Review Article

Management of cardiovascular disease in haemophilia

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Abstract

Improvements in the management of haemophilia have led to a significant increase in the life expectancy of haemophilia patients, which is now close to the life expectancy in the general male population. Therefore, age-related conditions, especially cardiovascular disease (CVD), have become increasingly common in these patients. The management of CVD, especially that of coronary artery disease (CAD), acute coronary syndrome (ACS) and atrial fibrillation (AF), is particularly challenging in patients with haemophilia due to the need to find an adequate balance between bleeding and ischemic risk, requiring close coordination between cardiologists and haemophilia specialists. However, specific recommendations and relevant literature and data are scarce. Therefore, we propose pragmatic and practical therapeutic suggestions, based on the available literature and our own experience, for the management of ACS, stable angina and AF in patients with haemophilia. Overall, evidence and experience suggest that they should be treated much in the same way as the general CVD population, following standard guidelines, while choosing available treatment options known to be associated with low rates of bleeding complications. Treatments advocated for patient with haemophilia include antiplatelet therapy (aspirin and P2Y12 inhibitors), antithrombin therapy such as heparin or bivalirudin, glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa inhibitors), transradial cardiac catheterization, and use of bare metal (BMS) or drug-eluting stents (DES). Antithrombotic agents with shorter half-lives that are reversible or have an antidote offer a safer choice in this setting. In addition, optimal clotting factor replacement therapy should be tailored to the increased risk of bleeding associated with invasive procedures and antithrombotic therapies, particularly during the acute phase of ACS.

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Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; CVD, cardiovascular disease; ECG, electrocardiogram; MI, myocardial infarction; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; UA, unstable angina.

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Introduction

Improvements in the management of haemophilia have led to a significant increase in the life expectancy of haemophilia patients, which is now close to the life expectancy in the general population [1–3]. Therefore, age-related conditions, especially cardiovascular disease (CVD), have become increasingly common in these patients [4]. One might expect that the hypocoagulable state and increased bleeding risk in haemophilia would protect against thrombotic risk but this does not appear to be the case particularly when several CV risk factors are present – even patients with haemophilia and other coagulation factor deficiencies are not protected from the development of atherosclerosis and the resulting thrombotic complications due to age [5–7].

Patterns of risk factors for CVD are different in haemophilia patients compared with the general population. A large European cross sectional study comparing CVD risk factors in haemophilia patients with the general population showed that hypertension was more common (49% vs. 40%), whereas obesity and hypercholesterolaemia were lower (15 vs. 20% and 44 vs. 68%, respectively), and diabetes and smoking were similar, giving a significantly more unfavourable CVD risk profile in haemophilia patients over 40 years [8]. A retrospective study found hypertension in 65.5%, diabetes in 10.3%, smoking in 12.5% and obesity in 19.6%, and 84.2% and 12.5% were receiving antihypertensive and lipid-lowering agents, respectively [9]. Another large US study found approximately double the prevalence of coronary artery disease (CAD), stroke and myocardial infarction (MI) in haemophilia patients compared with non-Hispanic white males [10]. However, another study has shown a decreased occurrence of MI in patients with severe haemophilia, suggesting a protective effect on thrombotic cardiac events [8].

In view of the background bleeding risk, managing CVD, particularly CAD and other coronary conditions in patients with haemophilia is a therapeutic challenge, considering the frequent need for antithrombotic medications such as antiplatelet and anticoagulant agents and invasive revascularisation strategies, such as percutaneous coronary intervention (PCI) [2–4]. Therefore, management benefits from close collaboration between cardiology and haemophilia specialists [9].

Overview of Types of Patients

CAD can be subdivided into acute coronary syndrome (ACS) and stable angina. ACS is related to a sudden thrombotic obstruction of a disrupted atheromatous coronary plaque, and reveals underlying CAD. Current classifications of ACS distinguish between patients with a persistent ST elevation on ECG (ST elevation myocardial infarction; STEMI), reflecting a complete coronary occlusion, and patients without this persistent ST elevation, which include unstable angina (UA) and non-ST elevation acute coronary syndrome (NSTEMI), both reflecting an incomplete coronary obstruction. Stable angina is chest pain associated with narrowing of the coronary arteries. Other CVD patients for whom the management in haemophilia can be particularly challenging are those with non-valvular atrial fibrillation (AF). AF is the most frequent type of cardiac arrhythmia, is associated with a significant increase in stroke risk and its prevalence increases with age. All require discussion of antithrombotic therapy and anti-ischaemic interventions to manage the morbidity and mortality risk, all of which are associated with an increased risk of bleeding complications.

