Multicentric and international study evaluating clinical and subclinical venous thrombosis in patients with haemophilia undergoing major orthopaedic surgery

Professor Cedric HERMANS

Haemostasis and Thrombosis Unit
Haemophilia Clinic

Division of Haematology

Cliniques Universitaires Saint-Luc
Catholic University of Louvain

Brussels, Belgium

Disclosures for:

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CONFLICT	DISCLOSURE — IF CONFLICT OF INTEREST EXISTS
RESEARCH SUPPORT : BAXALTA, BAYER, PFIZER	
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HONORARIA : BAYER, BAXALTA, PFIZER, SOBI BIOGEN, CSL BEHRING, LFB, OCTAPHARMA, NOVO NORDISK, CAF-DCF	
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CONSULTANT : BAYER, BAXALTA, PFIZER, SOBI BIOGEN, CSL BEHRING, LFB, OCTAPHARMA, NOVO NORDISK	

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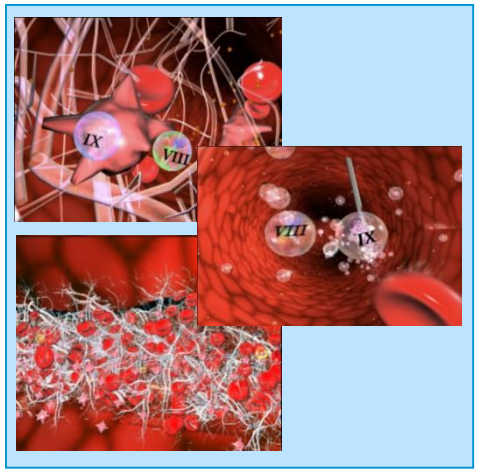
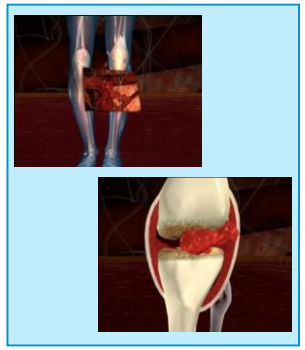
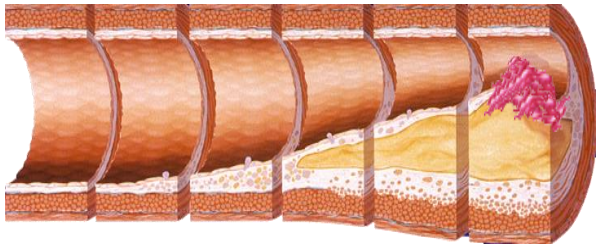
Consequences of haemophilia



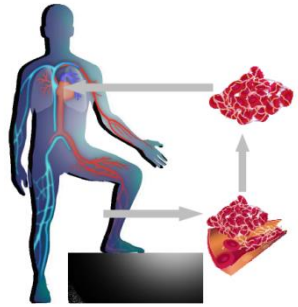
Partial or complete Clotting factor deficiency (FVIII or FIX)



Joint bleeds Debilitating arthropathy



Protection against arterial thrombosis?



Protection against venous thrombosis?

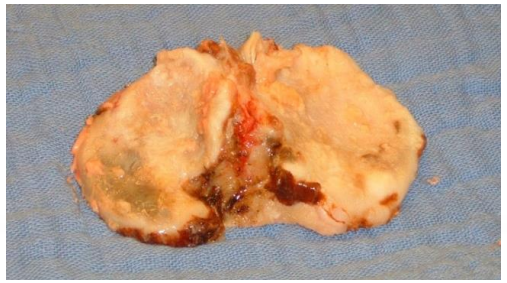
Background

- Venous thromboembolism (VTE) is a common postoperative complication in patients undergoing major orthopaedic surgery of the lower limbs.

- In absence of thromboprophylaxis, the risk of asymptomatic deep venous thrombosis (DVT) is 40 to 60% after hip replacement and 40 to 85% after total knee replacement.

- Few properly sized studies have objectively evaluated the incidence of VTE in haemophiliacs after orthopaedic surgery.

- The need, appropriate timing, dosage, duration of mechanical or pharmacological thromboprophylaxis in this setting remain unclear.



