Netherlands
The Journal of Medicine

REVIEW

The effect of haemophilia and von Willebrand disease on arterial thrombosis: a systematic review

S. Biere-Rafi[1*], M. Zwiers[2], M. Peters[3], J. van der Meer[2†], F. R. Rosendaal[4], H.R. Büller[1], P.W. Kamphuisen[1]

[1]Department of Vascular Medicine, Academic Medical Centre, Amsterdam, the Netherlands, [2]Department of Haematology, University Medical Centre, Groningen, the Netherlands, [3]Department of Paediatric Haematology, Emma Children's Hospital AMC, Amsterdam, the Netherlands, [4]Departments of Clinical Epidemiology and Thrombosis and Haemostasis, Leiden University Medical Centre, Leiden, the Netherlands, *corresponding author: tel.: +31 (0)20-566 70 50, fax: +31 (0)20-69343, e-mail: s.rafi@amc.uva.nl

ABSTRACT

Background: Patients with haemophilia and von Willebrand disease (VWD) may have a reduced cardiovascular mortality, due to a hypocoagulable state or decreased atherogenesis. We performed a systematic review to assess the association between haemophilia and VWD, and fatal and nonfatal arterial thrombosis and asymptomatic atherosclerosis.

Methods: Medline and PubMed were searched to identify studies that assessed the incidence of cardiovascular mortality and morbidity in haemophilia and VWD, and that measured asymptomatic atherosclerosis with intima media thickness (IMT) of the carotid and femoral arteries, or flow-mediated dilatation (FMD) of the brachial artery. Weighted standardised mortality ratios (SMR) and mean differences (WMD) were calculated and pooled using a random effects model.

Results: 15 longitudinal and cross-sectional studies consisting of 19,242 patients were included. Mortality due to arterial thrombosis was nonsignificantly reduced in patients with haemophilia compared with healthy controls (SMR 0.51, 95% CI 0.24 to 1.09). Haemophilia reduced nonfatal coronary events, and severe haemophilia offered better protection, but these results were based on a single study. No results were available for VWD. Although IMT of the carotid and femoral arteries was similar between VWD and haemophilia patients and healthy controls, atherosclerotic plaques of the large arteries were less prevalent in haemophilia patients. Only two studies assessed FMD and the results were inconsistent.

Conclusion: Haemophilia may reduce arterial thrombosis, but this association should be further studied in haemophilia patients with a higher prevalence of cardiovascular risk factors.

KEYWORDS

Atherosclerosis, arterial thrombosis, flow mediated dilatation, haemophilia, intima media thickness, von Willebrand disease

INTRODUCTION

The concept of risk factors in cardiovascular disease (CVD) has been well established. Smoking, hypertension, obesity, hypercholesterolaemia, diabetes mellitus, and a positive family history for CVD are all associated with an increased risk of morbidity and mortality due to CVD. A prothrombotic state contributes to the development of CVD.[1] Increased levels of fibrinogen, von Willebrand factor (VWF), and factor VIII have all been linked to arterial disease.[2,3] VWF is essential for platelet adhesion and aggregation. Furthermore, VWF acts as the carrier protein for coagulation factor VIII. Factor VIII contributes to the formation of a fibrin-rich clot, and also has a role in the formation of occluding thrombi in stenotic vessels. Patients with haemophilia A, who have a congenital deficiency of clotting factor VIII, are thought to be protected against mortality due to arterial thrombosis.[4,5] This protection may be due to hypocoagulability, which is associated with decreased thrombin generation and results in inhibition of thrombus formation.

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On the other hand, haemophilia or VWD may also decrease the formation of atherosclerotic plaques. Studies evaluating preclinical atherosclerosis by measurement of intima media thickness (IMT) and flow-mediated dilatation (FMD) are, however, conflicting.[6,7] Moreover, autopsy findings have found extensive atherosclerotic plaques in subjects with VWD and haemophilia, and case reports have been published about patients with occlusive arterial thrombi.[8-15]

Although this subject was recently reviewed,[16] a systematic review assessing these studies has not been performed. We therefore systematically evaluated all literature to determine whether patients with haemophilia or VWD are protected against arterial thrombosis, and whether the prevalence of asymptomatic atherosclerosis is reduced. In order to thoroughly investigate this association, we first analysed fatal arterial thrombosis, followed by nonfatal events, and finally we addressed preclinical atherosclerosis.

