Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial

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Summary

Background Recombinant activated factor VII (factor VIIa) has prohaemostatic effects in bleeding patients with coagulation abnormalities. We aimed to test the hypothesis that recombinant factor VIIa could reduce perioperative blood loss in patients with normal coagulation systems. Therefore, we assessed safety and efficacy of this drug in patients undergoing retropubic prostatectomy, which is often associated with major blood loss and need for transfusion.

Methods In a double-blind, randomised placebo-controlled trial, we recorded blood loss and transfusion requirements in 36 patients undergoing retropubic prostatectomy, who were randomised to receive an intravenous bolus of recombinant factor VIIa (20 μg/kg or 40 μg/kg) or placebo in the early operative phase.

Findings Median perioperative blood loss was 1235 mL (IQR 1025–1407) and 1089 mL (928–1320) in groups given recombinant factor VIIa 20 μg/kg and 40 μg/kg, respectively, compared with 2688 mL (1707–3565) in the placebo group (p=0·001). Seven of twelve placebo-treated patients were transfused, whereas no patients who received 40 μg/kg recombinant factor VIIa needed transfusion. The odds ratio for receiving any blood product in patients treated with recombinant factor VIIa compared with control patients was 0 (95% CI 0·00–0·33) No adverse events arose.

Interpretation An injection of recombinant factor VIIa can reduce perioperative blood loss and eliminate the need for transfusion in patients undergoing major surgery.

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Introduction

Retropubic transabdominal prostatectomy is a common surgical procedure for patients with prostate cancer or enlargement of the prostate due to other causes (such as benign prostate hypertrophy) that cannot be treated by a transurethral procedure. Despite refinement of surgical operation techniques and increased surgical experience, abdominal prostatectomy is still associated with substantial perioperative blood loss, ranging from 800 mL to 3500 mL.[1–4] This loss is mainly due to the complicated anatomical location of the prostate in a densely vascularised area, which can hamper adequate surgical haemostasis. Moreover, the prostate is removed by blunt dissection, which unavoidably causes blood loss that cannot be dealt with by standard haemostatic procedures. Consequently, transfusion of red blood cells and other blood products during and after operation is often needed.[5,6] Although important improvements to safety have been achieved, patients who receive allogeneic blood transfusions or other blood products can still have serious immunological or infectious complications.[7,8] Hence, much effort is devoted to reduction of perioperative blood-loss and need for blood transfusion, for which several strategies have been assessed.[2,9]

Recombinant activated factor VII (factor VIIa) is a highly potent prohaemostatic agent, as shown by the successful treatment of haemophiliac patients who fail to respond to other coagulation agents because they have formed antibodies against factors VIII or IX, and of patients with idiopathic acquired inhibitory antibodies to factor VIII.[10,11] Several investigators have reported successful treatment with recombinant factor VIIa of bleeding patients with other coagulopathies, such as factor VII deficiency, acquired von Willebrand's disease, thrombocytopenia, and platelet function disorders,[12–14] and of patients with coagulation disorders caused by liver cirrhosis, in whom it corrected prolonged clotting times,[15] and substantially reduced blood loss and blood-product requirements in patients who underwent orthotopic liver transplantation.[16]

The effect of recombinant factor VIIa in individuals without coagulation abnormalities is unknown apart from anecdotal experience.[17,18] Since the haemostatic effect of recombinant factor VIIa is immediate, short lasting, and probably localised to the site of vascular injury, this agent might also be beneficial for patients without pre-existing coagulation disorders who undergo surgical procedures that are associated with major blood loss. Therefore, we assessed the safety of this agent and its effect on perioperative blood loss and transfusion requirements in patients undergoing transabdominal prostatectomy.

Methods

Patients

Patients aged 18–85 years who were scheduled to undergo radical retropubic prostatectomy (for prostatic cancer) or prostatectomy by Millin and MacAlister's method[19] (Millin prostatectomy) for prostate hypertrophy were eligible.

Exclusion criteria were: treatment with any anticoagulant agent within 48 h preoperatively; treatment with aspirin fewer than 7 days before operation; known congenital or acquired haemostatic disorder; unstable coronary artery disease or angina pectoris class III/IV (New York Heart Association classification); history of venous thromboembolism or known thrombophilic state; known (advanced) liver disease, liver cirrhosis, or acute hepatitis; and participation in any other trials within 30 days before operation. We screened all study participants 24 h before the operation, took medical histories, and did physical examination and routine laboratory tests for haematology and biochemistry. The study protocol and consent procedure were approved by the institutional review board of the Academic Medical Centre, Amsterdam, the Netherlands. Written informed consent was obtained from all patients before entry.

