bjh research paper

Role of clinical and laboratory parameters for treatment choice in patients with inherited FVII deficiency undergoing surgical procedures: evidence from the STER registry

Matteo N. D. Di Minno,[1] Mariasanta Napolitano,[2] Alberto Dolce[3] and Guglielmo Mariani,[4] on behalf of the STER Study Group*

[1]Department of Advanced Biomedical Sciences, Federico II University, Naples, [2]Haematology Unit, Thrombosis and Hemostasis Reference Regional Center, University of Palermo, Palermo, [3]Istituto Nazionale di Statistica, Palermo, Italy and [4]Faculty of Science and Technology, University of Westminster, London, UK

Received 28 July 2017; accepted for publication 9 October 2017

Correspondence: Matteo N. D. Di Minno, Department of Advanced Biomedical Sciences, Federico II University, Via S. Pansini 5, 80131 Naples, Italy.
E-mail: dario.diminno@hotmail.it
A complete list of the members of the Seven Treatment Evaluation Registry (STER) Study Group appears in the acknowledgements section.

Summary

Perioperative bleeding is a major concern in patients with factor VII (FVII) deficiency. Evaluating data of 95 FVII-deficient patients undergoing 110 surgical procedures (61 major, 49 minor), we assessed the impact of type of surgery, bleeding phenotype and FVII coagulant activity (FVII:C) levels on perioperative replacement therapy (RT). Compared to those with higher FVII:C levels, patients with <3% FVII:C received a higher number of RT doses (8 vs. 2, $P = 0{\cdot}003$) for a longer RT duration (3 days vs. 1 day, $P = 0{\cdot}001$), with no difference in RT dose. Similarly, patients with a history of major bleeds received a higher number of RT doses (8·5 vs. 2–3, $P = 0{\cdot}013$) for a longer RT duration (2 days vs. 1 day, $P = 0{\cdot}005$) as compared to those with a history of minor bleeds or to asymptomatic patients. No difference in RT was found among major and minor surgical procedures. Overall, multivariate analysis showed that history of major bleeding was the only independent predictor of number of RT doses ($\beta = 0{\cdot}352$, $P = 0{\cdot}001$) and RT duration ($\beta = 0{\cdot}405$, $P = 0{\cdot}018$). Overall, a ≈20 μg/kg perioperative RT was efficacious in 95·5% of cases. The infusion should be repeated ≈8 times in high-risk subsets (i.e. patients with a history of major bleeding).

Keywords: factor VII deficiency, bleeding disorders, surgery.

Inherited factor VII (FVII) deficiency is the most common of the rare autosomal recessive bleeding disorders, with an estimated prevalence of 1:300 000 in European countries (Mannucci *et al*, 2004; Mariani & Bernardi, 2009; Perry, 2002). Affected individuals display a wide range of clinical phenotypes. About 50% of patients experience a mild clinical picture (i.e. mucocutaneous bleeds) that mimics that of a platelet disorder, but in 15–20% of cases life- or limb-threatening haemorrhages [i.e. central nervous system (CNS) bleeds, gastrointestinal (GI) bleeds or haemarthrosis] are consistently seen (Perry, 2002; Mariani & Bernardi, 2009). On the other hand, up to one-third of individuals with FVII deficiency is asymptomatic (Mariani *et al*, 2005). These individuals are mainly diagnosed during family studies or after a haemostatic screen prior to surgery.

The relationship between the severity of clinical phenotype and FVII coagulant activity (FVII:C) has been recently demonstrated for non-surgical bleeds (Di Minno *et al*, 2013). For surgical patients, a number of other variables (e.g. type of surgery, tissue/organ involved, type of anaesthesia) should be taken into account to define bleeding risk (Mariani *et al*, 2011).

In our experience, perioperative bleeding is a major concern in patients with FVII deficiency (Kitchens & Lawson, 2013), and validated recommendations about the perioperative management of replacement therapy (RT) with FVII are currently lacking.

In this study, by analysing the large database of the Seven Treatment Evaluation Registry (STER), we have evaluated whether specific clinical and laboratory characteristics could influence the clinical choice of the perioperative RT schedule in subjects with inherited FVII deficiency undergoing major and/or minor surgery.

Methods

STER is an international, prospective, observational, multicentre, web-based registry created to collect demographic,

First published online 12 December 2017
doi: 10.1111/bjh.15055

clinical baseline information and describe data on treatment modalities and outcomes in patients with congenital FVII deficiency. The registry was proposed by the International F7 Study Group (www.targetseven.org) and approved by the Ethics Committees of all of the institutions involved. The STER protocol is available at http://www.targetseven.org and published on http://clinicaltrials.gov (# NCT01269138). The STER Registry completed enrolment in February 2012 and included information related to 225 patients. Clinical and demographic data were collected for each patient. In each case, the type of bleeding was defined by the treating physicians, and patients were carefully characterized with respect to their bleeding phenotype by recording the number and type of bleeding events. FVII:C levels for the STER were assessed in a centralized European Quality Assurance (ISO 9001) certified laboratory.

