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SISET SOCIETA' ITALIANA PER LO STUDIO DELL'EMOSTASI E DELLA TROMBOSI

Il rischio di inibitore, prevenzione e trattamento nell'emofilia lieve

Giancarlo Castaman

Centro Malattie Emorragiche e della Coagulazione,
Dipartimento Oncologico
Azienda Ospedaliero-Universitaria Careggi, Firenze

Inhibitors in hemophilia

- IgG inhibiting clotting activity of FVIII/FIX
- Usually < 20 exposure days to concentrate, rare later
- ~ 30 % severe hemophilia A patients, <5% severe hemophilia B (risk of severe allergic reactions)
- Often transient, sometimes occurring during hemostatic challenges (e.g. surgery)

blood

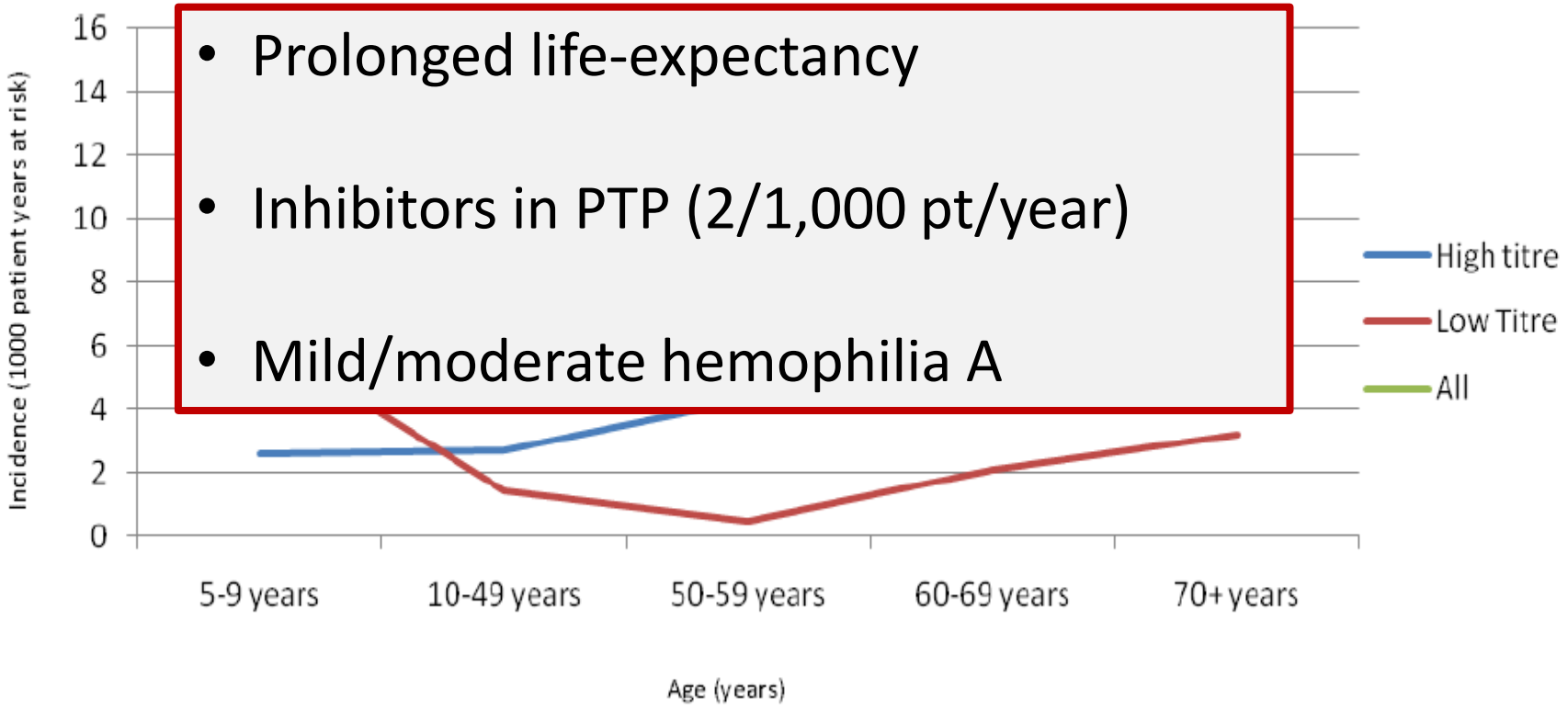
Prepublished online April 6, 2011;
doi:10.1182/blood-2010-09-308668

The incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom

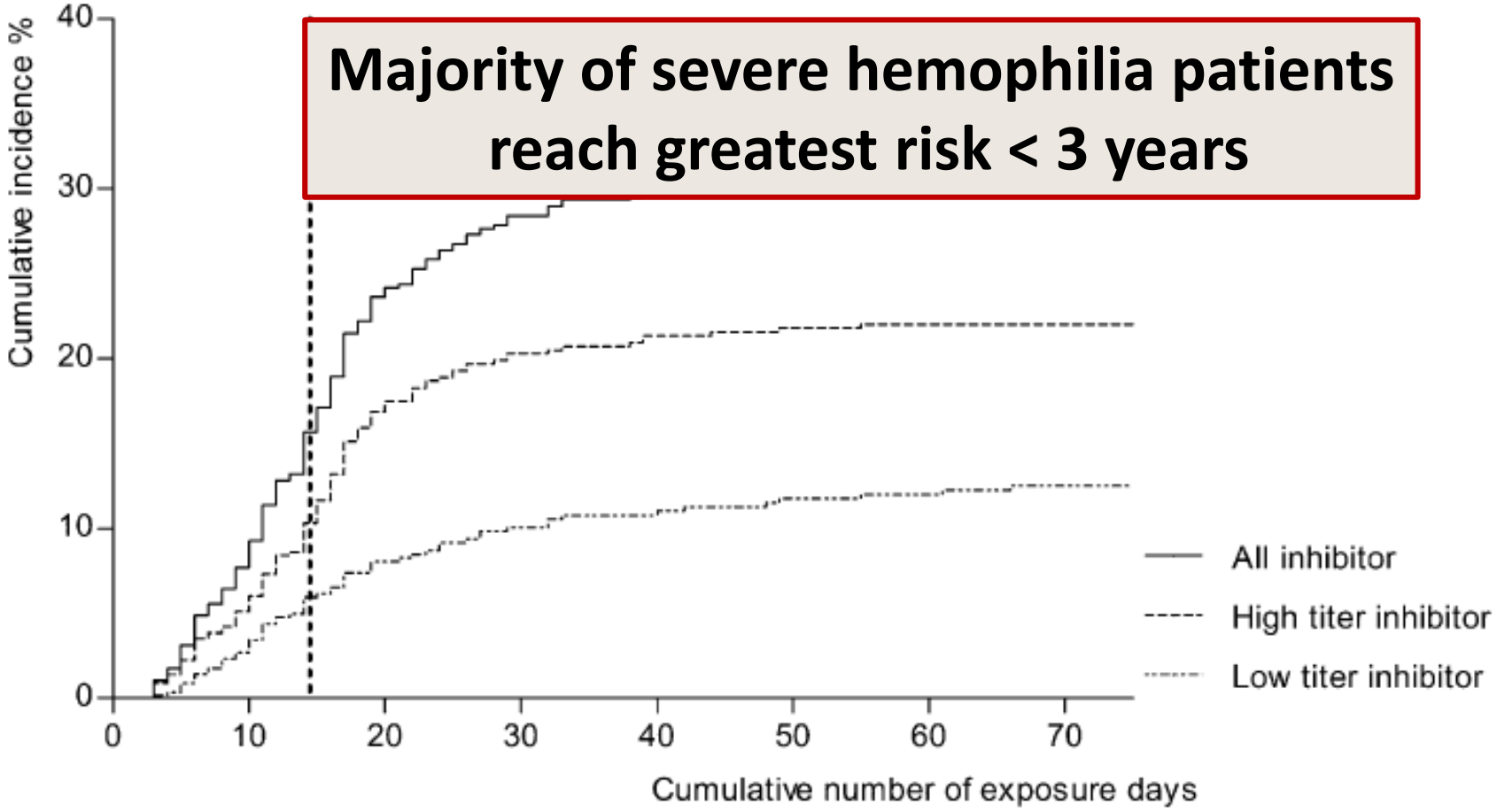
Charles RM Hay, Ben Palmer, Elizabeth Chalmers, Ri Liesner, Rhona Maclean, Savita Rangarajan, Michael Williams and Peter W Collins

Blood 2011; 117: 6367

- Prolonged life-expectancy
- Inhibitors in PTP (2/1,000 pt/year)
- Mild/moderate hemophilia A

