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ORIGINAL ARTICLE

Cardiovascular risk factors among adult patients with haemophilia

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Abstract

Since the introduction of episodic and prophylactic treatments with safer factor concentrates, the life expectancy of people with haemophilia (PwH) has improved considerably. Ageing-related diseases such as cardiovascular disease (CVD) have also become more prevalent in PwH. This cross-sectional study aimed to evaluate CVD risk factors and estimate 10-year risk for CVD events among PwH. Male patients ≥ 30 years were interviewed and examined. Blood tests were performed at the local laboratory. Eighty-two patients were included, of whom 83% had haemophilia A and half had severe disease. Median age at study entry was 43.0 years (interquartile range [IQR], 36.0–51.3). Prevalence of obesity, systemic arterial hypertension (SAH) and diabetes mellitus were 16%, 60% and 16%, respectively. Hypertriglyceridaemia, hypercholesterolaemia and low HDL blood levels were present in 18%, 41% and 30% of patients, respectively. Metabolic syndrome was found in 37%. The Framingham Risk Score showed that 39% of PwH had a high risk of developing cardiovascular events in the following 10 years. We conclude that, in this cohort, PwH have a higher prevalence of SAH when compared with Brazilian men without haemophilia and about two-fifths have a high risk of developing a CVD event in the following 10 years.

Keywords Haemophilia · Cardiovascular disease · Cardiovascular risk · Framingham Risk Score

Introduction

Hereditary haemophilia A and B are rare bleeding disorders caused by reduced or absent activity of the coagulation factors VIII (FVIII) and IX (FIX), respectively [1]. Replacement of the deficient factor is required to treat (episodic) and prevent bleeding (prophylaxis) [1]. Since the introduction of safer factor concentrates, life expectancy of people with haemophilia (PwH) has reached rates similar to the general population [2–4].

In 2016, there were 12,119 PwH in Brazil, of whom 43% were 30 years or older [5]. Haemophilia treatment is publicly funded by the Brazilian National Health System. From 2006 to 2018, there was a dramatic increment in the use of FVIII and FIX concentrates, from 1.0 to 4.0 and 0.2 to 0.7 IU per capita, respectively [6]. Considering the improvement of haemophilia care in Brazil, life expectancy of PwH has also increased [3, 4].

As PwH are living longer, cardiovascular diseases (CVD) may increasingly occur. Several reports have shown that PwH have higher systolic (SBP) and diastolic blood

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pressures (DBP) and more frequently dyslipidaemia compared with individuals without haemophilia [7, 8]. CVD is an important issue in PwH because its management often demands the use of anti-thrombotic drugs further affecting the risk of bleeding. Besides, there are no specific guidelines for the management of stroke nor myocardial infarction in PwH. Therefore, identifying and treating CVD risk factors is a key step to prevent CVD later in life in this population. The aim of our study was to evaluate the CVD risk factor profile and to estimate the 10-year risk for CVD events among Brazilian PwH, according to the Framingham Risk Score (FRS). This score predicts the 10-year risk of major CVD events (coronary disease — chronic arterial disease, stroke, peripheral obstructive arterial disease, or heart failure). To the best of our knowledge, this is the first time FRS is evaluated among PwH in Latin America.

Methods

Setting

In Brazil, the Ministry of Health centrally purchases and distributes clotting factors for all the 27 Brazilian states. Each state allocates a comprehensive haemophilia treatment centre (CHTC), in its capital, and several haemophilia treatment centres (HTC), throughout the territory, which are responsible for haemophilia care. Each CHTC coordinates a net of HTCs in surrounding cities [9]. This study enrolled patients attended at HEMOPE (Centre of Haematology and Haemotherapy of Pernambuco) which allocates the CHTC in its capital, Recife. Pernambuco is a state located in North-eastern Brazil.

In 2016, a total of 711 PwH were registered in HEMOPE [5]. Patients are free to choose the HTC of their preference, but they can be registered only in one of them.

Study design and patients

The HemoCardio Study is a cross-sectional study aimed to evaluate CVD risk factors and estimate the 10-year risk for CVD events among PwH registered at CHTC of HEMOPE in Recife, Brazil. This centre is responsible for haemophilia care of about one-third of PwH in the state, i.e. approximately 240 PwH, of whom 120 are 30 years or older. All male PwH aged ≥ 30 years and registered at the outpatient clinic were invited to participate in the study during their elective consultation at the CHTC between 1/Aug/2018 and 31/Jul/2019. The assisting physician/nurse provided the study information and asked for informed consent. HEMOPE Committee on Ethics and Research approved the project.

