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Clinical Investigation

The Cardioprotective Potential of von Willebrand Disease in Ischemic Heart Disease

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von Willebrand factor (vWF) aids coagulation at sites of vessel injury. Elevated vWF levels have been associated with an increased risk of ischemic heart disease (IHD); however, it is unclear whether vWF deficiency, seen in patients with von Willebrand disease (vWD), protects people against IHD. We determined and compared the prevalence and risk of IHD in patients with versus without vWD by using data from the National Inpatient Sample (2009–2014), excluding patients younger than 18 and older than 75 years. The primary outcome was the odds ratio (OR) of IHD in patients with versus without vWD. Secondary outcomes were major medical comorbidities and demographic characteristics in patients with vWD.

Of 224,475,443 weighted hospital-discharge samples, we identified 82,809 patients with a vWD diagnosis. The odds of IHD were lower in patients with vWD than in those without (OR=0.54; 95% CI, 0.52–0.56). After multivariable logistic regression analysis and adjustment for age, sex, and typical IHD risk factors (hypertension, smoking, diabetes, hyperlipidemia, chronic kidney disease, obesity, and family history of IHD), the likelihood of IHD remained lower in patients with vWD than in patients without (OR=0.65; 95% CI, 0.63–0.67). Our study shows that vWF deficiency, as seen in patients with vWD, is associated with a decreased prevalence of IHD. Further investigation may confirm these findings.
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Ischemic heart disease (IHD) is the leading cause of death in developed countries. However, in the last few decades, primary and secondary prevention strategies for IHD have led to fewer deaths. In the United States (US), 16.5 million people have IHD.[1] Multiple risk factors for IHD, including diabetes mellitus (DM), hypertension, hyperlipidemia, chronic kidney disease (CKD), obesity, old age, cigarette smoking, and family history of coronary artery disease (CAD),[2] can cause endothelial dysfunction and atherosclerotic plaque formation in the coronary arteries that can lead to IHD. Unstable plaque can rupture, leading to platelet activation and clot formation.[3,4] von Willebrand factor (vWF) is integral in platelet adherence to endothelial cells at the site of vessel injury.[5] Elevated vWF levels have been associated with an increased risk of IHD; however, it is unclear whether vWF deficiency is associated with protection from IHD. To examine this possibility, we used the National Inpatient Sample (NIS) to determine and compare the prevalence and risk of IHD, including myocardial infarction (MI), angina pectoris, acute coronary occlusion, and intermediate coronary syndrome, in a large sample of patients with versus without von Willebrand disease (vWD).

Patients and Methods

We retrospectively reviewed data from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) NIS database (2009–2014).[6] The NIS, the largest publicly available, deidentified, all-payer administrative claims database in the US, contains data from 5 to 8 million hospital discharges

annually, approximately 20% of US hospital admissions. The NIS is compiled yearly by the HCUP of the AHRQ to include all patients from involved hospitals who have Medicare, Medicaid, private insurance, or no insurance. We used the entire database, from 2009 through 2014, excluding only patients younger than 18 and older than 75 years. We defined IHD as any MI event or a diagnosis of IHD (angina pectoris, acute coronary occlusion, and intermediate coronary syndrome), using the International Classification of Disease, 9th revision (ICD-9).[7] In October 2015, ICD-9 was updated to ICD-10 with subsequent changes in coding, so to avoid selection bias, we confined our data to the time period before 2015. Up to 30 ICD-9 diagnosis codes available for each observation were evaluated and classified on the basis of comorbidity groups.

Statistical Analysis

All measured criteria were adjusted for applicable sampling weights. Descriptive analyses were performed to describe demographic characteristics and IHD risk factors of patients with versus without IHD. Normally distributed continuous data were described in terms of mean, SD, median, and range. The primary outcome of interest was the odds ratio (OR) of IHD in patients with versus without vWD. As potential confounders for the multivariable logistic regression, hypertension, hyperlipidemia, CKD, obesity, smoking or history of tobacco use, and family history of IHD were included in the final model as risk factors for IHD.[2] Associations were reported as the OR and the corresponding 95% CI. We used SAS version 9.4 (SAS Institute Inc.) for data analyses.

Results

The NIS contained weighted hospital-discharge samples for 224,475,443 patients from 1 January 2009 through 31 December 2014. Of those patients, 82,809 (0.04%) had a diagnosis of vWD, and 224,392,634 (99.96%) did not. Table I contains information pertaining to vWD, IHD, and IHD risk factors determined on the basis of the ICD-9 coding system.

