In-stent Restenosis of a Bare Metal Stent in a Patient with Hemophilia A

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BACKGROUND

- Hemophilia A: factor VIII deficiency
- X-linked recessive or spontaneous mutations
- Patients with hemophilia (PWH) generally have a higher risk of bleeding but still need coronary intervention followed by effective dual antiplatelet therapy (DAPT) in acute coronary syndrome (ACS)
- Variable risk for bleeding based on extent of factor deficiency
- Mild (5-40% activity), moderate (1-5% activity), severe (<1% activity)
- Challenges involve antithrombotic management, antiplatelet therapy, and stent choice; further complicated by the severity of hemophilia and the presence of alloantibody inhibitors
- Limited evidence-based guidelines on treatment of PWH who present with ACS or those who are candidates for elective percutaneous coronary intervention (PCI)

CASE

55-year-old male with mild Hemophilia A, HTN, and 60-pack-year smoking history → Presented to the ED with chest pain and dyspnea for 2 months → Precordial T-wave inversions and negative troponins → Pharmacological nuclear stress test (+) for anterolateral wall ischemia

Recombinant factor VIII (2,862U) → 99% m-LAD lesion on coronary angiography → Bare metal stent to m-LAD → Aspirin 81 mg, Clopidogrel 75 mg, Lisinopril 5 mg, Atorvastatin 40 mg

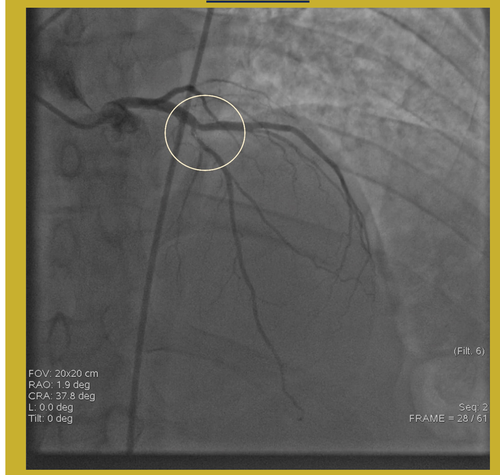
Patient stopped DAPT 3 months later due to superficial bleeding → 14 months later presents with chest pain and DOE → Pharmacological nuclear stress test (+) for anteroseptal ischemia at outside hospital

DECISION MAKING

- Patient had baseline 8-10% factor VIII activity
- Given recombinant factor VIII replacement with peak target of 80% activity level prior to further management
- Patient received unfractionated heparin per standard protocol
- Coronary angiogram showed 99% in-stent restenosis of the bare metal stent (BMS) (2.5 mm x 15 mm) in the mid-left anterior descending (LAD) artery (Figure 1)
- PCI with a second generation Zotarolimus drug-eluting stent (DES) (2.5 mm x 18 mm) post dilated to 2.78 mm (Figure 2)
- Loaded with aspirin 324 mg and clopidogrel 300 mg, then initiated aspirin 81 mg daily and clopidogrel 75 mg daily
- After 10 months, patient reported no angina and improved exercise tolerance

