HHS Public Access

Author manuscript

Thromb Res. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Thromb Res. 2016 August ; 144: 236–238. doi:10.1016/j.thromres.2016.05.029.

Association of von Willebrand factor deficiency with prevalent cardiovascular disease and asymptomatic carotid atherosclerosis: The Atherosclerosis Risk in Communities Study

Craig D. Seaman, MD, MS[1,2], **Kristen M. George, MPH**[3], **Margaret Ragni, MD, MPH**[1,2], and **Aaron R. Folsom, MD, MPH**[3]

[1]Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[2]Hemophilia Center of Western Pennsylvania, Pittsburgh, Pennsylvania, USA

[3]School of Public Health, Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN

Dear Editors,

Von Willebrand factor (VWF), a large multimeric glycoprotein, plays a critical role in hemostasis. It binds to subendothelial collagen at the site of vascular injury where it facilitates platelet activation. Given the role of VWF in platelet activation, and the role of platelets in cardiovascular events, such as myocardial infarction (MI) and ischemic stroke, VWF may influence the risk of cardiovascular disease (CVD). In addition, evidence suggests that VWF may affect CVD risk by playing a role in atherogenesis by direct participation in plaque formation [1].

Several observational studies have looked at the role of VWF in atherosclerotic CVD, and most have concluded a positive, albeit weak, association exists between VWF levels and CVD [2–4]. Given the potential role of elevated VWF levels in CVD, VWF deficiency may in turn protect against CVD. Von Willebrand disease (VWD) is an inherited bleeding disordered characterized by VWF deficiency or dysfunction. Patients with VWD primarily experience easy bruising and mucocutaneous bleeding, such as epistaxis and menorrhagia. While several studies have shown reduced aortic and carotid atherosclerosis in VWF deficient pigs, results have been inconclusive in humans [5]. More recently, a cross-sectional study in the Netherlands performed by Sanders *et al* reported a reduced prevalence of arterial

Reprint Requests: Craig Seaman, MD, Assistant Professor of Medicine, Division Hematology/Oncology, University of Pittsburgh, Associate Director, Hemophilia Center of Western Pennsylvania, 3636 Boulevard of the Allies, Pittsburgh, PA 15213-4306, Telephone: 412-209-7280, Fax: 412-209-7281, seaman@upmc.edu.

Authorship: CDS, ARF and MVR designed the research. CDS, ARF, and MVR performed the research. KMG performed the statistical analysis. CDS, ARF, KMG, and MVR analyzed the data and formulated the conclusions. CDS, ARF, KMG, and MVRJ wrote the paper.

Disclosure of Conflicts of Interest: The authors declare no competing financial interests.

thrombosis in VWD compared with the general population [6]. Similarly, a cross-sectional analysis of a national discharge register by Seaman *et al* found a 15% decrease in the odds of CVD in VWD patients providing evidence that VWF deficiency may protect against CVD [7].

While a great deal of research has been done evaluating whether elevated VWF levels increase the risk for cardiovascular events, little research has been done to determine if VWF deficiency is protective against CVD. The Atherosclerosis in Communities (ARIC) Study previously showed VWF levels were positively correlated with prevalent CVD; however, VWF deficiency was not assessed [8]. We used data from the ARIC Study to examine the cross-sectional association of VWF deficiency with CVD by assessing carotid artery intima media thickness (IMT), a marker of generalized atherosclerosis positively correlated with prevalent and incident coronary heart disease (CHD), and history of acute cardiovascular events, including CHD, stroke, and intermittent claudication.

Methods

The ARIC Study is a prospective investigation of atherosclerosis and related diseases in a cohort of 15,792 persons 45 to 64 years of age at the time of recruitment sampled from Minneapolis, Minnesota; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi.

Hemostatic variables were determined in the ARIC Central Hemostasis Laboratory using previously published procedures [9]. Fibrinogen was measured by the thrombin-titration method, factor VIII (FVIII) activity was determined using clotting assays, and VWF antigen was assessed with ELISA.

Body mass index (BMI) was calculated as the ratio of weight in kilograms to height in meters squared. Overweight and obesity were defined as a BMI of 25 to <30.0 and >=30.0, respectively. Blood pressure was measured in the right arm three times while sitting and calculated based on the mean of the second and third measurements. Hypertension was defined as a systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg, and/or use of antihypertensive medication. Total cholesterol and triglycerides were measured by enzymatic method and low-density lipoprotein was calculated. Glucose was determined using the hexokinase method. Diabetes mellitus was defined as a fasting glucose >=126 mg/dL, non-fasting glucose >=200 mg/dL, and/or self-reported history of physician-diagnosed diabetes mellitus or use of hypoglycemic medication. Smoking status was obtained from interviews and consisted of current, former, or never smoker. Prevalent CVD was defined as CHD (history of angina pectoris by the Rose questionnaire, self-reported history of physician-diagnosed heart attack, evidence of prior MI by ECG, or history of coronary revascularization), self-reported history of a physician diagnosed stroke, or intermittent claudication according to the Rose questionnaire.

