3° CONGRESSO INTERREGIONALE

Aggiornamenti nell'ambito delle malattie emorragiche congenite ed acquisite

Catania, 20-21 Maggio 2017

Nuovi approcci terapeutici in emofilia

Renato Marino

Centro Emofilia e Trombosi
Bari

La terapia dell'emofilia ieri e oggi

Nuovi farmaci

Terapia genica

FVII attivato ricombinante

Prodotti ricombinanti

Concentrati plasmatici ad elevata purezza

Concentrati plasmatici ad intermedia purezza

Crioprecipitati

Plasma fresco

Sangue intero

Nuovi approcci terapeutici in emofilia

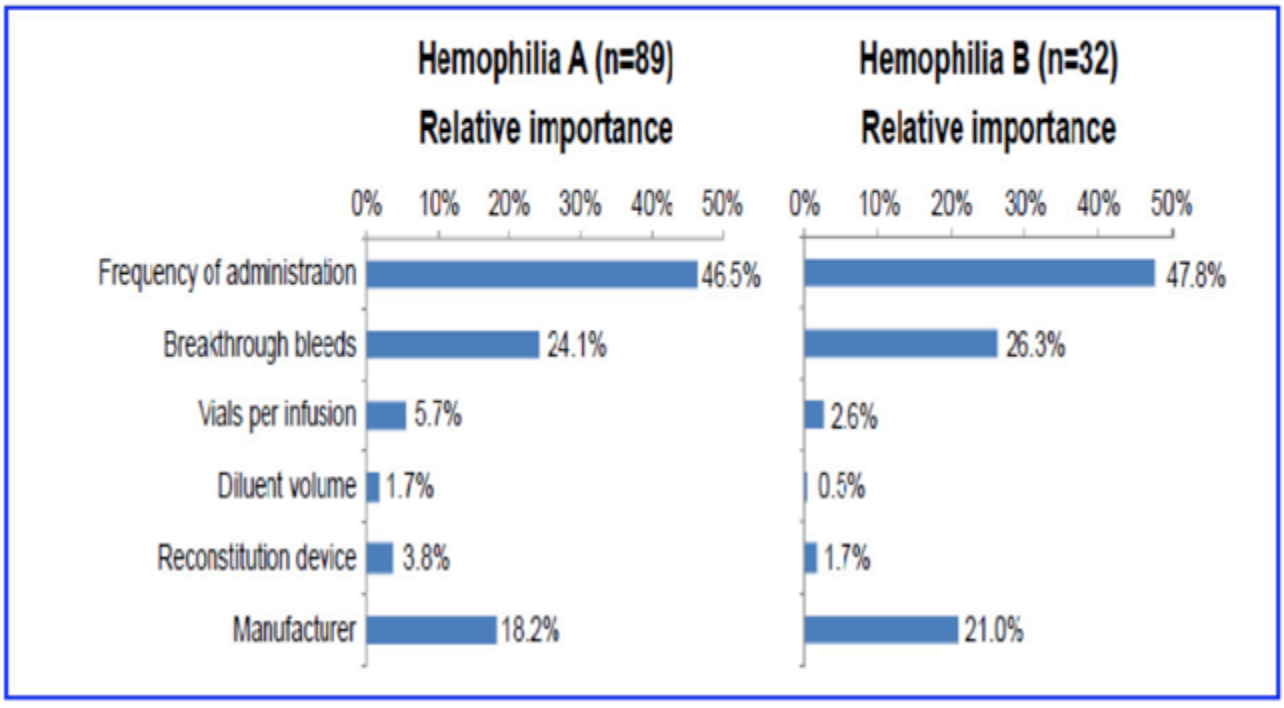
Limiti dei concentrati di fattore "standard"

Emivita plasmatica breve
FVIII: 8-12 h FIX: 18-24 h

- Frequenti infusioni (2-3 volte/sett, a dì alterni)
- Difficoltà di reperimento accessi venosi periferici
- Necessità di accessi venosi alternativi (Broviac, port-a-cath, FAV)
- Ritardo nell'inizio della profilassi
- Interruzione transitoria o definitiva della profilassi
- Peggioramento della qualità di vita

Patient and parent preferences for characteristics of prophylactic treatment in hemophilia

Furlan et al Patient Preference and Adherence 2015:9 1687–1694



Nuovi approcci terapeutici in emofilia

Concentrati ad emivita prolungata

- Identificare la metodologia ottimale
- Preservare l'attività biologica
- Garantire l'efficacia emostatica
- Ridurre l'immunogenicità
- Tollerabilità

Estensione dell'emivita plasmatica

Minor numero di infusioni

"Trough levels" piu elevati

Maggiore protezione dal rischio di emorragie articolari

Phenotype according to baseline FVIII acti

The current classification compared well with
ters age of diagnosis, first treatment and first j
according to FVIII activity (Fig. 1). This ob
was confirmed by the joint bleeding frequenc
ing to baseline FVIIII activity (Fig. 2) Above
age at diagnosis, onset of treatment and joint

12 UI/dL

Haemophilia (2011), 17, 849–853

Den Uijl IEM, Haemophilia 2011:17:849-853

Nuovi approcci terapeutici in emofilia

Strategie per allungare l'emivita dei farmaci

1. Modificazione chimica del fattore che conserva la sua struttura e la sua funzione ma che viene legato ad alcune sostanze che prolungano la sua permanenza nel sangue

2. Tecnica di ingegneria genetica in cui il fattore viene "fuso" con due proteine a lunga emivita: albumina o immunoglobuline

3. Modificazione chimica che aumenta la stabilità del fattore senza l'aggiunta di sostanze esogene

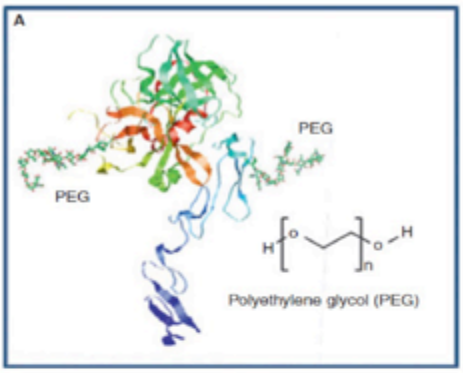
Nuovi approcci terapeutici in emofilia

Modificazione chimica	Fattori
Pegilazione	FVIII, FIX
Glicopegilazione	FVIII, FIX

Proteine di fusione	Fattori
Regione costante(FC) delle Ig	FVIII, FIX
Albumina	FIX, FVIII

