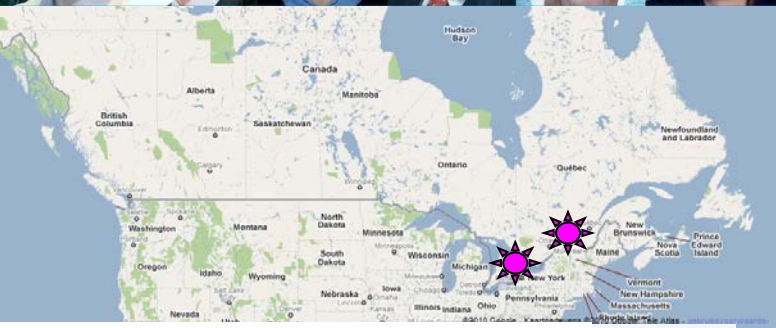
PedNet Haemophilia Registry

PedNet Registry

Workshop on registries
EMA / CHMP / BPWP

Rolf Ljung for the PedNet study group



PedNet Haemophilia Registry

PedNet Registry
31 centers
Europe, Canada and Israel

PedNet and Pednet registry

- PedNet started 1996
- PedNet Registry started 2003
- The RODIN study was the first satellite study in the PedNet Registry (+ 8 “non-PedNet” centers)
- 2010 former “ex-PedNet centers joined PedNet

Pednet registry
Inclusion criteria

- Diagnosis of haemophilia A or B, all severities;
- Factor VIII/IX activity <25% (25 IU/dL);
- Data available form the first treatment onwards;
- Born during the study period and treated from diagnosis onwards at a participating centre. (Cohort 1: 2000-2009; Cohort 2: 2010 – ongoing)

Pednet registry
Exclusion criteria

- Cases with inhibitors diagnosed at another center and referred to a PedNet treatment center
- Cases not diagnosed at a PedNet center
- Informed consent not obtained.

Collection of data

Baseline – type of haemophilia, diagnostic symptoms, mode of delivery, neonatal haemorrhage, type of mutation, baseline FVIII/FIX, etc.

50 first exposure days (ED) – detailed information on immunological “danger signals”, such as vaccinations, surgery, etc. Type of concentrate, dose, bleeds, inhibitor etc.

Follow up – quarterly and annual follow up of development of inhibitors, mode of treatment, type of concentrates, dose, frequency, joint bleeds, serious bleeds, etc.

Cohort 1 - born Jan. 1, 2000 - Dec 31, 2009 (original 22 PedNet centres)

Cohort 2 – born Jan. 1, 2010 - Dec. 31, 2019 (22 PedNet + 8 previous non-PedNet Rodin centers; 31 centres. Same slightly revised CRFs.

RODIN – first satellite study on determinants for inhibitor development in *severe hemophilia A* on Cohort 1 in PedNet + additional 8 ex-PedNet centers (born 2000-2009).

Data update
January 1st 2015

Cohort 1
Born 2000-2009

- Total 1118 PID
  - HA: 958
  - HB: 160
- 64 Excluded (6%)
- 759 (68%) reached 50 ED or CRI (=inhibitor)
- 67 (6%) are Lost to FU, of which 36 (54%) after ED 50 or CRI
- Still open for new patients born <2010