In the present report, data about patients with FVII deficiency undergoing major and/or minor surgical procedures were analysed. The concomitant presence of reduced clotting factors other than FVII, von Willebrand factor deficiencies/abnormalities, abnormal platelet counts or platelet dysfunction were considered as exclusion criteria from the present study. Patients with missing data about perioperative RT, FVII:C, clinical phenotype and surgery outcome were also excluded. To avoid a relevant source of heterogeneity, only patients receiving recombinant activated FVII (rFVIIa, NovoSeven®; Novo Nordisk, Bagsværd, Denmark) were included in the current analysis. Surgical procedures were classified as major or minor according to standard criteria (Kitchens & Lawson, 2013). In agreement with previously published criteria (Di Minno *et al*, 2013), patients were stratified in tertiles according to FVII:C level (<3% cFVII, 3–20%, >20%) and, according to the clinical phenotype, as major bleeders (patients with a history of bleeding in a critical area or organ, i.e. CNS, GI and intra-articular), minor bleeders [patients with an history of mucocutaneous bleeds (excluding GI): epistaxis, gum bleeding, easy bruising, ecchymosis, umbilical cord stump bleeding, haemorrhoidal bleeding, subcutaneous or muscle haematoma, menorrhagia and haematuria] and asymptomatic subjects (non-bleeders: individual with a confirmed diagnosis of FVII deficiency who never experienced any spontaneous minor or major bleeding episode). Only bleeding episodes occurring before the index surgical procedure were taken into account to define the severity of the clinical phenotype.

For each surgical procedure, data about type of surgery, RT dose, number of RT doses and RT duration were evaluated. The occurrence of a perioperative bleed (until hospital discharge) and concomitant medical interventions have been recorded.

STER study was approved by the ethics committee of the University of L'Aquila and registered in ClinicalTrials.gov: NCT01269138.

Statistical analysis

Continuous data were expressed as means ± SD, and categorical variables were expressed as percent. To compare continuous variables, an independent sample *t* test was performed. Because of skewed distribution of values, data on RT have been presented as median with inter-quartile range (IQR) and the Mann–Whitney *U* test (for comparing 2 groups) and the Kruskal–Wallis test (for comparing more than 2 groups) were used to compare non-parametric continuous variables. The chi-square test was employed to analyse categorical data. However, when the minimum expected value for categorical data was <5, the Fisher exact test was used. The whole population was stratified into quantitatively comparable tertiles according to FVII:C levels (1st: <3%; 2nd: 3–20%; 3rd: > 20%). A linear regression analysis was used to identify predictors of RT dose, number of RT doses and RT duration. In addition, separate logistic regression analyses were used to identify predictors of the use of a single-dose RT administration and concomitant use of anti-fibrinolytic drugs. In these multivariate analyses, gender, age, age at first bleeding episode, age at diagnosis, FVII:C levels, type of surgery and bleeding phenotype were the independent variables. This also allowed us to test the potential collinearity between bleeding phenotype and FVII:C levels. All results are expressed as 2-tailed values with statistical significance if *P* values <0·05. Statistical analysis was performed with the SPSS 17 software (SPSS Inc., Chicago, IL, USA).

Results

Study population

Data on 113 patients with FVII deficiency undergoing surgery have been recorded in the STER registry. After excluding those treated with plasma-derived FVII (pd-FVII, $n = 16$) or fresh frozen plasma (FFP, $n = 2$), a total of 95 patients (52 females and 43 males with a similar mean age, Table I) undergoing surgical procedures and receiving perioperative RT with rFVIIa were included in the present study. In this population, FVII:C levels ranged from <1% to 48·7% (mean: 14·14 ± 13·35). Stratifying for residual FVII:C levels, tertiles yielded the following result: 30 subjects (31·6%) exhibited <3% FVII:C, 31 (32·6%) between 3% and 20% and the remaining 34 (35·8%) had >20% FVII:C.

Stratification according to life-long bleeding tendency showed that 15 subjects (15·8%) had a history of major bleeds, 32 (33·7%) of minor bleeds and 48 (50·5%) had always been asymptomatic. Among the 15 subjects with a history of major bleeds, 2 had experienced umbilical cord bleeding, 5 CNS, 7 haemarthrosis and 5 GI bleeds.

Among the 32 subjects with a history of minor bleedings, 5 had haemorrhoidal blood loss, 16 easy bruising, 25

Table I. Demographic characteristics at presentation.

