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ORIGINAL STUDIES

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Coronary angiography with or without percutaneous coronary intervention in patients with hemophilia—Systematic review

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Abstract

Objectives: We aimed to summarize the evidence for periprocedural and long-term strategies to both minimize the bleeding risk and ensure sufficient anticoagulation and antiaggregation in hemophilia patients undergoing coronary angiography with or without percutaneous coronary interventions (PCI).

Background: Hemophilia patients undergoing coronary angiography and PCI are at risk of bleeding due to deficiency of the essential clotting factors VIII or IX combined with the need of peri-interventional anticoagulation and antiaggregation and dual antiplatelet therapy (DAPT) after PCI.

Methods: We report on a patient with moderate hemophilia B undergoing single-vessel PCI with administration of factor IX concentrate during the procedure and during the 1-month DAPT period. In addition, a systematic review of patients ($n = 54$, mean age 58 ± 10 years) with hemophilia A ($n = 45$, 83%) or B ($n = 9$, 17%) undergoing coronary angiography with or without PCI is presented.

Results: Peri-interventional factor substitution was performed in the majority (42 of 54, 78%) but not all patients. In 38 of 54 (70%) patients undergoing coronary angiography, PCI with balloon dilation ($n = 5$), bare metal ($n = 31$), or drug-eluting stents ($n = 2$) was performed. For PCI unfractioned heparin ($n = 24$), low molecular weight heparin ($n = 2$), bivalirudin ($n = 4$), or no periprocedural anticoagulation at all ($n = 8$) were used. PCI was successful in all cases. After stenting, the majority (28 of 33; 85%) was treated with DAPT (median duration 1 month). Major periprocedural bleeding episodes occurred in 3 of 54 (6%) patients. Bleeding during follow-up occurred in 11 of 54 (20%) patients.

Conclusions: Coronary angiography and PCI in patients with hemophilia are effective and safe when applying individualized measures to prevent bleeding.

KEYWORDS

anticoagulants/antithrombins, antiplatelet therapy, bleeding, coronary heart disease

1 | INTRODUCTION

Hemophilia A and B [deficiency of clotting factor VIII (FVIII) and IX (FIX) respectively] are rare, most often inherited coagulation disorders usually occurring in males leading to increased bleeding risk. Hemophilia A and B affect about 1 in 5,000 to 10,000 and 1 in 40,000 males at birth. Disease severity depends on the plasma concentrations of FVIII or FIX, where severe, moderate, and mild disease are characterized by plasma concentrations <1% activity of normal (<0.01 U/l; usually associated with spontaneous unprovoked bleeding episodes), 1–5% activity of normal (0.01–0.05 U/l), and 5–40% of normal (0.05–0.3 U/l) respectively [1,2]. Patients with moderate or mild disease typically present with bleeding after trauma or surgery. The main treatment principle in hemophilia patients is to substitute the missing clotting factor into the bloodstream during periods of increased bleeding risk or when bleeding occurs (on demand treatment). In severe

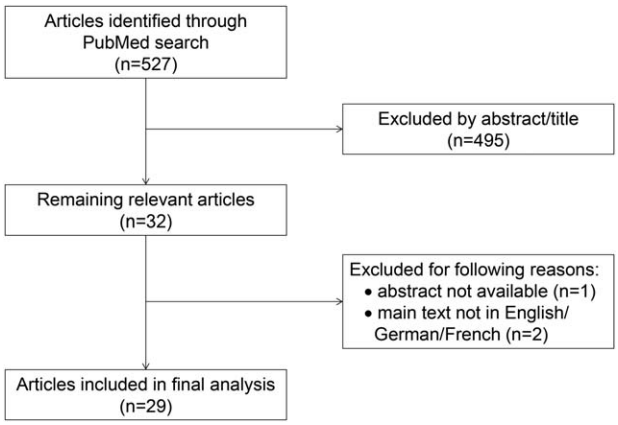

FIGURE 1 Flow chart showing the process of article search and selection

forms, clotting factors are injected on a regular schedule in order to prevent spontaneous bleeding episodes (continuous prophylaxis) [2]. Despite the presence of a significant coagulation disorder patients with hemophilia are neither protected from coronary artery disease (i.e., atherosclerosis) nor from myocardial infarction (i.e., coronary thrombosis) [3]. However, the management of patients with both hemophilia and coronary artery disease is complex since despite the presence of a coagulation disorder thrombocyte count and thrombocyte function are normal, and antiplatelet therapy is required, particularly after percutaneous coronary intervention (PCI). Hemophilia patients undergoing coronary angiography and PCI are at risk of bleeding during the periprocedural period but also during follow-up due to the combination of a natural clotting factor deficiency combined with the need of periinterventional anticoagulation and dual antiplatelet therapy (DAPT) after PCI [1,4,5]. Evidence and recommendation for periprocedural strategies during PCI in these patients is based on case reports and small case series [1,4–6]. In this article, we present an up-to-date systematic review of patients with hemophilia A or B undergoing coronary angiography with or without PCI.

2 | MATERIALS AND METHODS

First, an illustrative and so far unpublished case of a patient with moderate hemophilia B and stable coronary artery disease undergoing coronary angiography and PCI is presented. Second, a literature search to assess cases of hemophilia A or B as listed in PubMed using the key words "hemophilia" or "haemophilia" and "PCI," "coronary artery disease," "coronary intervention," or "myocardial infarction" was performed by two authors (C.B. and M.T.M.). Patients were included in the analysis if coronary angiography with or without PCI was performed in patients with an established diagnosis of hemophilia. Only reports with the main text in English, German, or French published until December 2016 were considered. The process of search and article selection is shown in Figure 1. Information for the present analysis was extracted from 29 articles (case reports and small case series) [5,7–34].

