By passing therapy in patients with inhibitors. Success and failure: what else is necessary?

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Patients with inhibitors: several clinical unmet needs

- ✓ A significant difference in bleeding frequency between inhibitor and non-inhibitor patients has not been demonstrated so far but the management of bleeding episodes in the presence of **high-titer inhibitors** is more problematic
- ✓ Inhibitor patients develop chronic and progressive arthropathy earlier and more frequently than non-inhibitor peers
- ✓ Prophylaxis as intended for non-inhibitor patients is not possible

	Pts with INH (n=38) ***Mean age 26 yrs***	*Pts without INH* (n=49) ***Mean age 25 yrs***	P value
Clinical examination			
Major joints	14.6 (± 12.2)	5.27 (± 6.2)	<0.05
All joints	15.4 (± 13.6)	5.46 (± 7.1)	<0.05
Radiological evaluation			
Major joints	22.9 (± 14.3)	8.0 (± 10.2)	<0.05

Morfini et al. Haemophilia 2007;13:606-12

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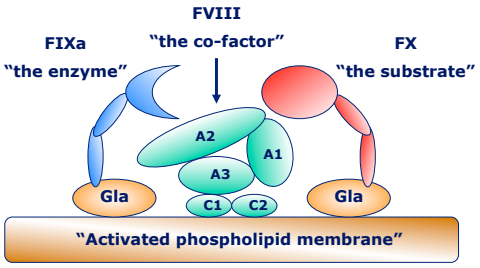
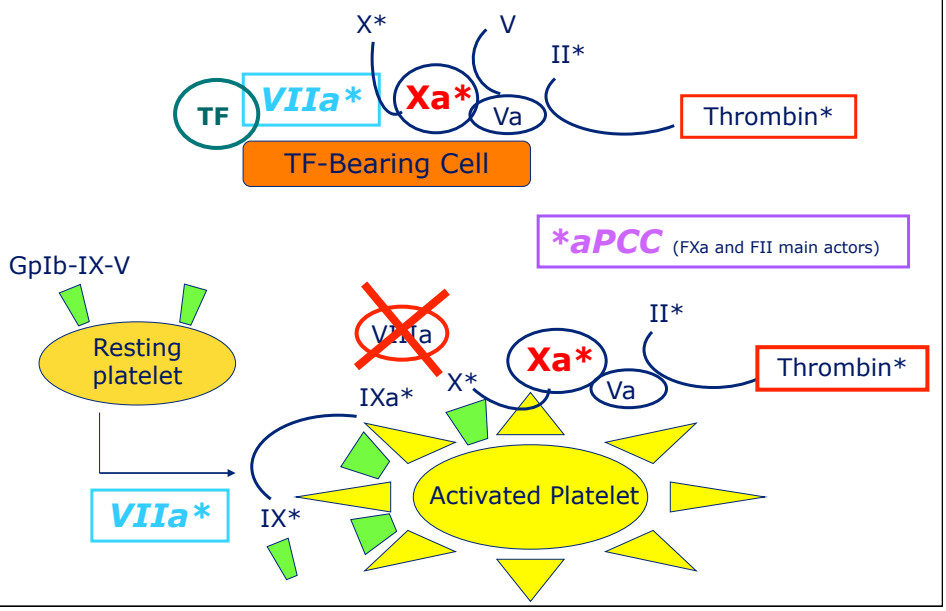
Why by-passing therapy in patients with inhibitors?

- Products that promote fibrin clot formation without the need for tenase complex



- The current choices include activated recombinant FVII (rFVIIa) and activated prothrombin complex concentrate (aPCC)

