Iceland Liechtenstein Norway grants

"Working together for
a green, competitive and inclusive Europe"

"HE-RO-IS strategic cooperation in hematology"

F SEE 2014-2021 No. 19-COP-0031

Curricula in hemophilia

Disclaimer: This curricula was realised with the EEA Financial Mechanism 2014-2021 financial support. Its content (text, photos, videos) does not reflect the official opinion of the Programme Operator, the National Contact Point and the Financial Mechanism Office. Responsibility for the information and views expressed therein lies entirely with the authors.

The Ageing Patient

A **case**

A 70-year old person with severe hemophilia was admitted to hospital in Sweden as he could not take care of himself or by his spouse. He was somewhat crippled because of joint bleeds but could walk. He was somewhat demented and had diabetes in need of insulin treatment. He had been on prophylactic factor VIII treatment since years and it was known that he would start to get painful joint bleeds if treatment was stopped. The alternative is only treatment according to need, something that is practiced in most other countries in adult patients. Should he be given prophylactic treatment for his hemophilia (which is expensive) or should he only be given treatment according to need (which is less expensive)?

How to proceed with this case? – suggestions

Ethical Analysis

- *The patient* probably wants the prophylactic treatment.
- *The relatives* want the prophylactic treatment.
- *The physician* believes that the prophylactic treatment should be given because that is what the physician believes to be in the best interest of the patient and that is what the relatives want. The physician is to decide and the decision made is to give the patient the prophylactic treatment.
- *The hospital nurse* disagrees and believes that the need of the patient after a bleeding should be satisfied and nothing more – even if the patient suffers. The reasons given are the age of the patient and his dementia. He also got diabetes.

Ethical Analysis

- *The assistant nurse* also disagrees and believes that the need of the patient after a bleeding should be satisfied and nothing more. She gives the same reason as the hospital nurse.
- It could reasonably be seen by *the other patients* as a utility cost and an injustice to them to offer the demented and old patient the prophylactic treatment (if they were told about the consequences).

Ethical principles

- *The principle of autonomy*, with its demand for protection of those that cannot protect themselves, honesty, and confidentiality (or anonymity in certain questionnaires), informed and voluntary consent, or refusal to participate. The principle is duty-oriented.

- *The principle of utility*, with its demand not to harm, to reduce suffering, to prevent suffering, and to increase wellbeing. The principle is consequentialistic, and it is sometimes formulated as two requirements. The first requirement is often called ”the principle of non-maleficence”. The second, third, and fourth requirements are often called ”the principle of beneficence”.

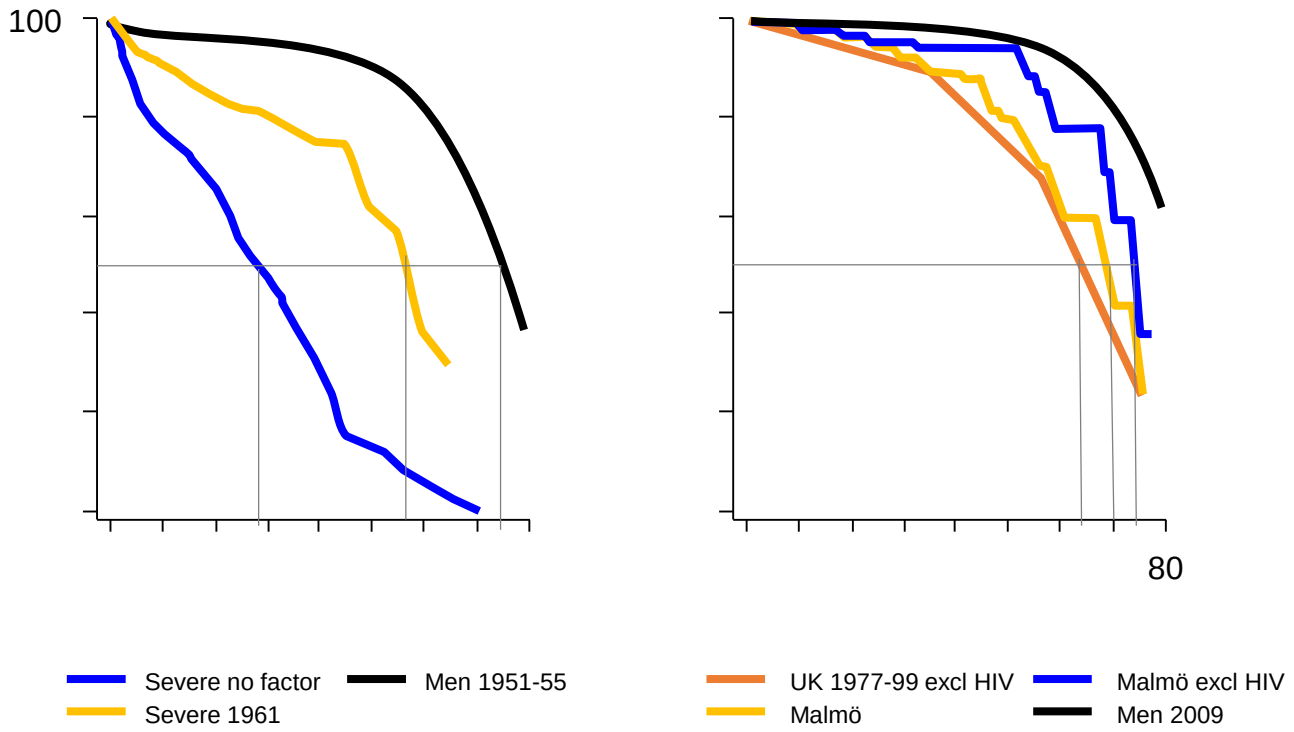
- *The principle of justice*, with its demand that no one should be discriminated against (for instance by reference to age and sex), and the obligation to show solidarity with vulnerable individuals. To impartially respect the right of everyone is usually understood as a duty-oriented principle.

Increased life expectancy in subjects with hemophilia

- Safe products for replacement therapy
- Comprehensive care
- Primary and secondary prophylaxis
- Improved treatment for inhibitor patients
- Improved antiviral therapy (HIV, HCV, HBV)
- Greater access to elective surgery

