Role of recombinant factor VIIa in the treatment of intractable bleeding in vascular surgery

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Background: **Most recent publications have shown that the recombinant form of activated factor VII (rFVIIa; NovoSeven, Novo Nordisk A/S, Bagsværd, Denmark) induces excellent hemostasis in patients with severe intractable bleeding caused by trauma and major surgery. The purpose of this study was to determine the influence of rFVIIa on the treatment of intractable perioperative bleeding in vascular surgery when conventional hemostatic measures are inadequate.**

Materials and Methods: **There were two groups of patients: the NovoSeven group (group N), 10 patients with ruptured abdominal aortic aneurysms (RAAAs) and 14 patients operated on due to thoracoabdominal aortic aneurysms (TAAAs); the control group (group C), 14 patients with RAAAs and 17 patients with TAAAs. All patients suffered intractable hemorrhage refractory to conventional hemostatic measures, while patients from group N were additionally treated with rFVIIa.**

Results: **Postoperative blood loss was significantly lower in group N treated with rFVII ($P < .0001$). Postoperative administration of packed red blood cells, fresh frozen plasma, and platelets was lower in patients from group N, ($P < .0001$). Successful hemorrhage arrest was reported in 21 patients (87.5%) treated with rFVIIa, and in 9 patients (29.03%) in group C ($P < .001$). Thirty-day mortality in these two groups significantly differed. The mortality rate was 12.5% (3 patients) in group N and 80.65% (25 patients) in group C ($P < .0001$).**

Conclusion: **Our findings suggest that rFVIIa may play a role in controlling the intractable perioperative and postoperative bleeding in surgical patients undergoing a repair of RAAAs and TAAAs. Certainly, prospective randomized trials are necessary to further confirm the efficacy and cost-effectiveness of rFVIIa in these patients. (J Vasc Surg 2011;53: 1032-8.)**

The most common cause of intraoperative hemorrhage is mechanical bleeding from surgically correctable sites. Surgical bleeding is usually localized, and is manifested by a visible jet. On the other hand, bleeding due to coagulopathy, termed intractable bleeding, is often diffuse and it is manifested as slow ooze that is difficult to control by local measures. Intractable bleeding during the operation and in the early postoperative period remains a significant problem that complicates extensive vascular procedures, such as repair of ruptured abdominal aortic aneurysms (RAAAs) and thoracoabdominal aortic aneurysms (TAAAs). Various mechanisms are thought to be implicated in this coagulopathy.[1-3] Blood loss cause platelet and clotting factor consumption, while prolonged operative time (causing heat loss to the environment), global hypoperfusion, and intraoperative replacement of large volumes of nonwarmed fluids are factors causing hypothermia. Hypoperfusion due to supraceliac aortic cross-clamping and subsequent bowel and liver reperfusion after unclamping, induce fibrinolysis and acidosis. Both hypothermia and acidosis may contribute to clotting factor dysfunction. It is the interaction of these mechanisms that results in intractable postoperative bleeding and, therefore, the treatment of this severe complication demands a combination of various measures. These include blood transfusion, correction of hypothermia (by body warming, warmed fluid infusion, and local warming of surgical field), and application of antifibrinolytic drugs (aminocaproic acid, tranexamic acid, and 1-Deamino-8-d-arginin vasopressin [DDAVP]), in patients with platelet dysfunction.[4] However, occasionally, all these interventions are not sufficient to control bleeding.

The recombinant form of activated factor VII (rFVIIa) is a prohemostatic drug approved for use in patients with hemophilia who develop antibodies to FVIII or FIX.[5,6] The most recent studies have shown that rFVIIa (NovoSeven; Novo Nordisk A/S, Bagsværd, Denmark) may produce an excellent hemostatic effect in patients with severe nonhemophilic bleeding caused by trauma,[7-9] cardiac,[1-3,10,11] and major orthopedic surgery.[12,13] However, the literature on the use of rFVIIa in major vascular surgical procedures is mainly anecdotal,[14-19] as available data are part of larger studies on mixed groups of patients, case series, and reports. However, the lack of controlled trials is a major limitation of these studies.