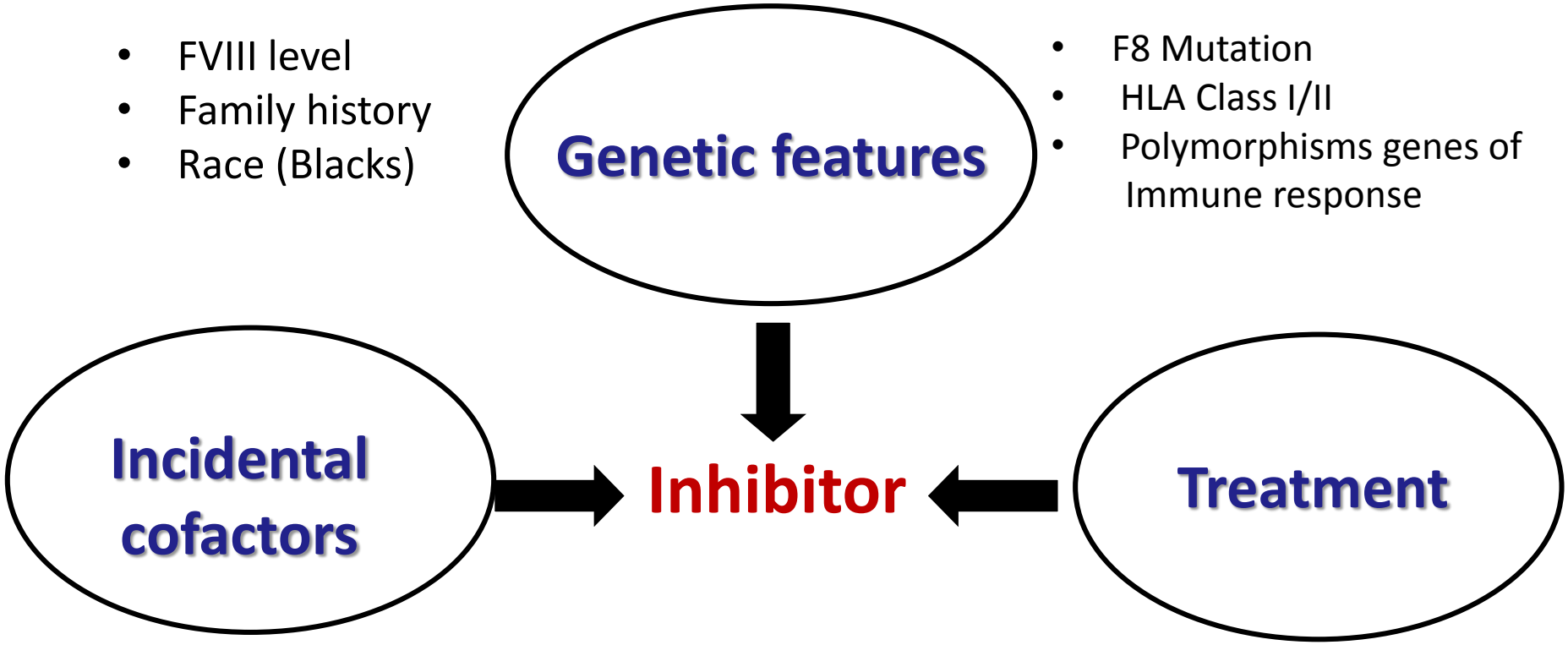


Inhibitor incidence in severe patients

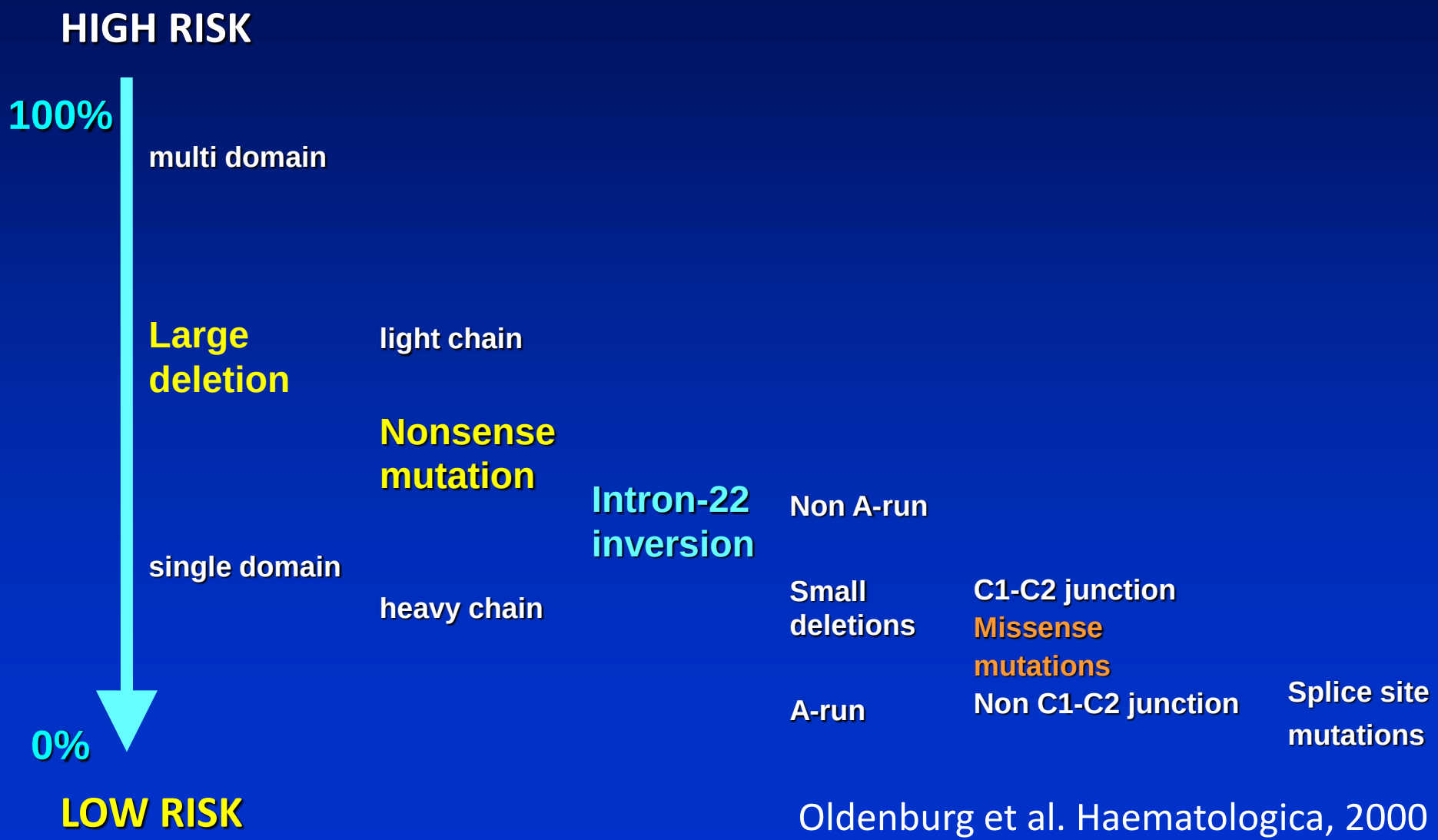


Gouw SC *et al*. Blood 2013;121:4046–55

Risk factors for inhibitor development



Inhibitor risk in PUPs e Type of F8 mutation



Oldenburg et al. Haematologica, 2000

Inhibitors in Mild Hemophilia A

- The cumulative incidence of inhibitor development is historically reported to be 3-13% in patients with MHA (Wight, 2003)

- Some adult patients with MHA may still have had less than 50 EDs to therapeutic factor VIII and be at risk of developing inhibitors in contrast to patients with severe hemophilia who generally reach 50 ED within the first years of life.

INSIGHT study

(**IN**ternational **S**tudy on etiology of inhibitors in moderate/mild hemophilia A: influences of **I**mmuno Genetic & **H**emophilia **T**reatment factors)