Treatment
Early Period of Replacement Treatment

Severe Haemophilia Malmö /UK

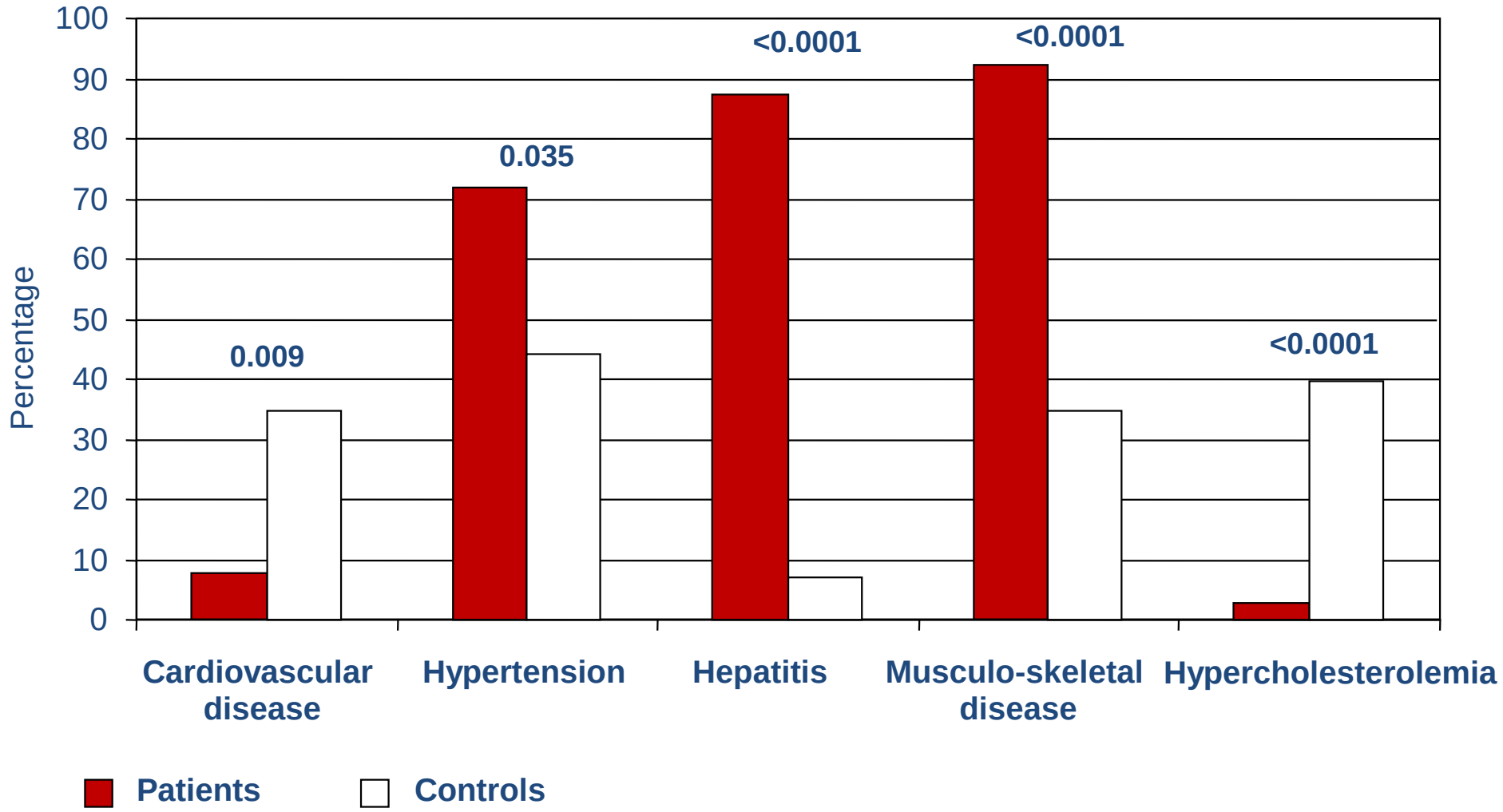


Steen Carlsson K. Personal communication; Larsson, S.A., *Hemophilia in Sweden. Studies on demography of hemophilia and surgery in hemophilia and von Willebrand's disease.* Acta Med Scand Suppl, 1984. **684**: p. 1-72; Darby, S.C., et al., *Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV.* Blood, 2007. **110**(3): p. 815-25

Clinical issues in elderly hemophiliacs

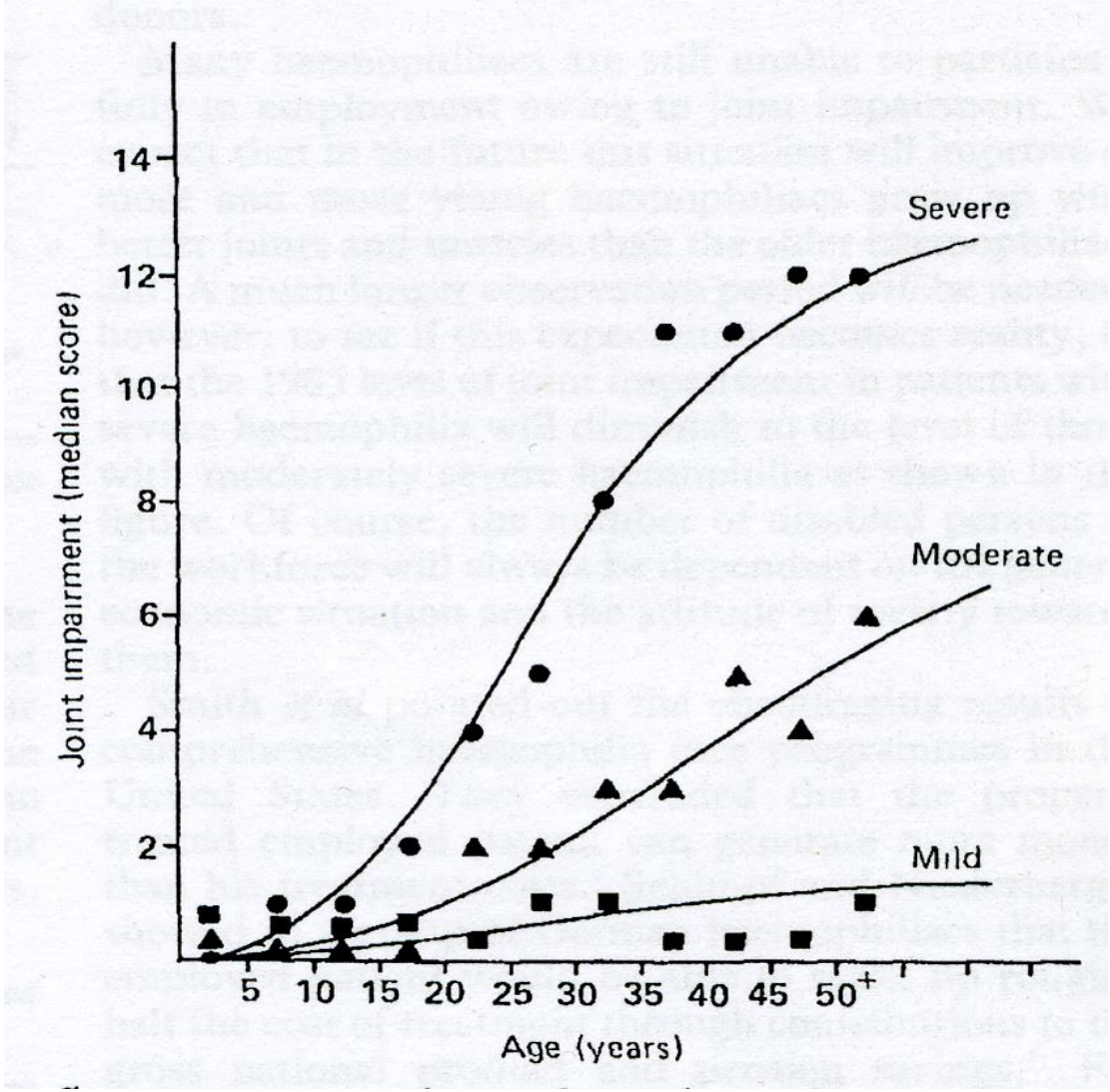
- **Hemophilia-related:**
  - disabling arthropathy
  - chronic pain
  - long-lasting HIV infection
  - cirrhosis
  - HCC
- **Other comorbidities:**
  - hypertension
  - diabetes
  - obesity
  - renal disease
- **Age-related:**
  - cardiovascular disease
  - cancer
  - arthritis
  - prostatic hypertrophy
  - osteoporosis
  - falls