In contrast to the group without IHD, the patients with IHD were older and had a greater number of specified IHD risk factors (Table II).

The prevalence of IHD was 3,500 (4.2%) in patients with vWD and 16,884,101 (7.5%) in patients without vWD. The odds of IHD were lower in patients with vWD than in patients without vWD (OR=0.54; 95% CI, 0.52–0.56) (Table III). After multivariable logistic regression analysis and adjustment for age, sex, and the IHD risk factors, the likelihood of IHD remained lower in patients with vWD than in patients without (OR=0.65; 95% CI, 0.63–0.67) (Table IV).

TABLE I. ICD-9 Codes Used to Evaluate Risk of Ischemic Heart Disease in Patients From the National Inpatient Sample (2009–2014)

Risks and Outcome	Specific Morbidities	ICD-9 Code
Primary risk factor	von Willebrand disease	286.4
Other risk factors		
Hypertension	Essential hypertension	401.*
Diabetes	Diabetes mellitus	250.*
Hyperlipidemia	Pure hypercholesterolemia	272.0
	Mixed hyperlipidemia	272.2
Obesity (adult)	BMI 25–29	V85.2*
	BMI 30–39	V85.3*
	BMI ≥40	V85.4*
	Overweight and obesity	278.0*
Smoking	Smoking	305.1
	Personal history of tobacco use	V15.82
Family history of IHD	Family history of IHD	V17.3
CKD stage	II (mild)	585.2
	III (moderate)	585.3
	IV (severe)	585.4
	V	585.5
	V, requiring chronic dialysis	585.6
	Unspecified	585.9
Outcome variable		
IHD	MI	410.*
	Old MI	412.*
	Intermediate coronary syndrome	411.1
	Acute coronary occlusion without MI	411.81
	Other acute and subacute forms of IHD	411.89
	Other and unspecified angina pectoris	413.9

BMI = body mass index; CKD = chronic kidney disease; ICD-9 = International Classification of Disease, 9th revision; IHD = ischemic heart disease; MI = myocardial infarction

*Indicates any suffix to the listed ICD code

Discussion

Primary hemostasis is achieved through the interaction among platelets, vWF, and the vessel wall. After vascular injury or atherosclerotic plaque rupture, such as in MI, vWF adheres to the exposed cells, leading to platelet activation and adherence to the surface of vWF.[4] Given the importance of vWF in coagulation, vWF is a potential target in managing the care of patients who have CAD. Elevated vWF levels have been investigated as

TABLE II. Demographic Characteristics and Risk Factors for Ischemic Heart Disease in 82,809 Patients With von Willebrand Disease

Variable	With IHD	No IHD
Admissions (n)	3,500	79,309
Mean age (yr) (median, interquartile range)	67.62 (68, 58–78)	44.72 (43, 26–63)
IHD risk factors		
Essential hypertension	1,832 (52) (50.7–54.0)	22,401 (28) (27.9–28.6)
Diabetes	1,044 (30) (28.3–31.4)	9,753 (12) (12.1–12.5)
Hyperlipidemia	282 (8) (7.2–9.0)	2,643 (3) (3.2–3.5)
Obesity	385 (11) (10.0–12.1)	5,687 (7) (7.0–7.5)
Smoking	1,032 (29) (28.0–31.0)	14,145 (18) (17.6–18.1)
Family history of IHD	175 (5) (4.3–5.8)	841 (1) (0.99–1.1)
Chronic kidney disease	674 (19) (18.0–20.6)	4,536 (6) (5.6 –5.9)

IHD = ischemic heart disease

Data are presented as number and percentage with 95% CI unless otherwise stated.

TABLE III. Unadjusted Odds Ratio of Ischemic Heart Disease in Patients With von Willebrand Disease

vWD	No IHD	IHD	Total
No	207,508,533 (92.5)	16,884,101 (7.5)	224,392,634
Yes	79,309 (95.8)	3,500 (4.2)	82,809
Total	207,587,842	16,887,602	224,475,443
Odds ratio (95% CI)	0.54 (0.52–0.56)	—	—

IHD = ischemic heart disease; vWD = von Willebrand disease

Data are presented as number and percentage unless otherwise stated.

an independent risk factor for IHD. In 3 large prospective studies, univariate analysis has shown that elevated vWF levels are significantly associated with the subsequent development of IHD.[8-10] Similarly, a meta-analysis of 6 prospective trials has shown that high vWF levels are associated with a moderately increased risk of CAD and death (OR=1.5; 95% CI, 1.1–2.9).[11] Of note, the authors of the meta-analysis could not definitively determine the cause of such an association.