PEGILAZIONE

GLICOPEGILAZIONE



Polimeri idrofilici di glicolpolietilene (PEG) legati direttamente o attraverso una catena glicidica al fattore VIII (o fattore IX) in maniera "random" o in alcuni siti ben precisi

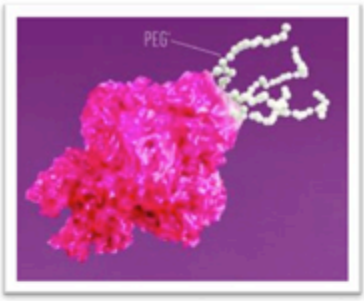
Aumentano il peso molecolare del fattore e riducono l' eliminazione attraverso il rene

Interferiscono con i recettori delle cellule deputate allo smaltimento dal sangue del FVIII

Protezione dalla stimolazione del sistema immunitario

Pegilazione

Legame "random" di 2 molecola di PEG di 20 KDa ad un residuo di lisina presenti su rFVIII "full lenght"



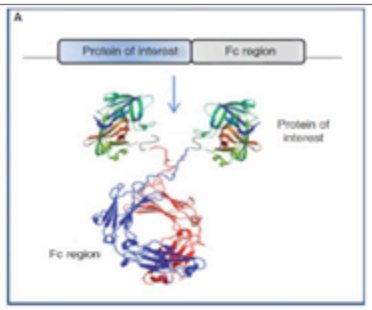
Legame selettivo (sito-specifico) di una molecola di PEG di 60 KDa ad un residuo di cisteina espresso su rFVIII-BDD

Glicopegilazione

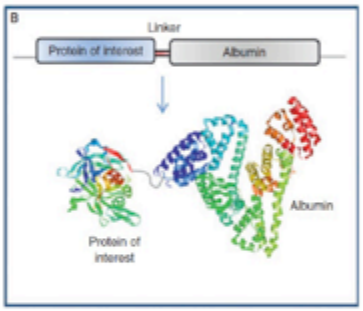
PEG 40 KDa legato ad un glicano nella porzione di dominio B del turoctocog

PEG 40 KDa legato al peptide di attivazione del FIX

PROTEINE DI FUSIONE



Fattore VIII | Immunoglobuline

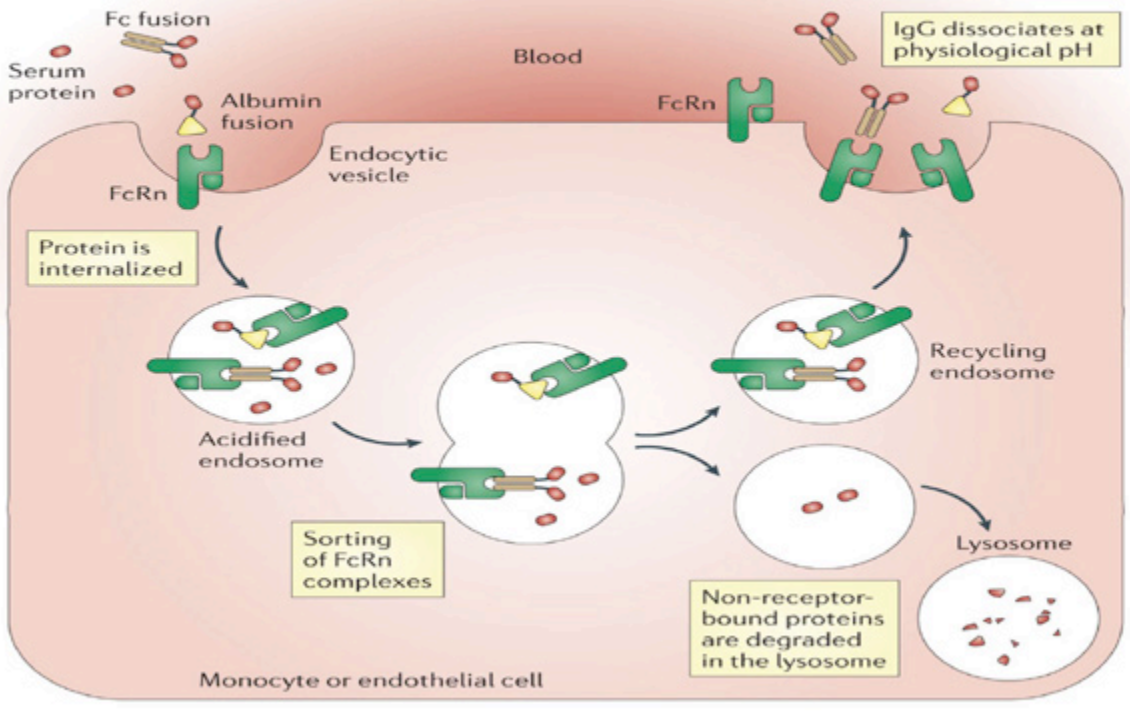


Fattore IX — Albumina

Sfruttano il legame dell'albumina e delle immunoglobuline ad un particolare recettore presente sulle cellule di rivestimento dei vasi sanguigni che le protegge dalla degradazione e li mantiene più tempo nella circolazione sanguigna

Emivita plasmatica: 21 giorni

PROTEINE DI FUSIONE



Nuovi approcci terapeutici in emofilia

Nuovi approcci terapeutici in emofilia

rFVIII-Fc

rFIX-FP

rFIX-Fc

2013-10-529974.

The online version of this article contains a data supplement.