METHODS

Data sources and study selection

We identified all published studies that evaluated the prevalence of atherosclerosis and arterial thrombosis in patients or carriers with haemophilia A or B, and VWD. A comprehensive literature search was conducted by a clinical librarian of Medline from 1950 to December 2009, and Embase from 1980 to December 2009. The following search terms were used: haemophilia, von Willebrand disease or coagulation disorder. The results of this search were combined with a subsequent search, in which the terms were arterial thrombosis, cardiovascular disease, arterial occlusive disease, atherosclerosis, cerebral vascular accident, stroke, myocardial infarction, acute coronary event, peripheral vascular event, peripheral artery disease, intima media thickness and flow-mediated dilatation. No language restrictions were initially applied to the search. A manual review of references from primary or review articles was performed to identify any additional relevant studies. The 'related articles' feature of PubMed was also used.

Study selection

Those studies that entailed observations of the same subjects over well-defined time periods were defined as longitudinal studies (e.g. prospective and retrospective cohort studies and registry studies). Longitudinal studies were included if they reported on mortality due to arterial thrombosis (i.e. ischaemic heart disease or ischaemic stroke) in carriers of haemophilia or patients with haemophilia or VWD. Carriers of haemophilia were also included in the analyses since they may have a bleeding tendency that can be similar to that of mild haemophiliacs. But, since pooling male haemophilia patients and female carriers may lead to heterogeneity, we analysed these groups separately. We further specified that every longitudinal study should either report a standardised mortality ratio (SMR) with 95% confidence interval (95% CI) or report sufficient data to estimate this. To adjust for differences in age with the reference population, SMRs were calculated, in which the incidence rates in the patients and the general population are standardised with the age distribution (in person-years) of the patients as weights. This leads to the calculation of an expected number of events, which is the number of events that would have happened in the patient group, if the population rates had applied to it. The SMR is the ratio of the observed over the expected number of events. Furthermore, all longitudinal studies reporting nonfatal arterial thrombotic events were also included. Only those cross-sectional studies that measured asymptomatic atherosclerotic disease in patients with haemophilia or VWD by means of ultrasonography, IMT or FMD were included in this review.

Study selection and quality assessment

After identifying relevant titles, the abstracts of these studies were read to decide if the study was eligible. The full article was retrieved when the information in the title or abstract appeared to meet the inclusion criteria of this systematic review. The list of articles was reviewed independently by two investigators (SB and MZ). Disagreement between the two reviewers was intended to be resolved by consensus or by the opinion of a third author if necessary. However, there was no disagreement during the review process.

Using a standardised data extraction sheet, the following data were collected from the articles: lead author, publication year, study design, sample size, years of follow-up, description of the study population, type of coagulation disorder and, if available, information on the classification of the coagulation disorders. In addition, the following baseline characteristics were extracted (if reported): mean age of the population and the number and proportion of male patients. From cross-sectional studies crude and adjusted (for cardiovascular risk factors) mean IMT thickness of carotid and femoral artery, and mean percent of flow-mediated dilatation were extracted. From longitudinal studies the SMR for fatal and nonfatal arterial thrombotic events was either calculated or extracted. The quality of cohort studies was assessed using a specific checklist consistent with the consensus recommendations by the Meta-analysis Of Observational Studies in Epidemiology group.[17] Cohort studies were assessed for quality according to four design features for each study: prospective data collection, consecutive patient enrolment, a clearly stated duration of follow-up and a description of losses during follow-up.

Statistical analysis

Review Manager (RevMan version 5.0, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and the Stata statistical software package 10.0 (Stata Corp., College Station, TX) were used to pool data for each outcome variable. Summary estimates, including 95% CIs were calculated. The cross-sectional studies consisted of continuous outcome data; therefore, means and standard deviations of IMT were used to calculate a weighted mean difference in the meta-analysis. Data were pooled using the random effect model, where appropriate. X^2- and I^2 statistics were used to assess between-study heterogeneity. The SMRs in the longitudinal studies were pooled using a random effects model and this was added in a Poisson regression model by calculating the ratio of the number of observed over expected events, in which the number of observed events is the sum of the observed events in all studies, and the number of expected events is the sum of the expected number of events in all studies. As for the SMRs of the individual studies, confidence intervals for the pooled SMR were based on a Poisson distribution of the observed number of events, whereas the expected number was considered invariant.