Data update
January 1st 2015

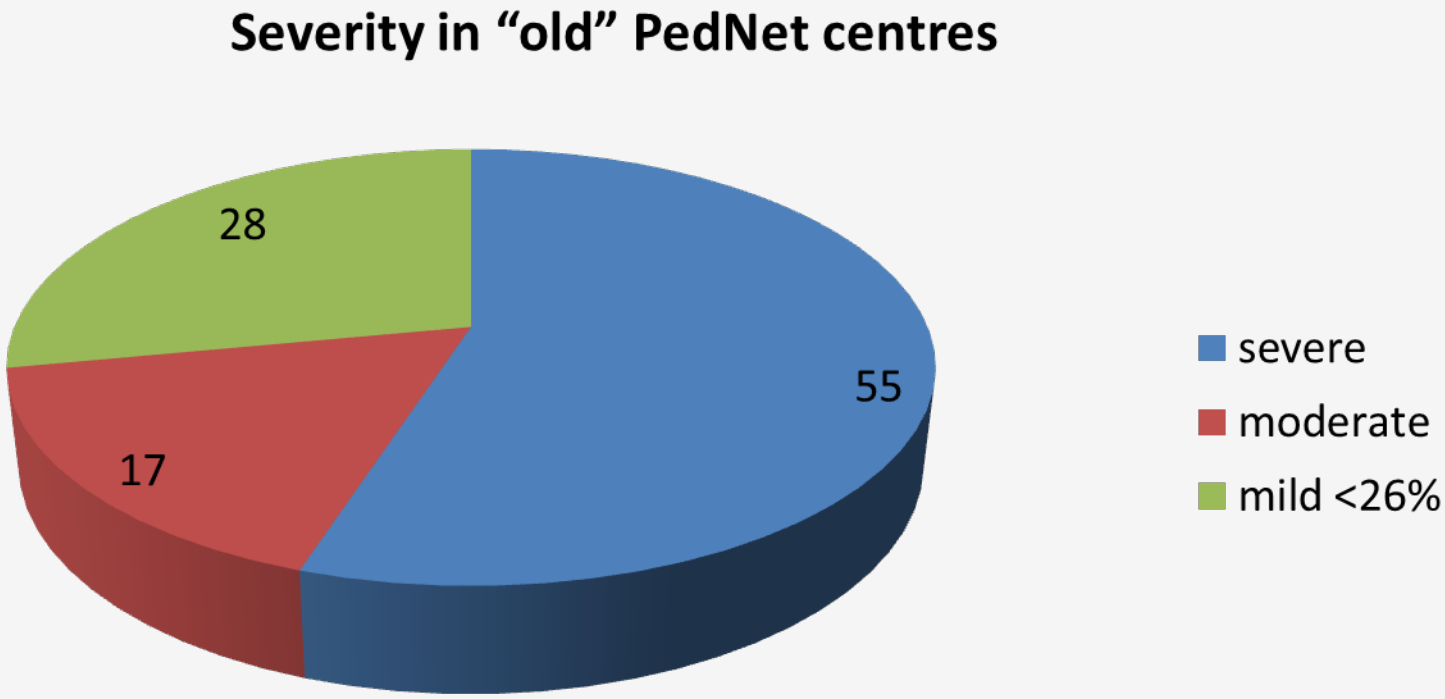
Cohort 1
Born 2000-2009

Type & Severity	N PID Included	> 50ED (%)	N Known Mutations (%)	N Lost Follow Up
Sev HA	628	594 (95%)	586 (93%)	46 (7%)/ 29*
Mod HA	118	57 (48%)	79 (67%)	5 /1*
Mild HA	212	22 (10%)	146 (69%)	4
Sev HB	80	74 (93%)	73 (91%)	9 (11%)/ 6*
Mod HB	34	11 (32%)	31 (91%)	1
Mild HB	46	1 (2%)	31 (67%)	2

*N of patients with End of FU after reaching ED 50 or CRI

Data update
January 2015

Cohort 1
Born 2000-2009



Infrastructure

- PedNet charter/regulations (steering and scientific cie)
- Registry (Web-based) is administered at Julius Center, UMC, Utrecht
- Funding from Bayer, Baxter, NovoNordisk
- Monitoring plan (Baseline 100%, follow up 10% random)
- Satellite study has to be approved by Steering Committeé after application
- All data used in a Satellite study has to be returned to the Registry

Infrastructure, cont.

- Principal Investigators: Marije van den Berg & Rolf Ljung
- Executive Director PedNet Registry: Marijke van den Berg (80% position at Julius Center, UMC, Utrecht
- Coordinator PedNet Registry: Ella Smink Hardeveld (almost 100%)
- Assistant coordinator (50%) (previously 3 Regional coordinators)
- Epidemiologist: Kathelijn Fischer (10%)
- Data manager/IT support

I. Inhibitors

- To study endogenous (genetic) and exogenous (treatment-related) determinants of inhibitor development
- To study inhibitor incidences, total high and low titre inhibitors over time.
- To define a risk profile (prediction model) for the development of inhibitors and to develop clinical strategies for patients with increased risk.
- To follow-up patients with inhibitors diagnosed in the CANAL and the RODIN study with respect to bleeding frequency, treatment, immune tolerance induction (ITI) and outcome, etc.

II. Perinatal studies

- To study the natural history and bleeding onset in neonates.
- To study the optimal mode of delivery of a child with haemophilia.

III. Studies on phenotype of haemophilia

- To study the correlation between genotype and phenotype in haemophilia.
- To compare the bleeding phenotypes of haemophilia A and haemophilia B.
- To study the short-term and long-term outcomes and to define the optimal regimen of prophylactic treatment.