3 | RESULTS

3.1 | Case Report

A 70-year-old man with mild hemophilia B (residual FIX activity 5%) was referred for coronary angiography because of typical angina and a pathological bicycle exercise stress test. His cardiovascular risk factors included hypertension, dyslipidemia, and a previous smoking. He had not required regular FIX administration. Due to occasional FIX replacement the patient had a chronic hepatitis C infection. No major abnormalities were noted on his blood count and chemistry (hemoglobin level was 16 g/dl, platelet count of 221 G/l). Coronary angiography was performed using a right radial approach 15 min after administration of 4,800 IU (70 IU/kg) of plasma-derived FIX (Immunine, Baxalta Schweiz AG) leading to a FIX activity of 92%. After local anesthesia with lidocaine and insertion of a 6F introducer sheath 5,000 IU of unfractionated heparin (UFH) were administered. Coronary angiography revealed single-vessel disease with a subtotal stenosis of the large first marginal branch of the left circumflex artery (Figure 2A). After ad hoc discussion with the patient and the hematologist the decision was made to proceed with PCI. After intravenous administration of 500 mg acetylsalicylic acid (ASA) and additional 3,000 IU of UFH to achieve an activated clotting time >250 s PCI was performed using an EBU 6F guiding catheter. A bare metal stent (BMS; 2.5 × 9 mm; postdilation with a 2.75 ×8 noncompliant balloon) was implanted with a good angiographic result (Figure 2B). An oral loading dose of 300 mg of clopidogrel was administered immediately after the procedure. The sheath was removed from the radial artery, and hemostasis was achieved with the use of a TR Band (Terumo Interventional Systems, Leuven, Belgium). Twelve hours after the procedure 1,200 IU (17 IU/kg) of FIX were administered. There was only minimal hematoma at the radial access site on the day after PCI. The patient was discharged home on 100 mg ASA, 75 mg clopidogrel, and 40 mg atorvastatin. During the 1-month period of DAPT the patient received 2,400 IU (35 IU/kg) of FIX every second day. No bleeding complications occurred. After 1 month, the patient was free of angina, and clopidogrel was stopped. Given the

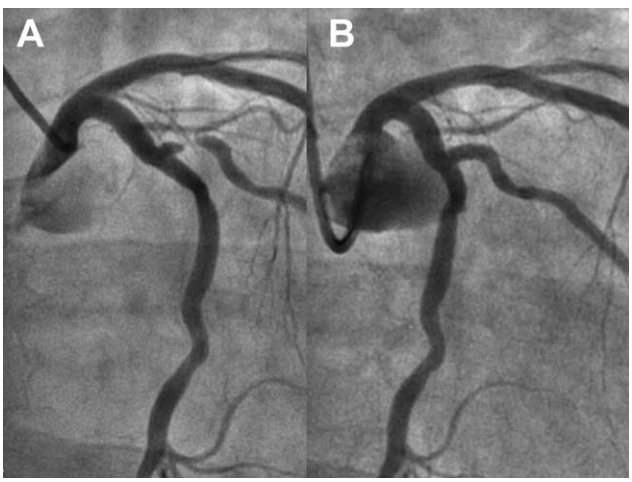

FIGURE 2 Coronary angiography (0°/0°) before (A) and after (B) percutaneous coronary intervention

patient's FIX activity of 5% and his reluctance to learn self-injection of factor concentrate, he did not receive further FIX substitution while on ASA monotherapy. Seven months later, the patient suffered from a tongue bite leading to a massive tongue and retropharyngeal hematoma. The episode resolved after intense FIX substitution concentrate and transient intubation due to airway obstruction. After that a prophylactic FIX replacement therapy was started [2,400 IU (35 IU/kg) of FIX concentrate twice weekly] while low-dose ASA was continued.

3.2 | Analysis of the Literature

We identified additional 53 cases fitting the inclusion criteria (Figure 1) [5,7–34]. Thus, the study population consisted of 54 male patients with a mean age of 58 ± 10 years. Another case of a patient with hemophilia A and anterior ST-segment-elevation myocardial infarction (STEMI) undergoing PCI of the occluded left anterior descending artery [35] was not included in the analysis as the report was not written in English and not enough details could be extracted. Hemophilia characteristics and management of each patient at the time of index procedure are described in Table 1.

3.3 | Patients

Hemophilia A was present in 45 of 54 patients (83%), 19 of 45 (42%) of whom had mild disease, 5 of 45 (11%) had moderate disease, and 20 of 45 (44%) had severe disease. For one patient with hemophilia A disease severity was not mentioned. Hemophila B was present in 9 of 54 patients (17%), 3 of 9 (33%) of whom had mild disease, 5 of 9 (56%) had moderate disease, and one patient (11%) had severe disease. The clinical presentation was STEMI in 14 of 54 (26%) patients, Non-ST-segment-elevation myocardial infarction (NSTEMI) in 11 of 54 (20%) patients, unstable angina in 16 of 54 (30%) patients, stable angina in 10 of 54 (19%) patients, and unknown in three patients. Percutaneous coronary intervention was performed in 38 of 54 (70%) patients, 8 of 54 (15%) patients were referred for coronary artery bypass grafting, and 8 of 54 (15%) patients were treated with medical therapy.

3.4 | Procedural Aspects of Coronary Angiography and PCI

Femoral access for coronary angiography was reported in 28 of 54 (52%) cases, radial access in 11 of 54 (20%) cases, and for the remaining 15 cases the access site was not reported and was not obvious from the angiographic images provided in the reports. Periprocedural factor substitution was performed in the majority (42 of 54, 78%) but in not all patients. Among the 38 patients undergoing PCI, plain balloon dilation ($n = 5$) or stenting ($n = 33$) was performed. In the majority of patients undergoing stenting BMS ($n = 31$, 94% of patients with stenting) were used. In only two patients, drug-eluting stents (DES) were implanted. For PCI periprocedural UFH was used in 24 of 38 (63%) patients, whereas low molecular weight heparin was used in two patients, and bivalirudin was used in four patients. In 8 of 38 (21%) patients no periprocedural anticoagulation at all was given. Factor supplementation was performed in 33 of 38 (87%) patients undergoing PCI. In four patients undergoing PCI for STEMI factor supplementation FVIII in three patients [32–34], recombinant factor VIIa in another patient with anti-FVIII antibodies [31] had precipitated STEMI. Glycoprotein inhibitor use (eptifibatide, abciximab) was reported in three cases [10,22,28].