On the other hand, it remains unclear whether vWD (due to either vWF deficiency or defective vWF function) is associated with a decreased prevalence of IHD.

TABLE IV. Odds Ratios for Ischemic Heart Disease in Patients With Risk Factors for Ischemic Heart Disease

Risk Factor	Unadjusted OR* (95% CI)	Adjusted OR** (95% CI)
von Willebrand disease	0.54 (0.52–0.56)	0.65 (0.63–0.67)
Essential hypertension	2.61 (2.61–2.61)	3.37 (3.37–3.38)
Diabetes	2.82 (2.81–2.82)	1.6 (1.59–1.6)
Hyperlipidemia	2.65 (2.65–2.65)	1.64 (1.63–1.64)
Overweight and obesity (BMI ≥25)	1.70 (1.70–1.70)	1.08 (1.08–1.08)
Smoking or history of tobacco use	2.32 (2.32–2.32)	1.83 (1.83–1.83)
Family history of IHD	5.63 (5.62–5.64)	3.86 (3.85–3.87)
Chronic kidney disease	2.92 (2.91–2.92)	4.7 (4.69–4.71)

BMI = body mass index; IHD = ischemic heart disease; OR = odds ratio

*Based on bivariate association between IHD and the risk factor

**Adjusted for all listed risk factors

We therefore performed a cross-sectional analysis of patients with versus without vWD, using NIS data from 2009 through 2014. We found that the prevalence of IHD was 3.3% lower in patients with vWD than in patients without vWD. In addition, in both univariable and multivariable logistic regression analyses, the likelihood of IHD was lower in patients with vWD. After adjustment for age, sex, and IHD risk factors, the likelihood of IHD was 35% lower in patients with vWD than in patients without. Aside from the differences in numeric values, these findings agree with those of Seaman and colleagues[12] and provide additional evidence that vWD may protect people against IHD.

To our knowledge, ours is the first study to corroborate the findings of Seaman and colleagues[12] in a large cohort of patients, but with noticeable differences. First, our analysis included a large number of patients for analysis, spanning several years of NIS data. Second, we attempted to reduce measurement errors by defining IHD as MI, angina pectoris, acute coronary occlusion, or intermediate coronary syndrome, rather than involving cerebrovascular and peripheral arterial disease as Seaman and colleagues did.[12] We did so because we were confident that the power of our sample size would accurately reflect the association of vWD with the odds of complications related to CAD. Last, we identified family history and CKD (well-known risk factors for IHD) as potential confounders, in addition to the others noted by Seaman and colleagues.[12]

Our findings also concur with those of other studies that have suggested a protective effect of vWD in

IHD, albeit a broadly defined one in most cases. A cross-sectional study in the Netherlands[13] compared the prevalence of arterial thrombosis between 635 patients with vWD and 2 reference populations in the Dutch general population and showed a decreased prevalence of arterial thrombosis in both reference populations. In addition, results of animal studies indicate that vWF deficiency protects against the development of atherosclerosis.[14-17] A nationwide study in Sweden of 2,790 patients with vWD showed a 0.4-fold (95% CI, 0.3–0.6) hazard of cardiovascular disease–related death in patients with vWD when compared with the general population.[18]

Study Limitations. Our study had several limitations. First, the NIS is an administrative database in which patients and procedures are classified by using ICD codes for billing purposes. Therefore, the data may be incomplete and subject to errors. Nonetheless, NIS data have been used extensively in research and are considered an accurate and validated tool.[19] Second, comorbidities are more likely to be underreported because they are not related to the administrative process. Third, from the NIS data available, we could not quantify IHD severity, vWF deficiency level, and other factors because the NIS uses hospital-discharge diagnoses with no patient-level information. Fourth, we could not eliminate selection bias. Finally, because patients with vWD can have bleeding complications, they may have had better care than did patients without vWD, resulting in fewer complications from CAD.