The purpose of the present study was to determine the possible effects of rFVIIa on intractable perioperative

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Table I. Clinical data of group C and group N

Variable	*Group C*	*Group N*	P *value*
Men	27 (87.10%)	23 (95.83%)	.37
Women	4 (12.90%)	1 (4.17%)	
Age (years)	68.58 ± 7.86	62.91 ± 10.3	.0246; .07[a]

[a]Fisher exact two tailed test.

bleeding in vascular surgery, when conventional hemostatic measures were inadequate.

MATERIALS AND METHODS

At the Clinic for Vascular Surgery of the Serbian Clinical Center, from January 1995 to January 2008, 723 patients were operated on for RAAAs (599) and TAAAs (124). Of these patients, 55 (7.60%) suffered massive perioperative (intraoperative and/or postoperative) bleeding with consecutive consumptive coagulopathy. To evaluate the clinical effectiveness of rFVIIa, we compared two groups of patients who were operated on for RAAAs and TAAAs and had intractable bleeding. In Serbia, the application of rFVIIa for clinical use in patients with intractable hemorrhage in vascular surgery was approved in 2003. Since then, this drug is routinely used in all patients who have intractable surgical bleeding when conventional measures are inadequate. Therefore, the first group of patients (the NovoSeven group [group N]) was gathered prospectively, from July 2003 to January 2008, from 376 patients who were operated on for either RAAAs (292 of 376 patients) or TAAAs (84 of 376 patients). This group consisted of 24 patients who suffered massive perioperative bleeding. Fourteen patients (58; 3%) were operated on for RAAAs, while 10 patients (41; 7%) were treated for elective TAAAs. The patients from group N have already been reported on by our group in 2008 as part of a bigger case series in a journal in a local language.[19] In the present study, we went further to compare the group of patients treated with rFVIIa with the historical group of patients who suffered from the same complication.

As a control group (group C), we considered all 31 patients with intractable bleeding that were operated on for RAAAs (17 of 307 patients) and TAAAs (14 of 40 patients) from January 1995 to July 2003 in the 8-year period when rFVIIa was not available.

Group N was comprised of 23 men (95.83%) and 1 woman (4.17%), whereas group C was comprised of 27 men (87.10%) and 4 women (12.90%). The mean age in group C was 68.58 years old, whereas in group N it was 62.9 years old. Clinical data of both groups are shown in Table I.

Inclusion criteria for both groups were the same: surgery for RAAAs or TAAAs type III or IV, massive blood loss (defined as intraoperative blood loss of more than 50% of circulatory volume or postoperative drainage with estimated blood loss of total circulatory volume in 24 hours), intraoperative usage of the cell saver, and the use of all conventional hemostatic measures. The only inclusion criterion for patients from group N was the treatment with rFVIIa.

Exclusion criteria were patients who had preoperative anticoagulant therapy or pre-existing congenital or acquired coagulopathy and patients re-operated on to control surgical bleeding.

In patients with RAAAs, urgent midline laparotomy and supraceliac aortic cross-clamping were performed, followed by aortic repair with tube or bifurcated graft, depending on the distribution of aneurysmal disease.[20,21] Repair of type III TAAAs was performed through a thoracophreno-laparotomy, whereas in cases of TAAA type IV, the left retroperitoneal approach with eleventh rib excision was used. During resection of TAAAs, it was necessary to reimplant the visceral arteries, whereas in case of type III TAAAs, additional reattachment of intercostal arteries was performed. The cell saver was routinely used in all procedures. Before aortic cross clamping, heparin 100 iu per kilogram of body mass was routinely administered intravenously. After aneurysm resection and restitution of arterial circulation, conventional hemostatic measures were applied: reversal of heparin with protamine (according to body mass and time passed after total distribution of heparin), transfusion of blood products and cryoprecipitate, local surgical hemostatic (Surgicel; Ethicon, Inc, Johnson & Johnson, New Brunswick, NJ), and correction of acidosis and hypothermia. We also used antifibrinolytic agents and procoagulant drugs, such as tranexamic acid and epsilon-aminocaproic acid, and 1-Deamino-8-d-arginin vasopressin (DDAVP) in patients with consumptive coagulopathy or platelet dysfunction.[4] Since 2003, in all patients with massive intraoperative bleeding, the standard protocol of administering rFVIIa was used, which consisted of administration of rFVIIa in a single bolus of 5 mL of NovoSeven (50-76 mg/kg, depending on the patients' body weight). In 2 patients, one more dose was added, due to inadequate effect of single bolus. Before administration of rFVIIa, platelet count ($>50 \times 109/L$), fibrinogen level (>1 g/L), and electrolytes disturbance (pH >7.2) were corrected.

