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BRIEF REPORT

Acute myocardial infarction in von Willebrand disease: characteristics and outcomes

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Abstract

Background: Von Willebrand disease (VWD) is the most common inherited bleeding disorder. As treatments have improved prognosis of VWD, age-related diseases, including acute myocardial infarction (AMI), have become more prevalent. The treatment of AMI includes antithrombotic therapies, which increase the risk of bleeding. Current guidelines suggest weighing risks/benefits of antithrombotic therapy in patients with VWD. However, data to inform these discussions are lacking.

Objective: To characterize outcomes of patients with VWD after AMI.

Methods: We conducted a retrospective cohort study utilizing the National Readmissions Database of patients with and without VWD admitted with AMI in 2017 and 2018. Primary outcomes were 90-day any-cause, bleeding-related, and arterial thrombosis-related readmissions. Case-control matching was performed for age, sex (male or female), ST-elevation myocardial infarction, percutaneous coronary intervention, diabetes, and chronic kidney disease. Time-to-event analysis was performed after matching using Cox proportional hazards regression.

Results: A total of 136 patients with VWD were matched with 3400 controls without VWD. At 90 days, there were no differences in all-cause (10.7% vs 11.5%; P = 1.00), arterial thrombosis (1.9% vs 3.1%; P = .77), and bleeding (1.9% vs 0.4%; P = .083) readmission in patients with VWD. VWD was associated with increased risk of 90-day bleeding (hazard ratio [HR], 4.75; 95% CI, 1.05-21.66) but not all-cause (HR, 0.91; 95% CI, 0.50-1.67) or arterial thrombosis (HR, 0.54; 95% CI, 0.39-2.19) readmission.

Conclusion: Among patients admitted with AMI, VWD was associated with higher risk of 90-day readmission for bleeding but not any-cause and arterial thrombosis-related readmissions. Further studies are needed to balance bleeding and thrombotic risks post-AMI in patients with VWD.

KEYWORDS
acute myocardial infarction, bleeding, readmission, von Willebrand disease

Essentials

- Von Willebrand disease (VWD) is a common bleeding disorder and myocardial infarction (AMI) may occur in these patients.
- AMI in patients with VWD poses a dilemma in balancing bleeding and clotting risk.
- We aimed to investigate readmissions for bleeding in patients with VWD and AMI.
- Our study suggests that patients with AMI and VWD are at higher risk of bleeding.

1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder with heterogeneous clinical manifestations ranging from asymptomatic to frequent, severe bleeding diathesis [1]. As treatments and bleeding prophylaxis strategies have improved the prognosis of inherited bleeding disorders, age-related comorbidities, including atherosclerosis and coronary artery disease, have become more prevalent in this patient population [2]. A complication of coronary artery disease is acute myocardial infarction (AMI), which can lead to death, cardiogenic shock, heart failure, and significant post-hospitalization morbidity and mortality [3].

Acute and long-term therapy for AMI includes percutaneous coronary intervention (PCI) and antithrombotic therapy, which increases risk of bleeding. Given the increased risk of bleeding associated with VWD and AMI therapies, managing patients with both conditions poses challenges for clinicians [4,5]. Current guidelines recommend that among patients with VWD and cardiovascular disease requiring antithrombotic therapy, treatment with antithrombotic therapy is suggested over no therapy [6]. The guidelines also suggest a multidisciplinary discussion with cardiologists, hematologists, and patients regarding risks and benefits of antithrombotic therapy [6]. However, data to inform these conversations is scarce, and the risk of readmission for bleeding and recurrent cardiovascular events is not well characterized in this patient population. Therefore, we investigated 90-day all-cause, bleeding, arterial thrombosis, and cardiovascular readmissions among patients admitted with AMI with and without VWD using the National Readmission Database (NRD).

2 | METHODS

We conducted a retrospective cohort study using the NRD from 2017 and 2018, which is part of the Healthcare Cost and Utilization Project and is sponsored by the Agency for Healthcare Research and Quality. The NRD captures approximately 50% of hospitalizations nationwide. The NRD assigns unique identifiers to individual patients in order to track readmissions within a given calendar year but does not track patients between years. We identified admissions with primary and secondary diagnoses of AMI, including ST-elevation myocardial infarction (STEMI) and non-STEMI, using the International Classification of Diseases 10th edition (ICD-10) codes. Patients <18 years of age or with unknown vital status were excluded. For patients with more than 1 admission for AMI, the first admission for AMI was considered the index AMI hospitalization. Patients with VWD were identified using administrative ICD-10 (D68.0*) codes. Administrative ICD-10 codes for the different subtypes of VWD were not available until 2021. Comorbidities, including atrial fibrillation, prior myocardial infarction, prior PCI, and prior coronary artery bypass grafting (CABG), were identified using ICD-9 and ICD-10 codes. Inpatient procedures, including left heart catheterization, transfusion of blood products, PCI, CABG, and mechanical circulatory support, were identified using ICD-10 procedure codes (Supplementary Table S1). The NRD does not include information on race or ethnicity. Our study was deemed exempt by the New York University Grossman School of Medicine Institutional Review Board, given that the data are publicly available and de-identified.