Prevalence of comorbidities in 39 severe PWHs aged ≥ 65 years



Siboni SM et al. J Thromb Haemost 2009; 7: 247-54

Joint impairment by age in hemophilia

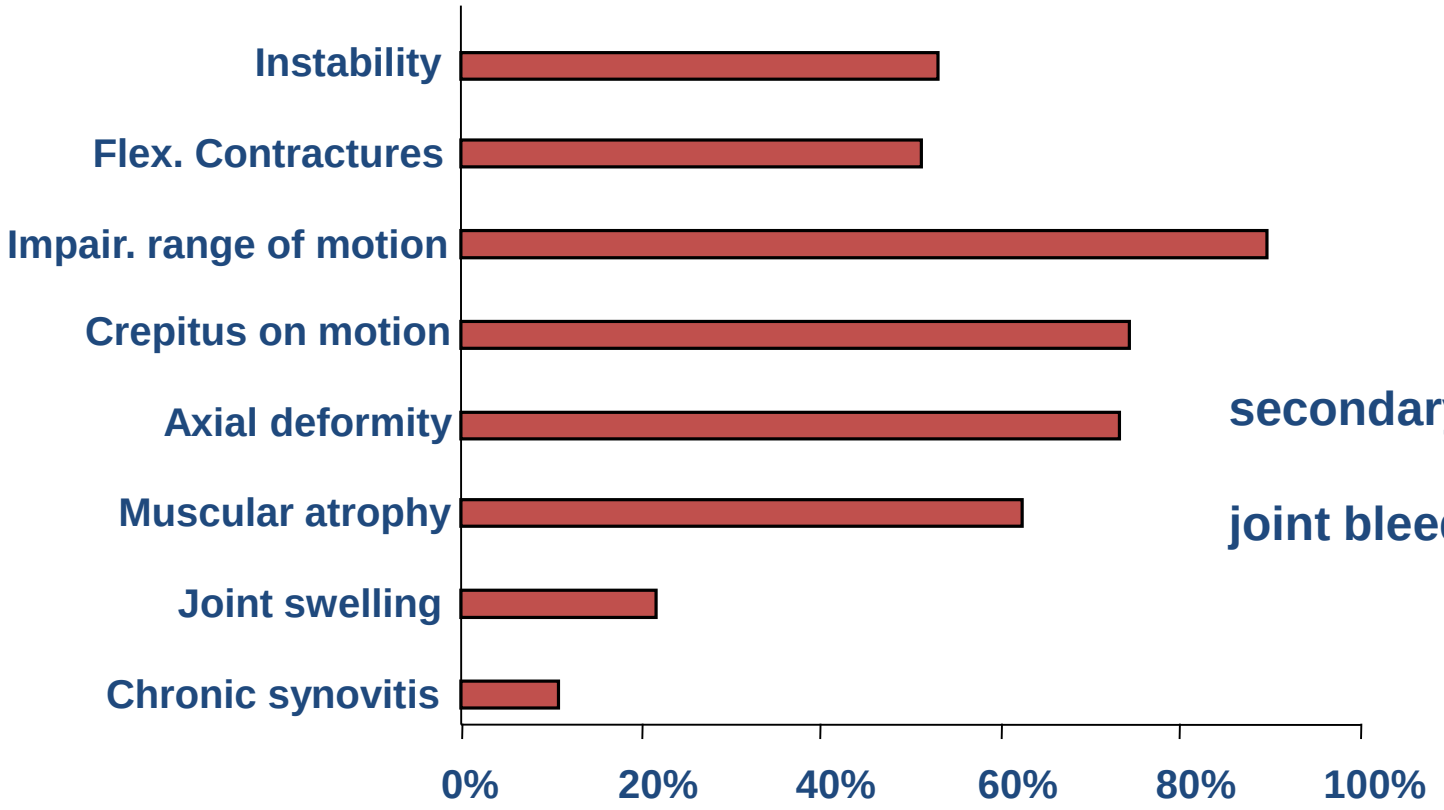


Smit C, Rosendaal FR et al. Brit Med J 1989, 298: 235-238

Arthropathy in elderly hemophiliacs

- What is the influence of sendentary life-style, arthritis, obesity and balance dysfunction on arthropathy and bleeding pattern?
- What is the need and the risk/benefit ratio for secondary prophylaxis?
- Greater need for orthopaedic surgery
  - Knee and hip replacement
  - Prosthesis revisions
  - Fractures
  - Should thromboprophylaxis be used?
- Chronic pain management

Orthopaedic joint score in 39 severe PWHs aged ≥ 65 years

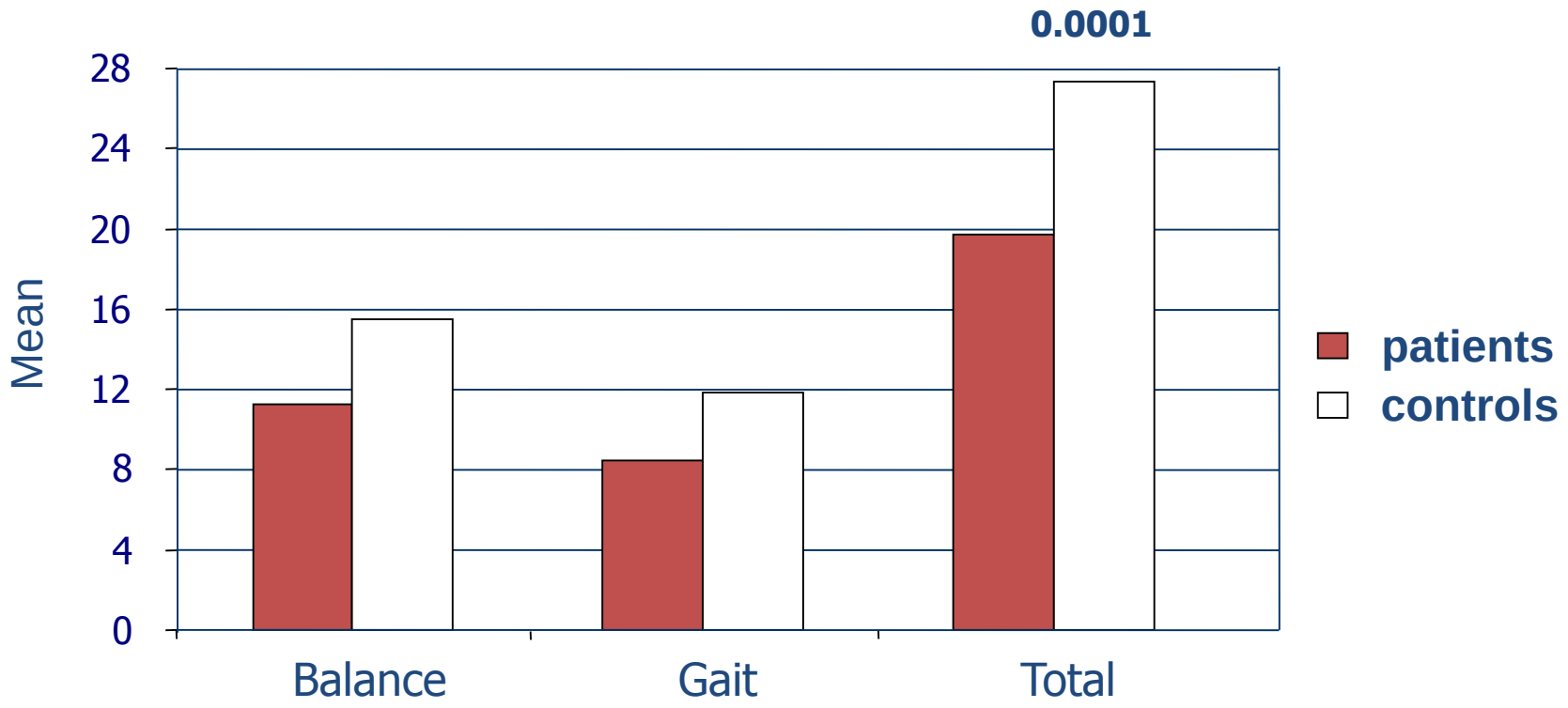


secondary prophylaxis: 8 (21%) #
joint bleeding: median 5 (0-40)

