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Hypertension and cardiovascular diseases in Swedish persons with haemophilia — A longitudinal registry study

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ABSTRACT

Introduction: Data on the prevalence of hypertension and cardiovascular diseases (CVD) among persons with haemophilia (PWH) vary. Sweden has a long tradition of maintaining population-based data registries, and there is extensive follow-up of haemophilia patients due to the use of prophylaxis over decades. We evaluated the prevalence of these diseases among Swedish PWH compared to matched controls using a longitudinal study design.

Methods: Data were obtained from the National Patient Registry and linked to records of persons with haemophilia enrolled in the haemophilia centres. For each subject, five gender and age matched controls were identified.

Results: We identified 193 (19.7%) diagnoses of hypertension in PWH born in 1978 or earlier over ≥30 years compared with 550 (11.2%) among controls. The median ages and interquartile ranges were 60.0 (42.8, 69.9) and 57.2 (42.6, 70.6) years. The hazard rate (HR) for hypertension, PWH vs. controls, was 2.1, 95% CI: [1.8; 2.5], $p < 0.001$. The findings were similar in subgroup analyses of patients with non-severe and severe haemophilia with or without HIV and/or viral hepatitis. Angina pectoris was diagnosed in 69 (4.8%) of patients censored at age 75 compared with 311 (4.3%) in controls, and myocardial ischemia in 84 (5.9%) compared with 442 (6.2%). As a cause of death, the HR for myocardial ischemia, comparing PWH and controls, was 0.58, 95% CI: [0.42, 0.80], $p = 0.001$.

Conclusion: Our data support an increased prevalence of hypertension among persons with haemophilia. The prevalence of CVD seems to be similar to that of controls, but with lower mortality.

1. Introduction

Haemophilia is a hereditary, X-linked recessive bleeding disorder caused by absent, deficient or dysfunctional coagulation factor VIII (FVIII) or factor IX (FIX). The hypocoagulable state due to coagulation factor deficiency has been suggested to protect against ischemic heart disease [1]. Consistent with this, a relatively low frequency of cardiovascular events as the cause of death has been reported among persons with haemophilia (PWH) [2–5] However, events do occur and as PWH have had a lower life-expectancy than the general population, the outcome over time is not clear. In addition, there is no indication that the arteriosclerotic process per se is diminished [5,6].

Hypertension, a well-known risk factor for cardiovascular diseases, has been more frequently encountered in PWH compared to the general population in several cohorts, especially among those with the more severe form of the disease [7–10]. These findings have, however, not been consistent. In some cases, a lower prevalence of hypertension has been observed [11,12]. In addition, although unfavourable cardiovascular risk profiles have been reported for PWH, no consistent association with well-established risk factors for hypertension, e.g. age, body mass index (BMI), cholesterol level, kidney function, diabetes, smoking, and race, have been found and the reasons for this are not clear

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[7,13–16]. The potential impact of blood transmitted viral diseases, e.g. HIV and hepatitis C, on the cardiovascular risk profile in patients with haemophilia has also not been established [17,18].

Patients with haemophilia in Sweden are characterized by a relatively advantageous treatment history in that prophylactic use of coagulation factor concentrates has been widely practiced for decades in more or less all patients with factor activity levels below 1–2%. With respect to hypertension and CVD, this type of treatment may theoretically offer both potential benefits and draw-backs. The benefit is the protection against clinical and subclinical bleeding in a variety of tissues, whereas the draw-backs, theoretically, may be a higher protein load and deposition affecting kidney function and the mechanisms of establishing adequate blood pressure levels. No prospective evaluation of the relatively well-treated Swedish cohort from young age into adulthood has been done. Therefore, we wanted to evaluate the prevalence of hypertension and fatal as well as non-fatal CVD in a longitudinal manner by taking advantage of Sweden's long tradition of data collection in the form of registers. Using the unique national identification number for each patient, data over time can be linked across registers. Moreover, the haemophilia care has been centralized in three haemophilia treatment comprehensive care centers (HTCC) in Malmö, Stockholm and Gothenburg, providing the advantages of accurate diagnosis, follow-up and management of the disease and co-morbidities. Data from both the National Patient Registry (NPR), as the source of outcomes, as well as the registers at the haemophilia treatment centers (HTCCs), for optimum coverage of patients with less severe disease, were collected. Subgroup analyses of patients with severe and non-severe haemophilia with and without HIV and/or viral hepatitis were performed.