By-passing therapy: mechanisms of action



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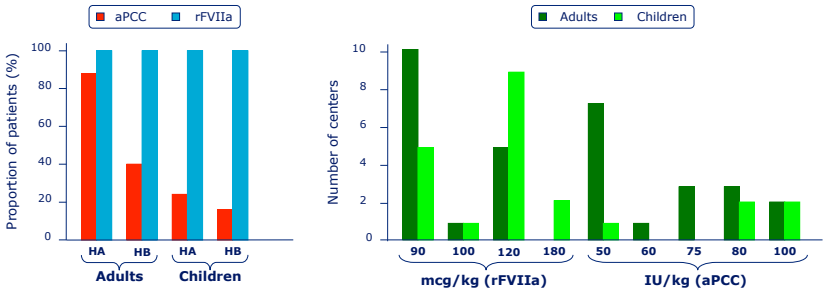
By-passing therapy: characteristics

rFVIIa	aPCC
✓ First used in 1988	✓ First experiences in 1974
✓ Recombinant DNA technology	✓ Plasma-derived
✓ Small volume	✓ Big volume
✓ Absence of anamnestic response	✓ Contains "some" FVIII
✓ Hemophilia B with allergic reactions	✓ Contains FIX
✓ Safe association with antifibrinolytics	✓ Possible association with antifibrinolytics
✓ Home therapy	✓ Home therapy
✓ Surgery	✓ Surgery
✓ Wide dosing range (90-270 mcg/kg)	✓ Maximum dose/injection (100 IU/kg)
	✓ Maximum daily dose (200 IU/kg)
✓ Short half-life	✓ Contains factors with longer half-life
✓ Used every 2-3 hours in the acute phase	✓ Used every 6-12 hours in the acute phase

By-passing therapy: how to choose?

- ✓ Previous exposure to blood components or plasma-derived products
- ✓ Site and severity of bleed
- ✓ Time elapsed between bleeding onset and therapy start
- ✓ Possible anamnestic response prior to ITI start
- ✓ Personal history of responsiveness to either products
- ✓ Venous access
- ✓ Availability and costs



Astermark et al. Haemophilia 2007;13:38-45

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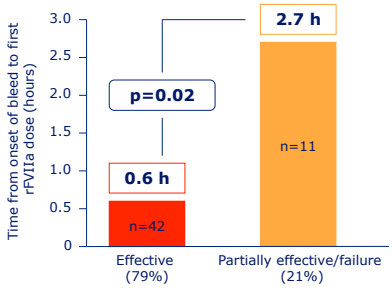
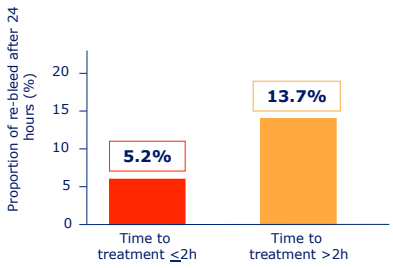
By-passing therapy for acute bleeds: efficacy

- ✓ Great inter- and intra-patient variability of treatment efficacy
- ✓ aPCC: success rates of **64-88%** with 1-3 doses (joint or muscle bleeds)
- ✓ rFVIIa: success rates of **74-92%** with 3*90 mcg/kg (mild/moderate joint bleeds; home)
- ✓ Efficacy and risk of re-bleeding is greatly dependent on the rapidity of treatment onset

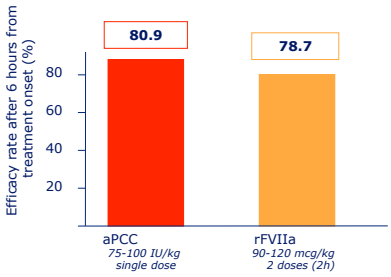


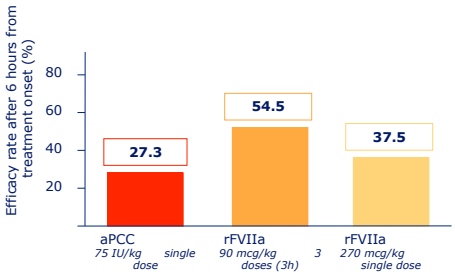


Lusher et al. Blood 1983;62:1135-8
Sjamsoedin et al. NEJM 1981;305:717-21
Key et al. TH 1998;80:912-8
Santagostino et al BJH 1999;104:21-6
Lloyd Jones et al. Haemophilia 2003;9:464-520
Santagostino et al. JTH 2006;4:367-71
Kavakli et al. TH 2006;95:600-5
Young et al. Haemophilia 2008;14:287-94
Salaj et al. Haemophilia 2009;15:752-9