Average temperature in the operating room was 18°C and 24°C in the intensive care unit. In all patients, body temperature was measured by nasopharyngeal tube.

Intraoperative blood loss was measured by using a canister with the volume recorded, while postoperative drainage was measured in a calibrated drain sac. Blood from sponges and pads was extracted into the container and aspirated into the canister, while blood loss into the operating drapes could not be counted. The drains were placed in the Douglas cavity and retroperitoneal hematoma in the cases of RAAAs, or in the thoracic cavity, retroperitoneal space close to the aneurysmatic sac, and nearby visceral and distal anastomosis, in the cases of TAAAs. Postoperative blood loss was measured after application of all hemostatic measures in group C, and after treatment with all hemostatic measures together with rFVIIa in group N.

We referred to the bleeding as intractable when there was general ooze in the operative field in the absence of major arterial bleeding, in the case of postoperative onset of

Table II. Intraoperative data

Variable	*Group C*	*Group N*	P *value*
Body weight (kg)	77.61 ± 9.03	83.08 ± 9.44	.0334
TBV (mL)[a]	5430 ± 680	5810 ± 650	.0431
IO blood loss[b]	1.07 ± 0.44	1.26 ± 0.45	.1239
PRBC (mL)	1830 ± 986	1541 ± 619	.2141
FFP (mL)	1716 ± 1259	1208 ± 522	.0207
Platelets (mL)	133 ± 87	294 ± 166	.000183

FFP, Fresh frozen plasma; *IO,* intraoperative; *PRBC,* packed red blood cells; *TBV,* total blood volume.
[a]TBV (mL) was counted by using Travenol's total blood volume predictor designed by Harry F. Weisberg (Travenol Laboratories, Inc, Morton Grove, Ill).
[b]Intraoperative blood loss is reported as a ratio with TBV blood loss (mL)/TBV (mL).

Table III. Postoperative data

Variable	*Group C*	*Group N*	P *value*
PO blood loss[a]	0.18 ± 0.11	0.06 ± 0.07	.0257
PRBC	1346 ± 401	593 ± 263	<.0001
FFP	1129 ± 312	433 ± 247	<.0001
Platelets	361 ± 209	110 ± 107	<.0001
Total blood loss[b]	1.24 ± 0.45	1.32 ± 0.45	.0592

FFP, Fresh frozen plasma; *PRBC,* packed red blood cells; *TBV,* total blood volume.
[a]Postoperative blood loss is reported as a ratio with TBV - amount of blood per hour (mL)/TBV (mL) in calibrated drain sac.
[b]Total blood loss was counted as the sum of intraoperative and postoperative blood loss and reported as a ratio with TBV.

anemia or hypotension, and an increased drainage rate in the wound suction drains, with laboratory parameters showing coagulopathy (increased prothrombin time and international normalized ratio [INR]). The decision to administer rFVIIa in group N was made in cases with massive intractable perioperative hemorrhage, when intraoperative blood loss was more than 50% of total blood volume (TBV) and/or when postoperative drainage was estimated as a blood loss of complete circulatory volume during 24 hours.[22-24]

After intraoperative data, we recorded intraoperative blood loss, the amount of blood product administration—fresh frozen plasma (FFP), packed red blood cells (PRBC), and cryoprecipitate and platelet concentrate (Table II).

In addition, after postoperative data were measured, postoperative blood loss, the amount of blood product administration—FFP, PRBC, cryoprecipitate and platelet concentrate, and the amount of postoperative drainage (Table III). Prothrombin time and INR were measured preoperatively, 30 minutes and 2 hours after reversal of heparin and administration of prohemostatic drugs, and 30 minutes and 2 hours after administration of rFVIIa in group N (Table IV).

Intraoperative, postoperative, and total blood loss were expressed in proportion to TBV, as blood loss (mL)/TBV (mL) and drained blood per hour (mL)/TBV (mL). TBV was estimated for every patient according to Travenol's surface area calculator and TBV predictor designed by Harry F. Weisberg (Travenol Laboratories, Inc, Morton Grove, Ill).

