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Review

Factor VIII: Long-established role in haemophilia A and emerging evidence beyond haemostasis

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ABSTRACT

Factor VIII protein (FVIII) as a coagulation replacement factor has for decades been used as the standard of care for management of people with haemophilia A. It is effective for treatment of bleeding events, as prophylaxis to prevent bleeding events and preserve joint function, and to support surgery in people with haemophilia A. Despite long experience in treating haemophilia A, we are only beginning to understand the functions of FVIII beyond its established role as a coenzyme to factor IXa to expedite thrombin generation through the intrinsic pathway of coagulation. Here, we review the current role of FVIII coagulant (FVIII:C) in haemophilia A management and emerging evidence for the role of FVIII across multiple systems, including the cardiovascular system, angiogenesis and maintenance of bone health. For instance, supraphysiological FVIII levels are a risk factor for venous thromboembolism. von Willebrand factor (VWF), which forms a non-covalent complex with circulating FVIII, is an established marker and regulator of angiogenesis. In a mouse model of haemophilia, treatment with FVIII decreased expression of receptor activator of nuclear factor kappa-B ligand (RANKL), a marker for bone turnover. Longitudinal follow-up data in people with haemophilia A are needed to confirm and extend these observations.

1. Introduction

People with haemophilia A (PwHA) may suffer spontaneous bleeding events (including those that are life-threatening) and develop joint damage (arthropathy) as a result of recurrent bleeding into joints [1]. In PwHA, prophylaxis with FVIII coagulant (FVIII:C) is well established as the standard of care for the treatment and prevention of bleeding episodes, and in surgeries [2]. This is supported by extensive clinical and real-world evidence demonstrating safety and effectiveness in bleed prevention and, above all, preservation of joint health. Additionally, preventing bleeding events improves quality of life (QoL) and allows PwHA greater participation in school, work and social activities [3-5]. The renewed interest in a patient-centred perspective has led to a shift in the paradigm of care in haemophilia. Knowledge of the pharmacokinetic profile of the various commercially available FVIII:C products in combination with the bleeding phenotype of each individual enables treatment to be tailored to patient conditions and lifestyles [6-8].

Observations derived from longitudinal studies of disease incidence in PwHA and studies in animal models have revealed potential additional roles for FVIII in several biological processes. These potential roles may be categorised as either secondary to the impact of impaired thrombin generation or as independent of the role of FVIII in haemostasis. In this review, we explore current evidence for the roles of FVIII.

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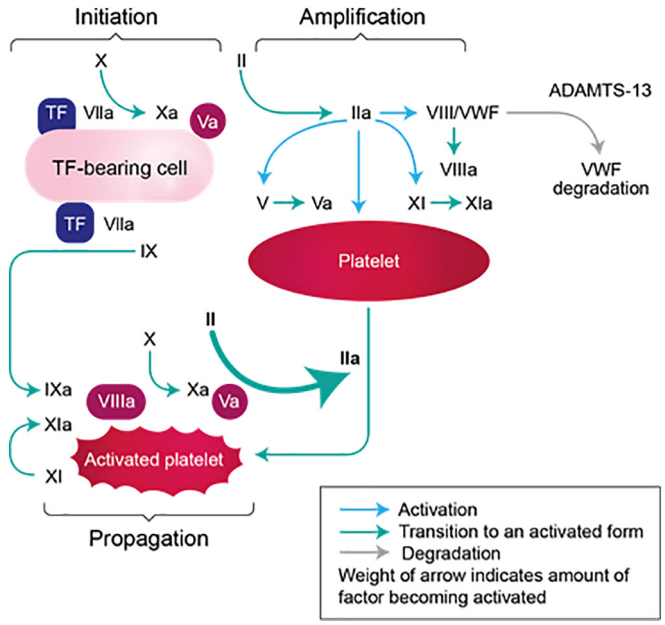

Fig. 1. Phases of coagulation.
TF, tissue factor; VWF, von Willebrand factor.