! **37%** of patients suffered from **chronic pain** with a mean **intensity of 74.1** (SD 27.1) on the VAS (0-100)

Siboni SM et al. J Thromb Haemost 2009; 7: 247-54

Tinetti Gait & Balance Assessment Scale



Total score < 1: not able to walk 0%
2-19: high falling risk 47%
20-24: moderate falling risk 23%
>24: low falling risk 30%

Siboni SM et al. J Thromb Haemost 2009; 7: 247-54

Changes in bleeding pattern

- Joint/muscles annual bleeding rate?
- Bleeding in other sites:
  - Hematuria (genitourinary diseases, prostatic hypertrophy/cancer)
  - ICH (hypertension, cerebrovascular disease)
  - GI (gastroduodenitis, malignancy)
  - Liver cirrhosis

Surgery in elderly PWHs

- Surgery in HIV+ve and HCV cirrhotic patients
- Surgery and other comorbidities
- Greater need for surgery (other than orthopaedic)
  - Cancer
  - Prostatectomy
  - Cholecystectomy
  - Hernioplasty
  - Cataract

Causes of deaths in UK

UKHCDO Annual Reports

	2004	2005	2006
Accident	2	1	na
AIDS	1	1	1
Cancer	14	16	16
HCC	2	1	2
Liver failure	2	1	3
Ischemic heart disease	9	13	10
Suicide	4	2	na
VTE	2	1	na
Infection	14	19	16
ICH	na	na	5
Miscellaneous hemorrhage	na	na	7

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

Haemophilia (2013), **19**, 362–369 DOI: 10.1111/hae.12092

ORIGINAL ARTICLE *Clinical haemophilia*

Incidence, mortality rates and causes of deaths in haemophilia patients in Sweden

S. LÖVDAHL,* K. M. HENRIKSSON,†‡ F. BAGHAEI,§ M. HOLMSTRÖM,¶ J.-Å. NILSSON,* E. BERNTORP* and J. ASTERMARK**

Table 4. Estimated hazard ratios for haemophilia patients compared with matched controls for all causes of death.

Group	HR	95% CI	*P*-value
Patients with all severities			
All			
Haemophilia control	2.2	[1.8; 2.7]	< 0.001
HIV-infected excluded			
Haemophilia control	1.6	[1.2; 2.0]	< 0.001
HIV-infected and viral hepatitis excluded			
Haemophilia control	1.7	[1.3; 2.2]	< 0.001
Patients with severe haemophilia			
All			
Haemophilia control	6.6	[4.5; 10.0]	< 0.001
HIV-infected excluded			
Haemophilia control	3.3	[1.9; 5.6]	<0.001
HIV-infected and/or viral hepatitis excluded			
Haemophilia control	8.2	[3.2; 20.8]	<0.001

Table 2. The most frequent causes of death for the total study group of haemophilia patients, for patients without HIV, for patients without HIV and/or viral hepatitis. The most frequent causes of death for patients with severe haemophilia, for severe haemophilia patients without HIV and/or for patients without HIV and/or viral hepatitis. The comparative numbers for their matched controls are also presented.

	Total study group		After exclusion of subjects with HIV infection		After exclusion of subjects with HIV infection and/or viral hepatitis	
Causes of death	Haemophilia, *n* (%)	Control, *n* (%)	Haemophilia, *n* (%)	Control, *n* (%)	Haemophilia, *n* (%)	Control, *n* (%)
All severities						
Number of deaths	382 (100)	1351 (100)	324 (100)	1294 (100	274 (100)	1100 (100)
Malignancies	83 (22)	306 (23)	77 (24)	296 (23)	62 (23)	254 (23)
Haemorrhage related	54 (14)	0 (0)	47 (15)	0 (0)	35 (13)	0 (0)
Ischaemic heart disease	48 (13)	391 (29)	48 (15)	378 (29)	45 (17)	322 (29)
Immunodeficiency including HIV/AIDS	29 (8)	0 (0)	4 (1)	0 (0)	4 (2)	0 (0)
Cerebrovascular disease	23 (6)	111 (8)	22 (7)	106 (8)	18 (7)	91 (8)
Severe haemophilia						
Number of deaths	78 (100)	102 (100)	31 (100)	63 (100)	14 (100)	24 (100)
Immunodeficiency including HIV/AIDS	24 (31)	0	1* (3)	0	1* (7)	0
Haemorrhage-related deaths/cerebrovascular disease	18 (23)	6 (6)	13 (42)	2 (3)	8 (57)	1 (4)
Malignancies	9 (12)	13 (13)	5 (16)	8 (13)	1 (7)	3 (13)
Viral hepatitis	5 (6)	0	3 (10)	0	0	0
Ischaemic heart disease	3 (4)	25 (25)	3 (10)	18 (29)	1 (7)	8 (33)

*ICD-9 (279)

Cardiovascular disease in hemophilia

review by Tuinenburg et al. epub JTH

- SMRs of ischaemic heart disease:
  - cohort studies: 0.2-0.6 (0.0-1.4)

    Rosendaal et al. 1989; Koumbarelis et al. 1994; Triemstra et al. 1995; Plug et al. 2006; Darby et al 2007
  - US cohort: 3.0 (95% CI: 1.5-5.8)