Table IV. Prothrombin time and INR were measured preoperatively

Variable	*Group C*	*Group N*	P *value*
Preoperative INR	1.10 ± 0.15	1.06 ± 0.17	.13
INR[a]	1.92 ± 0.29	1.85 ± 0.47	.3181
INR30	1.82 ± 0.30	1.19 ± 0.26	<.0001
INR 120	1.60 ± 0.23	1.11 ± 0.24	<.0001

INR, International normalizing ratio.
[a]Postoperative INR after reversal of Heparin with protamine; INR30, international normalizing ratio 30 minutes after administering hemostatic drugs including rFVIIa in group N; INR120, international normalizing ratio 120 minutes after administering hemostatic drugs including rFVIIa in group N.

The main end points of the study were survival or death.

We made comparisons between groups N and C regarding parameters that express intraoperative and postoperative blood loss and blood product administration, INR value, bleeding tendency, and outcome. Statistical analysis was made by *t* test, Pearson's χ^2 test, Fischer exact two-tailed test, Mann-Whitney *U* test, Kruskal-Wallis analysis of variance (ANOVA), non-parametric test, and logistic regression analysis, depending on data compared. Mean and SD values were reported for continuous data with normal distribution. Difference was significant when $P < .05$.

RESULTS

Patients from group C were significantly older ($P = .024$), but univariate analysis revealed that it was not associated with survival ($P = .07$).

The two groups did not differ in the gender distribution and the surgical diagnosis ($P > .05$).

Intraoperative results. There was no significant difference between the groups in terms of intraoperative blood loss ($P = .1239$), or intraoperative transfusion of PRBCs ($P = .2141$). There was a significant difference in terms of intraoperative transfusion of FFP ($P = .0207$), and regarding intraoperative transfusion of platelets ($P = .000183$; Table II). Univariate analysis revealed that transfusion of FFP was not associated with survival, while platelet transfusion was significantly associated with survival ($P = .04$). However, multivariate analysis revealed that platelet transfusion had no association with survival ($P = .11$).

Postoperative results. Patients from group N had significantly lower postoperative blood loss ($P = .0257$), postoperative transfusion of PRBC ($P < .0001$), postoperative transfusion of FFP ($P < .00001$), and postoperative transfusion of platelets ($P < .0001$; Kruskal-Wallis ANOVA nonparametric test). Total blood loss (expressed as a ratio of TBV) was 1.24 among patients in group C and 1.32 in group N ($P = .0592$; Table III). Multivariate analysis revealed that these parameters did not have influence on survival rates ($P > .05$); nevertheless, postoperative blood loss significantly influenced survival ($P = .02$).

All patients had normal preoperative and increased postoperative INR and there was no significant difference in terms of preoperative ($P = .13$) or postoperative INR ($P = .3181$) between groups. INR was significantly lower in group N compared to group C, as measured 30 minutes ($P < .0001$), and 2 hours ($P < .0001$) after the operation (Kruskal-Wallis ANOVA nonparametric test; Table IV).

Among patients in group N, 10 (41.67%) received one, and 14 (58.33%) received both hemostatic drugs (antifibrinolytics and DDAVP), while in group C, 9 (29.03%) received one, while 20 (64.53%) were treated with both hemostatic drugs. There was no statistical difference between the groups regarding this treatment ($P = .32$). Moreover, univariate and multivariate analysis revealed that therapy with antifibrinolytics and DDAVP had no significant influence on survival. In 22 patients, we used a single bolus dose of 5 mL of NovoSeven that was 50 to 76 mg/kg according to the patients' body weight. In addition, there was no significant influence of the dosage of the rVIIa used in group N on the INR value improvement or on the survival.

Outcome. Therapeutic benefit of all hemostatic measures, including therapy with rFVIIa was estimated by a decrease in the postoperative amount of wound drainage, normalization of INR, and a decreased need for inotrope drugs and blood transfusions. The successful cessation of bleeding was present in 21 of 24 patients (87.5%) who were treated with rFVIIa, and in 9 of 31 patients (29.03%) in group C ($P < .001$).

Finally, the mortality of these two groups was significantly different; 3 patients (12.55%) from group N and 25 patients (80.65%) from group C died ($P < .0001$).

