Coronary interventions in patients with bleeding and bleeding tendency

Thach Nguyen, Lan Nguyen

Corresponding author: Dr. Thach Nguyen, MD, St. Mary Medical Center, 1500 South Lake Park Ave, Hobart IN 46342, USA. E-mail: thach@jgcard.com

In general, percutaneous coronary intervention (PCI) is contra-indicated in patients with bleeding and those that are easy to bleed because during PCI the patients need full anticoagulation to counter any thrombotic formation caused by introduction and manipulation of devices in the vascular system. The patients who currently bleed may not tolerate any short term anticoagulant effect. The patients who are easy to bleed may have annoying and prolonged bleeds especially at the surgical or vascular access site while on long term antiplatelet drugs such as clopidogrel or aspirin (ASA). These patients in critical situations such as acute myocardial infarction (AMI) or unstable angina may need to undergo PCI, in spite of the fact that the operators have difficulty in predicting the risk of or controlling further bleeding before or during PCI. Any patients whose bleeding cannot be controlled after PCI should not undergo PCI because they will succumb from hemorrhagic shock. These patients are listed in Table 1.

There are many options for reperfusion of the infarct-related artery (IRA) in AMI patients with bleeding. These options differ or complement each other. Their benefits and risks, advantages and disadvantages will be presented and discussed (Table 2).

Angioplasty alone without stenting

In general, PCI is contra-indicated for patients with bleeding or bleeding diathesis because full anticoagulation is needed during PCI. However, if the risk of mortality from AMI is higher than the risk of complications from bleeding during PCI, then the AMI patient should undergo percutaneous transluminal coronary angioplasty (PTCA) with or without stenting in the IRA. The benefits and risks of PTCA alone without stenting are highlighted in the case study below.

Case study: Angioplasty without stenting for AMI patients with recurrent gastro-intestinal bleeding

An elderly patient with AMI was admitted with chest pain and mild hematemesis. The electrocardiogram (ECG) showed ST segment elevation. The gastroenterologist refused to do gastroscopy because of ongoing AMI. As the risk of mortality from AMI is estimated to be higher than the risk of complications from further bleeding, the patient successfully underwent PTCA of the IRA with a single bolus dose of unfractionated heparin (UFH) and ASA. After PTCA, the condition of the patient was more stabilized, so the patient could undergo successfully gastroscopy for ligation of the bleeding artery with a Hemoclip device (Medtronic, Natick, MA). Because the patient had only PTCA, the patient was given ASA, without UFH and clopidogrel after the procedure.

The practical implication is that when a patient has bleeding problems with prolonged anticoagulant or antiplatelet therapy, the patient should undergo PTCA without stenting. After the procedure, only ASA (without clopidogrel) is needed. This is the most appropriate strategy for AMI patients with 1) recurrent and active bleeding, 2) after recent surgery or 3) after an ischemic stroke. However how long the beneficial effect of an open IRA by PTCA alone last? What is the main concern in the short term for AMI patient undergoing PTCA without stenting?

Re-occlusion for AMI patients undergoing PTCA

The main concern for AMI patients undergoing only PTCA without stenting is re-occlusion. This question was asked in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. In this trial, 2,082 patients who had AMI were randomized in a 2 × 2 factorial design to primary stenting or to balloon angioplasty, each with and without abciximab. At a median of 2 days (range 0 to 23), early re-occlusion occurred in 0.5% of patients who had been randomized to undergo stenting versus 1.4% of those who underwent PTCA alone (P = 0.04). So after PTCA, these patients should be followed-up closely for early re-occlusion because they require and benefit from repeat PTCA. Complex baseline lesion morphology and small vessel size are angiographic predictors of early re-occlusion for the patient undergoing only PTCA without stenting. ¹

PTCA alone for AMI patients after recent surgery

Besides for the patient with bleeding, the strategy of

1 PTCA alone for AMI patients after recent surgery

Corresponding author: Dr. Thach Nguyen, MD, St. Mary Medical Center, 1500 South Lake Park Ave, Hobart IN 46342, USA. E-mail: thach@jgcard.com
PTCA alone without stenting could be also applied for patients in whom AMI happens after a recent surgical procedure. The proximity of the surgery to PCI placed this patient at high risk for hemorrhagic complications at the operative site.