Characteristic	Value
Individuals, *N*	95
Males, *n* (%)	43 (45·3%)
Females, *n* (%)	52 (54·7%)
Age (years), mean ± SD	36·7 ± 21·1
Males, *n* (%)	37·6 ± 22·2
Females, *n* (%)	36·0 ± 20·3
Body weight (kg), mean ± SD	61·9 ± 22·4
Males	68·3 ± 22·3
Females	56·2 ± 21·2
Life-long bleeding phenotype, *n* (%)	
Minor bleeding	32 (33·7%)
Major bleeding	15 (15·8%)
Asymptomatic	48 (50·5%)
FVII:C (%), mean ± SD	14·7 ± 13·2
Males	17·3 ± 11·9
Females	11·5 ± 13·1
FVII:C group, *n* (%)	
<3%	30 (31·6%)
3–20%	31 (32·6%)
>20%	34 (35·8%)

Minor bleeding, major bleeding and non-bleeding: definitions in Methods section.
Age: similar among male and female subjects, $P = 0{\cdot}731$.
Body weight: significantly higher in men than in women, $P = 0{\cdot}010$.
Factor VII coagulant activity (FVII:C) significantly higher in males than in females, $P = 0{\cdot}018$.

epistaxis, 18 gum bleeds, 6 haematuria, 5 haemoperitoneum, 18 menorrhagia, 6 muscle haematomas and 13 subcutaneous haematomas.

Among the 95 patients enrolled, a history of previous post-operative bleeding was reported in 13 (13·7%) subjects (2 with a history of major bleeding, 7 with a previous minor bleeding and 4 in asymptomatic subjects).

Surgical procedures (major surgery and minor surgery)

In these 95 subjects, 110 surgical procedures were carried out: 61 (55·5%) major and 49 (44·5%) minor. Surgical procedures were elective in all the cases but nine in whom an emergency surgery was performed. Surgical interventions performed are listed in Table II.

Replacement therapy dose was 18·0 μg/kg (IQR: 12·6–30·0), the number of RT doses was 2·0 (IQR: 1–8) and RT duration was 1 day (IQR: 1–3). A single-dose RT with rFVIIa was used in 42 (38·2%) procedures and a concomitant treatment with anti-fibrinolytic agents was reported in 29 procedures (26·4%). Perioperative antithrombotic prophylaxis with heparin (in all cases low-molecular weight heparin) was used in six major and three minor surgical procedures (in 4 subjects with 3–20% FVII:C and in 5 subjects with >20% FVII:C).

Type of surgery (minor versus *major)*

No difference was found in RT dose, number of RT doses and RT duration among major and minor surgical procedures (Table III). A single-dose RT was used in 22 subjects {36·1% [95% confidence interval (CI): 25·1–48·8%]} undergoing major surgery and in 20 subjects [40·8% (95% CI: 28·1–54·9%)] undergoing minor surgery [odds ratio (OR): 0·818 (95% CI: 0·378–1·772), $P = 0{\cdot}694$]. The concomitant treatment with anti-fibrinolytic was used in 12 subjects [19·7% (95% CI: 11·5–31·5%)] undergoing major surgery and in 17 subjects [34·7% (95% CI: 22·8–48·9%)] undergoing minor surgery [OR: 0·461 (95% CI: 0·194–1·092), $P = 0{\cdot}086$]. A sub-analysis showed that, as compared to elective surgery procedures, patients undergoing emergency surgery received a similar RT dose [34·4 μg/kg (IQR: 13·6–67·9) vs. 18·0 μg/kg (IQR: 12·5–27·2), $P = 0{\cdot}148$], with a higher number of RT doses [8·0 (IQR: 3·0–53·0) vs. 2·0 (IQR: 1·0–7·0), $P = 0{\cdot}015$] and a trend toward longer RT duration [3·0 (IQR: 1·0–10·0) vs. 1·0 (IQR: 1·0–2·5), $P = 0{\cdot}073$].

FVII:C levels (<3%, 3–20%, >20%)

By stratifying results according to FVII:C levels, the number of RT doses and RT duration were higher in subjects with <3% FVII:C as compared to those with 3–20% or with >20% FVII:C, but no difference was found in RT dose (Table III).

Of interest, these results were confirmed in those undergoing major surgical procedures, but not in those undergoing minor surgery (Fig 1).

A single-dose of FVII was used in 10 procedures [27·0% (95% CI: 15·2–43·3%)] in patients with <3% FVII:C, in 16 [43·2% (95% CI: 28·4–59·4%)] with 3–20% FVII:C and in 16 [44·4% (95% CI: 29·3–60·7%)] with >20% FVII:C (P for within group difference = 0·229). A similar prevalence of concomitant treatment with anti-fibrinolytic agents was also reported in those with FVII:C < 3%, 3–20% and >20% [35·1% (95% CI: 21·6–51·5%), 21·6% (95% CI: 11·2–37·6%) and 22·2% (95% CI: 11·5–38·5%), respectively; P for within group difference = 0·331].

Bleeding history (major bleeds, minor bleeds and asymptomatic patients)

Those with a history of major bleeds received a higher number of RT doses and had a longer RT duration compared to those with a history of minor bleeds as well as to asymptomatic patients, without a difference in RT dose (Table III). Of interest, these differences were confirmed in those undergoing major surgical procedures, but not in those undergoing minor surgery (Fig 2).

Evaluating the bleeding history, a single-dose of FVII replacement was used in 2 [12·5% (95% CI: 3·10–38·6%)] of those reporting a history of major bleeding, in 13 [33·3% (95% CI: 20·4–49·3%)] of those with previous minor

Table II. Summary of surgical procedures stratified in major and minor surgical interventions.