Efficacy evaluation: a big challenge

- ✓ Tested in small controlled clinical trials
- ✓ Efficacy assessment is patient-reported
- ✓ Larger series derived from registries (non homogeneous patient populations)
- ✓ Lack of a validated laboratory marker useful to predict and monitor the clinical response
- ✓ Head-to-head comparisons:
  - a randomized non-blinded cross-over trial (n=48)
  - a 3-way randomized cross-over double-blind comparison of high-, standard dose of rFVIIa and aPCC (n=27)





Astermark et al. Blood 2007;109:546–51
Young et al. Haemophilia 2008;14:287–94

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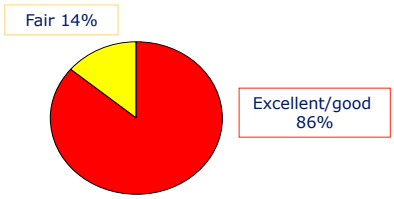
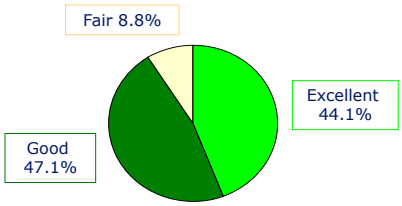
By-passing therapy in the surgical setting

✓ Both aPCC and rFVIIa have been successfully used to cover major and minor orthopedic and non-orthopedic surgical procedures in inhibitor patients



Hemostatic efficacy in 50 orthopedic procedures [46 major] and 151 non-orthopedic procedures covered with **rFVIIa**



Hemostatic efficacy in 34 surgical procedures [13 major] covered with **aPCC**

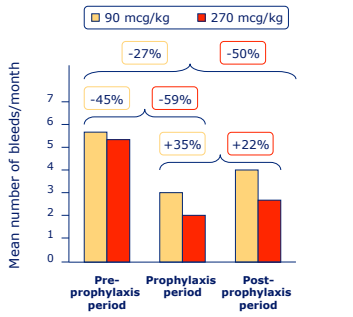
✓ Different dosing regimens have been used for either drugs

✓ rFVIIa continuous infusion has been used with controversial results

Nègrier et al. Haemophilia 2013;19:e143–50
Santagostino et al. Blood Reviews 2015;29(S1):S9–18

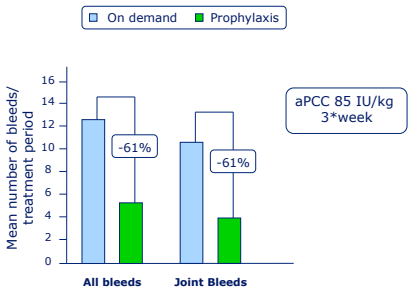
By-passing therapy and prophylaxis

✓ Both aPCC and rFVIIa have been used to prevent bleeding episodes and reduce bleeding frequency with good results although not comparable to standard prophylaxis in non-inhibitor patients



22 patients; 16 yrs (5-56); 3 months of treatment

Randomized, double-blind, parallel group



26 patients; 29 yrs (3-63); 6 months of treatment

Randomized, open-label, cross-over

✓ In the PRO-PACT study a 50% reduction in bleeding frequency was observed

Konkle et al. JTH 2007;5:1904–13 Leissinger et al. NEJM 2011;365:1684–92 Young et al. Thromb Res 2012;130:864-70

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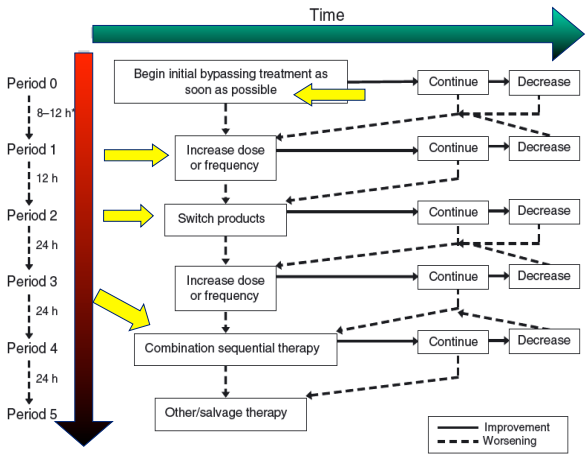
Unresponsiveness to by-passing therapy

