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Haemophilia and ageing

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Summary

Advances in the development of effective and safe treatments for haemophilia over the last 50 years have resulted in a significant increase in the life expectancy of persons with haemophilia (PWH). The management of this new cohort of middle-aged and elderly PWH is challenging because of the opposing risks of haemophilia and age-related cardiovascular disease and malignancy. Furthermore, this cohort of ageing PWH have the additional comorbidities of HIV/hepatitis C and chronic haemophilic arthropathy. This article reviews the prevalence, underlying mechanisms, and treatment strategies for managing these comorbidities. International collaboration is essential for registry data and further prospective trials to inform optimal evidence-based management for this rare disorder in the future.

Introduction

Haemophilia is due to reduced or absent factor VIII or IX activity and is characterised by bleeding primarily into joints and muscles. The development and availability of clotting factor concentrates and home treatment allows the rapid administration of the missing factor to stop the bleeding once it occurs. Although this improved the lives of persons with haemophilia (PWH), it was the introduction of prophylaxis in the 1990s that dramatically changed the quality of life of most patients and allowed survival into older age with minimal or no bleeds. We now have individuals with severe disease reaching older age which presents new challenges in managing PWH. This review addresses the problems (table 1) and associated management questions which PWH experience as they get older.

Increasing life expectancy of PWH

As treatment became more widely available, the life expectancy of PWH improved in parallel. In Sweden, the median life expectancy of persons with severe haemophilia (PWSH) increased from 11 years during the period 1831-1920 to 57 years during 1961-80, whilst for moderate patients it increased from 28 to 72 years(Larsson 1985). Proportionally this was a much greater increase than the general male population over the same period (62 to 76 years). A subsequent UK study of 6,018 PWH during the period 1977-1999 found higher median life expectancy: 63 years for PWSH, and 75 years in mild/moderate haemophilia (Darby*, et al* 2007). Crucially this was in a population who were not infected with HIV although it did include those infected with hepatitis C (HCV). All-cause mortality for hemophilia A and hemophilia B was similar. Compared with mortality in the general population, mortality from bleeding and its consequences, and from liver disease and Hodgkin disease, was increased, but for ischemic heart disease it was lower, at only 62% of the general population rates (Darby*, et al* 2007).

HIV and hepatitis C

The dramatic initial increase in life expectancy which corresponded to the more widespread availability of replacement therapy, and plasma derived factor concentrates in the mid-1970s and early 1980s, was unfortunately associated with the catastrophic contamination of these concentrates with HCV and then with HIV in the early 1980s. Viral inactivation of plasma derived factor concentrates was not introduced until 1985. Out of a total of 7250 PWH registered in the UK Haemophilia Centre Doctors' Organisation database during 1977-1998 (Darby*, et al* 2004a), more than 90% were infected with HCV and 1246 were infected

with HIV. For PWSH who contracted HIV, annual mortality was 0.9% before HIV, and this increased progressively from 1985 reaching over 10% during 1993-1996 before falling to 5% in 1997-1999 with the advent of treatment (Darby*, et al* 2004a). It is largely because so many PWSH died of HIV during this period that it is only recently, following both viral inactivation of concentrates and effective treatment for HIV, that there is a relatively large cohort of aging PWSH. Nowadays HIV-positive PWH should be under the care of HIV specialist physicians and almost all are on highly active anti-retroviral therapy (HAART). HAART means that HIV is now a chronic disease, although patients must also be managed for the side effects of treatment such as increased risk of cardiovascular disease associated with protease inhibitors (Friis-Moller*, et al* 2007, Shah*, et al* 2018).

A retrospective review of 863 HCV infected patients with inherited bleeding disorders from the Netherlands and the UK with a median follow-up since HCV infection of 31 years, showed that 19% of patients spontaneously cleared the virus and 81% developed chronic HCV infection (Fransen van de Putte*, et al* 2014). Of the patients with chronic HCV, 13% developed end-stage liver disease (ESLD) and 3% developed hepatocellular carcinoma during this timeframe. Concomitant HIV infection promotes hepatitis C viral replication and hepatic inflammation, accelerating the progression to end-stage liver disease (cumulative incidence ESLD 14% v 2.6%)(Goedert*, et al* 2002) and associated death from liver failure (Darby*, et al* 2004a). Treatment for hepatitis C aims to clear the virus and prevent progression to cirrhosis and ESLD. Interferon and ribavirin treatment regimens, resulted in approximately 40% of PWH achieving sustained virological remission (Holmstrom*, et al* 2016). Recently however, new even more effective direct-acting antivirals have been introduced, enabling interferon-free treatment with high rates of sustained virological