Conclusion

Using the NIS, we have shown in a large cohort of patients that vWD is associated with a decreased prevalence of IHD. We think that further prospective investigation and clinical trials with clear patient-level information are warranted to confirm these findings, identify possible causes, and determine the usefulness of vWF as a potential therapeutic target in managing IHD.

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References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation 2020;141(9):e139-596.
2. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines [published errata appear in Circulation 2019;140(11):e649-50, Circulation 2020;141(14):e60, and Circulation 2020;141(16):e774]. Circulation 2019;140(11):e596-646.
3. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20(5):1262-75.
4. Yamashita A, Sumi T, Goto S, Hoshiba Y, Nishihira K, Kawamoto R, et al. Detection of von Willebrand factor and tissue factor in platelets-fibrin rich coronary thrombi in acute myocardial infarction. Am J Cardiol 2006;97(1):26-8.
5. NHLBI von Willebrand disease expert panel. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda (MD): National Heart Lung and Blood Institute. NIH publication no. 08-5832 (2007 Dec).
6. HCUP National Inpatient Sample (NIS). Healthcare cost and utilization project (HCUP). 2009-2014. Agency for Healthcare Research and Quality (Rockville, MD). Available from: www.hcup-us.ahrq.gov/nisoverview.jsp
7. Centers for Disease Control and Prevention. Classifications of diseases, functioning, and disability. International classification of diseases, ninth revision, clinical modification (ICD-9-CM). Hyattsville (MD): National Center for Health Statistics. Available from: http://www.cdc.gov/nchs/icd/icd9cm.htm
8. Cortellaro M, Boschetti C, Cofrancesco E, Zanussi C, Catalano M, de Gaetano G, et al. The PLAT study: hemostatic function in relation to atherothrombotic ischemic events in vascular disease patients. Principal results. PLAT Study Group. Progetto Lombardo Atero-Trombosi (PLAT) Study Group. Arterioscler Thromb 1992;12(9):1063-70.
9. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 1997;96(4):1102-8.
10. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N Engl J Med 1995;332(10):635-41.
11. Whincup PH, Danesh J, Walker M, Lennon L, Thomson A, Appleby P, et al. von Willebrand factor and coronary heart disease: prospective study and meta-analysis. Eur Heart J 2002;23(22):1764-70.
12. Seaman CD, Yabes J, Comer DM, Ragni MV. Does deficiency of von Willebrand factor protect against cardiovascular disease? Analysis of a national discharge register. J Thromb Haemost 2015;13(11):1999-2003.
13. Sanders YV, Eikenboom J, de Wee EM, van der Bom JG, Cnossen MH, Degenaar-Dujardin MEL, et al. Reduced prevalence of arterial thrombosis in von Willebrand disease. J Thromb Haemost 2013;11(5):845-54.
14. Fuster W, Bowie EJ, Lewis JC, Fass DN, Owen CA Jr, Brown AL. Resistance to arteriosclerosis in pigs with von Willebrand's disease: spontaneous and high cholesterol diet-induced arteriosclerosis. J Clin Invest 1978;61(3):722-30.
15. Fuster V, Fass DN, Kaye MP, Josa M, Zinsmeister AR, Bowie EJ. Arteriosclerosis in normal and von Willebrand pigs: long-term prospective study and aortic transplantation study. Circ Res 1982;51(5):587-93.
16. Badimon L, Steele P, Badimon JJ, Bowie EJ, Fuster V. Aortic atherosclerosis in pigs with heterozygous von Willebrand disease: comparison with homozygous von Willebrand and normal pigs. Arteriosclerosis 1985;5(4):366-70.
17. Griggs TR, Reddick RL, Sultzer D, Brinkhous KM. Susceptibility to atherosclerosis in aortas and coronary arteries of swine with von Willebrand's disease. Am J Pathol 1981;102(2):137-45.
18. Holm E, Osooli M, Steen Carlsson K, Berntorp E. Cardiovascular disease-related hospitalization and mortality

among persons with von Willebrand disease: a nationwide register study in Sweden. Haemophilia 2019;25(1):109-15.
19. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, Faiz OD. Systematic review of discharge coding accuracy. J Public Health (Oxf) 2012;34(1):138-48.
20. Mihyawi N, Ajmal M, Hung J, Yeneneh BT. The prevalence of cardiovascular disease in patients with von Willebrand disease: a potential therapeutic target [abstract]. Circulation 2020;142:A13941. Available from: https://doi.org/10.1161/circ.142.suppl_3.13941