2. Coagulation function of FVIII (FVIII:C)

FVIII has a well-established role in the promotion and maintenance of haemostasis after injury, due to its pivotal role in the coagulation cascade [1]. Sequential activation of clotting factors, both zymogens and cofactors (including FVIII), drives coagulation to form thrombin (FIIa; Fig. 1). FVIII is a coenzyme critical in accelerating the generation of Xa and subsequently of thrombin. FVIII is therefore central to propagation of a haemostatic response. Circulating FVIII is bound to von Willebrand factor (VWF), which stabilises FVIII and binds to the subendothelial matrix to mediate platelet adhesion at sites of injury, hence localising FVIII at these sites. Following activation by FXa or FIIa-mediated proteolysis via amplification and feedback loops, activated FVIII (FVIIIa, which becomes detached from VWF) forms the Xase complex with FIXa on the surface of platelets to potentiate FXa generation.

A secondary role of FVIII in coagulation is regulation of VWF. FVIII stabilises VWF multimers and renders them more susceptible to degradation by the metalloprotease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), while FVIIIa, which is not VWF-bound, does not have this effect [9,10].

Deficiency in FVIII due to mutations in the *F8* gene causes haemophilia A (HA), a condition affecting 1/5000 live male births [1]. In PwHA, it is recommended that bleeding events are treated as rapidly as possible after detection, optimally within 2 h, replacing missing FVIII:C [2,11]. Dosing protocols for FVIII:C use in different bleeding scenarios are well established [2], and optimal dosing relies on monitoring FVIII levels using accurate assays. However, there is inter-laboratory variability in the results obtained and there is evidence that assays routinely used in laboratories may under- or overestimate FVIII levels provided by different FVIII products [12-14]. The optimum methods for monitoring each new product will need to be assessed in each laboratory [12-14].

Replacement therapy delivered as prophylactic treatment offers better patient outcomes (maintained joint health, improved QoL) than on demand treatment at any age [15-17].

The Joint Outcomes Study demonstrated that children treated with FVIII primary prophylaxis had less joint damage and were more likely to remain free from joint damage as compared with peers treated on-demand [17]. The 10-year ESPRIT study confirmed these observations,

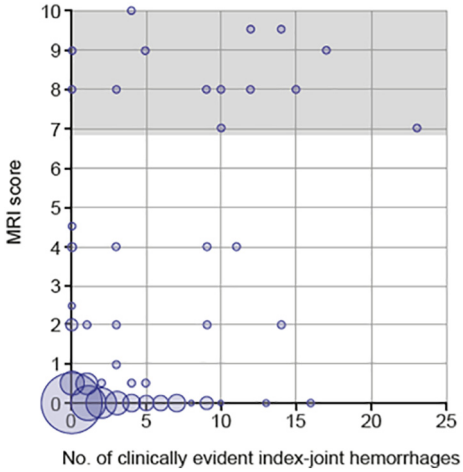

Fig. 2. Comparing MRI score for index joints with number of joint haemorrhages. MRI score of 0 = normal joint, MRI score > 7 = bone/cartilage damage by MRI. Sizes of circles correspond to the number of cases.
MRI, magnetic resonance imaging.

finding fewer joint bleeding events and improved QoL in children treated with early secondary prophylaxis versus on-demand treatment [3].

The SPINART and POTTER studies both found improved joint outcomes and reduced bleeding in adolescent/adult patients starting prophylaxis, compared with on-demand treatment [4,18]. Despite the clear evidence of significant reduction in bleeding frequency in patients receiving regular prophylaxis, breakthrough bleeds and subclinical bleeds may both occur. The former may be related to poor adherence, while the latter to the need for increased protection. Therefore, both result from insufficient haemostatic coverage provided by attainable trough levels with traditional and “not individualized” prophylaxis regimens. The accumulation of such bleeds may impact on long-term joint health [19], even in patients always treated with prophylaxis, which further underlines the importance of tailoring treatment. In addition, the early detection of such microbleeds and concurrent inflammation is crucial to further optimize treatment. This can be achieved through the use of sensitive tools such as magnetic resonance imaging or thermography (Fig. 2 [20]) [17,21], although these are not universally available.