Type of surgery	Major surgical procedures (n = 61)	Minor surgical procedures (n = 49)	Total (n = 110)
Cardiac	2	0	2
Neurosurgery	6 (3 emergency)	0	6
Eye surgery	2	1	3
General surgery	18	5 (1 emergency)	23
Gynaecological	4 (1 emergency)	4* (2 emergency†)	8
Plastic surgery	2	0	2
Ear nose throat	8 (1 emergency)	3	11
Orthopaedic	8† (1 emergency)	3	11
Urological	8	0	8
Vascular	3	1	4
Endoscopic/biopsies	0	12	12
Oral surgery	0	20†	20

*Two with peri-operative bleeding.
†One with peri-operative bleeding.

bleedings and in 27 [49·1% (95% CI: 36·2–62·1%)] of asymptomatic subjects (P for within group difference = 0·022). In detail, asymptomatic patients were treated with a single-dose of FVII more frequently than those with a history of major bleeding (OR: 6·75, 95% CI: 1·40–32·54, P = 0·010), with no significant difference as compared to patients with a history of minor bleeding (OR: 1·93, 95% CI: 0·824–4·513, P = 0·144). The prevalence of a concomitant treatment with anti-fibrinolytic agents was significantly higher in those with a history of major or minor bleeds as compared to asymptomatic subjects [56·3% (95% CI: 32·4–77·5%) vs. 12·7% (95% CI: 6·20–24·4%), OR: 8·85 (95% CI: 2·48–31·25), P = 0·001 and 33·3% (95% CI: 20·4–49·3%) vs. 12·7% (95% CI: 6·20–24·4%), OR: 3·42 (95% CI: 1·22–9·61), P = 0·022, respectively].

Multivariate analyses. In a multivariate analysis (linear regression model), after adjusting for all co-variates (see Methods section) and for the potential collinearity between bleeding phenotype and FVII:C levels, a history of major bleeding was the only independent predictor of number of RT doses (β = 0·352, P = 0·001) and RT duration (β = 0·405, P always = 0·018).

A logistic regression analysis confirmed that asymptomatic subjects were more likely to receive a single-dose RT as compared to those with a history of major bleedings [OR: 6·76 (95% CI: 1·40–32·3), P = 0·017]. The difference was not confirmed comparing those with a history of minor bleedings with asymptomatic subjects [OR: 1·93 (95% CI: 0·82–4·50), P = 0·130].

In a separate regression model, those with a history of major or minor bleeds received more often a concomitant treatment with anti-fibrinolytic agents as compared to

Table III. Perioperative replacement therapy with rFVIIa (μg/kg) – stratification according to type of surgery, FVII levels, and bleeding history.

	Type of surgery		
	Major surgery (n = 61)	Minor surgery (n = 49)	P
RT dose (μg/kg)	16·1 (13·9–25·2)	20·0 (12·4–30·0)	0·457
RT doses (n)	2·0 (1–8·5)	2·0 (1·0–6·0)	0·203
Total RT dose (μg/kg)	47·3 (20·0–159·0)	40·0 (20·0–102·0)	0·745
RT duration (days)	1 (1–5·0)	1 (1–2·5)	0·101

	FVII:C levels			
	<3% FVII:C (n = 37)	3–20% FVII:C (n = 37)	>20% FVII:C (n = 36)	P
RT dose (μg/kg)	19·0 (7·3–27·7)	20·0 (15·0–28·5)	16·0 (12·1–30·0)	0·357
RT doses (n)	8·0 (1–17)	2·0 (1–6·5)	2·0 (1–3)	0·001
Total RT dose (μg/kg)	77·6 (25·5–332·4)	32·0 (20·0–127·5)	30·0 (16·2–63·0)	0·015
RT duration (days)	3 (1–9)	1 (1–1)	1 (1–1)	<0·001

	Bleeding history			
	Major bleeding (n = 16)	Minor bleeding (n = 39)	Asymptomatic (n = 55)	P
RT dose (μg/kg)	25·0 (11·3–50·2)	16·0 (10·0–25·0)	18·0 (15·0–27·5)	0·281
RT doses (n)	8·5 (2–15·5)	3·0 (1–9)	2·0 (1–4)	0·003
Total RT dose (μg/kg)	95·6 (54·7–307·5)	60·0 (20·0–150·0)	30·0 (18·0–60·0)	0·002
RT duration (days)	2 (1–8·2)	1 (1–4)	1 (1–1)	0·007

All values are presented as median (IQR); P values for non-parametric comparisons by using Mann–Whitney U test (for comparing 2 groups) and Kruskal–Wallis test (for comparing more than 2 groups).
FVII:C, factor VII coagulant activity; IQR, interquartile range; rFVIIa, recombinant activated factor VII; RT, replacement therapy.