Case study: PCI for AMI patient after recent surgery
A patient underwent knee surgery. One hour later, while the patient was in the recovery room, the patient complained of chest pain. An ECG showed ST elevation in V leads. An emergency coronary angiography showed complete occlusion of the left anterior descending artery (LAD). The patient was then given an initial 0.75 mg/kg bolus of bivalirudin, a direct thrombin inhibitor (DTI), followed by a 1.75 mg/kg/h infusion and underwent a successful PCI with ASA and clopidogrel.

This case study raises 2 questions: 1) Do all the patients benefit from PCI for AMI which happens after a surgical procedure? 2) Do these patients have less local and intra-cranial bleeding with UFH or with DTI?

Benefit and risks of PCI for AMI patients after a recent surgery Between 1990 and 1998, 48 consecutive patients at Mayo Clinics underwent emergent coronary angiography and interventions due to AMI within 7 days after a non-cardiac surgery. The types of surgery included intra-abdominal, orthopedic, vascular, urologic, and neurologic procedures. Shock was present in 21 patients, and cardiac arrest occurred in 12 before angiography. Of the 41 patients who underwent angioplasty, the procedure was successful in 30 patients. None had bleeding at the surgical site in the catheterization laboratory. Thirty-one patients (65%) survived to be discharged. Of the 21 patients with shock before catheterization, 11 survived. Nine of 12 patients with cardiac arrest before angiography survived. Although 9 patients required red blood cell transfusion, only 1 developed bleeding at the surgical site requiring treatment. Survival of 11 of 21 patients with profound cardiogenic shock is encouraging when compared with the outcome of patients receiving reperfusion therapy in the SHOCK trial.

Steps to minimize bleeding at the surgical site, including weight adjustment of UFH or DTI, should be taken to decrease risk. Between UFH and DTI, which one causes less bleeding?

UFH vs. DTI for PCI in AMI patients At this present time, the risks of any anticoagulation by UFH or bivalirudin, or of antiplatelet agents such as ASA or clopidogrel, for AMI patients after a recent non-cardiac surgery, an ischemic stroke or with gastrointestinal bleed are clearly not quantifiable from the scarce data available in the literature. For these patients, only anecdotal reports showed that bivalirudin and clopidogrel in the immediate post-operative period did not impose an increased risk of bleeding. The understandings and rationale of treatment in these cases are translated from data of patients in large clinical trials in which the majority of high risk patients were excluded. In the REPLACE-2 trial of patients undergoing PCI without high-risk features, bivalirudin, a hirudin analog, was tested against UFH and a
glycoprotein (GP) IIb/IIIa inhibitor. The primary end point at 30 days included major bleeding plus the usual end points of death, MI, and urgent revascularization. These events occurred in 9.2% of the bivalirudin group and 10% of the group given UFH plus GP IIb/IIIa inhibitors (P >0.05). The secondary end point was freedom from death, MI, and urgent revascularization and occurred in 7.6% of the bivalirudin group and 7.1% of the group given UFH plus GP IIb/IIIa inhibitors (also P >0.05), but bleeding (combined major and moderate bleeding) was significantly reduced in the bivalirudin group (from 7.1% to 2.4%, P <0.001). 5 So the rationale of using bivalirudin as antithrombotic is because DTI was not inferior to UFH in clinical outcomes, while it caused less bleeding. Bivalirudin also has a rapid onset of action, a short 25-minute half-life and a predictable dose response that allowed for early sheath removal. 6

As PTCA alone could be done successfully with DTI without the need of long term clopidogrel, for AMI patients after recent surgery, does UFH or DTI provide a better outcome for PCI in AMI patient with recent stroke?

Concern of further bleeding by anticoagulant during PCI for AMI patients with recent stroke If the patient with recent ischemic stroke develops AMI, the patient could undergo PCI under coverage of short term anticoagulant (UFH or DTI) and long term oral antiplatelet drug. However there are two concerns: 1) The risk of hemorrhagic conversion of the ischemic stroke with anticoagulant therapy and 2) risk of cerebral emboli from the protruding plaque in the aortic arch if they were the cause of emboli stroke in the first place.

