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.

Case 1

Male born 1966

Case 1

- No bleeding history
- No family history
- Football player
- Several tooth extractions

Case 1

- Multiple sclerosis
- Bilateral necrosis of caput femoris
  - High dose steroid treatment + interferon in the past
  - Is now on Tysabri (natalizumab)

Case 1

- Sample sent to us 2004 because of prolonged APTT 64 seconds
- FIX 2% and FXI 29%
- No inhibitor or lupus anticoagulant

Case 1

- Coagulation check up confirmed
  - No bleeding history
  - FIX 3-4 % and FXI 27 %. APTT 67 seconds. No inhibitor.
- Minor ankle artopathi according to HJHS

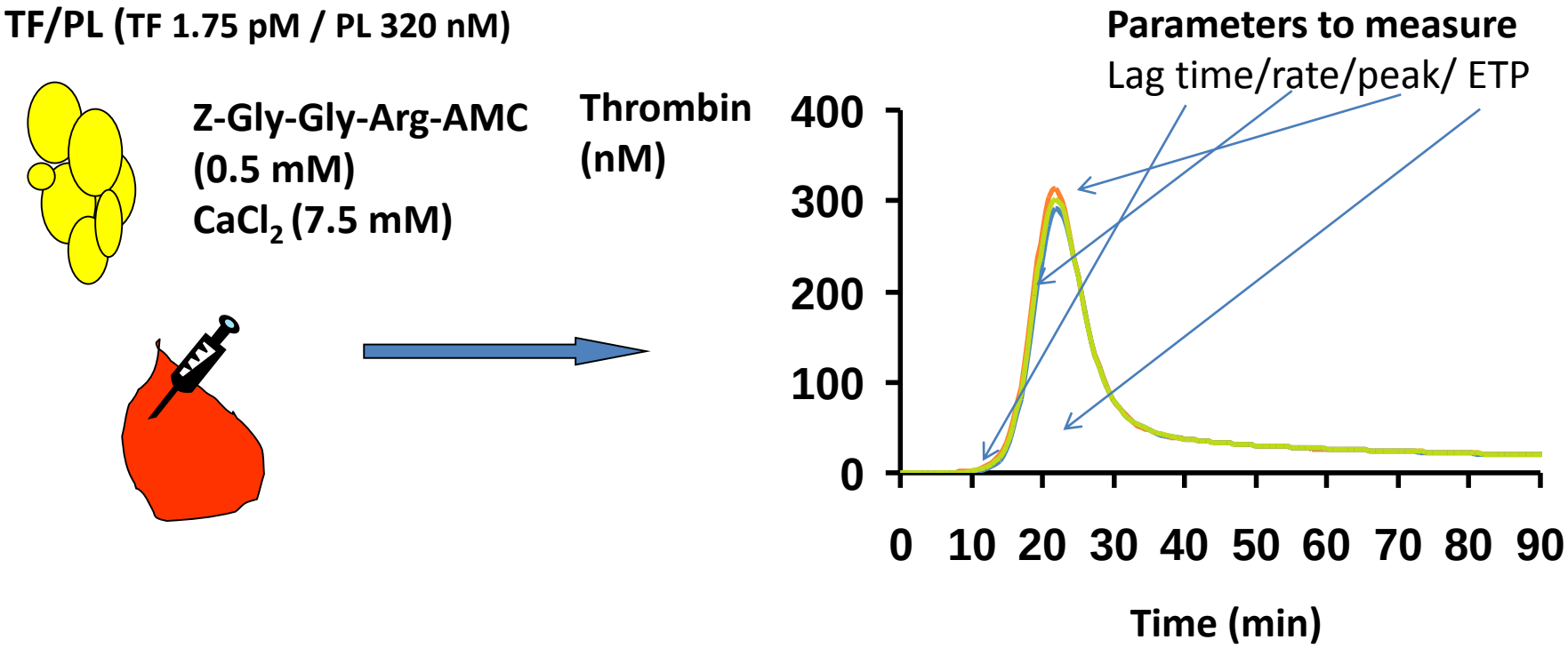
Case 1. What to do?

