Treating symptomatic coronary artery disease in patients with Von Willebrand disease

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There is limited data on the occurrence of coronary artery disease (CAD) in patients with Von Willebrand disease and the literature is even scarce on their management. We at our institute reviewed the medical records of 198 patients with Von Willebrand disease over a period of 15 years, of which 6 were found to have symptomatic CAD. Acute coronary syndrome was noted in 3 patients while the remaining 3 had stable angina. Cardiac catheterization showed that left main coronary artery was the culprit vessel in all of these patients. In terms of management, stents were placed in 3 patients, two of them underwent coronary artery bypass grafting, and the remaining one patient was medically managed. Aspirin, and in some patients clopidogrel, was well tolerated with minimal side effects.

With better quality of treatment and treatment options, patients with congenital bleeding disorders now enjoy increased life expectancy.1,2 A byproduct of this longevity is increased age-related co-morbidities particularly cardiovascular and cerebrovascular disease.3–5 Although clear consensus from the American College of Cardiology and American Heart Association is available for the management of coronary artery disease (CAD) in the general population, such evidence-based guidelines are lacking for the bleeding population.6 All we have are recommendations based on expert opinion.7 Due to paucity of data on this subject, physicians are faced with increased challenges of managing thrombotic conditions with the use of anti-platelet therapy which can significantly increase the risk of bleeding.

Von Willebrand disease (VWD) is the most common congenital bleeding disorder in which there is either a quantitative or qualitative defect in the Von Willebrand factor.8 Here, in this case series, we report our center’s experience in the management of CAD in this specific patient population.

METHODS

This is a single center, retrospective case study conducted at Henry Ford Hospital in Detroit, Michigan. This study was approved by the institutional review board of the hospital. Initially, 350 patients with the diagnosis of presumed VWD were identified from the hospital’s administrative database using the ICD-9 code (286.4), from January 1985 to December 2010. Medical records were reviewed to confirm the diagnosis. Patients with uncertain diagnosis and/or incomplete medical records were excluded from the study. Additionally, patients with acute coronary syndrome within 7–10 days of administration of VWF/FVIII or desmopressin were excluded.

Inclusion criteria

Patients diagnosed with VWD in the setting of a personal history and/or family history of bleeding along with laboratory criteria of VWF:RCo<50 IU/dL; VWF:Ag<50 IU/Dl and low to normal levels of FVIII.9,10

Outcomes

Primary outcome was the incidence of symptomatic coronary artery disease (CAD) in this patient population.

Definitions

Patients were considered to have acute coronary syndrome (ACS) if there was documentation of myocar-
dial infarction, either STEMI (ST segment elevation), NSTEMI (non-ST segment elevation) or unstable angina. Characteristics of chest pain along with changes on the ECG (pathological Q waves, ST-T segment changes, new onset left bundle branch block) with or without serial elevation in troponin (cTn) were used to define it. Patients with features of angina pectoris along with one or more cardiovascular risk factors were classified as stable angina.

Statistical analysis
Categorical variables were expressed as absolute values and percentages, whereas the continuous variables were expressed as mean ± standard deviation. Statistical analysis was carried out using the PASW v18 (Cary, NC, USA).

RESULTS
Of the 350 patients identified over the 15-year period, 198 patients met the inclusion criteria, of which six (3%) patients had CAD (combination of ACS and stable angina). The mean age at the time of diagnosis was 65.5 ± 10.6 years; four out of the six patients were females. All of them had type-1 VWD. The mean Framingham score was found to be 17.43 ± 4.32. Among the risk factors, hypertension was seen in all six patients, followed by hyperlipidemia in three. Four patients had extensive smoking history, with three of them being active smokers at the time of diagnosis. VWF/FVIII replacement was given both before and after the procedure. The given dose of Humate-P was 50U/kg body weight one hour before the procedure and subsequently the same dose 12 h after the procedure for the first 24–48 h during the hospital stay.

Below is the detailed description of patient characteristics and management of their CAD.

Patient A
A 75-year-old female with a history of hypertension, hyperlipidemia and type-1 VWD (VWF:Ag 45%; VWF:RCo 13%; FVIII:60%). On initial presentation, she was found to have chest pain and cardiac troponin elevation. There was no ST segment elevation on the ECG. Cardiac catheterization showed 80–95% stenosis of proximal and mid left anterior descending artery (LAD). As this was an acute presentation requiring immediate intervention, she received VWF/FVIII replacement after the procedure. The decision was made for her to undergo coronary artery bypass grafting (CABG), following which she started on aspirin-81 mg. No bleeding episodes were noted during either procedure. She continued to be on aspirin and was followed for a period of five years, with no recurrence of symptoms.

Patient B
A 58-year-old male with a history of hypertension, and type-1 VWD (VWF:Ag 14%; VWF:RCo 3%; FVIII:50%). He was found to have anterior myocardial ischemia on a stress echocardiogram after having complaints of typical chest pain, though without any ECG changes and with a normal troponin. Following this, he underwent cardiac catheterization which showed 80% occlusion of the LAD, in which a bare metal stent was placed. He received VWF/FVIII replacement both before and after the procedure. There were no bleeding episodes during his hospital stay. He was started on aspirin-81 mg and clopidogrel 75 mg. Minor bruising was noted within the next month, at which point clopidogrel was discontinued. He is close to ten months post operative, with no major bleeding episodes.