In the REPLACE 2 trial, AMI patients receiving bivalirudin did better than patients receiving UFH. However, no patients had recent stroke, so the questions of hemorrhagic conversion could not be definitively answered. 5 Because of the risk of intracranial bleed from single or double antiplatelet agents, placement of a DES or BMS should be avoided if possible. Both kinds of stent obligate the patient to take ASA and clopidogrel. An adequate PTCA result would have accomplished the acute goal of restoring flow to salvage the myocardium without the need for clopidogrel. The higher rate of restenosis associated with PTCA in comparison to stenting would have been less of an acute concern than the increased risk of bleeding associated with the addition of clopidogrel. 4 However, the 1.4% rate of early acute and subacute thrombosis at the PTCA site is a REAL great concern.

In the OASIS-6 trial, the goal was to evaluate the treatment with fondaparinux compared with control (UFH or placebo) among ST-elevation myocardial infarction (STEMI) patients. Patients were randomized to either fondaparinux (2.5 mg/day for up to 8 days or hospital discharge; n=6,036) or control (n=6,056). Patients were classified as Stratum 1, meaning UFH was not indicated, or Stratum 2, meaning UFH was indicated. Patients in Stratum 1 received fondaparinux or placebo; patients in Stratum 2 received fondaparinux or UFH. The primary endpoint of death or MI at 30 days was lower in the fondaparinux group compared with the control group (9.7% vs. 11.2%, hazard ratio [HR] 0.86, P =0.008). Among the components of the composite at 30 days, mortality was lower in the fondaparinux group (7.8% vs. 8.9%, HR 0.87, P =0.03), and reinfarction trended lower (2.5% vs. 3.0%, HR 0.81, P =0.06). Guiding catheter thrombosis in the primary PCI cohort occurred significantly more frequently with fondaparinux (n=22 vs. n=0, P <0.001), as did coronary complications (n=270 vs. n=225, P =0.04). There was no difference in severe bleeding at 9 days by treatment group (1.0% with fondaparinux vs. 1.3% with control, P =NS). Intracranial hemorrhage occurred in 0.2% in each group. Further investigations are needed to elucidate the effectiveness of fondaparinux in the subsets of AMI patients after recent surgery, stroke or having bleeding. 7

Even after successful PCI or only PTCA with UFH or DTI, with or without clopidogrel, the ideal scenario is still how PCI could be done without anticoagulation or without the concern of short or long term complications from UFH or DTI. Are there any reliable data addressing this question?

**PCI without anticoagulant**

In some patients with AMI or with bleeding tendency (after recent surgery), even a short term anticoagulant could cause bleeding with long term sequelae. These patients could benefit from a new stent coated with GP IIb/IIIa inhibitor. This strategy was verified in the ReoPro-coated stent trial. In this prospective randomized trial comparing the outcomes of 96 patients with AMI treated with abciximab (ReoPro)-coated stents (n=48) and DES (control, n=48). PCI was performed by standard technique without UFH in group 1 and with UFH as usual in group 2. The results showed that after PCI, one patient in group 2 had reinfarction and target lesion reintervention during the hospital stay. No AMI was seen in group 1. A year later, two patients in group 2 (4.1%) had AMI, whereas no patient in group 1 suffered AMI. So abciximab-coated stent implantation was safe and effective in AMI patients without the need of an anticoagulant. 8

This strategy could be applied perfectly for patients with high risk of bleeding from even short term anticoagulation such as an AMI patient with recent surgery or a concurrent or recent stroke.

Besides the typical cases of AMI patients with bleeding or bleeding diathesis, there are many other complex, complicated non-cardiac conditions on top of the bleeding problems which need to be solved before, during or after PCI. The general strategy is to have temporary control of the bleeding so PCI for AMI could proceed. Once the IRA is recanalized and the patient general condition improves then the cause of bleeding could be definitively corrected.

**Comprehensive angioplasty and stenting for AMI patients who need subsequent surgery**

**Case study: Angioplasty and stenting of AMI patients**
with bleeding and need for subsequent surgery An elderly patient had AMI when driving a car. The patient lost control of his car and hit the incoming one on the opposite lane. The patient suffered a fracture in the left femur and tibia with profuse bleeding. In the emergency room, the orthopedic surgeon applied a pressure dressing to stop the bleeding and splints to stabilize the fractured bones. Because of ongoing AMI, the patient could not undergo extensive surgery. The patient was brought to the cardiac catheterization laboratories and had a bilateral femoral angiogram. The results showed no laceration in the arterial system. So the patient was prepared for PCI and underwent successfully angioplasty and stenting of the IRA under the cover of one bolus dose of UFH (5000 units) and clopidogrel. After PCI, the patient’s condition was stabilized enough to undergo definitive surgery for the fractured leg.

