Percutaneous Coronary Intervention and the Management of Acute Coronary Syndromes in Patients With von Willebrand Disease

Sulaiman Rathore, MD1, Dexter Deleon, MD1, Hafsa Akram, MD2, David Sane, MD1, Timothy Ball, MD, PhD1

ABSTRACT: Background. Von Willebrand disease (vWD) results from quantitative or qualitative deficiency of von Willebrand factor (vWF). The occurrence of myocardial infarction is very rare in patients with vWD. A few case reports of acute coronary syndrome (ACS) in vWD patients are present in the literature, but no definite management recommendations are available for such patients. Case report. We report a case of successful percutaneous coronary intervention (PCI) with bare-metal stent (BMS) implantation in a 46-year-old woman with type 1 vWD and history of coronary artery disease (CAD). She received periprocedural dual-antiplatelet therapy for 2 weeks and then continued aspirin without any bleeding complications. Management proposal. The optimal management of patients with vWD and ACS is complex and presents a therapeutic challenge. We propose that dual-antiplatelet therapy can be used safely in most vWD patients presenting with ACS as most of them are type 1 vWD. PCI with BMS can be done safely. Long-term management of these patients requires a systemic approach including hematological consultation, ascertaining vWF levels, as well as patient education and close outpatient follow-up.

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Key words: vWD, DAPT, dual-antiplatelet therapy, bleeding

Von Willebrand disease (vWD) results from quantitative or qualitative deficiency of von Willebrand factor (vWF). In developed countries, introduction of clotting factor concentrates has significantly increased life expectancy for patients with vWD. In this aging patient population, the occurrence of ischemic cardiovascular disease has been on the rise and the presence of coronary artery disease has been demonstrated in autopsies of vWD patients.1 The occurrence of myocardial infarction is very rare in patients with vWD.

To our knowledge, a few case reports are present in the literature, but no definite management recommendations are available for vWD patients presenting with acute coronary syndrome (ACS). In this article, we review the literature and report the case of a vWD patient undergoing percutaneous coronary intervention (PCI). Finally, we present a proposal for antplatelet and antithrombotic therapy in vWD patients presenting with ACS.

Case Report
A 46-year-old woman with history of diabetes mellitus, hypertension, hypercholesterolemia, tobacco use, and type 1 vWD disease was referred to our hospital with chest pain and abnormal nuclear stress test. Her cardiac history included coronary artery disease (CAD) status post balloon angioplasty of the left circumflex artery in 2005. She was not on any antiplatelet therapy since then due to risk of bleeding. She was diagnosed with vWD in 1993 with factor VIII activity of 25% (normal, 50%-150%). Her surgical history was significant for cholecystectomy and total abdominal hysterectomy complicated by excessive bleeding that was controlled with factor VIII/vWF complex. Physical examination was unremarkable and cardiac catheterization with possible intervention was scheduled. After hematological consultation, two doses of desmopressin 12 hours apart were given. She was given aspirin 325 mg and clopidogrel 600 mg pre catheterization. The patient was taken to the cardiac catheterization laboratory, where the right radial approach was favored over femoral because of bleeding risks.

At the time of arterial cannulation, 3000 units of intravenous heparin were administered. After sheath placement, nitroglycerin 100 µg and verapamil 2.5 mg were administered. Her starting activated clotting time (ACT) was 121 seconds. Prior to advancing the extra back-up (EBU) guide catheter to the aortic root, bivalirudin was administered and her ACT was >300 s. Judkin’s left and right curved catheters were used for left and right coronary angiography and EBU 3.5 curved guide catheter was advanced for left main cannulation and intervention.

Coronary angiography showed widely patent left main and left anterior descending (LAD) arteries. Right coronary artery (RCA) was 100% occluded, which was consistent with her previous cardiac catheterization findings in 2005. Left circumflex artery showed stenosis up to 95% at the site of prior angioplasty. It was decided to stent this lesion and a 3.5 x 18 mm bare-metal stent (BMS) was deployed without any complications. The final angiograms showed excellent angiographic results without any evidence of edge dissections or thrombus (Figure 1).

There were no periprocedural complications and she was discharged the next day on clopidogrel 75 mg daily for 1 month and aspirin 325 mg daily. She was followed at our office and completed clopidogrel 75 mg and aspirin 325 mg daily therapy.
for 4 weeks without any bleeding sequelae. Aspirin 325 mg daily was continued and on last check 9 months after her PCI, she was tolerating aspirin without any bleeding complications.