Current guidance for PwHA undergoing surgery is to raise FVIII levels as appropriate prior to surgery and use FVIII:C postoperatively as needed [2]. Standard FVIII:C products may be delivered by continuous infusion in major surgery [22], while to date there is no experience with continuous infusion of extended half-life FVIII:C.

Over 50 years of clinical experience with FVIII:C as a treatment for HA means that the safety profile is well understood. Modern manufacturing processes for FVIII:C products have minimised the risk of blood-borne viral disease transmission [23]; morbidity and mortality from such transmission was previously a serious concern with FVIII:C use [15]. For example, between 1979 and 1998, of 4781 deaths in people with haemophilia (PwH) in the US, 2254 were related to HIV [24], while chronic hepatitis C infection has been the dominant cause of morbidity in adult people with haemophilia until now [25]. Another major concern with FVIII:C use is the potential for patients to develop inhibitors – antibodies that completely or partially neutralise FVIII clotting activity and render FVIII:C infusions less effective. Inhibitors occur in up to 30% of previously untreated patients [26,27].Inhibitors may be eradicated through immune tolerance induction (ITI), based on regular FVIII:C infusions; however, this may be burdensome and may not be successful in around 20% of patients [28,29]. Due to the high frequency of infusions, very often children undergoing ITI may require central venous access devices (CVADs), which are also used in older patients with poor venous access. CVAD use is often complicated by

infections and/or thrombosis that requires CVAD removal, which can impair treatment outcome and further increase haemophilia-related morbidity [30].

3. Impact of impaired thrombin generation beyond haemostasis

3.1. Haemophilia may influence the risk of cardiovascular disease

Many studies have investigated possible links between haemophilia and cardiovascular disease (CVD). Intuitively, a reduced risk of thrombotic events in PwHA might be expected. A review of 15 longitudinal and cross-sectional studies, including 19,242 patients with coagulation disorders (14,754 of whom had HA), found no significant reduction in arterial thrombosis-related mortality versus the general population [31]. HIV or hepatitis C infection (or the therapy for these infections), which affect many adult PwH, are both risk factors for arterial disease, and this may confound studies of CVD in PwH [32,33]; in a study of CVD in PwH without HIV, ischaemic heart disease mortality was lower than expected [34]. Based on a small study, severe haemophilia appears to offer greater protection from arterial disease than moderate or mild haemophilia [35]; thrombin generation (though not specifically FVIII) is likely to play a role in the formation of atherosclerotic plaques [36]. In terms of acute thrombosis, supraphysiological FVIII level (upstream of thrombin generation) is an established risk factor for venous thromboembolism [37]. The influence of regular FVIII:C infusions on CVD risk in HA has not been studied.

3.2. FVIII and brain function in patients with haemophilia

Despite studies suggesting an association between cognitive or behavioural problems in patients with both haemophilia A and B, a direct role for FVIII or FIX in brain function has not been demonstrated. There are findings of reduced academic achievement [38], a higher incidence of attention-deficit/hyperactivity disorder [39-41] and a greater need for special educational services [40,41] in PwH compared with their peers; the studies, however, do not allow us to conclude whether these observations are the impact of a chronic disease or a clinical feature of FVIII deficiency.

It is possible that cerebral bleeding events directly impact brain function in PwH: intellectual functioning, visual-spatial skills and fine motor skills were scored lower in a small group of haemophilia patients with intracranial haemorrhage (ICH) compared with controls [42]. Even clinically non-evident bleeding events (microbleeds) detectable only on magnetic resonance imaging influence cognitive function [43,44]. Recently, it has been demonstrated that intracranial microbleeds are more frequent in PwH as compared with age-matched general population controls [45]. While prophylaxis with FVIII reduces the incidence of ICH compared with on-demand treatment [46], and improves work and school performance in PwHA, it may reflect enhanced participation in work and school rather than a direct effect of FVIII on cognitive function [47].