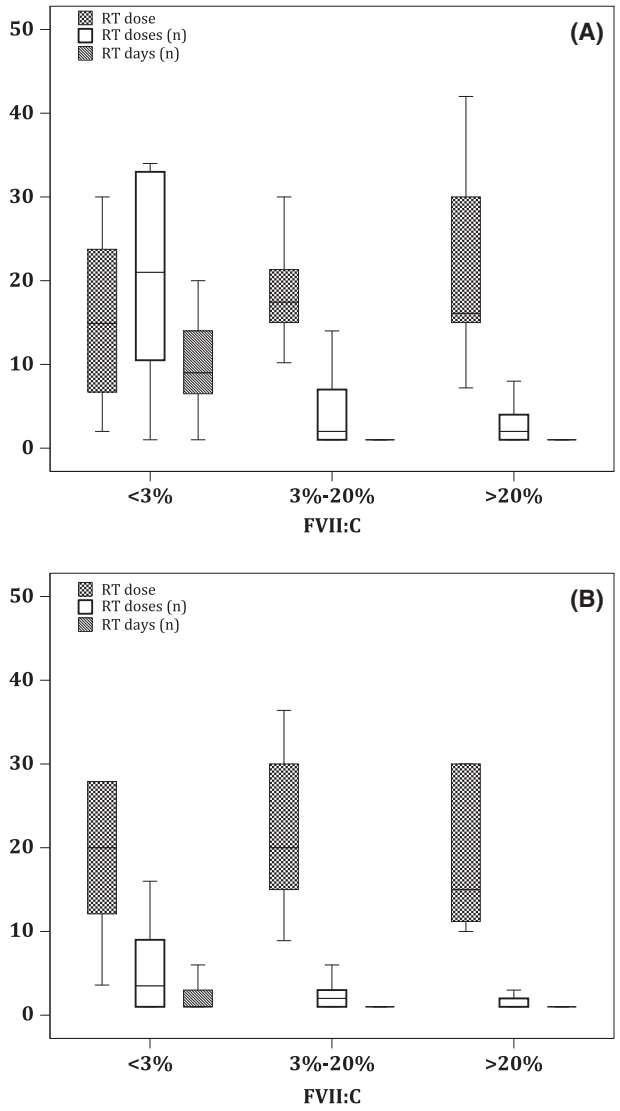

Fig 1. RT dose, number of RT doses and RT duration (days) in patients with <3%, 3–20% and >20% FVII:C undergoing (A) major surgical procedures and (B) minor surgical procedures. FVII:C, factor VII coagulant activity; RT, replacement therapy. Differences among the 3 FVII:C tertiles: RT dose: $P = 0{\cdot}185$ in major surgical procedures and $P = 0{\cdot}597$ in minor surgical procedures. Number of RT doses: $P < 0{\cdot}001$ in major surgical procedures and $P = 0{\cdot}180$ in minor surgical procedures. Number of RT days: $P < 0{\cdot}001$ in major surgical procedures and $P = 0{\cdot}103$ in minor surgical procedures.

asymptomatic subjects [OR: 8·816 (95% CI: 2·484–31·289), $P = 0{\cdot}001$ and OR: 3·429 (95% CI: 1·217–9·656), $P = 0{\cdot}020$].

Surgical procedure outcome

RT with FVII was efficacious in 95·5% of surgical procedures. Perioperative bleeding was reported by five subjects (4 females and 1 male), but only one of these required transfusion (2 units). Thus, three out of these five perioperative bleedings occurred in patients undergoing minor elective surgery (2 gynaecological and 1 oral surgery), one during a minor gynaecological emergency intervention and one during major elective orthopaedic surgery. The patient undergoing major elective surgery also received nadroparine (0·3 ml once daily) for perioperative antithrombotic prophylaxis.

As detailed in Fig 3, when patients with perioperative bleeding were stratified according to life-long bleeding phenotype, two were asymptomatic, two were minor bleeders and one was a major bleeder. As to FVII:C categories, three