**Von Willebrand Disease Pathophysiology and Classification**

Von Willebrand disease is the most common inherited bleeding disorder, with an estimated prevalence of 1% in general population by laboratory screening, although less than 5% of these individuals are symptomatic. Most cases are transmitted as an autosomal dominant trait that affects males and females equally, but there are some acquired forms of vWD as well. vWD is classified in three main phenotypes. Mechanisms, diagnostic basis, and treatment options are different in every phenotype (Table 1). Diagnostic test levels for vWD include vWF ristocetin cofactor activity (vWF:RCo <30 IU/dL), vWF antigen (vWF:Ag <30 IU/dL), and factor VIII (decreased or normal). vWD type 1 is the most common type, accounting for approximately 75% of cases.

**Von Willebrand Factor**

Von Willebrand factor plays an important role in platelet adhesion, aggregation, and thrombus formation. It has three important functions in thrombus formation: (1) binding to platelets; (2) binding to subendothelium; and (3) carrier function for factor VIII. This requires activation of vWF that can occur with exposure to subendothelial structures after vascular injury or high shear stress present in atherosclerotic arteries (shear rates >1000/second).

Von Willebrand factor is synthesized mostly in endothelial cells, but it can be found in alpha-granules of platelets with no interchange between the two compartments. Although plasma and platelet vWF differ significantly from each other, both factors play an important role in securing primary hemostasis. There is evidence of significant heterogeneity of platelet vWF levels in vWD types with platelet-low and platelet-normal phenotypes identified.

**vWF in Coronary Artery Disease**

Many studies have shown that high levels of plasma vWF are associated with risk of coronary heart disease and increased levels of vWF have been found in patients with acute myocardial infarction. Probably, this elevation of vWF level is also seen in vWD patients presenting with ACS as evident by their baseline and ACS vWF levels in case reports (Table 2). vWF levels rise in ST-elevation myocardial infarction (STEMI) up to 1.5-2 fold in the first 24 hours and peak at 48 to 72 hours, with levels returning to baseline within 14 days.

**Safety of Antiplatelet and Antithrombotic Therapy in vWD and ACS**

Dual-antiplatelet therapy with aspirin and a thienopyridine (eg, clopidogrel) is currently the standard of care for the majority of patients undergoing PCI. Usually, antiplatelet medications are avoided in vWD patients due to risk of bleeding and the safety of such agents is not well studied in patients with vWD and ACS. However, there are a few case reports describing the use of antiplatelet and antithrombotic agents in patients with vWD undergoing PCI (Table 2) and cardiac surgery. Increase in vWF levels with ACS, as a result of catecholamine surge, may play a role in better tolerance of antiplatelet and antithrombotic medications during ACS in vWD patients.

There are studies on aspirin-vWF interactions and tolerance in vWD patients, but data are lacking for thienopyridines. Aspirin therapy results in a minor decrease in vWF levels and significantly lengthens bleeding time only in less prevalent severe vWD type patients.
Heparin does not decrease vWF levels in a normal population and multiple reports have described use of heparin in vWD patients undergoing PCI and cardiac surgery without significant bleeding complications (Table 2). Direct thrombin inhibitor (eg, bivalirudin) use has been reported in hemophilia A patients undergoing PCI.

Glycoprotein (GP) IIb/IIIa inhibitor (tirofiban) use has been reported in patients with vWD and ACS during PCI with BMS in a patient with vWD without major bleeding complications. Thrombolytic therapy poses a greater risk of bleeding in vWD patients and ACS. These agents can degrade vWF, further reducing the levels and increasing bleeding risk. Fragasso et al reported use of rtPA in a vWD patient and STEMI associated with significant extracerebral bleeding.

There are two main therapies available for treatment of spontaneous bleeding episodes and for bleeding prophylaxis: desmopressin (DDAVP) and factor VIII/vWF concentrates. Desmopressin raises endogenous factor VIII and vWF up to 3-5 times and corrects the defects. In severe diseases like type 3 and in most type 2 cases, DDAVP is ineffective and factor VIII/vWF concentrates is the best choice (Table 1).21

Proposition of Management of Acute Coronary Syndrome in vWD

The optimal management of patients with vWD and ACS is complex and requires detailed history and laboratory work-up including factor levels that may not be available quickly especially while treating STEMI. Patients with vWD can have a variable degree of vWF deficiency and therefore management should be individualized. If recent evaluation of vWF including typing, vWF activity, and factor VIII levels are available, these can help in making decisions. vWF activity levels above 30% in vWD patients are considered safe for minor surgeries. However, given the fact that prompt initiation of antiplatelet and antithrombotic therapy is associated with improved outcomes in patients with ACS, it is reasonable to proceed carefully with initiation of such therapies in ACS-vWD patients. We suggest that antiplatelet therapy can be given with aspirin and clopidogrel both in STEMI and unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) in vWD patients, as 75% of them are type 1 vWD (Figure 2).

As in the case of non-vWD patients with CAD, indications for cardiac intervention should be the same in vWD patients presenting with ACS. In STEMI and vWD, where the outcomes are time-dependent, primary PCI should be preferred.