3.5 | Postprocedural Treatment

Patients treated with balloon dilatation were treated with ASA monotherapy or no antiplatelet therapy at all. Patients undergoing stenting were treated with DAPT consisting of ASA and clopidogrel in most (28 of 33; 85%) but not all cases (Table 1). In some patients the information was not available, and thus it was assumed that they had no DAPT. However, it is likely that despite lack of information some of these patients received DAPT, particularly those treated with DES [20,21]. Thus, the number of patients treated with DAPT after PCI is probably underestimated. The median duration of DAPT was one month (interquartile range 1–6 months). Dual antiplatelet therapy was started after PCI in most cases, but there are also reports with DAPT including loading doses of clopidogrel before PCI [5,8,10,14,15,18,19]. We found one case of a patient treated with a loading dose of prasugrel [12], and two cases with loading doses of ticagrelor [5], but thereafter DAPT consisting of ASA and clopidogrel was used during follow-up. Factor substitution during the period of DAPT was performed in 21 of 28 (75%) patients.

3.6 | Procedural Outcomes

Good angiographic and clinical results were reported after all PCI procedures. In one patient not given any antiplatelet therapy before and during the procedure stent thrombosis occurred immediately after stent implantation which required the use of abciximab and UFH to achieve a good final result [23].

3.7 | Bleeding Complications During and After Coronary Angiography and PCI and During Follow-Up

Information on follow-up and complications is shown in Table 2. Median follow-up time was 12 (interquartile range 4–23) months. Bleeding was a rare periprocedural complication with only 3 of 54 (6%) patients with a major bleeding. Two patients had an excessive bleeding at the femoral access site [9,31], and in one patient with a previous trauma an intramuscular hemorrhage occurred [7] (Table 2). In 11 of 54 (20%) patients, bleedings were reported late after coronary angiography/PCI, the majority representing minor bleeds (Table 2). However, at least two patients (including the patient presented in the case report) experienced severe bleeding episodes months after PCI. Another patient with mild hemophilia A experienced excessive gastrointestinal bleeding during monotherapy with ASA requiring discontinuation [9]. In this patient no bleeding had occurred during the preceding 6 months of DAPT without prophylactic factor replacement.

TABLE 1 Clinical and procedural characteristics, bleeding prevention measures, and antithrombotic therapy in patients with hemophilia undergoing coronary angiography and percutaneous coronary intervention ($n = 54$)

Reference	Case	Hemophilia type and severity	Age (years)	Clinical presentation	Baseline factor level (%)	Baseline hemostatic regimen	Trough factor levels during PCI/FU	Antithrombotic management and factor substitution		Revascularization strategy	Access site	Access site management
								Peri-interventional	Follow-up			
Present case	1	B, moderate	70	Stable AP	FIX 5%	On demand	≥80%/DAPT: ≥10%, ASA mono: 4%	FIX boluses, ASA 500 mg, clopidogrel 300 mg, UFH 8,000 IU	DAPT: 1 month (ASA 100 mg, clopidogrel 75 mg); LT: ASA 100 mg	PCI (BMS): 1. Marginal branch (LCX)	Radial	Compression band
Chang et al., 2016 [7]	2	A, severe	56	Unstable AP	n.a.	On demand	>80% for 48 h; DAPT: initially 15%, after bleeding increased to 20%; LT: >1%	FVIII, ASA 300 mg, clopidogrel 300 mg, UFH 8,000 U	DAPT: 2 mo (ASA 100 mg, clopidogrel 75 mg); LT: ASA 100 mg; FVIII 3×/wk	PCI (BMS): middle and distal LCX, ostium of LAD, RCA and posterolateral branch	Radial	n.a.
Koklu et al., 2015 [8]	3	B, mild	41	NSTEMI	FIX 8%	FIX 1,000 IU 3×/wk	>70%/54% (d1), 49% (d2), 59% (d3)	FIX 3,500 IU, ASA 300 mg, clopidogrel 300 mg	DAPT: 1 mo (ASA, clopidogrel), FIX 1,000 IU d1–2, 500 IU d3, 1,000 U 3×/wk	PCI (BMS): Posterolateral branch (RCA)	Femoral	Manual compression
Fogarty et al., 2015 [9]	4	B, mild	66	Unstable AP	FIX 14%	On demand	n.a.	ASA	ASA	CABG	n.a.	n.a.
	5	A, mild	57	STEMI	FVIII 11%	On demand	n.a.	FVIII bolus and infusion, ASA	DAPT: 6 mo (ASA, clopidogrel), LT: ASA	PCI (BMS): Two-vessel disease, information on treated vessel n.a.	Femoral	n.a.
	6	A, moderate	68	STEMI	FVIII 2%	On demand	≥100%/n.a.	FVIII bolus and infusion ASA, UFH	DAPT: 6 mo (ASA, clopidogrel), LT: ASA, FVIII 3×/wk	PCI (BMS): Two-vessel disease, information on vessel n.a.	Femoral	n.a.
	7	A, mild	47	Unstable AP	FVIII 26%	On demand	n.a.	ASA	ASA	CABG	n.a.	n.a.
	8	A, moderate	62	Unstable AP	FVIII 3%	On demand	n.a.	None	none	CABG	n.a.	n.a.
	9	A, mild	48	NSTEMI	FVIII 20%	On demand	n.a.	ASA, LMWH	ASA	CABG	n.a.	n.a.
	10	A, severe	48	NSTEMI	FVIII <1%	On demand	n.a.	FVIII bolus and infusion, ASA, LMWH	DAPT: 6 wk (ASA, clopidogrel), LT: ASA, FVIII daily (6 wk)	PCI (BMS): Triple-vessel disease, information on vessel n.a.	Femoral	n.a.