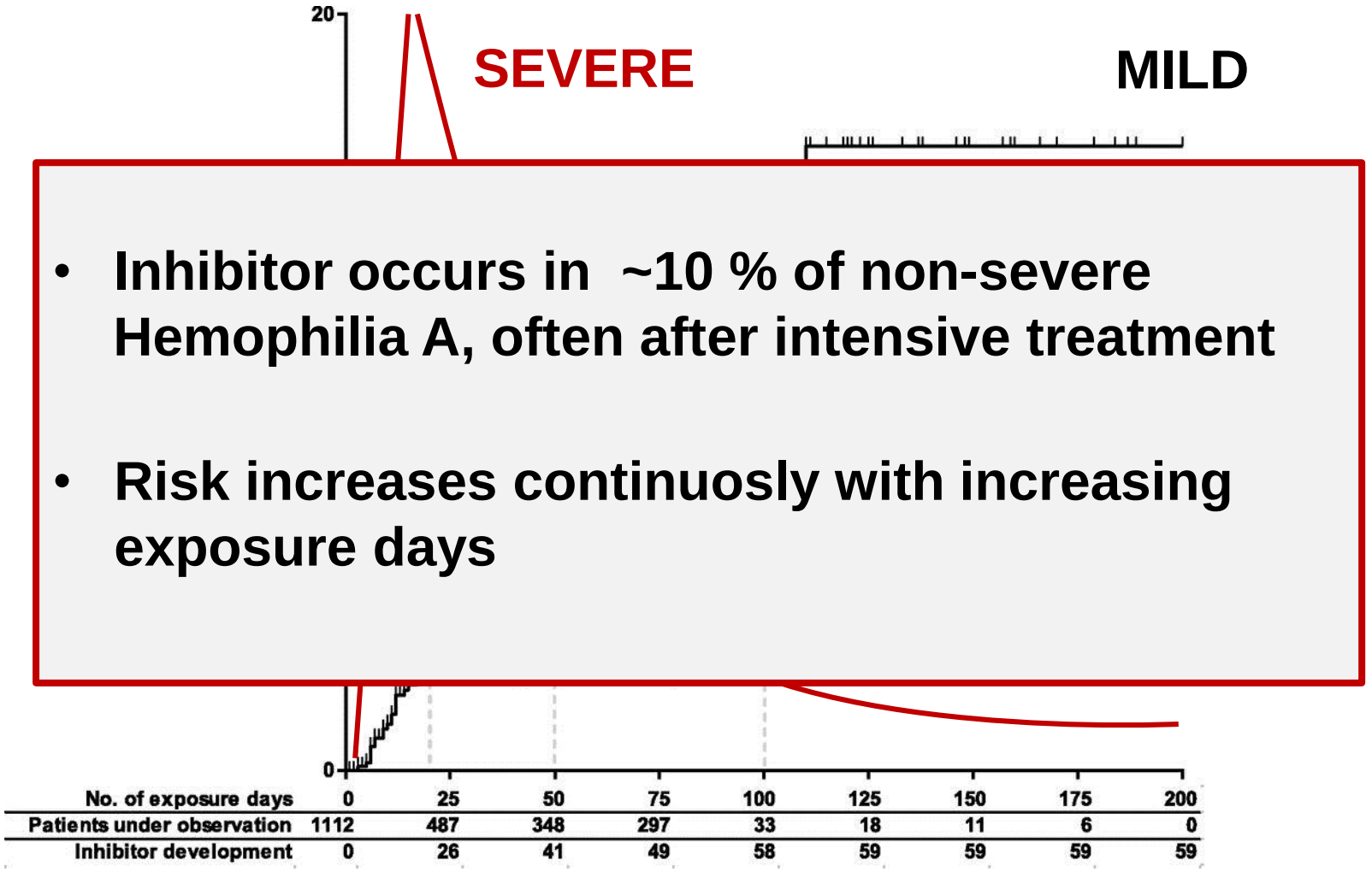
- Observational study (2,711 moderate and MHA patients (FVIII 0.02-0.40 IU/mL) from 34 Hemophilia Treatment Centers in Europe and Australia who received at least one exposure to factor VIII concentrate between 1980 and 2011

- The risk of inhibitor development was calculated adjusting for the number of ED