For UA and NSTEMI, where more time is available, heparin in addition to dual-antiplatelet therapy can be given. Hematological consultation and factor levels may be considered unless a decision for urgent PCI is made. In case of urgent PCI, follow the STEMI track (Figure 1).

Similarly, in patients with abnormal cardiac stress test and vWD, appropriate medical treatment including antiplatelets, factor levels, and hematological opinion may be considered before proceeding to PCI (Figure 1).

Bleeding is the most feared complication in the treatment of ACS in vWD patients and can be associated with poor immediate and long-term outcomes. We suggest the following to minimize bleeding risks in such patients undergoing PCI: (1) a radial approach should be preferred over femoral approach for cardiac catheterization for better hemostatic control; (2) direct thrombin inhibitors like bivalirudin alone or in combination with heparin can be used for angiography and PCI; (3) BMSs should be preferred to reduce the duration of dual-antiplatelet therapy; (4) use of GP IIb/IIIa inhibitors should

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Table 1. Classification, mechanism, and treatment of von Willebrand Disease.

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>vWF Activity*</th>
<th>RIPA**</th>
<th>Multimer Pattern***</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Partial quantitative deficiency of vWF</td>
<td>decreased</td>
<td>decreased</td>
<td>uniform decrease: all present</td>
<td>Desmopressin or Factor VIII-vWF concentrate</td>
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<td>Type 2</td>
<td>qualitative defects</td>
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<td>Type 2A</td>
<td>defective platelet-dependent vWF functions</td>
<td>decreased</td>
<td>decreased</td>
<td>decreased large multimers</td>
<td>Factor VIII-vWF concentrates</td>
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<tr>
<td>Type 2B</td>
<td>Increased platelet-dependent vWF functions</td>
<td>decreased</td>
<td>increased</td>
<td>decreased large multimers</td>
<td>Factor VIII-vWF concentrates</td>
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<tr>
<td>Type 2M</td>
<td>defective platelet-dependent vWF functions</td>
<td>decreased</td>
<td>decreased</td>
<td>uniform decrease: all present</td>
<td>Factor VIII-vWF concentrates</td>
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<tr>
<td>Type 2N</td>
<td>defective vWF binding to factor VIII</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>Factor VIII-vWF concentrates</td>
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<tr>
<td>Type 3</td>
<td>severe deficiency of vWF and moderate factor VIII deficiency</td>
<td>markedly decreased or absent</td>
<td>markedly decreased or absent</td>
<td>undetectable</td>
<td>Factor VIII-vWF concentrates or recombinant Factor VIII</td>
</tr>
</tbody>
</table>