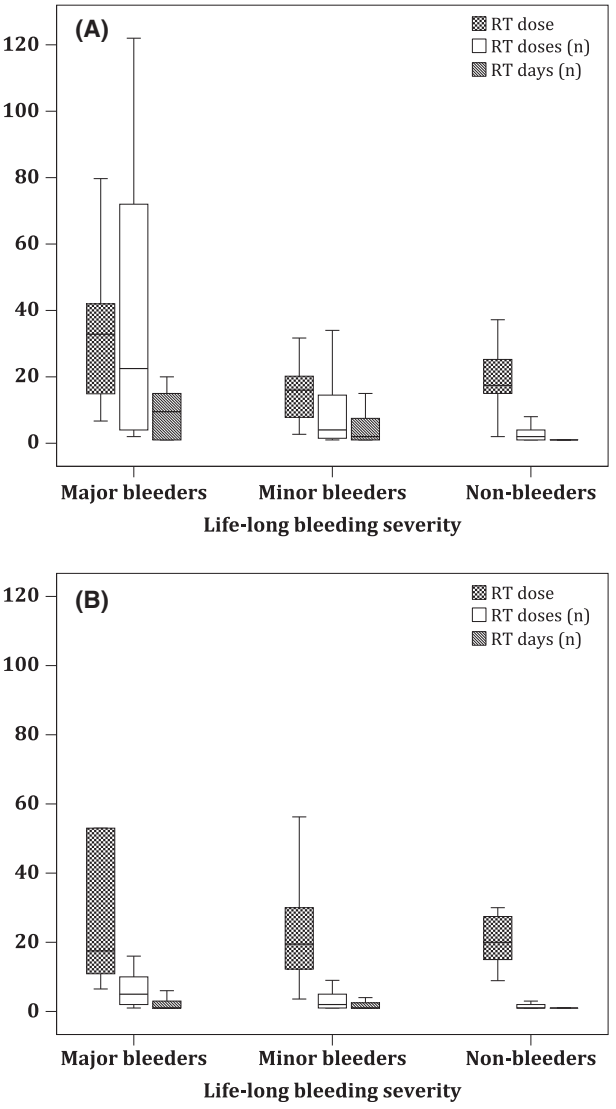

Fig 2. Replacement therapy (RT) dose, number of RT doses and RT duration (days) in major bleeders, minor bleeders and non-bleeders undergoing (A) major surgical procedures and (B) minor surgical procedures. Differences among the three life-long bleeding severity groups: RT dose: $P = 0{\cdot}127$ in major surgical procedures and $P = 0{\cdot}960$ in minor surgical procedures. Number of RT doses: $P = 0{\cdot}005$ in major surgical procedures and $P = 0{\cdot}110$ in minor surgical procedures. Number of RT days: $P = 0{\cdot}002$ in major surgical procedures and $P = 0{\cdot}336$ in minor surgical procedures.

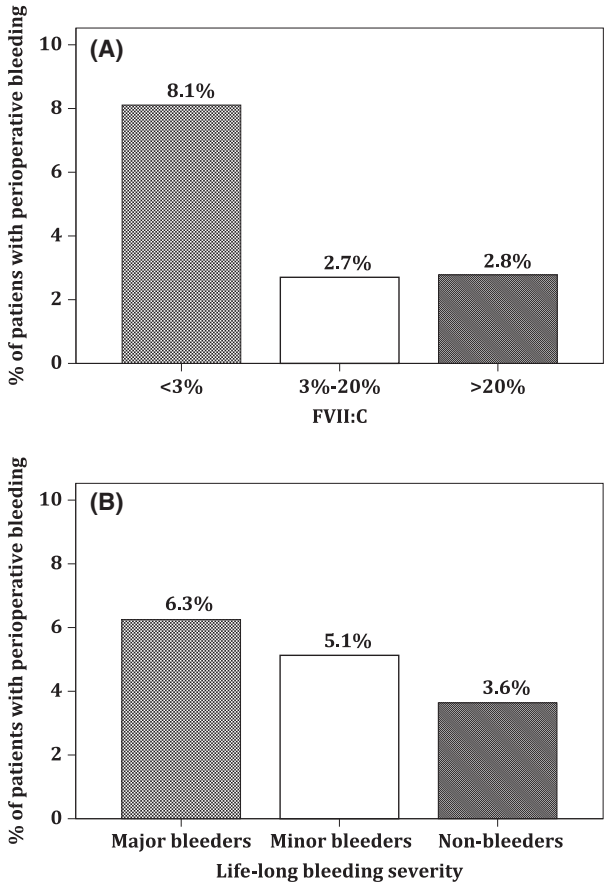

Fig 3. Distribution of perioperative bleeding episodes in the study population according to factor VII coagulant activity (left panel) and life-long bleeding phenotype (right panel).

out of five patients experiencing postoperative bleeding had <3% FVII:C, the other two patients having 3–20% and >20% FVII:C, respectively. The five patients reporting perioperative bleeding received a 27·9 μg/kg RT dose (IQR: 20·2–113·9) with eight RT doses (IQR: 1·5–9·5) and a RT duration of 1 day (IQR: 1–2).

Perioperative thrombosis occurred in two subjects undergoing major surgery (1 urological and 1 orthopaedic) and not receiving perioperative antithrombotic prophylaxis with heparin.

The cumulative in-hospital stay was 5·0 days (IQR: 2–9), which was higher in those who underwent major rather than minor surgery [6·0 days (IQR: 3–10) vs. 2·0 days (IQR: 1–6), $P < 0{\cdot}001$].

No difference was found in the cumulative in-hospital stay according to FVII:C levels [<3% FVII:C: 7·5 days (IQR: 2–12); 3–20% FVII:C: 3·5 days (IQR: 1·25–6·0); >20% FVII:C: 4·5 days (IQR: 2·0–7·0), *P* for within group difference = 0·224] or to a history of bleeding [major bleeders: 4·0 days (IQR: 1·5–11·5); minor bleeders: 5·0 days (IQR: 2·0–9·0); asymptomatic: 4·5 days (IQR: 1·75–8·25), *P* for within group difference = 0·874].

Discussion

This is the first study reporting on the relationship between clinical and laboratory factors and the perioperative RT management of patients with FVII deficiency.