2. Materials and methods

The characteristics of the study cohort have previously been described and a summary is provided in Table 1 [4]. In short, the cohort was created by identifying PWH from the national In- and Out-patient Registry and from the treatment centres in Malmö, Gothenburg and Stockholm who were born before 2009. *International Classification of Disease* (ICD) codes were used to identify PWH. The severities of haemophilia were only available for those registered at the local haemophilia centers, as the ICD-codes do not distinguish between severities. For each PWH five controls, matched on age and gender, were randomly chosen from the Population Registry. Cardiovascular events were identified from the national In- and Out-patient Registry. Diagnoses were identified using the following ICD-codes; ICD-8/ICD-9: (400–405, 410–414); ICD-10: (I10-I15, I20-I25). The codes were stratified into three groups: hypertension: (400–405, I10-I15); angina pectoris: (413, I20) and myocardial ischemia: (410–412, 414), (I21-I25). The presence of one or more occurrence was coded as 1 and no occurrence as 0. Causes of death due to cardiovascular events were extracted from the national Cause of Death Registry. The investigation of hypertension was completed only for those born in 1978 or earlier to permit a follow-up period of at least 30 years.

Table 1
Description of the study population.

	Haemophilia	Control
All severities		
Total number	1431	7150
Mean birth year, range	1960, 1884–2008	1960, 1884–2008
Follow-up (year), median (IQR)	44.3 (22.3–65.8)	43.8 (22.2–65.3)
HIV-positive, n (%)	96 (6.7)	2 (0.0)
Viral hepatitis infected, n (%) (*with or without HIV*)[a]	337 (23.5)	35 (0.5)
Non-infected, n (%)	1067 (74.6)	*5331* (*n.d.*)[d]
Overall deaths, n (%)	382 (26.7)	1351 (18.9)
Mild or moderate form		
Total number	550	2749
Follow-up (year), median (IQR)	41.8 (20.9–62.1)	40.5 (20.4–61.5)
HIV- positive, n (%)	17 (3.1)	1 (0.0)
Viral hepatitis infected, n (%) (*with or without HIV*)[b]	134 (24.4)	17 (0.6)
Non-infected, n (%)	410 (74.5)	*2050* (*n.d.*)[d]
Overall deaths, n (%)	90 (16.4)	389 (14.2)
Severe form		
Total number	384	1918
Follow-up (year), median (IQR)	26.9 (14.0–47.2)	27.2 (13.5–48.5)
HIV-positive, n (%)	78 (20.3)	1 (0.1)
Viral hepatitis infected, n (%) (*with or without HIV*)[c]	167 (43.5)	9 (0.5)
Non-infected, n (%)	196 (51.0)	*980* (*n.d.*)[d]
Overall deaths, n (%)	78 (20.3)	102 (5.3)

[a] No. of patients with only viral infection = 268.
[b] No. of patients with only viral infection = 123.
[c] No. of patients with only viral infection = 110.
[d] Control cohort defined by the patients with no infection (n.d., not determined).

2.1. Statistical analysis

The median age at the first registered event of hypertension, angina pectoris and myocardial ischemia was calculated together with the interquartile range (IQR). Cox proportional-hazards regression models stratified on birth date were used to investigate hypertension, angina pectoris and both fatal and non-fatal myocardial ischemia with estimation of hazard ratios (HR) and their corresponding 95% confidence intervals (CI). The follow-up time was from date of birth until date of event, date of emigration, date of death, or end of study (Dec 31, 2008). To meet assumptions regarding proportional hazards, age was censored at 75 years for angina pectoris and myocardial ischemia. Analyses were performed if the number of events was ≥ 10. A p-value below 0.05 was considered to demonstrate statistical significance. SPSS version 21 was used for all tests.