2.1 | Outcomes

Primary outcomes were 90-day any-cause, bleeding-related, arterial thrombosis-related, and cardiovascular readmissions. Readmissions for bleeding were a composite of readmission with a primary diagnosis of gastrointestinal bleeding, nontraumatic intracranial bleeding, retroperitoneal bleeding, epistaxis, hemoptysis, musculoskeletal bleeding, and hemarthrosis [7,8]. Arterial thrombosis readmission was defined as readmission with a primary diagnosis of AMI, arterial thromboembolism, or ischemic stroke. Cardiovascular readmission was defined as readmission with a primary diagnosis of arterial thrombosis or heart failure. Readmission diagnoses were identified using ICD-10 codes (Supplementary Table S1). Given the NRD does not track patients across years, admissions after September were excluded from readmission analysis.

2.2 | Statistical analysis

Categorical variables were compared between patients with and without VWD using Fisher exact or chi-squared tests, as appropriate. Continuous variables were compared using Wilcoxon rank sum test.

We performed case-control matching (1 VWD case to 25 controls) on age and sex, as well as variables that were different between groups (defined as $P < .15$). These variables include STEMI presentation at index hospitalization, PCI during index hospitalization and history of chronic kidney disease or diabetes. Time-to-event analysis of first readmission was performed using Cox proportional hazards modeling to estimate the hazard ratio (HR) of outcomes in the matched cohort. As a sensitivity analysis, a multivariable Cox

TABLE 1 Patient characteristics and in-hospital outcomes during index hospitalization among matched patients with and without von Willebrand disease.

Characteristic	No VWD, N (%) N = 3400	VWD, N (%) N = 136
Characteristic		
Age (y)	65.3 (13.6)	65.3 (13.6)
Female sex, N (%)	2050 (60.3)	82 (60.3)
Index hospitalization characteristics, N (%)		
STEMI	500 (14.7)	20 (14.7)
PCI	1275 (37.5)	51 (37.5)
CABG	385 (11.3)	13 (9.6)
Mechanical circulatory support	132 (3.9)	5 (3.7)
Cardiogenic shock	174 (5.1)	7 (5.1)
Large or medium hospital bed size	2953 (86.8)	116 (85.3)
Urban teaching hospital	2371 (69.7)	112 (82.3)
Length of stay, days, mean (SD)	4.9 (5.7)	5.5 (6.5)
Comorbidities, N (%)		
Prior PCI	531 (15.6)	21 (15.4)
Prior CABG	310 (9.1)	14 (10.3)
Hypertension	2737 (80.5)	108 (79.4)
Heart failure	1362 (40.1)	57 (41.9)
Anemia	833 (24.5)	35 (25.7)
Liver disease	132 (3.9)	8 (5.9)
Obesity	744 (21.9)	33 (24.3)
CKD	600 (17.6)	24 (17.6)
Diabetes	1125 (33.1)	45 (33.1)
Thrombocytopenia	167 (4.9)	8 (5.9)
Atrial fibrillation	626 (18.4)	29 (21.3)
Medicare or Medicaid	2298 (67.6)	92 (67.6)
Long-term antiplatelet use	967 (28.4)	35 (25.7)
Long-term anticoagulation use	234 (6.9)	7 (5.1)
In-hospital outcomes		
Death	135 (4.0)	7 (5.1)
Any bleeding	474 (13.9)	26 (19.1)
GI bleeding	79 (2.3)	2 (1.5)
Intracranial bleeding	9 (0.3)	1 (0.7)
Other bleeding	59 (1.7)	4 (2.9)
Procedure-related bleeding	286 (8.4)	12 (8.8)
Transfusion	187 (5.5)	15 (11.0)

CABG, coronary artery bypass grafting; CKD, chronic kidney disease; GI, gastrointestinal; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; VWD, von Willebrand disease.

TABLE 2 Postindex hospitalization for 90-day readmissions rates.

Characteristic	Non-VWD N = 2427	VWD N = 103	p value
Any readmission	280 (11.5)	11 (10.7)	1.00
Bleeding readmission	10 (0.4)	2 (1.9)	.083
Arterial thrombosis readmission	76 (3.1)	2 (1.9)	.77
Cardiovascular readmission	84 (3.5)	3 (2.9)	1.00

Patients who were admitted after the month of September were excluded. VWD, von Willebrand disease.

proportional hazards regression was performed to estimate HR of outcomes in patients with VWD using variables that differed between groups ($P \leq .10$) in the before case-control matching as covariables.

