Anticoagulation therapy in haemophilia

Managing the unknown

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Summary
Patients with haemophilia (PWH) are relatively protected from cardiovascular death. Recent insights have shown that this is not due to less formation of atherosclerosis than in non-haemophilic men, therefore protection from the final occlusive thrombus will be the major determinant. Prevalence and incidence rates of cardiovascular disease (especially non-fatal events) are scarce, although ongoing studies are addressing this issue.

Meanwhile, because the haemophilia population is aging, we are increasingly confronted with cardiovascular events. The main cardiovascular risk factors that should be part of regular screening programs are hypertension, overweight, lipometabolic disorders and smoking. Anticoagulation therapy in haemophilia is feasible, provided that individual tailored coagulation therapy and close monitoring is provided.

Here, we present our view on anticoagulation management in PWH. There is an absolute need for risk assessment tools and prospective validation of suggested anticoagulation management strategies in PWH. Until then, we are managing the unknown.

Keywords
Haemophilia, anticoagulation, aspirin, coumarin, cardiovascular disease, atrial fibrillation

Antikoagulatorische Therapie bei Hämostaseologie

Schlüsselwörter
Hämophilie, Antikoagulation, Azetlysalizylsäure, Cumarin, kardiovaskuläre Erkrankung, Vorhofflimmern

Zusammenfassung
Patienten mit Hämophilie sind relativ geschützt vor kardiovaskulär bedingtem Tod. Nach neuen Erkenntnissen ist dies nicht darauf zurückzuführen, dass die Arteriosklerose geringer ausgeprägt ist als bei Männern ohne Hämophilie, daher wird der Schutz vor dem letztlich okklusiven Thrombus der ausschlaggebende Faktor sein. Daten zur Prävalenz und Inzidenz kardiovaskulärer Erkrankungen (besonders für nicht tödliche Ereignisse) liegen kaum vor, jedoch werden zurzeit Studien dazu durchgeführt.


Hier legen wir unsere Sicht der antikoagulatorischen Behandlung von Hämophilie-Patienten dar. Es besteht ein Bedarf an Methoden zur Risikobeurteilung und zur prospektiven Validierung der für Hämophilie-Patienten vorgeschlagenen Behandlungsstrategien zur Antikoagulation. Bis dahin bewegen wir uns auf unbekanntem Terrain.

Atherosclerosis is an inflammatory disease of large and medium-sized arteries, which develops in response to injury of the endothelium and leads to thickening of the vessel walls through plaque formation. Following atherosclerotic plaque rupture, thrombus formation occurs. When the thrombus occludes the vessel lumen, it can result in an acute cardiovascular event.

The development of atherosclerosis is influenced by several well known risk factors, including:
• aging,
• hypertension,
• diabetes mellitus,
• hypercholesterolaemia,
• smoking,
• positive family history and
• obesity.

In atherogenesis, endothelial cells, vascular smooth muscle cells, monocytes, macrophages, platelets and cytokines are involved and closely interact (1–3). Current evidence supports considerable crosstalk between molecular and cellular components of thrombosis and inflammatory pathways that initiate atherosclerosis, contribute to plaque expansion and promote degradation and rupture of the fibrous cap (4–8).

Platelets, the cellular components of thrombosis, are recruited to the endothelium and release pro-inflammatory products and growth factors stimulating atherosclerosis progression. In addition, platelets direct leukocyte incorporation into plaques through platelet-mediated leukocyte adhesion.

Thrombin is the main effector of the coagulation cascade and links coagulation to inflammation by having pro-inflammatory effects, via protease-activated receptors, on endothelial cells, smooth muscle cells, monocytes, macrophages and platelets.
In addition, the inflammatory mediators stimulate tissue factor expression within the atheroma resulting in more thrombin formation (9,10).

In patients with haemophilia (PWH), activation of prothrombin into thrombin is lower as compared to non-haemophilic subjects. This might reduce the formation of a final thrombus and the stimulation of pro-inflammatory pathways supporting atherogenesis. Indeed, several cohort studies comparing cardiovascular mortality between PWH and the general male population have shown standard mortality ratios < 1.0 (11–16) (Tab. 1). Recently, it has become clear that this observation cannot be explained by less formation of atherosclerosis in PWH than in non-haemophilic men (17,18), indicating that protection of the final occlusive thrombus could be the major determinant.

