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blood advances

Reduced cardiovascular morbidity in patients with hemophilia: results of a 5-year multinational prospective study

Paul Van Der Valk,[1] Michael Makris,[2] Kathelijn Fischer,[1] Robert C. Tait,[3] Pratima Chowdary,[4] Peter W. Collins,[5] Karina Meijer,[6] Lize F. D. van Vulpen,[1] Eveline Mauser-Bunschoten,[1] and Roger E. G. Schutgens[1]

[1]Benign Hematology Center, Van Creveldkliniek, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands; [2]Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, United Kingdom; [3]Department of Haematology, Royal Infirmary, Glasgow, United Kingdom; [4]Katharine Dormandy Haemophilia and Thrombosis Centre Royal Free Hospital, London, United Kingdom; [5]Arthur Bloom Haemophilia Centre, University Hospital of Wales School of Medicine, Cardiff University, Cardiff, United Kingdom; and [6]Department of Haematology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Key Points

- In this prospective study, PWH have a lower-than-predicted incidence of CVD.
- The QRISK-2011 risk predictor is not valid for PWH.

Hemophilia is a congenital bleeding disorder caused by low levels of clotting factor VIII or IX. The life expectancy of people with hemophilia (PWH) has increased with the availability of clotting factor concentrates. At the same time, the incidence of cardiovascular disease (CVD) has increased; in retrospective studies, there are conflicting data regarding if, despite this increase, the incidence is still lower than in the general population. We prospectively compared the incidence of CVD in PWH vs the predicted incidence. This prospective, multicenter, observational study included adult PWH (aged >30 years) from The Netherlands and United Kingdom. They were followed up for a 5-year period, and CVD incidence was compared with a predicted event rate based on the QRISK2-2011 CVD risk model. The primary end point was the observed fatal and nonfatal CVD incidence after 5 years compared with the estimated events and in relation to severity of hemophilia. The study included 709 patients, of whom 687 (96.9%) completed 5 years' follow-up or reached an end point. For 108 patients, the QRISK score could not be calculated at inclusion. For the remaining 579, fewer CVD events were observed than predicted: 9 vs 24 (relative risk, 0.38; 95% confidence interval, 0.18-0.80; $P = .01$), corresponding with an absolute risk reduction of 2.4%. Severe hemophilia treated on demand had the highest risk reduction. There was no statistically significant relation between severity of hemophilia and incidence of CVD. In hemophilia, a lower-than-predicted CVD incidence was found, supporting the theory that hemophilia protects against CVD. The study is registered at www.clinicaltrials.gov as #NCT01303900.

Introduction

Hemophilia is an X-linked hereditary congenital disorder causing low levels of clotting factor VIII (hemophilia A) or factor IX (hemophilia B), resulting in a clinical presentation of bleeding tendency. The severity of the disease is directly correlated to plasma concentrations: factor levels >5 to 40 IU/dL confer mild hemophilia; factor levels of 1 to 5 IU/dL are considered moderate; and factor levels <1 IU/dL indicate severe hemophilia. Severe hemophilia is characterized by spontaneous, recurrent bleeding into the joints (hemarthrosis) and muscles, as well as intracranial hemorrhage, which is the most serious event, resulting in high rates of mortality and disability. With the availability of viral safe clotting factor concentrates,

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bleeds can be prevented or effectively treated, and in high-income countries, the life expectancy of patients with hemophilia (PWH) has increased considerably over recent decades.[1] Consequently, the number of PWH aged >60 years has increased significantly in the United Kingdom from ~500 (in 1988) to ~1350 (in 2018).[2] In The Netherlands, 23% of the PWH in the national registry were aged >60 years in 2019.[3]

