agent use. For analyses of AF incidence, Model 1 adjusted for age, sex and race/ARIC field center; and Model 2 adjusted additionally for educational attainment, body mass index, hypertension, diabetes mellitus, smoking status, drinking status, eGFR, ECG-based left ventricular hypertrophy, time-varying coronary heart disease and heart failure that occurred in the cohort sample during later follow-up, and a time-varying antiplatelet agent use. Because of the difference of risk factors between coronary heart disease/heart failure/ischemic stroke and AF, we conducted separate analyses.

RESULTS

Baseline Plasma β -thromboglobulin and Risk Factors for Cardiovascular Disease

As shown in Table 1, individuals with higher concentrations of plasma β -thromboglobulin were more likely to have CVD risk factors such as male sex, higher body mass index, lower HDL cholesterol, higher LDL cholesterol, diabetes, lower eGFR, and left ventricular hypertrophy. They were less likely to use antiplatelet agent.

Association of Plasma β -thromboglobulin with Risk of Coronary Heart Disease, Heart Failure and Ischemic Stroke

During the 14,387 person-years of follow-up for the 746 cohort random sample participants, we identified 229 first-ever CVD events (140 coronary heart diseases, 123 heart failures, and 54 ischemic strokes) (Table 2). The age-, sex-, and race-adjusted model (Model 1) showed no associations of tertiles of or continuous β -thromboglobulin with CVD, regardless of subtypes (coronary heart disease, heart failure and ischemic stroke). After further adjustment for other CVD risk factors (Model 2), β -thromboglobulin remained unassociated with CVD risk. The analysis stratified by antiplatelet agent use at baseline also showed no association between β -thromboglobulin and CVD risk (Table 3).

Association of Plasma β -thromboglobulin with Risk of Atrial Fibrillation

We found 126 AF cases and no association between plasma β -thromboglobulin and AF risk (Supplemental Table I). The analysis stratified by antiplatelet agent use also showed no association between β -thromboglobulin and AF risk (Supplemental Table II).

DISCUSSION

In this population-based prospective study in the U.S., we tested the hypothesis that activated platelet activity, measured by higher plasma levels of β -thromboglobulin, is associated with increased risk of incident CVD. We found β -thromboglobulin was not associated with CVD.

Previously, ARIC suggested no association between β -thromboglobulin and coronary heart disease risk during short-term follow-up (13). The present study with extended follow-up also found no association between β -thromboglobulin and atherosclerotic CVD risk, even after adjusting for and stratifying participants by antiplatelet agent use [plasma β -thromboglobulin concentrations can be affected by antiplatelet agent use (27)]. Although

activated platelets may be a key contributor to atherothrombosis and thromboembolic events (1, 2), it may be difficult to predict future CVD events by measuring β -thromboglobulin in general populations.

There is growing evidence on the association between atherosclerosis and AF (14). Recent studies have suggested that even subclinical atherosclerosis, in addition to heart failure and coronary heart disease, may be a risk marker for AF (14, 28–31). Based on this background, we also examined the association between plasma β -thromboglobulin and AF incidence, but similarly found no association.

Some limitations of our study need to be mentioned. Firstly, because our sample size was relatively small, we cannot negate the possibility of missing a modest association, due to limited statistical power. Secondly, we had only a single measurement of β -thromboglobulin; changes in β -thromboglobulin during follow-up could have led to the misclassification, which would likely bias the observed HRs toward the null. Thirdly, based on a previous report (32), almost all participants (over 95%) had “normal” values of β -thromboglobulin. Although this narrow distribution of β -thromboglobulin might be partially because our participants were CVD-free at baseline, this may also be due to poor techniques of β -thromboglobulin measurements in 1980’s, compared to current techniques. Thus, it is not clear whether our results are also applicable to individuals with “abnormal” values of β -thromboglobulin. Finally, the possibility of confounding by unmeasured CVD and AF risk factors that might be associated with platelet activation cannot be negated.

In conclusion, in the prospective population-based ARIC cohort, β -thromboglobulin was not associated with CVD risk. Thus, ARIC data do not support the hypothesis that a blood marker of higher platelet activity reflect increased future risk of CVD in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Evidence for the association of platelet activity markers with CVD risk is limited.
- We examined the association of β -thromboglobulin with CVD risk.
- β -thromboglobulin was not associated with CVD risk.
- A higher platelet activity marker did not reflect increased CVD risk.

Table 1Baseline Characteristics of Participants Across Tertiles of Plasma β -thromboglobulin, ARIC, 1987–1989.