Rationale of the anticoagulation strategy For any patient with bleeding or bleeding tendencies, if there is no severe arterial bleeding or if the venous bleeding could be controlled by pressure dressings, then the patient can undergo coronary interventions. A diagnostic coronary angiogram would not require any anticoagulation. The preferred anticoagulant for PCI is UFH because its short half life (4 hours for a bolus dose of 5,000 units) and its effect can be reversed by protamine. ASA can be given without immediate worsening of bleeding. A 300-600mg bolus of clopidogrel is given after PCI and its effect does not start for at least 6 to 8 hours later. Its therapeutic effect (>80% of platelets blocked) does not reach its peak until 24 hours later. During the time window after the effect of UFH wears off and before the full therapeutic effect of clopidogrel starts, any surgery could be done with minimal concern of bleeding.

The strategy of using the window of low anticoagulation level during transition between UFH and clopidogrel was also applied in case of PCI followed by aortic valve replacement or carotid artery stenting followed by coronary bypass graft surgery (CABG). In case of aortic stenosis, if the elderly (>75 years of age) patients undergo aortic valve replacement (AVR) and CABG in the same session, their mortality was estimated to be very high (>20%). So the strategy was to perform PCI and right after, the patient would go for minimally invasive AVR. 9

Anemia and re-occlusion after PCI

As seen in previous cases, many AMI patients with bleeding benefit from PTCA with or without stenting, with or without ASA or clopidogrel, with UFH or DTI, who are the patients who cannot tolerate PCI?

Case study: Risk of re-occlusion after transfusion for patient just undergoing PCI A patient with AMI was treated with tenecteplase. The patient underwent successful rescue PCI of the right coronary artery (RCA). Due to a history of chronic anemia, the patient was pre-treated with aspirin and clopidogrel. After PCI, the patient was found to have persistent significant anemia (hemoglobin 6.5 mg/dl). Therefore, two units of blood were transfused with substantial increase of hemoglobin levels (up to 10.1 mg/dl). Nine hours later, the patient developed chest pain and ST elevation in leads 2, 3, and aVF. Emergency angiogram showed re-occlusion of the RCA stent. In order to reduce the risk of stent re-thrombosis, the patient received abciximab infusion and 300 mg of clopidogrel at the time of repeat PCI. 10

Stent thrombosis after blood transfusion Does blood transfusion carry increased risk of stent thrombosis? Acute and subacute stent thrombosis is a hard-to-predict complication of PCI. Anemia, i.e., with the decrease in hematic concentration of antiplatelet agents, and a blood transfusion, i.e., with the administration of fully functioning platelets, may act synergistically to increase the risk of stent thrombosis. The risk for stent thrombosis is the highest in the first 14 days after insertion, particularly in the first 96 hours, and decreases thereafter. 11 With the latest data in the literature, bleeding after PCI is really a reliable marker of long term higher mortality. The patient who gets transfusion also has higher mortality and morbidity. One best option is to stent the patient with a Reopro-coated stent, if it is commercially available. However, the best management in this present time is to administer a second ‘load’ of clopidogrel at the time of blood transfusion in anemic patients with recent PCI regardless of their hemorrhagic risk. 11

Practical management

In general, the principle is that PCI can be performed if any bleeding can be stopped before, during and mainly after PCI. The patient also needs to tolerate 4 hours of anticoagulant without excessive further bleeding during PCI. If the bleeding cannot be stopped after PCI, then PCI is contra-indicated. If the patient needs surgery after PCI, then the appropriate time window is between the end of the effect of UFH and before the full effect of clopidogrel. If there is concern about long term effect of clopidogrel, then PTCA without stenting is the best option. If there is a Reopro-coated stent available then this is the best scenario for patients who need PCI without anticoagulant. The advantages and disadvantages of each option are highlighted in Table 3. So in real life, each option should be selected according to the specific clinical requirement for a best expected outcome.