Objective

There are currently no evidence-based or consensus guidelines for the treatment of CVD in patients with haemophilia. This motivated us to present practical therapeutic suggestions for specific interventions commonly used in CVD patients and which have the potential to be problematic in patients with haemophilia due to bleeding risks or other issues relating to therapy, in the form of a narrative review of recent literature data [11] supplemented by the authors’ own experience.

It should be noted that, although the issue of correction of CV risk factors is outside the scope of this review, it being primarily concerned with the acute phase treatment of CVD, the correction of modifiable risk factors is crucial in the secondary prevention of CVD, particularly given the high and probably increasing prevalence of CVD risk factors in the haemophilia population.

Methodology

A literature search of the MEDLINE (PubMed) database was conducted using terms related to CVD, CAD, ACS, STEMI, NSTE-ACS, stable angina or AF and haemophilia using both MesH terms and free text searches. Papers were selected manually for inclusion in this paper. The bibliographies of the retrieved papers were also manually screened for relevant papers.

Overview of CVD Management in Patients with Haemophilia

There are few specific evidence-based guidelines for the management of CVD in haemophilia and current treatment strategies are often based on local clinical experience and adaptation of general guidelines used in the non-haemophilic population.

The following recommendations are based on individual initial assessment and stratification of both ischemic and bleeding risks. In general, patients with haemophilia should be considered to be at high risk for bleeding events.

Management of CAD (ACS and Stable Angina)

Existing guidelines, such as those of the European Society of Cardiology for STEMI [12] and NSTE-ACS patients [13], have allowed for standardized management of ACS in most patients. However, whether or not these guidelines are relevant for patients with haemophilia and other bleeding disorders remains to be elucidated.

The decision nodes and main components of the overall management process for CAD in patients with haemophilia are shown in Fig. 1.

Treatments advocated for a patient with haemophilia include antiplatelet therapy (aspirin or dual therapy with aspirin plus...
clopidogrel), antithrombin therapy such as unfractionated heparin (UFH) or low-molecular weight heparin (LMWH), GPIIb/IIIa inhibitors, transradial cardiac catheterization, bare metal stents (BMS) and correction of clotting factor levels [1].

In general, continuous infusion is preferred to bolus injections, shorter half-lives to longer and agents that are easy to reverse (or have an antidote in case of bleeding complications) are preferred to non-reversible [5,14].

Evidence-based recommendations for haemophilia control prior to an invasive procedure in haemophilia patients advise target factors levels of 60% to 80% [15,16].

Radial Vascular Access

With the improvement in risk stratification and treatments, one of the main areas for improvement now lies with reducing bleeding complications related to vascular access [17].

When an invasive approach is indicated, use of radial artery access has demonstrated a dramatic 60% reduction in puncture-related bleeding events, as compared with the traditional femoral access for cardiac catheterization [15,18,19]. Radial access is associated with a reduction cardiac mortality in patients with ST elevation [20]. The main advantage of transradial cardiac catheterization and intervention is the reduced risk of access-site bleeding complications; and the ease by which bleeding can be stopped due to the small size and compressibility of the radial artery [17]. Therefore, it must be proposed as the default access site in haemophilia patients.

Correction of the Coagulation Defect (Replacement Therapy)

According to the literature on haemophilia management, no invasive procedure should be performed without replacement therapy to correct the clotting factor deficiency, but the evidence guiding optimal targets in terms of percentage clotting factor levels prior to and during invasive cardiovascular procedures and duration of therapy is limited [15]. For example prior to PCI the aim should be a peak level of 80% clotting factor concentrate infused before PCI and continued for 48 hours after PCI depending on the choice of stent and the need for dual clopidogrel and aspirin therapy [1].