Publication overview of PedNet registry 2013-2015

- Gouw SC, et al. *Factor VIII products and inhibitor development in severe haemophilia A : the RODIN study*. N Engl J Med 2013;368:231-9.

- Gouw SC, et al. *Intensity of factor VIII treatment and inhibitor development in children with severe haemophilia A: the RODIN study.* Blood 2013;121:4046-55.

- Carcao MD, van den Berg HM, Ljung R, Mancuso ME; PedNet and the Rodin Study Group. *Correlation between phenotype and genotype in a large unselected cohort of children with severe haemophilia A.* Blood 2013;121:3946-52, S1.

- Clausen N, et al. *Similar bleeding phenotype in young children with haemophilia A or B: a cohort study.* Haemophilia 2014;20:747-55.[Epub].

Publication overview of PedNet registry 2013-2015

- Fischer K, et al. *Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry.* Haemophilia 2014l;20:e280-6.

- Nijdam A, et al. *Bleeding before prophylaxis in severe hemophilia: paradigm shift over two decades.* Haematologica 2014 Dec 19 [Epub].

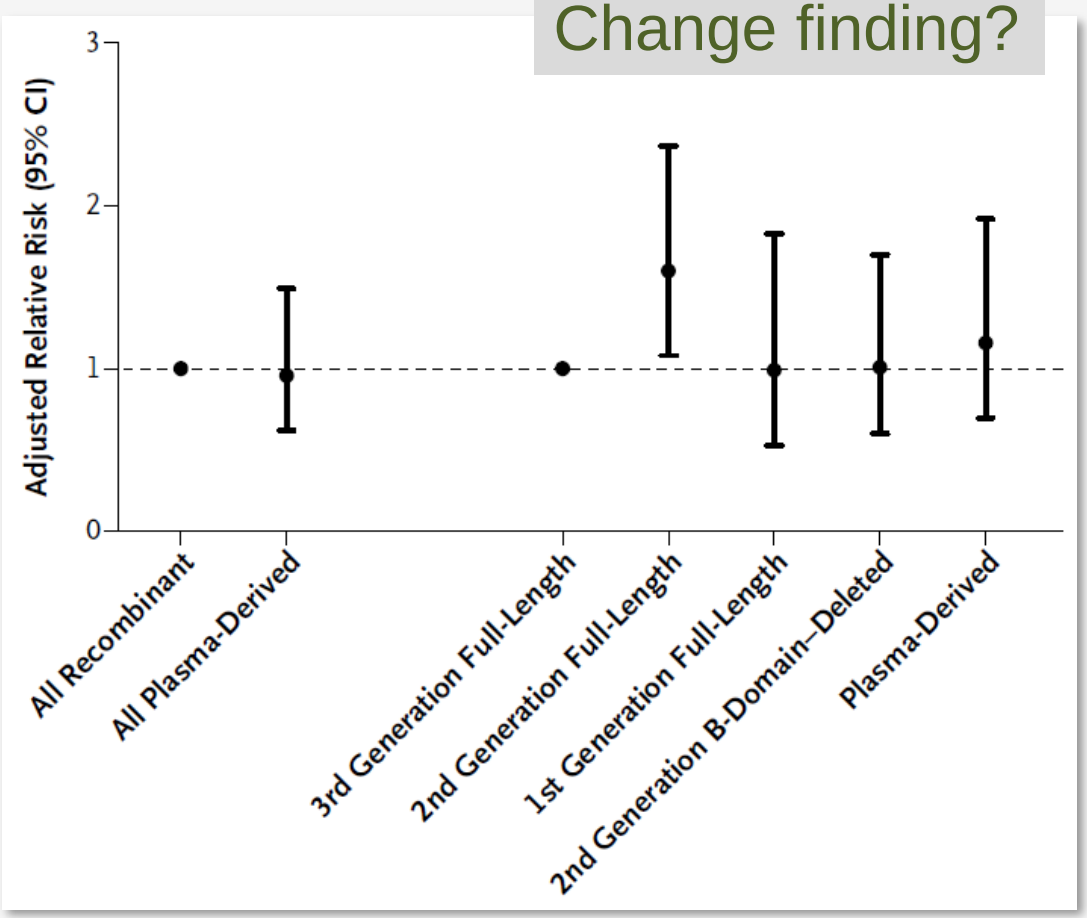
- Hashemi SM, et al *Improved prediction of inhibitor development in previously untreated patients with severe haemophilia A.* Haemophilia 2014 Dec 11 [Epub].

- Nijdam A, et al. *How to achieve full prophylaxis in young boys with severe haemophilia A: different regimens and their effect on early bleeding and venous access.* Haemophilia 2015 Jan 13 [Epub].