Angioplasty and stenting for patients on warfarin

During PCI for a patient taking warfarin, coronary angiography, angioplasty and stenting can be performed in the usual fashion. Care is taken to access the femoral artery below the inguinal ligament and above the inferior margin of the femoral head while avoiding posterior wall puncture. When PCI is needed, an activated clotting time (ACT) should be measured before and after the administration of UFH. Target ACT is ≥ 300 sec. Patients can receive ASA and
Table 3. Advantages and disadvantages of PCI for patients with bleeding or bleeding tendency

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>Best long term results</td>
<td>Need UFH, ASA, clopidogrel</td>
</tr>
<tr>
<td>BMS</td>
<td>No UFH after CPI</td>
<td>1 month clopidogrel, ASA forever</td>
</tr>
<tr>
<td>Only PTCA</td>
<td>No UFH after PCI</td>
<td>Re-occlusion rate of 1.4%</td>
</tr>
<tr>
<td>Reopro-coated stent</td>
<td>No need of UFH</td>
<td>1 month of clopidogrel, ISR same as BMS</td>
</tr>
<tr>
<td>UFH</td>
<td>Short ½ life, can be reversed</td>
<td>Uncertain pharmacokinetic</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Short ½ life</td>
<td>Cannot be reversed</td>
</tr>
</tbody>
</table>

clopidogrel as usual. Hemostasis by vascular closure device is preferred because only a platelet plug is formed to stop the bleeding at the vascular access site when the sheath is removed and manual pressure is held. Cardiac catheterization and PCI without interrupting warfarin is beneficial for patients at high risk for thrombotic and embolic complications such as those with prosthetic mechanical valves in the mitral position or those with a history of a recent embolic event. 12

Does aspirin and thienopyridine cause more bleeding for patients on warfarin after PCI? The main complication of oral anticoagulant therapy is bleeding, and the risk is related to the intensity of anticoagulation. In a meta-analysis, the relationship between international normalized index (INR) and major bleeding events was assessed; an INR > 3, compared with an INR ≤ 3, was associated with an odds ratio for bleeding events of 3.21 (95% CI, 1.24-8.28). 13 The Atrial Fibrillation, Aspirin, Anticoagulation Study 14 reported major bleeding annual rates of 1.1% during treatment with aspirin and adjusted-dose warfarin. Increasing INR value was an independent risk factor for bleeding complications. The Aspirin and Coumadin After Acute Coronary Syndromes study 15 demonstrated that by using a low-intensity warfarin regimen (INR 2.0-2.5) and aspirin, there was an increase only in minor, but not major, bleeding complications compared to aspirin-treated patients. In contrast, the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting trial after Intracoronary Stenting trial, comparing antiplatelet with anticoagulant treatment in high-risk patients, aimed for a target INR of 2.5-3, and reported a higher incidence of bleeding complications with anticoagulation treatment. 16 So short-term triple therapy after PCI was not associated with prohibitively high bleeding complication rates, and thus should be favorably considered in patients with a clear indication for warfarin and clopidogrel. 17

PCI for patients with thrombocytopenia

Thrombocytopenia is any disorder in which there are not enough platelets and it is sometimes associated with abnormal bleeding. Three major causes of low platelets are 1) low production of platelets in the bone marrow, 2) decreased breakdown of platelets in the bloodstream (intravascular), 3) increased breakdown of platelets in the spleen or liver (extravascular). Disorders that involve low production in the bone marrow include aplastic anemia, cancer in the bone marrow, infections in the bone marrow (rare), and drugs (very rare). Disorders that involve the breakdown of platelets include immune thrombocytopenic purpura (ITP), drug-induced immune thrombocytopenia, drug-induced nonimmune thrombocytopenia, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation (DIC). The breakdown of platelets by the spleen is called hypersplenism. 18

Catheterization in patients with thrombocytopenia due to liver disease In a study by Vaitkus et al., an acceptably low risk of bleeding related to diagnostic cardiac catheterization in patients with advanced liver failure associated with thrombocytopenia and coagulopathy was demonstrated. Infusion of blood products is largely unnecessary in the pursuit of adequate hemostasis. The vast majority of patients in this study did not receive antecedent platelet or plasma infusions and nevertheless did not experience bleeding. So with appropriately careful technique during vascular access, cardiac catheterization can be safely performed in patients with severe liver disease despite significant thrombocytopenia and coagulopathy. Adjunctive blood product transfusions are not necessary in the majority of cases. 19

PCI in patients with thrombocytopenia If a patient has mild symptom of thrombocytopenia, PCI can be performed with close follow-up of the platelet level and complications.