Results

Our initial search yielded 4450 potential literature citations (*figure 1*). Of these, 4349 were excluded after scanning titles. A total of 86 studies were excluded after reading the articles: 60 studies were case reports, ten citations were letters, three were autopsy studies, two studies only reported venous thrombosis, another two were reviews, and in one study the SMR was not reported and could not be calculated. The interobserver agreement for study selection and quality assessment was 100%. So, 15 studies were included in the present review, with a total number of 19,242 patients, with 14,754 haemophilia A patients, 3408 haemophilia B patients, 965 carriers of haemophilia A and B, and 115 VWD patients (*table 1*).[4-7,18-28] The number of patients in the various studies ranged from 24 to 6018. The mean age of the patients in the various studies varied between 35 and 54 years. Eight longitudinal studies[22-26,28] and three cross-sectional studies[6,18,19] investigated males. In the remaining three cross-sectional studies the percentage of male subjects ranged between 43 and 60%.[7,20,21] In the remaining longitudinal study all patients were female carriers.[27]

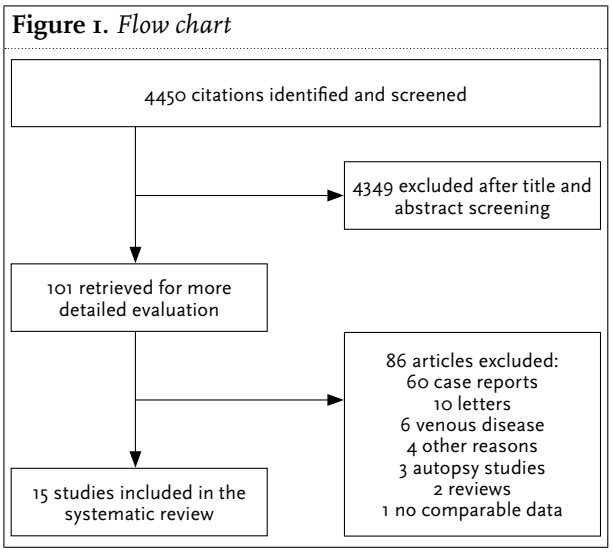


Figure 1. *Flow chart*

CARDIOVASCULAR MORTALITY IN PATIENTS WITH HAEMOPHILIA

All longitudinal studies[4,5,22-25,27,28] described cause-specific mortality. All studies reported on both haemophilia A and B patients, but the influence of the type of haemophilia was not analysed separately. One of these studies, by Srámek and colleagues, studied carriers of haemophilia A and B.[27] None of the longitudinal studies analysed patients with VWD. The duration of follow-up varied between two and 21 years. Follow-up was complete in two studies,[4,24] and nearly complete (lost to follow-up <5%) in six other studies.[5,22,23,25,27,28] In one study, no information on completeness of follow-up was provided.[26] Information on various parameters in the longitudinal studies was usually obtained through surveys supplemented with data from the haemophilia treatment centres, treating or attending physicians, municipal registries and death certificates. All studies compared cause-specific mortality with that of the general male population obtained through either the Central Bureau of Statistics or the World Health Organisation.

Most longitudinal studies[4,5,22-25,27] assessed cardiovascular mortality due to ischaemic heart disease, whereas one study[5] also mentioned mortality due to ischaemic stroke. One longitudinal study[28] reported on mortality due to circulatory disease without further specifying the underlying causes, and was therefore left out from the pooled analysis. Three longitudinal studies[4,22,23] assessed Dutch haemophilia patients from 1976 to 2001.