In addition to hemophilia-related morbidity, age-related comorbidity such as malignancies and cardiovascular disease (CVD) are becoming increasingly common. Management of thromboembolic CVD with antiplatelet or anticoagulation therapy is a major challenge in PWH. For an adequate strategy in the prevention of CVD, the incidence of CVD in PWH should be known and ideally be predictable on an individual level based on underlying characteristics. For the general population, CVD risk tools such as the QRISK score have been developed for this purpose. They predict the chance that an individual will develop CVD in a specific time frame. This allows the individuals identified as at high risk for CVD the option of more intensive treatment. However, risk scores are not validated for PWH and are expected to overestimate the risk. Theoretically, a protective effect of low levels of clotting factor would be expected. Indeed, in some retrospective studies, a lower-than-expected CVD mortality in PWH was found.[4] This is not associated with fewer risk factors, because in an international study, PWH had an unfavorable risk profile compared with that of the general population.[5] Furthermore, PWH are not protected from the development of atherosclerosis, as the same degree of atherosclerosis burden as the general population has been found.[6,7]

However, prospective studies on CVD mortality and morbidity in PWH are lacking. To determine the effect of lower levels of clotting factor on CVD, correction for the CVD risk factors is needed. A CVD risk tool such as the QRISK2-2011 score can be used for this calculation. The aim of the current prospective, multicenter, observational study was to describe the incidence of fatal and nonfatal CVD in PWH from The Netherlands and United Kingdom during 5 years' follow-up compared with a predicted event rate based on a general cardiovascular risk model (QRISK2-2011).[8]

Materials and methods

All male patients with hemophilia aged ≥30 years who attended 1 of the 6 participating hemophilia treatment centers between January 2009 and July 2011 were invited to take part in a prospective CVD study. The participating centers were the Van Creveldkliniek, University Hospital Utrecht, and University Hospital Groningen, Department of Hematology in The Netherlands; and the Sheffield Haemophilia and Thrombosis Centre, Glasgow Adults Haemophilia Centre (Royal Infirmary), Katharine Dormandy Haemophilia and Thrombosis Center (Royal Free Hospital), and Cardiff Haemophilia Centre (University Hospital of Wales) in the United Kingdom.

At inclusion, hemophilia characteristics, ethnic background, data on medical history, medication use, smoking habits, alcohol use, and family history of CVD were collected from patient files and by direct interviews. Parameter definitions and results and risk profiles (QRISK2-2011) were reported previously.[5] QRISK2-2011 is a risk model for predicting the risk of a first thrombotic CVD event (coronary heart disease, stroke, or transient ischemic attack) in the general population for the age group of 30 to 84 years, based on multiple factors (Table 1). One of these risk factors (postal code) could not be used for the Dutch patients, as the Townsend deprivation score is based on a UK postal code. The 10 years' QRISK score is mostly used for CVD management, and patients are frequently divided into 3 risk groups: low (<10%), intermediate (10%-20%), or high (>20%) risk. For this study, the 5 years' QRISK was used and compared with the 5 years' prospective follow-up data on the occurrence of thrombotic cardiovascular events. According to the QRISK model, CVD events were defined as myocardial infarction, ischemic heart disease, ischemic stroke, and transient ischemic attack. In this model, hemorrhagic stroke and peripheral artery disease are not considered as an event. Based on the QRISK score, an expected CVD event rate can be calculated per group. Furthermore, treatment schedule and annual clotting factor consumption were recorded. Data were stored anonymously in a central database at the University Medical Center Utrecht, Utrecht, The Netherlands.

Table 1. Cardiovascular risk factors for calculating QRISK2-2011

Age
Sex
Smoking status
Ethnicity
Systolic blood pressure
Ratio of total serum cholesterol to high-density lipoprotein
Body mass index
Family history of coronary heart disease in a first-degree relative <60 y of age
Townsend deprivation score (optional)
Treated hypertension
Diagnosis of
Rheumatoid arthritis
Atrial fibrillation
Type 2 diabetes
Chronic renal disease

The Townsend deprivation score was omitted in this study.

This study was approved by the Medical Ethics Review Boards of all participating hospitals. All participating patients provided written informed consent. The study is registered at www.clinicaltrials.gov as #NCT01303900.

Statistical analysis

For comparing the predicted vs the observed event rate, the relative risk (RR) (with 95% confidence interval [CI]), the absolute risk reduction, and a two-sided Fisher's exact test were calculated; a P value <.05 was considered significant. Subjects who were lost to follow-up were excluded from analysis. Patients who died of a non-CVD cause were included in the analysis until their death. Because only 2 and 5 years' QRISK scores were available, their predicted CVD risk during their follow-up period could not precisely be calculated. Risk was estimated by adjusting their 5 years' QRISK score with their time at risk. For subgroup analysis, patients were divided into severe, nonsevere (combination of mild and moderate severe), and mild hemophilia.