Paradoxically, haemophilia caregivers are increasingly confronted with cardiovascular events, as the haemophilia population grows older.

Several papers addressed the issue of cardiovascular management in haemophilia and proposed guidelines (19–23). The main problem is that these guidelines are based on expert opinions and theoretical evidence as solid clinical data from scientific studies are lacking. Although haemophilia specialists observe an increase in haemophilia patients with ischaemic cardiovascular disease, these patients are still uncommon. This makes it very unlikely that well-designed randomised clinical trials can be performed to find the optimal therapy for these complex patients.

In this paper we describe how our institute deals with anticoagulation therapy in PWH. We focus on the rationale of our therapeutic choices, which is based on the experience from laboratory and clinical studies.

### Haemophilia in age

#### Atherosclerosis and cardiovascular disease

Until recently, it was still a matter of debate if and to what extend PWH form less atherosclerosis. Autopsy studies observed coronary atherosclerosis in several PWH (24,25). Although these studies provide evidence that PWH are not fully protected against development of atherosclerosis, they do not provide insight into the potential partial protection, nor do they give us information about the extent of atherosclerosis in a living and aging haemophilia population. Studies comparing carotid and femoral intima-media thickness (IMT) between PWH and subjects without bleeding disorders reported conflicting results (26–30). The interpretation of these results is hampered by small samples sizes, heterogeneous study populations also including patients with other bleeding disorders than haemophilia, ill-defined comparison populations, and variability in tests and outcome parameters.

The strength of both studies are that they were done in haemophilia patients at high risk for atherosclerosis (i.e. high age and obese) and that well-matched controls were used.

The effect of bleeding disorders on cardiovascular disease is subject of several publications. There are multiple case reports describing myocardial infarction in haemophilia patients and several cohort studies comparing cardiovascular mortality rates (Tab. 1) between PWH and the general male population (31). There is, however, less data on the incidence and prevalence of non-fatal ischaemic cardiovascular disease in haemophilia.

- The CACHÉ study demonstrated equal amounts of coronary calcium deposits in PWH > 59 years as compared to well matched controls (17).
- The IDAHO study found no differences in carotic intima media thickness between obese haemophilia patients and matched controls (18).

Two recent multicenter trials have clearly elucidated that factor FVIII deficiency does not protect against formation of atherosclerosis.

- Kulkarni et al. evaluated medical records of 3422 PWH who were admitted to the hospital between 1993 and 1998 (32). They found that in 184 patients, aged 60 years or older, the prevalence of ischaemic heart disease was 15.2%. The rate of ischaemic heart disease discharges among haemophilia patients 65 years or older was nearly 30% lower than that of non-haemophilic men.
- Siboni et al. described co-morbidities in 39 PWH aged ≥ 65 years and 5% of their patients had prevalent cardiovascular disease (33).
- Miesbach et al. found ischaemic cardiovascular disease in 6 (21%) out of 29 PWH aged ≥ 60 years (34).
- Another report describes yearly prevalences of hospital admissions for atherosclerotic heart disease in 1380 patients between 2001 and 2006 (35). The authors found prevalences to be 6.5% to 10.5%, with a clear age-related increase where PWH aged 75 years and older had a prevalence of 31.8% (35).

<table>
<thead>
<tr>
<th>reference</th>
<th>period</th>
<th>number of PWH</th>
<th>SMR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Rosendaal et al. (14)</td>
<td>1973–1986</td>
<td>717</td>
<td>0.2</td>
</tr>
<tr>
<td>Koumbarelis et al. (12)</td>
<td>1972–1993</td>
<td>531</td>
<td>0.25</td>
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<tr>
<td>Triemstra et al. (16)</td>
<td>1986–1992</td>
<td>919</td>
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<tr>
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<td>1990–1999</td>
<td>nr</td>
<td>0.25</td>
</tr>
<tr>
<td>Plug et al. (13)</td>
<td>1992–2001</td>
<td>967</td>
<td>0.5</td>
</tr>
<tr>
<td>Darby et al. (11)</td>
<td>1977–2000</td>
<td>6018</td>
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<td>Tagliaferri et al. (15)</td>
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nr: not reported.