2.2. Ethics

The study was approved by the regional ethics committee of Lund, Sweden (registration number 706/2008). For study purposes, all data were de-identified and analysed at the group level.

3. Results

A summary of the characteristics of the study cohort is provided in Table 1.

3.1. Hypertension

As shown in Table 2, 196 (13.7%) of the entire study population of PWH ($n = 1431$) had a diagnosis of hypertension compared with 551 (7.7%) of the controls ($n = 7150$). As described in Material and Methods, the primary end-point for hypertension was an evaluation of the subgroup of patients born in 1978 or earlier to allow an observation period of at least 30 years. Among these patients ($n = 981$), 193 (19.7%) had been diagnosed with hypertension compared with 550 (11.2%) of the controls. The median ages and IQR at diagnosis were 60.0 (42.8, 69.9) and 57.2 (42.6, 70.6) years, respectively. The distribution of cases by age is shown in Fig. 1. Overall, the hazard rate (HR) was significantly higher for PWH than controls; 2.1, 95% CI: [1.8; 2.5], $p < 0.001$.

In subgroup analysis of patients born in 1978 or earlier with non-severe haemophilia, hypertension was diagnosed in 53 (15.1%) of the patients compared with 195 (11.1%) of the controls (Table 3). The corresponding median ages and IQR at diagnosis were 60.0 (36.8, 87.7) and 65.0 (9.1, 93.9) years, and the corresponding HR was 1.5, 95% CI: [1.1, 2.1], $p = 0.02$. In the corresponding subgroup of patients with

Table 2
Diagnoses of hypertension, angina pectoris and myocardial ischemia. Figures for the total cohort of PWH (n = 1413) and matched controls (n = 7150) are shown as well as for those with and without HIV and/or viral hepatitis as described in Table 1. As mentioned in Material and Methods, hypertension was primarily evaluated in patients born 1978 or earlier and the diagnosis of angina pectoris and myocardial ischemia censored at the age of 75 years. The total number of patients for each calculation is given. (Pts, patients). **The control cohorts were defined by the patients with or without infections.*

	Total Study Group			Non-infected*			Infected*					
							HIV			Viral hepatitis		
	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*
Hypertension												
Total	196 (13.7)	551 (7.7)		132 (12.4)	400 (7.5)		12 (12.5)	48 (10.0)		52 (19.4)	103 (7.7)	
	n_{pat} = 1431	$n_{control}$ = 7150		n_{pat} = 1067	$n_{control}$ = 5331		n_{pat} = 96	$n_{control}$ = 480		n_{pat} = 268	$n_{control}$ = 1340	
Pts born 1978 or earlier	193 (19.7)	550 (11.2)	< 0.001	130 (19.8)	399 (12.1)	< 0.001	12 (12.9)	48 (10.3)	< 0.001	51 (22.1)	103 (8.9)	< 0.001
	n_{pat} = 981	$n_{control}$ = 4903		n_{pat} = 657	$n_{control}$ = 3285		n_{pat} = 93	$n_{control}$ = 465		n_{pat} = 231	$n_{control}$ = 1155	
Angina Pectoris												
Total	85 (5.9)	398 (5.6)		75 (7.0)	297 (5.6)		2 (2.1)	24 (5.0)		8 (3.0)	77 (5.7)	
	n_{pat} = 1431	n_{pat} = 7150		n_{pat} = 1067	$n_{control}$ = 5331		n_{pat} = 96	$n_{control}$ = 480		n_{pat} = 268	$n_{control}$ = 1340	
Pts censored at age 75	69 (4.8)	311 (4.3)	0.61	60 (5.6)	225 (4.2)	0.14	2 (2.1)	20 (4.2)	n.a	7 (2.6)	66 (4.9)	n.a
	n_{pat} = 1431	n_{pat} = 7150		n_{pat} = 1067	$n_{control}$ = 5331		n_{pat} = 96	$n_{control}$ = 480		n_{pat} = 268	$n_{control}$ = 1340	
Myocardial ischemia												
Total	117 (8.2)	578 (8.1)		105 (9.8)	452 (8.5)		2 (2.1)	27 (5.6)		10 (3.7)	99 (7.4)	
	n_{pat} = 1431	n_{pat} = 7150		n_{pat} = 1067	$n_{control}$ = 5331		n_{pat} = 96	$n_{control}$ = 480		n_{pat} = 268	$n_{control}$ = 1340	
Pts censored at age 75	84 (5.9)	442 (6.2)	0.46	73 (6.8)	332 (6.2)	0.68	2 (2.1)	22 (4.6)	n.a	9 (3.4)	88 (6.6)	n.a
	n_{pat} = 1431	n_{pat} = 7150		n_{pat} = 1067	$n_{control}$ = 5331		n_{pat} = 96	$n_{control}$ = 480		n_{pat} = 268	$n_{control}$ = 1340	