There is an Inside *Blood* commentary on this article in this issue.

marked "advertisement" in accordance with 18 USC section 1

BLOOD, 16 JANUARY 2014 • VOLUME 123, NUMBER 3

sobi

rFVIII-Fc

165 pazienti PTPs

Profilassi individualizzata (25-65 UI/kg ogni 3 -5 gg)
Profilassi settimanale (65 UI/kg)
A domanda (10-65 UI/kg)

No inibitori (110 pz > 110 ED)

87 % delle emorragie risolte con 1 infusione

ABR (mediana)	Profilassi individualizzata	Profilassi settimanale	A domanda
Totali	1.6	3.6	33.6
Spontanee	0	1.9	20.2

Journal of Blood Medicine 2016:7

rFVIII-Fc

71 pazienti PTPs

Profilassi iniziale bisettimanale (G1 25 UI/kg, G4 50 UI/kg)

↓

↓intervallo di infusione (min. ogni 48 h) o ↑ dose (max 80 UI/kg)

46% dei pazienti: nessun sanguinamento

93 % delle emorragie risolte con 1-2 infusioni

ABR (mediana)	< 6aa	6-12 aa
Totali	0	2
Spontanee	0	0

A fine studio: 90 % dei pazienti in profilassi bisettimanale con dosaggio medio di 88 UI/kg /week

No inibitori

Accepted after revision 5 June 2015

onstrated in previously treated adults, adol

rFVIII-Fc

No inibitori

150 pazienti (studio A-LONG) e 61 pazienti (Kids A-LONG) con > 100 EDs

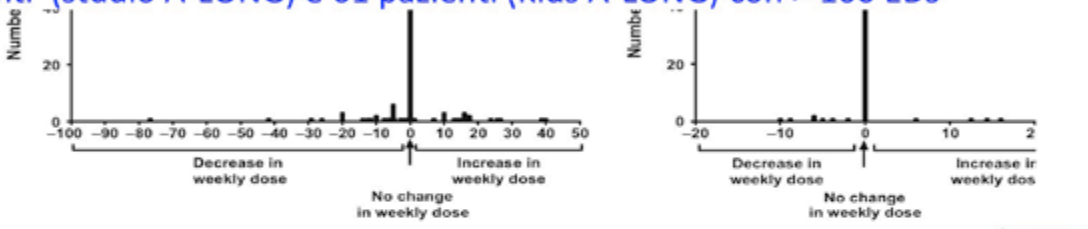


Fig. 4. Change in total weekly prophylactic dose during ASPIRE among subjects treated prophylactically in A-LONG and Kids A-LONG majority of A-LONG (64.1%) and Kids A-LONG (78.7%) subjects had no change in their total weekly prophylactic dose during the extension to their total weekly prophylactic dose at the end of the parent study. The median change in weekly prophylactic dose was 0.0 IU kg^{-1} we A-LONG subjects, 20.3% reduced and 15.6% increased their total weekly prophylactic dose on ASPIRE. Among Kids A-LONG subjects, 1 and 9.8% increased their total weekly prophylactic dose on ASPIRE.

ABR	Profilassi individ.	Profilassi sett.	A domanda	< 6 aa	6-12 aa
Totale	0.66	2.03	18.36	0	1.54
Spontanee	0	1.9	20.2	0	0

Accepted after revision 27 November 2015

should mainly be based on the clini

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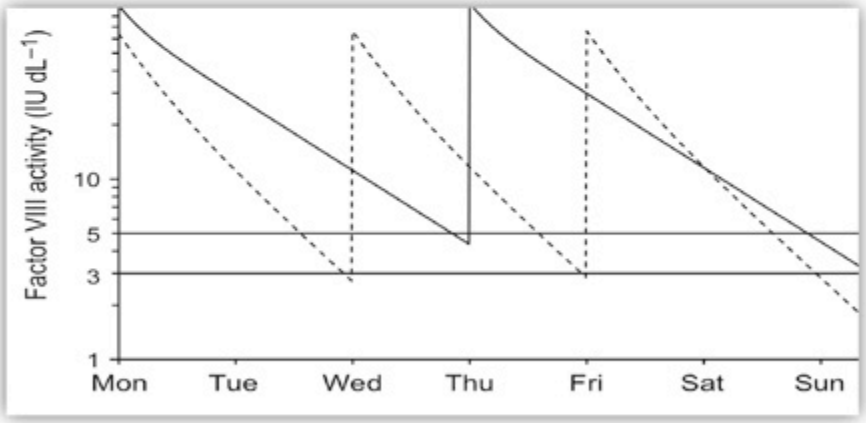
rFVIII-Fc



Haemophilia (2016), **22**, 389–396

Accepted after revision 27 November 2015

should mainly be based on the clini

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Pioneer in Rare Diseases

rFVIII-Fc

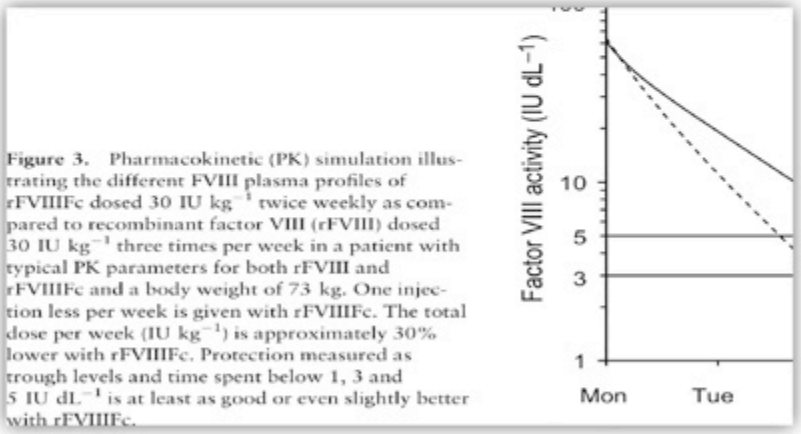
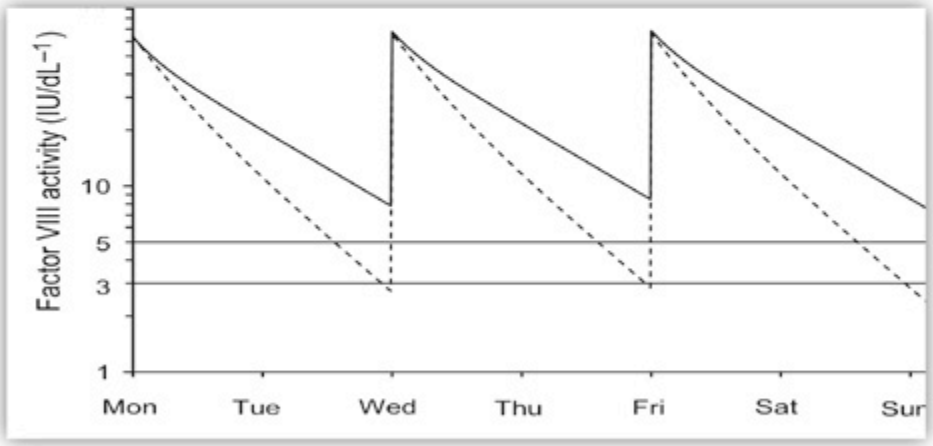