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We recently showed that patients with severe haemophilia had lower rates of myocardial infarction as compared to the general population (1.7% versus 4.0%), but in non-severe haemophilia the prevalence was similar (3.6% versus 4.0%) (36).

In summary, the prevalence of cardiovascular disease in PWH lies between 1.7 and 32%, indicating that the occurrence of cardiovascular disease in PWH cannot be ignored. The broad range of prevalences can largely be explained by differences in study population.

Although solid data about the risk of events are lacking, haemophilia caregivers should establish specific management guidelines for their patients at risk for and with ischaemic cardiovascular disease.

**Cardiovascular risk factors**

Several studies have evaluated cardiovascular risk factors in PWH as compared to the general population (35, 37). Two risk factors should be emphasized in particular, as they have shown to be emerging.

First, hypertension has been reported to be more common in haemophilia in recent papers with prevalences ranging from 29 to 71% (25, 33–35, 37, 38).

Differences in prevalence between these studies may be due to a large heterogeneity and small samples sizes of the studied populations, and differences in the definition of hypertension. However, in general they reflect the increasing burden of disease. As hypertension plays a crucial role in atherosclerosis development, it is of importance that adult PWH have their blood pressure regularly measured.

Second, the prevalence of overweight and obesity are increasing, both in the general population and haemophilia population (37, 39–41).

Mean body mass index (BMI) was 30.2 kg/m² in one study in PWH (41) and median BMI was 26 in another (37). In the Netherlands, the prevalence of overweight in PWH (BMI > 25 kg/m²) is reported to be 35% (39), where obesity is 8–19% (37, 39).

In the United States, these proportions are even larger with 68% and 36% respectively (40). Haemophilia treatment centers should systematically promote activity in both young and elderly PWH.

**Managing anticoagulation therapy**

It is obvious that managing anticoagulation treatment in PWH is a difficult task, which arises from two uncertainties.

1. The goal of anticoagulation therapy is primary or secondary prevention of thrombotic diseases. While there is ample data in non-haemophilia patients on the risk for future ischaemic heart disease or stroke, we cannot predict the real thrombotic risk in PWH. On the other hand, this does not mean that PWH should not receive thromboprophylaxis, as is reflected by the multiple published case reports of myocardial infarction in PWH (42, 43).

2. Whereas there is abundant evidence for efficacy and safety of anticoagulation therapy in non-haemophilia patients over a broad range of indications, these data are completely lacking in PWH. Even more so, safety of anticoagulation therapy is of major concern as the bleeding risk in PWH will certainly differ from that in the normal population.

Therefore, a proper consideration of individual risk-benefit profiles in PWH is virtually impossible. However, using the data from non-haemophilic patients we have to find a way to balance between the two uncertainties. At the Van Creveldkliniek, we developed a tool to guide us in deciding which anticoagulation therapy would be appropriate (Fig. 1). In the small patient population that we used it in so far, it appeared to be safe and feasible (data submitted). This tool should be used in a tailored approach, in which the overall medical condition of the patient, his bleeding phenotype and the indication for anticoagulation therapy should constantly be re-evaluated.

**Aspirin**

In patients with FVIII or FIX levels >5%, we have the experience that low dose aspirin (80 mg) is well tolerated. On the other hand, at clotting factor levels <1%, the risk of spontaneous bleeding when using aspirin is very high and the use of antiplatelet agents should be avoided unless a patient is using prophylaxis with clotting factor concentrate (CFC). At clotting factor levels of 1–5%, the choice to start with aspirin should be based on characteristics of the individual patient. Two examples:

- A high aged patient with arthropathy, dizziness, a high risk of falling and factor levels of 2% is not a good candidate for antiplatelet therapy.
- A patient of 50 years without joint problems and a factor level of 4% will probably tolerate aspirin very well.

![Fig. 1](http://www.haemostaseologie-online.com)
In our centre, we do not start clotting factor replacement therapy merely to increase basal levels high enough to start aspirin. When starting aspirin in PWH, we always prescribe proton pump inhibitors concomitantly.