Study design

The study was a randomised, double-blind, placebo-controlled, single-centre trial. All surgical interventions were done at the Academic Medical Centre in Amsterdam. Consecutive groups of 12 patients were randomised to recombinant factor VIIa treatment or placebo, with a computer-generated 2 to 1 randomisation scheme (eight patients recombinant factor VIIa, four patients placebo). Sample size was based on the assumption that perioperative blood loss would be 1500–2500 mL in the placebo group and would be reduced by 35% in patients treated with recombinant factor VIIa, with 80% power and at a 5% significance level. Recombinant factor VIIa (Novo Nordisk, Bagsværd, Denmark) and placebo (saline) were provided as indistinguishable solutions in numbered vials for every participant. Treatment allocation was concealed from the investigators. A sealed envelope for every patient, containing the details of treatment, was available in case of emergency. All envelopes were unopened at end of study.

The study was designed according to a dose-escalating protocol. In the first group of 12 patients, recombinant factor VIIa was given intravenously at a dose of 20 μg/kg bodyweight, versus placebo. In the next group of 12 patients the dose of recombinant factor VIIa was 40 μg/kg bodyweight, and the third group was to receive recombinant factor VIIa at a dose of 80 μg/kg bodyweight. An independent safety committee did an interim analysis for every group of 12 patients. We decided before the start of the study that progression to the next dose should not take place if serious adverse events arose at the previous dose, or if the efficacy of the previous dose was judged sufficient (defined as a trend towards lower transfusion requirements that would be significant [at the $p<0·05$ level] in the treatment group). If the dose was sufficient, all further patients who were randomised for recombinant factor VIIa would be treated with this dose.

We gave the study drug during operations as an intravenous bolus dose, after lymph-node biopsy in patients undergoing radical retropubic prostatectomy, or after placement of guiding sutures in those undergoing Millin prostatectomy. We gave standard postoperative treatment, including low-molecular weight heparin at a prophylactic dose (nadroparin calcium once daily, 2850 aXa IU subcutaneously), starting 1 day after operation.

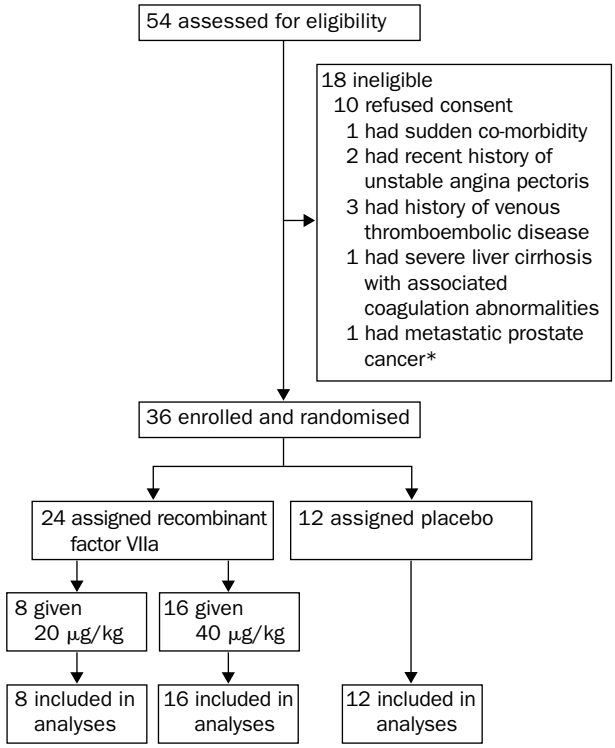

Figure 1: **Trial profile**
*Discovered immediately at beginning of surgery (before randomisation), on which procedure was aborted.

Outcome assessment

Primary outcomes were safety and efficacy in terms of reduction of perioperative blood-loss and transfusion requirements. During and after operation, we measured: total volume of perioperative blood-loss up to 24 h after surgery, estimated by measurement of blood volume that originated from the operation area and was collected in suction containers and wound drains; blood volume in swabs that were used during operation; and volume of additional blood loss, which included blood in operation drapes. We recorded number of red-cell transfusions and need for other blood components. Red-cell transfusion was given only if haemoglobin was below 4·5 mmol/L intraoperatively or 5·5 mmol/L postoperatively. Administration of other blood components (such as plasma or platelets) was at the discretion of the attending physician.