Of 3 patients (12.55%) in group N, one died intraoperatively (RAAA), when rFVIIa was not expected to have any visible effect on nonsurgical hemorrhage, while 2 patients (both with TAAAs) had multiple organ failure syndrome (MOFS) due to hypoperfusion. and died in the first postoperative day. Postmortem examination did not reveal any evidence of acute thrombotic events in 2 of 3 cases.

The cause of death in 25 patients from group C was myocardial infarction in 9 patients (36%), MOFS in 8 patients (32%), acute respiratory distress syndrome in 6 patients (24%), and renal failure in 2 patients (8%).

Univariate analysis showed that platelet transfusion, the amount of postoperative blood loss, MOFS, and application of rFVIIa were significantly associated with survival. Multivariate analysis revealed that factors associated with survival were postoperative blood loss, treatment with rFVIIa ($P < .001$, odds ratio, 0.04; confidence interval, 95% 0.006-0.28), and MOFS ($P < .05$; odds ratio, 13.9; confidence interval, 0.92-210.6).

The overall mortality rate after RAAA repair in our hospital, in the period from 1995 to 2003 was 53%, while mortality in group C, operated in the same time period, was 87%. On the other side, overall mortality in the period from 2003 to 2007 was 38%, while mortality in N group, operated in the same period of time, was 7.14%.

DISCUSSION

The rFVIIa was introduced to the clinical practice in 1980s and has been shown to be a highly effective hemostatic agent in patients with hemophilia.[25,26] Recent reports on rFVIIa application in the cases of severe posttraumatic bleeding or bleeding associated with different surgical procedures suggest its efficacy even in patients without pre-existing hemorrhagic diatheses.[27-29] However, more liberal use of rFVIIa in vascular patients is limited by a lack of randomized controlled trials on its safety and efficacy, by absence of dosing guidelines and by poorly defined indications.

Our results show that all patients had an increased value of INR before the treatment with rFVIIa. According to the recent study, rotational thromboelastography contributed even more in revealing the cause of hemorrhage in order to choose adequate therapy; however, we did not use this method until 2009 due to technical insufficiency of our laboratory.[30,31] Several studies showed that reversal or rapid decrease of INR value can be used as a parameter of effective treatment with rFVIIa, which is supported by our own results.[32] Administration of rFVIIa correlated with normalization of INR and with clinical improvement.[33,34]

There is no consensus on the dosage of rFVIIa in vascular patients. Moreover, there are special concerns in vascular patients because of the higher exposure of tissue factor in circulation, which may predispose them to the greater incidence of adverse events. Therefore, Abshier et al[35] suggested a dose of 41 to 90 mg/kg, which is less than the dose recommended in patients with hemophilia. Accordingly, we used a single bolus of 5 mL of NovoSeven, which is 50 to 76 mg/kg and only in 2 patients was an additional dose added, due to inadequate effect.[6]

According to published data, side effects of rFVIIa are rare.[36-41] These were mainly inflammation and pain at the site of administration and skin irritation. Considering the mechanism of action rFVIIa, one should be aware of possible thromboembolic complications when using this drug. As a side effect, thrombosis is most commonly reported in patients who already had a tendency toward thrombotic complications due to conditions such as diabetes, malignancy, or atherosclerotic cardiovascular diseases. In our study, we did not observe these complications in clinical or postmortem examinations.

Reconstruction of TAAAs and urgent surgical treatment of RAAAs are associated with massive blood loss.[42,43] Blood transfusions related to these procedures are associated with an increased incidence of complications, including adult respiratory distress syndrome and MOFS.[44,45] In our study, in the group of patients additionally treated with rFVIIa, incidence of these complications was significantly lower. Multivariate analysis of our data revealed that factors contributed to outcome were treatment with rFVIIa and incidence of MOFS. We argue that significantly reduced postoperative blood loss and consequently lesser need for transfusion therapy contributed to a reduced incidence of

postoperative MOFS, adult respiratory distress syndrome, and myocardial infarction.

Among patients included in the present study, there was no significant difference in demographic, preoperative, and postoperative data. There was a significant difference in age between our two groups of patients; still multivariate analysis showed that age was not significantly associated with survival. In addition, there was a significant difference in intraoperative platelet transfusions between the two groups; however, this may be explained by the lack of platelets in the Serbian transfusion service due to the economical crisis that was affecting our national health system in the 1990s. All patients had intractable bleeding and were treated with the same hemostatic measures and agents. Patients from group N differed since they were additionally treated with rFVIIa, suggesting that this additional therapy contributed to cessation of bleeding. The rFVIIa was used as a "last option" in those patients in whom regular measures did not improve hemostasis and INR was showing coagulation disorder.