severe haemophilia, 35 (18.2%) suffered from hypertension compared with 76 (7.9%) of the controls (Table 4). The median ages and IQR in this subgroup were 51.2 (25.1, 74.8) and 58.2 (23.4, 81.3), respectively, and the HR was 4.9, 95% CI: [2.6, 9.4], $p < 0.001$.

Of the 382 PWH that died during the study period, hypertension was reported as the cause of death in three (0.8%) cases with an equally low proportion among controls (0.8%).

3.1.1. Non-infected subgroups

Among patients born in 1978 or earlier without viral hepatitis and/or HIV (n = 657), 130 (19.8%) cases of hypertension were registered compared with 399 (12.1%) in the control group. This corresponds to a HR of 1.8, 95% CI: [1.5, 2.3], $p < 0.001$. As seen in Table 3, no significant difference was found in the subgroup containing only those with non-severe haemophilia (p = 0.35). Only five cases of hypertension were identified for subjects with severe haemophilia according to Table 4. Thus, no statistical tests were performed.

3.1.2. Infected subgroups

Considering all severities, 51 (22.1%) cases of hypertension were reported in 231 PWH with viral hepatitis born in 1978 or earlier, excluding those co-infected with HIV, compared with 103 (8.9%) of the controls (Table 2). The HR were 3.3, 95% CI: (2.3, 4.9), $p < 0.001$ and consistently > 1 in subgroup analyses of patients with non-severe haemophilia, as well severe haemophilia, compared to the controls, e.g. 1.9, 95% CI: [1.1, 3.4], $p = 0.02$ and 4.9, 95% CI: [2.6, 9.4], $p < 0.001$, respectively.

Twelve (12.9%) of 93 patients infected with HIV had a diagnosis of hypertension compared with 48 (10.3%) of the controls ($p < 0.001$). In the corresponding subgroup of patients with non-severe haemophilia, 3/16 (18.8%) had a diagnosis of hypertension compared with 10/80 (12.5%) of the controls (Table 3). The figures in the subgroup of patients with severe haemophilia were 9/76 (11.8%) and 38/380 (10.0%), respectively (Table 4). Given the relatively small sample sizes, no additional statistical testing was done.

3.2. Angina pectoris

Angina pectoris was diagnosed in 85 (5.9%) of all PWH included in the study (Table 2). Their median age (range) was 65.6 years (40.7–89.0). The corresponding outcome for controls were 398 (5.6%) and 66.7 years (32.8–94.9). As mentioned in Material and Methods, the HR was estimated for events occurring before 75 years of age in the two cohorts. Sixty-nine (4.8%) of the patients and 311 (4.3%) of the controls had angina pectoris corresponding to a HR of 1.1, 95% CI: [0.82, 1.41] (p = 0.61).

In subgroup analysis of persons with non-severe haemophilia censored at age 75, 18 (3.3%) suffered from angina pectoris compared with 112 (4.1%) among controls at median ages of 64.2 (47.9, 87.0) and 64.7 (40.9, 91.0) years, respectively (Table 3). The HR in this subgroup was 0.72, 95% CI: [0.44, 1.20], p = 0.21. Only five (1.3%) of the persons with severe haemophilia had a diagnosis of angina pectoris compared to 49 (2.6%) of the controls (Table 4).