Fisher's exact testing was performed for analyzing the effect of factor level on the event rate. A two-sided P value <.05 was considered

significant for the Fisher's exact test. Testing was done in all patients and also only in patients with a calculable QRISK score. This was studied because a relation between severity and treatment form of hemophilia and CVD risk cannot not be ruled out or corrected in the absence of a QRISK score. For exploration about this possible bias regarding type of hemophilia on CVD risk, QRISK means were compared and were analyzed by using independent Student *t* testing. Comparisons were conducted in the patients with severe hemophilia: on-demand vs on-prophylactic therapy and between patients with severe hemophilia treated on-demand vs all other patients. Treatment regimen at inclusion was used in this analysis.

A logistic regression analysis was performed to analyze the effect of the QRISK score on the occurrence of CVD events and to evaluate the influence of factor levels. In addition, a comparison was conducted within patients with severe hemophilia (on-demand vs on-prophylactic therapy) and between patients with severe hemophilia treated on-demand vs all other patients.

Results

A total of 709 patients were included in the study, of whom 687 (96.9%) completed 5 years' follow-up or reached an end point. The characteristics of the PWH included in the study are shown in Table 2. Twenty-two patients were lost to follow up (3.1%). Table 2 also presents the data of people who were lost to follow-up compared with those with complete follow-up. PWH lost to follow-up commonly had mild hemophilia (17 of 22).

The QRISK score could not be calculated at inclusion for 108 patients. This was mostly due to statin use (n = 46 [42.6%]) or history of CVD (n = 43 [39.8%]). The CVD incidence in these 108 patients was 11.1%.

A complete data set was available for 579 PWH that allowed comparison with the predicted event rate (Table 3). One patient with a factor VIII level of 20 IU/dL was on a vitamin K antagonist because of a history of aortic valve replacement. Another patient with severe hemophilia A was on aspirin therapy because of nonischemic heart failure. PWH had a significantly lower number of fatal and nonfatal CVD events than predicted: 9 vs 24 (RR, 0.38; 95% CI, 0.18-0.80; $P = .01$), corresponding with an absolute risk reduction of 2.4%. This risk reduction was seen in all types of hemophilia severities. In all cardiovascular risk groups, a considerable risk reduction was found: high-risk group RR, 0.33 (95% CI, 0.11-0.99); intermediate-risk group RR, 0.43 (95% CI, 0.11-1.61); and low-risk group RR, 0.17 (95% CI, 0.020-1.38). Table 4 provides an overview of these 9 cases.

In severe, nonsevere, and mild hemophilia, there was a risk reduction in CVD with an RR of 0.33 ($P = .04$), 0.38 ($P = .05$), and 0.20 ($P = .02$), respectively. In people with severe hemophilia, the RR was dependent on treatment modality. For those treated

Table 2. Patient characteristics

Characteristic	Total	Lost to follow-up	No QRISK	QRISK
Number	709	22	108	579
Age, mean ± SD, y	48 ± 13.4	47 ± 15.0	64 ± 14.0	46 ± 11.7
From the United Kingdom	45.3% (321)	72.7% (16)	59.3% (64)	41.6% (241)
Hemophilia A	83.8% (594)	72.7% (16)	82.4% (89)	84.5% (489)
Severity				
Severe	48.5% (344)	13.6% (3)	59.3% (64)	52.5% (304)
Moderate	11.7% (83)	9.1% (2)	6.5% (7)	12.8% (74)
Mild	39.8% (282)	77.3% (17)	59.3% (64)	34.7% (201)
QRISK (5 y), mean ± SD	2.0 ± 5.41	1.30 ± 4.91	NA	2.0 ± 5.42
Previous CVD	8.6% (61)	9.1% (2)	46.3% (50)	1.6% (9)*
Cholesterol/HDL ratio, mean ± SD	4.31 ± 1.54	4.15 ± 1.36	4.0 ± 1.13†	4.36 ± 1.60
Systolic blood pressure, mean ± SD, mm Hg	135 ± 16.6	135 ± 20.6	137 ± 19.5	134 ± 15.8
Hypertension	48.8% (346)	45.5% (10)	78.7% (85)	43.4% (251)
HIV infection	10.7% (76)	4.5% (1)	7.4% (8)	11.6% (67)
Active HCV infection	32.2% (228)	27.2% (6)	17.6% (19)	35.1% (203)
Diabetes mellitus	6.1% (43)	4.5% (1)	17.6% (19)	4.0% (23)
Rheumatoid arthritis	1.1% (8)	0	1.9% (2)	1% (6)
Active smoking	27.6% (196)	18.2% (4)	18.5% (20)	29.7% (172)
BMI, mean ± SD, kg/m^2	25.7 ± 4.1	26.37 ± 4.3	26.9 ± 4.5	25.5 ± 4.0
Family history coronary heart disease	35% (248)	36.4% (8)	45.4% (49)	33.0% (191)
Atrial fibrillation	2.3% (16)	0% (0)	9.3% (10)	1.0% (6)
Chronic kidney disease (stage 4 or 5)	0.1% (1)	0% (0)	0.9% (1)	0% (0)