**Coumarin derivates**

When starting coumarin derivates, we consider clotting factor levels of ≥30% to be appropriate. This means replacement therapy with CFC is needed in most haemophilia patients, depending on basal factor levels. In nearly all cases were we aim for trough levels ≥30% through replacement therapy, the medical need for coumarin derivates is temporary, for instance during and after cardiac intervention. At levels <20%, we do not consider coumarin therapy. Patients with levels 20–30% should undergo the same individual approach as described above when prescribing aspirin at factor levels 1–5%.

**A practical example**

A man (age: 47 years) with mild haemophilia (FVIII level 21%) never experienced bleeding problems due to his haemophilia and he is in general good condition. He underwent an aortic valve replacement in 1999 and thromboprophylaxis with vitamin K antagonist was started since. No CFC prophylaxis was started to support anticoagulation therapy after surgery. This patient never experienced any bleeding episode since the start of anticoagulation therapy.

**Dual antiplatelet therapy**

Similar bleeding risks are reported between patients using coumarin derivates compared to patients taking aspirin combined with clopidogrel (44). Therefore, when starting dual antiplatelet therapy we use the same cut-off as for coumarin derivates. Comparable with coumarin derivates, the medical need for trough levels ≥30% is temporary, for instance during four weeks after placement of a bare-metal stent.

We do not use coumarin derivates in combination with antiplatelet agents in PWH.

**Angina pectoris**

When a patient develops stable angina pectoris, one or more of the coronary vessels is partially occluded due to atherosclerosis. In addition to management with beta-blockers and/or calcium-antagonists and statins, the main question for haemophilia specialists is when to give aspirin.

We start low dose aspirin in mild haemophilia patients (Fig. 1) and do not give it to severe PWH without CFC prophylaxis.

In moderate haemophilia and in severe haemophilia with CFC prophylaxis, it is based upon the individual patient, taking into consideration his

- bleeding phenotype,
- overall physical state and
- considering clinical changes over time.

A special note on CFC prophylaxis should be made. Most of our elderly patients use prophylaxis with 12–13 U FVIII/kg body weight three times a week. This results in peak levels of 25% and trough levels of approximately 1% (and sometimes <1%). Considering our own preliminary data on the occurrence of myocardial infarction (45), more than half of the events occurred in patients with FVIII levels >10%. On the other hand, when a patient develops angina pectoris, there is a clear indication for antiplatelet therapy, where we do not want to have trough levels of ≤1%. Therefore, an adapted CFC prophylaxis regimen should be considered for these patients ideally using daily injections of 6–7 U FVIII/kg body weight to avoid high peaks and low troughs. The feasibility of this approach in the elderly patient however is sometimes hampered by poor venous access.

**Acute coronary syndrome**

In a PWH developing an acute coronary syndrome (ACS), our aim is to guide him through cardiac intervention comparable to non-haemophilic patients (23). A percutaneous coronary intervention (PCI) is certainly feasible, when several aspects are taken into account.

Correction of the clotting factor deficit should take place aiming at peak levels of 80–100%.

We use bolus injections of 40–50 U/kg body weight in severe haemophilia, followed by 20–25 U/kg every 12 hours for 48 hours. This results in trough levels >45% and provides safe support for arterial access and treatment with anticoagulant drugs. As most major bleedings in PCI occur at the femoral access site, we strongly recommend a radial approach (23). We are willing to use heparin as long as clotting factor substitution with trough levels >30% is achieved. The choice for unfractionated heparin or low-molecular weight heparin (LMWH) might be in favour of LMWH as this does not require monitoring.

Even more so, the use of bivalirudin is reported to be safer than combination of heparin and GPIIb/IIIa inhibitors (46), but not every center has experience in using bivalirudin.

When a coronary stent is needed, a bare metal stent (BMS) is recommended as this requires a shorter period of dual antiplatelet therapy. During dual antiplatelet therapy, trough levels of >30% are required (Fig. 1) for at least four weeks after a BMS. In most patients, this requires intensive CFC substitution.

**A man with haemophilia and ACS**

A short description of one of our patients illustrates the feasibility of this approach. The man (age: 69 years) with mild haemophilia (FVIII level 15%) developed an acute coronary syndrome for which he was treated with PCI where a BMS was placed.