    Soucie et al. Blood 2000, 96: 437-442

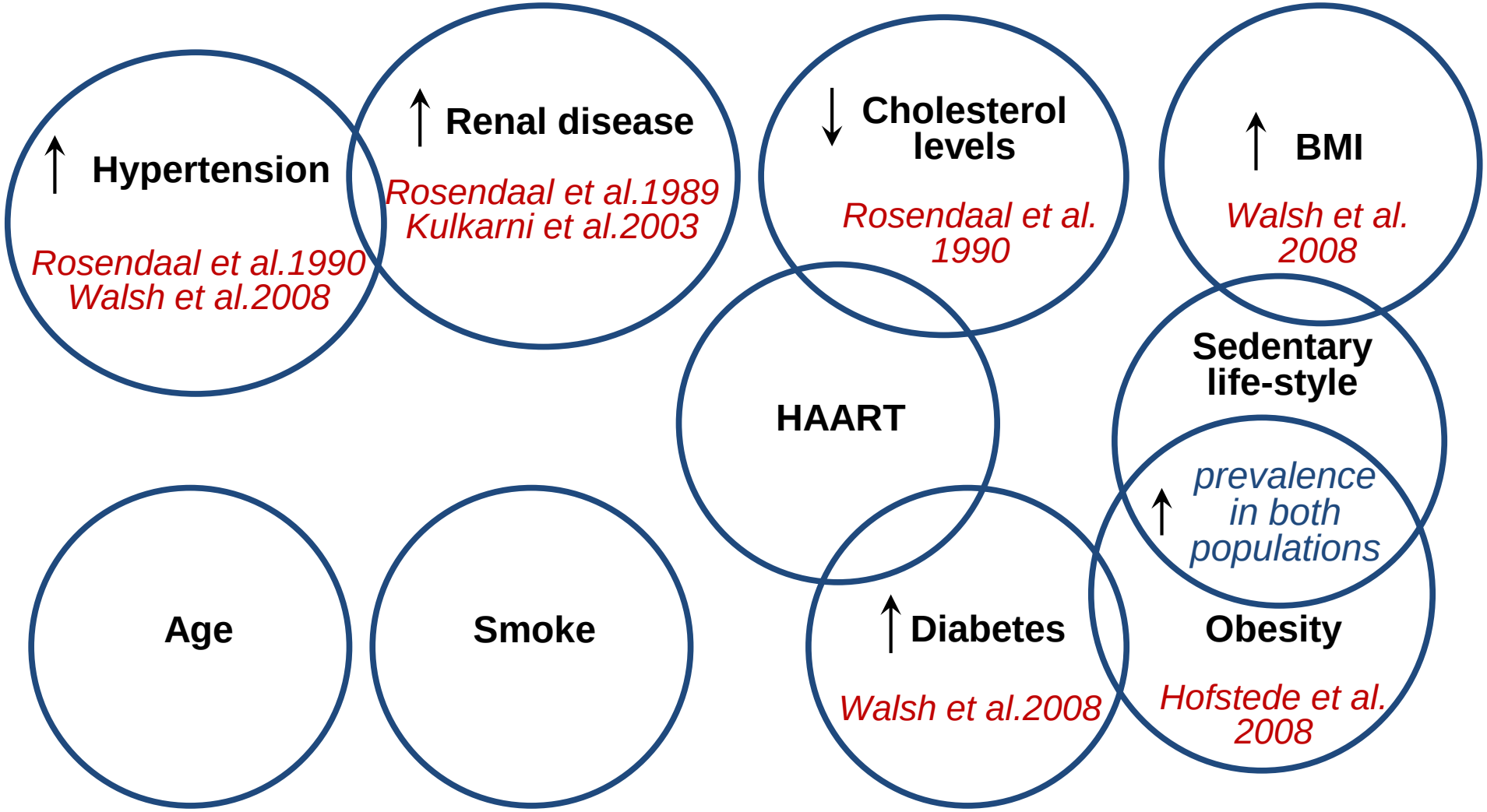
Protection against atherosclerosis?

- No difference in intima-media thickness (IMT) between patients with hemophilia/VWD and healthy controls *(Sramek et al. Circulation 2001; Sartori et al. Haemophilia 2008)*
- Significant difference in IMT between patients with hemophilia/VWD and healthy controls *(Bilora et. 1999, 2001, 2006)*

Protection against occlusive thrombosis?

- In vitro experiments and animal models suggest that FVIII/FIX deficiency reduces the tendency to form occlusive arterial thrombi *(Mizuno et al. Thromb Res 2008; Wang et al. JTH 2005)*
- Normal and hemophilic dogs in which thrombosis was induced similarly developed arterial occlusion *(Nichols et al. Blood 1993)*

Cardiovascular risk factors in hemophiliacs *vs* general population



Treatment of cardiovascular disease in hemophilia

- No evidence-based guidelines

  Few case reports; unreported events

- Comprehensive care team/cardiologist

  Anticoagulant/antiplatelet medications increase bleeding risk; cardiovascular interventions are frequently complicated by bleeding

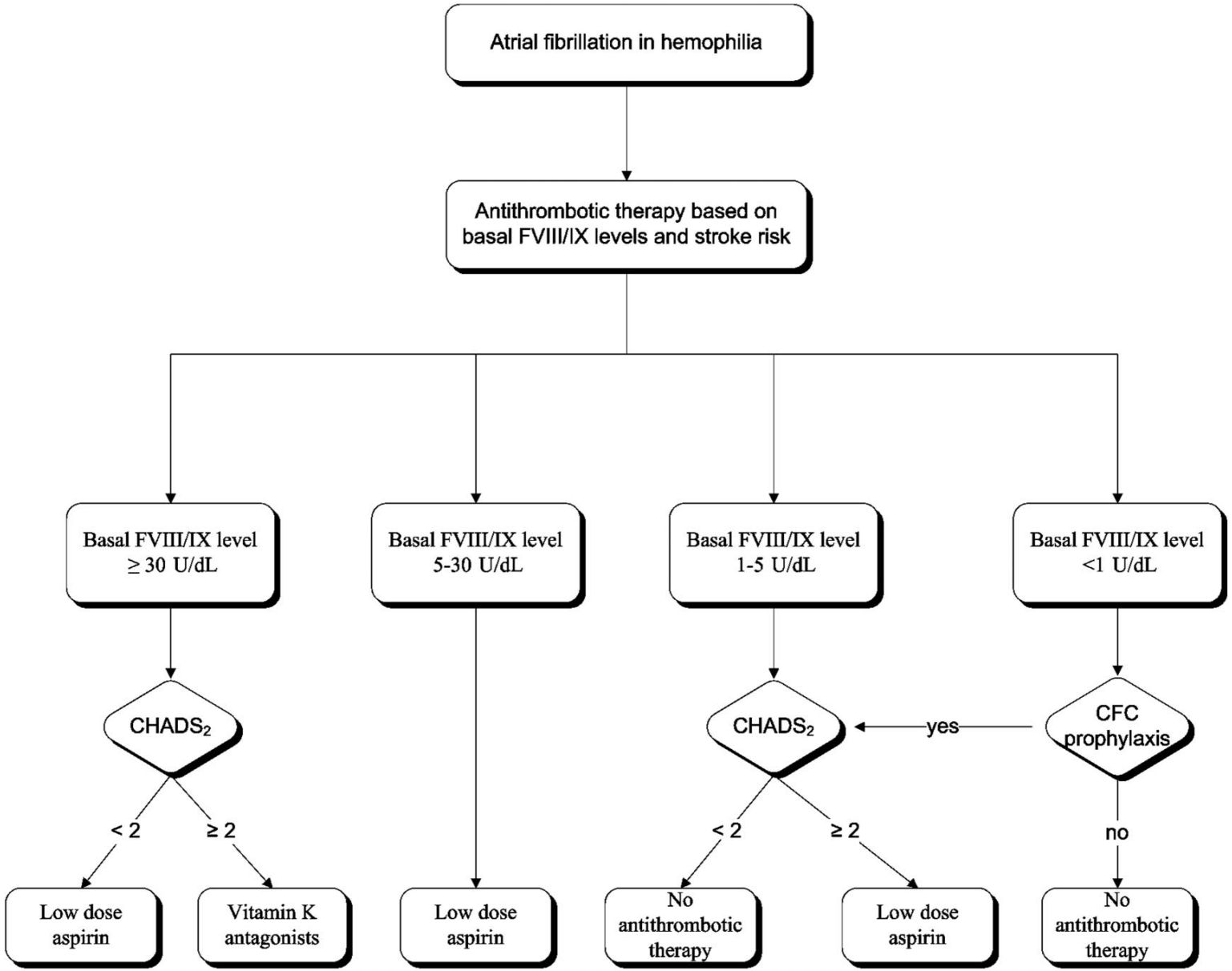
- Wide prospective surveillance

  Registries (EUHASS; www.euhass.org); controlled studies to build up evidence

Severe hemophilia. 65y. Artrial fibrillation

- Treatment
  - If no thromboembolic event
  - If a thromboembolic event

- If moderate hemophilia?
- If mild hemophilia?