- Does he have moderate hemophilia B?
- Does he need replacement therapy during surgery?

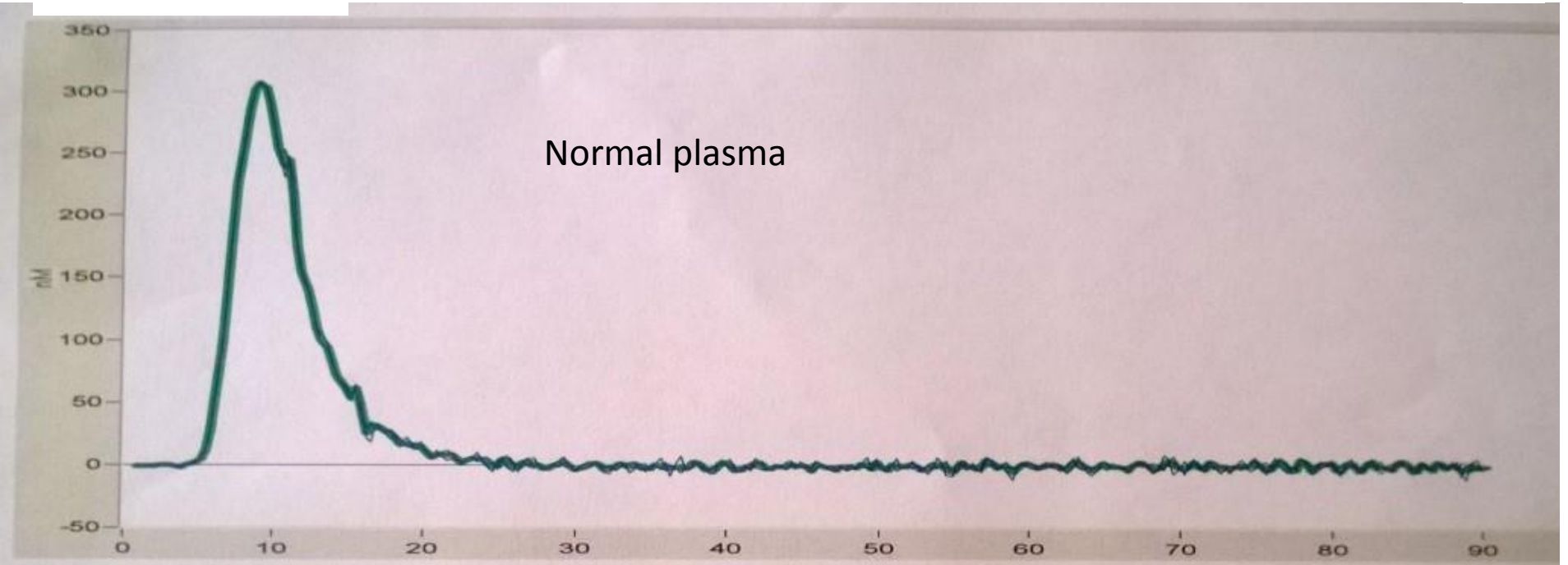
Case 1. What did we do?