Measurements and definitions

Data collection

Patients were interviewed and underwent physical examination. Clinical data were collected from medical files using a standardised questionnaire. The variables collected were age, ethnicity, haemophilia type and severity, inhibitor status, replacement factor regimen (either exclusively episodic, or prophylaxis with clotting factor concentrates, to prevent spontaneous bleedings) [1], and human immunodeficiency virus (HIV) and hepatitis C status. HIV and hepatitis C status are routinely evaluated at HEMOPE, according to international recommendations [10–12].

Mild, moderate and severe haemophilia were defined as plasma factor activities between 5 and 40 IU/mL, 1 and 5 IU/mL, and below 1 IU/mL, respectively [1]. PwH were considered as inhibitor positive if they presented two titres 0.6 BU/mL or higher, at least 2 weeks apart from each other [1]. HIV infection was confirmed if, after two positive screening tests for HIV antibody, there was a positive result on a confirmatory test [12]. Patients were considered to have a current or previous HCV infection if they had a reactive HCV-antibody test confirmed by a positive quantitative RNA for HCV [11].

Using a standardised form, we collected medication use, smoking status, history of dialysis, atherosclerotic disease, or cardiovascular tests. Patients were examined to obtain their weight, height, and waist circumference. Waist circumference was measured with a tape at the midpoint between the iliac crest and the lowest rib. Blood pressure (BP) was measured by only one researcher with a calibrated mercury sphygmomanometer. For this, patients remained seated in a comfortable position for at least 15 min, before the first measurement. SBP and DBP were measured three times and 5 min or more apart one from another. The mean of these three measurements was considered as the final BP and included in the analyses. A patient was considered obese if his body mass index (BMI) was ≥ 30 kg/m^2 [13, 14]. Abnormal waist circumference was considered when values were 90 cm or above [14, 15]. SAH was considered when the mean SBP was ≥ 140 mmHg and/or DBP was ≥ 90 mmHg, or when patients were on medication for SAH [16].

We defined as having previous CVD those PwH with (1) history of clinically evident disease of coronary or cerebrovascular disease or peripheral artery obstruction, documented by a diagnostic method and/or a medical report; (2) history of significant subclinical disease, documented by a diagnostic method; (3) history of arterial revascularization procedures, documented by a diagnostic method and/or a medical report; (4) diabetes mellitus; (5) chronic

kidney disease (CKD); or (6) history of familial hypercholesterolaemia [17]. Family history of premature CVD was considered positive when it occurred in a first-degree relative, at an age < 65 years for men and < 55 years for women [18].

Laboratory

Blood tests performed at the Laboratory Department of the CHTC 1 year before until 6 months after the inclusion were considered. Twelve-hour fasting blood glucose, triglycerides (TG), total cholesterol (Tc), low- (LDLc) and high-density lipid cholesterols (HDLc), urea and creatinine tests were performed. A patient was considered to have diabetes mellitus if fasting blood glucose levels were ≥ 7.0 mmol/L or if he was on treatment for diabetes mellitus with hypoglycaemic agents [19]. Hypertriglyceridaemia was considered when TG ≥ 2.3 mmol/L, hypercholesterolaemia as Tc ≥ 5.2 mmol/L and hypoHDLaemia as HDLc < 1.0 mmol/L [17].

Estimated Glomerular Filtration Rate (eGFR) was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. CKD was defined according to KDIGO (Kidney Disease Improving Global Outcomes) as eGFR ≤ 60 mL/min/1.73 m^2 [20].

Metabolic syndrome was considered to be the presence of increased waist circumference and at least two of the following criteria: SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or SAH on treatment; fasting glucose ≥ 5.6 mmol/L, use of antidiabetic medication or previous diagnosis of diabetes mellitus; TG ≥ 1.7 mmol/L or on treatment; or HDLc ≤ 1.0 mmol/L or use of nicotinic acid or fibrate [15, 21].