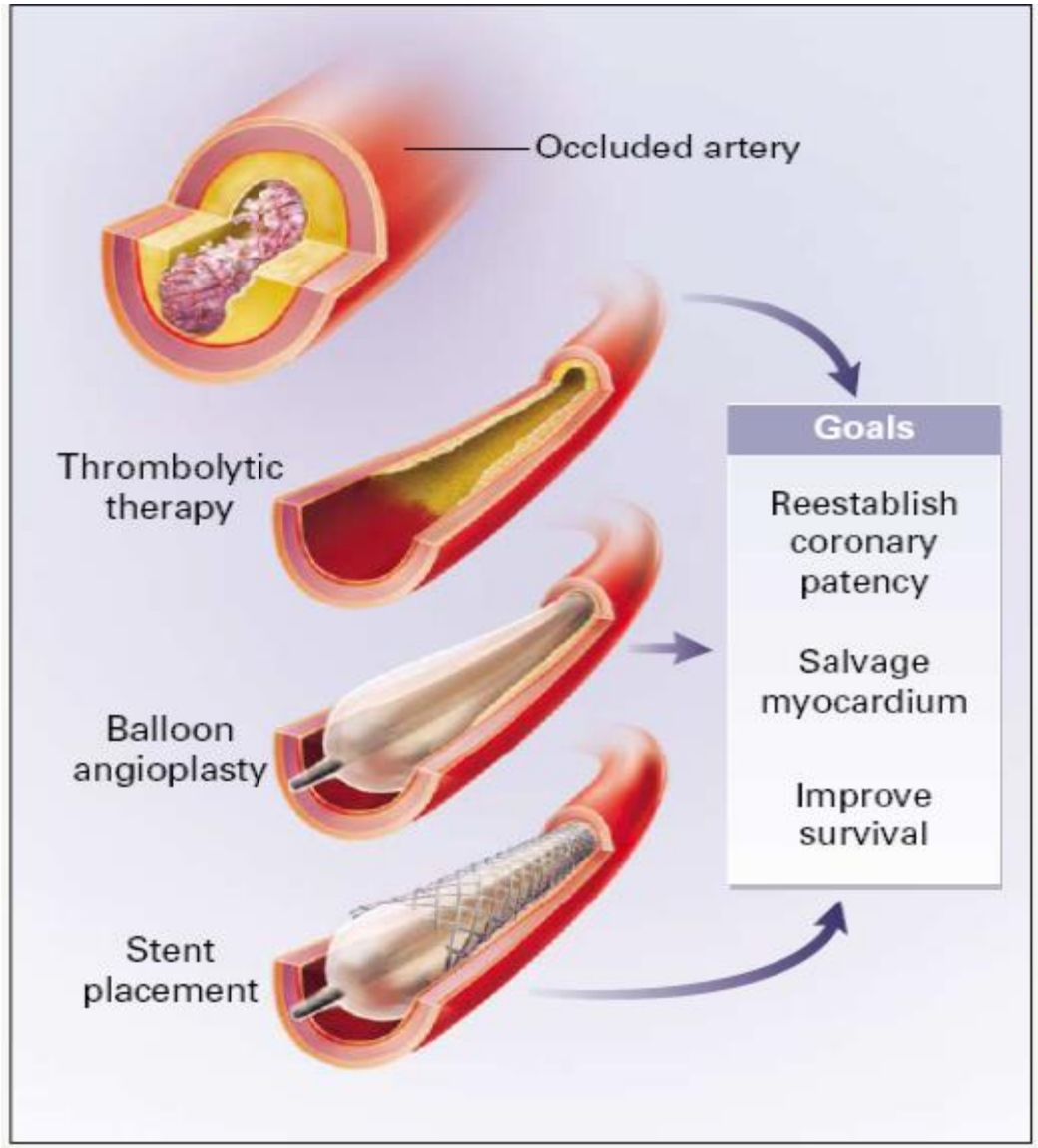


Mannucci et al Blood 2009

Table 5. $CHADS_2$ score: risk for stroke in nonhemophilia patients

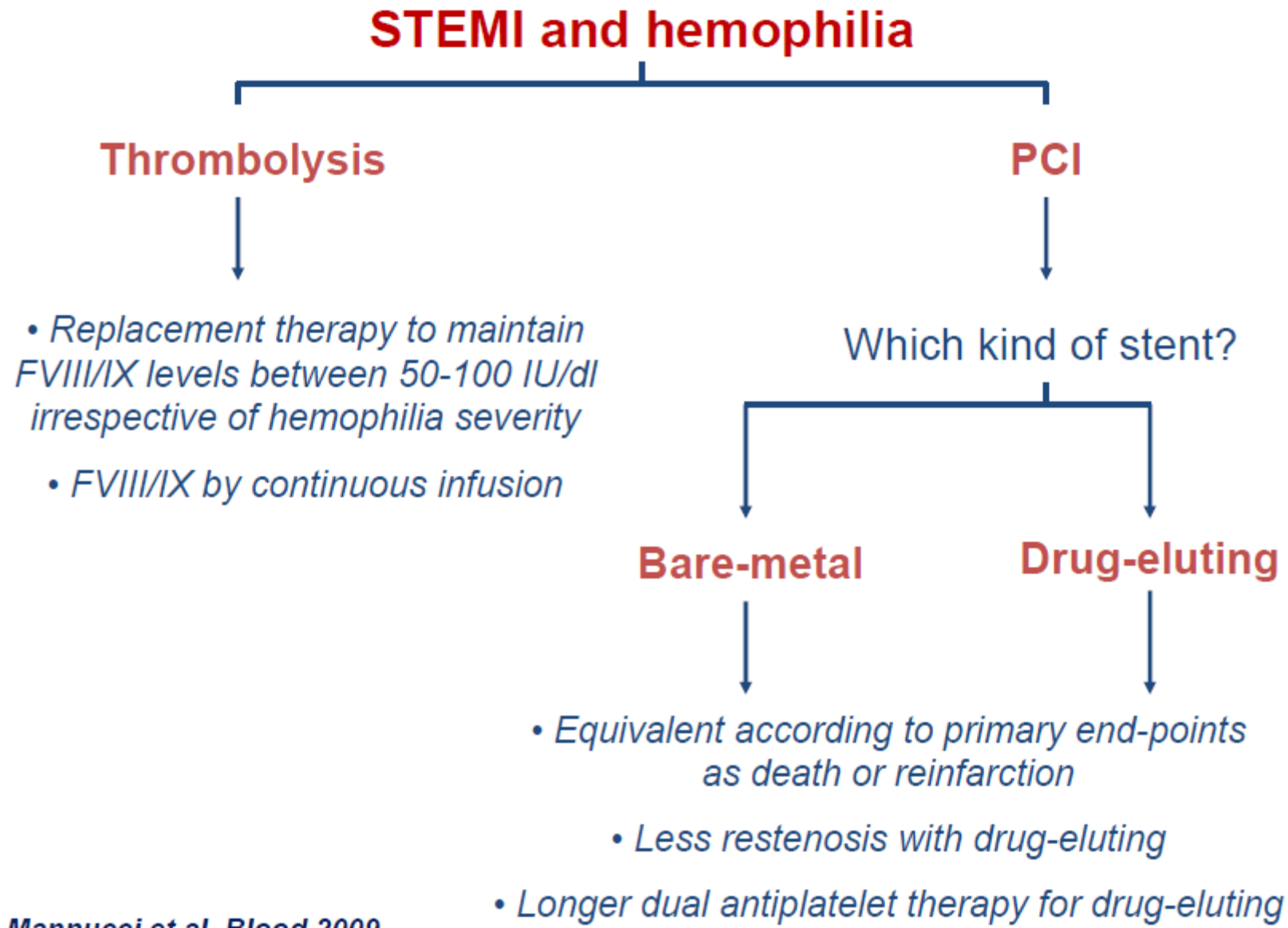
$CHADS_2$ score	Adjusted stroke rate per 100 patient-years
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