Characteristics of all patients included, lost to follow-up, patients with complete follow-up in whom a QRISK score was calculable, and those without a QRISK score.
BMI, body mass index; HCV, hepatitis C virus; NA, not available; SD, standard deviation.
*Nine patients had a history of nonthrombotic CVD, such as nonischemic heart failure, atrial fibrillation, and hemorrhagic stroke. A QRISK score was therefore applicable.
†A significant portion of patients without a QRISK score are on statin therapy, lowering the cholesterol/high-density lipoprotein (HDL) ratio.

Table 3. Predicted vs observed CVD events

Variable	N	CVD events expected	CVD events observed	RR (95% CI)	Fischer exact test, *P*	Absolute risk reduction
Total	579	4.1% (24)	1.7% (9)	0.38 (0.18-0.80)	.01	2.4%
CVD risk group						
Low	401	1.5% (6)	0.2% (1)	0.17 (0.02-1.38)	.12	1.3%
Intermediate	100	7.0% (7)	3.0% (3)	0.43 (0.11-1.61)	.17	4.0%
High	78	15.3% (12)	6.4% (5)	0.42 (0.15-1.13)	.06	8.9%
Severity						
Mild	201	5.0% (10)	1.0% (2)	0.20 (0.04-0.90)	.02	4.0%
Nonsevere*	275	4.7% (13)	1.8% (5)	0.38 (0.14-1.06)	.045	2.9%
Severe	304	3.9% (12)	1.3% (4)	0.33 (0.11-1.02)	.04	2.6%
On-prophylaxis therapy	182	3.8% (7)	2.2% (4)	0.57 (0.17-1.92)	.27	1.7%
On-demand therapy	122	4.1% (5)	0% (0)	0.00	.03	4.1%

Fisher exact test with a two-sided *P* value. CVD risk groups are divided by their 10 years' risk (<10%; 10%-20%; and >20% risk); the expected risk for 5 years' follow-up is therefore lower.

*Combination of mild and moderate to severe disease.

on-demand (n = 122), no CVD events were observed (predicted, 5; RR, 0; $P = .03$), whereas for those on prophylaxis therapy (n = 182), 4 CVD events were observed (predicted, 7; RR, 0.57; 95% CI, 0.17-1.92; $P = .27$). In a head-to-head comparison for treatment type, no significant difference in CVD events was found between PWH treated on-demand and on-prophylaxis ($P = .127$); there was also no significant difference in QRISK score ($P = .286$) (Table 5). No significant differences were found between PWH treated on-demand vs the whole group.

Logistic regression analysis revealed a significant correlation between QRISK score and the occurrence of CVD events: odds ratio, 1.118; 95% CI, 1.043-1.198; $P = .002$. Adjustment for factor level did not change this result. When severity of hemophilia in relation to CVD occurrence was analyzed, we found no differences; particularly, severe hemophilia with on-demand therapy did not differ from mild hemophilia (data not shown).