3.3. Hypertension and renal impairment in HA

3.3.1. Hypertension

An increased prevalence of hypertension among PwH compared with the general population has been reported [48-51]. As in the general population, age and body mass index are major risk factors for hypertension in PwH [52]. Neoangiogenesis/altered vascular architecture is seen in response to bleeding events in the joints, as a response to prolonged local inflammation [53] (discussed in 4.1). Similar neoangiogenesis in the kidney may perpetuate future bleeding events and result in the hypertension observed among PwH [54,55]. Whether replacement therapy with FVIII:C will impact neoangiogenesis is not known. The propensity of PwH to suffer from hypertension is of immediate concern as risk of ICH, which is 20–50 times more common among PwH than in the general population, increases with the severity of hypertension [49].

3.3.2. Renal function

Haematuria is more common in PwH than in the general population, with a reported prevalence of 66% among PwH, compared with 0.19–16.1% among healthy young adults [56]. PwH are reported to have a 50-fold greater risk of developing chronic kidney disease compared with the general population [57]. However, a large EU observational study did not find a correlation between haematuria and renal dysfunction in PwH [32]. Small-vessel disease and renal microbleeds are suspected to underlie poor renal function [58], but have yet to be comprehensively studied in PwH. The US Hemophilia Surveillance System reported high rates of death from kidney disease among PwH: data from 2950 studied males showed that renal disease was responsible for 4.2% of recorded deaths [57]. The American Thrombosis and Hemostasis Network (ATHN) 1, a cross-sectional observational study, will seek to investigate the risk factors associated with kidney disease [59]; currently, the precise role of FVIII, and a mechanism for its influence, is not defined.

3.4. Thrombin generation and cancer metastasis

Three decades of follow-up in Sweden found an increased incidence of cancer in PwH A or B, mainly haematological malignancies and urinary organ cancers [60]. The observation that this increased incidence is common to both haemophilia A and B could be interpreted to suggest that decreased thrombin generation, rather than FVIII or FIX per se, may be associated with malignancy. Inflammation following bleeding may also contribute to carcinogenesis/metastasis [61].

The interplay between coagulation and tumourigenesis and/or metastasis is complex. In contrast to the observation from the Swedish study in PwH A or B, some preclinical evidence suggests a role for normal or supranormal thrombin generation in cancer metastasis. In a mouse model of HA, lung tumour seeding was significantly reduced in the presence of lepirudin, a direct thrombin inhibitor [62]. In patients with advanced malignancy, the low-molecular-weight heparin anticoagulant dalteparin was found to improve survival in a subgroup of those with a better prognosis [63,64]. Downstream of thrombin generation, formation of a cancer-cell-platelet-fibrin complex is thought to promote cancer-cell adhesion to the vascular endothelium, which then provides a matrix for tumour-associated angiogenesis [62,65,66].

A comprehensive mechanistic picture of cancer risk in PwH remains to be established [67].

4. Physiological roles for FVIII beyond coagulation

4.1. FVIII and VWF in angiogenesis

Marked neoangiogenesis and abnormal vascular architecture have been observed in arthropathic HA joints specifically, but not in those damaged by other conditions, such as rheumatoid arthritis [54]. Moreover, the degree of arthropathy is more severe in PwHA compared with PwHB [68]. Markers of vascular remodelling (α-smooth muscle actin, endoglin [CD105] and vascular endothelial growth factor) are strongly expressed after joint bleeding events and are postulated as targets of FVIII signalling by an unknown mechanism(s) [53,54].

Additionally, VWF is established as a marker and regulator of angiogenesis [69], and ADAMTS13, the enzyme responsible for its degradation, has been shown to be proangiogenic [70,71]; however, a connection between angiogenesis, these two proteins and FVIII has not been established.

4.2. Bone health in haemophilia and FVIII in bone remodelling

In joint bleeding events, haemoglobin-related iron deposits have

Table 1
Systems/processes impacted by haemophilia and the role of FVIII.