For 10 days postoperatively, patients were visited daily by a study physician to assess any treatment-related side-effects. Electrocardiograms were done at 1, 3, 5, and 7 days, and venous ultrasound of both legs was done at 3 and 7 days postoperatively. Laboratory tests included daily measurement of haemoglobin and perioperative measurement of prothrombin time, factor VII clotting activity (by one-stage clotting assay), and concentration of factor VIIa in plasma (by an enzyme capture assay with an anti-factor VIIa monoclonal antibody and a chromogenic substrate, as previously described[20]). We assessed generation of thrombin by measurement of prothrombin activation fragment F1+2

	Placebo (n=12)	Recombinant factor VIIa 20 μg/kg (n=8)	Recombinant factor VIIa 40 μg/kg (n=16)
Age* (years)	63 (8·3, 49–76)	61 (8·9, 55–79)	64 (8·5, 50–79)
Weight* (kg)	82·1 (11·8, 66–87)	76·8 (9·2, 60–105)	82·0 (13·1, 67–101)
Radical/Millin prostatectomy†	5 (42%)/7 (58%)	4 (50%)/4 (50%)	7 (44%)/9 (56%)
Preoperative haemoglobin (mmol/L)‡	8·4 (0·9)	8·7 (0·9)	8·1 (0·7)

Data are *mean (SD range). †number (%), and ‡mean (SD).

Table 1: **Clinical characteristics**

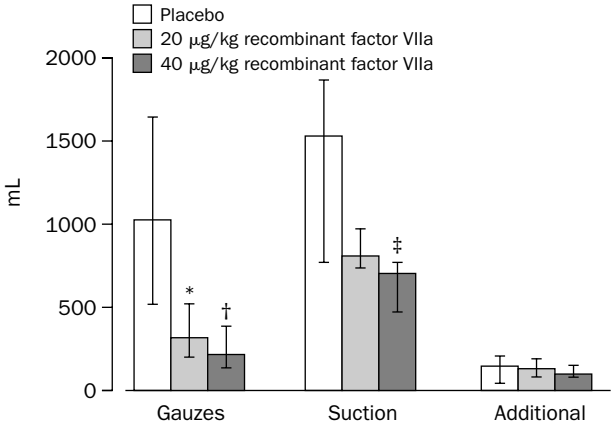

Figure 2: **Median perioperative blood loss in gauzes and swabs, suction containers, and wound drains, and additional blood loss**
*p=0·017, †p=0·012, ‡p=0·034 (recombinant factor VIIa treatment *vs* placebo). Vertical bars=IQR.

and thrombin-antithrombin complexes (both by ELISA, Behring, Marburg, Germany).

Statistical analysis

Data were expressed as median and IQR, or as mean and SD or SE. We used analysis of variance, Newman Keuls test, and the Mann Whitney test to examine volume of perioperative blood-loss, number of red cell units transfused, and laboratory indices. All analyses were corrected for multiple comparisons. The proportion of patients needing any transfusion in each group was compared by calculation of odds ratios and 95% CI.

Role of the funding source

Recombinant factor VIIa and placebo were provided by Novo Nordisk A/S, Bagsværd, Denmark. This company was not involved in the design of the study, collection of the data, or analysis and interpretation of the results.

Results

54 consecutive patients were scheduled to undergo retropubic prostatectomy and were screened for participation in the study, 18 were excluded (figure 1). After inclusion of the second group of 12 patients, the safety committee advised not to proceed to a higher dose group, but to complete the study with the recombinant factor VIIa dose of 40 μg/kg instead. Hence, the study included eight patients who were treated with recombinant factor VIIa at a dose of 20 μg/kg, 16 patients who received 40 μg/kg recombinant factor VIIa, and 12 who were given placebo. Table 1 shows the characteristics of these 40 patients.