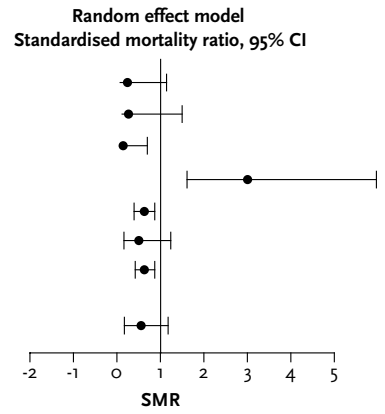
The mean age of mortality in the various studies ranged between 44 and 54 years. Overall, the number of fatal arterial thrombotic events was low. Compared with the general population, patients with haemophilia had a nonsignificant reduced mortality due to arterial thrombosis. For the seven studies, the overall SMR using a random effect model was 0.51 (95% CI 0.24 to 1.09). There was considerable, but not significant, heterogeneity between the studies (p=0.12) (*figure 2*). All longitudinal studies,[4,5,22-24,27] with the exception of the study by Soucie and colleagues,[25] found a reduced mortality due to arterial

Table 1. *Characteristics of studies included in the systematic review*

Source	Population							Design	Outcome	Follow-up	
	Total	Haemophilia A	Haemophilia B	Severe	Mild	Moderate	VWD			Years	(n) loss to follow-up
Rosendaal et al. (1989)[4]	717	616	101	321	227	169	na	Longitudinal	Mortality	10.9	0
Koumbarelis et al. (1994)[24]	531	460	71	212	227	92	na	Longitudinal	Mortality	21	0
Triemstra et al. (1995)[22]	919	796	123	381	366	172	na	Longitudinal	Mortality	6.4	38
Walker et al. (1998)[28]	2450	1985	465	857	1127	465	na	Longitudinal	Mortality	15	53
Bilora et al. (1999)[20]	76	64	na	nr	nr	nr	12	Cross-sectional	IMT	na	na
Soucie et al. (2000)[25]	2950	2334	616	1252	902	717	na	Longitudinal	Mortality	2.6	71
Sramek et al. (2001)[18]	76	52	7	20	34	5	17	Cross-sectional	IMT	na	na
Bilora et al. (2001)[6]	40	25	na	nr	nr	nr	15	Cross-sectional	IMT	na	na
Sramek et al. (2003)[27]	965#	nr	nr	nr	nr	nr	na	Longitudinal	Mortality	15	33
Sramek et al. (2004)[7]	47	na	na	na	na	na	47	Cross-sectional	IMT	na	na
Kulkarni et al. (2005)[26]	3422	2.714	708	1419	1083	827	na	Longitudinal	Arterial events	6	nr
Plug et al. (2006)[23]	967	796	171	386	414	167	na	Longitudinal	Mortality	9	2
Bilora et al. (2007)[21]	24	na	na	na	na	na	24	Cross-sectional	IMT	na	na
Darby et al. (2007)[5]	6018	4874	1144	3222	1320	1476	na	Longitudinal	Mortality	21	194
Sartori et al. (2008)[19]	40	38	2	nr	nr	nr	na	Cross-sectional	IMT, FMD	-	-
Total	19,242	14,754	3408				115				

nr = not reported; na = not applicable; #: carriers of haemophilia.

Figure 2. *The influence of haemophilia on cardiovascular mortality*



Study	Events Observed	Expected	SMR	95% CI
Rosendaal 1989	1	5	0.20	0.0-1.1
Koumbarelis 1994	1	4	0.25	0.0-1.4
Triemstra 1995	0	5.2	0	0.0-0.58
Soucie 2000	8	2.7	3	1.50-5.80
Sramek 2003	39	60.5	0.64	0.47-0.88
Plug 2006	6	12	0.50	0.20-1.10
Darby 2007	104	167	0.62	0.51-0.76
	Heterogeneity p=0.12			
	Overall SMR		95%	0.24-1.09

SMR = standardised mortality ratio.

thrombosis in carriers and patients with haemophilia, but due to the low number of events, confidence intervals were wide. Exclusion of the study with haemophilia carriers resulted in a SMR of 0.59 (0.33 to 1.05). When restricting analyses to studies with a follow-up period of ten years or longer and that had complete follow-up,[4,5,24] the association between a lower cardiovascular mortality and haemophilia became more consistent (overall SMR 0.59, 0.48 to 0.72). In the only study that investigated the influence of haemophilia on ischaemic stroke,[5] the SMR was 0.63, with a wide confidence interval (0.17 to 1.62). The influence of the severity of haemophilia on cardiovascular mortality was assessed in one study, by Darby and colleagues.[5] A similar reduction in cardiovascular mortality was found in patients with severe, moderate and mild haemophilia but, again, the number of fatal cardiovascular events was too

low to detect potential differences (1.2% in patients with severe haemophilia, and 1.9% for patients with moderate and mild haemophilia).

