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Review Article

Challenges in treating elderly patients with haemophilia: A focus on cardiology

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ABSTRACT

Seventy years ago, the average life expectancy for patients with severe haemophilia A was less than 17 years. Today, due to the availability of safe and effective clotting factor concentrates, life expectancy is nearly normal, at least in patients without viral infections. More individuals are living into their 70s and 80s, acquiring a range of diseases that are common in elderly persons. One of the most important challenges includes the treatment of comorbidities, especially cardiovascular diseases. Although most evidence suggests that haemophilia, at least the severe manifestation, partially protects against myocardial infarction, stroke and venous thromboembolism, typical cardiovascular risk factors can still be present despite the clotting defect. Patients with haemophilia are equally or even more prone to obesity, hypertension, diabetes, and dyslipidaemia, and this is especially true for HIV-infected individuals using highly active antiretroviral therapy. The management of elderly haemophilia patients with cardiovascular comorbidities is hampered by a lack of evidence-based guidelines. Nevertheless, experience in treating cardiovascular disease is growing amongst the haemophilia community, and several authors have published their own recommendations for managing a variety of commonly encountered cardiovascular scenarios in haemophilia patients. Basic recommendations exist for risk-factor management, the adaptation of factor replacement therapy in the at-risk elderly, management of coronary revascularization, the management of acute coronary syndrome and atrial fibrillation. This review outlines our current knowledge about cardiovascular risk in elderly haemophilia patients, recommendations for clinical decision making, and our own experiences of managing individuals with coronary heart disease and atrial fibrillation.

Contents

Abbreviations: ADVANCE, Age-related DeVelopments ANd ComborbiditiEs in haemophilia; APCC, activated prothrombin complex concentrate; $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; DVT, deep-vein thrombosis; FVIII, factor VIII; FIX, factor IX; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MI, myocardial infarction; PCI, percutaneous coronary intervention; rFVIIa, activated coagulation factor VII.

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Introduction

Seventy years ago, the average life expectancy for patients with severe haemophilia A was less than 17 years [1]. Today, following the availability of safe and effective clotting factor concentrates and other major advances in care, most individuals with haemophilia can expect to reach retirement age, with many living into their 70s and 80s [2–5]. Even in haemophilia patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections under highly active antiretroviral therapy (HAART) and interferon treatment, life expectancy has improved and they can expect to live for several decades after their diagnosis [2,6].

An increasing ageing haemophilia population presents a range of new challenges for healthcare professionals. In addition to the challenges of managing premature arthropathy, a growing number of elderly people with haemophilia can be expected to develop significant comorbidities, such as liver disease, renal disease, and cancer [7]. Until recently, reports of cardiovascular disease in haemophilia patients were relatively rare, probably as a result of their shortened lifespan [8,9]. This situation is now changing, and growing numbers of patients with cardiovascular risk factors and cardiac comorbidities are presenting to our haemophilia centres or to other hospitals. In the absence of evidence-based management guidelines, it is extremely important that haemophilia professionals share their experiences, enhance their cardiovascular expertise, and collaborate on areas of best practice – a concerted action, which is starting now [7,10–12].

Does Haemophilia Protect Against Cardiovascular Disease and Venous Thromboembolism?

A review of the literature seems to suggest that haemophilia at least partially protects against myocardial infarction, possibly due to the low factor VIII (FVIII) levels (for a comprehensive review, see Tuinenburg et al. [11]). In the first longitudinal study of its kind, Rosendaal et al. documented an 80% lower mortality in patients with ischaemic heart disease in a Dutch haemophilia population in the late 1980s [3]. Plug et al. confirmed these findings in a comparable cohort of patients approximately 10 years later [5]. Darby et al., Srámek et al. and Lövdahl et al. also reported a lower incidence of deaths due to ischaemic heart disease in haemophilia populations compared to the general male population [2,13,14]; however, Walsh et al. found a higher prevalence of heart disease in a haemophilia population (18%) than a control group (9%) [15]. The lower incidence of deaths due to ischaemic heart disease found in most studies has been attributed to the hypocoagulable state of these patients compared with the general population, potentially leading to a decreased tendency to form occlusive thrombi.

Attempts have also been made to determine whether or not haemophilia protects against the development of atherosclerosis, but, again, results have been conflicting [16–18]. Srámek et al. found no clinically relevant differences in intima-media thicknesses of the carotid artery or the femoral artery between patients with bleeding disorders and healthy controls [18]; however, a more recent study [17] showed the mean intima-media thickness was significantly lower in patients with severe or moderate haemophilia than in controls.