Subclinical carotid atherosclerosis was determined with B-mode ultrasound. Trained technicians scanned the carotid arteries bilaterally, which were divided into three segments each, the distal 1.0 cm portion of the common carotid artery, carotid bifurcation, and the

proximal 1.0 cm of the internal carotid artery. The mean IMT of the far wall of the six carotid artery segments was averaged to produce an overall mean IMT. Only 13% of the sample had a mean IMT for all six carotid sites as a result of poorly visualized carotid boundaries; therefore, imputation from sex and race specific multivariate linear models as a function of age, BMI, and arterial depth fit by maximum liklihood methods was done to determine missing values.

Demographics (age, sex, and race), hypertension, hyperlipidemia, diabetes mellitus, tobacco use, BMI, fibrinogen, and FVIII activity were compared between VWF and non-VWF deficient groups (VWF deficiency was defined as <0.50), using the Rao-Scott chi-square test and Student's *t*-test for categorical and continuous variables, respectively. The primary outcome was mean IMT of the far wall of the six carotid artery segments. The secondary outcome was the prevalence of CVD as defined above. Outcomes were compared between subjects with and without VWF deficiency. Mean carotid IMT was compared using multiple linear regression with adjustment for major risk factors - age, sex, race, systolic blood pressure, use of antihypertensive medication, total cholesterol, high-density lipoprotein cholesterol, use of antihyperlipidemics, diabetes mellitus, smoking status, BMI, and fibrinogen. Odds ratios for prevalent CVD were determined after adjustment for the same variables using a logistic regression model. Carotid IMT analysis was restricted to subjects without prevalent CVD.

Results

The ARIC Study sample consisted of 15,792 persons. We excluded 273 persons due to missing VWF levels, leaving 15,519 participants, 310 of whom were VWF deficient. The study population is described in Table 1. The VWF deficient cohort was younger than the non-VWF deficient cohort. Mean carotid IMT was similar among VWF deficient and non-VWF deficient groups, 0.72 +/− 0.18 mm vs 0.74 +/− 0.19 mm, p-value=0.08, respectively. The prevalence of CVD was lower in VWF deficient subjects than subjects without VWF deficiency, 5.8% vs. 9.3%, p-value=0.04, respectively. CVD risk factors, including hypertension, diabetes mellitus, and obesity, were more prevalent in non-VWF deficient participants than participants with VWF deficiency. Table 2 (supplementary) illustrates the association between VWF deficiency and cardiovascular outcomes following adjustment for CVD risk factors. There was no statistically significant difference in mean carotid artery IMT between VWF and non-VWF deficient groups, 0.017 mm, 95% CI −0.001–0.036. The odds of CVD were similar in subjects with and without VWF deficiency, OR 0.83, 95% CI 0.45–1.53.

Discussion

In this study, we demonstrated a 17%, but statistically nonsignificant, reduced odds of CVD in VWF deficient patients compared with non-VWF deficient patients. Further, we found no difference in mean carotid IMT between patients with and without VWF deficiency.

VWF has a well-established role in platelet activation, which contributes to the pathophysiology of MI, ischemic stroke, and other arterial thrombotic events that occur via

atherosclerotic plaque rupture. We recently illustrated in a cross-sectional analysis of a national discharge register that VWD patients had a 15% decrease in the odds of CVD, after adjustment for several CVD risk factors, compared with non-VWD patients [8]. While VWF plays a clear role in acute cardiovascular events via platelet activation, what part, if any, it plays in atherosclerotic disease development is less certain. Animal studies have demonstrated reduced rates of atherosclerosis; however, it has not been shown VWF deficiency is protective against atherosclerotic disease in humans. Comparably, persons with hemophilia have a similar prevalence of atherosclerosis compared to the general population despite decreased cardiovascular mortality, indicative of a protective effect during acute cardiovascular events, such as myocardial infarction, ischemic stroke, etc. [10]. Given our current findings, VWF deficiency may function in a similar role, protecting against acute cardiovascular events without retarding the development of atherosclerosis, a largely inflammatory process.

Our study has a few limitations that warrant consideration. First, the study was cross-sectional rather than prospective, since VWF antigen was only collected during the first ARIC Study visit. Second, VWF deficiency alone, in the absence of clinical manifestations, is not sufficient to diagnose VWD; therefore, we cannot be certain if each VWF deficient patient truly has VWD. Third, the small number of VWF deficient participants may have limited the study's power to detect modest associations. The major strength of our study lies in the fact that it is a large population-based study with well-standardized measurements.

In conclusion, we have investigated the association of VWF deficiency and CVD using a large population-based study and found a 17% statistically nonsignificant lower odds of prevalent cardiovascular events and no difference in atherosclerotic disease in the VWF deficient participants. These findings complement those of analogous studies and provide further evidence that a large, prospective observational study of VWD patients is warranted to more completely evaluate the role of VWD in CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C) with the ARIC carotid MRI examination funded by U01HL075572-01. The authors thank the staff and participants of the ARIC study for their important contributions.