- **6.7%** (95%CI, 4.5-8.9) at 50 ED

  13.3% (95%CI, 9.6-17.0) at 100 ED, with greater risk for particular genotypes

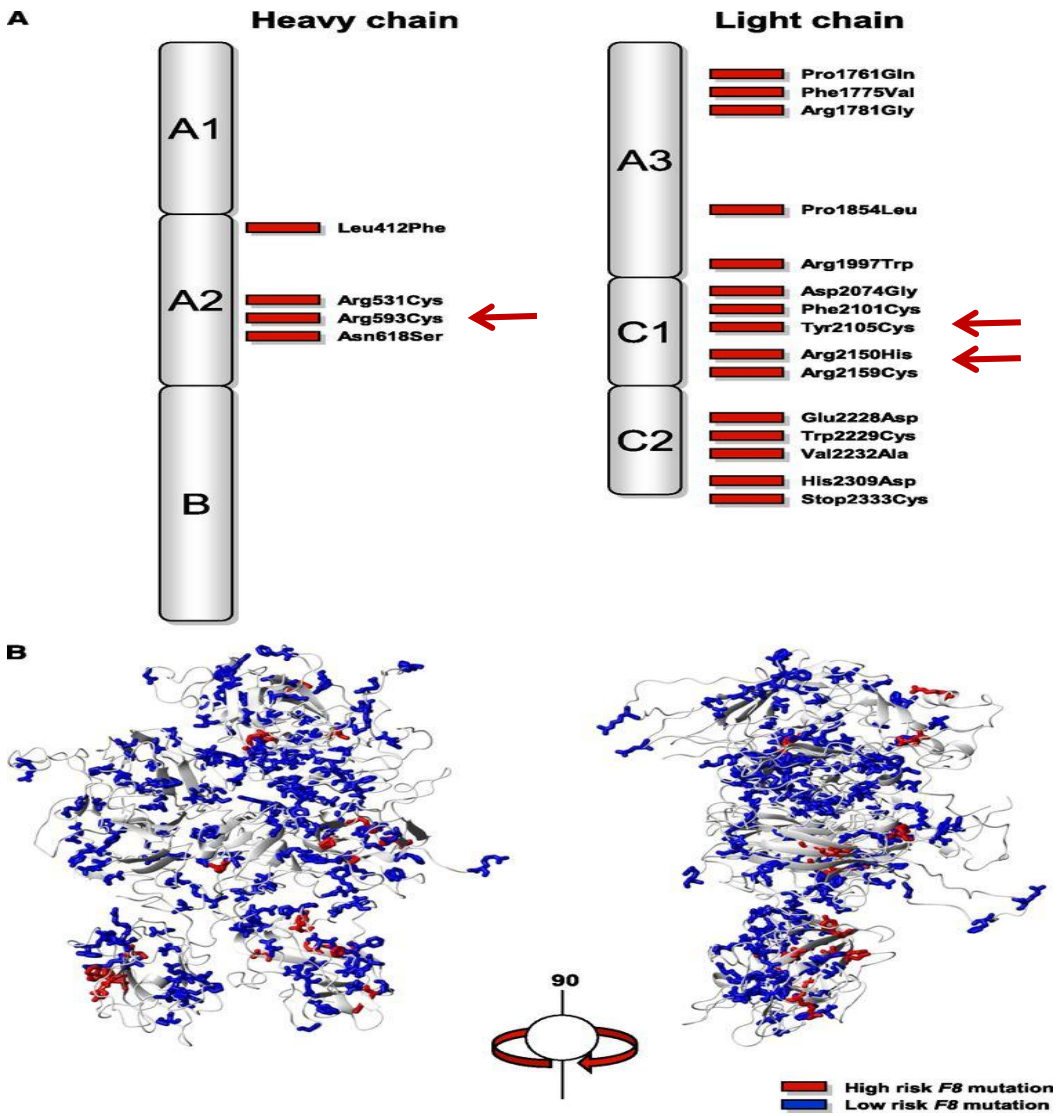
Cumulative inhibitor incidence in 1,112 nonsevere hemophilia A patients, according to cumulative exposure days to factor VIII concentrates