Discussion

Estimating the risk of a future cardiovascular event is of utmost importance for proper preventive management and counseling. In the general population, the QRISK has proven to be a valuable tool in this aspect and has been implemented in routine practice in the United Kingdom. The QRISK score has not been validated in patients with hemophilia. In this first long-term prospective study on fatal and nonfatal CVD in a large cohort of adult PWH, we documented a lower-than-predicted CVD incidence during a 5-year follow-up. This finding indicates that the QRISK overestimates CVD events in patients with hemophilia. It seems that all PWH might be reclassified to a lower cardiovascular risk group (Table 3).

To date, there have been no other prospective studies on nonfatal CVD in PWH published. Retrospective studies report a decreased prevalence of CVD, mostly lower CVD mortality but conflicting data on CVD risk factors. In the ARCHER (Age-Related CVD in Haemophilia Epidemiological Research) study,[9] a retrospective multicenter Canadian study for PWH aged >35 years (n = 294), risk factors were common (hypertension, 31.3%; diabetes mellitus, 10.5%; smoking, 21.8%; obesity, 27.6%; dyslipidemia, 22.4%; family history, 8.5%; antiretroviral therapy, 12.2%). The mean time to follow-up was 5.86 years, during which 18 CVD events (excluding atrial fibrillation) occurred: 14 coronary artery disease events and 4 ischemic cerebrovascular disease events. There was no comparison with a control group and no predicted number of events based on a risk score. Therefore, the effect of hemophilia on CVD cannot be assessed in this study. Because QRISK excludes high-risk patients (previous CVD, old age, and statin use), the higher CVD incidence compared with our study (18 events per ±1650 patient-years vs 9 events per ±2400 patient-years) could be explained by the higher risk population in the ARCHER study.

Humphries et al[10] conducted a retrospective chart review in Detroit, Michigan, comparing cardiovascular risk factors between PWH and control patients from the same hospital group. They found lower risk factors in PWH and a trend to lower prevalence of hypertension and less common history of coronary artery disease. Data on outcome were not given. Another retrospective study, by Sood et al,[11] showed a significantly lower prevalence of self-reported, nonfatal CVD compared with the ARIC (Atherosclerosis Risk in Communities) cohort (RR, 0.58; $P < .001$) despite the presence of more risk factors. In this study, no risk score was calculated. The RR is comparable to our study. In a retrospective registry study in Sweden,[12] an increased prevalence of hypertension was found, as in our cohort,[5] with a similar prevalence of CVD but with lower mortality compared with a matched control group. Using retrospective chart review, a study by Soucie et al[13] found a higher cardiovascular mortality rate compared with the general population. Previous studies on mortality in PWH in the United Kingdom[14] and The Netherlands[1] showed a lower incidence of fatal CVD compared with the general population.

Patients with severe hemophilia treated on demand had the highest risk reduction (RR, 0) in the current study. This finding supports the theory that very low factor VIII or IX activity levels protect against thrombotic CVD. We found no statistically significant effect of severity of disease or factor level on CVD events. However, due to the low event rate and short period of follow-up, the lack of an association between hemophilia severity and cardiovascular events should be validated. It is possible that data after 10 years' follow-up will be

Table 4. Characteristics of the 9 patients who experienced a CVD

Event	Time, wk	Age, y	Factor level, %	QRISK, %	Smoking	CVD in family (aged <60 y)	DM	HCV	HIV	BMI, kg/m^2	BP, mm Hg	aHT	Cholesterol ratio	Creatinine, μmol/L
Stroke	98	77	<1	10.8	No	No	No	Spontaneous clearance	Yes	17.7	146/86	No	3.36	62
IHD	49	47	<1	6.3	No	Yes (no)	Yes	Treated	Yes	23.0	120/90	Yes	5.00	202
Stroke	188	58	<1	13.8	No	Yes (yes)	No	Negative	No	25.4	162/55	No	9.27	103
TIA	149	62	<1	22.8	Stopped	Yes (yes)	Yes	Treated	No	34.3	143/87	Yes	4.41	65
Stroke*	16	42	3	2.4	Yes	Yes (yes)	No	Unsuccessful treated	No	19.6	95/62	No	4.08	66
MI	193	64	3	6.5	Yes	Yes (no)	No	Yes, never treated	No	19.9	122/86	Yes	2.93	80
Stroke	115	65	5	7.4	No	No	No	Yes, never treated	No	22.0	126/64	Yes	4.55	75
MI	146	66	10	9.8	No	Yes (no)	No	Negative	No	24.3	163/98	No	6.74	79
IHD	198	63	25	19.7	Yes	Yes (yes)	No	Negative	No	27.8	166/107	Yes	4.26	70