	β-thromboglobulin (ng/mL)		
	5–14.1	14.2–19.5	19.6–517.3
Participants, n	249	247	250
Age, y	52.6 \pm 0.4	54.3 \pm 0.4	54.0 \pm 0.4
Female, %	75.9	49.8	42.0
African American, %	22.8	18.6	25.9
High school graduation, %	78.1	78.7	78.3
Current smoker, %	24.6	27.0	26.2
Current drinker, %	56.0	58.8	57.3
Body mass index, kg/m ²	26.2 \pm 0.5	26.5 \pm 0.4	27.1 \pm 0.4
Hypertension, %	27.0	25.7	31.3
HDL cholesterol, mmol/L	1.5 \pm 0.05	1.4 \pm 0.04	1.3 \pm 0.04
LDL cholesterol, mmol/L	3.3 \pm 0.08	3.5 \pm 0.10	3.6 \pm 0.09
Diabetes, %	5.4	8.1	10.0
eGFR, ml/min/1.73m ²	106.0 \pm 1.3	100.9 \pm 1.0	100.0 \pm 1.6
ECG-left ventricular hypertrophy, %	0	0.03	2.0
Antiplatelet agents use, %	51.0	43.8	38.3

Values are weighted mean \pm standard error for continuous variables and weighted % for categorical variables.

Table 2
 Hazard Ratios and 95% Confidence Intervals for Coronary Heart Disease, Heart Failure, and Ischemic Stroke According to Plasma β -thromboglobulin Concentrations, ARIC, 1987–2013.

	Log(β -thromboglobulin)*	Tertiles of plasma β -thromboglobulin (ng/mL)			P for trend
		5–14.1	14.2–19.5	19.6–517.3	
Number at risk	746	249	247	250	
Person-years	14,387	5,131	4,733	4,524	
First-ever coronary heart disease, heart failure or ischemic stroke, cases	229	66	67	99	
Model 1	1.10 (0.93–1.30)	1	0.86 (0.52–1.40)	1.07 (0.67–1.72)	0.727
Model 2	1.16 (0.94–1.41)	1	0.95 (0.57–1.59)	1.08 (0.67–1.74)	0.714
Coronary heart disease, cases	140	41	39	60	
Model 1	0.94 (0.75–1.18)	1	0.91 (0.49–1.67)	1.10 (0.63–1.92)	0.708
Model 2	0.97 (0.77–1.21)	1	1.00 (0.54–1.85)	1.15 (0.67–1.97)	0.604
Heart failure, cases	123	40	31	52	
Model 1	1.07 (0.82–1.39)	1	0.66 (0.35–1.25)	0.86 (0.49–1.25)	0.621
Model 2	1.05 (0.81–1.37)	1	0.67 (0.34–1.32)	0.81 (0.46–1.40)	0.481
Ischemic stroke, cases	54	15	21	18	
Model 1	1.18 (0.89–1.58)	1	1.02 (0.36–2.91)	0.92 (0.29–2.96)	0.881
Model 2	1.34 (0.81–2.19)	1	0.99 (0.30–3.31)	0.78 (0.23–2.60)	0.664

Model 1: Adjusted for age, sex, race/ARIC field center.

Model 2: Adjusted for Model 1 + educational attainment, body mass index, hypertension, diabetes mellitus, HDL cholesterol, LDL cholesterol, smoking status, drinking status, eGFR, and a time-varying antiplatelet agent use.

* Per 1 SD increment.

Table 3

Hazard Ratios and 95% Confidence Intervals Associated with 1 SD increment in log(β -thromboglobulin) for Coronary Heart Disease, Heart Failure, and Ischemic Stroke According to Plasma β -thromboglobulin Concentrations, Stratified by Antiplatelet Agent Use, ARIC, 1987–2013.

	Antiplatelet agent use	
	No	Yes
Number at risk	413	333
Person-years	7,941	6,447
First-ever coronary heart disease, heart failure or ischemic stroke, cases	127	102
Model 1	1.08 (0.86–1.36)	1.13 (0.90–1.44)
Model 2	1.21 (0.93–1.58)	1.13 (0.81–1.58)
Coronary heart disease, cases	78	62
Model 1	0.91 (0.63–1.32)	1.03 (0.80–1.34)
Model 2	0.95 (0.65–1.37)	1.03 (0.72–1.49)
Heart failure, cases	68	55
Model 1	1.05 (0.74–1.51)	1.11 (0.75–1.65)
Model 2	1.11 (0.81–1.52)	1.00 (0.51–1.95)
Ischemic stroke, cases	31	23
Model 1	1.10 (0.73–1.68)	1.28 (0.89–1.84)
Model 2	1.24 (0.68–2.28)	1.35 (0.57–3.16)

Model 1: Adjusted for age, sex, race/ARIC field center.

Model 2: Adjusted for Model 1 + educational attainment, body mass index, hypertension, diabetes mellitus, HDL cholesterol, LDL cholesterol, smoking status, drinking status, eGFR and a time-varying antiplatelet agent use.