Cardiovascular risk tool

CVD risk scores were estimated according to the FRS tool [22]. This tool predicts the 10-year risk of major CVD events (coronary disease — chronic arterial disease, stroke, peripheral obstructive arterial disease, or heart failure). The following variables were entered into the web-based calculator: age, gender, Tc, HDLc, SBP and treatment for SAH, diabetes mellitus and smoking status. A specific score is assigned to a characteristic (e.g. "yes" or "no") or a value for each variable. The sum of these points provides the patient's risk estimate. The estimated cardiovascular FRS was categorised into high (> 20%), intermediate (5–20%) and low risk (< 5%). For the purpose of this study, the original FRS [22] was adapted according to Jellinger et al. [17]. We classified all PwH with a history of coronary artery, cerebrovascular, or peripheral obstructive atherosclerotic disease, with subclinical (i.e. documented by diagnostic methodology) or clinical manifestations (CVD events); arterial revascularization procedures; diabetes mellitus; or CKD into the high-risk category regardless of the FRS estimation [17]. Furthermore, individuals with an estimated intermediate CVD risk who had metabolic syndrome, or a family history of premature CVD were recategorized as high risk [17]. Patients with an estimated low risk with a positive family history of premature CVD were reclassified to the intermediate risk category [22].

Literature search

Literature was reviewed to compare our data with data published on healthy Brazilian men. One researcher performed the literature search for Brazilian data on each specific cardiovascular risk factor on PubMed, Lilacs and Scielo. The articles should have been released in the last 10 years. English, Spanish, and Portuguese languages were accepted. Only studies which described the general male population at the same age range of PwH from HemoCardio Study were included. The terms "Brazil*" or "Pernambuc*" were crossed with "registry" and a variety of other terms, as stated: "obesity", "hypertension", "diabetes", "dyslipidaemia" (and related, as "hypercholesterolaemia"), "kidney disease", "metabolic syndrome", and "cardiovasc*". The articles were selected for comparison, if the definitions of the variables in common were the same we applied in the HemoCardio Study.

Data analyses

Quantitative variables were expressed as medians and interquartile range (IQR), unless otherwise stated. Categorical variables presented as absolute and relative frequencies.

Medians (IQR) and frequencies of CVD risk factors were reported for the study population and compared with the population without haemophilia reported in the literature research. For the FRS analysis, one missing variable was present in seven patients. For each of these missing data, we inputted empirical values corresponding to zero additional risk for the correspondent variable, according to the FRS. Descriptive statistical analysis was performed using SPSS® Statistical software, version 26 (IBM, Armonk, USA).

Results

Patients

All invited PwH agreed to participate in the HemoCardio Study. Eighty-two PwH were included, corresponding to 70% (82/120) of all PwH aged > 30 years registered at the CHTC. The 38 PwH who were not included did not visit the outpatient clinic during the study period of enrolment. Detailed characteristics of the cohort are shown in

Table 1 Characteristics of the patients included in the study*

Characteristic	Total ($n=82$)
Age at study inclusion (y)	43.0 [36.0–51.3]
White	89% (73/82)
Age at haemophilia diagnosis (y)	11.0 [3.0–20.0]
Haemophilia A	83% (68/82)
Haemophilia inhibitor	7% (6/82)
Severe haemophilia	51% (42/82)
On prophylaxis	56% (46/82)
HIV positive	5% (4/82)
Current or previous HCV	54% (44/82)

y years, *HIV* human immunodeficiency virus, *HCV* hepatitis C virus

*Continuous variables were expressed as median [interquartile range] and frequencies were expressed as percentage (cases/total sample without missing data)

Tables 1 and 2. Median age at study entry was 43.0 years [IQR, 36.0–51.3]. Most patients had haemophilia A (83%), about half of the patients had severe haemophilia, and 56% were on prophylaxis.

Cardiovascular risk factors

Thirteen (16%) PwH were obese. The prevalence of SAH and diabetes mellitus were 60% and 16%, respectively. The frequencies of hypertriglyceridaemia, hypercholesterolaemia and hypoHDLaemia were 18%, 41% and 30%, respectively. Twenty-five (37%) PwH had metabolic syndrome. Previous atherosclerotic disease was reported by 7%, and familial history of early CVD by 24% of the patients.