All tests were 2-sided, and a P value $< .05$ was considered statistically significant. Statistical analyses were performed with SPSS software version 27.0 (IBM Corporation) and STATA version 15.1 (STATA Corporation).

3 | RESULTS

3.1 | Baseline characteristics and outcomes during index hospitalization of patients with and without VWD

A total of 638 276 patients hospitalized with AMI were included (638 140 without VWD and 136 patients with VWD). Patients with VWD were more likely to be female (60.3% vs 37.3%; $P < .001$) and less likely to present with STEMI (14.7% vs 28.3%; $P < .001$) and undergo PCI (37.5% vs 52.0%; $P = .001$).

During index hospitalization, patients with VWD had similar rates of in-hospital death compared with patients without VWD (5.1% vs 5.2%; $P = 1.00$). However, patients with VWD had an increased risk of bleeding or transfusion (19.1% vs 12.3%; $P = .015$). Patient characteristics and outcomes prior to case-control matching are summarized in Supplementary Table S2.

A total of 136 patients with VWD were matched with 3400 patients without VWD. After case-control matching, there was no significant difference in baseline patient characteristics between patients with and without VWD. The rate of bleeding or transfusion during index hospitalization was not statistically significant between patients with and without VWD (19.1% vs 13.9%; $P = .10$). Among the matched cohort, there was no difference in the rate of bleeding readmission in patients with VWD (1.9% vs 0.4%, $P = .083$). Patient characteristics and outcomes after case-control matching are summarized in Tables 1 and 2, respectively. The most common first readmissions at any time for patients with VWD after index AMI hospitalization were non-STEMI (5 patients, 3.7%), chronic obstructive lung disease

TABLE 3 Cox proportional hazard modeling of readmission rates in patients with and without von Willebrand disease.

Characteristic	Total cohort unadjusted HR (95% CI)	Total cohort adjusted HR (95% CI)[a]	Matched cohort HR (95% CI)
Any readmission	1.01 (0.56 -1.83)	1.00 (0.56-1.81)	0.91 (0.50-1.67)
Bleeding readmission	4.97 (1.24-19.88)	5.12 (1.28-20.48)	4.75 (1.04-21.66)
Arterial thrombosis readmission	0.61 (0.15-2.45)	0.64 (0.16-2.56)	0.54 (0.39-2.19)
Cardiovascular readmission	1.02 (0.33-3.15)	1.05 (0.34-3.24)	0.84 (0.27-2.65)

[a]Adjusted for age, sex, ST-elevation myocardial infarction, percutaneous coronary intervention, liver disease, chronic kidney disease, diabetes, long-term antiplatelet use, and long-term anticoagulation.

(3 patients, 2.2%), hypertension and heart failure (3 patients, 2.2%), and sepsis (2 patients, 1.5%) (Supplementary Table S3).

3.2 | Time-to-event analyses

Among the matched cohort, after Cox proportional hazards regression modeling, patients with VWD were associated with increased risk of 90-day readmission for bleeding (HR, 4.75; 95% CI, 1.04-21.66). There was no difference in the risk of 90-day all-cause, arterial thrombosis, or cardiovascular readmission between patients with and without VWD (Table 3). Of the 2 patients with VWD who had a 90-day readmission for bleeding, no patients had long-term antiplatelet or anticoagulation use at the time of readmission.

After sensitivity analysis utilizing multivariable Cox proportional hazards regression in all patients with AMI with age, sex, race, STEMI, PCI, liver disease, diabetes, chronic kidney disease, and long-term antiplatelet or anticoagulation as covariables, patients with VWD were associated with increased risk of 90-day (adjusted HR, 5.12; 95% CI, 1.28-20.48) readmission for bleeding. There was no difference in 90-day risk of all-cause, arterial thrombosis, and cardiovascular readmissions.

4 | DISCUSSION

These findings suggest that among patients admitted for AMI, VWD was associated with increased risk of 90-day readmission for bleeding. Additionally, patients with VWD had increased rates of in-hospital bleeding or transfusion compared with those without VWD. Patients with AMI with and without VWD had similar risks of 90-day all-cause, arterial thrombosis, and cardiovascular readmission.

In people with VWD, data on outcomes after AMI hospitalization are scarce, with readmission rates and posthospitalization outcomes of patients with VWD and AMI not well described. One study of 264 patients with VWD and over 700 000 patients with non-VWD hospitalized for AMI between 2004 and 2010 suggested that patients with VWD had similar rates of in-hospital death and bleeding (6.4% vs 3.8%, P = .16) compared with patients without VWD. However, only procedure-related bleeding was included in the definition of bleeding complication in that study [9]. Readmissions and posthospitalization outcomes of patients with VWD and AMI are not well characterized in the literature. Our findings suggest that the presence of concurrent VWD is associated with an increased risk of in-hospital bleeding and 90-day readmission for bleeding, although the absolute number of patients readmitted for bleeding was low.