Overall, RT with rFVIIa was efficacious in 95·5% of cases, as only five perioperative bleeds were reported, three of which occurred in subjects with <3% FVII:C and only one requiring blood cell transfusion.

Interestingly, we found that neither severity of FVII deficiency nor type of surgery (major *versus* minor) are determinants of the perioperative RT. In contrast, we showed that the severity of bleeding phenotype significantly impacted on RT, patients with an history of major bleeding receiving higher number of RT doses with a longer RT duration as compared to those with minor bleeding or to asymptomatic subjects. Of interest, these results were mainly confirmed in major but not in minor surgical procedures.

Further confirming this finding, besides results on the number of RT doses, we found that the concomitant use of anti-fibrinolytic agents progressively increased with increasing severity of bleeding phenotype (12·7%, 33·3% and 56·3%, in asymptomatic subjects, minor bleeders and major bleeders, respectively). Although these results support the pro-haemostatic efficacy of anti-fibrinolytic agents and their good safety profile when concomitantly used with rFVIIa (Levi *et al*, 2002), we do not have any data about the use of anti-fibrinolytic without concomitant treatment with rFVIIa.

Overall, these results argue for a history of major bleeding as a relevant risk factor for a more severe bleeding tendency in the perioperative period. These findings confirm and extend some of our recent data (Di Minno *et al*, 2013) showing that a history of major bleedings is a strong predictor of clinical severity of FVII deficiency.

It is important to highlight that these results were mainly confirmed in major but not in minor surgical procedures. This additional finding is useful to address the issue of perioperative RT in minor surgical procedures.

In most of cases, regardless of FVII:C levels, severity of bleeding phenotype and type of surgery, the perioperative RT was performed with a ≈20 μg/kg median dose.

Overall, this approach was efficacious in more than 95% of cases, with only five perioperative bleedings reported, three of which occurred in subjects with <3% FVII:C and only one required blood cell transfusion. However, the lack of a group not receiving RT hampers the possibility to assess efficacy and safety of perioperative RT.

Given the lack of recognized standard recommendations, the perioperative management of patients with FVII deficiency is particularly complex and RT is widely variable in terms of doses and length.

Although further studies are needed to address this issue, we can state that, based on data of the STER registry, the current choice is to treat patients with FVII deficiency

undergoing surgical procedures with ≈20 μg/kg RT, repeating infusions (up to 8–10 times) in patients with a history of major bleeding episodes and in those with <3% FVII:C.

These results confirm and extend previous data showing that haemostasis could be secured by RT with at least 13 μg/kg repeated for three or more administrations/day (Mariani *et al*, 2011).

Of interest, the efficacy of low-dose RT has been also supported by an experimental study (Brummel Ziedins *et al*, 2004), in which 1–2 μg/kg rFVIIa was suggested to produce a competent haemostasis as measured by surrogate markers. However, this study was performed in a few selected FVII patients, in a non-bleeding state, and the computerized models and the ex-vivo and para-vivo experiments cannot be directly extended to surgical patients.

Our study included only surgical procedures carried out with rFVIIa. An additional number of 18 surgical procedures conducted on 16 FVII-deficient patients by using pd-FVII in the perioperative period are reported in the STER registry. In this subgroup, RT dose was 500·0 iu/kg (IQR: 29·7–1018·4), the number of RT doses was 3·5 (IQR: 1–16·7) and RT duration was 1·5 days (IQR: 1·0–6·0). However, given the small sample size of the subgroup, it was not possible to perform stratification of results according to clinical (type of surgery and bleeding phenotype) and laboratory (FVII levels) characteristics.

An interesting sub-analysis needing to be further addressed is on minor surgery. This type of surgical intervention is progressively more frequently used in daily practice, and its inherent bleeding risk cannot be ignored. Indeed, in minimally invasive procedures, local haemostasis is not always possible. Thus, an adequate perioperative RT is mandatory in patients undergoing minor surgical procedures. In line with some of our recent data on minor surgery in FVII-deficient patients (Mariani *et al*, 2012), no difference in perioperative RT was found between minor and major surgical procedures. In detail, RT dose, number of RT doses and RT duration were similar in major and minor surgical procedures, as was the prevalence of concomitant use of anti-fibrinolytic agents.

The results of the present report suggest that perioperative RT is safe and efficacious also in asymptomatic patients. In this clinical setting, a single-dose RT was efficacious in about 50% of asymptomatic patients enrolled. A single-dose RT was used also in more than 30% of those with a history of minor bleedings, resulting efficacious in all cases.

Although the lack of asymptomatic patients not receiving perioperative RT hampers a direct comparison, our results may help address the question whether perioperative RT should be prescribed only in previously symptomatic patients (Giansily-Blaizot *et al*, 2002; Benlakhl *et al*, 2011).

In conclusion, despite inherent limitations, the results of this study suggest that a low-dose (≈ 20 μg/kg) perioperative RT is efficacious in 95·5% of cases to obtain competent haemostasis in patients with FVII deficiency. In high-risk clinical subsets (i.e. patients with a history of major bleeding), the same dosage should be repeated up to ≈8 times. In addition, a single-dose RT is a valuable option in patients without a previous history of bleeding episodes.