The systematic literature search revealed six studies on CVD risk factors in the male reference population performed in Pernambuco and Brazil (Table 3). All studies were cross-sectional, and the results refer to males only. Lyra et al. [23] investigated 68 men from the hinterlands of Pernambuco and described prevalence of SAH in 52%. A lower prevalence of SAH among men (30%) was described in the semi-arid region of Pernambuco [24]. Three articles from the ELSA-Brasil (Brazilian Longitudinal Study of Adult Health) described a prevalence of SAH among men ranging from 36 to 40% [25–27]. We have found a higher prevalence of SAH in our study among the haemophilia population (60%). Furthermore, among 46 patients with SAH, 15 (33%) were not on treatment. Smoking was also more prevalent among PwH in Pernambuco than among men in the ELSA-Brasil cohort [26], but obesity, diabetes mellitus and metabolic syndrome prevalence were less frequent in PwH than in those described in the ELSA cohort [25, 26, 28].

Table 2 Cardiovascular profile of the haemophilia patients included in the HemoCardio Study*

Characteristic	Total ($n=82$)
Physical examination and behavioural characteristics	
BMI (kg/m^2)	25.0 [21.5–28.5]
Obesity	16% (13/81)
Waist circumference (cm)	90.0 [82.0–101.0]
SBP (mmHg)	126.0 [116.0–140.0]
DBP (mmHg)	83.0 [76.8–93.0]
Hypertension treatment	42% (31/74)
SAH	60% (46/77)
Smoking (last 6 months)	20% (16/82)
Metabolic measurements	
Plasma glucose level (mmol/L)	5.5 [5.1–6.3]
Antidiabetic treatment	11% (8/72)
Diabetes mellitus	16% (10/61)
Plasma triglycerides level (mmol/L)	1.3 [1.0–2.0]
Hypertriglyceridaemia	18% (11/61)
Plasma total cholesterol levels (mmol/L)	4.8 [4.1–5.8]
Hypercholesterolaemia	41% (24/59)
Plasma HDL level (mmol/L)	1.3 [1.0–1.5]
HypoHDLaemia	30% (17/57)
Plasma LDL levels (mmol/L)	2.9 [2.2–3.6]
Familial hypercholesterolaemia	1% (1/72)
Statin treatment	0% (0/72)
Metabolic syndrome	37% (25/67)
Atherosclerotic disease	
Previous atherosclerotic disease	7% (5/72)
Significant asymptomatic atherosclerotic disease	0% (0/71)
Previous arterial revascularization	0% (0/72)
Familial history of premature cardiovascular disease	24% (17/72)
Kidney function	
Plasma urea levels (mmol/L)	4.7 [3.7–5.7]
Plasma creatinine levels (µmol/L)	70.7 [61.9–80.0]
eGFR (mL/min/1.73 m^2)	113.9 [106.4–132.3]
CKD	2% (1/66)
Peritoneal dialysis	0% (0/72)
Haemodialysis	0% (0/72)

*Continuous variables were expressed as median [interquartile range] and frequencies were expressed as percentage (cases/total sample without missing data)

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *SAH* systemic arterial hypertension, *HDL* high-density lipid, *LDL* low-density lipid, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease

Framingham risk score

We calculated FRS for 76% (62/82) of the studied PwH (Fig. 1). We inputted a value equivalent to zero risk,

Table 3 Cardiovascular risk factors among HemoCardio and studies with non-haemophilia Brazilian population*

Characteristic	Current*	Lyra et al. [23]	Santiago et al. [24]	Chor et al. [27]	Santos et al. [25]	Pinto Filho et al. [26]	Cardinal et al. [28]	
Study	HemoCardio	–	–	ELSA				
Year	2017–2019	2008–2009	2015	2008–2010				
City(ies)/state(s)	Several/PE	Triunfo/PE	Serra Talhada, Custodia and Belem de Sao Francisco/PE	Belo Horizonte/MG, Porto Alegre/RS, Rio de Janeiro/RJ, Salvador/BA, Sao Paulo/SP, Vitoria/ES				
Males (*n*)	82	68	146	6,888	6,787	5,341	3,663	
Age range (y)	30–68	30	20–59	35–74				
BMI (kg/m^2)	25.0 [21.5–28.5]	NA	NA	NA	NA	$27 \pm 4^{\dagger}$		NA
Obesity	16% (13/81)	NA	NA	NA	21%	20%		21%
SAH	60% (46/77)	52%	30%	40%	40%	36%		NA
Smoking (last 6 months)	20% (16/82)	NA	NA	NA	14%	14%		NA
Diabetes mellitus	16% (10/61)	9%	NA	NA	23%	21%		NA
Plasma triglycerides level (mmol/L)	1.3 [1.0–2.0]	NA	NA	NA	$1.5 \pm 1.1^{\dagger}$	NA		NA
Plasma total cholesterol levels (mmol/L)	4.8 [4.1–5.8]	NA	NA	NA	$5.4 \pm 1.4^{\dagger}$	$5.5 \pm 1.1^{\dagger}$		NA
Plasma HDL cholesterol levels (mmol/L)	1.3 [1.0–1.5]	NA	NA	NA	$1.2 \pm 0.4^{\dagger}$	$1.3 \pm 0.3^{\dagger}$		NA
Plasma LDL cholesterol levels (mmol/L)	2.9 [2.2–3.6]	NA	NA	NA	$3.3 \pm 1.1^{\dagger}$	$3.4 \pm 1.0^{\dagger}$		NA
Metabolic syndrome	37% (25/67)	NA	NA	NA	NA	NA		54%
CKD	2% (1/66)	NA	NA	NA	NA	NA		NA