3.2.1. Non-infected subgroups

Seventy-five (7.0%) of all non-infected patients and 297 (5.6%) of their controls had a diagnosis of angina pectoris (Table 2). For PWH, the numbers of events that occurred before the age of 75 years was 60 (5.6%) and for controls 225 (4.2%) (HR = 1.3, 95% CI: [0.93, 1.68], p = 0.14). In the subgroup of patients with non-severe haemophilia, the corresponding figures were 15 (3.7%) and 78 (3.8%), respectively, and the HR was estimated to be 0.86, 95% CI: [0.49, 1.51], p = 0.60. Among those with severe haemophilia only one case was reported (0.5%) compared with 8 cases (0.8%) in controls.

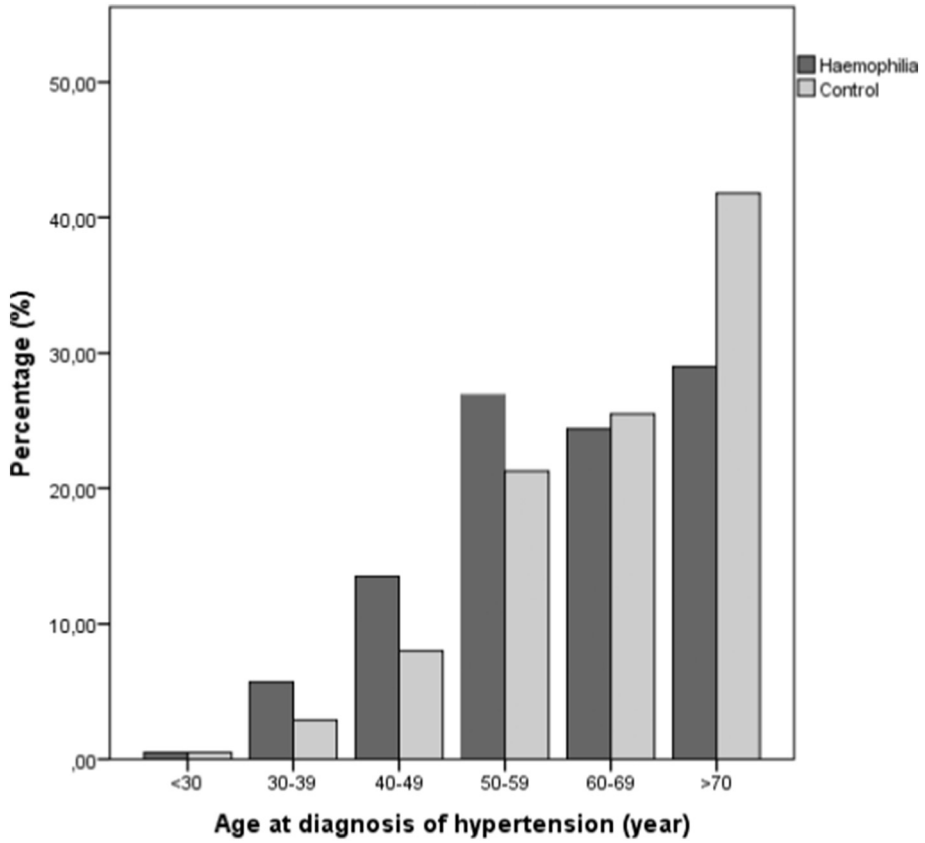

Fig. 1. Distribution of age at diagnosis of hypertension for patients with haemophilia and controls born 1978 or earlier.

3.2.2. Infected subgroups

Seven (2.6%) of the 268 censored patients with viral hepatitis and 2 (2.1%) of the 96 HIV infected patients suffered from angina pectoris compared with 66 (4.9%) and 20 (4.2%) of the controls. No statistical testing was performed. Among those with non-severe haemophilia, angina pectoris was only found in 3 (2.4%) patients with viral hepatitis compared with 29 (4.7%) of the corresponding controls (Table 3). As shown in Tables 4, 2 (2.6%) of the patients with severe haemophilia infected with HIV and 2 (1.8%) with viral hepatitis had been diagnosed with angina pectoris.