Acknowledgements

STER Study Group: Guenter Auerswald, Angelica Batorova, Francesco Bernardi, Giovanni Di Minno, Matteo Nicola Dario Di Minno, Alberto Dolce, Muriel Giansilly-Balizot, Jorgen Ingerslev, Guglielmo Mariani, Uri Martinowitz, Massimo Morfini, Mariasanta Napolitano, Mirko Pinotti, Amy Shapiro, Sergio Siragusa, Jean Francois Schved and Benny Sørensen.

Rosanna Scala performed final editing and proof reading.

Disclosures

Financial support for the study was granted by a number of sources (charities, industry, institutional) through the Department of Medicine and Public Health of the University of L'Aquila. MNDDM received grants and honoraria from Pfizer, Biotest, Bayer, Novo-Nordisk. GM, as co-ordinator of the International FVII Study Group, collected financial support from institutional research organisations and unrestricted funding from Novo Nordisk and charities, administered by the Internal Medicine Department of the University of L'Aquila. The other authors reported no potential conflicts of interest.

Author's contribution

Di Minno MND designed the study, interpreted results and drafted the manuscript. Napolitano M retrieved data, revised the manuscript and performed critical revisions. Dolce A prepared the dataset, performed the statistical analysis and revised the manuscript. Mariani G drafted the manuscript and performed critical revision. All authors approved the final version of the manuscript.

References

Benlakhl, F., Mura, T., Schved, J.K., Giansily-Blaizot, M. & on behalf of the French Study Group of FVII Deficiency. (2011) A retrospective analysis of 157 surgical procedures performed without replacement therapy in 83 unrelated factor VII-deficient patients. *Journal of Thrombosis and Haemostasis*, **9**, 1149–1156.

Brummel Ziedins, K., Rivard, G.E., Pouliot, R.L., Butenas, S., Gissel, M., Parhami-Seren, B. & Mann, K.G. (2004) Factor VIIa replacement therapy in factor VII deficiency. *Journal of Thrombosis and Haemostasis*, **2**, 1735–1746.

Di Minno, M.N., Dolce, A., Mariani, G. & for the STER Study Group. (2013) Bleeding symptoms at disease presentation and prediction of ensuing bleeding in inherited FVII deficiency. *Thrombosis and Haemostasis*, **109**, 1051–1059.

Giansily-Blaizot, M., Biron-Andreani, C., Aguilar-Martinez, P., de Moeloose, P., Briquel, M.E.,

Goudemand, J., Stieltjes, N., Barrot, C., Chambost, H., Durin, A., Gay, V., Peynet, J., Pouymayou, K. & Schved, J.F. (2002) Inherited factor VII deficiency and surgery: clinical data are the best criteria to predict the risk of bleeding. *British Journal of Haematology*, **117**, 72–75.

Kitchens, C.S. & Lawson, J.W. (2013) Surgery and hemostasis. In: Consultative Hemostasis and Thrombosis, chapter 36, 3rd edn (eds by C.S. Kitchens, C.M. Kessler & B.A. Konkle), pp. 651–672. Elsevier, Philadelphia.

Levi, M.M., Vink, R. & de Jonge, E. (2002) Management of bleeding disorders by prohemostatic therapy. *International Journal of Hematology*, **76** (Suppl 2), 139–144.

Mannucci, P.M., Duga, S. & Peyvandi, F. (2004) Recessively inherited coagulation disorders. *Blood*, **104**, 1243–1252.

Mariani, G. & Bernardi, F. (2009) Factor VII deficiency. *Seminars in Thrombosis and Hemostasis*, **35**, 400–406.

Mariani, G., Herrmann, F.H., Dolce, A., Batorova, A., Etro, D., Peyvandi, F., Wulff, K., Schved, J.F., Auerswald, G., Ingerslev, J., Bernardi, F. & for the International Factor VII Deficiency Study Group. (2005) Clinical phenotypes and factor VII genotype in congenital factor VII deficiency. *Thrombosis and Haemostasis*, **93**, 481–487.

Mariani, G., Dolce, A., Batorova, A., Auerswald, G., Schved, J.F., Siragusa, S., Napolitano, M., Knudsen, J.B., Ingerslev, J. & STER and the International Factor VII Deficiency Study Groups. (2011) Recombinant, activated factor VII for surgery in factor VII deficiency: a prospective evaluation – the surgical STER. *British Journal of Haematology*, **152**, 340–346.

Mariani, G., Dolce, A., Napolitano, M., Ingerslev, J., Giansily-Blaizot, M., Di Minno, M.D., Auerswald, G., De Saez, A.R., Tagliaferri, A., Batorova, A. & STER (Seven Treatment Evaluation Registry). (2012) Invasive procedures and minor surgery in factor VII deficiency. *Haemophilia*, **18**, e63–e65.

Perry, D.J. (2002) Factor VII deficiency. *British Journal of Haematology*, **118**, 689–700.