*vWF activity: ristocetin cofactor activity; it can be performed on plasma as well as platelet vWF; **RIPA: ristocetin-induced platelet aggregation; ***Multimer pattern: vWF multimer pattern assay on gel electrophoresis.
### Table 2. Case reports of ACS in vWD patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>ACS</th>
<th>Periprocedure Medication</th>
<th>Intervention</th>
<th>Complications and Course</th>
<th>Factor Levels *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al²⁶</td>
<td>1996</td>
<td>69</td>
<td>female</td>
<td>STEMI</td>
<td>Received rtPA initially followed with intervention. She received intravenous heparin,</td>
<td>Angioplasty was done initially without stenting</td>
<td>No major bleeding complications. Second PCI</td>
<td>Factor VIl level</td>
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<td></td>
<td>nitroglycerin, oral aspirin and metoprolol. 2000 units of vWF/Factor VIII given</td>
<td>and 2 months later PCI with BMS was done for</td>
<td>was done without Factor VIII transfusion and</td>
<td>of 42% (normal</td>
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<td>precatheaterization.</td>
<td>restenosis of LAD and patient was placed on</td>
<td>discharge home in 3 days.</td>
<td>range 60%-200%)</td>
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<td>aspirin and ticlopidine.</td>
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<td>(normal range 45%-125%)</td>
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<tr>
<td>Fragasso et al²⁵</td>
<td>1998</td>
<td>61</td>
<td>male</td>
<td>STEMI</td>
<td>Known three-vessel coronary artery disease on list for CABG, received rtPA followed</td>
<td>Known history of coronary artery disease taken</td>
<td>Mild gum bleeding after 1 hour, epistaxis and</td>
<td>vWD type 1 with</td>
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<td>by heparin drip and continued for 48 hours. Finally underwent CABG on factor VIII drip.</td>
<td>directly for coronary artery bypass graft surgery.</td>
<td>hematuria after 5 hours of rtPA and dropped</td>
<td>ristocetin cofactor activity 20%</td>
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<td>Hgb from 14.7 g/dL to 8.9 g/dL in 48 hours. No</td>
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<td></td>
<td>complications during CABG surgery on factor VIII</td>
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<td></td>
<td></td>
<td>concentrate.</td>
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<tr>
<td>James et al²⁷</td>
<td>2002</td>
<td>70</td>
<td>female</td>
<td>STEMI</td>
<td>Aspirin 300 mg given without standard preprocedural heparin. Angioplasty without</td>
<td>Angioplasty without stent placement was done</td>
<td>No complications and patient symptomatic 2</td>
<td>Factor VIII (VIIIC) of 137 IU/dL (range 50-200), vWF activity 51 IU/dL (range 50-200) and vWF Ag 40 IU/dL (50-200) at admission and baseline 2 months after FVIII:C 124, vWF 43 and vWF Ag 55%</td>
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<td>stent placement was done in the right coronary artery.</td>
<td>months post procedure.</td>
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<tr>
<td>Arjomand et al²⁸</td>
<td>2002</td>
<td>45</td>
<td>female</td>
<td>STEMI</td>
<td>Pretreatment with aspirin, metoprolol, and nitroglycerin. Also received heparin to</td>
<td>PTCA with bare-metal stents placed in the left</td>
<td>No major bleeding complications were noticed.</td>
<td>Factor VIII activity 36% (normal 50%-150%) and vWF Ag 73% (normal &gt;50%) on last evaluation 10 years ago and during hospitalization factor VIII 82% and vWF Ag 74%</td>
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<td>maintain ACT &gt;300 s and GP IIb/IIIa inhibitor (tirosiban) up to 48 hours.</td>
<td>anterior descending.</td>
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<tr>
<td>Macdonald et al²⁸</td>
<td>2006</td>
<td>56</td>
<td>male</td>
<td>NSTEMI</td>
<td>Received vWF/Factor VIII 48 hours preprocedure. Loading dose of clopidogrel given and</td>
<td>PTCA with drug-eluting stent (paclitaxel) placed</td>
<td>Mild epistaxis resolved without any intervention.</td>
<td>vWD Type 1</td>
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<td>ACT of 250-350 s maintained during the procedure. No GP IIb/IIIa given.</td>
<td>in left anterior descending and right coronary</td>
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<td>arteries.</td>
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</table>

* vWF, Factor VIII levels, and vWD type if reported by authors.
be minimized; and (5) for bleeding prophylaxis, desmopressin should be avoided preprocedure in acute events due to greater risk of hypertension and thrombosis with DDAVP.\(^{22,23}\) However, DDAVP can be used preprocedure in elective procedures under suitable hemodynamic conditions. Desmopressin infusion at a dose of 0.3 µg/kg 30 minutes preprocedure increases plasma factor VIII and vWF levels by 3-5 times, suitable for minor surgeries.\(^{3}\) In case of severe vWD and periprocedural bleeding, cryoprecipitate (may require up to 8-12 bags and contains both factor VIII and vWF) can be used.\(^{24}\) Factor VIII/vWF complex, a commercially available concentrate, can also be used in consultation with a hematologist.

It is probably safe to continue aspirin (ASA) 81 mg/day after PCI indefinitely or as tolerated, like a non-vWD disease patient.\(^{25}\) Clopidogrel 75 mg/day after BMS implantation for 1 month or at least 2 weeks if increased risk of bleeding\(^{26}\) as with severe vWD, can be given. Antiplatelet agents should be stopped if bleeding occurs. Also, factor VIII and vWF levels should be checked during the ACS if available in the hospital, as well as after 4-6 weeks to guide long-term antiplatelet therapy with hematological consultation. Close outpatient follow-up and patient education are necessary.

### Summary

ACS occurs rarely in vWD patients, but presents a therapeutic challenge. The rare occurrence of vWD and ACS together makes it difficult to develop evidence-based guidelines based on clinical trials for such patients. In this article, we describe the case of a patient with vWD undergoing elective PCI and periprocedural management. There are a few case reports of myocardial infarction in vWD patients treated with antiplatelet and antithrombotic therapy without significant bleeding complications. Antiplatelet and antithrombotic therapy can be given in most vWD cases presenting with ACS. Long-term management of these patients requires a systematic approach, hematological consultation, vWF levels, platelet-vWF type, and antiplatelet therapy decisions in association with hematological consultation.

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**Figure 2.** Management proposal of acute coronary syndrome in vWD patients. *Clopidogrel load of 300-600 mg orally. "Femoral approach can be used if vWF level >30%; "Factor levels for antiplatelet therapy decisions in association with hematological consultation.*
patient education, and close outpatient follow-up. There are currently no definite recommendations or guidelines for use of antiplatelet therapy for primary and secondary prevention of ischemic heart disease in patients with vWD.

References