3.3. Myocardial ischemia

Myocardial ischemia was reported in 117 (8.2%) of the entire study population in PWH compared to 578 (8.1%) in controls (Table 2). The median ages (range) were 67.2 (13.0, 91.4) and 67.1 (17.9, 101.3) years, respectively. Prior to the age of 75, the numbers of events were 84 (5.9%) in the patients and 442 (6.2%) in the controls. The corresponding HR was 0.91, 95% CI: [0.72, 1.16], $p = 0.46$.

In the subgroup analyses censored at age 75, 17 (3.1%) patients with non-severe and 6 (1.6%) with severe haemophilia had a diagnosis of myocardial ischemia compared with 139 (5.1%) and 50 (2.6%) of the controls (Tables 3 and 4). The HR of patients with non-severe haemophilia vs. controls was 0.55, 95% CI: [0.33, 0.91], $p = 0.02$.

Myocardial ischemia was registered as the cause of death in 47 (12.3%) of all PWH compared to 388 (28.7%) of the controls, corresponding to a HR of 0.58, 95% CI: [0.42, 0.80], $p = 0.001$.

3.3.1. Non-infected subgroups

We identified 105 (9.8%) of all PWH in the non-infected group with a diagnosis of myocardial ischemia compared with 452 (8.5%) among controls (Table 2). The numbers decreased to 73 (6.8%) and 332 (6.2%)

Table 3
Diagnoses of hypertension in patients born 1978 or earlier, as well as angina pectoris and myocardial ischemia censored at age 75 as described above for persons with *non-severe* haemophilia with and without HIV and/or viral hepatitis according to Table 1. The total number of patients for each calculation is given. (Pts, patients)
**The control cohorts were defined by the patients with or without infections.*

	All included			Non-infected*			Infected*					
							HIV-infected			Viral hepatitis		
	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*
Hypertension	53 (15.1) $n_{pat} = 352$	195 (11.1) $n_{control} = 1760$	0.02	30 (13.2) $n_{pat} = 227$	126 (11.1) $n_{control} = 1135$	0.35	3 (18.8) $n_{pat} = 16$	10 (12.5) $n_{control} = 80$	n.a.	20 (18.3) $n_{pat} = 109$	59 (10.8) $n_{control} = 545$	0.02
Angina Pectoris	18 (3.3) $n_{pat} = 550$	112 (4.1) $n_{control} = 2749$	0.21	15 (3.7) $n_{pat} = 410$	78 (3.8) $n_{control} = 2050$	0.60	0 (0) $n_{pat} = 17$	5 (5.9) $n_{control} = 85$	n.a.	3 (2.4) $n_{pat} = 123$	29 (4.7) $n_{control} = 615$	n.a.
Myocardial ischemia	17 (3.1) $n_{pat} = 550$	139 (5.1) $n_{control} = 2749$	0.02	13 (3.2) $n_{pat} = 410$	86 (4.2) $n_{control} = 2050$	0.17	0 (0) $n_{pat} = 17$	6 (7.1) $n_{control} = 85$	n.a.	4 (3.3) $n_{pat} = 123$	47 (7.6) $n_{control} = 615$	n.a.

Table 4
Diagnoses of hypertension in patients born 1978 or earlier, as well as angina pectoris and myocardial ischemia censored at age 75 as described above for persons with *severe* haemophilia with and without HIV and/or viral hepatitis according to Table 1. The total number of patients for each calculation is given. (Pts, patients) *The control cohorts were defined by the patients with or without infections.