It should also be mentioned that, in patients with haemophilia, a potential increased risk of MI, is associated with replacement factor concentrate transfusion therapy [21]. Of note, the risk of MI with replacement therapy is probably similar to the general population.

Stent Type and Platelet Aggregation Inhibition

Systematic use of dual antiplatelet therapy (usually aspirin plus another antiplatelet agent) is a major recommendation after stenting [18,22]. Since ACS is a life-threatening condition, there is no strong argument for contraindicating antiplatelet agents, even in haemophilia patients. However, haemophilia raises specific issues regarding the choice of antiplatelet agents and the duration of treatment, depending on the type of stent used, the substitution therapy regimen (i.e. on-demand or prophylactic) and associated treatments [22]. As with all antithrombotic therapy, the duration of dual antiplatelet therapy should be as short as possible.

The choice of stent is less of an issue than it used to be. In the past, bare metal stents (BMS), which needed only four to six weeks of dual antiplatelet therapy, were preferred to drug-eluting stents (DES) since the latter required six to twelve months of dual antiplatelet therapy [18]. However, new generation DES do not need long-term dual antiplatelet therapy making treatment duration similar to that required for BMS [23]; one study is ongoing with the new generation DES and a shorter duration of dual antiplatelet therapy (ClinicalTrials.gov number:NCT01623180). Also, the lesion type and haemophilia severity should also be taken into account when selecting the type of stent [22].

Regarding the choice of antiplatelet prophylaxis, it has been shown that new drugs, namely prasugrel or ticagrelor, reduce ischemic complications after an ACS, as compared to the standard agents aspirin and clopidogrel, but are also associated with an increased incidence of
spontaneous bleeding events [24–26]. These new agents have been strongly recommended by the NSTE-ACS and STEMI guidelines for the general population with an ACS [13,27]. However, no specific data are available on their use in haemophilia patients. Considering the increased rate of minor and major bleeding events, these agents should not be used in haemophilia patients [26]. Instead, clopidogrel is preferred, using loading doses of 300 mg up to 600 mg, followed by a daily dose of 75 mg for four to six weeks, associated with low-dose aspirin (≤100 mg daily). As recommended by the guidelines, gastric protection with a proton pump inhibitor should be employed for the duration of dual antiplatelet therapy in patients at high risk of bleeding [28]. Antiplatelet therapy may be adapted to the severity of haemophilia: severe haemophilia (<1% FVIII or IX) generally requires classical prophylaxis: for haemophilia A, 25 to 30 IU/Kg 3 times a week; for haemophilia B, 30 to 40 IU/Kg twice a week. For less severe haemophilia (moderate to minor), prophylaxis may not be required. The decision relies on the tolerance of antiplatelet therapy. If the antiplatelet agent does not induce recurrent ecchymoses or bleeding, no prophylaxis is necessary. If recurrent ecchymoses, hematomas or other bleeding events occur, tailored prophylaxis could be proposed, beginning at 1 or 2 infusions a week to reach the schedule of classical prophylaxis.

The GPIIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban, etc.) should be limited to patients with a high-burden thrombus during coronary angiography or in cases of slow or no-reflow or thrombotic complications [27].

During this period, prophylactic replacement therapy by antihaemophilic concentrates should be used according to usual protocols (e.g. 20 to 30 IU/kg of factor VIII concentrate three times a week; or 30 to 40 IU/kg factor IX concentrate twice a week). When dual antiplatelet therapy is no longer necessary, a single-agent therapy based on aspirin or clopidogrel does not systematically require prophylactic replacement therapy. The decision may depend on the dose used, but mainly depends on the safety of this monotherapy.

It has been suggested that platelet-function monitoring and adjustment of antiplatelet therapy could be used to reduce ischemic and bleeding risks in patients undergoing stenting; however, the ARCTIC study showed no significant difference in the rate of major bleeding events between patients receiving platelet-function monitoring and treatment adjustment, and those receiving standard antiplatelet therapy without monitoring or adjustment [29]. The ANTARTIC study/Assessment of a Normal versus Tailored Dose of Prasugrel after Stenting in Patients Aged >75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic Complications; ClinicalTrials.gov number:NCT01538446 is ongoing and will assess the value of platelet function testing in older patients, with a focus on the prevention of bleeding events.