References

1. Vischer UM. Von Willebrand factor, endothelial dysfunction, and cardiovascular disease. Journal of Thrombosis and Haemostasis. 2006; 4:1186–1193. [PubMed: 16706957]
2. Willeit P, Thomson A, Aspelund T, Rumley A, Eiriksdottir G, Lowe G, Gudnason V, Di Angelantonio E. Hemostatic factors and risk of coronary heart disease in general populations: new prospective study and updated meta-analysis. PLoS ONE. 2013; 8:e55175. [PubMed: 23408959]

3. Sonneveld MAH, de Maat MPM, Leebeek FWG. Von Willebrand factor and ADAMTS13 in arterial thrombosis: a systematic review and meta-analysis. Blood Reviews. 2014; 28:167–178. [PubMed: 24825749]

4. Whincup PH, Danesh J, Walker M, Lennon L, Thomson A, Appleby P, Rumley A, Lowe GDO. Von Willebrand factor and coronary heart disease: prospective study and meta-analysis. Eur Heart J. 2002; 23:1764–1770. [PubMed: 12419296]

5. Van Galen KPM, Tuinenburg A, Smeets Em, Schutgens REG. Von Willebrand factor deficiency and atherosclerosis. Blood Reviews. 2012; 26:189–196. [PubMed: 22721874]

6. Sanders YV, Eikennboom J, De Wee EM, van der Bom JG, Cnossen MH, Degenaar-Dujardin ME, Fijnvandraat K, Kamphuisen PW, Laros-van Gorkom BA, Meijer K, Mauser-Bunschoten EP, Leebeek FW. Reduced prevalence of arterial thrombosis in von Willebrand disease. Journal of Thrombosis and Haemostasis. 2013; 11:845–854. [PubMed: 23506463]

7. Seaman C, Yabes J, Comer D, Ragni MV. Does deficiency of von Willebrand factor protect against cardiovascular disease? Analysis of a national discharge register. Journal of Thrombosis and Haemostasis. 2015; 13:1999–2013. [PubMed: 26368360]

8. Folsom AR, Wu KK, Shahar E, Davis CE. for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Association of hemostatic variables with prevalent cardiovascular disease and asymptomatic carotid artery atherosclerosis. Arterioscl Thromb. 1993; 13:1829–1836. [PubMed: 8241104]

9. Papp AC, Hatzakis H, Bracey A, Wu KK. ARIC hemostasis study, I: development of blood collection and processing system suitable for multicenter hemostatic studies. Thromb Haemost. 1989; 61:15–19. [PubMed: 2526384]

10. Kamphuisen PW, ten Cate H. Cardiovascular risk in patients with hemophilia. Blood. 2014; 123:1297–1301. [PubMed: 24385539]

Highlights

- VWF deficiency is associated with a decreased prevalence of cardiovascular disease
- Subclinical carotid atherosclerosis is not reduced in VWF deficiency
- VWF deficiency may prevent cardiovascular events but not affect atherosclerosis

Table 1

Baseline characteristics of patients with and without VWF deficiency.*

	VWF deficiency (<0.50 IU/dL) N=310	**Non-VWF deficiency (>=0.5 IU/dL) N=15,209**	***P* value**
Age, years	51.7 +/− 5.2	54.2 +/− 5.8	<0.001
Female %	183 (59.0)	8,347 (54.9)	0.146
White %	243 (78.4)	11,187 (73.6)	0.056
Hypertension %	89 (28.7)	5,268 (34.8)	0.026
Systolic blood pressure, mmHg	118.8 +/− 17.9	121.3 +/− 18.8	0.022
Antihypertensive use %	76 (24.5)	4,649 (30.6)	0.022
Hyperlipidemia %	78 (25.2)	4,047 (26.6)	0.528
Total cholesterol, mg/dL	210.9 +/− 42.1	215.1 +/− 42.1	0.087
Antihyperlipidemic use %	3 (1.0)	447 (3.0)	0.039
Diabetes mellitus %	13 (4.2)	1,495 (9.9)	<0.001
Tobacco use			
Current smoker %	87 (28.1)	3,967 (26.1)	<0.001
Former smoker %	103 (33.2)	4,912 (32.3)	
Never smoker %	120 (38.7)	6,315 (41.6)	
Body mass index, kg/m^2	26.7 +/− 4.4	27.7 +/− 5.4	<0.001
Obese %	56 (18.3)	4,185 (27.8)	<0.001
Overweight %	131 (42.8)	5,989 (39.8)	
Normal weight %	119 (38.9)	4,886 (32.4)	
Factor VIII, IU/dL	0.77 +/− 0.18	1.33 +/− 0.39	<0.001
Fibrinogen, mg/dL	272 +/− 59.2	304.1 +/− 65.4	<0.001
Mean carotid artery IMT, mm	0.72 +/− 0.18	0.74 +/− 0.19	0.077
High carotid artery IMT (>90^{th} percentile) %	21 (7.1)	1,158 (8.2)	0.248
CVD %	15 (5.8)	1,083 (9.3)	0.038

VWF: von Willebrand factor; IMT: intima media thickness; CVD: cardiovascular disease

*Values are expressed as means +/− standard deviation or N (%).