Figure 3. Pharmacokinetic (PK) simulation illustrating the different FVIII plasma profiles of rFVIIIFc dosed 30 IU kg^{-1} twice weekly as compared to recombinant factor VIII (rFVIII) dosed 30 IU kg^{-1} three times per week in a patient with typical PK parameters for both rFVIII and rFVIIIFc and a body weight of 73 kg. One injection less per week is given with rFVIIIFc. The total dose per week (IU kg^{-1}) is approximately 30% lower with rFVIIIFc. Protection measured as trough levels and time spent below 1, 3 and 5 IU dL^{-1} is at least as good or even slightly better with rFVIIIFc.

Accepted after revision 27 November 2015 should mainly be based on the clini

rFVIII-Fc

Haemophilia (2016), 22, 389–396 © 2016 T



Haemophilia (2016), 22, 389–396 © 2016 The

rFVIII-Fc

24 chirurgie maggiori (adulti) 52 chirurgie minori (adulti e bambini)

1-2 infusioni il giorno dell'intervento

Efficacia emostatica: eccellente (19 magg e 25 min) – buona (3 magg e 7 min)

Perdite ematiche secondi le attese

Endpoints were summarised using descriptive statistics. The investigator/surgeon assessment of a subject's haemostatic response to rFVIIIFc was summarised as the number of surgeries at each rating on the four-point scale (i.e. excellent, good, fair, poor/none).

Results

Subjects

Demographics and baseline characteristics for subjects who underwent major or minor surgery in all three studies (A-LONG, Kids A-LONG, and ASPIRE) were representative of a population with severe haemophilia A (▶ Table 1).

mophilia in which the most common type of surgery roplasty (1).

Minor surgeries

Across studies, 41 subjects underwent a total of 52 s geries. Ten minor surgeries were performed in paediati (Kids A-LONG, n = 7; ASPIRE, n = 3). The other 42 s geries were performed in adults and adolescents. rFVIII administered for three of the 42 surgeries (no dose either on the day of surgery or as treatment related to th these three subjects were on rFVIIIFc prophylaxis regin studies. For the 49 minor surgeries across the three s which subjects were administered rFVIIIFc, the mos

No inibitori

Shire

165 pazienti PTPs 12-65 aa

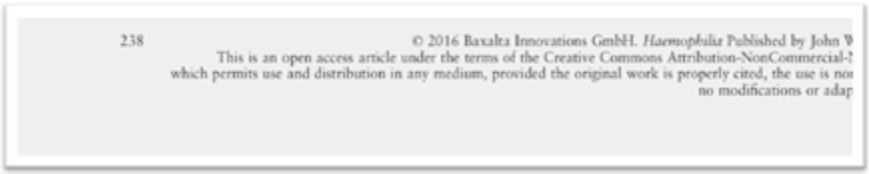
Profilassi bisettimanale (45± 5 UI/kg)

A domanda (10-65 UI/kg)

96 % delle emorragie risolte con 1-2 infusioni

Nessun caso di inibitore

ABR (mediana)	Profilassi	A domanda
Totali	1.9	41.5



66 pazienti PTPs ≤ 12 aa

Profilassi bisettimanale (50± 10 UI/kg)

38 % dei pazienti: nessun sanguinamento

Nessun caso di inibitore

ABR (mediana)	Profilassi
Totali	2.0
Spontanee	0
Articolari	0

novo nordisk®

186 pazienti PTPs 12-65 aa

Profilassi bisettimanale (50 UI/kg ogni 4 giorni)

A domanda (20-75 UI/kg)

40% dei pazienti: nessun sanguinamento

ABR (mediana)	Profilassi	A domanda
Totali	**1.33**	**30.87**

95.5 % delle emorragie risolte con 1-2 infusioni

1 caso di inibitore anti-FVIII dopo 93 EDs

Studio pediatrico in corso

Final decision: F. R. Rosendaal, 25 November 2016 the benefits of prophylaxis, adherence

134 pazienti PTPs

Profilassi 30-40 UI/Kg due giorni alla settimana
Profilassi 45-60 UI/Kg ogni 5 giorni
Profilassi 60 UI/kg ogni 7 giorni
A domanda

ABR mediana	Profilassi ogni 5 gg	Profilassi ogni 7 gg.	Profilassi 2 gg/sett
	1.9	0.96	4.1

Studio pediatrico in corso di pubblicazione

BLOOD, 20 SEPTEMBER 2012 • VOLUME 120, NUMBER 12

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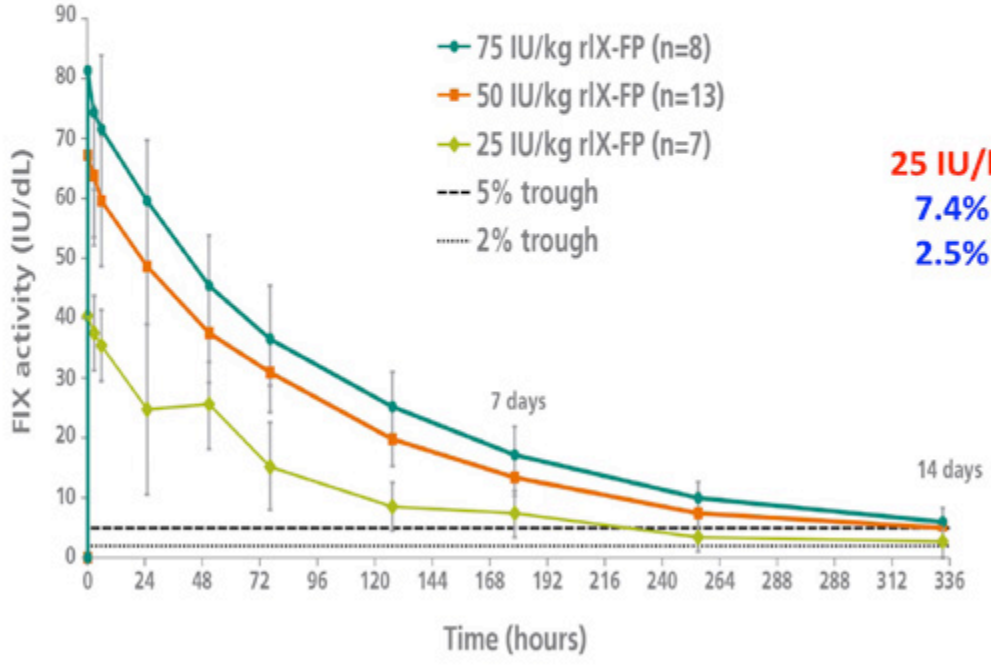
rFIX-FP