Clotting factor levels were corrected using a bolus injection of 3000 U followed by 1500 U every 12 hours for 48 hours. Dual antiplatelet therapy was started with aspirin 80 mg and clopidogrel 75 mg daily. CFC prophylaxis was started using 1000 U/day for four weeks.

With this approach, trough levels of 32% were achieved. He did not experience bleeding episodes. After four weeks, clopidogrel was stopped, as was the CFC pro-
Atrial fibrillation

In a previous paper, we described a flowchart for anticoagulation management in PWH developing atrial fibrillation based on clotting factor levels and stroke risk (22) (Fig. 2). It is apparent how this flowchart was build up. Again, prospective evaluation of this flowchart has not been performed and it should act as a guidance tool, not as a protocol. Although the CHADS2 score has proven its usefulness in predicting stroke risk in non-haemophilia patients, there is no evidence to support or reject the hypothesis that the CHADS2 score is equally useful in PWH. However, as there are no other tools, an adopted strategy in PWH seems plausible.

In patients with basal FVIII/IX levels of > 30%, we base the choice of anticoagulation drug upon the CHADS2 score. Patients with a
- CHADS2 score ≥ 2 are able to receive coumarin derivate;
- CHADS2 score < 2, low dose aspirin is the recommended anticoagulation drug.

Recently, the CHADS2 score has been refined by the CHADSVasc score, in an attempt to finetune those patients with CHADS2 scores < 2. As we believe that haemophilia patients with CHADS2 scores < 2 should not receive coumarin derivate anyway, we do not incorporate the CHADSVasc score in our patients yet to decide whether or not to give coumarin.

In mild PWH with basal factor levels of 5–30%, we do not consider coumarin derivatives. Therefore, we use low dose aspirin regardless of the CHADS2 score, as we feel levels > 5% are sufficient to tolerate aspirin. It should be noted, however, that although we assume low dose aspirin is tolerated well with factor levels > 5%, the patient’s choice has a strong influence as well.

We have educated our patients for years that aspirin and other anti-inflammatory drugs are strictly forbidden. Prescription of aspirin to the same patients as they grow older is not always appreciated. Furthermore, there is currently no evidence that PWH benefit from aspirin therapy. This is illustrated by a case of mild PWH (FVIII 14%) with atrial fibrillation since two years and a CHADS2 score of 0. He does not take aspirin (because the cardiologist did not find the need) and fares very well with it. Even more so, the recent ECS guidelines of AF reconsider the role of aspirin in AF as the benefits are small. But considering the fact that PWH with factor levels < 20 are not able to use coumarin derivate anyhow, the option of aspirin is considerably different from that of the general population.

In moderate haemophilia with factor levels 1–5%, we decide to start with aspirin based on the CHADS2 score, where patients with a score ≥ 2 receive aspirin and patients with a score < 2 are not treated with any anticoagulation drug at all. Off course, an individualised approach is mandatory. For instance, we regularly see a man (age: 45 years) with moderate haemophilia (FVIII 2%) with on demand CFC. He developed atrial fibrillation four years ago with a CHADS2 score of 0. We decided not to treat him with aspirin and until now, there have been no problems.

In severe haemophilia, we do not give anticoagulation when patients are not on regular CFC prophylaxis. Patients on CFC prophylaxis are managed similar to moderate haemophilia.

Conclusion

The incidence of cardiovascular disease is increasing as patients with haemophilia are aging. Education and screening programs for cardiovascular risk factors should be part of routine care for such patients.

We developed a tool that can be useful to decide whether therapy with an anticoagulation drug is feasible and which drug might be preferred. The major problem is that guidelines and tools in this respect have not been validated prospectively. Only when efficacy and safety outcomes of anticoagulation management strategies are prospectively gathered, we will be able to be more confident in our approach to the elderly patient. In the meantime, we can only rely on the experiences from others and from patients without bleeding disorders.
We encourage following the same cardiac procedures in haemophilia patients as in the non-haemophilia population, but with clotting factor correction and with slight modifications in stent and drug choices as described.

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RS, AT, KF, and EM-B all wrote the paper.

Conflict of interest

The authors disclose no financial interests in any company or institution that might benefit from this publication.

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