ELSA Brazilian Longitudinal Study of Adult Health, *PE* Pernambuco, *MG* Minas Gerais, *RS* Rio Grande do Sul, *RJ* Rio de Janeiro, *BA* Bahia, *SP* Sao Paulo, *ES* Espirito Santo, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *SAH* systemic arterial hypertension, *HDL* high-density lipid, *LDL* low-density lipid, *CKD* chronic kidney disease

*Continuous variables were expressed as median [interquartile range] and frequencies were expressed as percentage (cases/total sample without missing data)

†Continuous variables were expressed as pooled mean ± standard deviation

according to the FRS references, for seven patients who had only one missing data. Twenty patients were excluded because there were two or more missing variables.

According to the predefined definitions of the 10-year-risk categories, fourteen (23%) patients were classified as having a high-risk due to diabetes mellitus ($n = 8$), previous atherosclerotic disease ($n = 4$), diabetes mellitus and atherosclerotic disease ($n = 1$), or chronic kidney disease ($n = 1$). Another 10 PwH had an estimated high risk of developing CVD events in the following 10 years, totalling 24/62 (39%) high-risk PwH. There were 22/62 (35%) and 16/62 (26%) PwH with estimated moderate- and low-risk of developing CVD events in the following 10 years, respectively.

Discussion

We evaluated the CVD risk factors and we estimated 10-year CVD risk according to the FRS among PwH 30 years or older. In this study, we found a high prevalence of CVD risk factors among PwH. When compared with the Brazilian male population without haemophilia, PwH had higher

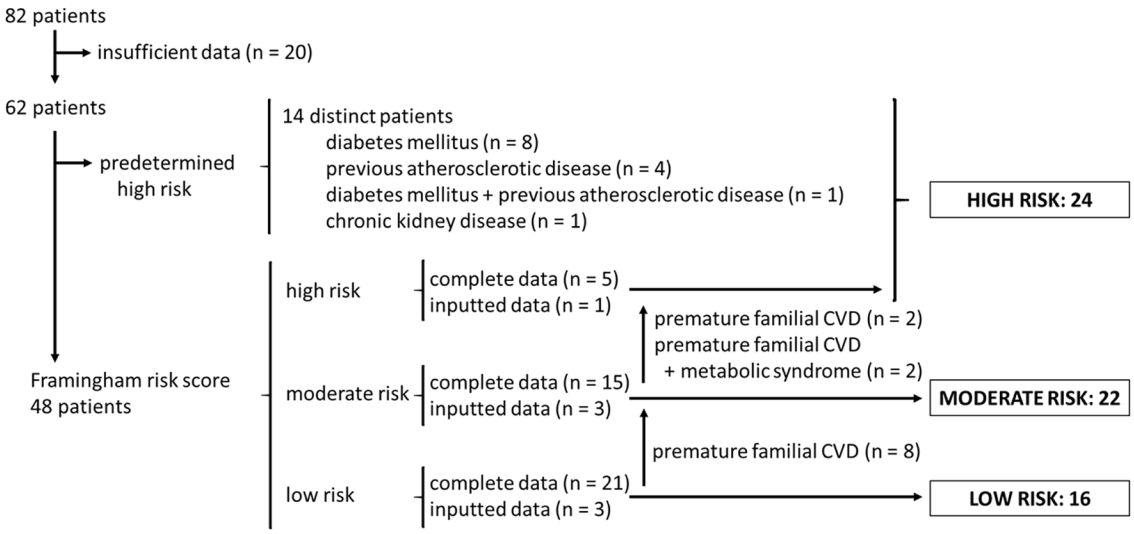

Fig. 1 Framingham Risk Score of the haemophilia patients included in the HemoCardio Study. Only patients who had ≤ 1 missing were suitable to have the missing value inputted, which should correspond to the 0-value in Framingham Risk Score of that specific variable. *CVD* cardiovascular disease

frequencies of SAH and smoking, and lower frequencies of obesity and metabolic syndrome. Consequently, 39% of PwH had an estimated high risk of developing CVD events in the following 10 years, according to the FRS.