25 IU/kg rIX-FP:
7.4% a 7 giorni
2.5% a 14 giorni

BLOOD, 20 SEPTEMBER 2012 • VOLUME 120, NUMBER 12

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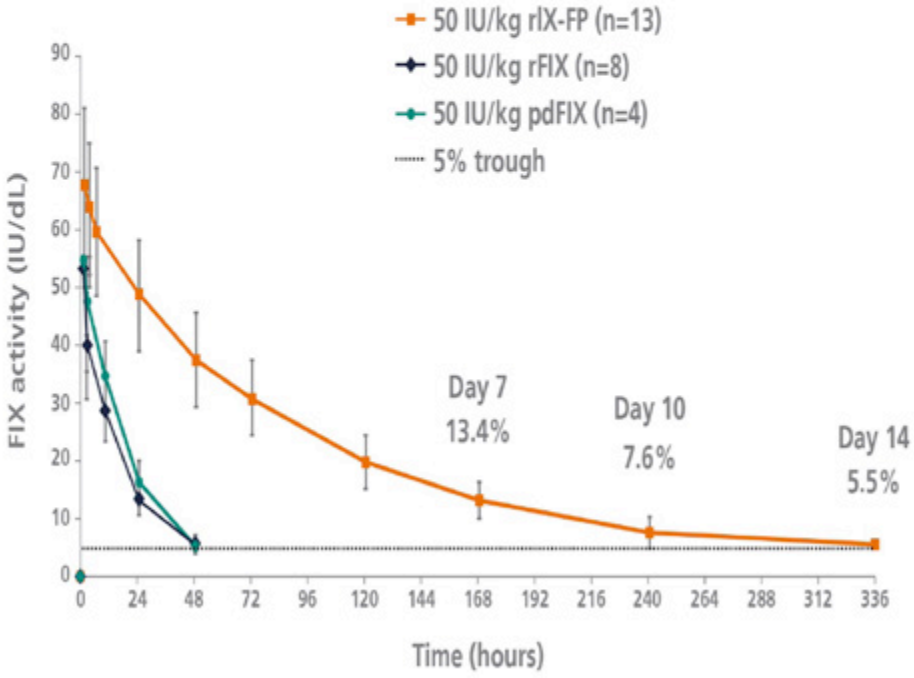
rFIX-FP



50 IU/kg rIX-FP:
13.4% a 7 giorni
5.5% a 14 giorni

BLOOD, 7 APRIL 2016 • VOLUME 127, NUMBER 14

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rFIX-FP

63 PTPs (12-61 aa)

Profilassi
35-50 UI/Kg ogni 7 gg

→ **35-50 UI/Kg ogni 7 gg**
→ **75 UI/Kg ogni 10 gg**
→ **75 UI/kg ogni 14 gg**

A domanda → **35-50 UI/Kg ogni 7 gg**

94 % delle emorragie risolte con 1 infusione

ABR (mediana)	Profilassi 7 gg n = 40	Profilassi 10 gg n=7	Profilassi 14 gg n=21
Totali	0	0	0
Spontanee	0	0	1.08

ABR (mediana)	A domanda n=19	→ Profilassi 7 gg n =19
Totali	19.22	1.58
Spontanee	15.43	0

Nessun caso di inibitore

skeletal function is the goal of routine prophylactic treatment (1). Current prophylactic therapy requires frequent intravenous injection of FIX replacement product, maintaining appropriate FIX (PK) and prolonged pharmacodynamic activity in ear trials conducted in adolescent and adult haemophilia B 6). The improved PK profile of rIX-FP, including ov

Thrombosis and Haemostasis

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rFIX-FP

27 pazienti PTPs < 12 aa

Profilassi 35-50 UI/kg ogni 7 giorni

93 % delle emorragie risolte con 1-2 infusioni

Nessun caso di inibitore

ABR (mediana)	Profilassi < 6 aa	Profilassi 6-11 aa
Totali	2.64	3.29
Spontanee	0	0.78
Articolari	0.50	1.13

Studio di estensione (in corso)

52 PTPs > 12 aa e 24 < 12 aa

Profilassi ad intervalli di 7, 10, 14 o 21 giorni (100 IU/kg)

45/52 (87%) dei pazienti (≥12 anni) sono passati dalla profilassi ogni 7 gg a 10-14 gg

10 pz (≥18 anni) sono passati da intervalli di 14 a 21 giorni

11/24 (46%) bambini (<12 anni) sono passati ad intervalli di 10 o 14 gg

Hospitalier Est, Hôpital Cardiologique Louis Pradel, 59 boulevard Pinel, Bron Cedex 69677, France.
Tel.: +33 4 72 11 88 22; fax: +33 4 72 11 88 17;
e-mail: claude.negrier@chu-lyon.fr

Accepted after revision 7 April 2016

FIX replacement during the period; FIX activity should be IU dL^{-1} in the first 3 days IU dL^{-1} on day 4 through 6 40 IU dL^{-1} from 7 to 14 days p

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rFIX-FP

19 procedure chirurgiche in 21 pazienti

Singola infusione intra-operatoria in 21/22 chirurgie

Efficacia emostatica: eccellente (n= 17)/ buona (n=4)

9 interventi di chirurgia ortopedica maggiore

Perdite ematiche in linea o inferiori alle attese

Nessun caso di inibitore

minor.

No FIX inhibitors or antibodies against detected in any of the subjects that partic surgical sub-study. All subjects continued

number, NCT01027364.)