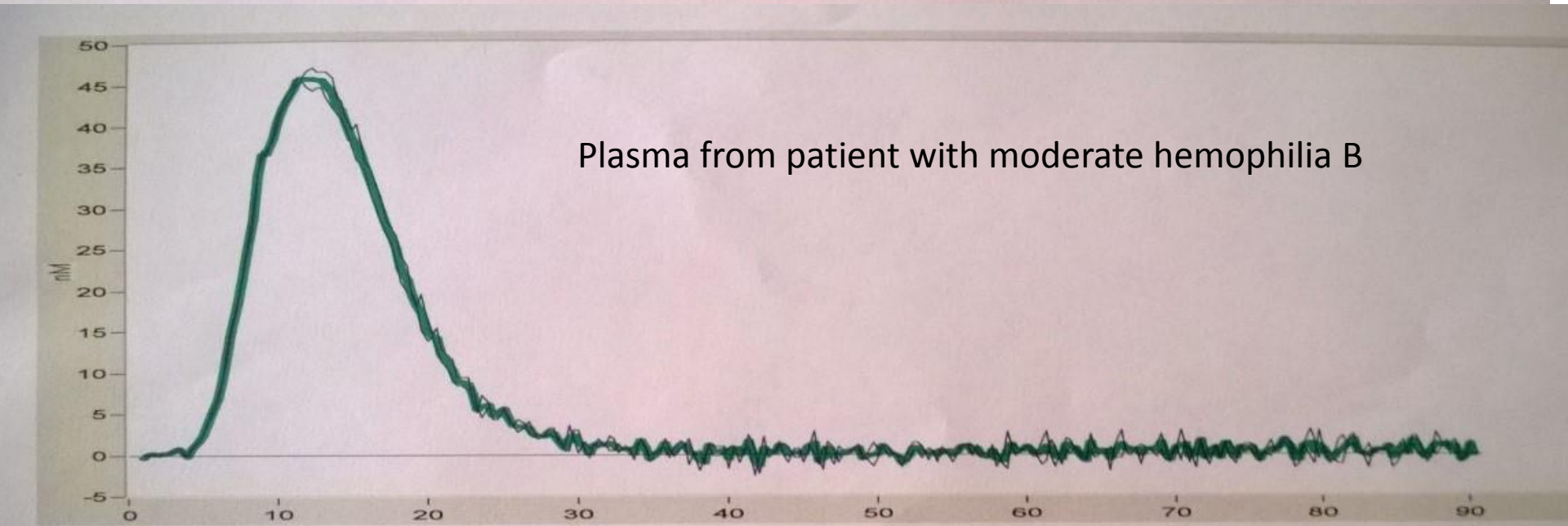
- DNA: known point mutation mild HB
- Thrombin generation

Thrombin generation assay (TGA)