NONFATAL CARDIOVASCULAR DISEASE

Only one study investigated the influence of haemophilia on nonfatal arterial thrombotic events.[26] The occurrence of ischaemic heart disease (consisting of acute myocardial infarction, acute/subacute coronary syndrome, angina pectoris, and chronic heart disease) in 3422 patients with haemophilia was based on hospital discharge diagnosis, and was compared with general US males based on the National Hospital Discharge survey. From 1993 until 1998, ischaemic heart disease was reported 79 times in 48 patients, corresponding with a prevalence of approximately 2.3%. Among 45- to 64-year-old haemophilic men, the discharge rate (per 1000) for ischaemic heart disease was 24.1, 50% lower compared with that of US males (48.9/1000). This difference was 28% among patients of 64 years and older (127.3 *vs* 175.6 respectively). In addition, the incidence of IHD was higher in patients with mild haemophilia (3.4%) than in moderately severe (0.7%) or severe (0.4%) types of haemophilia (p<0.001). When haemophilia A and B were analysed separately, IHD was more prevalent in patients with haemophilia B (2.4%) than haemophilia A (1.1%) (p<0.05). No studies assessed the prevalence of peripheral arterial disease or stroke.

PREVALENCE OF ASYMPTOMATIC ATHEROSCLEROSIS IN HAEMOPHILIA AND VWD

Of the six cross-sectional studies[6,7,18-21] that assessed endothelial function or preclinical atherosclerotic disease, one study[19] involved patients with haemophilia A and B, two studies[6,20] involved patients with haemophilia A and VWD, one study haemophilia A and B and VWD[18], whereas one study[21] described patients with type IIb VWD, and one study[7] investigated type III VWD patients. None of the studies were performed on either the same or an overlapping patient group. The ultrasonographers were not blinded for the severity of the bleeding disorder in any of the studies.

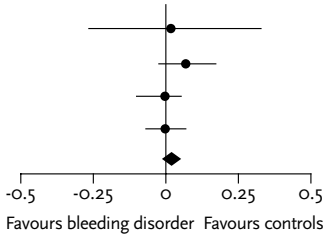
Intima media thickness

Four studies assessed the presence of asymptomatic atherosclerosis by measuring IMT of the carotid artery,[7,18,19,21] with a total of 187 patients (99 haemophilia patients and 88 patients with VWD) and 290 control subjects, whereas three studies also assessed the femoral artery.[7,19,21] Overall, mean IMT of the carotid artery was 0.75 mm in patients with haemophilia and VWD and 0.74 mm in healthy controls, matched for age and sex (WMD 0.01 mm, 95% CI -0.02 to 0.04). The mean IMT of the femoral artery was 0.75 mm in patients with a coagulation disorder and 0.79 mm in controls (WMD -0.04 mm, 95% CI -0.10 to 0.02). Statistical heterogeneity was not present in either of the two analyses (*figure 3*).

The presence of atherosclerotic lesions and extent of the occlusion of the arteries was assessed by ultrasonography in two studies,[6,20] without quantification of the IMT. The presence of atherosclerotic plaques was analysed in various arteries (common carotid, bifurcation, brachial, femoral and abdominal aorta) of patients with haemophilia A or VWD. In the first study, atherosclerotic plaques of the carotid artery were present in 13.1% of 76 patients with haemophilia A and VWD (mean age 58 years), and in 27.2% of the 77 controls (p<0.05).[20] This difference was more pronounced in patients older than 60 years. In the second study,[6] atherosclerotic plaques in the abdominal aorta were present in 7.5% of the 40 patients with haemophilia A and VWD (mean age 48 years) and in 27.5% of the 40 controls (p<0.001). 12.5% of the 40 patients and 42.5% of the 40 control subjects had plaques in the leg arteries (p<0.001).