There are several limitations of our study; the number of patients in the control group could be greater, but all patients with positive inclusion and negative exclusion criteria operated on in our institute were analyzed. The groups we compared were not parallel, as patients were treated in different time periods. Since 2003, in our clinical practice, we routinely use rFVIIa in patients with intractable surgical bleeding when conventional measures are inadequate and, therefore, we considered it ethically to offer rFVIIa treatment to all of our patients with appropriate indications. Therefore, the control group had to be collected retrospectively. Additionally, groups are heterogeneous, consisting of a mixed population of patients with RAAAs and TAAAs who had severe bleeding. We chose patients with the same complication, regardless of the performed surgical procedure. However, statistical analysis showed that surgical procedure had no significant influence on survival rate. One may argue that better survival rates of patients in group N (treated between 2003 and 2008) may be the consequence of better experience of the staff and better technical amenities, which were not fully available in the period when patients from group C were operated on (1995-2003). Finally, it might be difficult to differentiate surgical from nonsurgical bleeding. However, we believe that all patients included in this study had nonsurgical bleeding, as the bleeding was detected intraoperatively during wound closing when possible surgical causes of bleeding were already excluded and patients with normal intraoperative hemostasis who had massive postoperative bleeding were excluded from the study.

CONCLUSION

In conclusion, our findings suggest that rFVIIa may play a role in controlling the intractable perioperative and postoperative bleeding in surgical patients undergoing a repair of RAAAs and TAAAs. Certainly, prospective randomized trials are necessary to further confirm the efficacy and cost-effectiveness of rFVIIa in these patients.

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INVITED COMMENTARY

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In 1999, the US Food and Drug Administration approved the use of rVIIa for the treatment of bleeding in patients with hemophilia A or B and inhibitors of factors VII and IX. Since then, rVIIa has been increasingly used off-label to treat surgical patients without hemophilia that have intractable bleeding. Končar et al describe the largest case series of vascular patients treated with rVIIa. Like numerous earlier case reports and case series, the current article describes the use of rVIIa to decrease blood transfusion requirements and correct coagulopathy after major operations associated with serious nonsurgical bleeding.[1,2] The current series also highlights a significant survival advantage for patients treated with rVIIa compared to a historical control group. Similarly, a meta-analysis of case series analyzing the use of rVIIa in major abdominal operations found a 73% mean reduction or cessation of bleeding and a 53% mean probability of survival after administration of rVIIa.[1]

Activated factor VII (VIIa) is believed to complex with tissue factor in the subendothelium at sites of injury, leading to the activation of factors IX and X and the generation of thrombin.[3] Because of its mechanism of action, there exists the potential for thrombotic complications which must be balanced with rVIIa's ability to control hemorrhage. Končar et al reported no thromboembolic complications in their historical control or treatment group. A review of the Food & Drug Administration's Adverse Event Reporting System between 1999 and 2004 for thromboembolic adverse events (TAEs) with rVIIa, led the authors to conclude that there was a substantial risk of TAEs.[4] The majority of TAEs occurred with the use of rVIIa for unlabeled indications, and arterial thrombotic complications were the most common. A subsequent meta-analysis of case series calculated a mean probability of 16.5% for thrombemboli associated with rVIIa use during abdominal surgery.[1] A recent meta-analysis of randomized controlled trials comparing rVIIa to placebo found that TAEs occurred in 8.6% of the rVIIa group compared to 6.4% in the placebo group.[2] However, arterial TAEs occurred more frequently in the rVIIa group compared to placebo. Despite the lack of TAEs in the current article, a review of the literature would suggest that an increased risk of thrombotic complications is suspected that can only be ascertained by randomized controlled trials.

Končar et al's routine use of rVIIa for intractable bleeding in patients treated for ruptured abdominal aortic aneurysms (RAAAs) and elective thoracoabdominal aortic aneurysms (TAAAs) resulted in a significant reduction in mortality rate (13%), a significant decrease in transfusion requirement, and rapid correction of international normalized ratio compared to their retrospective historical control group. However, these results are not sufficient to