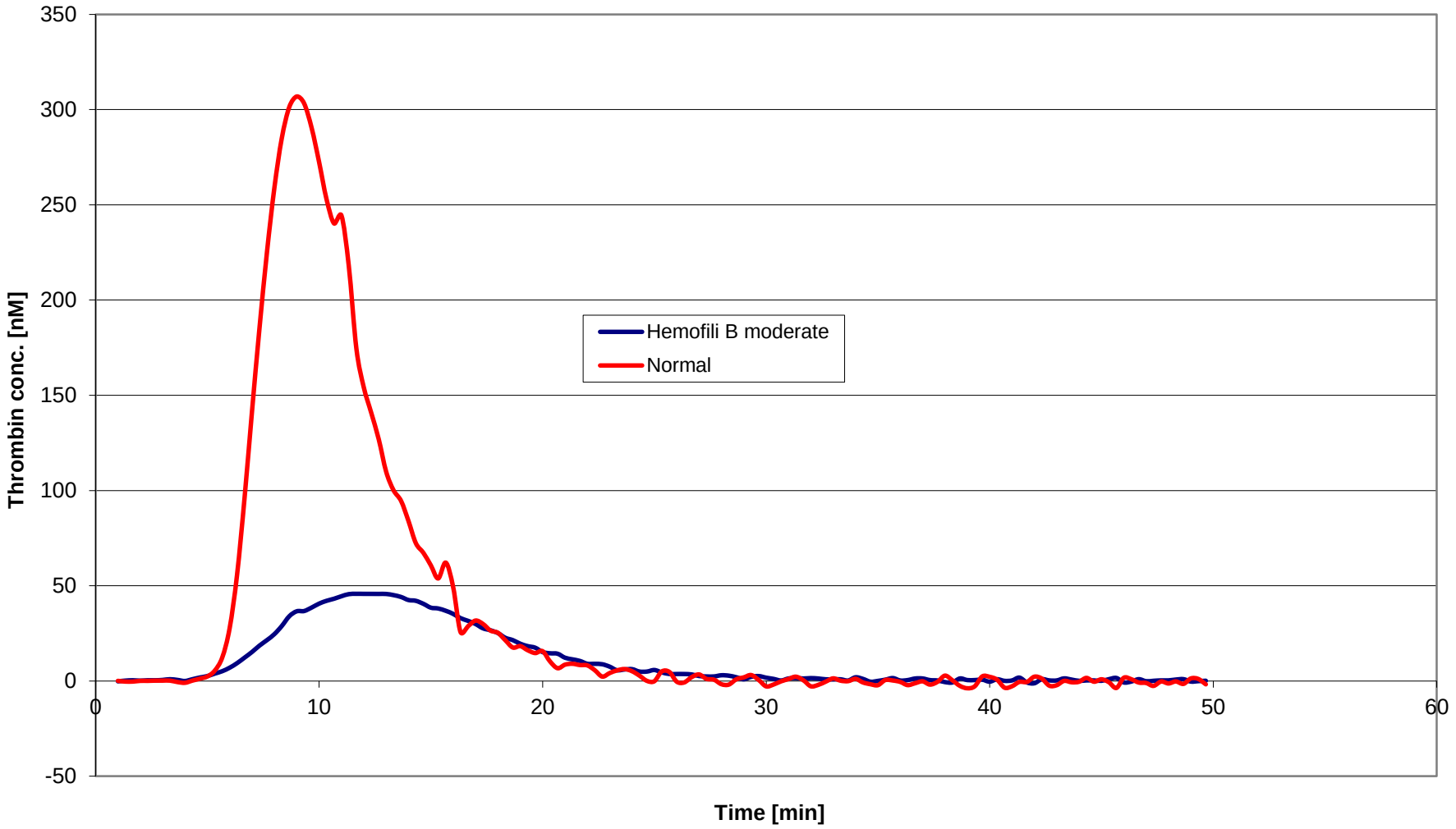


TF, tissue factor; PL, phospholipid; Pos, positive; Co, control sample;
Váradi et al 2003


Normal plasma
nM
350
300
250
200
150
100
50
0
-50
0
10
20
30
40
50
60
70
80
90


Plasma from patient with moderate hemophilia B
nM
50
45
40
35
30
25
20
15
10
5
0
-5
0
10
20
30
40
50
60
70
80
90

Thrombogram



Case 1. Surgery

- Under cover with Benefix, FIX level 40-70%
- Surgery uneventful
- Hemoglobin drop after 5-8 days when replacement was tapered to FIX level of around 20%
- Blood transfusion needed

Case 1. Key points

- Always trust the lab or never trust the lab?
- Global assays e.g. TGT may be of value in situations when lab and phenotype diverge
- This case is an example of a mild phenotype which upon a more severe hemostatic challenge may become more severe. Both the FIX level and reduced/absent TG indicate that the patient has a potential to bleed

Questions

1. Hemophilia B has a milder bleeding type than hemophilia A
2. Thrombin generation better reflects hemostasis than e.g. FIX in this patient
3. This is not a rare case
4. If pdFIX had been used instead of rFIX he had never started to bleed

Case 2

Male born 1978

Case 2

- No family history
- Easy bruising
- Aged 1 ½ years prolonged bleeding from the lip caused by a traumatic wound. Blood transfusion
- APTT 39 sec, normal bleeding time and routine hematological labs
- Referred to Malmö

Case 2.

- Coagulation check up revealed a mild hemophilia A with VIII:C values 9-10%. One stage assay
- During the coming years joint bleeds in ankles, knees and right hip
  - Treated on demand because of ”mild hemophilia”
- 1987-88 (10 years old) FVIII 4-5% using one-stage assay
- Prophylaxis started 1991 (13 years old) after referral to Malmö

Case 2

- Arthrodesis right ankle 2005 and left ankle 2006
- Knee problems

Case 2

- FVIII 2006
  - 3 % chromogenic assay
  - 10 % one-stage assay
- Mutation: missense

Case 2. Key points

- Consider assay issues
- Phenotype has to direct mode of treatment
  - Prophylaxis not only restricted to severe hemophilia
- Centralized hemophilia care!

Questions

1. Clot assay and chromogenic assay always show different results in patient plasmas
2. Arthropathy may be reversible
3. At FVIII levels above 15% arthropathy practically never develops
4. Starting prophylaxis at the age of 13 is useless ”The train is gone”