In this cohort, patients with AMI and VWD were more likely to be female, although the burden of cardiovascular risk factors, including age, hypertension, prior PCI, heart failure, and diabetes, were not different between groups. Although all forms of inherited VWD are autosomal and therefore affect men and women equally, there is a burden of VWD on women compared with men, given that women may experience mucosal bleeding with menses and postpartum bleeding [10,11]. Another observation in our study is the association of a lower rate of STEMI among patients with VWD compared with patients without VWD. While the difference in gender may partially explain this difference given that women are less likely to have STEMI than men, this difference was persistent in our study among males (14.8% vs 31.2%; P = .008) and females (14.6% vs 23.2%; P = .067) [12,13]. The most common pathophysiology of STEMI involves either atherosclerotic plaque rupture or erosion, leading to thrombosis and complete coronary artery occlusion. Given that von Willebrand factor plays an important role in hemostasis and thrombus formation through both platelet binding and stabilization of factor VIII, it is plausible that patients with VWD are less susceptible to STEMI due to an impairment in intracoronary thrombus formation. A study of 374 patients (209 who had AMI and 165 healthy controls) suggested that elevated mean plasma von Willebrand factor antigen levels were elevated in patients with AMI and were associated with increased risk of subsequent major adverse cardiovascular events [14]. However, further investigation is warranted to test the hypothesis that VWD might be protective against STEMI.

Patients with hereditary bleeding disorders admitted for AMI present a clinical challenge, given that antiplatelet and antithrombotic therapy are a mainstay in treatment of AMI, especially post-PCI, and these therapies increase the risk of bleeding. One large trial investigated short duration (1 month vs 3 months) of dual antiplatelet therapy (DAPT) in patients at high risk of bleeding after PCI [15]. Among the inclusion criteria was hematologic disease or coagulopathy, of which 13.3% of patients included in the trial had present. There was a significant reduction in bleeding at 12 months in the abbreviated 1-month DAPT arm compared with the 3-month DAPT arm (6.5% vs 9.4%), with no difference in ischemic events. Further investigation in patients with VWD and AMI is needed in order to better balance bleeding and thrombotic risk in this patient population.

Limitations to consider when interpreting these results include that the NRD relies on administrative ICD-10 codes, limiting the granularity

of the data obtained, which may be a source of unmeasured confounding. Additionally, medications, such as anticoagulant or antiplatelet therapies, are not captured at the time of index hospitalization or afterward; therefore, antithrombotic strategies are unknown in this study. The NRD does not capture race or ethnicity; therefore, our study is unable to evaluate how socio-cultural determinants of health affect our results. As noted in the methods, all patients with VWD may not have been captured during the study period, given that the NRD does not track patient information across calendar years. Another limitation is that the NRD is unable to confirm the diagnosis of VWD or provide information about its severity. VWD is a heterogeneous disorder with several subtypes based on quantitative or qualitative functional abnormalities with a wide spectrum of bleeding risk. Administrative ICD-10 codes for the different subtypes of VWD were not available until 2021. Therefore, we do not know how many of our patients had type 3 VWD, which is associated with high risk of bleeding. Our study is also limited by the small number of events, particularly bleeding events. This precludes any definitive conclusions.

5 | CONCLUSION

Despite the bleeding risk associated with VWD, patients with VWD can and do present with AMI, posing clinical challenges for management as bleeding risk with interventions and antithrombotic treatments may be increased. These findings suggest that VWD is associated with an increased risk of both in-hospital bleeding and bleeding within 90 days of an AMI event. However, VWD was not associated with an increased risk of any readmission or arterial thrombosis-related readmission. Further investigation is warranted to confirm these results and to optimize treatment approaches with requisite antithrombotic strategies in combination with potential strategies to mitigate bleeding in patients with VWD.

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AUTHOR CONTRIBUTIONS

O.L., J.M.C., N.T.C., and J.S.B. designed the study. O.L. performed statistical analysis and drafted the initial manuscript. J.M.C., N.T.C., and J.S.B. critically reviewed or edited the manuscript. O.L. and J.S.B. had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

DECLARATION OF COMPETING INTERESTS

J.C. reports scientific advisory board and consulting fees from Abbott, Anthos, Alnylam, Bristol Myers Squibb, Five Prime Therapeutics, and Pfizer, and research funding from CSL Behring. N.T.C. reports consulting from Takeda and Genentech and honoraria from Octapharma and Equity in Doximity. O.L. and J.S.B. have no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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