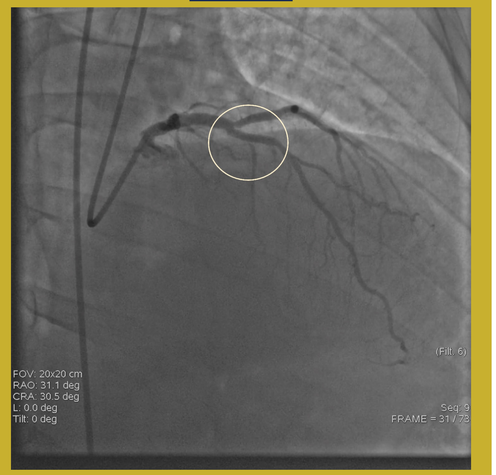
RUTGERS

FIGURE 1



IN-STENT RESTENOSIS OF BMS IN M-LAD

FIGURE 2



PCI WITH 2ND GEN ZOTAROLIMUS DES POST-DILATED TO 2.78 MM

FIGURE 3

	First PCI	Second PCI	Recommendations
Initial management	Factor VIII given at 35u/kg with peak target 80% activity level prior to PCI		Factor VIII with target 80% activity level prior to PCI
Arterial access site	Radial	Femoral (radial vasospasm)	Radial
Stent choice	BMS (2.5 mm x 15 mm)	DES (2.5 mm x 18 mm)	DES
Antithrombotic therapy	Unfractionated heparin	Unfractionated heparin	Unfractionated heparin
Antiplatelet therapy	• Aspirin and clopidogrel load • DAPT x 3 months • Trough factor level of ≥30%	• Aspirin and clopidogrel load • DAPT continued • Trough factor level of ≥30%	• Aspirin and clopidogrel indefinitely as tolerated • Trough factor level goal ≥30%

FIGURE 4

	ZEUS	LEADERS FREE
Type of study	Randomized, single-blind	Randomized, double-blind
Number of enrolled participants	1,606	2,466
Study arms	Zotarolimus-eluting stent versus BMS	Polymer-free umirolimus-coated stent versus BMS
Inclusion criteria regarding PWH	Systemic conditions associated with increased bleeding risk	Hospital admission for bleeding in previous 12 months
Conclusions regarding primary outcomes	At 12 months, ZES superior to BMS with respect to MI, target vessel revascularization rate, and definite or probable stent thrombosis	At 390 days, polymer-free umirolimus-coated stent superior to BMS with respect to cumulative incidence of a composite of cardiac death, MI, or definite or probable stent thrombosis
Bleeding outcomes	No difference with the Bleeding Academic Research Consortium (BARC) classification	

DISCUSSION

Hemophilia for the Cardiologist

- PWH may appear to have a reduced risk of mortality from ischemic cardiovascular disease due to a deficiency in the coagulation cascade, but the number of deaths from this cause is increasing
- Largely thought to be due to increasing hemophilia treatment centers leading to increased life expectancies in PWH and age-related comorbidities such as atherosclerotic cardiovascular disease
- Factor VIII deficiency is not necessarily protective against the development of atherosclerosis
- Cross-sectional study of hemophilia cohort suggests that PWH may have a higher calculated 10-year risk for MI or stroke and may have similar cardiovascular disease risk factor profiles to patients without hemophilia

Management Overview

- Replacement factor therapy is the cornerstone for initial management with correction peak level of 80% for 48 hours and trough level of 30% during DAPT
- Bypassing agents for patients with alloantibody inhibitors, especially in patients with severe disease who receive frequent factor infusions
- Standard heparin protocol and radial access preferred
- General guidelines regarding DAPT duration can be used as initial benchmarks, but the duration of DAPT should be individualized while monitoring for symptoms of bleeding and in close coordination with a hematologist for the tracking of factor trough levels

Stent Choice

- Challenge due to limited data and variability in disease
- Risk for restenosis in PWH unknown and experts previously suggested that bleeding associated with prolonged DAPT outweighed any benefit a DES offered in terms of restenosis
- BMS were always preferred, and DES used only in special circumstances in patients with symptomatic restenosis, those considered high risk for restenosis, or mild disease due to higher baseline factor activity
- ZEUS and LEADERS FREE trials: Zotarolimus-eluting stents (ZES) and umirolimus-coated stents superior to BMS in high bleed-risk patients after a 1-month course of DAPT, and no difference in bleeding (Figure 4)
- Further studies needed but with refined techniques, contemporary DES may reduce risk of subsequent revascularization of BMS in PWH

TAKE HOME POINTS

1. **Contemporary DES** may provide more benefits than BMS in PWH.
2. Factor VIII **peak and trough levels** should be monitored both in the acute and outpatient settings while on DAPT and individualized accordingly.
3. **Risk factors for CAD** should be **aggressively managed** in PWH.