	All included			Non-infected*			Infected*					
							HIV-infected			Viral hepatitis		
	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*	Haemophilia, n (%)	Control, n (%)	*p-Value*
Hypertension	35 (18.2)	76 (7.9)	< 0.001	5 (17.2)	12 (8.3)	n.a.	9 (11.8)	38 (10.0)	n.a.	21 (24.1)	26 (6.0)	< 0.001
	n_{pat} = 192	$n_{control}$ = 960		n_{pat} = 29	$n_{control}$ = 145		n_{pat} = 76	$n_{control}$ = 380		n_{pat} = 87	$n_{control}$ = 435	
Angina Pectoris	5 (1.3)	46 (2.4)	n.a.	1 (0.5)	7 (0.7)	n.a.	2 (2.6)	15 (3.8)	n.a.	2 (1.8)	24 (4.4)	n.a.
	n_{pat} = 384	$n_{control}$ = 1918		n_{pat} = 196	$n_{control}$ = 960		n_{pat} = 78	$n_{control}$ = 390		n_{pat} = 110	$n_{control}$ = 550	
Myocardial ischemia	6 (1.6)	43 (2.2)	n.a.	2 (1.0)	6 (0.6)	n.a.	2 (2.6)	16 (4.1)	n.a.	2 (1.8)	21 (3.8)	n.a.
	n_{pat} = 384	$n_{control}$ = 1918		n_{pat} = 196	$n_{control}$ = 960		n_{pat} = 78	$n_{control}$ = 390		n_{pat} = 110	$n_{control}$ = 550	

when only those younger than 75 years were included. The corresponding HR was 1.1, 95% CI: [0.81, 1.38], $p = 0.68$.

Thirteen (3.2%) patients with non-severe haemophilia compared with 86 (4.2%) of the corresponding controls had myocardial ischemia in subgroup analysis with a HR of 0.66, 95% CI: [0.37, 1.20], $p = 0.17$ (Table 3). The corresponding figures for patients with severe haemophilia were 2 (1.0%) and 9 (0.9%), respectively, and due to the low numbers, no further statistical calculation was made (Table 4).

3.3.2. Infected subgroups

Among the patients infected with HIV, 2 (2.1%) cases of myocardial ischemia were identified compared with 22 (4.6%) of the controls censored at the age of 75 (Table 2). In patients with viral hepatitis, the corresponding figures were 9 (3.4%) vs. 88 (6.6%), respectively. Given the small sample sizes, no statistical testing was done. In subgroup analysis of persons with non-severe haemophilia, only 4 (3.3%) cases among those with viral hepatitis were identified compared with 47 (7.6%) of the controls (Table 3). Two (2.6%) patients with severe haemophilia infected with HIV and 2 (1.8%) with viral hepatitis were identified as shown in Table 4.

4. Discussion

This longitudinal registry-based study of Swedish PWH born 1978 or earlier with an observation period of at least 30 years identified hypertension in 19.7% of patients – all severities included – compared to 11.2% in the matched controls. This supports previous findings of a higher frequency of hypertension among PWH compared to persons without haemophilia [7–10]. The difference was more or less consistent in the subgroup analyses of patients with non-severe and severe haemophilia with or without the co-infection of viral disorders. The reasons for the observed higher risk of hypertension among patients with haemophilia remain unclear, but may be multifactorial. In previous studies, common risk factors for hypertension, such as BMI, kidney function, smoking, and diabetes, have not been consistently associated with hypertension in the population with haemophilia. In Sweden, the use of prophylaxis in patients with factor VIII and IX activity below 1–2% began in a smaller scale in the 1950s. Overall, Swedish patients with haemophilia have had relatively beneficial access to treatment over the years. Theoretically, a relatively high protein load with the deficient coagulation factor over time may have an impact on the renal function and the risk of developing hypertension due to protein accumulation and deposition. Even though this potentially could explain part of the difference identified in our study, this pathophysiological mechanism has not been possible to show and/or confirm in other studies [13]. We did observe a slightly higher frequency of hypertension in the subgroup of patients with severe haemophilia (18.2%) born in 1978 or earlier compared to those with non-severe disease (15.1%), but this difference is small and should be interpreted with caution. In fact, our findings may instead argue against the amount of factor replacement per se to increase the risk for hypertension. In addition, the frequency of hypertension in our population is not higher than reported for other cohorts – in fact, in most cases, it is even lower. We could also not identify renal failure as a significant cause of death in our previous study [4]. Therefore, one could not exclude the possibility that adequate prophylaxis may actually be of some benefit due to the prevention of subclinical bleeds in the renal tissue. This should be further evaluated using a prospective approach. Importantly, the prevalence of patients diagnosed with hypertension receiving primary health care in Sweden has been reported to be approximately 11% [19] which correlates very well with the figure of 11.2% in the entire control group. It is also important to take into account that patients with haemophilia in Sweden have had relatively close follow-up in their treatment centers over decades, including blood pressure measurement, which, despite the same diagnostic criteria for patients and controls over the years, could influence the proportion of patients diagnosed with hypertension

in this study. In addition, the data presented in Fig. 1 on the age at diagnosis of hypertension may indicate a somewhat earlier detection compared with the controls, which, if so, may also be due to a closer and more regular follow-up.