Case study: PCI in a patient with thrombocytopenia due to myelodysplastic syndrome An old patient presented with unstable angina. Admission laboratories results showed severe thrombocytopenia (platelet count of 47×10^9/L). Diagnostic angiography showed a severe lesion in the mid-LAD. To minimize the risk of bleeding, PCI was performed
with bivalirudin, instead of UFH. Clopidogrel (300 mg) and ASA (365 mg) were given 2 hours before the procedure. He was given an intravenous (IV) bolus of bivalirudin followed by a maintenance infusion for the duration of the procedure. Baseline ACT was 120 seconds. Five minutes after the bivalirudin bolus and infusion, the ACT was 365 seconds. PCI was performed successfully in the mid-LAD without bleeding complication.

In patients with more severe symptoms of thrombocytopenia, PCI can still be performed under coverage of UFH or DTI. The oral antiplatelet agents (ASA or clopidogrel) can be given and empirically withheld when there is complication from low platelet level. In this situation, DES stenting is not favored because of uncertainty of long term complication profile with clopidogrel.

Case study: PCI in a patient with thrombocytopenia due to myelodysplastic syndrome A patient with history of spontaneous gingival hemorrhage and petechiae came with chest pain. The platelet level was 20 x 10^9/L. The patient underwent a bone marrow biopsy which confirmed the diagnosis of myelodysplastic syndrome involving both granulocytic and megakaryocytic series, with preservation of the erythroid series. The patient was then medicated with folic acid, pyridoxin, and cyanocobalamin. The number of platelets was maintained at approximately 40 x 10^9/L, and no further hemorrhagic events were observed. Coagulogram results were within normal limits: INR was 1.09 (normal range = 0.90-1.26), and the activated partial thromboplastin time (APTT) was 28 seconds (normal range 5-25 seconds). The patient underwent coronary angiography 2 hours after transfusion of 10 units of platelets. The result showed an obstruction of 80% in the RCA ostium. Six days later, after 75 mg/day of clopidogrel and 2 hours after new transfusion of 10 units of platelets, the patient underwent successful stenting of the RCA ostium with 6,000 units of UFH. The result showed an obstructed diffuse petechiae and a spontaneous nose bleed at a site of the previous LCX angioplasty. Two bare metal stents were deployed. There was no excessive bleeding during or after the procedure and the patient had prompt relief of symptoms. Three weeks later, the patient developed diffuse petechiae and a spontaneous nose bleed at a time when his platelet count had decreased to 84 x 10^9/L. Clopidogrel was discontinued and aspirin held for 4 days. Since that time, he has had no further bleeding problems and continues on aspirin (81 mg q.d.). His platelet count is 79 x 10^9/L. PCI in a patient with ITP presents a unique situation in which platelet function needs to be inhibited sufficiently to perform PCI safely but not to the extent that bleeding complications result. 21

Cutting balloon was selected because there is no need for long term clopidogrel after PCI. Stent is not favored as initial therapy because of the risk of subacute stent thrombosis in a patient in whom it was unknown whether he would be tolerant of ASA plus clopidogrel therapy. 21

PCI for patients with hemophilia B

Hemophilia B is a severe inherited coagulopathy caused by mutations in the gene that encodes factor IX. Surgical and invasive procedures in patients suffering from this congenital disease are to be considered as being at high risk of bleeding. Regularly, the patient with hemophilia was administered recombinant factor VIII pre- and post-procedure to maintain activity levels between 60-80% in order to prevent bleeding. When a patient with hemophilia B had AMI undergoing PCI, anticoagulation was maintained with a direct thrombin inhibitor, bivalirudin, a thrombin-specific anticoagulant. There were no complications. Bivalirudin can be safely used in patients with hemophilia B undergoing PCI. 22

PCI for patients with hemophilia A
Hemophilia A is a sex-linked genetic bleeding disorder resulting in deficiency of plasma factor VIII coagulant activity. Patients with severe hemophilia A have factor VIII levels of about 1% of normal and tend to bleed frequently on minimal or unrecognized trauma, especially into joints or muscle or less frequently intracerebrally. Modern management of hemophilia A includes safe and early treatment of bleeding and prophylactic use of factor VIII concentrate in prevention of bleeding. Major surgery may be performed quite safely in hemophilic patients if hemostasis is achieved by transfusion of factor VIII, with the aim of achieving a target concentration of 100% factor VIII activity during the perioperative period.

