Individualisation of prophylaxis in severe haemophilia:

starting, dosing, tapering/stopping

Kathelijn Fischer
Van Creveldkliniek,
Dept of Haematology
UMCU, Utrecht, Netherlands
Outline

- Goals of prophylaxis
- Changes in treatment over the last decades
- When to start prophylaxis
- How to start prophylaxis
- Pilot study on frequency of infusions at start
- Discontinuing prophylaxis
- Computer models in long term outcome assessment
Prophylaxis: Goals

Prevention of bleeds
↓
↓
Joint damage
↓
loss of function & pain
↓
preservation of HRQoL & ability to work
Prophylaxis: Goals

- Prevention of bleeds
  - Joint damage
  - Loss of function & pain
  - Preservation of HRQoL & ability to work

For all patients who have bleeds.
Prophylaxis: Goals

Prevention of bleeds
↓
↓
Joint damage
↓
loss of function & pain
↓
preservation of HRQoL & ability to work

Feasible & important

-patients’ perspective
-societal perspective
Prophylaxis in the Netherlands

Sweden
Since 1958
High dose
Early start

Netherlands
Since 1969
Lower dose
Started later
Dutch prophylactic regime

Tailored according to bleeding pattern:

- **Start →**
  *after first joint bleed(s)*

- **Dosing →**
  *increase in case of bleeding*

- **Stop →**
  *if dose is low and*
  *bleeds are rare*

Intensified over the last decades
Outcome parameters

Short term outcome

- annual number of joint bleeds

Long term outcome

- clinical score (Gilbert, 6 main joints, max 90)
- radiological score (Pettersson, 6 main joints, max 78)

Treatment cost

- annual clotting factor use (IU/kg/yr)
Young adults (20 yrs): changes in treatment

<table>
<thead>
<tr>
<th>Evaluation year</th>
<th>1980 (n=45)</th>
<th>1990 (n=46)</th>
<th>2000 (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start prophyl. (yrs)</td>
<td>14.7</td>
<td>8.7</td>
<td>4.4</td>
</tr>
<tr>
<td>On Home Treatment</td>
<td>53%</td>
<td>91%</td>
<td>100%</td>
</tr>
<tr>
<td>On full prophylaxis</td>
<td>64%</td>
<td>61%</td>
<td>89%*</td>
</tr>
<tr>
<td>Total use (IU/kg/yr)</td>
<td>855 (411-1121)</td>
<td>1319 (769-1667)</td>
<td>2036 (1554-2425)</td>
</tr>
</tbody>
</table>

Median values (IQR)

* 11% had stopped prophylaxis
1970-2000

Prophylaxis ↑

↓

Bleeds ↓ & Function ↑
Tailoring: Start of prophylaxis

When: early, before arthropathy (Nilsson ‘92)

\[ \Downarrow \]

Individualised (Astermark ‘99, Fischer ‘02)

How: 2-3x/wk (Nilsson ‘92, WHO ‘95, Fischer ‘02)

\[ \Downarrow \]

1x/wk (Astermark ‘99, Petrini ‘01)
Tailoring: Onset of joint bleeds

median: 1.7 yrs
range: 0.2-5.8

Van Dijk, et al. Haemophilia ’05
Tailoring: start according to bleeding pattern

- delay prophylaxis: Pettersson score at age 20: + 8% / year
- start before 3rd joint bleed

<table>
<thead>
<tr>
<th>Joint bleeds&lt; prophylaxis</th>
<th>&lt;3 (n=10)</th>
<th>3-14 (n=11)</th>
<th>≥15 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>15.8</td>
<td>17.5</td>
<td>17.2</td>
</tr>
<tr>
<td>Age start prophylaxis (yrs)</td>
<td>1.4</td>
<td>4.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Pettersson score (max 78)</td>
<td>0</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>% with Pettersson =0</td>
<td>70%</td>
<td>17%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Median values

Fischer et al, Blood 2002
Astermark (‘99): effects start & frequency

Br J Haematol 1999;105:1109-13

<table>
<thead>
<tr>
<th>Joint bleeds/jr</th>
<th>Start proph 0-2 jr</th>
<th>Start proph 3-5 jr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis 1x/wk</td>
<td>1.1 (0.3)</td>
<td>2.1 (0.4)</td>
</tr>
<tr>
<td>Prophylaxis 2-3x/wk</td>
<td>0.8 (0.2)</td>
<td>1.2 (0.4)</td>
</tr>
</tbody>
</table>
## Tailoring: frequency of infusions at start of prophylaxis

<table>
<thead>
<tr>
<th>Decade of birth</th>
<th>1970s (n=43)</th>
<th>1980s (n=44)</th>
<th>1990s (n=39)</th>
<th>2000s (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start prophylaxis (yr)</td>
<td>5.4</td>
<td>4.5</td>
<td>2.8</td>
<td>1.5*</td>
</tr>
<tr>
<td>Bleeds&lt; prophylaxis (n)</td>
<td>22</td>
<td>6.5</td>
<td>2.0</td>
<td>1*</td>
</tr>
<tr>
<td>% start prophylaxis 1x/wk</td>
<td>7%</td>
<td>5%</td>
<td>19%</td>
<td>67%*</td>
</tr>
</tbody>
</table>

Median values
* 14 patients did not start prophylaxis yet
Considered for Dutch Protocol