We did not observe any statistically significant differences for angina pectoris and myocardial ischemia in the entire study population compared to controls. However, in subgroup analysis, myocardial ischemia was encountered significantly less frequently in patients with non-severe haemophilia. Among patients with severe haemophilia, a similar trend was observed, but the numbers of events were low and no statistical comparison could be made. In our previous report, ischemic heart disease as the cause of death among those with haemophilia was found to be 57% less likely than that for controls [4]. A lower mortality rate has also been reported by Kamphuisen et al. [3]. It appears as if the arteriosclerotic process per se is similar in subjects with or without haemophilia [5,6]. The hypocoagulability state with less thrombin produced in PWH may, as suggested, be beneficial and preventive for a fatal outcome [1,16]. Interestingly and noteworthy, however, the opposite outcome has also been reported. Soucie et al. reported a 3-fold (95% CI: 1.5–5.8) higher standardized mortality ratio for acute myocardial infarction for patients with haemophilia from six US states compared to US males without haemophilia of similar age [20]. The reason for this is unclear.

Our study design has strengths and weaknesses. The strengths include the size of the cohort and absence of selection bias, in that all subjects with registered diagnoses of hypertension and/or CVD were enrolled including those with non-severe haemophilia, not registered at the national haemophilia center. Undiagnosed cases of hypertension, due to lack of exposure to regular follow-up, may influence the results, whereas the symptoms of CVD would most likely result in hospital care for almost all. The follow-up of individuals in Sweden over the years, both PWH and the general population within the primary health care system, is considered to be relatively good which increases the validity of our data. In addition, the frequency of hypertension observed among controls correlates very well with the expected value based on our studies. Additional weaknesses are the inability to review medical records and adjust for important behavioral risk factors and/or family history to rule out the possibility that the prevalence of these risk factors differs between patients and controls. We also cannot examine the measurements and definitions of hypertension in each case, but must rely on the clinicians` expertise and knowledge of the diagnostic setting. The same diagnostic criteria according to national guidelines and ICD codes should, however, have been used for both patients and controls over the years, so we think a significant bias in this context will be unlikely. Finally, the relatively small number of cardiovascular events did not permit complete subgroup evaluation.

In conclusion, Swedish PWH with decades of relatively good access to factor concentrates seem, as described for other study cohorts, to experience more hypertension than the general population. The amount of protein load due to replacement therapy as part of the explanation for this higher prevalence cannot be completely ruled out, but the figures in patients with severe haemophilia is more or less similar to those observed in the non-severe group in our study and also relatively low compared to other study populations with access to less treatment. Therefore, we argue that the higher frequency of hypertension in PWH will likely have other causes, yet to be identified. Finally, myocardial ischemia appears to be as common among patients with haemophilia as in the general population, but the outcome, in terms of mortality, may be lower, despite the relatively extended use of prophylactic treatment.

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Author contribution

S Lövdahl has designed and performed the research, interpreted and analysed data, written the manuscript and given her final approval of the version to be published. KM Henriksson has designed the research, interpreted data, revised the manuscript and given her final approval of the version to be published. M Holmström has contributed data, interpreted data, revised the manuscript and given her final approval of the version to be published. F Baghaei has contributed data, interpreted data, revised the manuscript and given her final approval of the version to be published. E Berntorp has designed and performed the research, interpreted and analysed data, written the manuscript and given his final approval of the version to be published. J Astermark has designed and performed the research, interpreted and analysed data, written the manuscript and given his final approval of the version to be published.

Declaration of Competing Interest

S Lovdahl, KM Henriksson, F Baghaei, M Holmstrom, E Berntorp and J Astermark stated that they had no interests which might be perceived as posing a conflict or bias for this manuscript.

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