Figure 3A. *Carotid IMT in patients with haemophilia and VWD compared with healthy controls*

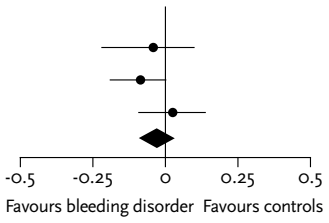
	Bleeding disorder			Controls				Mean difference, random, 95% CI
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	
Bilora, et al. 2007	0.87	0.38	24	0.86	0.21	24	3.0%	0.01 [-0.16, 0.18]
Sartori, et al. 2008	0.74	0.09	24	0.7	0.11	24	28.0%	0.04 [-0.02, 0.10]
Sramek, et al. 2001	0.76	0.18	76	0.77	0.18	142	36.0%	-0.01 [-0.06, 0.04]
Sramek, et al. 2004	0.63	1.17	47	0.63	0.09	84	33.1%	0.00 [-0.05, 0.05]
Total (95% CI)			171			274	100.0%	0.01 [-0.02, 0.04]



Heterogeneity: Tau²=0.00, Chi²=1.80, df=3 (P=0.61), I²=0%; Test for overall effect: Z=0.51 (P=0.61).

Figure 3B. *Femoral IMT in patients with haemophilia and VWD compared with healthy controls*

Study or subgroup	Bleeding disorder Mean	SD	Total	Controls Mean	SD	Total	Weight	Mean difference, random, 95% CI
Bilora, et al. 2007	0.92	0.23	24	0.96	0.23	24	21.0%	-0.04 [-0.17, 0.09]
Sramek, et al. 2001	0.75	0.31	76	0.83	0.3	142	45.5%	-0.08 [-0.017, 0.01]
Sramek, et al. 2004	0.59	0.31	47	0.57	0.23	84	33.5%	0.02 [-0.08, 0.12]
Total (95% CI)			171			274	100.0%	0.01 [-0.02, 0.04]



Heterogeneity: Tau²=0.00, Chi²=2.19, df=2 (P=0.33), I²=9%; test for overall effect: Z=1.22 (P=0.22).

Four cross-sectional studies[6,18-20] analysed the relation between the severity of the coagulation defect and atherosclerosis. In the study by Srámek and colleagues[18] mean IMT of the femoral arteries was similar in patients with moderate and severe haemophilia (0.74 mm, 95% CI 0.64 to 0.87) and in individuals with a mild form (0.76 mm, 95% CI 0.69 to 0.84). Also in the study by Sartori and colleagues, IMT of the carotid artery was not different between patients with moderate to severe compared with mild haemophilia.[19] Two studies by Bilora *et al.*[6,20] showed less atherosclerotic plaques in patients with a more severe coagulation defect.

Flow-mediated dilatation

Endothelial dysfunction, assessed with flow-mediated dilatation (FMD), was analysed in two studies.[19,21] FMD was lower in 40 haemophilia patients compared with 40 controls (3.8±5.2% *vs* 20.3±13.0%, p<0.0001) in the first study, and this difference remained after adjustment for viral infections.[19] In this study, severity of haemophilia did not affect FMD. In the second study, the percentage of vasodilatation was 15.2±3.1% in 24 type IIb VWD patients and 14.1±2.9% in 24 controls, which was not different.[21]

DISCUSSION

Our findings suggest that mortality due to ischaemic heart disease is 50% lower in patients with haemophilia when compared with the general population. This association is more consistent in studies with longer and complete follow-up. Asymptomatic atherosclerosis as measured by IMT of the carotid and femoral arteries in patients with VWD and haemophilia was not different from healthy matched controls, but atherosclerotic plaques of the large arteries were less prevalent in these patients. Interestingly, in the only (large) study assessing nonfatal cardiovascular events, haemophilia not only reduced cardiovascular events, but patients with severe haemophilia had fewer events than those with mild or moderate haemophilia. Haemophilia B patients had more cardiovascular events than those with type A. The influence of VWD on cardiovascular events has not been studied.