Published reports of symptomatic VTE in patients with haemophilia undergoing major orthopaedic surgery

Number of procedures	Thromboprophylaxis	VTE	Authors
71	Compression stockings (all), intermittent compression device (6), LMWH (2)	One symptomatic DVT	Perez et al. 2015
23	12 compression device, 1 LMWH, 10 none	No clinical VTE	Raza et al. 2014
34	Not used	No clinical VTE	Miles et al. 2008
35	Not used	No clinical VTE	Rodriguez-Merchan et al. 2007
90	Not used	1 non-fatal PE	Silva & Luck et al. 2005
44	Not used	No clinical VTE	Krause et al. 2005
32	Not used	No clinical VTE	Franchini et al. 2004
27	Not used	No clinical VTE	Djulbegovic et al. 1995
72	Not used	No clinical VTE	Kasper 1973

C. Hermans. Perioperative thromboprophylaxis in patients with hemophilia and von Willebrand disease undergoing major orthopedic surgery; Hematology Education: the education program for the annual congress of the European Hematology Association | 2015; 9(1)

Incidence of symptomatic VTE in hemophilia patients undergoing arthroplasty : *analysis of pooled data from published series*

- **Detailed review of 35 published studies.**
  - 843 patients had 1,107 THA or TKA procedures
  - 8 of 843 patients (0.9%) had VTE 95% CI [0.26, 1.54%]

- **Inconsistent reporting and/or use of VTE prophylaxis.**
  - 9 reports addressed VTE prophylaxis in the methods section (2 only administered LMWH to all patients)

  - 26 studies did not address thromboprophylaxis in the methods section. It is reasonable to conclude that pharmacologic thromboprophylaxis likely was not used.

Perez BJ, et al. Incidence of symptomatic venous thromboembolism in patients with hemophilia undergoing joint replacement surgery: a retrospective study Thromb Res 2015; 135(1):109-113.

Subclinical DVT in patients with haemophilia undergoing major orthopaedic surgery

Subclinical deep venous thrombosis observed in 10% of hemophilic patients undergoing major orthopedic surgery

C. HERMANS,* F. HAMMER,† S. LOBET* and C. LAMBERT*
*Division of Haematology and †X-Ray Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

JTH2010, 8(5): 1138-1140

Haemophilia The Official Journal of the World Federation of Hemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society

Haemophilia (2015), 1–4 DOI: 10.1111/hae.12643

ORIGINAL ARTICLE

Deep venous thrombosis was not detected after total knee arthroplasty in Japanese patients with haemophilia

H. TAKEDANI,* K. OHNUMA† and J. HIROSE*
*Department of Joint Surgery Research Hospital, The Institute of Medical Science, The University of Tokyo; and †Department of Therapy Development and Innovation for Immune Disorders and Cancers, Graduate School of Medicine, Juntendo University, Tokyo, Japan

46 cases of TKA in 33 Japanese patients with haemophilia

Ultrasonography was used to determine the prevalence of lower extremity DVT

No subclinical DVT was detected

Coagulation and Fibrinolysis

Prospective, multicenter study of postoperative deep-vein thrombosis in patients with haemophilia undergoing major orthopaedic surgery

Tyler W. Buckner[1]; Andrew D. Leavitt[2]; Margaret Ragni[3]; Christine L. Kempton[4]; M. Elaine Eyster[5]; Adam Cuker[6]; Steven R. Lentz[7]; Jonathan Ducore[8]; Cindy Leissinger[9]; Mike Wang[1]; Nigel S. Key[10]

51 subjects enrolled, 46 of whom completed the study.

1 distal symptomatic distal DVT, 1 PE

No case of subclinical DVT by US

Current practice of thromboprophylaxis in haemophilic surgical patients

- There is currently a lack of consensus and no clear guidelines for thromboprophylaxis for persons with haemophilia without inhibitors.
- Three surveys of current practice in haemophilia centers have been conducted.
- Despite the absence of data, half of haemophilia comprehensive centers in Europe report the use thromboprophylaxis (compression stockings, mechanical compression devices, pharmacological treatment) in such setting.