- **Inhibitor occurs in ~10 % of non-severe Hemophilia A, often after intensive treatment**
- **Risk increases continuosly with increasing exposure days**

Eckhardt C L et al. Blood 2013

Distribution of F8 missense mutations associated with inhibitor development



Eckhardt C L et al. Blood 2013

GENETIC RISK FACTORS FOR INHIBITOR DEVELOPMENT (I)

- In patients with MHA type of F8 mutation is an important risk factor for inhibitor development

- Nineteen F8 missense mutations were associated with inhibitor development among a total of 214 F8 missense mutations

- Patients with MHA carrying one of these 19 mutations had inhibitor risks comparable to patients with severe hemophilia A

F8 genotype and adjusted inhibitor risk

***F8* mutation**	**Patients** *n*	**Inhibitor** *n (%)*	**Inhibitor risk at 20 ED** *% (95%CI)*	**Inhibitor risk at 50 ED** *% (95%CI)*
Mutations in >10 patients				
R531C	35	1 (2.9)	.0	.0
N618S	58	1 (1.7)	3 (0-9)	3 (0-9)
R2150H	57	9 (15.8)	2 (0-7)	12 (1-24)
R593C	104	12 (11.5)	9 (2-17)	19 (7-30)
D2074G	11	3 (27.3)	21 (0-47)	21 (0-47)
R2159C	21	3 (14.3)	9 (0-26)	39 (3-75)
W2229C	10	5 (50.0)	42 (5-78)	42 (5-78)

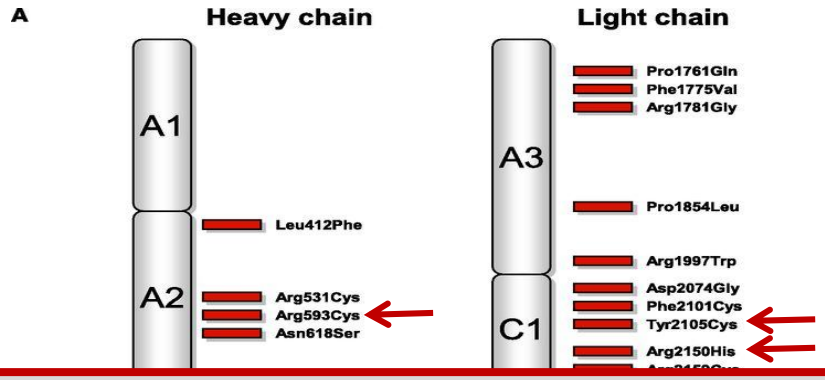
GENETIC RISK FACTORS FOR INHIBITOR DEVELOPMENT (III)