N ENGL J MED 369;24 NEJM.ORG DECEMBER 12, 2013

The New England Journal of Medicin
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rFIX-Fc

123 pazienti PTPs ≥ 12 aa

G1. Profilassi settimanale (dose iniziale: 50 UI/kg)
G2. Profilassi individualizzata (100 UI/kg ogni 10 gg)
G3. A domanda (20-100 UI/kg)

dix). Among the particip:
in the study for 6 or more
(53.8%) had a dosing inte
days during the last 3 m
The reduction in the
with prophylaxis as c
treatment was consisten
and disease-based subgr
group analyses (Fig. 3 a
who received prophyla:

ABR (mediana)	Profilassi individualizzata	Profilassi settimanale	A domanda
Totali	1.4	3.0	17.7
Spontanee	1.0	0.9	11.8

2318

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90 % delle emorragie risolte con 1 infusione

Nessun caso di inibitore

Paz G1: dosaggio 45 UI/Kg (mediana)

Paz G1: intervallo infusioni: 12.5 giorni (mediana)

54 % dei paz G2 negli ultimi 3 mesi dello studio: intervallo ≥ 14 giorni

A FIX molecule with a prolonged half-life might improve prophylaxis adherence and positively affect therapeutic outcomes in children with haemophilia B.[7] Recombinant factor IX Fc fusion protein (rFIXFc), composed of a single, monomeric molecule of recombinant factor IX (rFIX)

We did this open-label, multicentre, phase 3 16 hospitals and academic institutions in A Hong Kong, Ireland, the Netherlands, South Af UK, and the USA. Additional details about th design are in the appendix (p 7).

www.thelancet.com/haematology Vol 4 February 2017

rFIX-Fc

30 PTPs (< 12 aa) → **50-60 UI/Kg ogni 7 gg**

33% dei pazienti: no emorragie

63% dei pazienti: no emartri

97 % dei pazienti: nessuna variazione di profilassi

ABR (mediana)	< 6aa	6-12 aa	Totali
Totali	1.1	2.1	2.0
Spontanee	0	0	0

Nessun caso di inibitore

bjh BRITISH JOURNAL OF HAEMATOLOGY

14 interventi di chirurgia maggiore in 12 pazienti

11/14: chirurgia ortopedica maggiore

Efficacia emostatica: eccellente (n= 13) / buona (n=1)

Perdite ematiche secondo le attese

Nessun caso di inibitore

recombinant FIX products typically require two to three intravenous prolong the half-life of FIX, in order to reduce pro

Thrombosis and Haer

sobi

rFIX-Fc

116 pazienti

73.1 % adulti

39.1% bambini

> 100 EDs

	Episodic treatment n = 19 (21.1%)	Every 5 days	Once weekly	Every 8–13 days	Every 14–21 days	n = 11 (12.2%)
A		0	5	2	1	11

B-YOND infusion frequency (interim data cut)

Kids B-LONG infusion frequency (end of study)	Twice weekly n = 1 (4.3%)	Every 5 days n = 0 (0%)	Once weekly n = 18 (78.3%)	Every 10–14 days n = 4 (17.4%)
Twice weekly n = 0 (0%)	0	0	0	0
Every 5 days n = 1 (4.3%)	1	0	0	0
Once weekly n = 22 (95.7%)	0	0	18	4[b]

B

Change ir infusion inte
Lengthe (n = 4, 17
No chan (n = 18, 7
Shorten (n = 1, 4.

Figure 3: Change in infusion frequency from end of parent study to B-YOND interim data cut. Changes in prophylactic infusion frequency from the end of B-LONG [A] and Kids B-LONG [B] to the time of the B-YOND interim data cut are shown for individual subjects. The majority of these subjects had either no change to (white boxes) or lengthened (dark grey boxes) their infusion interval during B-YOND. The infusion frequency at the time of the B-YOND interim data cut is also shown for subjects pr sodic arm of B-LONG (n = 19). [b]Excludes three subjects wh surgery arm in B-LONG. The B-YOND interim data cut dosi three subjects was twice weekly, every four days, and ev 10 days, n = 3; every 14 days, n = 1.

Thrombosis and Haemostasis 3/2017

C

Nessun caso di inibitore

ABR	Profilassi individ.	Profilassi sett.	A domanda	< 6 aa	6-12 aa
Totale	2.30	2.30	11.3	0	2.7

There is an Inside *Blood* Commentary on this article in this issue.

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Nonacog beta pegol

72 PTPs (12-65aa)

- 10 UI/Kg ogni 7 gg
- 40 UI/Kg ogni 7 gg
- A domanda

Nessun caso di inibitore

ABR (mediana)	10 UI/Kg/sett	40 UI/Kg/sett	A domanda
Totali	2.9	1.0	15.6
Spontanee	0.97	0	11.1

Nonacog beta pegol in previously treated children with hemophilia B: results from an international open-label phase 3 trial

M. CARCAO,* M. ZAK,† F. ABDUL KARIM,‡ H. HANABUSA,§ S. KEARNEY,¶ M.-Y. LU,**P. PERSSON,† S. RANGARAJAN†† and E. SANTAGOSTINO‡‡

25 PTPs (< 12 aa) → 40 UI/Kg ogni 7 gg

ABR	Tutti	0-6 aa	7-12 aa
	1.0	0	2.0

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http://dx.doi.org/10.1016/j.thromres.2013.06.017

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rFVIII-single chain

rFVIII-B troncato con legame covalente catene pesante-leggera

disegnato specificamente per

Maggiore stabilità molecolare

Prolungata durata d'azione

Aumentato legame di affinità al fattore von Willebrand

Miglior profilo PK senza l'aggiunta di molecole esogene

Blood First Edition paper, June 21, 2016; DOI 10.1182/blood-2016-01-687434.

The online version of this article contains a data supplement.

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146 PTPs (12-65aa) in profilassi

- 20-40 UI/Kg a dì alterni 6%
- 20-50 UI/Kg 3 gg/sett 54%
- 20-50 UI/kg 2 gg/sett 32%
- Altri regimi 8%

Nessun caso di inibitore

27 PTPs (12-65aa) → A domanda

93.5 % delle emorragie risolte con 1-2 infusioni

ABR (mediana)	Tutti i tipi di profilassi	3gg/sett	2gg/sett	A domanda
Totali	1.14	1.93	0	19.64
Spontanee	0	0	0	11.73

43% dei pazienti: no emorragie

Nuovi farmaci in emofilia

FIX standard

104 infusioni/anno → 18-52 infusioni/anno

FIX long-acting

FVIII standard

156-182 infusioni/anno → 73-122 infusioni/anno

FVIII long-acting

Benefici

- Maggiore aderenza alla terapia
- Minore utilizzo di accessi venosi alternativi
- Inizio più precoce della profilassi
- Protezione più duratura dalle emorragie
- Miglioramento della qualità di vita

Hospital of Wales, Heath Park Cardiff CF14 4XN, UK.
Tel.: +44 02920742155; fax: 02920744221; e-mail: peter.collins@wales.nhs.uk

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may wish to test more frequently in pa
past history of an inhibitor.