System/process	Influence of haemophilia	Specific role of FVIII
Coagulation	Impaired clotting: bleeding and joint damage	Forms the Xase complex with FIXa on the surface of platelets to potentiate FXa generation [1] Treatment and prophylaxis of bleeding events
Cardiovascular system	Lower incidence of arterial disease in some studies [34,92-94]	Supraphysiological FVIII levels are a risk factor for venous thromboembolism [37]
Brain	Reduced academic achievement [38] Higher incidence of attention-deficit/hyperactivity disorder [39-41] Poor intellectual functioning [42] Cerebral bleeding events [42,45,47]	Not established
Hypertension	Higher incidence of hypertension [48-51]	Not established (see angiogenesis)
Kidney	Haematuria and increased risk of kidney disease [56,57]	Not established
Cancer incidence and spread	Increased incidence of haematological malignancies and urinary organ cancers [60] Decreased metastasis in a mouse model [62]	Not established
Angiogenesis	Neoangiogenesis and abnormal vascular architecture [54]	FVIII binding partner VWF is a regulator of angiogenesis [69]
Bones	Increased fracture risk [81] Decreased bone mineral density [74-80]	RANKL (which increases bone breakdown) expression is decreased by FVIII treatment [86]
Macrophages	Impaired function and differentiation [90]	Not established
Haematopoiesis	*F8*-knockout mice have altered proportions of haematopoietic stem cell progenitors, with functional impairments [91]	Not established

FVIII, factor VIII; FIXa, activated factor IX; FXa, activated factor X; RANKL, receptor activator of nuclear factor kappa-B ligand; VWF, von Willebrand factor.

been shown to increase inflammatory cytokines (interleukin [IL]-1α, IL-6 and tumour necrosis factor-α) and proangiogenic factors, enhancing articular cartilage and subchondral bone destruction [72]. Adequate long-term prophylaxis with replacement FVIII or FIX has been suggested to preserve bone mineral density (BMD) in PwH [73], potentially because it supports patients participating in physical activity, particularly during the years (childhood and adolescence) when most bone mineralisation occurs.

An association between haemophilia and reduced BMD has been observed in both children and adults in various studies [74-80]. As might be expected, there is also a greater risk of bone fracture in PwH A or B compared with the general population, with risk increasing with increasing haemophilia severity [81]. It is challenging to understand if this fracture risk is due to an unsteady gait/joint disease leading to more falls, or decreased bone density making fracture more likely in the event of a fall. Two factors common to all PwH, namely a sedentary lifestyle [78,82] and bleeding into joints [72], contribute to poor bone health.

In addition to a general effect of haemophilia on BMD, animal models have provided evidence for a specific role of FVIII in bone remodelling. Bone remodelling is controlled by bone formation and resorption, primarily induced by osteoblasts and osteoclasts, respectively. Receptor activator of nuclear factor kappa-B (RANK) on the surface of osteoclasts and their precursors is activated by RANK ligand (RANKL), which stimulates osteoclastogenesis and enhances the breakdown of bone tissue. Conversely, bone tissue formation is aided by osteoprotegerin (OPG), which, by acting as an alternative receptor for RANKL, inhibits the activation of RANK and thus osteoclast activity [83]. Bone formation may be indirectly affected by FVIII via thrombin generation, which has been associated with the activation of osteoblasts in a rabbit leg-lengthening model [84]. In addition, a direct role in bone remodelling has been observed for the FVIII–VWF complex. FVIII–VWF binds to OPG and RANKL, enhancing the inhibitory effect of both RANKL- and OPG-induced osteoclastogenesis [85]. Osteoblasts differentiated from primary mesenchymal cells from FVIII-deficient mice treated with FVIII-replacement therapy had a 25% reduction in RANKL, with increased osteoblast formation [86]. Together, these data suggest that, despite other aggravating factors, FVIII deficiency is an independent risk factor in the osteoporosis observed in PwH.

There is a paucity of data on whether there are differences between PwH A and B in terms of bone health, as the two conditions are often studied as one patient population [87]. FIX-deficient mice have reduced BMD compared with wild-type mice; although the mechanism behind this finding is unclear, the RANKL/OPG data are consistent with aberrant osteoblast-osteoclast signalling [88]. In blood plasma samples from PwHA, PwHB and controls, patients with FVIII deficiency but not FIX deficiency have evidence of increased bone resorption (as measured by carboxy-terminal collagen crosslinks [CTX-1]) compared with control samples [89]. Increased OPG levels are present in FIX-deficient plasma and may contribute to the differences seen in CTX-1 production between subjects with FIX and FVIII deficiency [89].