✓ The subjective (patient/caregiver) and objective (physician) assessment of pain (joint bleeds), swelling/tension (muscle bleeds) and mobility after 24 hours from treatment onset has been proposed

✓ No universal objective, measurable criteria



Teitel et al. Haemophilia 2007;13:256-63

By-passing therapy: safety

✓ ***Thrombotic adverse events*** have been reported with either drugs but are rare in congenital hemophilia

Source	# of TE	Period	Type
• Baxter's pharmacovigilance[1]	16/55 AEs	10 years	MI, DIC, PE/DVT
• Retrospective postlicensure survey of FEIBA	0/63 pts	6 years	-
• FDA MedWatch pharmacovigilance[2]	83	3 years	CVE, MI, DIC, PE
• FDA's AE reporting system – rFVIIa[3]	246	7 years	arterial & venous
• Novo Nordisk safety database – PMS[4]	195	18 years	arterial & venous

[1] 3 AHA; 8 overdoses; 4.05 events/10^5 infusions
[2] 67 with rFVIIa: 3 AHA, 2 congenital; 16 with aPCC: 3 AHA, 4 congenital
[3] 81% related to unlabeled use; only 24 events in congenital (70% venous)
[4] 84 in congenital hemophilia, 44% venous TE, 60% recovered

✓ Trasmission of blood-borne infections has not been reported with aPCC (vapour heating)

✓ aPCC may carry the risk of anamnestic response that does not affect the efficacy of aPCC

Ehrlich et al. Haemophilia 2002;8:83-90 *Aledort. JTH 2004;2:1700-8*
DiMichele et al. Haemophilia 2006;12:352-62 *O'Connell et al. JAMA 2006;295:293-8* *Neufeld et al. Blood Rev 2015;29(S1):S34-41*

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By-passing therapy: costs

- ✓ Both aPCC and rFVIIa are costly drugs
- ✓ Patients usually require prolonged treatment
- ✓ Hospitalizations are more frequent for inhibitor than non-inhibitor patients

Resource	Cost per pt-month, €
rFVIIa	8491.9
aPCC	2982.0
Visits, surgeries, hospitalizations	209.9
FVIII concentrates	6251.3

64%

Total: 17,935 € per pt-month

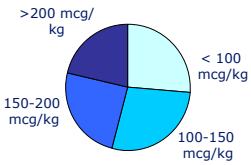
- ✓ The vast majority of comparative economic analyses of aPCC vs rFVIIa are based on decision models
- ✓ Cost-utility analysis vs cost-effectiveness models
- ✓ Efficacy assumptions, dosing assumptions and cost per unit

Gringeri et al. Blood 2003;102:2358-63

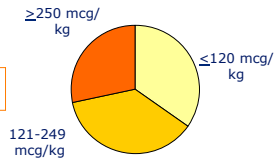
By-passing therapy: ongoing issues

- ✓ ***Optimal dosing***

HTRS registry – median total dose/ bleed

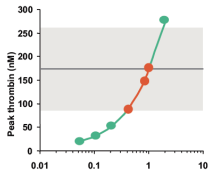


ONE registry – median initial dose

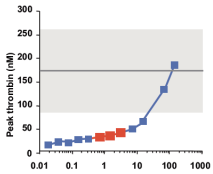


- ✓ ***Laboratory monitoring***

aPCC U/ml



rFVIIa mcg/ml



Parameswaran et al. Haemophilia 2005;11:100-6
Chambost et al. Haemophilia 2013;19:571-7

Turecek et al. Pathophysiol Haemost Thromb 2003;33:16-22

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Concluding remarks

- ✓ aPCC and rFVIIa are equally effective for the treatment of acute bleeds
- ✓ Both have been successfully used in the surgical setting
- ✓ The risk of thrombotic AEs is similar and quite low in congenital hemophilia
- ✓ BUT still their use needs to be optimized/investigated:

- Prophylaxis  primary in children with pristine joints, larger cohorts
- Understanding the reasons for varied hemostatic responses
- The role for sequential therapy
- Cost-utility analyses considering immune tolerance induction

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