- For some mutations (**p.Arg2169, p.Arg2178 and p.Ala2220**), antibodies elicited by treatment with exogenous FVIII concentrate can discriminate the therapeutic wild type FVIII and the patient's endogenous FVIII , reflecting the specificity of the T-cell epitope (Jacquemin, 2003; James, 2007)

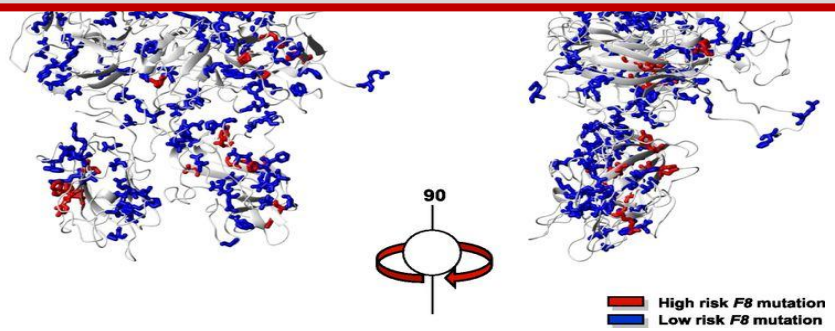
- The risk of inhibitor formation associated with FVIII missense mutations is significantly higher when amino acid substitution belongs to another physicochemical class than the original residue (Schwaab, 2013)

- However, the association between an intronic mutation (IVS10-18 G>A) and inhibitor occurrence after intensive replacement treatment and more than 90 ED again suggests that the pathogenesis may be heterogeneous (Santoro, 2013)

Distribution of F8 missense mutations associated with inhibitor development



- **Genotyping advised at diagnosis also in mild hemophilia A**
- **Use desmopressin**



Eckhardt, Blood 2013; Castaman, Blood 2014

Mutations with increased risk of inhibitor and response to desmopressin

Amino acid substitution (previous nomenclature)	Domain	Cases/tested reported with FVIII level ≥30 U/dL after desmopressin, n (%)	Cases/tested reported with FVIII level ≥50 U/dL after desmopressin, n (%)
IVS10-18 G>A*	A2	0/3 (0%)	0/3 (0%)
p.Arg550Cys (Arg531Cys)	A2	5/5 (100%)	2/5 (40%)
p.Arg612Cys (Arg593Cys)	A2	26/27 (96%)	15/27 (56%)
p.Asn637Ser (Asn618Ser)	A2	10/10 (100%)	10/10 (100%)
p.Pro1873Leu (Pro1854Leu)	A3	3/3 (100%)	2/3 (66%)
p.Tyr2124Cys (Tyr2105Cys)†	C1	4/4 (100%)	4/4 (100%)
p.Arg2169His (Arg2150His)‡	C1	11/11 (100%)	7/11 (64%)
p.Arg2178Cys (Arg2159Cys)	C1	9/9 (100%)	9/9 (100%)

Castaman, Blood 2014

MORBIDITY AND MORTALITY (I)

- The inhibitor frequently cross-reacts with the patient's endogenous FVIII, reducing the endogenous FVIII plasma levels below 0.01 IU/mL

- Consequently, most of these patients suffer from severe spontaneous bleeding

- In a large national UK study (1977-99), inhibitor development in patients with MHA was associated with a more than two fold increase of the all-cause death-rate (Darby et al, 2004)

MORBIDITY AND MORTALITY (II)

- In the INSIGHT study (1980-2011), including 2,709 patients with MHA (107 with inhibitors) the all-cause mortality rate in inhibitor patients was more than five times increased compared to those without inhibitors (age-adjusted mortality rate ratio, 5.6) (Eckhardt et al, 2016)

- In 70% of the patients with MHA in whom the inhibitor was present at time of death, severe bleeding complications were the cause of death

TREATMENT OF BLEEDING IN INHIBITOR PATIENTS (I)

- Two-thirds of MHA patients with inhibitors needed treatment for bleeding episodes. (van Velzen et al, 2016)

- Their annual bleeding rate was 1.1 (IQR, 0.1 -2.5), 10 times increased as compared to the period before the inhibitor developed

- In 40% of the MHA patients with clinically relevant inhibitors the bleeding phenotype resembled the phenotype of acquired hemophilia, with soft tissue bleeds, mucosal bleeds, hematuria and melena

TREATMENT OF BLEEDING IN INHIBITOR PATIENTS (II)

- Patients with high titer inhibitors, endogenous FVIII:C levels below ≤1 U/dL, or those who received eradication therapy required treatment with bypassing agents

- Importantly, there is a great inter-individual variation in response to the different therapies , in which several patient-related factors (e.g. inhibitor titre, FVIII level, bleeding phenotype) seem to play a central role

Treatment according to inhibitor titer

Low Titer
< 5 BU/mL

- Factor VIII
- APCC
- FVIIa
- Desmopressin

High titer
> 5 BU/mL

- APCC
- FVIIa
- Immunoadsorption for untractable bleeding ?