$CHADS_2$ score is calculated by adding 1 point for congestive heart failure, hypertension, age $\geq$ 75 years, or diabetes mellitus, and 2 points for prior stroke or transient ischemic attacks. Low risk = 0; moderate risk = 1; high risk $\geq$ 2.



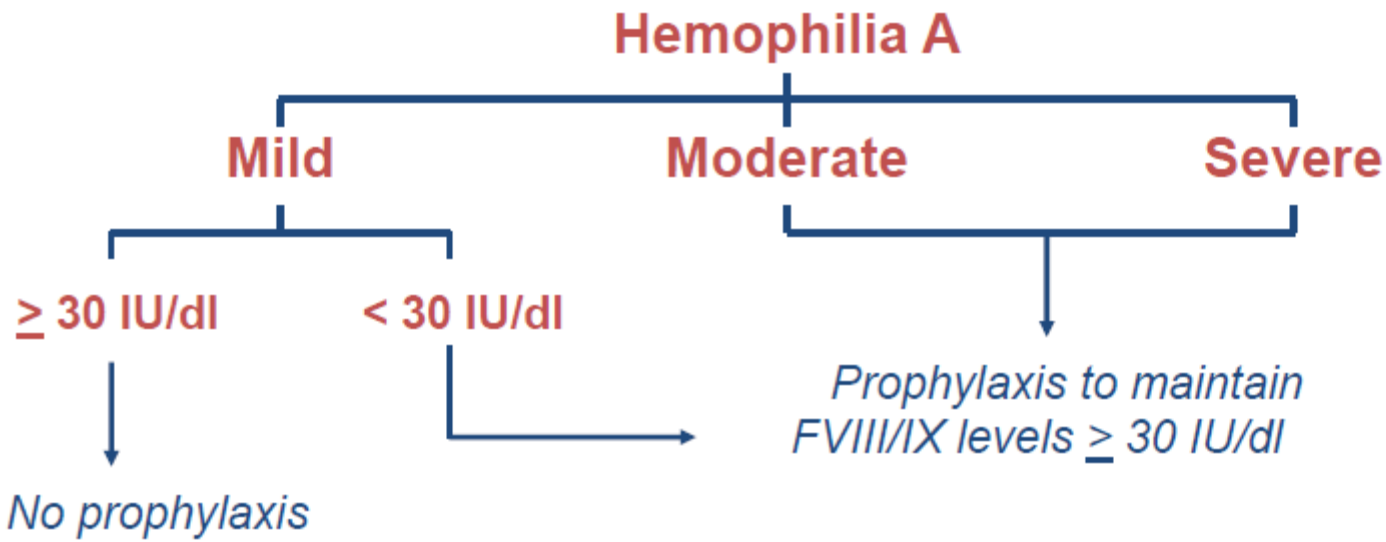
Methods of Reperfusion in Patients with Acute Myocardial Infarction.

Treatment of cardiovascular disease in hemophilia



Mannucci et al. Blood 2009

Oral anticoagulant therapy and hemophilia



Hemophilia B – specific issues:

- OAT converts mild patients into moderate/severe
- May FIX replacement interfere with anticoagulation ?

Mannucci et al. Blood 2009

ADVANCE Working Group
Age-related DeVelopments ANd
ComorbitiEs in hemophilia

Objectives

- ADVANCE aims to:
  - Highlight key issues and identify treatment strategies that will benefit the elderly hemophilia population
  - Encourage further research into this specific population
  - Generate Guidelines that can be used as a reference across Europe
- Currently, the key interests of the ADVANCE Working Group are elderly PwH and the impact of:
  - Epidemiology
  - Cardiovascular Disease
  - Hypertension
  - Hematuria

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

Haemophilia (2013), **19**, 833–840 DOI: 10.1111/hae.12189

ORIGINAL ARTICLE *Clinical haemophilia*

Applicability of the European Society of Cardiology guidelines on management of acute coronary syndromes to people with haemophilia – an assessment by the ADVANCE Working Group

P. STARITZ,* P. DE MOERLOOSE,† R. SCHUTGENS‡ and G. DOLAN§ ON BEHALF OF THE ADVANCE WORKING GROUP

Table 2. Statements relating to revascularization.

Questions	Response	Percentage agreement	Final statement/interpretation
Should early percutaneous coronary intervention (PCI) be postponed until replacement factor has been administered for a person with haemophilia (PWH) presenting with NSTE-acute coronary syndrome (ACS)?	Yes 12/15	80	PCI should be performed as soon as possible. Depending on the severity of the bleeding disorder, the urgency of the procedure and the availability of clotting factor concentrates, replacement therapy should be initiated in parallel or be started as soon as possible and before sheath removal. Replacement therapy should be supervised by a haemophilia specialist. Bare metal stents are preferred to drug-eluting stents.
When a PWH presents with an ACS, should treatment for the ACS be			
• Delayed until the factor VIII/IX level is known	No 15/15	100	
• Initiated after replacement therapy is given based on the patient's last known level	Yes 10/15	67	
Should early PCI (primary PCI) be postponed until replacement factor has been administered for a PWH presenting with an acute MI?	Yes 11/15	73	
What peak level of clotting factor should be achieved in PWH prior to PCI to provide adequate protection?	≥30% 1/15	7	
	≥50% 2/15	13	
	≥80%12/15	80	
In PWH undergoing PCI, are bare metal stents preferred to drug-eluting stents?	Yes 14/15	93	
Should CABG be considered in PWH with ACS?	Yes 12/15	80	
Is CABG preferred to PCI when either option is indicated for a PWH with stable coronary artery disease?	Yes 4/15	27	
	No 11/15	73	

Haemophilia (2014), 20, e399–e443

Management of atrial fibrillation in people with haemophilia – a consensus view by the ADVANCE Working Group