Patient C
A 74-year-female with a history of hypertension, hyperlipidemia, insulin dependent diabetes mellitus and type-1 VWD (VWF:Ag 15%; VWF:RCo 9%; FVIII:39%) who presented to the emergency department (ED) with complaints of chest pain. There were no ECG changes or troponin elevation. Further work-up including a cardiac catheterization showed 50% stenosis of the LAD; no intervention was undertaken at that time and the decision was made to medically manage her CAD. She received Humate-P before and after the procedure, resulting in no bleeding complications. Keeping her bleeding disorder in mind, no aspirin was given. Five years later, the patient continues to follow with us, with no recurrence of cardiac complaints.

Patient D
A 76-year-old female with a history of hypertension, peripheral vascular disease and type-1 VWD (VWF:Ag 9%; VWF:RCo 13% FVIII:98%). She suffered a massive ischemic stroke involving the left middle cerebral artery with residual right sided hemiparesis. Two years later, nuclear stress test was done for routine preoperative evaluation for an elective total knee replacement surgery, which showed anterior wall ischemia. A decision was made to proceed with cardiac catheterization, which showed 90% occlusion of the mid LAD, following which a drug-eluting stent (DES) was placed. She received factor replacement before and after the procedure.
and was started on aspirin-81 mg and clopidogrel 75 mg. She was followed up for 12 months, during which she tolerated the dual antiplatelet therapy well. The only complication noted was self resolving spontaneous bruising 6 months into the therapy. However, she died one year later secondary to failure to thrive.

**Patient E**
A 52-year-old female with a history of hypertension, hyperlipidemia and type-I VWD (VWF:Ag 15% VWF:RCo 18%; FVIII:46%) presented to ED with complaints of shortness of breath and chest pain, and was found to have ST segment elevation on the ECG. She was then sent for cardiac catheterization, was found to have 85% stenosis of the left main artery, and continued to have chest pains in the lab. An intra-aortic balloon pump was placed and two days later the patient underwent CABG. She was given VWF/FVIII replacement during both the procedures, without significant bleeding. She was then started on aspirin 81 mg and continues to be on it, and has been doing well for the past 10 years. At this time, she has no history of bleeding or cardiac complaints.

**Patient F**
A 58-year-old male with a known history of hypertension and type-I VWD (VWF:Ag 46%; VWF:RCo 14%; FVIII:70%), presented to ED with complaints of general tiredness, shortness of breath and fatigue. He was found to have elevated cardiac troponin with non ST segment changes on ECG. He underwent cardiac catheterization which showed 60% occlusion of the distal LAD; a bare metal stent was placed and the patient was started on aspirin 81 mg along with clopidogrel 75 mg. He continued the dual antiplatelet regimen for a month, during which he noted spontaneous bruising on his arms. Clopidogrel was discontinued after one month but aspirin was continued. He was followed up for a period of six years during which no major or minor bleeding episodes were noted.

**DISCUSSION**
To the best of our knowledge, this is the single largest case series on the management of CAD in VWD patients. A Medline search was carried out to identify similar case reports or case studies, and only eight independent reports were found in which therapeutic approaches to ACS in VWD patients were discussed.13–18 In our population, the incidence of symptomatic CAD was found to be 3%, which is lower than seen in the general population. Most of the patients were elderly females. Hypertension, hyperlipidemia and smoking were the most common risk factors. The cardiovascular risk factor profile in this bleeding population is similar to the general population. Finally, the duration of follow up was 45.6 ± 27.2 months.

In all our patients, the femoral artery was the choice of access. Factor VWF/FVIII was given in most cases, both before and after the procedure. Neither thrombotic nor bleeding complications were observed throughout hospital stay. In some cases reported in the literature, groin hematoma was noted after cardiac catheterization. In hemophiliacs, radial artery access is recommended as there is some data of lower risk of bleeding, alongside the fact that the radial artery is easily compressible.19 However, we believe that if adequate factor replacement is given before and after the procedure, the risk of bleeding is minimized even with the femoral approach. In one reported case, a small groin hematoma was noted in spite of VWF/FVIII replacement.16

Interestingly, occlusion of the left coronary artery was observed in all six symptomatic patients. This is the first study in which the culprit vessel is reported. This also suggests that, although ACS rarely occurs in this population, when it does, it becomes a serious, life-threatening condition involving the main blood supply to the heart. We do not have a rationale to explain this.

Percutaneous coronary artery intervention was carried out in three patients, while CABG was successfully performed in two patients. Aspirin was well tolerated; however, use of dual antiplatelet therapy lead to spontaneous bruising in two of the three patients to whom it was administered. This is similar to other cases reported in the literature where aspirin is well tolerated but the addition of a second antiplatelet agent can lead to incidence of spontaneous bleeding.20 Bare metal stent is preferred in cases of coronary stenting for it precludes the need for longer duration of antiplatelet therapy.21 One of the patients in our study received a drug eluting stent (DES), and was able to tolerate the dual antiplatelet therapy for 12 months. DES could therefore be an option, if needed.

**CONCLUSION**
CAD is uncommon in patients with VWD. In our study, we found that patients in ACS emergencies had safely undergone cardiac catheterization with minimal complications and tolerated the antiplatelet therapy well.
CONFLICT OF INTEREST

All authors report no conflict of interest.

REFERENCES