Type of event (fatal event marked with *) included ischemic stroke, IHD, TIA, and MI. Time indicates timing after inclusion (weeks). Age is at the time of event. QRISK indicates 5 years' QRISK2011 score. CVD in family indicates positive family history of CVD (aged <60 years [premature CVD]). Creatinine indicates level at inclusion.
aHT, antihypertensive medication; BP, blood pressure at inclusion; Cholesterol ratio, total cholesterol/high-density lipoprotein cholesterol ratio; DM, diabetes mellitus; HCV, hepatitis C virus; IHD, ischemic heart disease; MI, myocardial infarction; TIA, transient ischemic attack.

more informative. Because this study was observational, causality between treatment of disease and number of CVD is difficult to assess. The question of whether prophylaxis should be stopped in PWH who have a high-risk profile cannot be answered by this study. There are considerable benefits to prophylaxis in this group with regard to bleeding prevention that directly affects quality of life and life expectancy. In our opinion, prophylaxis should therefore not be stopped to prevent CVD. Evaluation, lifestyle education, and, if appropriate, treatment of CVD risk factors are more logical for the prevention of CVD in PWH.

The QRISK2-2011 was chosen because this tool only scores for ischemic stroke and not hemorrhagic ones.[15] By excluding hemorrhagic strokes, this scoring system is more suitable for hemorrhagic diseases such as hemophilia when exploring thrombotic events. This was underscored by the finding of a relatively high percentage (50% [2 of 4]) of hemorrhagic strokes in our study (data not shown), whereas in the general population, ischemic strokes are far more dominant (88%).[16]

The strength of the current study is its very high patient participation: 97% of all eligible patients were included. This means that the study cohort reliably represents the PWH population in The Netherlands and the United Kingdom, with limited selection bias. Furthermore, the retention was very high (97%) over a prolonged period of time. It is likely that most subjects who were lost to follow-up did not experience a CVD; the hemophilia center would have been consulted for medical advice in such a case, and in case of a fatal event, cause of death would have been known.

One of the weaknesses of the current study is the use of the QRISK2-2011 score for the predicted outcome. The alternative of comparisons vs a matching control group was not feasible, as this group should have comparable medical care such as frequent outpatient clinic visits. The QRISK model was used because of the availability for 5-year results, broad age range (30-84 years), both CVD mortality and morbidity as outcomes, and exclusion of hemorrhagic strokes. This is in contrast to another widely used risk score, SCORE (Systematic Coronary Risk Evaluation), which only has mortality as outcome. The QRISK score has not been validated for the general Dutch population.[15] However, we assume the QRISK to be a good predictor, as we earlier found a strong correlation between QRISK2 ten-year risks and SCORE results. This was the case irrespective of country of origin.[5] Because SCORE results are validated for both countries, and because the same validated low-risk chart is used for both countries, we found it feasible to use the QRISK score.

A confounding effect may be that, in this study, patients who were found to have severe hypertension or severe dyslipidemia were treated for these conditions, and lifestyle education was given to all patients. This drop-in effect is seen in most studies, and risk scores do not address these modifiers, and thus the precise impact of these possible differences is unknown.[17]

Another weakness is that the optional Townsend deprivation score was not used, as it is not available for Dutch postal codes. It was assumed that there was no difference in social economic status for PWH compared with the general population. There are no published data on the Townsend score in PWH, and other indicators for social economic status suggest a normal or below average status,[18,19] causing a possible underestimation of the QRISK score.