4.3. FVIII has defined roles in specific cell types

Two studies have highlighted possible roles of FVIII in the development/function of specific cell types.

4.3.1. Macrophage function

Preliminary evidence indicates that macrophages derived from PwH display poorer regenerative functions, such as blood clot infiltration and red blood cell phagocytosis, than macrophages derived from healthy controls. Moreover, the impaired clotting characteristic of PwH leads to increased inflammation and a deregulation in macrophage differentiation, which may explain the commonly observed deficits in wound healing and tissue regeneration [90]. Whether FVIII replacement therapy corrects this defect is still unknown.

4.3.2. Haematopoiesis

A single study in *F8*-knockout mice indicated a potential role for FVIII in the regulation of haematopoiesis. These mice had altered proportions of haematopoietic stem cell (HSC) progenitors, which had functional defects: reduced long-term repopulating capacity and enhanced granulocyte-colony-stimulating factor-induced mobilisation. The mechanism underlying this dysregulation lies downstream of FVIII, with thrombin/protease-activated receptor 1 signalling [91].

5. Discussion

We have described the central role that FVIII plays in coagulation via thrombin generation; the broader impact of impaired thrombin generation in HA on CVD, the central nervous system, hypertension and renal disease and metastasis; and emerging evidence for a role of FVIII in regulating processes beyond thrombin generation, as summarised in Table 1. The potential impact of FVIII beyond coagulation is supported

by the fact that plasma concentrations of FVIII are typically much higher than the levels required to trigger coagulation.

In studying data from PwHA, it is difficult to isolate the coagulation-dependent and -independent roles of FVIII. A difficulty in determining causal roles for FVIII in some systems is that they can be affected by a complex interplay of biological confounding factors, as in the case of bone health. This issue is further compounded by the generally low number of patients in many studies, which is a limiting factor when investigators wish to use subanalyses or multivariate analysis to remove confounding factors. The studies discussed above suggest that the majority of the tissues or systems affected by a lack of FVIII in haemophilia are affected because of a coagulation impairment in some way; examples of a role for FVIII beyond coagulation appear to be HSC maturation, macrophage function (contributing to joint health), bone formation [86,91], and potentially neoangiogenesis [54]. The evidence for these has come not just from retrospective or correlative data gathered in PwH, but also from specific mouse models in which signalling pathways can be unravelled.

A direct role for FVIII in the maintenance of bone health, via RANKL and independent of its role in coagulation, has been established through mouse research [85,86]. This interaction may partly explain the restored bone health observed in children who receive FVIII-replacement therapy [73,95,96], though studies of their osteoblast function would be required to confirm the hypothesis.

Currently, FVIII:C prophylaxis is the standard of care for PwHA, and maintenance of FVIII levels suited to a patient's activity offers protection from bleeding events by compensating for FVIII deficiency. The goal of haemophilia therapy has now shifted prevention of clinically evident bleeds to protection from subclinical bleeds allowing for better long-term joint health outcomes, and to improving patient QoL through a decreased burden of infusion and increased efficacy [7,97]. A key benefit of using FVIII:C prophylaxis is the high degree of control offered by manipulating the time/level of FVIII dosing [23].

