As a result of safer blood products and more effective treatments for human immunodeficiency virus (HIV) and hepatitis C infection (HCV), the life expectancy of those with haemophilia is approaching that of the general population. This was predicted over 20 years ago by Dutch epidemiologists who assessed the mortality of haemophilic men, after controlling for HIV and HCV infections (1). Thus, if trends in haemophilia follow the world population, 20% will be over 60 years of age by the year 2050 (2). To meet the challenges of the aging haemophilia population, it will be critical to plan for the treatment and prevention of diseases previously uncommon in haemophilia, but not uncommon in the general population, chief among which is the major cause of morbidity and mortality in Western society, atherosclerotic heart disease (ASHD).

This may seem counter-intuitive, given the well-known 50% to 80% lower ASHD mortality in men with haemophilia than in the general population (1, 3, 4). The protection against ASHD mortality is attributed to hypocoagulability, that is, low factor VIII or IX, which reduces thrombus formation on a ruptured atherosclerotic plaque and fatal myocardial infarction (5, 6). Yet, whether hypocoagulability is protective against development of ASHD the disease, and whether ASHD will increase as the haemophilia population ages is controversial.

What is the evidence that haemophilic men may be at risk for ASHD? At a molecular level, atherosclerosis is a chronic inflammatory response directed at the arterial wall, at specific sites where fatty streaks have progressed to lipid plaques, with lipid accumulation in macrophages, so-called macrophage foam cells, and foam cell trapping within the arterial intima (2, 7). In animal models, in fact, it is mice deficient in regulators of lipid trafficking, not those with haemophilia or von Willebrand disease, that are protected against atherosclerosis. Specifically, hyperlipidaemic mice deficient in CD36, a scavenger receptor that modulates migration of macrophages and traps oxidised LDL in arterial intima (2), are protected from lipid atheroma, but atherosclerotic-prone apolipoprotein E – factor VIII knockout mice (8) and pigs with von Willebrand disease (9) develop atherosclerotic plaques indistinguishable from unaffected animals. Thus, hypocoagulability in animals does not appear to protect against ASHD. Is this true for the aging man with haemophilia?

Evidence has been increasing that both atherosclerosis and atherosclerotic risk factors are not uncommon or new in haemophilia. First, the frequency of pathogenic coronary atherosclerosis was recently shown to be similar to that in the general population. In an autopsy study of men with haemophilia, most of whom died of HIV or hepatitis, the degree of intraluminal coronary stenosis was similar to that in age-, sex-, race-matched controls (10). Cardiovascular risk factors, including hypertension, smoking, diabetes, and hyperlipidaemia, in those cases were similar to controls (10). These findings were further supported by a statewide analysis of inpatient ASHD discharge data in haemophilic men showing disease prevalence and cardiovascular risk factors are similar to controls (11). Further, a six-state CDC (Centres for Disease Control) study of hospitalised haemophilic men found that 15% over age 60 had ischaemic heart disease, independently associated with traditional risk factors, as well as factor infusion and HIV disease (12). Regarding the former, activated clotting factors, including FEIBA are most commonly associated with myocardial risk (13), while regarding the latter, CD4+ T cell count below 200/μl (14) and use of highly active antiretroviral therapy (HAART) (15) are risk factors for heart disease among those with HIV infection.

An outstanding addition to the emerging evidence that ASHD in haemophilic men is comparable to the general population is the paper by Biere-Rafi et al. (16) in this issue of Thrombosis and Haemostasis, entitled "Cardiovascular risk assessment in haemophilia patients.” In their prospective ASHD risk assessment study, the investigative team enrolled 100 men at least 18 years of age with haemophilia A or B from haemophilia treatment centers (HTC) in Amsterdam and Rotterdam. Data collected included clinical history, physical exam, and laboratory studies during routine outpatient HTC visits. The comparison group included 200 age- and sex-matched healthy controls from the general Dutch population. None of the subjects had a history of cardiovascular disease. Individual patient cardiovascular mortality risk was determined by a European risk prediction algorithm, known as the Systemic Coronary Risk Evaluation (SCORE) (17). This score, calculated based on age, sex, smoking history, blood pressure, and cholesterol level, indicated comparable cardiovascular disease and risk factors between cases and controls. Further, the proportion with a SCORE of 10%, indicating similar risk for cardiovascular mortality, was also comparable, and independent of haemophilia severity or medications.

What are the implications of these findings? First, cardiovascular risk factors appear to be increasing in the haemophilia population similar to the general population. Hypertension and hyperglycaemia...
are not uncommon in individuals with haemophilia at least by age 47 years, based on the Biere-Rafi study in haemophilic men from the Netherlands. When coupled with the well recognised immobility due to chronic haemophilic arthropathy and disability, these findings are particularly concerning in those with haemophilia. Obesity has been recognised in children with haemophilia, and standard cardiovascular risk reduction and prevention recommendations are not standard at many HTCs. In an age when health care costs are high, and haemophilia patients may not seek care outside the HTC, it appears the HTC is the critical link to provide a standard cardiovascular risk reduction message. While long-term follow-up will be necessary to see the full spectrum of ASHD disease in the aging haemophilia population, the findings of Biere-Rafi et al. indicate that cardiovascular disease and risk factors are increasing for individuals with haemophilia as the general population. These findings suggest the need for an aggressive approach to cardiovascular disease prevention, including anti-hypertension medications, glucose- and cholesterol-lowering medications, weight optimisation, reduced fat intake, and smoking avoidance. This requires prospective, ongoing surveillance of risk factors in all patients with haemophilia, beginning in young adulthood.

Finally, in the absence of clinical trials and any evidence-based guidelines to guide the approach to management, and with the unlikely opportunity to conduct phase III randomised, controlled trials of anti-platelet and anticoagulant therapies in this orphan population with potential life-threatening adverse bleeding complications, comparative effectiveness and in silico modelling may be required to establish optimal care for those with haemophilia.

References