Table 5. Comparing CVD events based on severity of hemophilia and treatment type

CVD event	Complete cohort (N = 687)	*P*	QRISK available (n = 579)	*P*
Severe, treated OD	2.2% (3/135)	Ref	0% (0/122)	Ref
Severe, treated on prophylaxis	3.9% (8/206)	.303	2.2% (4/182)	.127
All patients, except those with severe hemophilia treated OD	3.3% (18/552)	.383	2.0% (9/457)	.117

No significant difference in CVD events was found between patients with severe hemophilia treated with on-demand (OD) therapy vs those on prophylaxis and vs all other patients (all patients except those with severe hemophilia treated with OD therapy). Analysis was done in in the complete cohort and exclusively in those with a QRISK score.

A constant risk increment per year was considered for patients who died during follow-up due to a non-CVD, as the QRISK only calculates risk after 2, 5, and 10 years' follow-up. Because the risk increment is not linear, this is an overestimation. However, this overestimation seems modest for this short follow-up time, and the number of non-CVD deaths was limited (18 PWH after a median follow-up of 144 weeks).

The QRISK could not be calculated for a subgroup, mostly due to prior CVD, statin use, or old age. Therefore, for this group, it is unknown if hemophilia protects against CVD. Today, CVD risk scores have become available that calculate risk for secondary prevention; for example, SMART (Second Manifestations of Arterial Disease)[20] and scores for elderly patients.[21] Analyzing this high-risk group should be part of future studies.

Are PWH really protected against CVD? In the current study, a lower-than-expected number of CVD events were observed. From previous studies, it is known that hemophilia does not protect against atherosclerosis.[6,7,22,23] We hypothesized that lower clotting factor levels diminish pathologic clot formation at sites of unstable plaques in PWH. Further supporting this theory is the efficacy of antithrombotic medications, which lower clot formation to reduce CVD in the general population with a high cardiovascular risk: in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial,[24] addition of an oral factor Xa inhibitor (rivaroxaban) to aspirin therapy for secondary prevention decreased the number of CVDs and death rate. In the ATLAS ACS 2–TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51) study,[25] the addition of rivaroxaban had a similar effect in patients with a recent acute coronary artery syndrome. However, not all studies with oral Xa inhibitors reported a reduced number of CVDs. The use of antithrombotic therapy in patients with hemophilia for primary or secondary prevention is beyond the scope of the current article.

No studies have examined the effect of hemophilia treatment on CVD. It is not yet known whether the risk of CVD will increase with the introduction of nonreplacement therapy and gene therapy.[26] Follow-up on CVD events in PWH on these new treatments is therefore necessary, preferably in prospective international cohort studies and in the context of a CVD risk score. As expected, also in PWH, an unfavorable CVD risk profile is associated with a higher incidence of CVD. Whether current risk assessment of CVD should be adapted for PWH is not known. The current study does provide evidence that standard risk scores might overestimate the CVD risk in PWH. However, the impact of having an ischemic event in PWH might be bigger than in the general population, as standard anticoagulation treatment is not always feasible. We therefore stress the importance of individualized risk assessment and early and proper preventive strategies.

In summary, this prospective, international multicenter study found a reduced incidence of CVD in PWH. However, events do occur, especially in people with a high risk for CVD. Assessment of CVD risk factors and the risk profile is advised for all PWH, as in the general population. This assessment could be the task of a comprehensive care center, which provides lifelong treatment and care for PWH. Treatment of risk factors and lifestyle education are mandatory.

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Authorship

Contribution: P.V.D.V. collected, analyzed and interpreted the data, and wrote the paper; M.M. designed the study, collected data, and revised the paper; K.F. analyzed and interpreted the data; R.C.T., P.C., P.W.C., K.M., L.F.D.V.V., and R.E.G.S. collected data and contributed to the paper; and E.M.-B. designed the study, collected and analyzed data, and contributed to the paper.

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ORCID profiles: P.V.D.V., 0000-0001-5292-166X; M.M., 0000-0001-7622-7939; K.F., 0000-0001-7126-6613; R.C.T., 0000-0003-4842-6783; P.C., 0000-0002-6690-8586; K.M., 0000-0001-9447-0465; L.F.D.v.V., 0000-0003-3242-5524; R.E.G.S., 0000-0002-2762-6033.

Correspondence: Paul Van Der Valk, University Medical Center Utrecht, Room F.02.127, PO Box 85500, 3508 GA Utrecht, The Netherlands; e-mail: p.r.vandervalk@umcutrecht.nl.

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