(Continues)

TABLE 1 (Continued)

Reference	Case	Hemophilia type and severity	Age (years)	Clinical presentation	Baseline factor level (%)	Baseline hemostatic regimen	Trough factor levels during PCI/FU	Antithrombotic management and factor substitution		Revascularization strategy	Access site	Access site management
								Peri-interventional	Follow-up			
	11	A, severe	53	NSTEMI	FVIII <1%	On demand	≥80%/≥60%	FVIII boluses, ASA, UFH	ASA, FVIII 2×/wk	None	n.a.	n.a.
	12	A, severe	70	Unstable AP	FVIII <1%	On demand	≥80%/≥60%	FVIII boluses ASA, UFH	DAPT: 1 mo (ASA, clopidogrel), LT: ASA, FVIII 3×/wk (1 mo)	PCI (BMS): Two-vessel disease, information on vessel n.a.	Femoral	n.a.
	13	A, severe	53	NSTEMI	FVIII <1%	On demand	≥80%/≥60%	FVIII boluses, ASA, UFH	ASA, FVIII 2×/wk (for 2 mo), then 3×/wk due to bleeding	None	n.a.	n.a.
	14	B moderate	48	NSTEMI	FIX 2%	On demand	≥70%/≥30%	FIX boluses, ASA	ASA, FIX 2×/wk	None	n.a.	n.a.
	15	A, severe	38	STEMI	FVIII <1%	FVIII 3×/wk	≥70%/≥50%	FVIII boluses and infusion, ASA, UFH	DAPT: 12 mo (ASA, clopidogrel), LT: ASA, FVIII daily	PCI (DES): Two-vessel disease, information on vessel n.a.	Femoral	n.a.
	16	B, moderate	42	Unstable AP	FIX 3%	On demand	n.a.	FIX bolus, ASA	DAPT: 12 mo (ASA, clopidogrel), LT: ASA, FIX 2×/wk	PCI (BMS): information on vessel n.a.	Radial	n.a.
	17	A, severe	54	STEMI	FVIII <1%	On demand	n.a.	ASA, UFH	DAPT: 1 mo (ASA, clopidogrel), LT: ASA, FVIII every other day (1 mo)	PCI (BMS): information on vessel n.a.	Femoral	n.a.
	18	A, mild	65	Unstable AP	FVIII 16%	On demand	n.a.	ASA, DDAVP	ASA	CABG	n.a.	n.a.
	19	A, mild	72	NSTEMI	FVIII 10%	On demand	n.a.	FVIII boluses	ASA	CABG	n.a.	n.a.
Fefer e tal., 2013 [10]	20	A, severe	63	STEMI	FVIII <1%	FVIII 2,000 U 2×/wk	n.a.	FVIII 2,000 IU, ASA 300 mg, clopidogrel 600 mg, bivalirudin	DAPT: 9 mo (ASA, clopidogrel), LT: ASA, FVIII 1,000 IU 2×/d during hospital stay, followed by 1,000 IU 2×/wk	PCI (BMS): LCX	Radial	Compression band
	21	A, severe	52	Unstable AP	FVIII <1%	FVIII 1×/wk	n.a.	FVIII 2,000 IU, ASA, clopidogrel, UFH, glycoprotein IIb/IIIa inhibitor	DAPT: 3 mo (ASA, clopidogrel), LT: ASA, FVIII 1,000 IU 2×/d (4d), then standard FVIII replacement	PCI (BMS): LAD	Radial	n.a.

(Continues)

TABLE 1 (Continued)

Reference	Case	Hemophilia type and severity	Age (years)	Clinical presentation	Baseline factor level (%)	Baseline hemostatic regimen	Trough factor levels during PCI/FU	Antithrombotic management and factor substitution		Revascularization strategy	Access site	Access site management
								Peri-interventional	Follow-up			
	22	A, mild	60	Unstable AP	FVIII 10%	On demand	n.a./10%	FVIII 2,000 IU, UFH	DAPT: 3 mo (ASA, clopidogrel), LT: ASA, FVIII 1,000 U 2×/d (4d)	PCI (BMS): LAD	Radial	n.a.
Patel et al., 2013 [11]	23	A, mild (+FV deficiency)	68	Stable AP	FV 11%; FVIII 7%	On demand	FVIII 31%/49%	FVIII 25 IU/kg 2×/d (1d), UFH 45 IU/kg, FFP 30 ml/kg	DAPT: 1 mo (ASA 81 mg, clopidogrel 75 mg), LT: ASA 81 mg	PCI (BMS): LAD	Femoral	Closure device
Reddy et al., 2013 [12]	24	A, information on severity n.a.	55	STEMI	n.a.	Tranexamic acid	60%/n.a.	ASA 300 mg, prasugrel 60 mg, UFH 5,000 IU	DAPT: 1 mo (ASA 75 mg, clopidogrel 75 mg), LT: ASA 75 mg, tranexamic acid prophylaxis (1 mo)	PCI (BMS): LAD	Radial	Compression band
Tuinenburg et al., 2013 [5]	25	B, moderate	65	Stable AP	FIX 5%	n.a.	130%/29–33%	FIX 5,000 IU, UFH 7,000 IU, ASA, ticagrelor	DAPT: 1 mo (ASA, clopidogrel), LT: ASA 100 mg, FIX 2,000 IU 2×/d (48 h), 2,000 IU daily (1 mo)	PCI (BMS): information on vessel n.a.	Radial	n.a.
	26	A, mild	72	STEMI	FVIII 15%	n.a.	80%/37%	FVIII 3,000 IU, ASA, clopidogrel, UFH	DAPT: 1 mo (ASA, clopidogrel), LT: ASA 80 mg, FVIII 1,500 IU 2×/d (48 h), FVIII 1,000 IU 1×/d (1 mo)	PCI (BMS): information on vessel n.a.	Femoral	n.a.
	27	A, mild	76	Stable AP	FVIII 28%	n.a.	126%/28%	FVIII 2,500 IU, ASA, clopidogrel, UFH 2,500 IU	DAPT: 6 mo (ASA, clopidogrel), LT: ASA, FVIII 1,000 IU 2×/d (48 h)	PCI (BMS): RCA	Femoral	n.a.
	28	A, mild	61	Stable AP	FVIII 20%	n.a.	80%/27%	FVIII 3,000 IU, UFH 10,500 IU	DAPT: 1 mo (ASA, clopidogrel), LT: ASA, FVIII 1,500 IU 2×/d (48 h), FVIII 2,000 IU 1×/d (1 mo)	PCI (BMS): LAD and diagonal branch	Radial	n.a.
	29	A, mild	57	Suspected CAD	FVIII 20%	n.a.	70%/n.a.	FVIII infusion, UFH 5,000 IU	None	None	n.a.	n.a.
	30	A, mild	49	NSTEMI	FVIII 25%	n.a.	125%/25%	FVIII 2,250 IU, ASA, ticagrelor, UFH 7,000 IU	DAPT: 12 mo (ASA, clopidogrel), LT: ASA, FVIII 750 IU (every 12 h)	PCI (BMS): RCA	Radial	n.a.