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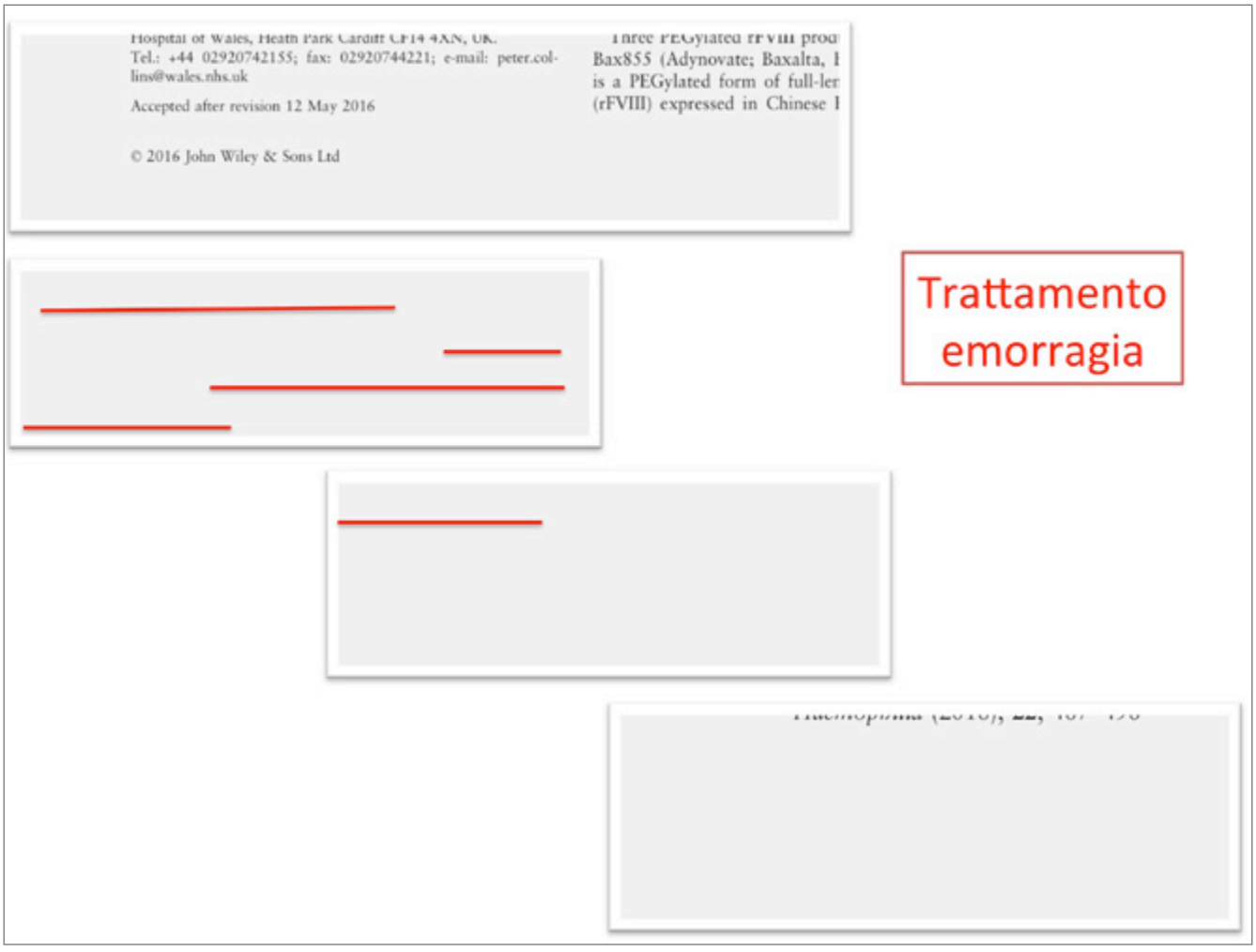
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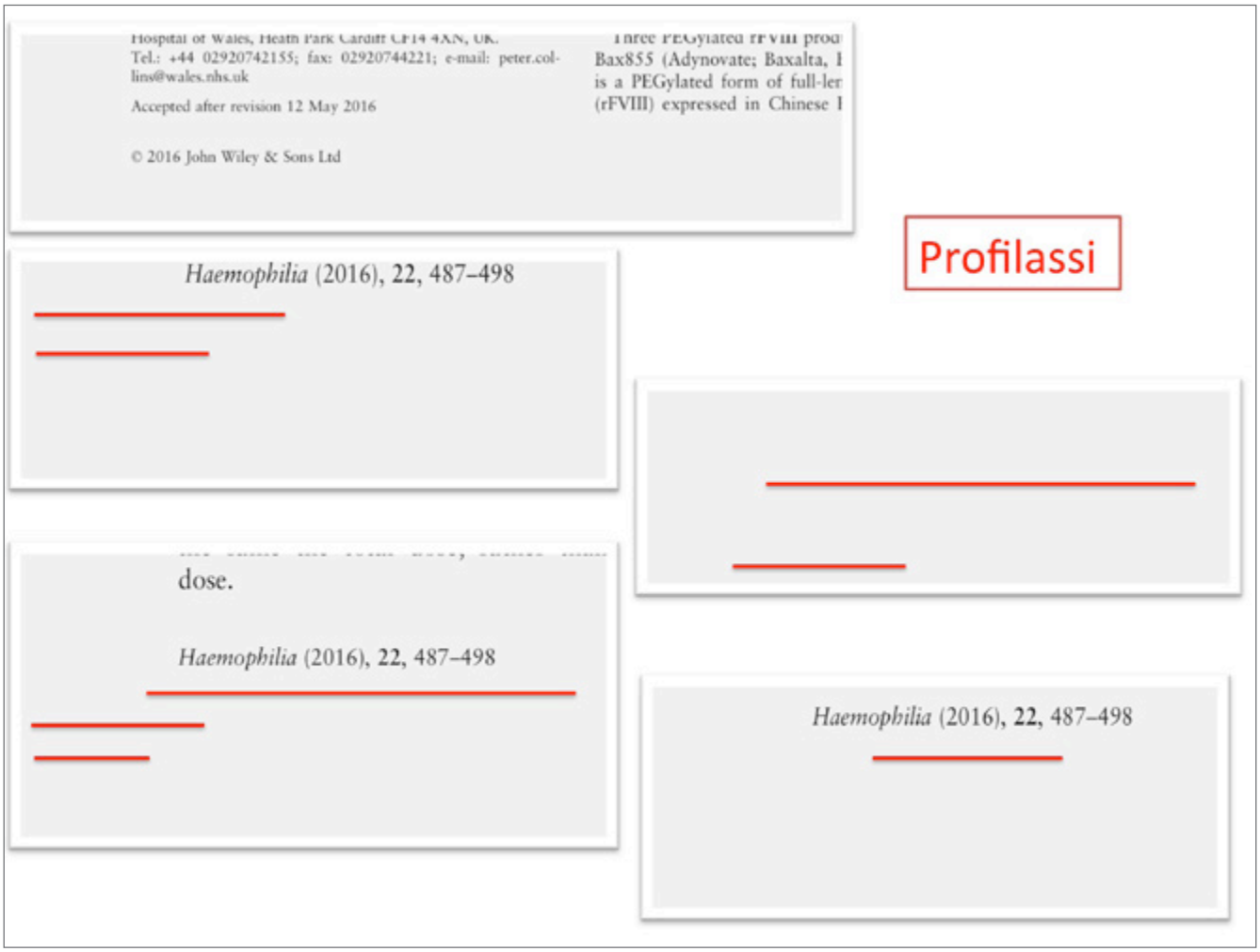
Trattamento emorragia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Profilassi
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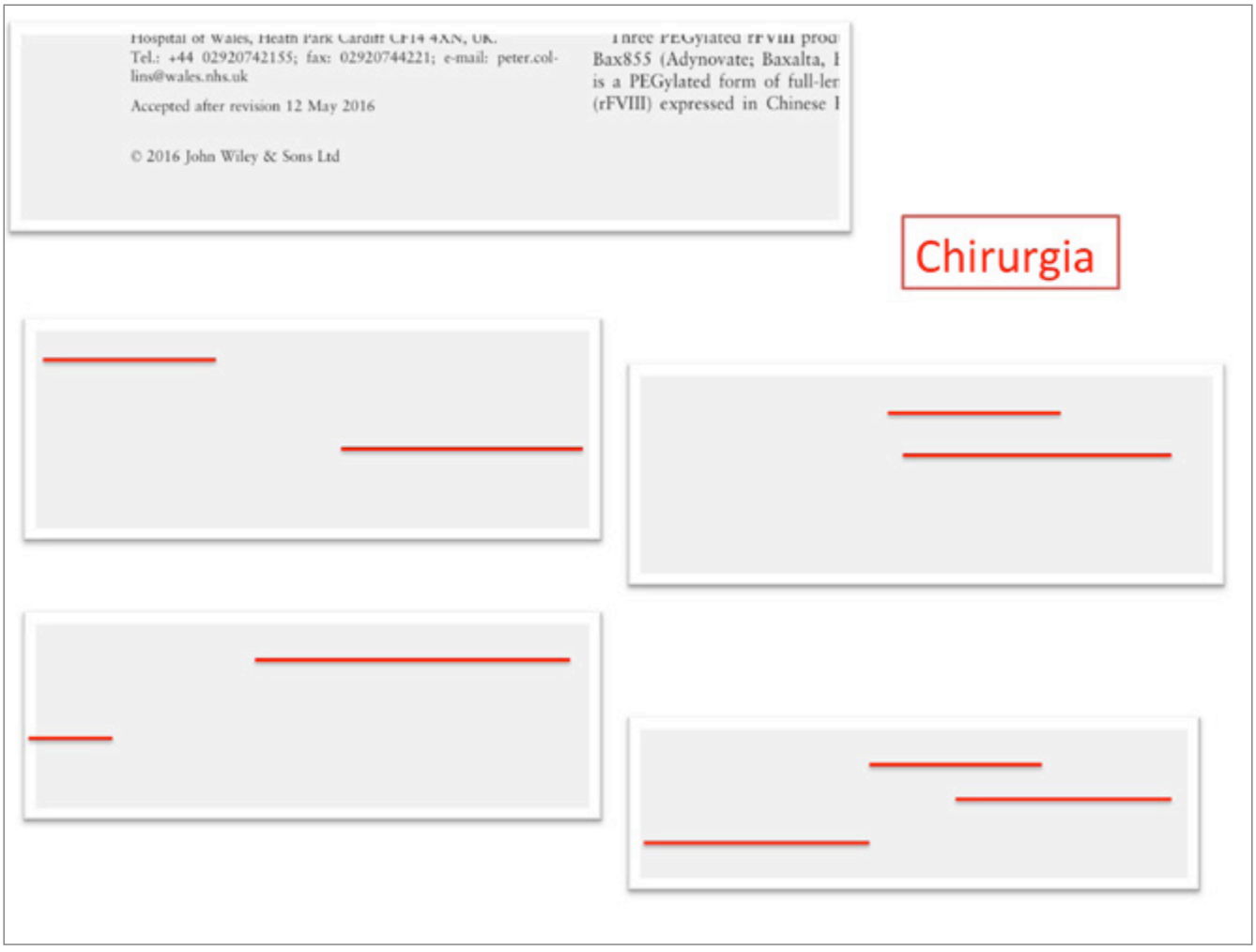
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Chirurgia

Uso dei nuovi farmaci nella "real life"

Valutazione caso per caso

- Età
- Stile di vita (sedentarietà, tipo di attività lavorativa, sport, esercizio fisico, vita sociale attiva)
- Considerare le esigenze e le difficoltà dei pazienti
- Studio farmacocinetico per decidere il trattamento ottimale per il singolo paziente (profilassi, emorragie acute, chirurgia)

PERSONALIZZAZIONE DEL TRATTAMENTO