Future: rFVIII porcine, ACE910 ?

Inhibitor Eradication (I)

- There are very limited and contradicting data on the optimal therapeutic approach to eradicate inhibitors in patients with MHA

- A better effect of rituximab than ITI on inhibitor eradication in a small selected group of patients has been reported (n= 32) with MHA (Kempton, 2012)

- An interesting finding in an observational study among 101 patients with MHA and inhibitors from the INSIGHT cohort was the spontaneous disappearance of inhibitors in the majority of the patients (Van Velzen, 2016)

Inhibitor Eradication (II)

- Only 28% of the 101 MHA inhibitor patients from the INSIGHT study received eradication therapy, with widely varying treatment protocols including immune tolerance induction, immune suppressive therapy or a combination of both.

- The outcome of both strategies (eradication or ’’wait-and-see”) was comparable: the inhibitor disappeared in 75% of the patients of the eradication group and 70% of the patient in the ’’wait-and-see” group.

- To evaluate sustained success in inhibitor eradication only 52 patients, who were rechallenged with factor VIII concentrates after inhibitor disappearance, could be analyzed.

- In 36 (69%) of them sustained success could be demonstrated, they remained inhibitor free.

Practical recommendations for Mild Hemophilia A

1. Patients with suspected MHA should be referred to a specialized hemophilia treatment center;
2. Perform genetic testing to identify patients with mutations potentially at risk for inhibitor;
3. Perform a desmopressin challenge in all patients unless a contraindication exists;
4. Use desmopressin where possible, and use caution with high-dose/prolonged courses of FVIII replacement therapy, especially in patients with mutations associated with inhibitor development;
5. Test for inhibitor after 4-6 wk from intensive treatment with FVIII concentrates, before surgery, or at least every 6 or 12 mo if sporadically treated with FVIII concentrates;
6. Record accurately the progressive number of ED to anticipate the onset of inhibitor, especially in patients with high-risk mutations.

Castaman, Blood 2014

Conclusions

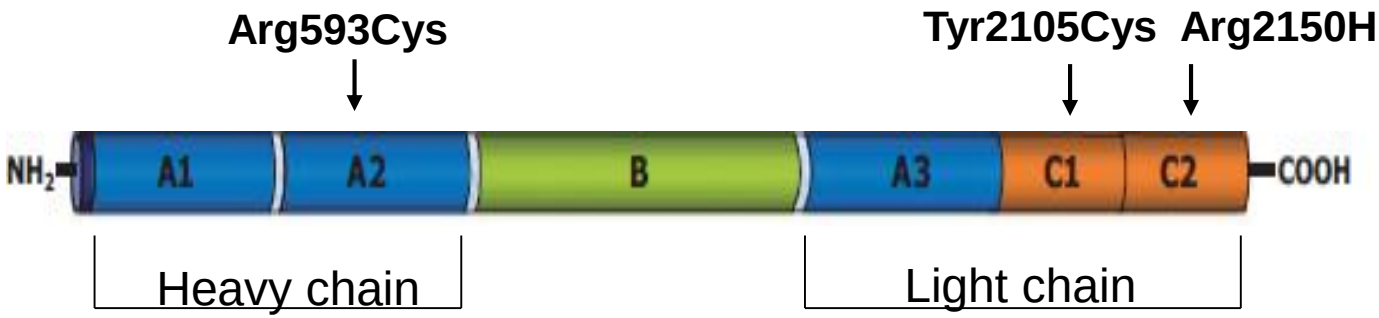
- Inhibitor risk in MHA is greater than previously believed

- The risk may be lessened by:

  - Knowing the mutation
  - Desmopressin use
  - Judicious use of replacement therapy

- Rechallenging with FVIII should be tried when treatment has not been used for years in a currently inhibitor negative patient

GENETIC RISK FACTORS FOR INHIBITOR DEVELOPMENT (II)



- p.Arg612Cys (Arg593Cys) in A2 domain, p.Tyr2124Cys (Tyr2105Cys), p.Arg2169His (Arg2150His) represent the most frequent mutations associated with this risk, with an inhibitor risk after 20 ED from 0 to 9.1% of patients

- Some rarer mutations (p.Asp2093Gly [Asp2074Gly] and p.Trp2248Cys [Trp2229Cys]) are particularly important since the risk of inhibitor at 20 ED (21.2 and 41.7%, respectively) parallels that of severe patients

Eckhardt, Blood 2013