Start: 1x joint bleed / severe bleed

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosing Schedule 1</th>
<th>Dosing Schedule 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-12 kg</td>
<td>500 U 1x/week</td>
<td>250 U 2x/week</td>
</tr>
<tr>
<td></td>
<td>↓ 1 joint bleed</td>
<td>↓ 1 joint bleed</td>
</tr>
<tr>
<td></td>
<td>250 U 3x/week</td>
<td>500 U 3x/week</td>
</tr>
<tr>
<td>12-15 kg</td>
<td>500 U 1x/week</td>
<td>500 U 2x/week</td>
</tr>
<tr>
<td></td>
<td>↓ 1 joint bleed</td>
<td>↓ 1 joint bleed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 U 3x/week</td>
</tr>
</tbody>
</table>
Severe haemophilia (<1% F VIII/IX)
Born 2000 until 2005
79 patients, 82% haemophilia A

Started prophylaxis: 53 (66%)
Start 1x/ wk 21 (39%) 
Start 2x/ wk 26 (48%) 
Start 3x/ wk 6 (13%)
Tailoring at the start of Prophylaxis: Conclusions

• Large variability in the onset of joint bleeds

• Arthropathy is best prevented if prophylaxis is started < 3rd joint bleed

Blood 2002;99:2237-31

• Increasingly started with 1x/week 50 IU/kg (≈ 500 IU) fewer CVL?
Tailoring II: Discontinuation of prophylaxis

Should prophylaxis be continued for life?

- Young adults stop taking prophylaxis, observed in the Netherlands & Denmark (Fischer’02, van Dijk’05)

- EHTSB 2005: (19 European Centres)

± 200 pts on prophylaxis

- 31% continued
- 27% tapered
- 42% stopped
- 12% restarted
- 30% continued OD
Discontinuation of Prophylaxis: design

Observational studies

Inclusion:
- Patients with severe haemophilia
- Born between 1970 and 1980
- No inhibitors

1st study (’99):
Van Creveldkliniek + prognostic score (N=49)

2nd study (’03):
2 Danish centres & Van Creveldkliniek (N=80)
Discontinuation of prophylaxis: 1st study

49 Young adults with severe haemophilia (born ’70-’80) treated with early prophylaxis:

- 69% discontinued prophylaxis one / more times
- 22% permanently stopped prophylaxis (mean 21 yrs)

This subgroup seems to have a milder phenotype

Haemophilia 2001;7:544-50
Discontinuation of prophylaxis: prediction

**SCORE**
2x weekdose +
3x joint bleeds/yr -
3x age start proph

Cut off: 44 points
Discontinuation of prophylaxis: 2nd study
## Discontinuation II: treatment

<table>
<thead>
<tr>
<th></th>
<th>Denmark (n=22)</th>
<th>Netherlands (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation (yrs)</td>
<td>26.2</td>
<td>26.5</td>
</tr>
<tr>
<td>Age start prophylaxis (yrs)</td>
<td>5.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Clotting factor use (IU/kg/yr)</td>
<td>2940</td>
<td>1855*</td>
</tr>
<tr>
<td>% Discontinued</td>
<td>45%</td>
<td>31%</td>
</tr>
<tr>
<td>Age at discontinuation (yrs)</td>
<td>21.5</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Median values, * p-value <0.01
Discontinuation III: Outcome

Median follow up since discontinuation 3.6 yrs

<table>
<thead>
<tr>
<th></th>
<th>Continued (n=52)</th>
<th>Discontinued (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint bleeds (n/yr)</td>
<td>1.8</td>
<td>3.2*</td>
</tr>
<tr>
<td>Clinical Score (0-90)</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Pettersson score (0-78)</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Median values, * p-value 0.04
Discontinuation of prophylaxis: Conclusions 2nd study

Young adults with severe haemophilia treated with early prophylaxis:

35% permanently stopped prophylaxis (median 21.5 yrs)
Experiencing only slightly more bleeds

Van Dijk, Br J Haem, ‘05
Discontinuation of prophylaxis: Conclusions

25% - 33% of patients: milder bleeding pattern
If joints intact after early prophylaxis
↓
May be able to taper/ stop prophylaxis in adulthood
(frequency and/ or dose)

Questions: long-term consequences
patient selection (age 1st joint bleed!)

→ Prospective study?
Long term results of discontinuation

Prospective studies are difficult

Computer simulation models for:
  - evaluation of different strategies
  - including long-term outcome

Based on real data, but extrapolated
Long term results of discontinuation II

Basic data from real distributions

1. life expectancy
2. age first joint bleed
3. average nr of joint bleeds
Long term results of discontinuation III

Figure 1: Simulation process. The model determines a patient's average annual number of joint bleeds but allows the actual annual number of joint bleeds to fluctuate around this average as is depicted by the bars.

<table>
<thead>
<tr>
<th>Patient i</th>
<th>Age first bleeding</th>
<th>Annual joint bleeds</th>
<th>t in years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average number of annual joint bleeds</td>
<td></td>
</tr>
</tbody>
</table>

Life expectancy + age first joint bleed + bleeding frequency & treatment regimen

Clotting factor use

Long term outcome Pettersson score (1 point/13 joint bleeds)
Long term results of discontinuation IV

4 strategies simulated

1. On demand only
2. Prophylaxis only

3. Single switch:
   PR until 18  →  On demand

4. Multiple switch:
   PR until 18  →
   OD if ≤ 1 joint bleed/yr (2 yrs)
   → return to PR:
   if 9 joint bleeds in any yr
   7-9 bleeds in 2 conseq. yrs
   6-9 bleeds in 3 conseq. yrs
   max 4 switches
In conclusion:

TAILORING PROPHYLAXIS

- Age at start
- Frequency at start
- Dose
- Duration

Patients are all different