responses (90-100%) and without the substantial side effects that were often associated with interferon and ribavirin (Makris and Konkle 2017, Walsh*, et al* 2017). All patients infected through blood products should be offered treatment with these new agents. Patients who had cirrhosis before they cleared HCV, remain at risk of hepatocellular carcinoma and require regular follow-up with liver ultrasound and alpha-fetoprotein monitoring.

Prophylaxis vs on demand therapy

Bleeding into joints results in synovial inflammation and ultimately a destructive arthropathy. Prophylaxis has been the standard of care in first-world countries since the early 1990s for PWSH in order to modify the phenotype to that of moderate patients. Many adults, however, remained on 'on demand' therapy, treating bleeds once they occurred. The SPINART study was a randomized controlled trial that investigated the impact of prophylaxis in adults with haemophilic arthropathy (Manco-Johnson*, et al* 2013, Manco-Johnson*, et al* 2017). Eighty-four adults with severe haemophilia who were not on prophylaxis were randomized to either continue 'on demand' therapy or to start regular prophylaxis. After 3 years, patients on prophylaxis had experienced a 94% reduction in bleeding episodes. Prophylaxis was associated with improved function, quality of life, activity and pain but there was no reduction in structural arthropathy documented by MRI suggesting that this is irreversible. These results are supported by those of the POTTER study which compared on-demand treatment and secondary prophylaxis in adolescents and adults (Tagliaferri*, et al* 2015). Prophylaxis improves function but PWSH must start before joint bleeding onset to prevent arthropathy. PWSH of all ages are therefore now

encouraged to use prophylaxis. Some adults, however, remain reluctant to commence prophylaxis for a variety of reasons including resistance to change a life-time way of treating haemophilia, dislike of alternate daily intravenous injections and concern for additional cost to National Health Service.

Additional benefits of prophylaxis in ageing PWH could be a reduced risk in intracranial bleeding. For PWH the risk of intracerebral haemorrhage (ICH) increases from about 40-50 years, with HR 3.7 (P=0.02) for PWH over the age of 50 compared to those aged 6-10 years (Nuss*, et al* 2001). There is developing interest in cerebral microbleeds (CMBs) although more data is required to understand their relevance. CMBs are clinically silent bleeds which are seen with ageing in the normal population but accumulating evidence suggests that they are associated with increased risk of ICH, a reduction in cognitive function and both vascular and all-cause dementia (Humphries and Mathew 2018, Husseinzadeh*, et al* 2018). In PWH (n=31), CMB were not clearly more prevalent than in controls, but they were associated with older age, HCV infection, cardiovascular risk factors, and the presence of an inhibitor (Husseinzadeh*, et al* 2018).

As PWH age, additional considerations balancing benefit of prophylaxis against feasibility should be considered. These include diminished activity (with reduced risk of bleeding), and potentially reduced ability to self-infuse due to poor venous access, poor vision, reduced dexterity, and dementia. Feasibility of continued prophylaxis depends on the availability of infusion assistance such as outreach nursing care and proximity of haemophilia treatment centres, although the development and recent licensing of **extended half-life** factors and novel haemostatic agents which can be given subcutaneously once a week will likely transform this care (Callaghan*, et al* 2018).