Anticoagulant Agents

As indicated in the guidelines, the duration of treatment with anticoagulant agents must be as short as possible and stopped after revascularization [18]. UFH or LMWH can be used for both STEMI and NSTE-ACS patients. However, UFH may probably be preferable to LMWH in this population as reversal of effect is easier and laboratory follow-up is quick and simple [5].

Newer antithrombotic agents fondaparinux and bivalirudin are both recommended by the NSTE-ACS treatment guidelines, and bivalirudin is also strongly recommended by the STEMI treatment guidelines [13,27]. Only two case reports of bivalirudin use in patients with haemophilia have been published [30,31]. Bivalirudin may be an alternative to heparin in patients with haemophilia given its very short half-life [30], but more data are needed in this specific population.

No publications are available on fondaparinux use, and no specific antidote exists.

Reperfusion Strategy in STEMI Patients

Reperfusion of STEMI patients should preferably be performed using a primary PCI approach considering the bleeding risk of thrombolysis. As mentioned above, the radial approach is preferable to femoral access to prevent retroperitoneal or groin bleeding complications [19].

As stated in recent guidelines [18], GPIIb/IIIa inhibitors are proposed only if there is angiographic evidence of a heavy thrombus burden.

Assessment of Platelet Reactivity in NSTE-ACS

A large prospective study has shown an association between low post-treatment platelet reactivity and increased occurrence of non-CABG-related TIMI major and minor bleeding in patients with NSTE ACS, suggesting that assessment of post-treatment platelet reactivity might be used to detect antiplatelet hyper-responders who have a higher risk of non-CABG related bleeding [32]. This may be particularly useful in patients with haemophilia to permit antiplatelet therapy to be tailored more accurately according to ischaemic and bleeding risk.

Coronary Artery Bypass Graft

Similarly to the recommended approach in the general population, bypass surgery should be proposed in the case of triple-vessel or left main artery CAD [2]. However, cardiac surgery remains a significant challenge in patients with haemophilia because of its specificities (sternotomy, total heparinization, extracorporeal circulation, etc.) [2]. Only case reports and small studies of haemophilia patients undergoing cardiac surgery have been published [33–36]. Since cardiac surgery is always a major intervention associated with a high risk of bleeding complications, high levels of replacement therapy are required in haemophilia patients for a few days after surgery to prevent bleeding events [2].

Management of Stable Angina

Stable angina in patients with haemophilia should be treated the same way as in the general population (Fig. 1) [1]. Low-dose aspirin should be proposed for patients with haemophilia. For patients with severe haemophilia, the use of clotting factor correction should be discussed in addition to low-dose aspirin. In the case of increased bleeding frequency, aspirin should be stopped (1).

Management of Non-valvular Atrial Fibrillation

Patients with AF are often treated with heart rate or rhythm control medications, synchronized electrical cardioversion and catheter-based ablation techniques, and require prophylactic anticoagulants to protect against stroke [37].

There is no evidence to suggest that patients with haemophilia are protected from thromboembolic complications, therefore, generally, patients with AF and haemophilia should be treated the same as AF patients without haemophilia.

Risk Stratification

Risk stratification is essential in AF patients to assess the risk of thromboembolic events and determine the treatment required. In the general population with AF, the individual stratification of the thromboembolic risk is based on the simple CHADS2 score [38] or the more recent CHA2DS2-VASc score [39] (Fig. 2). These scores are not directly applicable to haemophilia patients with AF as they do not include assessment of bleeding risk; nevertheless, they may prove useful as an aid to decision-making.

Recent ESC guidelines have stressed the need for stratification of the bleeding risk [40]. A recently devised method of assessing bleeding risk
in AF is the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly (HAS-BLED) bleeding risk schema (Fig. 3) [39,41,42]. Use of this scale in addition to the CHADS2 or CHA2DS2-VASc score to adjust treatment for bleeding risk seems sensible in patients with haemophilia.