Difference between products?

Adjusted for
- Ethnicity
- FVIII genotype
- Family history
- Time between
- Exposure days
- Dosage
- Body weight

Change finding?

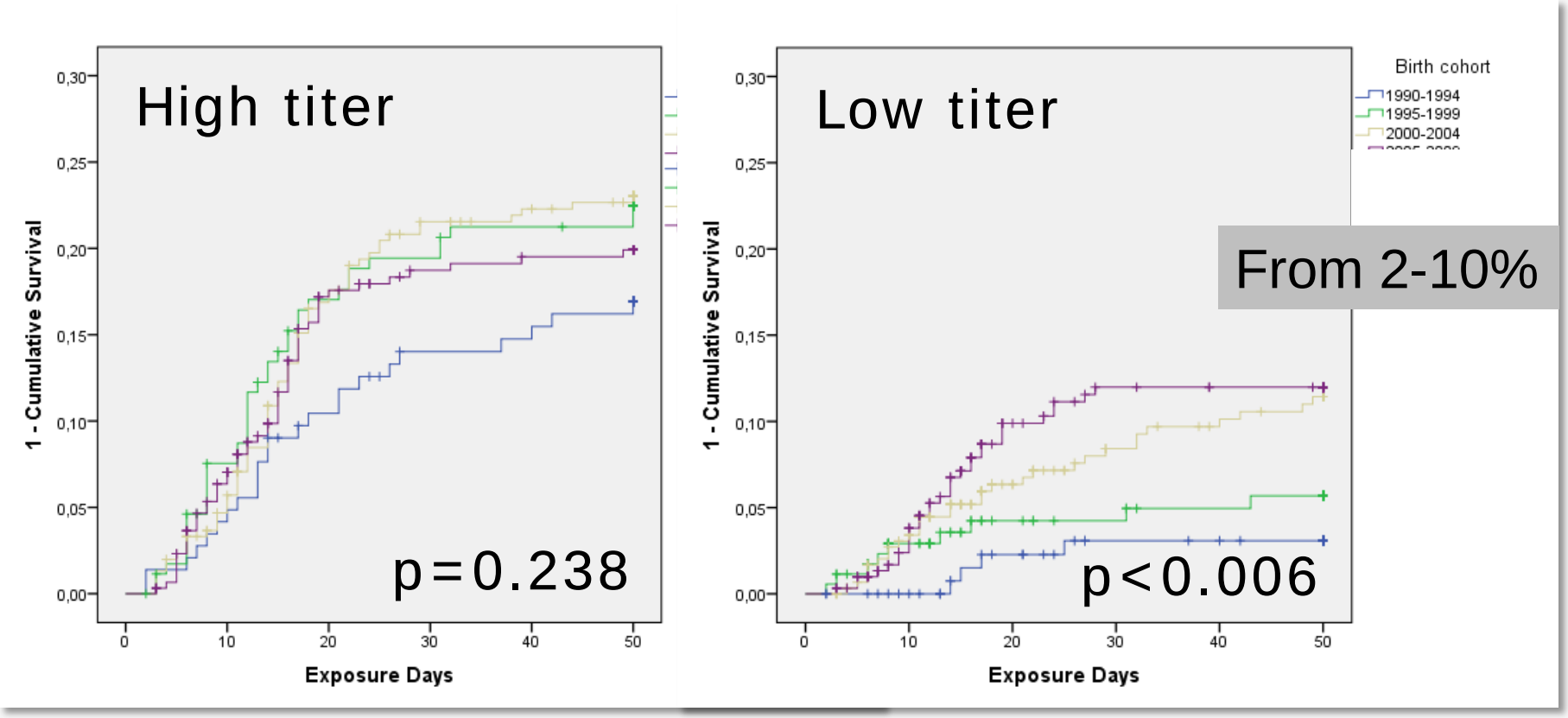


Definition of an inhibitor in both CANAL and RODIN study

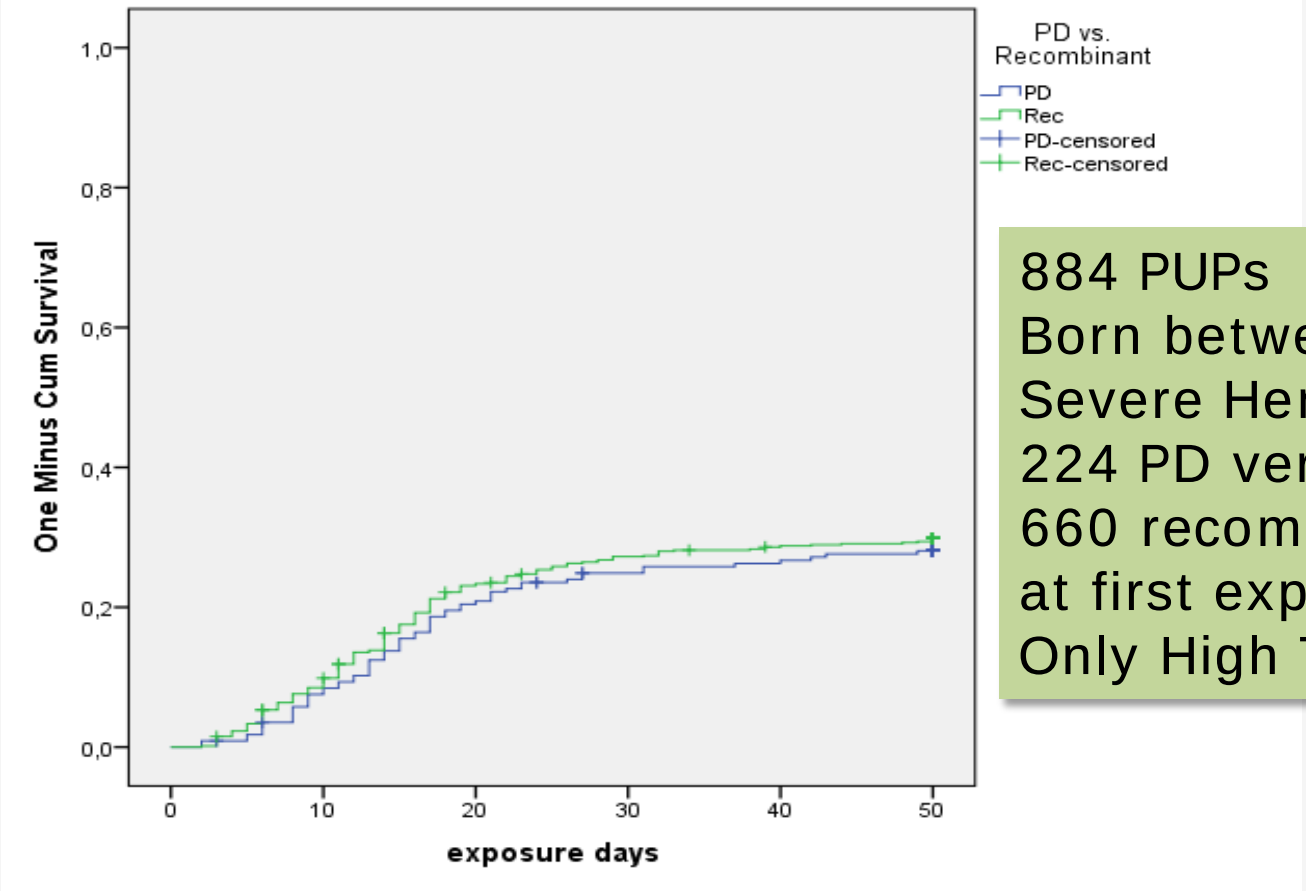
- Clinically relevant inhibitor development
  - ≥ 2 positive titers
  - In combination with decreased FVIII recovery
- High-titer inhibitor development
  - Clinically relevant inhibitor with peak titer ≥ 5 BU/ml

Gouw S.C. et al Blood 2007, Gouw S.C. et al. NEJM 2013, Gouw S.C. et al. Blood 2013
Blanchette et al. New SCC/ ISTH guidelines. JTH, 2014

Development of inhibitors in 1990-2009 N=926 PUPs



No difference in frequency of inhibitors between pd and rFVIII products



884 PUPs
Born between 1990-2009
Severe Hemophilia A
224 PD versus
660 recombinant
at first exposure
Only High Titer

Strengths of PedNet Registry

- Well-established infrastructure
- Prospective data on >95% of all patients diagnosed in 31 centers over a 15 year period … ongoing. Known denominator.
- Web based CRF forms, definitions of data collected
- Centers are monitored (“GCP-like”)
- Data on all bleeds, products, etc. up to ≥ 50 exposure days and data on gene mutations, intensive treatment, surgery

Weaknesses of PedNet Registry

- Dependent on industry funding
- Limited to PedNet centers
- No central testing of inhibitors

Questions ?

PedNet Haemophilia Registry

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