(Continues)

TABLE 1 (Continued)

Reference	Case	Hemophilia type and severity	Age (years)	Clinical presentation	Baseline factor level (%)	Baseline hemostatic regimen	Trough factor levels during PCI/FU	Antithrombotic management and factor substitution		Revascularization strategy	Access site	Access site management
								Peri-interventional	Follow-up			
Arzu et al., 2011 [13]	31	B, moderate	77	Unstable AP	FIX 3.8%	On demand	3.8%/3.8%	UFH 7,500 IU, ASA 100 mg, clopidogrel 75 mg	DAPT: 1 mo (ASA 300 mg, clopidogrel 75 mg), LT: ASA 300 mg	PCI (BMS): Left main	Femoral	Closure device
Petrillo et al., 2011 [14]	32	A, severe	38	NSTEMI	FVIII <1%	On demand	n.a.	ASA 500 mg, UFH 2,500 IU, clopidogrel 300 mg	DAPT: 19 days (ASA 100 mg, clopidogrel 75 mg), LT: ASA 100 mg, FVIII 1,000 IU 1×/d (5d)	PCI (BMS): LAD and RCA	Femoral	Closure device
Kim et al., 2010 [15]	33	A, severe	52	Unstable AP	FVIII <1%	on demand	n.a.	FVIII 2,500 IU, UFH 70 IU/kg, clopidogrel 300 mg	DAPT: 1 mo (ASA 100 mg, clopidogrel 75 mg), LT: ASA 100 mg; FVIII 1,500 U 2×/d (d1), FVIII 1,500 U 1×/d (d2), then regular FVIII substitution	PCI (BMS): LAD	Femoral	Manual compression
Coppola et al., 2010 [16]	34	A, severe	63	Unstable AP	n.a.	On demand	64%/20–35%	FVIII 30 IU/kg + FVIII 1 IU/kg/h infusion, clopidogrel 75 mg, UFH 2,500 IU, infusion UFH 600 IU/h	UFH, FVIII 1 U/kg/h infusion until death	CABG planned	Femoral	n.a.
Ergelen et al., 2009 [17]	35	A, severe	60	STEMI	FVIII <1%	On demand	n.a.	None	None	Medical therapy, CABG suggested	n.a.	n.a.
Quintero et al., 2008 [18]	36	A, severe	44	STEMI	FVIII 1.7%	On demand	60–80%/60–80% (3 d after PCI)	FVIII 2,500 IU, ASA 325 mg, clopidogrel 600 mg, bivalirudin 0.7 mg/kg	DAPT: 4 mo ASA 325 mg, clopidogrel 75 mg), LT: ASA 325 mg, FVIII (d2 + 3)	PCI (BMS): RCA	n.a.	n.a.
Smolka et al., 2007 [19]	37	A, moderate	62	Unstable AP	FVIII 2–3%	On demand	73%/n.a.	FVIII 2,500 IU, clopidogrel 300 mg, UFH 70 IU/kg	DAPT: 1 mo (ASA 75 mg, clopidogrel 75 mg), LT: ASA 75 mg, FVIII 1,500 IU 2×/d (d1), FVIII 1,500 IU 1×/d (d2), periodically etamsylate and ascorbic acid	PCI (BMS): LAD	Femoral	Closure device

(Continues)

TABLE 1 (Continued)

Reference	Case	Hemophilia type and severity	Age (years)	Clinical presentation	Baseline factor level (%)	Baseline hemostatic regimen	Trough factor levels during PCI/FU	Antithrombotic management and factor substitution		Revascularization strategy	Access site	Access site management
								Peri-interventional	Follow-up			
Krolick, 2005 [20]	38	A, severe	54	Stable CAD	n.a.	n.a.	n.a.	FVIII 3,500 IU, ASA 325 mg, clopidogrel 300 mg, bivalirudin 0.75 mg/kg bolus, 1.7 mg/kg/h infusion	FVIII 2,000 IU 3×/d (duration unknown). Information on DAPT n.a.	PCI (DES): LCX, and RCA	Femoral	n.a.
Arora et al., 2004 [21]	39	A, severe	64	Unstable AP	n.a.	Daily FVIII infusions	100%/n.a.	FVIII 4,500 IU, bivalirudin 56.5 mg bolus, 8.9 mg infusion	Information on DAPT n.a.	PCI (BMS): LCX and LAD	Femoral	n.a.
Virtanen et al., 2004 [22]	40	A, mild	59	STEMI following DDAVP administration	n.a.	on demand	81%/35% (d1), 26% (d3)	ASA 250 mg, DDAVP 0.19 μg/kg Eptifibatide, clopidogrel 75 mg	DAPT: 6 days (ASA 100 mg, clopidogrel 75 mg), LT: clopidogrel 75 mg (2 mo)	PCI (BMS): LAD	Radial	Manual compression
Bovenzi et al., 2003 [23]	41	B, severe	73	Unstable AP	FIX <1%	n.a.	n.a.	FIX 30 IU/kg, UFH 5,000 IU, initially no antiplatelet therapy; treatment with abciximab + UFH because of thrombus formation immediately after stenting	Clopidogrel for 1 mo (information on ASA use n.a.)	PCI (BMS): LAD	n.a.	n.a.
Mackinlay et al., 2000 [24]	42	A, mild	73	n.a.	FVIII 15%	n.a.		FVIII 6,500 IU (2 d)	None	None	Femoral	n.a.
	43	A, moderate	52	n.a.	FVIII 2%	n.a.		FVIII 17,000 IU (5 d)	ASA	None	Femoral	n.a.
	44	A, mild	56	n.a.	FVIII 15%	n.a.		FVIII 21,000 IU (5 d)	None	CABG after left main dissection during coronary angiography	Femoral	n.a.
Forman e tal., 1986 [25]	45	A, moderate	45	Stable AP	FVIII 2–4%	Monthly FVIII infusions	200%	FVIII bolus 20 IU/kg, infusion 5 IU/kg per hour. UFH 15,000 IU	None	PCI (ballon dilatation, no stenting) LCX	Femoral	Manual compression
Ferrario et al., 2007 [26]	46	A, severe	57	NSTEMI				ASA 100 mg, clopidogrel 300 mg, then 75 mg, UFH. FVIII 75 IU/kg, then infusion (total dose 39,000 IU)	DAPT: 1 mo (ASA 100 mg, clopidogrel 75 mg), ASA long-term, FVIII for 4 mo	PCI (BMS) RCA	n.a.	n.a.