All patients completed the study without any adverse event. Repeated physical examination, laboratory testing, electrocardiogram, and duplex ultrasound of the venous system of the legs up to 10 days after operation did not show any abnormality. One patient, who had received a 20 μg/kg dose of recombinant factor VIIa, developed acute

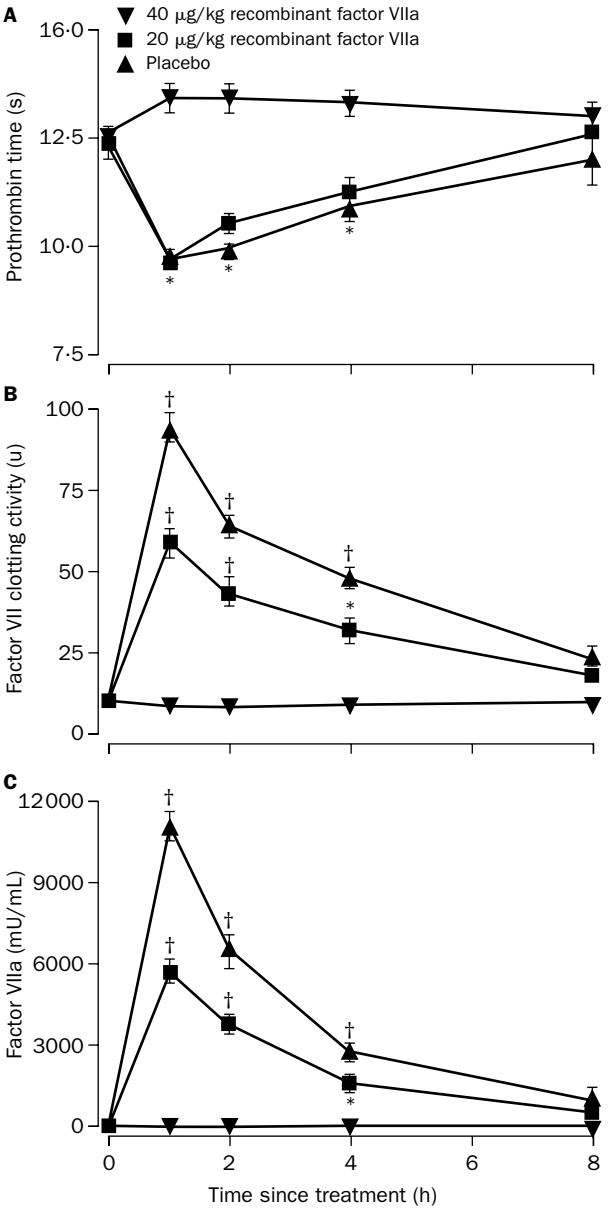

Figure 3: **Prothrombin time (A), factor VII clotting activity (B) and plasma concentration of factor VIIa (C)**
*p=0·008, †p=0·001 (treatment with recombinant factor VIIa *vs* placebo). Data are mean values; vertical bands are SD.

myocardial infarction 14 days after the operation (ie, after the predefined 10-day study period). In view of the short half-life of factor VIIa and the long interval between the treatment and the myocardial infarction, we did not think that this event was related to the use of the drug.

Perioperative administration of recombinant factor VIIa resulted in a dose-dependent reduction of total perioperative blood-loss compared with placebo. Median total blood loss was 1235 mL (IQR 1022–1407) in patients who received recombinant factor VIIa at 20 μg/kg, and 1089 mL

	Placebo (n=12)	Recombinant factor VIIa			
		20 μg/kg (n=8)	p*	40 μg/kg (n=16)	p*
Units of packed red cells	1·5 (0·4)	0·6 (0·3)	0·047	0 (0)	0·0003
Number (%) of patients needing any transfusion	7 (58%)	3 (38%)	0·651	(0%)	0·001
Duration of operation (min)	180 (16)	126 (21)	0·035	120 (15)	0·014
Length of hospital stay (days)	12 (1·7)	13 (1·3)	0·662	11 (0·7)	0·350

Data are mean (SD), unless otherwise indicated. *Versus placebo.

Table 2: **Transfusion requirements, duration of operation, and hospital admission in the three study groups**