Biere-Rafi et al. have recently conducted a systematic review to assess the association between haemophilia, arterial thrombosis, and asymptomatic atherosclerosis [19]. The group reported that, overall, mortality due to arterial thrombosis was 50% lower in patients with haemophilia compared to the general population [19]. They also reported that, although intima-media thicknesses of the carotid and femoral arteries were similar in haemophilia patients and healthy controls, atherosclerotic plaques of the large arteries were less prevalent in haemophilia patients [19]. The authors suggest that the favourable effects of haemophilia on arterial thrombosis could be the result of reduced thrombin formation, with resulting beneficial effects on both the formation of thrombi and the atherosclerotic arterial remodelling processes.

Cases of myocardial infarction (MI) are rare in the haemophilia population [20], but they do occur [21]. Girolami et al. undertook a systematic review of the literature and collected all reports of arterial occlusion in patients with haemophilia A [21]. These investigators reported that, of the 42 cases published so far, nine (21%) occurred in individuals aged 65 years or more. An association between the occurrence of MI and the recent administration of clotting factor concentrates was identified; the strongest association appeared to be in connection with administration of bypassing agents (i.e. recombinant activated coagulation factor VII [rFVIIa] and FVIII inhibitor bypassing activity [activated prothrombin complex concentrate [APCC]) for the treatment of bleeding episodes in patients with FVIII inhibitors, especially in elderly individuals [21]. Ischaemic cerebrovascular accidents occurred in six cases identified by Girolami et al.; four of these were associated with the use of cryoprecipitate, rFVIIa or APCC [21].

The occurrence of venous thromboembolism in patients with haemophilia A or B has also been reviewed by Girolami et al. [22]. A total of 27 cases (aged 9–67 years) were identified in the literature: 10 cases of deep-vein thrombosis (DVT), eight patients with pulmonary embolism with or without DVT, five cases of superficial vein thrombosis, three cases of thrombosis at unusual sites, and one case of multiple thromboses. Administration of APCC or rFVIIa in patients with inhibitors was the most common risk factor for thrombosis in haemophilia A; surgery plus prothrombin complex concentrates was the most frequent cause of thrombosis in haemophilia B.

Major orthopaedic surgery was also identified as a risk factor for DVT in a prospective study conducted by Hermans and Lambert in Belgium [23]. These investigators evaluated the occurrence of DVT of the lower limb in 36 haemophilia patients who were treated with clotting factor concentrate as continuous infusion during major orthopaedic procedures, but did not receive thromboprophylaxis. No cases of clinical DVT or pulmonary embolism were reported during follow-up; however, three patients (6%) developed uncomplicated subclinical distal DVT that either resolved spontaneously or with a short course of low-molecular-weight heparin (LMWH). Similarly, a study by Holme et al. reported a very low risk for thromboembolic complications in patients with haemophilia [24]. No cases of DVT were observed [24].

Overall, the available literature demonstrates that thrombotic complications in patients with haemophilia are very rare, even in those at high risk of thrombosis. Thus, for this population of patients, the use of medical thromboprophylaxis does not appear to be warranted.

Cardiovascular Risk Factors in Haemophilia

Girolami et al. have suggested that the only conclusion that can be drawn from reviewed studies is that haemophilia does not necessarily prevent the occurrence of arterial occlusions, and that factors known to predispose to developing atherosclerosis and arterial thrombosis (e.g. hypercholesterolaemia, smoking, diabetes, and hypertension) can predominate despite the clotting factor defect [21]. Older individuals with haemophilia may be particularly prone to developing metabolic syndrome, which is driven by obesity and physical inactivity – both of which are frequently encountered in elderly haemophilia patients due to severe haemophilic arthropathy [7,24].

Little is known about the prevalence of cardiovascular risk factors in the haemophilia population [11]. Hypertension seems to occur more frequently in haemophilia patients than in the general population [25], and this has been associated with both acute and chronic renal disease [26]. Hyperlipidaemia was found to be significantly less common in haemophilia patients than in non-haemophilia patients with atherosclerotic heart disease (myocardial infarction, angina, coronary disease) [27]. Mean cholesterol concentrations were found to be lower in a Dutch haemophilia population than in the general population [25]. This could be related to HCV infection, which is known to be associated with lower cholesterol levels [25]. The