(Continues)

TABLE 1 (Continued)

Reference	Case	Hemophilia type and severity	Age (years)	Clinical presentation	Baseline factor level (%)	Baseline hemostatic regimen	Trough factor levels during PCI/FU	Antithrombotic management and factor substitution		Revascularization strategy	Access site	Access site management
								Peri-interventional	Follow-up			
Helft et al., 1997 [27]	47	B, mild	58	Unstable AP	FIX 9%	none	n.a.	FIX 8,000 IU. UFH 10,000 IU	None	PCI (BMS) RCA	femoral	Manual compression
Kerkhoffs et al., 2004 [28]	48	A, mild	62	Stable AP	FVIII16%	On demand	76%	FVIII 4,000I UI abciximab LMWH	Clopidogrel for 4 wk, thereafter ASA. FVIII for 1 wk	PCI (BMS) LCX because of STEMI during FVIII infusion	n.a.	n.a.
Meili et al., 1968 [29]	49	A, mild	72	NSTEMI	FVIII 14%	None	n.a.	None	None	Medical therapy (LAD occluded)	femoral	Manual compression
Paolini et al., 1993 [30]	50	A, mild	53	Stable AP	FVIII 14.5%	None	n.a.	FVIII 1,000 IU. ASA 450 mg	ASA	PCI (balloon dilatation) RCA	femoral	Manual compression
Peerlinck and Vermylen, 1999 [31]	51	A, severe	72	STEMI after administration of recombinant FVII and tranexamic acid	FVIII <1%	Activated prothrombin complex and tranexamic acid on demand (anti-FVIII antibody)	n.a.	UFH 10,000 IU. ASA. Recombinant FVII	Recombinant FVII for 5 days otherwise information n.a.	PCI (balloon dilatation) LAD	femoral	Manual compression
Lickfett et al., 1998 [32]	52	A, severe	69	STEMI after FVIII application	FVIII <1%	On demand	110%	Thrombolysis with recombinant tissue plasminogen activator, FVIII 6,000 IU, UFH 5,000 IU, ASA 250 mg	ASA 100 mg. FVIII for 5 days	PCI (balloon dilatation) RCA	femoral	Manual compression
Gunaldi et al., 2009 [33]	53	A, severe (+FV Leiden mutation)	49	STEMI after FVIII and tranexamic acid application	FVIII <1%	On demand		LMWH 100 IU/kg, ASA 100 mg, FVIII	Initially DAPT (ASA 100 mg, clopidogrel 75 mg), switch to clopidogrel monotherapy (9 mo)	PCI (BMS) RCA	femoral	
Alsolaiman et al., 2000 [34]	54	A, mild	44	STEMI after FVIII application	FVIII 6%	n.a.	n.a.	FVIII	ASA	PCI (balloon dilatation) LAD	femoral	Manual compression

AP: angina pectoris; ASA: acetylsalicyl acid; BMS: bare metal stent; CA: coronary angiography; CABG: coronary artery bypass graft; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; DDAVP: desmopressin acetate; DES: drug eluting stent; FFP: fresh frozen plasma; FVIII: factor VIII; FIX: factor IX; n.a.: not available; LAD: left anterior descending artery; LCX: left circumflex artery; LMWH: low molecular weight heparin; LT: long term; NSTEMI: Non-ST segment elevation myocardial infarction. PCI: percutaneous coronary intervention; RCX: right coronary artery; STEMI: ST segment elevation myocardial infarction; UFH: unfractionated heparin.

TABLE 2 Follow-up and complications (n = 54).

Reference	Case	Follow-up	Complications
Present case	1	12 mo	Tongue and retropharyngeal hematoma 7 mo after PCI on ASA monotherapy
Chang et al., 2016 [7]	2	15 mo	Serious hematuria and intramuscular hemorrhage (after 48 h following PCI when FVIII trough was reduced from 80 to 15% during DAPT); Restenosis of the posterolateral branch of the RCA at 7 mo, treated with PCI, second course of DAPT for 1 mo
Koklu et al., 2015 [8]	3	8 mo	None
Fogarty et al., 2015 [9]	4	1 mo	None
	5	24 mo	Gastrointestinal bleeding on ASA monotherapy, requiring discontinuation of ASA
	6	5 mo	None
	7	8 mo	None
	8	n.a.	n.a.
	9	19 mo	None
	10	26 mo	Excessive bleeding at the puncture site (early after PCI)
	11	13 mo	None
	12	17 mo	None
	13	13 mo	Bruising and epistaxis (on ASA monotherapy), increase of FVIII replacement from 35 IU twice a week to 25 IU three times a week
	14	49 mo	None
	15	18 mo	None
	16	14 mo	None
	17	11 mo	None
	18	1 mo	None
	19	109 mo	None
Fefer et al., 2013 [10]	20	9 mo	None
	21	24 mo	Recurrent minor bleeding episodes over 6 mo FU after instent stenosis; recurrent severe instent re-stenosis (LAD) with unstable AP (12 mo after index PCI). Treatment with cutting balloon, clopidogrel continued for 1 mo
	22	15 mo	Minor bleedings
Patel et al, 2013 [11]	23	36 mo	None
Reddy et al., 2013 [12]	24	n.a.	None
Tuinenburg et al., 2013 [5]	25	n.a.	None
	26	n.a.	Minor bleedings (hematuria) after 10 weeks; treatment with single bolus FVIII 2000 IU, ASA continued
	27	n.a.	Minor bleedings (small hematomas on his hands), no discontinuation of DAPT (for 6 mo)
	28	24 mo	Instent re-stenosis of diagonal branch
	29	10 mo	None
	30	3 mo	None
Arzu et al., 2011 [13]	31	6 mo	None
Petrillo et al., 2011 [14]	32	1 mo	Minor bleedings during first month
Kim et al., 2010 [15]	33	10 mo	50% re-stenosis (10 mo)
Coppola et al, 2010 [16]	34	4 d	sudden death on day 4 while waiting for coronary artery bypass
Ergelen et al., 2009 [17]	35	n.a.	n.a.
Quintero et al., 2008 [18]	36	24 mo	Gingival bleeding, ecchymoses (month 4), therefore clopidogrel was discontinued