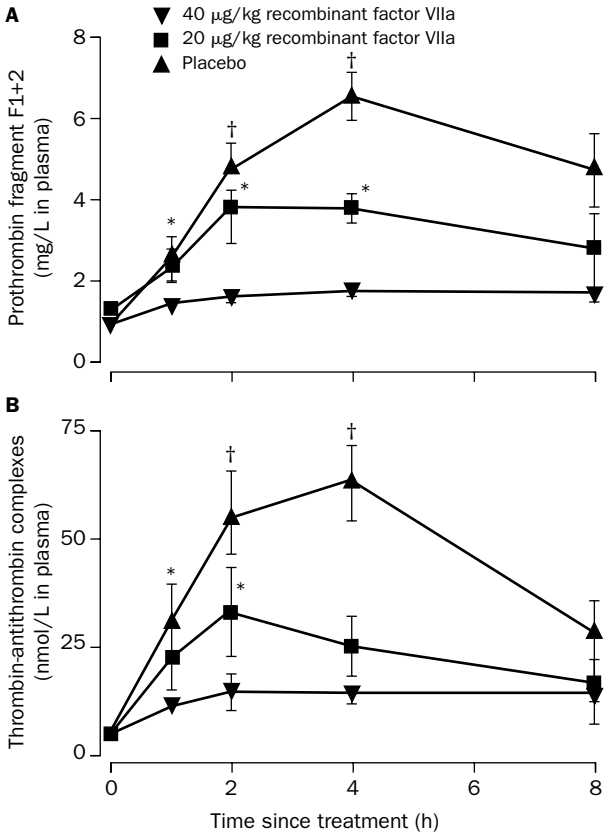

Figure 4: **Thrombin generation, shown by plasma concentrations of prothrombin activation fragment F1+2 and thrombin-antithrombin complexes**
*p=0·045, †p=0·009.

(928–1320) in those who received 40 μg/kg, whereas median total blood loss in the placebo group was 2688 mL (1707–3565; p=0·001 for each of the two dose groups compared with placebo). Figure 2 shows blood loss in the three groups. Overall, patients undergoing radical retropubic prostatectomy had significantly more blood loss than those undergoing Millin prostatectomy (median 2250 mL [IQR 1339–3250] *vs* 1128 mL [900–1300], respectively, p=0·001). Effect of recombinant factor VIIa did not differ between the two procedures.

None of the 16 patients who received 40 μg/kg recombinant factor VIIa needed red-cell transfusion, compared with seven of 12 (58%) patients on placebo (odds ratio *vs* placebo 0, 95% CI 0–0·33; table 2). Of the eight patients who received 20 μg/kg of recombinant factor VIIa, three (38%) were transfused (0·5, 0·05–3·67). No transfusions violated the predefined transfusion requirements. No patients received transfusion with other blood components, such as platelets or plasma.

Mean duration of operation in patients treated with recombinant factor VIIa (20 μg/kg dose) was 54 min shorter than in those on placebo (table 2). Duration of operation did not differ between the two dose groups of recombinant factor VIIa, or between surgeons. Mean duration of hospital stay in placebo-treated patients did not differ from that in recombinant factor VIIa-treated patients (table 2).

Administration of recombinant factor VIIa at both doses resulted in a short-lasting reduction of mean prothrombin time, from 12·5 s (SD 0·1) to 9·7 s (0·1; figure 3). This reduction coincided with a dose-dependent increase in both factor VII clotting activity and plasma concentrations of activated factor VII. Peak amounts of factor VII clotting activity were 58·3 U (SD 4·7) and 94·1 U (3·9) in patients receiving recombinant factor VIIa at 20 μg/kg and 40 μg/kg, respectively. The plasma concentration of activated factor VIIa increased from 72 mU/mL (SD 8) to 5885 mU/mL (369) in the 20 μg/kg group and to 11 155 mU/mL (599) in the 40 μg/kg group 1 h after infusion. Hereafter, it rapidly fell, with an elimination half-life of about 2 h. Thrombin generation, indicated by an increase in prothrombin activation fragment F1+2 and formation of thrombin-antithrombin complexes, was also dose dependently stimulated by factor VIIa, and peaked 4 h after the bolus injection (figure 4). 8 h after the drug was given, markers of thrombin generation decreased and thrombin-antithrombin complexes had almost returned to normal concentrations. Platelet counts and fibrinogen concentrations were in the normal range, and did not significantly change over time in all three study groups.

Discussion

In our randomised trial, in which recombinant factor VIIa was given to individuals with normal haemostatic function and undergoing major surgery, administration of a bolus dose of recombinant factor VIIa (20 or 40 μg/kg bodyweight) resulted in a dose-dependent significant reduction in perioperative blood loss, compared with placebo. Moreover, treatment with recombinant factor VIIa at a dose of 40 μg/kg eliminated the need for red cell transfusion in all patients, whereas more than half of the patients on placebo required a transfusion.