R. E. G. SCHUTGENS,* R. KLAMROTH,† I. PABINGER‡ and G. DOLAN§ ON BEHALF OF THE ADVANCE WORKING GROUP

um, Berlin, Germany;
, UK

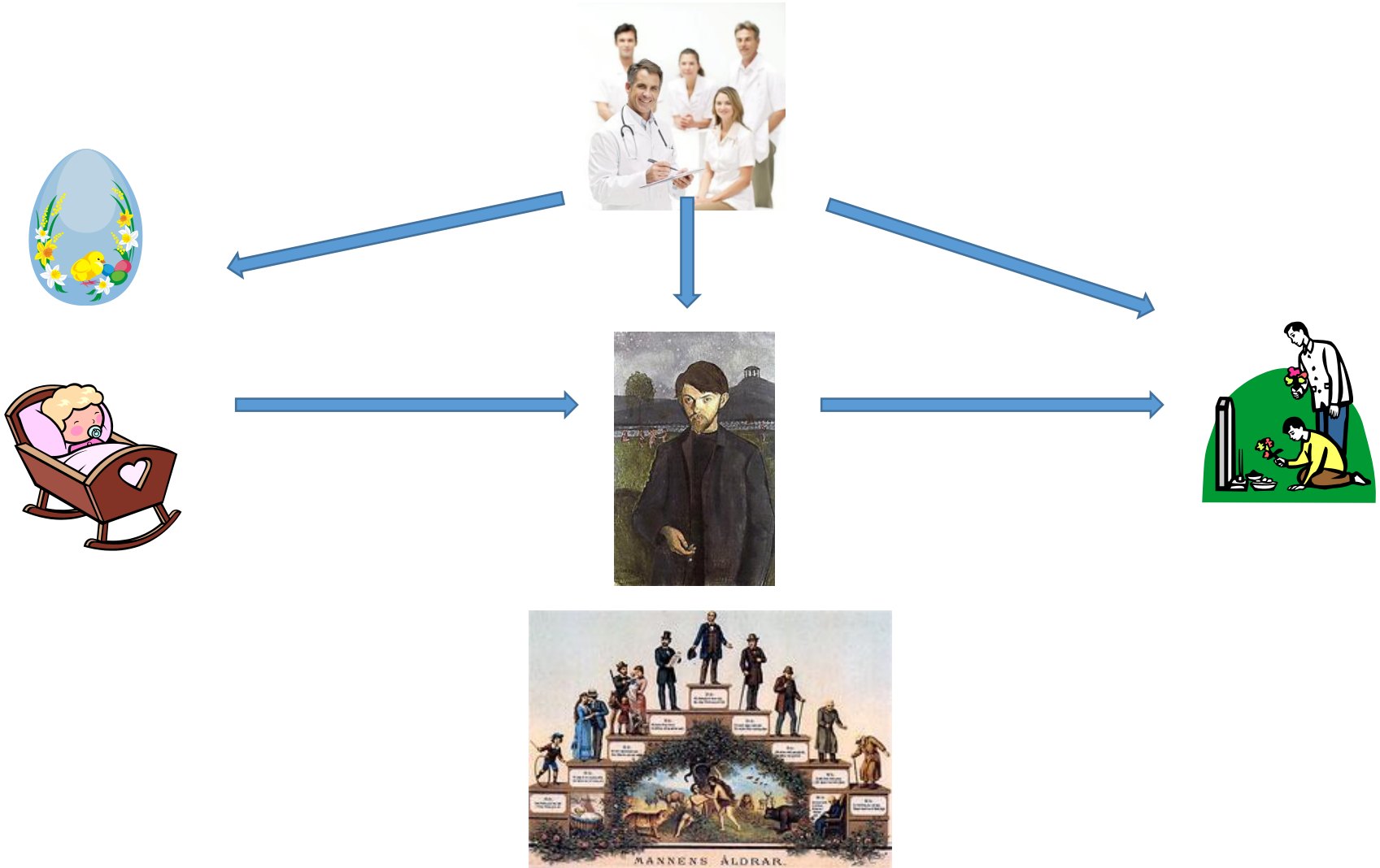
Table 1. Management of atrial fibrillation in haemophilia.

Questions	Response	Agreement (%)	Final statement/interpretation
Who should treat PWH found to have AF?	General physician 0 Haemophilia doctor 3 Cardiologist 1 Multidisciplinary team 12	75	PWH diagnosed with AF should be treated by a multidisciplinary team
Should vitamin K antagonists be considered for PWH?	Yes, in those at high risk for stroke 0 Yes, in those at high risk for stroke, only with a high enough trough CF level 14 No 2	88	The use of vitamin K antagonists may be considered for PWH at high risk for stroke with a high enough trough CF level
Is dual antiplatelet therapy considered an alternative to VKA treatment in the long-term?	No 12 Yes 2 Don't know 2	75	The indication for cardioversion in PWH is the same as in the NHP
Should the new oral anticoagulants be used in PWH	No 11 Yes 2 Don't know 3	69	Cardioversion in a patient with severe haemophilia requires a therapeutic dose of heparin, but should only be carried out after administration of clotting factor
Can cardioversion be performed in PWH in the presence of CF therapy?	Yes 16 No 0 Don't know	100	
Does cardioversion in a patient with severe haemophilia require a therapeutic dose of heparin?	Yes 11 No 2 Don't know 3	69	
Should clotting factor be given prior to cardioversion?	Yes 13 No 2 Don't know 1	81	
Is atrioventricular node ablation feasible in PWH with uncontrolled AF	No, never 1 Yes, given adequate CF replacement 15	94	While AV node ablation is feasible in a PWH with uncontrolled ASF, its long-term effects are unknown

AF, atrial fibrillation; PWH, people with haemophilia; NHP, non-haemophilia population; CF, clotting factor.

Do current models of hemophilia care need to be modified to accomodate the needs of aging patients?

Comprehensive hemophilia care



”Malmö Haemophilia Training and Treatment Centre”
World Federation of Haemophilia 1976

- Hematologist (3)
- Pediatrician (3)
  - Molecular genetics
  - Genetic counceling
  - Children with hemophilia
- Nurse (2)
- Ortopedic surgeon (1)
- Social worker (1)
- Physical therapist (1)
- (Dentist)
- (Infectious disease specialist)

Present annual check up in adults

- Comprehensive medical history
- SF-36
- Physical examination
  - General
  - Joint assessment (HJHS/US)

Annual check up in adults

- Labs
  - FVIII/IX, Bethesda if relevant
  - Hematology
  - Liver tests (enzymes)
  - Electrolytes, creatinine
  - Cystatin C
  - U-albumin
  - Blood lipids
  - Virology (if appropriate)
- Bone mineral density and physical activity (previous research project)

Strategy for the future

- All severe adults PWHs (with few exceptions) should be on continuous replacement theray
  - Implemented at our center since decades
- Much of what we already do will screen for problems in the elderly population
  - Awareness very important
- If a problem is present and cannot be handled according to state of the art at our center the patient is referred to relevant specialist
  - Team-work important and is implemented ad hoc

Additional thoughts

- Should the comprehensive care team be enlarged?
  - Probably not, but should be educated concerning problems in the elderly
- Is anything lacking?
  - Certainly: guidelines
    - CV interventions
    - Care of the mentally disabled (dementia etc)
    - Ethical considerations
      - Ethical analysis
    - And more…….
  - Registries
- Research important in order to establish appropriate guidelines

Conclusion

- A program that discloses age related problems is important
  - Many PWHs do only see the hemophilia center
- Refer the patients to the appropriate specialist
  - But do not leave the patient alone with the problem
- Prophylaxis important, even more important, for the patient who suffers from comorbidities
  - Do not destroy what you achieved during childhood/adolescence

The Future PWH