**Prophylaxis**

In haemophilia patients, no prophylaxis is proposed if the CHADS2 score is \( \leq 1 \) [11], whereas low-dose aspirin is proposed when the CHADS2 score is \( \geq 2 \). In patients with moderate haemophilia at high risk for thromboembolic events, vitamin K antagonists targeted at low levels of international normalized ratio (INR; around 2.0) can be proposed in addition to replacement therapy. Haemophilia B is probably more difficult to manage because factor IX is vitamin K-dependent.

**Treatment**

Prophylaxis for stroke prevention is essential in non-valvular AF. Vitamin K antagonists are very effective as stroke prophylaxis but are burdened with difficulties in maintaining the required INR, inconvenience of coagulation monitoring, numerous drug and food interactions and concerns about the bleeding risk [43], hence they are under used in patients with haemophilia.

Several new oral anticoagulant agents such as oral direct thrombin inhibitors (e.g., dabigatran etexilate) and oral anti-Xa inhibitors (apixaban, edoxaban, rivaroxaban, etc.) are or will soon be available for the general population. Compared with vitamin K antagonists, some of these agents seem to reduce major bleeding complications, especially intracerebral bleeding complications [44–47]. Of note, these agents avoid the high INR values observed in some patients with VKA. Given that no specific antidotes are yet available, their use may be limited in haemophilia patients; however, they all have short half-lives compared to warfarin [48].

Given the bleeding risks with oral anticoagulation, left-atrial appendage (LAA) closure or occlusion may be possible alternative for patients with a contraindication for oral anticoagulation like in patients with haemophilia [49]. LAA closure has been shown to be non-inferior to oral anticoagulation in the prevention of all-cause stroke, cardiac death, and systemic embolization in patients with AF [50]. Although associated with an early safety hazard related to peri-procedural complications (which can be minimized by experienced operators), LAA may avoid some bleeding risk seen with long-term oral anticoagulation; however, recent European AF guidelines [37] state that evidence that LAA occlusion reduces stroke risk in AF is inconsistent and antithrombotic therapy may be required even after LAA closure.

As with ACS therapy, clotting factor replacement therapy is essential in AF to control the increased risk of bleeding due to antiplatelet and anticoagulant drug use [3].

**Ongoing/Planned Trials and Directions for Future Research**

Patients are being enrolled into a prospective multicentre study designed to assess the occurrence of age-related co-morbidity, especially CVD, associated risk factors and QRISK2 CV risk scores, in a large cohort of 700–800 male patients with haemophilia from the UK and The Netherlands (ClinicalTrials.gov number: NCT01303900). Data on the occurrence of CVD events from 5 and 10 years' follow-up

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>C= congestive heart failure/ LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>H= hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A= Age= 75</td>
<td>1</td>
</tr>
<tr>
<td>D= diabetes</td>
<td>1</td>
</tr>
<tr>
<td>S= stroke</td>
<td>2</td>
</tr>
<tr>
<td>Maximum: 6 points</td>
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<table>
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<tr>
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<tr>
<td>H= hypertension</td>
<td>1</td>
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<tr>
<td>A= Age= 75</td>
<td>2</td>
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<tr>
<td>D= diabetes</td>
<td>1</td>
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<tr>
<td>S= stroke</td>
<td>2</td>
</tr>
<tr>
<td>Vasculardisease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
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</tr>
<tr>
<td>Sexe category (ie: female gender)</td>
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</tr>
<tr>
<td>Maximum: 9 points</td>
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<table>
<thead>
<tr>
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<th>Score</th>
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<tr>
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<tr>
<td>Abnormal major liver or renal function (1 point each)</td>
<td>1-2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)</td>
<td>1-2</td>
</tr>
<tr>
<td>Maximum</td>
<td>9</td>
</tr>
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Fig. 2. The CHADS2,CHA2DS2-VASc scores and HAS BLED score [38,42,51].
patients should be treated in the same way as the general CVD population, following standard published guidelines, while choosing medications and procedures known to be associated with low rates of bleeding complications. With regard to prescribing antithrombotic agents, those with shorter half-lives and a convenient antidote would provide better management of possible bleeding complications and offer a safer choice of therapy in this setting. In addition, optimal substitution therapy should be provided during all invasive procedures and during the acute phase of ACS and tailored to the individual patient.

### Conflict of Interest Statement

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