(Continues)

TABLE 2 (Continued)

Reference	Case	Follow-up	Complications
Smolka et al., 2007 [19]	37	5 mo	Two to three hemorrhages to joints and subcutaneous bleeding (during first month on DAPT) periodically etamsylate, ascorbic acid
Krolick, 2005 [20]	38	n.a.	n.a.
Arora et al., 2004 [21]	39	n.a.	n.a.
Virtanen et al., 2004 [22]	40	24 mo	None
Bovenzi et al., 2003 [23]	41	n.a.	None
Mackinlay et al., 2000 [24]	42	n.a.	None
	43	n.a.	None
	44	n.a.	Left main dissection during coronary angiography, emergency bypass surgery (uncomplicated)
Forman et al., 1986 [25]	45	6 mo	None
Ferrario et al., 2007 [26]	46	4 mo	None
Helft et al., 1997 [27]	47	3 mo	None
Kerkhoffs et al., 2004 [28]	48	n.a.	None
Meili et al., 1968 [29]	49	None	n.a.
Paolini et al., 1993 [30]	50	2 mo	Recurrent angina
Peerlinck and Vermylen, 1999 [31]	51	5 d	Large groin hematoma three days after procedure
Lickfett et al., 1998 [32]	52	5 d	None
Gunaldi et al., 2009 [33]	53	6 mo	Hemorrhages of oral mucosa during DAPT, switch to clopidogrel monotherapy
Alsolaiman et al, 2000 [34]	54	3 yr	None

ASA: acetylsalicyl acid; DAPT: dual antiplatelet therapy; n.a.: not available. LAD: left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery; FVIII: factor VIII; FU: follow up.

3.8 | Coronary Artery Disease-Related Outcomes

One patient with severe coronary artery disease died 4 days after coronary angiography while waiting for coronary artery bypass surgery [16]. Four patients experienced in-stent-restenosis after BMS implantation [5,7,10,15] (Table 2), which were treated with PCI in three cases.

4 | DISCUSSION

The present so far largest data collection and analysis of patients with hemophilia undergoing coronary angiography and PCI indicates that PCI is effective in these patients and that these procedures and subsequent DAPT are generally relatively safe provided that the problem is recognized, and appropriate preventive measures are undertaken. Many different approaches were used to both minimize the bleeding risk and to ensure sufficient anticoagulation and antiaggregation for PCI during the periprocedural period, while the longer-term management was relatively uniform. The data suggest that in general the same antithrombotic strategies and bleeding prevention methods can and should be used in hemophilic as in nonhemophilic patients provided that factor replacement is performed with adequate dosing and timing.

Several authors have published recommendations for the management of patients with hemophilia and coronary artery disease [1,2,4–6]. A summary of these recommendations is provided in Table 3. Authors agree that myocardial revascularization should be managed by a multidisciplinary team including a hemophilia expert (hematologist) and a cardiologist. In patients with acute coronary syndrome, PCI should be performed as soon as possible under adequate clotting factor protection.

Unfractionated heparin is preferred to low molecular weight heparin for PCI for hemophilia. The effect of anticoagulation can be measured in the cath lab by the activated clotting time (point-of-care test), the half-life is short, and protamine sulfate as an antidote is available. Before administration of UFH appropriate clotting factor correction should be achieved. We found several cases where factor substitution precipitated STEMI, i.e., coronary thrombosis in patients with coronary artery disease and presumably plaque rupture. Thus, optimal dosing and timing of FVIII or FIX administration depending on hemophilia severity is crucial. Notably, desmopressin acetate (DDAVP) may be more prothrombotic than FVIII concentrate in patients with coronary injury because it releases ultralarge von Willebrand factor multimers from storage sites which are known to be most effective in primary hemostasis, which is crucial in injured vessels, especially at high shear rates [22]. Based on this we usually do not use DDAVP in patients with hemophilia and established atherosclerosis, i.e., coronary artery disease or previous stroke.

TABLE 3 Recommendations for percutaneous coronary intervention (PCI) in hemophilia patients [modified according to Ferraris (1), Mannucci (2), Schutgens (4), Tuinenburg (5), and Staritz (6)]