In addition to FVIII replacement, alternative technologies are being developed to treat HA, including the FIXa-FX bispecific antibody emicizumab [98], anti-tissue factor pathway inhibitor (TFPI) monoclonal antibodies, such as concizumab [99-101], and the antithrombin RNA interference therapy, fitusiran [102]. In the phase III studies of emicizumab in PwHA with or without inhibitors, the annualised rate of treated bleeds was significantly lower in all groups receiving emicizumab compared with patients treated on demand or versus prior prophylaxis (in non-inhibitor patients in an observational arm) [98,103]. Thrombotic microangiopathy has been reported as a serious adverse event with emicizumab (when used together with activated prothrombin complex concentrate), whereas replacement FVIII:C therapy has not been associated with this complication [103]. In a phase Ib study, concizumab given to PwHA without inhibitors for 42 days was well tolerated without serious adverse events [101]. The trial was not powered to evaluate efficacy, though a trend towards lower bleeding rates was observed in patients in the highest dose cohort. Coagulation-related parameters, including D-dimer and prothrombin factor 1 + 2, were above the normal reference range in this cohort, but the significance of this finding is uncertain. No thrombotic events were reported (nine subjects observed for 42 days). Future longer-term studies of efficacy and safety, and ideally studies of putative thrombin-independent roles of FVIII in patients receiving emicizumab or concizumab, are needed. Although additional treatment options are likely to offer patients greater flexibility in terms of administration method or frequency, the long-term efficacy/safety profiles of these newer treatments have not yet been established [103,104]. In particular, the impact on joint health of not replacing FVIII as a molecule is yet to be established. Finally, the best protocols to manage breakthrough bleeding events or surgery-related bleeding are still being developed. Moreover, standardised/optimal protocols for laboratory monitoring of coagulation activity with non-replacement therapies are not yet clearly defined. A further consideration is the treatment of inhibitor patients with non-replacement therapy. Without being maintained on FVIII:C following immune tolerance induction, it is possible that tolerance will be lost, a concept that remains to be explored. We anticipate that data on the incidence of secondary pathology, such as impaired renal function, from PwH treated with non-replacement therapies will be informative on the coagulation-dependent and -independent roles of FVIII, and such findings may ultimately inform treatment choices.

The changing demographic among PwHA should also be noted [105]. In an ageing haemophilia population, the effects that FVIII replacement has on age-related illnesses such as cancer, or comorbidities associated with altered coagulation or vascular biology (e.g. atrial fibrillation and type 2 diabetes), may become apparent [106,107]. Such observations will not only improve our mechanistic understanding of the role of FVIII in comorbidities, but could also inform treatment choice for PwHA who have an increased susceptibility to comorbidities.

6. Conclusion

In the elucidation of the role of FVIII, three aspects, namely impaired coagulation and joint sequelae, a wider impact of impaired thrombin generation and lifestyle consequences, and putative coagulation-independent roles of FVIII, are becoming better defined. Clinically, based on extensive experience of its effectiveness and safety, FVIII:C for treatment of bleeding events and in surgery is the standard of care for PwHA worldwide. For bleeding prophylaxis, FVIII replacement remains the standard of care in many countries, though in some, the treatment paradigm is evolving. Based on the evidence presented in this review, now is the time for clinicians and researchers interested in the non-haemostatic role of FVIII to determine if the data presented above hold up and whether non-replacement treatments may have a differential effect compared with FVIII. In the US, ATHN has launched a large, multi-institutional, multi-year natural history study of PwHA who are treated with FVIII:C or non-replacement therapies in order to investigate these types of questions [108]. These real-world data will be valuable, but the study will take years to accumulate sufficient data and requires extensive data collection to address potential confounders during analyses. In the interim, further research using in vitro and animal models of HA is essential to improve our understanding and the mechanism of the coagulation-dependent and -independent role of FVIII.

Practice points

- FVIII replacement remains the standard of care in many countries, though the treatment paradigm of haemophilia A is evolving and now includes the use of both FVIII and non-FVIII therapies for bleeding prophylaxis in patients with and without inhibitors.
- FVIII may have a role in regulating processes beyond thrombin generation; the potential clinical implications of this are currently unknown.

Research agenda

- Data on the incidence of secondary pathology in patients with haemophilia receiving non-FVIII replacement therapy.
- Preclinical data on the role of FVIII in angiogenesis.
- Further preclinical data on the role of FVIII in bone remodelling.

Future considerations

- Longitudinal follow-up data on the potential link between FVIII and bone health in patients with haemophilia A.
- Preclinical data on the physiological roles of FVIII beyond coagulation.

Conflicts of interest

Author name	Disclosure information
Bethany Samuelson Bannow	Nothing to disclose
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Cedric Hermans	Paid consultancies or invitations to give lectures for: Shire, Pfizer, Bayer, Octapharma, LFB, CAF-DCF, Roche, Novo Nordisk, CSL Behring, Sobi/Bioverativ, Kedrion, Roche
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