New Inhibitors in older age

Clinicians need to remain vigilant to the risk of inhibitor formation in older age. Inhibitory allo-antibodies against the replaced factor VIII or factor IX are a serious complication of treatment, precluding standard treatment and are associated with more bleeds, arthropathy, pain and time off work/school. They develop in approximately 30% of PWH A and 5% of PWH B. The peak time for developing inhibitors in PWSH is within the first 20-50 exposure days and subsequently there is only a very small accumulation with time (Darby*, et al* 2004b). In contrast the international INSIGHT study found that the risk of inhibitors in mild and moderate haemophilia accumulated with increasing exposure: 6.7% at 50 ED, rising to 13.3% after 100 EDs (Eckhardt*, et al* 2013). Patients with mild and moderate haemophilia often do not require treatment with factor concentrate and the risk of developing an inhibitor accumulates with age (cumulative risks of inhibitor development at ages 5, 15, 50 and 75 years were 5%, 6%, 10% and 12%, respectively(Darby*, et al* 2004b). Increased risk of inhibitors is associated with certain mutations and periods of intensive treatment(Castaman and Fijnvandraat 2014). In moderate/mild hemophilia the development of inhibitors remains deleterious, with patients at risk of severe bleeding and all-cause mortality similar to that in severe hemophilia. Whilst some inhibitors resolve spontaneously, many patients will require treatment for bleeds with bypassing agents and consideration of immune tolerance or immunosuppression in order to eradicate the inhibitor.

Musculoskeletal issues

A bleed into a joint, especially if recurrent, results in synovial hypertrophy, cartilage damage and ultimately bone damage (Van den Berg*, et al* 2006). Older patients, who grew up initially without treatment, or only limited on demand treatment, invariably have chronic haemophilic arthropathy. This may result in crepitus, reduced range of movement, joint instability, flexion contractures, and muscle wasting, as well as pain. The most commonly effected joints are knees, ankles and elbows (Siboni*, et al* 2009). Chronic haemophilic arthropathy affects people with both haemophilia A and B. Whilst haemophilia A and B have been considered clinically indistinguishable, with phenotype dependent on the level of factor VIII or IX, there are suggestions severe haemophilia A has a more severe phenotype than severe haemophilia B and therefore that PWSH A may have poorer joint health in older age compared to PWSH B (Melchiorre*, et al* 2016, Soucie*, et al* 2018, Tagariello*, et al* 2009). However rather than an inherent difference between FVIII and FIX deficiency, this could be the result of the current laboratory definition of 'severe' (Makris 2009).

A multidisciplinary approach is essential for joint health. In the ageing population who already has chronic arthropathy, it can be difficult to distinguish pain due to chronic arthropathy from the pain of acute bleeds, which may lead to over use of factor replacement (Timmer*, et al* 2015, Timmer*, et al* 2016). Point of care ultrasound can be used to help evaluate whether pain is secondary to an acute bleed. Whilst promising, this is operator dependent and the patient would still be required to attend a haemophilia centre (Stephensen*, et al* 2018). Physiotherapists play a key role both in rehabilitation for acute musculoskeletal bleeding, and also in maximizing mobility and function in chronic arthropathy (Stephensen*, et al* 2018).

Pain control is important and patients frequently use paracetamol (acetaminophen). As inflammation plays a significant role in synovitis and the development of chronic arthropathy, it would be appealing to use non-steroidal anti-inflammatory drugs (NSAIDs) to reduce both pain and inflammation. NSAIDs, however, are not recommended in PWH due to increased risk of bleeding, especially gastrointestinal. Cyclooxygenase-2 (COX-2) selective inhibitors preferentially inhibit the COX-2 enzyme rather than COX-1. As a result they do not affect platelet thromboxane production or platelet function, and have reduced gastrointestinal side-effects. In small studies they have been reported to be efficacious for the pain associated with haemophilic arthropathy and to be well tolerated (Boban*, et al* 2016, Tsoukas*, et al* 2006). PWH have a higher risk of gastrointestinal bleeding compared to the general population and clinicians should consider using the lowest effective dose of COX-2 inhibitor, ideally for a limited period, and in conjunction with a protein pump inhibitor. This is particularly important in PWH with additional risk factors for gastrointestinal bleeding such as reflux symptoms or liver disease (Arachchillage and Makris 2016) .