In our study, more than half of PwH had SAH. Surprisingly, about a third was not on any anti-hypertension medication. SAH prevalence in other cohorts of PwH varied between 21% and 52%, which is above the frequency described for the individuals without haemophilia [7, 8, 29–31]. Chronic haematuria leading to CKD and SAH was a proposed mechanism, but recent data did not confirm this association [32, 33]. Besides that, only one patient in our study had CKD, a similar frequency found in other studies with PwH [31–33]. A possible defect in the endothelium itself and in the surrounding tissues in the PwH has also been suggested [34].

Metabolic status is still an undefined issue in haemophilia. The prevalence of obesity in HemoCardio Study was 16%, similar to the prevalence reported in other haemophilia cohorts (13%–21%) [29, 30, 32, 33]. However, although we showed a lower prevalence of obesity in PwH when compared with men without haemophilia described in other Brazilian studies (20%–21%) [25, 26, 28], literature data are inconsistent. One of the reasons which could explain a lower BMI in our study is the late introduction of prophylaxis for PwH in Brazil, in comparison with developed countries [6, 9]. As a consequence of repeated haemarthroses, several adult PwH in Brazil suffer from disability and hypotrophic muscle mass, and therefore, low body weight. The prevalence of diabetes mellitus in different Brazilian men without haemophilia ranged from 9% to 23% [25, 26], while it was 16% in PwH in this study, consistent with several reports on PwH ranging from 6% to 24% [29–32]. TG, Tc, HDLc and LDLc levels seemed similar between Brazilian PwH and men without haemophilia [25, 26]. Although some non-Brazilian studies showed different lipid profiles between PwH and men without haemophilia [7, 8, 30], other stated they may be similar [29].

The ELSA-Brasil Study described a much higher prevalence of metabolic syndrome among men without haemophilia in comparison with PwH from our study [28]. This may be a result of a combination of factors, since prevalence of obesity and diabetes among PwH in this study seemed to be lower than among men from ELSA-Brasil Study, with at least a similar lipid profile (TG and HDLc) [25–28]. On the contrary, there is a higher prevalence of SAH in PwH in our study.

Finally, 39% of the PwH in our study were categorised as high-risk for developing CVD-related death, coronary artery disease, stroke (including transient ischaemic attack), intermittent claudication and heart failure in the following 10 years [18, 35]. Considering only the CVD-related mortality, these results seem to reflect the demographic transition in Brazil: whilst CVD-related mortality in men without haemophilia has decreased in Pernambuco (− 40%) and in the country (− 27%) from 1990 to 2015 [36], CVD has been reported as an increasing cause of mortality among Brazilian PwH from 2000–2002 (14%) to 2012–2014 (26%) [3, 4]. Although not defined as a CVD event in the FRS, we should also highlight the potential risk of haemorrhagic stroke among PwH, which is higher than in people without haemophilia and increases with age [7]. Haemorrhagic

Table 4 Comparative results of Framingham Risk Score between HemoCardio and North-American individuals with haemophilia

Characteristics	Current	Sait et al. [40]
Study	HemoCardio	–
Year of test performances	2017–2019	2004–2012
City(ies)/state	Several/PE	San Diego/CA (USA)
Males (*n*)	82	89
Age (y)	30–68 (range)	42.1 ± 14.8 (mean ± SD)
Framingham Risk Score		
Low risk	26%	77%
Moderate risk	36%	15%
High risk	39% (21%)[†]	8%

Frequencies were expressed as percentage

PE Pernambuco, *CA* California, *USA* the United States of America, *SD* standard deviation

[†]The frequency of high-score individuals when PwH with previous CVD event are excluded from the analysis is 21% (10/48)

stroke is related to SAH in many registries [37]. Since PwH have also a higher risk of SAH than people without haemophilia [3, 4, 8, 29–31], uncontrolled high BP associated with ageing in a population with a high bleeding tendency may worsen the risk of haemorrhagic stroke.