Recent insights into the mechanism of blood coagulation have shown that the initiation of blood coagulation proceeds mainly by the tissue factor-factor VIIa complex-mediated activation of factor X to factor Xa, which subsequently converts prothrombin into thrombin.[21,22] The tissue factor-factor VIIa complex also activates factor IX, resulting in an amplification of coagulation activation by generation of additional factor Xa. On the basis of this knowledge, recombinant factor VIIa has been developed as a pro-haemostatic agent. Studies with non-human primates and phase I/II clinical trials in man have shown that infusion of recombinant factor VIIa indeed results in short-term, local generation of thrombin.[20,23]

Several possible mechanisms of action of recombinant factor VIIa have been proposed. One consists of formation of complexes between tissue factor and recombinant factor VIIa at sites where tissue factor is exposed, such as vessel-wall injury during surgical procedures.[11] Pharmacological doses of recombinant factor VIIa will displace the inactive zymogen factor VII from tissue factor by competitive binding.[24] Subsequently, the tissue factor–recombinant factor VIIa complex generates thrombin by activation of factors X and IX in the presence of activated platelets. This process will induce only local thrombin generation, since tissue factor and activated platelets are not present in the systemic circulation.

An alternative mechanism consists of recombinant factor VIIa-mediated activation of factor X and subsequent thrombin generation independent of tissue factor in the presence of sufficient phospholipid surface on activated platelets.[25] Evidence of recombinant factor VIIa-induced activation of factor X on human monocytes without tissue factor lends support to this notion.[26] Similarly, other findings showed tissue-factor-independent generation of thrombin by recombinant factor VIIa on the surface of activated platelets.[27] We have shown that administration of recombinant factor VIIa to healthy individuals resulted in thrombin generation that could be partly blocked by an inhibitor of the tissue factor/factor VIIa complex.[11]

Thrombin generation was much lower in this investigation (despite a higher dose of recombinant factor VIIa) than in the trial we report here. Thus, both the proposed mechanisms might be operational, and factor VIIa-induced thrombin generation seems to be predominantly, but not exclusively, dependent on tissue factor.

Extensive use of recombinant factor VIIa has shown that the product is safe in individuals with coagulation disorders, and is associated with few treatment-related adverse events, with 0·8% of serious adverse events reported as possibly or probably related to recombinant factor VIIa treatment.[28] The administration of recombinant factor VIIa to people without coagulation disorders might raise concerns that systemic coagulation could be activated, with subsequent disseminated intravascular coagulation or thromboembolic events. We noted no laboratory evidence for sustained systemic activation of coagulation, since platelet count and fibrinogen concentration did not change over time during the study, and clotting times returned to normal shortly after administration of recombinant factor VIIa.

Additionally, we did not encounter thromboembolic or other adverse events that could be associated with recombinant factor VIIa treatment, although the study was not large enough to allow definite conclusions. If recombinant factor VIIa is indeed active only where tissue factor is exposed or activated platelets are present, this mechanism could partly explain the absence of a systemic effect. Moreover, the short elimination half-life of recombinant factor VIIa (about 2 h) causes only a short-lasting activation of coagulation. Patients undergoing prostatectomy have a 2–4% risk of venous thromboembolism,[1,4] although we are not told whether these values come from series of patients who received heparin prophylaxis, as did our patients. The safety of recombinant factor VIIa should be precisely assessed in large controlled clinical trials.[29]

We conclude that treatment of patients undergoing surgery associated with significant blood loss with recombinant factor VIIa seems to be effective and safe. Naturally, blood loss does not exclusively depend on the coagulation system, because type and duration of operation, individual patient characteristics, surgical skill, and postoperative patient-care are important variables that affect perioperative blood-loss and transfusion requirements. Nevertheless, promotion of haemostatic function could be a promising option that needs further exploration, in particular in situations of severe perioperative bleeding when surgical haemostasis is difficult to achieve.

Contributors

All authors took part in all stages of the study, from design to writing and editing the manuscript. P Friederich, E Messelink, and K-H Kurth were directly involved in patient recruitment and undertaking of the study. C Henny, M Geerdink, and T Keller were responsible for perioperative parts of the study and monitoring patients. H Büller and M Levi were mostly responsible for the design of the study, analysis and interpretation of the data, and writing of the manuscript.

Conflict of interest statement

P Friederich and M Levi have been invited speakers at symposia organised by Novo Nordisk. No other conflicts of interest are declared.

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