Whether factor VIII transfusions are pro-atherogenic remains to be investigated. There are however, case reports of patients having AMI after receiving factor VIII transfusions. To avoid excess bleeding during surgery in patients with hemophilia type A, administration of factor VIII is necessary. However, since factor VIII is an important component of clot formation and high factor VIII activity has been identified as a risk factor for thrombosis, effective, reliable anticoagulation is also required during PCI.

Case report: PCI in patients with hemophilia A A 64-year-old white male with a medical history of severe hemophilia A (factor VIII-dependent) presented with acute non-ST elevation MI. After appropriate hematology consultation and prior to cardiac catheterization, the patient was administered 4,500 Units of factor VIII to maintain factor VIII activity around 100%. For PCI, the patient was anticoagulated with 11.3 cc bolus of bivalirudin (5 mg/ml) via peripheral IV followed by 1.78 cc bivalirudin (5 mg/ml) infusion. Coronary angioplasty of the LAD was performed successfully.

**PCI for patients with von Willebrand disease**

von Willebrand factor (vWF) is a large glycoprotein encoded on chromosome 12 produced by vascular endothelial cells and megakaryocytes. It is also contained in alpha granules within the platelets and plays a crucial role in the formation of a platelet plug at sites of endothelial damage. It binds to exposed collagen-containing subendothelium and forms a bridge between the subendothelium and platelets, allowing platelet adhesion. Platelet aggregation is also partly mediated by vWF, as it binds to platelets via the Ib/IX/V and IIb/IIIa GP complexes.

vWF stabilizes the circulating procoagulant factor VIII by forming a noncovalent complex with it. Factor VIII is an essential cofactor in the activation of factor X, leading ultimately to the formation of thrombin and fibrin.

von Willebrand disease (vWD) affects approximately 1% of the US population and is the most common congenital bleeding disorder. It is subdivided into three types. The majority of cases are type I (75%), which is inherited in an autosomal-dominant fashion. A mutation at the vWF gene on chromosome 12 impairs the export of vWF out of storage organelles, thus resulting in a reduction in circulating levels of vWF. This slows platelet plug formation and reduces circulating levels of Factor VIII (which rapidly degrades in the absence of vWF). Typical clinical manifestations include epistaxis, menorrhagia and difficult hemostasis following surgery. Type II vWD is caused by the production of flawed vWF due to point, insertion or missense mutations. A moderate bleeding risk results and there are several subtypes. A major gene deletion causing a complete lack of vWF results in a severe bleeding tendency (Type III).

**Clinical manifestations**
The clinical manifestations of vWD vary from features secondary to platelet dysfunction or factor VIII deficiency, according to the clinical subtype.

Typically, there is easy bruising and mucosal bleeding such as epistaxis and menorrhagia in milder forms of vWD. The latter may only occur associated with aspirin or nonsteroidal anti-inflammatory drug use or after minor surgery or dental extractions. In the most severe cases of vWD, such as in Types III and 2N there may be hemarthroses and hematomas secondary to the deficiency in factor VIII. Bleeding episodes in Type III are characterized by GI bleeding in 20%, hemorrhages in 37%, postoperative bleeding in 41%, muscle hematomas in 52%, menorrhagia in 69%, oral cavity bleeding in 70% and severe nosebleeds in 77%.

**Laboratory diagnosis**

Initial screening tests typically include bleeding time, platelet count and the APTT. The bleeding time is prolonged in severe forms of vWD but may be normal or minimally prolonged in the milder forms. The platelet count is decreased in type 2B. The APTT is prolonged in patients with vWD when Factor VIII levels are decreased. Normal values of the aforementioned test do not exclude vWD, especially in milder forms of the disease. Therefore, in patients with a bleeding history, especially with ASA associated bruising or when there is a family history of vWD, more specific tests that include vWF antigen (vWF: Ag), ristocetin cofactor activity, and factor VIII coagulant activity tests may be required to confirm or exclude the diagnosis. Plasma vWF:Ag levels and the immunoreactive proteins are decreased in Type I. The binding activity between vWF and platelet glycoprotein Ib is assessed via the ristocetin activity assay. Levels are decreased in types 2A and 2M. Factor VIII activity levels usually parallel vWF: Ag. There are also assays to assess the multimeric pattern of vWF protein but usually these are not necessary to make the diagnosis.