There is only one report describing the FRS among PwH (Table 4) [38]. A North-American (San Diego/CA) retrospective study calculated the CVD risk profile in 89 PwH, using the FRS. The authors reported a prevalence of high-risk category in 8% of PwH [38]. However, the study did not evaluate kidney function, occurrence of metabolic syndrome, revascularization procedures, nor family history of premature CVD [38], as we did in the present study. Besides that, although age, prevalence of haemophilia A, and HCV-positive individuals were similar to the HemoCardio cohort, the prevalence of hypertensive, smokers, and diabetic patients was relatively higher in the HemoCardio Study than in the North-American cohort [38]. These may be the reasons why the prevalence of the high-risk category in PwH in the current study was almost five times higher than in the North-American study.

A prediction tool is useful to estimate the event risk, mainly when the disease has a silent progress, as is the case of CVD [22]. It should be highlighted that the FRS tool was developed based on a prospective cohort of 3969 asymptomatic men aged 30–74 years who were followed for a maximum of 12 years [35]. There were 718 (18.09%) CVD events during follow-up, and the tool predicts with an adequate accuracy the 10-year risk of event [35, 39]. However, the need of recalibration for correctly estimating the risk among Latin Americans has been discussed by many authors [40, 41].

Since the prevalence of CVD risk factors are common among PwH and there are no controlled clinical trials on the treatments of CVD risk factors or events among these individuals, based on our findings, we suggest that the same care of the general population should be provided to PwH. Access to elective consultation, integrated care, and simple screening routine blood tests for identifying risk factors should be offered to all PwH. In Brazil, physicians at the HTC may be the only healthcare reference for PwH, both because of socioeconomical restrictions and because culturally Brazilian men do not feel comfortable seeking preventive health care [42, 43]. Since guidelines on the management of prothrombotic states such as CVD among PwH is not yet available, it becomes even more important to predict and prevent CVD events in this population. We recommend that the multiprofessional team should actively evaluate CVD risk factors of every PwH 30 years or older and initiate treatment and/or refer PwH accordingly, with special focus on SAH and smoking status.

This study has some limitations. First, the population of PwH studied is from one centre, which may be a barrier to generalisation of our results. Inhabitants of this Brazilian location are ethnically admixed, with diverse cultural aspects, and economic discrepancy. Second, we did not perform comparison between subgroups of PwH due to small size of the population included in the study. Therefore, further studies are needed to investigate the risks of CVD between severe and non-severe PwH, and the risks between PwH treated exclusively on demand and on prophylaxis. Third, the FRS was not originally designed for people with bleeding disorders [35], and may not be the best prediction tool for PwH. Therefore, results should be considered cautiously. Prospective studies should be performed to confirm the estimated risks, considering the current treatment recommendations. Finally, literature about CVD risk profile among general Brazilian population is scarce, and Pernambuco inhabitants were not included in the ELSA-Brasil Study cohort, which is the study we used for some comparisons.

Conclusion

We described a higher prevalence of SAH among PwH in comparison with Brazilian men without haemophilia. Moreover, 39% of the PwH had an estimated high risk of developing a CVD event in the following 10 years.

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Author contributions RMC, BPD, AMV and TMR designed the study. RMC, BPD, MCBM, NCMC, IMC and CGPR collected data. RMC and CCD analysed data. RMC, CCD, SG, SMR and JvdB wrote the original manuscript. All the authors revised the manuscript and accepted the final form for submission.

Declarations

Conflict of interest RMC received honoraria for participating as a speaker at scientific and educational meetings and travel support for scientific meetings from Takeda and Hoffman-La Roche. NCMC received honoraria for participating as a speaker at scientific and educational meetings from Takeda and travel support for scientific meetings from Takeda and Novo Nordisk. IMC received honoraria for participating as a speaker at scientific and educational meetings from Takeda and travel support for scientific meetings from Takeda and Hoffman-La Roche. AMV received honoraria for participating as a speaker at scientific and educational meetings from Takeda and travel support for scientific meetings from Takeda, Hoffman-La Roche, Novo Nordisk and BioMarin. TMRG received travel support for scientific meetings from Takeda. SG received an unrestricted research grant from Sobi. JvdB received reimbursement for educational activities from Bayer. CCD, BPD, MCBM, CGPR, and SMR declare they have no interests which might be perceived as posing a conflict of bias.

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