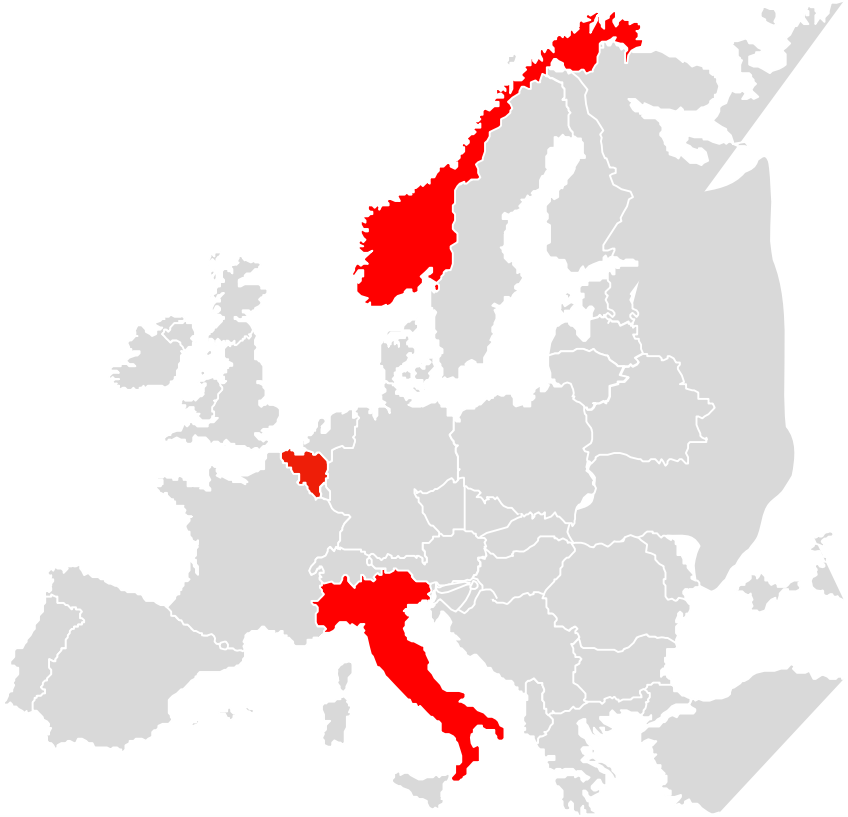
	Countries	Number of centers	% use of prophylaxis
C. Hermans (2009)	Europe	25	50 %
Zakarija and Aledort (2009)	USA	19	47 %
Pradhan (2009)	USA	60	67 %

Hermans C, et al. Haemophilia 2009;15(3): 639-58.
Zakarija A, et al. Haemophilia 2009;15(6):1308-10.
Pradhan SM, et al. Haemophilia 2009;15(6):1337-8.

Objective of the study

Evaluation of the incidence of **sub-clinical deep venous thrombosis** in patients with haemophilia undergoing major orthopaedic surgery and not receiving pharmacological thromboprophylaxis.

Multicentric and international study evaluating clinical and subclinical venous thrombosis in patients with haemophilia undergoing major orthopaedic surgery



- ***BELGIUM:***
  - *Cliniques universitaires Saint Luc, Brussels*
- ***ITALY :***
  - *Dipartimento Funzionale Riabilitativo, Fondazione Teresa Camplani, Brescia,*
  - *Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Ospedale Maggiore Policlinico, University of Milan, Italy*
- ***NORWAY :***
  - *Division of Haematology, Rikshospitalet, Oslo University Hospital.*

Population and methods (1)

- Prospective multicentric study: all consecutive haemophilic patients referred for major orthopaedic surgery for more than 10 years in three major centres from Italy, Belgium and Norway.
- In total, 214 patients with haemophilia undergoing 231 major orthopaedic procedures of the lower limbs mainly have been enrolled.
- None had a personal or family history of venous thrombosis.
- No thrombophilia work-up was performed.
- Patients were treated with continuous infusion or bolus of concentrates.
- No heparin was administered with the concentrate.

Population and methods (2)

- Factor levels were maintained between 80 and 100 % in the immediate post-operative period.
- The patients were not treated with antifibrinolytics (Tranexamic acid) post-operatively.
- None of the patients received pharmacological thromboprophylaxis.
- Most wore grade 1 stockings.
- Revalidation was initiated on the first post-operative day, in most cases.
- Bilateral US-doppler was performed on inferior limbs between day 5 and 10 by an experienced radiologist.