The potential beneficial effect of haemophilia on arterial thrombosis could be the result of reduced thrombin formation. Thrombin is the key player in both fibrin formation and platelet activation. Thrombin cleaves fibrinogen to form fibrin, but can also trigger platelet activation through protease-activated receptors (PAR) 1 and 4.[29] This may lead to the formation of thrombi and ultimately to vascular occlusion. Importantly, thrombin may also influence the process of atherosclerosis. Tissue factor and PARs are highly expressed in human atheroma and are induced in response to injury in animal models.[30] *In vitro,* PAR activation induces leucocyte chemotaxis, smooth muscle cell proliferation and migration, which may lead to arterial remodelling and stenosis of the injured artery.[31] In addition, coagulation factors and PARs are also involved in inflammatory responses and repair after injury.[32] These data suggest that local arterial damage may trigger both platelet activation and thrombin formation, which may further lead to arterial remodelling. It may well be that patients with haemophilia, who have a decreased thrombin formation, are relatively protected from these atherosclerotic processes.

Our systematic review cannot answer the question whether the association between haemophilia and arterial thrombosis is causal. The observed reduction in mortality, for instance, could be explained by a difference in cardiovascular risk factors between individuals with and without haemophilia. As previously shown by Rosendaal and colleagues, this does not seem to be an explanation.[33] As a prerequisite for causality, the association between haemophilia and arterial thrombosis seems biologically plausible. In addition, the association was consistent in different studies: only the study by Soucie and colleagues found no reduction in cardiovascular mortality.[25] Furthermore, there seemed to be a dose-response gradient, in the sense that a more severe deficiency of factor VIII offered better protection. Although this was not

apparent in two longitudinal studies,[5,27] a more severe type of haemophilia also seemed to reduce nonfatal events and atherosclerotic plaques compared with mild haemophilia.[6,18-20,26] However, these data were based on a small number of patients and events, affecting the strength of the association. Finally, also carriers of haemophilia had a 36% reduction in mortality due to ischaemic heart disease.[27]

Life-long hypocoagulability may be an interesting model to investigate the role of haemostasis in the occurrence of arterial thrombosis and the formation of atherosclerotic plaques. Further studies on this subject could serve two goals. First, the role of coagulation in the formation of atherosclerotic plaque formation could be further explored. If low factor VIII levels reduce atherogenesis and this is mediated through decreased thrombin generation, specific anticoagulants, such as thrombin inhibitors, may be beneficial. Next, if patients with haemophilia and cardiovascular risk factors are not protected against atherosclerosis, cardiovascular prevention will also be applicable to haemophilia patients, since the life expectancy of these patients has considerably increased.[34]

However, we noticed some methodological drawbacks of the studies included in this systematic review. In general, the number of fatal cardiovascular events was low, mostly due to the relatively young age of the patients, and therefore confidence intervals were wide. Nonfatal cardiovascular events, which are more prevalent than fatal ones, were only reported in one longitudinal study.[26] Furthermore, the low life expectancy of haemophilia patients as a result of bleeding complications and poor treatment regimens in the 1970s and 1980s may have affected cause-specific mortality ratios. Also HIV, a well-known cardiovascular risk factor, may have influenced cardiovascular mortality, but was seldom mentioned in the studies. However, Darby and colleagues showed a 40% reduction in cardiovascular mortality in haemophilia patients without HIV.[5] Also in the IMT studies, the number of participants was small, whereas the detection of significant differences in IMT requires large populations. Together with the relative young age of the participants and a low prevalence of cardiovascular risk factors, an inverse association between hypocoagulability and atherosclerosis is difficult to detect. Since IMT is clearly affected by age[35] and atherosclerotic risk factors,[36] the question whether a hypocoagulable state protects against atherosclerosis should be studied in older patients with a higher prevalence of cardiovascular risk factors.

In conclusion, this systematic review suggests that patients with haemophilia have a reduced cardiovascular mortality. Whether this reduction is mediated by a lesser formation of atherosclerosis should be investigated in patients with a higher prevalence of cardiovascular risk factors.

ACKNOWLEDGEMENT

We would like to thank Dr. S. Le Cessie for help with the statistical analysis.

Poster presentation of manuscript at the International Society on Thrombosis and Haemostasis (ISTH) in Boston on 15 July 2009.

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