When pain remains significant, despite optimal medical therapy, joint replacements are a useful option and are now carried out routinely. Post-replacement there may also be an improvement in joint function but this is also affected by contractures and baseline muscle strength. Because of the bleeding pattern in haemophilia, the most frequent joints replaced are knees but elbow and ankle joint replacements are also performed. As the incidence of osteoarthritis increases with age, total hip replacements are likely to become more common, even though this joint is less commonly affected in haemophilia. When these

surgeries are carried out by experienced surgeons in specialist centres, the risk of complications including infections is fairly low (Anderson*, et al* 2018, Eckers*, et al* 2018), although the risk is significantly higher in PWH with inhibitors. The risk of post-operative thrombosis needs to be considered in ageing patients undergoing this surgery. Whilst there are not consistent guidelines, most centres would consider pharmacological prophylaxis whilst a patient is receiving factor replacement therapy, certainly for PWH B as in these patients their own FVIII will increase post-operatively which is associated with increased risk of thrombosis (Mannucci*, et al* 2009). Recurrent joint replacement is associated with increased complexity and complications and as PWH grow older this will be required to be undertaken in increasing frequency.

Haemophilia has been associated with low bone mineral density (BMD) with two thirds of patients with moderate or severe haemophilia older than 50 years having osteoporosis (Kiper Unal*, et al* 2017). BMD showed significant correlation with the haemophilia joint health score (Kiper Unal*, et al* 2017) and it is thought that this is related to associated reduction in physical activity. Chronic HCV/HIV infection is additionally associated with reduction in BMD (Iorio*, et al* 2010). Therefore clinicians should consider screening patients with significant joint disease for reduced BMD. A recent systematic review and meta-analysis demonstrated that there is no benefit to routine vitamin D supplementation, including in high risk subgroups such as renal and liver disease (Bolland*, et al* 2018). Vitamin D supplementation did not have meaningful effects on fracture, falls, or bone mineral density. It is of note that in a study of haemophilia patients, whilst 78% had 25-hydroxyvitamin D concentration (25(OH)D) of less than 50 nmol/L, this was not correlated with BMD (Kiper Unal*, et al* 2017). Therefore, there appears to be little justification for the

routine use of vitamin D supplements to maintain or improve musculoskeletal health in PWH, except for the prevention or treatment of the rare condition of osteomalacia, which can occur after a prolonged lack of exposure to sunshine that leads to 25(OH)D concentrations lower than 25 nmol/L.

In the general population the risk of falls increases with age due to a number of factors including reduced balance and eyesight. Due to the comorbidites of haemophilia, it is possible that the risk of falling is higher in PWH. An exploratory study of falls risk in PWH with average age 54 years (range 41–79 years), found that 32% had fallen within the past year and with 42% of them falling more than once (Sammels*, et al* 2014). Living conditions, physical activity, orthopaedic status, urinary incontinence and mobility impairments were considered fall risk factors. Screening and fall prevention practices should be considered as part of routine review in the aging haemophilic population.

Cardiovascular disease

a) Hypertension

Hypertension is associated with an increased risk of ICH and cardiovascular disease in the general population. PWH have a significantly higher prevalence of hypertension compared to the general population (approximately 50% compared to 40%) (Fransen van de Putte*, et al* 2012, von Drygalski*, et al* 2013). The prevalence of hypertension in patients with severe haemophilia was higher than in those with mild disease. The mechanism for this increased risk of hypertension in haemophilia is unknown. However, of particular concern was the finding that of the people treated for hypertension, only 27.1% of PWH were controlled, compared to 47.7% in the general population (von Drygalski*, et al* 2013). All patients with

haemophilia should have their blood pressure measured and controlled preferably by general practitioners in the same manner as the general population.

b) Coronary artery disease

A systematic review of 15 studies which included 19,242 PWH demonstrated a trend for reduced mortality due to arterial thrombosis compared with healthy controls (standardised mortality ratio, SMR 0.51, 95% CI 0.24 to 1.09); this was significant when the analysis was restricted to studies with at least 10 years follow-up (SMR 0.59, 95%CI 0.48-0.72) (Biere-Rafi*, et al* 2010). Interestingly intima media thickness (IMT) of the carotid and femoral arteries, a marker of atherosclerotic disease, was similar between haemophilia patients and healthy controls and the traditional risk factors for ischemic heart disease such as hypertension, diabetes mellitus and hyperlipidemia, were also found to be risk factors for IHD in hemophilia (Biere-Rafi*, et al* 2010). Two subsequent relatively small studies also support the view that patients with haemophilia develop atherosclerosis at a similar rate to the normal population. The first (Biere-Rafi*, et al* 2012) demonstrated no differences in mean carotid and femoral IMT between obese hemophilic patients and obese controls. Thirty-five per cent of the obese hemophilic patients and 29% of the obese controls had an atherosclerotic plaque (P =0.49). The second study (Zwiers*, et al* 2012) evaluated the presence and extent of atherosclerosis by coronary artery calcification score (CACS) derived from computed tomography and carotid IMT intima media thickness (IMT) in patients with haemophilia. This again showed that CACS and carotid IMT were similar to control individuals; haemophiliacs who had had previous cardiovascular events had higher CACS and IMT scores. Given cardiovascular risk factors and atherosclerosis are the similar in PWH and the general population, what is the reason for reduced cardiovascular mortality? A