	Preprocedure	1–48 h Postprocedure	>48 h Postprocedure
Factor replacement		• Factor trough levels around 50% should be pursued until 24 h after cardiac catheterization (15 IU/kg FVIII or FIX every 12 h).	• In patients with mild or moderate hemophilia factor trough levels of 25–30% can be obtained with once daily infusions during DAPT. • In patients with a residual clotting factor level of 25% or higher no factor replacement is needed during DAPT. Minimum trough levels should be kept at 5–15% during DAPT. • On long-term treatment with ASA alone, trough factor levels of ≥1% are thought to be acceptable.
	• Factor target levels (peak) around 80% (40 IU/kg FVIII or 80 IU/kg FIX followed by 20 IU/kg FVIII or FIX every 12 h) during the highest bleeding risk phase (PCI and combined anticoagulant/antiplatelet treatment, 48 h after PCI). • Continuous infusion might be an alternative to bolus therapy (possible reduction in factor usage, and avoidance of wide fluctuations in factor levels).		
Anticoagulation	• Single bolus infusion of UFH (70–100 IU/kg) before PCI. • Bivalirudin as an option instead of UFH (data available with bolus of 0.7–0.75 mg/kg, followed by continuous infusion during PCI).	• No additional treatment with UFH after intervention.	
Antiplatelet therapy	• Loading dose of 325 mg ASA and 600 mg clopidogrel before PCI. • Ticagrelor or prasugrel are not recommended for DAPT due to higher bleeding risk.		• DAPT with 80 to 100 mg ASA and 75 mg clopidogrel after placement of a BMS during 4 weeks with adequate factor replacement. • Extension of DAPT as an option (e.g. after acute coronary syndrome), if no bleeding occurs, but generally as short as possible. • Longer DAPT after DES (currently 6 mo, probably less possible with modern DES). • Long-term antiplatelet therapy with ASA 75–325 mg was frequently reported and seems to be safe. • Usage of proton pump inhibitors during DAPT recommended.
Glycoprotein IIb/IIIa inhibitors	• Very little experience, generally not recommended, has been used rarely in bailout situations • Tirofiban (bolus of 10 μg/kg, followed by 0.15 μg/kg/min for 12 h). • Abciximab (bolus of 0.25 mg/kg, followed by 0.125 μg/kg/min for 12 h). • Eptifibatide theoretically preferred (shorter half-life and lower risk of thrombocytopenia) but sparse data.		
Access site for PCI	• Radial access theoretically preferred, but femoral access more frequently reported without significant bleeding.		
Coronary stent type	• BMS more frequently reported, probably to minimize the duration of DAPT. • The use of a DES should be considered in patients with prior restenosis (little data on DES in hemophilia). • Newer DES requiring shorter duration of DAPT as an option in patients with residual clotting factor level of ≥25%. • Plain balloon dilation/drug-eluting balloon as an option		

BMS: bare metal stent; DAPT: dual antiplatelet therapy; DES: drug eluting stent; PCI: percutaneous coronary intervention; ASA: acetylsalicylic acid; FXIII: factor XIII; FIX: factor IX; UFH: unfractioned heparin.

Bivalirudin is a direct thrombin inhibitor (half-life 25 min in patients with normal renal function), which was safely used as the only antithrombotic strategy during PCI in several hemophilia patients as shown in the present analysis. For unselected patients, there is evidence for a lower risk of major bleeding complications in patients receiving bivalirudin instead of UHF for PCI [36]. However, it is unknown whether this holds true also for hemophilia patients. Importantly, peri-interventional antiplatelet therapy is required and safe despite the presence of a significant coagulation disorder.

Radial access has been recommended to minimize bleeding complications in these high risk patients, because of better compressibility and earlier detection of bleeding [4,5]. Interestingly in most of the cases in the literature a femoral approach was used (as shown in Table 1), and still major bleedings were rare, although a meta-analysis of randomized clinical trials showed that radial artery access reduced major bleeding as compared with femoral artery access in a nonhemophilic population [37]. This may indicate that the interventional cardiologists treating the patients included in this analysis were very experienced "femoralists." Although overall the radial access is recommended in patients with high bleeding risk (i.e., those with acute coronary syndrome and also patients with hemophilia), this should be done only by trained "radialists"; otherwise the expected benefit of radial access will not be achieved.

Although the coagulation cascade is impaired in patients with hemophilia, both thrombocyte count and thrombocyte function are normal. Thus, DAPT is recommended for prevention of stent thrombosis after PCI [1,5]. However, this results in an overall significantly increased bleeding risk due to the combination of an inherited severe coagulation disorder and a drug-induced significant "platelet function disorder." Thus the period of DAPT should be kept as short as possible, and prophylactic factor replacement is indicated depending on hemophilia severity. The bleeding complications of varying severity several months after PCI in the patients of our case series highlight that these patients indeed have a high bleeding risk not only during the periprocedural period but also during follow-up when patients are on DAPT or even ASA monotherapy. Bare metal stents are therefore recommended to facilitate a short duration of dual antiplatelet therapy [4,5]. A recent study has clearly shown that BMS remain an option for the majority of patients undergoing PCI for stable and unstable coronary artery disease [38]. In patients with hemophilia, the risk of prolonged DAPT (currently still 6 months for DES versus 1 month for BMS in elective PCI) must be weighed against this risk of repeat revascularization with all the procedural challenges as discussed here. Data about the risk for restenosis in patients with hemophilia are limited. However, we found four patients with in-stent-restenosis after BMS implantation indicating that the problem is not irrelevant. Thus, the use of new generation DES requiring less than 6 months of DAPT could be an option in hemophilia patients with a residual factor level $\geq$25% without additional clotting factor infusions [5]. Especially in patients with previous in-stent restenosis or higher risk of restenosis due to diabetes, a DES should be considered. The minimal DAPT duration in this setting remains to be determined, however. A potentially interesting option for PCI in hemophilia patients is the use of drug-eluting balloons (DAPT for only 1 month, potentially less restenosis than BMS), which are currently used for the treatment of in-stent restenosis but also de novo lesions [39]. However, there are currently no data for drug-eluting balloon in hemophilia patients.

5 | LIMITATIONS

The present analysis is mainly limited by the small number of patients. However, to the best of our knowledge this represents the so far largest data collection on a rare constellation. We assume that in clinical practice the problem is not exceptionally rare, however, and that the present dataset may be of interest for a significant number of clinicians. The second limitation is related to the exclusion of some reports because of the language of the main text. However, as shown in Figure 1, only two case reports were excluded for this reason.

6 | CONCLUSIONS

Our analysis of published cases and case series suggests that coronary angiography and PCI are effective and safe also in patients with hemophilia if individualized measures to prevent bleeding are applied. However, DAPT and even ASA monotherapy confers a long-term bleeding risk. The optimal treatment strategy (BMS, DES, drug-eluting balloon, DAPT duration) in these patients remains to be determined.

CONFLICT OF INTEREST

No conflicts of interest to declare by any author.

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