**Replacement therapy**

Humate-P, an intermediate purity concentrate, is currently available for treatment. Typically 1 IU/kg of humate-P will increase plasma VIII:c levels by 2 U/dl.

Very high plasma VIII:c levels (> 200%) have been associated with deep venous thromboses post surgery in some rare instances. Monitoring bleeding time is not necessary since no laboratory test accurately predicts hemostatic
response. In general, there is agreement that the goal of therapy is to maintain ristocetin cofactor levels between 50-100% with replacement therapy for a period of 3-10 days following major surgery and less following percutaneous procedures. The length of time required post catheterization has not been studied and there are no evidence-based guidelines. Platelet transfusions may also be required to achieve hemostasis in cases where bleeding is not corrected by the preceding pharmacologic maneuvers and in severe cases of type III vWD.

**Treatment of acute coronary syndromes** ASA is standard therapy in acute coronary syndromes (ACS). This has safely been administered and described in case reports documenting various approaches to management of ACS in patients with vWD. Thrombolytic therapy has been administered in the case of vWD and an ST elevation MI, but was associated with a significant decrease in hemoglobin requiring transfusion. Successful PCI was reported without the use of anticoagulation in a patient with Type I vWD. A 70-year-old female with a history of menorrhagia and recurrent epistaxis presented with an acute inferior MI. ASA was administered. Cardiac catheterization was performed and right coronary artery angioplasty, without stent placement, was performed without preprocedural heparin. In this patient, factor VIII levels were 137 IU/dl (range 50-200 IU/dl), vWF: Ag was 40 IU/dl (50-200 IU/dl), and vWF activity was 51 IU/dl (50-200 IU/dl). There were no bleeding complications. Others have noted the safe use of full antithrombotic and antplatelet therapy in a patient with vWD and an anterior infarct and ventricular fibrillation arrest. Arjomand et al. reported their experience in performing primary PCI with the deployment of a bare metal stent and the use of full anticoagulation with heparin to maintain an ACT greater than 300 seconds. Glycoprotein IIb/IIIa therapy with tirofiban was also administered during the procedure and continued for 24 hours after the procedure. Tirofiban was chosen secondary to its shorter half life as compared with other GP IIb/IIIa inhibitors. The patient was also treated with aspirin and clopidogrel. The patient’s Factor VIII activity level was 82 percent (normal 50-100 percent) and vWF antigen was 74 percent (normal greater than 50 percent). There were no bleeding complications.

**PCI in patients with von Willebrand disease** For elective procedures, most patients with vWD do not present a significant risk of bleeding and require no prophylactic pharmacologic replacement therapy, especially if they have Type I disease and their ristocetin cofactor levels are more than 50% of normal. If the ristocetin cofactor level is less than 50%, patients should receive weight-adjusted doses of factor VIII-vWF prior to and after the procedure to maintain their cofactor levels more than 50% of normal. This overall approach should be modulated by any prior history of spontaneous mucosal bleeding or excessive bleeding with any prior procedure. All patients who come to the cardiac catheterization laboratory have baseline coagulation studies performed. In addition, specific questions should be a routine part of the pre-procedure evaluation to assess a history of bleeding in all patients and their first degree relatives since vWD can be present even with normal aPTT and bleeding times. Although bleeding time is not generally a part of the routine screening process, it probably should be done in anyone with a positive or suggestive history. For patients who present with ACS there are a number of options to help decrease the risk of bleeding. The data suggest the use of aspirin, UDH or DTI with the adjunctive use of short-acting glycoprotein IIb/IIIa inhibitors at the operator’s discretion based on the perceived risk for cardiac morbidity and mortality. In terms of catheterization approach, there may be some advantage to reduce the risk of bleeding that favors the radial compared to the femoral approach. Caution in sheath management with early sheath removal may also decrease bleeding complications. Finally, Factor VIII-vWF can be administered prophylactically in patients with an increased risk of significant clinical bleeding or in the treatment of peri- or post-procedural bleeding. For patients with Type I vWD, long-term management of the patients post percutaneous revascularization with aspirin and clopidogrel should continue with careful monitoring and clear instructions for immediate follow-up at the first sign of any mucosal bleeding. For patients with other subtypes, individual decisions in consultation with a hematologist is necessary to tailor the type of revascularization (balloon alone, BMS, PES) for the patient.

**References**