Table 1. Characteristics of study population

Number or patients	214
Type and severity of Haemophilia (Severe/Moderate/Mild)	HA/HB (N = 191 and 23) 195 / 17 /2
Age distribution	18 – 81
Number of orthopaedic procedures	231
Types of orthopaedic procedure	Knee arthroplasty (n=136) Ankle arthrodesis (n=49) Hip arthroplasty (n=24) Femoral fracture (n=4) Lumbar (n=1) Elbow (n=4) Multiple fractures (n=3)

Table 2. Study population

	Brussels	Oslo	Brescia	Total
Patients	39	29	146	214
Procedures	54	29	148	231
HA	35	26	130	191
HB	4	3	16	23
Severe	*28*	*29*	*138*	*195*
Moderate	*9*	*0*	*8*	*17*
Mild	*2*	*0*	*0*	*2*
Procedures	54	29	148	231
Knee	*32*	*11*	*93*	*136*
Ankle	*9*	*12*	*28*	*49*
Hip	*8*	*2*	*24*	*34*
Femur	*4*	*0*	*0*	*4*
Lumbar	*1*	*0*	*0*	*1*
Elbow	*0*	*4*	*0*	*4*
Multiple Fractures	*0*	*0*	*3*	*3*
DVT	**4**	**1 uncertain**	**6**	**11**

Results

- No patient developed clinical signs of DVT or PE in the immediate or delayed post-operative period.

- In total 11 cases of distal and subclinical DVT involving 1 (5) or 2 (6) calf veins were detected, of which 6 were treated with a low-dose and a short course of LMWH.

- The overall incidence of subclinical DVT was 4,7 % (11/231) and ranged in the three recruiting centres from 3,4 % in Norway (1/29), 4 % in Italy (6/148) and 7,4 % in Belgium (4/54).

Table 3. Characteristics of the 11 patients who developed a subclinical distal DVT

Haemophilia type and severity	Age	Location of DVT	Type of surgery	Other thrombotic risk factor(s)	Treatment / follow-up
HB moderate	71	Calf – 2 veins	Lumbar stenosis	Haemophilia B ?	Enoxaparin, 5000 anti-Xa, twice daily during 2 weeks
HA severe	37	Calf – 1 vein	TKR	HIV	Spontaneous resolution
HA severe	52	Calf – 1 vein	TKR	-	Spontaneous resolution
HA moderate	81	Calf – 1 vein	TKR	Severe chest infection Delayed revalidation	Nadroparin, 5700 anti-Xa units during 10 days
HA severe	59	Calf – 1 vein	TKR	-	Enoxaparin, 2000 anti-Xa, 22 days
HA severe	66	Calf – 2 veins	TKR	-	Spontaneous resolution
HA moderate	61	Calf – 2 veins	TKR	-	Spontaneous resolution
HA severe	67	Calf – 2 veins	TKR	-	Enoxaparin, 3000 anti-Xa, 13 days
HA severe	53	Calf – 2 veins	TKR	-	Enoxaparin, 3000 anti-Xa, 4 days
HA severe	56	Calf – 2 veins	TKR	-	Spontaneous resolution
HA severe	38	Short thrombus ?	TKR	-	No treatment