plausible explanation is that reduced thrombin generation at the point of plaque rupture results in reduced risk of vessel occlusion (Makris and Van Veen 2012). It is not known whether the increasing use of prophylaxis in aging PWSH, will result in an increase in cardiovascular mortality.

Clinicians can play an important role in educating PWH on cardiovascular risk, encouraging risk reduction (smoking, obesity, exercise), optimising other factors (hypertension, hyperlipidaemia) and using COX-2 selective inhibitors with caution. Whilst evidence based guidelines exist for management of cardiovascular disease in the general population, it is unclear to what extent they apply to haemophilia. The clotting factor level at which PWH would benefit from antiplatelet agents without an unacceptably high bleeding risk is unknown. Expert opinion is often to consider factor prophylaxis if factor level is less than 5% but this does not have a firm evidence base (de Raucourt*, et al* 2015, Schutgens*, et al* 2016). A recent study found that antiplatelet and anticoagulant drugs increased severe bleeding in PWH [HR = 3.55](Desjonqueres*, et al* 2018). On multivariate analysis the key risk factor for a severe bleed on antiplatelet/anticoagulant drugs was a history of non-severe bleeding in the preceding year(Desjonqueres*, et al* 2018). Patients are currently managed on an individualised basis following multidisciplinary team discussion and counseling and where possible the duration and intensity of antiplatelet/anticoagulant medications are minimised; for example PWH who require coronary stenting are advised to have a bare metal or a second generation drug-eluting stent where possible in order to minimise the required duration of dual anti-platelet therapy and optimise outcomes (Schutgens*, et al* 2016).

c) Atrial fibrillation

A European study analysed the prevalence of atrial fibrillation (AF) in 3,952 PWH (Schutgens*, et al* 2014). It found the overall prevalence of AF was 0.84% and increased with age (3.4% in patients over the age of 60). This prevalence is similar to historical prevalence in the general population (0.95%)(Go*, et al* 2001). However, it is now estimated that the prevalence in the general population is about 2% and that the prevalence was previously underestimated due to under detection of AF and also the increasing age of the population with more cardiovascular risk factors (Wilke*, et al* 2013). It therefore remains unclear as to whether the prevalence of AF in PWH is the same as the general population. For the normal population, guidelines advice consideration of anticoagulation for stroke prevention in AF if the CHADS2VASC score in men is 1 or more based on studies in people without haemophilia (Lip*, et al* 2017). PWH, however, will have a reduced thrombin generation potential and higher bleeding risk so it is unclear whether data from the general population apply to PWH. How to safely manage PWH and AF is unknown and expert opinion may differ (Martin and Key 2016, Schutgens*, et al* 2016).

Obesity

The World Health Organisation has estimated that the prevalence of obesity has tripled since 1975. Meta-analysis has shown that the prevalence of obesity/overweight in PWH in Europe and North America is currently similar to the general population at 31%, and that there has been a significant increase in paediatric PWH (Wilding*, et al* 2018). In the general population, obesity is associated with increased risk of hypertension, type 2 diabetes, stroke, coronary artery disease, osteoporosis and clinical depression. In PWH obesity has additionally been associated with reduced range of movement in joints and increased chronic pain (Biere-Rafi*, et al* 2011, Wilding*, et al* 2018, Witkop*, et al* 2017). The

increased prevalence of obesity in PWH therefore significantly increases the risk of developing additional co-morbidities with age. Patient education, involvement of the multi-disciplinary team and the patient's general physician is crucial for both prevention and treatment of overweight/obesity (Wilding*, et al* 2018).