REFERENCES

1. Kulkarni R, Soucie JM. Pediatric hemophilia: a review. *Semin Thromb Hemost*. 2011;37(7):737-744.
2. Lim MY, Pruthi RK. Cardiovascular disease risk factors: prevalence and management in adult hemophilia patients. Blood Coagul Fibrinolysis. 2011;22(5):402-406.
3. Kulkarni R, Soucie JM, Evatt BL; Hemophilia Surveillance System Project Investigators. Prevalence and risk factors for heart disease among males with hemophilia. *Am J Hematol*. 2005;79(1):36-42.
4. Pocoski, J., Ma, A., Kessler, C. M., Boklage, S., & Humphries, T. J. (2014). Cardiovascular comorbidities are increased in U.S. patients with haemophilia A: a retrospective database analysis. *Haemophilia : the official journal of the World Federation of Hemophilia*, *20*(4), 472–478.
5. Fransen van de Putte, D. E., Fischer, K., Makris, M., Tait, R. C., Chowdary, P., Collins, P. W., Meijer, K., Roosendaal, G., Schutgens, R. E., & Mauser-Bunschoten, E. P. (2013). Unfavourable cardiovascular disease risk profiles in a cohort of Dutch and British haemophilia patients. Thrombosis and haemostasis, 109(1), 16–23.27.
6. Biere-Rafi S, Tuinenburg A, Haak BW, Peters M, Huijgen R, De GE, et al. Factor VIII deficiency does not protect against atherosclerosis. J Thromb Haemost 2012; **10**: 30–7.
7. Cayla G, Morange PE, Chambost H, Schved JF. Management of cardiovascular disease in haemophilia. *Thromb Res*. 2013;132(1):8-14.
8. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-e47.
9. Staritz, P.; de Moerloose, P.; Schutgens, R.; Dolan, G.; ADVANCE Working Group. Applicability of the European Society of Cardiology guidelines on management of acute coronary syndromes to people with haemophilia—An assessment by the ADVANCE Working Group. Haemophilia 2013, 19, 833–840.
10. Mannucci PM, Mauser-Bunschoten EP. cardiovascular disease in haemophilia patients: a contemporary issue. Haemophilia. 2010;16(suppl 3):58–66.
11. Fefer P, Gannot S, Lubetsky A, Martinowitz U, Matetzky S, Guetta V, Segev A. Percutaneous coronary intervention in patients with haemophilia presenting with acute coronary syndrome: an interventional dilemma: case series, review of the literature, and tips for management. J Thromb Thrombolysis. 2013 Feb;35(2):271-8.
12. Fogarty PF, Mancuso ME, Kasthuri R, et al. Presentation and management of acute coronary syndromes among adult persons with haemophilia: results of an international, retrospective, 10-year survey. Haemophilia. 2015;21(5):589-597.
13. Mannucci PM, Schutgens re, Santagostino e, et al. How I treat age-related morbidities in elderly persons with hemophilia. Blood. 2009;114:5256–5263.
14. Schutgens RE, Tuinenburg A, Roosendaal G, Guyomi SH, Mauser-Bunschoten EP. Treatment of ischaemic heart disease in haemophilia patients: an institutional guideline. *Haemophilia*. 2009;15(4):952-958.
15. Valgimigli M, Patialiakas A, Thury A, McFadden E, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Airoldi F, Ferlini M, Listro F, Dellavalle A, Vranckx P, Briguori C, ZEUS Investigators. *J Am Coll Cardiol. 2015 Mar 3; 65(8):805-815.*
16. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC, LEADERS FREE Investigators. *N Engl J Med. 2015 Nov 19; 373(21):2038-47.*
17. Ferraris VA, Boral LI, Cohen AJ, Smyth SS, White GC 2nd. Consensus review of the treatment of cardiovascular disease in people with hemophilia A and B. *Cardiol Rev*. 2015;23(2):53-68.
18. Jabbar, A. Y., Baydoun, H., Janbain, M., & Ferdinand, K. C. (2018). Current concepts in the management of stable ischemic heart disease and acute coronary syndrome in patients with hemophilia. *Annals of translational medicine*, *6*(15), 299.