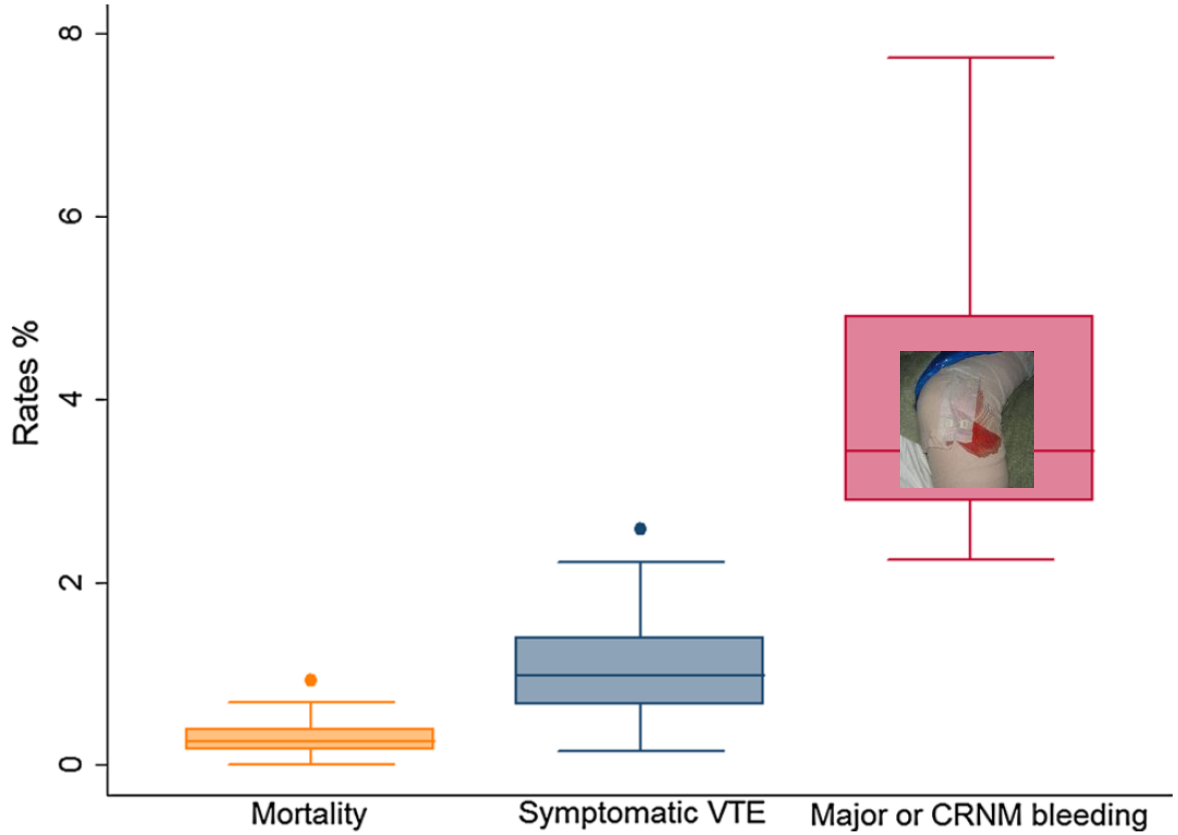
Interpretation of the study

- These data provide additional evidence that the risk of DVT following major orthopaedic surgery among patients with haemophilia is very low.

- The incidence is lower than that in patients without haemophilia undergoing major orthopaedic surgery and receiving pharmacological thromboprohylaxis with LMWH or NOAC and screened by imaging.

Combined patient important event rates for new anticoagulants and enoxaparin.

Box-plots of the mortality, symptomatic VTE and major or clinically relevant non-major bleeding rates



Chan NC, Siegal D, Lauw MN, Ginsberg JS, Eikelboom JW, Guyatt GH et al. A systematic review of contemporary trials of anticoagulants in orthopaedic thromboprophylaxis: suggestions for a radical reappraisal
J Thromb Thrombolysis 2014

VTE disease :
Non-haemophilic on thromboprophylaxis versus haemophilic patients without thromboprophylaxis

Haemophilia	Pharmacological Thrombo-prohylaxis	Mortality	Clinical VTE	Subclinical VTE	Bleeding complications
No	Yes	0.26 (0-0,92 %)	0,99 % (0,15-2,58)	6,95 -8,58 %	2.25-7,74 %
Yes	No	0	0,9 % (0.26-1,54)	0 to 7 % (only distal DVT)	38,8 %

Chan NC, Siegal D, Lauw MN, Ginsberg JS, Eikelboom JW, Guyatt GH et al. A systematic review of contemporary trials of anticoagulants in orthopaedic thromboprophylaxis: suggestions for a radical reappraisal - J Thromb Thrombolysis 2014

Limitations of the study

- The patients were studied in the immediate post-operative period.
- Us-doppler is less sensitive than phlebography for the detection of distal clots.
- One may not ruled out that some distal clots were undetected.

Conclusions

- Multicentric and imaging-based evidence that the risk of DVT following major orthopaedic surgery in the largest population of patients with haemophilia ever reported is very low.

- Systematic pharmacological thromboprophylaxis in this specific population is for most patients not required.

- In the future, more older individuals with haemophilic arthropathy will require orthopedic surgery and an increased proportion of haemophilic patients will also live long enough to need revision surgery.

Conclusions

- Further studies involving large sample sizes will be necessary to establish an individualized risk assessment of VTE and determine whether or not pharmacological thromboprophylaxis is required in some patients with haemophilia following major orthopaedic surgery.

- Appropriate type, timing, dosage, and duration of treatment should also be clearly defined.

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- ***NORWAY :***
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