Neurological/psychological disease

Compared with age matched controls elderly PWH (aged 65-78) had worse values for physical functioning as measured by the Activities of Daily Living (ADL) with significant differences for dressing, bathing, transport and shopping (Siboni*, et al* 2009). PWH reported more moderate pain, depression and a worse health-related quality of life (Siboni*, et al* 2009). It seems likely that the pain, musculoskeletal impairment and the burden of blood-borne viruses contribute to increased risk of depression; health professionals should be on high awareness to be able to offer support.

Despite concern about CMBs and dementia (Zanon*, et al* 2014) there is currently no evidence to support a reduction in cognitive status (measured by MiniMental Sate Examination, MMSE) in PWH compared to age-matched controls (Siboni*, et al* 2009).

Variant Creutzfeldt-Jakob disease (vCJD) may be transmitted through blood transfusion and factor concentrate. There is no reliable test or a method for destroying the prions before transfusion. In the UK, a study of 17 PWH who were neurologically asymptomatic but considered to be at increased risk of vCJD, reported that 1 PWH had prions detected in the spleen at autopsy. This patient had received multiple blood transfusions as well as factor VIII concentrate, and the potential contribution of each was uncertain. There has been no

evidence of any symptomatic disease or death from vCJD in a PWH (Darby*, et al* 2007, Zaman*, et al* 2011). However as the transmissibility of vCJD by concentrates is uncertain, the UK PWH remain under close surveillance for this (Lassila and Makris 2016).

Cancer

With certain clear exceptions the risk of malignancy in haemophilia is similar to that in the general population. The two main exceptions are HCV associated hepatocellular carcinoma and HIV related malignancy (Biron-Andreani*, et al* 2014, Dunn 2010). As PWH get older, diagnosing and treating cancer in PWH will become more common. Patients may present with bleeding earlier, especially for urogenital tract and gastrointestinal tumors and clinicians should be alert to this (Biron-Andreani*, et al* 2014). Haemostatic cover needs to be provided for invasive investigations including biopsy and surgery. Oncological treatments such as chemotherapy should not be withheld and haemostatic replacement may be required during periods of thrombocytopenia (Astermark*, et al* 2012).

Sexual dysfunction

The physical and psychological comorbidities associated with haemophilia, may exacerbate the sexual dysfunction which is experienced relatively commonly in ageing men. Chronic pain and joint arthropathy, recurrent bleeding, HIV and HCV, and adverse effects from medications contribute to the problem (Bar-Chama*, et al* 2011, Gianotten and Heijnen 2009). Although haemophilia professionals need to be alert to the issue, referral to specialists or general practitioners may be required.

Renal disease

Elderly people in general are at increased risk of both acute renal disease (ARD) and chronic renal disease (CRD). PWH have an increased baseline risk of renal disease. A review of the medical records of 2,075 PWH in the USA who were hospitalised at least once over a 6-year period, found that 60 (2.9%) were diagnosed with either acute renal disease (29/60) or chronic renal disease (31/60)(Kulkarni*, et al* 2003). On multivariate analysis HIV infection and hypertension were strongly associated with both ARD and CRD whilst inhibitors were associated with ARD, and increasing age with CRD. Although a recent European epidemiological study did not find a correlation between haematuria and renal dysfunction in PWH (Holme*, et al* 2016), the risk of haematuria increases with age and can be a significant problem for PWH and health care professionals. Urology referral is recommended for patients with haematuria and mild haemophilia or recurrent haematuria in patients of any severity; it should also be considered for elderly patients in order to exclude an underlying malignancy.

Polypharmacy

Whilst it might be assumed that due to multiple comorbidities, ageing PWH would be at risk of polypharmacy, a recent multi-centre observational study of PWH over the age of 60 years found that, after excluding factor replacement therapy and antiviral drugs against HIV/HCV, PWHs had a trend to take on average less daily drugs than controls (2.4 +/- 2.5 vs 3.0 +/- 2.4) and had more appropriate prescriptions as indicated by a lower rate of potential drug-drug interactions (16.7% vs 27%) (Mannucci*, et al* 2018). The reason for this is unclear although the authors suggest that this may be a result of prescription review by haemophilia centres at the time of their regular visits.

Altered bleeding risk with age

Certain coagulation parameter changes with age, such as an increase in factor VIII and von Willebrand factor, are well documented (Favaloro*, et al* 2014, Laffan 2017). It is also known that the risk of venous thrombosis increases with age, as does the risk of bleeding for patients on anticoagulation. In the Leiden cohort of patients on anticoagulation, both thromboembolic and bleeding risk increased with age (HR major haemorrhage 2.7 for patients over 80 years compared to those less than 60 years) (Torn*, et al* 2005). Specific bleeding problems such as haematuria and bleeding from angiodysplasia increase with age in the general population (Moudi*, et al* 2016, Sharma and Gorbien 1995). However, the overall balance of haemostatic changes as one ages in the normal population, and in PWH, is not currently well understood. A better understanding of this, and how bleeding risk alters with age in PWH, would likely help support optimal management of comorbidities.

Conclusions

As the life-expectancy of PWH has improved dramatically, it is now critical for haemophilia specialists to be alert to the associated comorbidities of ageing. Regular routine review by a multidisciplinary team in a haemophilia centre provides an important opportunity to reduce morbidity for our patients through education and prevention (hypertension, obesity, falls) and early detection (atrial fibrillation, bone mineral density, screening for hepatocellular carcinoma in patients with cirrhosis). Because of regular prophylaxis with safe concentrates from a young age, the next generation of PWSH are likely to age without significant chronic haemophiliac arthopathy and without HIV/HCV, however the challenges of the other

comorbidities of ageing such as cardiovascular disease will remain. Given the relatively small number of patients experiencing specific co-morbidities, international collaboration is essential for registry data and future prospective trials to inform optimal evidence-based management of this rare disease in the future.

Author contributions

SS wrote the first draft of the manuscript. MM critically reviewed and revised each draft. Both authors approved the final version.

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Conflicts of interest

The authors declare no relevant conflicts of interest for the work presented in this manuscript.

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Table 1

Key issues faced by the current cohort of ageing persons with haemophilia (PWH) including those directly related to haemophilia and its treatment, and those related in general to ageing. Recommendations for management are outlined. *Patient education and the multidisciplinary team are crucial to all management recommendations.

Issues faced by ageing PWH	Recommendations for management*
Chronic arthropathy and loss of bone mineral density	Regular review by a physiotherapist specialising in haemophilia. Offer COX-2 inhibitor rather than NSAIDs for pain control when needed, use lowest effective dose and consider additional proton-pump inhibitor. Measure bone mineral density in PWH who have significant arthropathy. Do not routinely give vitamin D supplementation.
Bleeds and risk of inhibitors	Consider regular prophylaxis as opposed to 'on demand' therapy for people with severe bleeding phenotype. Remain vigilant to risk of inhibitor formation, particularly in patients with moderate-mild haemophilia.
Hepatitis C, cirrhosis, hepatocellular carcinoma	Offer all PWH who have active hepatitis treatment to clear hepatitis C with the newer agents as appropriate. PWH who had cirrhosis before they cleared HCV, remain at risk of hepatocellular carcinoma and require regular hepatology follow-up with liver ultrasound and alpha-fetoprotein monitoring.
HIV	PWH should be under the care of a specialist physician in HIV.
Cardiovascular disease (hypertension, ischaemic heart disease, atrial fibrillation)	Prevention: Educate patients with regards to cardiovascular risk and encourage and support interventions to reduce this risk (smoking, obesity, exercise, hypertension, cholesterol) Treatment: Manage patients on an individualised basis following multidisciplinary team discussion and counseling. Where possible minimise the duration and intensity of antiplatelet/anticoagulant medications
Malignancy	Provide haemostatic cover for invasive investigations including biopsy and surgery. Oncology treatments such as chemotherapy should not be withheld and haemostatic replacement may be required during periods of thrombocytopenia.
Renal disease	Check renal function at least annually. For patients with haematuria, consider urology referral for patients with mild haemophilia, recurrent haematuria, and elderly patients
Sexual dysfunction	Be alert to this issue. Referral to specialists or general practitioners may be required.

Depression, dementia	Screen for depression at clinic visits. Offer appropriate support and referral.
Reduced mobility, dexterity, and visual acuity	Screen for mobility problems at clinic visits in order to offer proactive MDT support.
Reduced access to health care, ability to self-treat	Be alert to changes at clinic visits in order to offer support through MDT and community teams.