NAC STATEMENT ON RECOMBINANT FACTOR VIIA

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RECOMMENDATION:

A literature search performed included publications from 2018-2023 confirmed that recombinant factor VIIa (rFVIIa) should be used for on-label indications only. A significant risk of thrombosis exists, which negates any benefit. Any use of (rFVIIa) outside of on-label indications should only be in the context of a clinical trial.

April 2012: On behalf of NAC, Dr. Yulia Lin et al. has revised the rFVIIa transfusion policy framework, which is available online as an open access publication: The evidence for the use of recombinant factor VIIa in massive bleeding: revision of the transfusion policy framework (nacblood.ca)

ACKNOWLEDGMENTS:

The National Advisory Committee on Blood and Blood Products would like to acknowledge and thank the Saskatchewan Health Authority Library and Librarian Mark Mueller for providing the literature search required to update this recommendation.

The following is the evidence search report performed by the Saskatchewan Health Authority Library which informed this recommendation.

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Evidence Search Report

Niastese (Factor 7A Recombinant) for hemorrhages

Request ID#: 3130991
Date Submitted: 7 DEC 2023
Date Completed: 27 DEC 2023
Librarian: mark.mueller@saskhealthauthoriy.ca

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Search Results

Journal Articles

1. Navarro R, Bojic S, Fatima R, et al. Recombinant Activated Factor VII (rFVIIa) for Bleeding After Thoracic Aortic Surgery: A Scoping Review of Current Literature. J Cardiothorac Vasc Anesth. 2024;38(1):275-84. DOI: 10.1053/j.jvca.2023.09.041

ABSTRACT: BACKGROUND: Bleeding after surgery on the thoracic aorta is a frequent complication, and can be associated with a significant increase in morbidity and mortality. Recombinant activated factor VII (rFVIIa) was developed initially for treating patients with hemophilia; however, it has been used increasingly "off-label" to achieve hemostasis after thoracic aortic procedures. OBJECTIVE: This scoping review aimed to present the available literature on the role of rFVIIa in the management of refractory postoperative bleeding after thoracic aortic surgery. METHODS/RESULTS: An electronic database search was conducted using Medline, Embase, Cochrane Library, and Google Scholar in June 2023. The authors included studies that reported the use of rFVIIa in patients undergoing surgical repair of ascending or descending aortic aneurysm or dissection. Single-case reports were excluded. Ten publications with a pooled number of 649 patients (319 patients received rFVIIa and 330 in the control groups) were identified: 3 case series, 6 retrospective studies, and 1 nonrandomized clinical trial. All studies reported the potential role of rFVIIa in correcting coagulopathy and reducing postoperative blood loss in this group of patients. Overall, there was not enough evidence to suggest that rFVIIa was associated with higher rates of thromboembolic complications or mortality. CONCLUSION: Limited evidence suggests that rFVIIa may be useful in managing postoperative refractory bleeding in patients undergoing thoracic aortic surgery. However, the impact of rFVIIa on thromboembolic complications and mortality rates remains unclear.

URL: https://www.ncbi.nlm.nih.gov/pubmed/38036397
DOI: https://dx.doi.org/10.1053/j.jvca.2023.09.041

2. Flynn BC, Steiner ME, Mazzeffi M. Off-label Use of Recombinant Activated Factor VII for Cardiac Surgical Bleeding. Anesthesiology. 2023;139(2):197-210. DOI: 10.1097/ALN.0000000000004569

URL: https://www.ncbi.nlm.nih.gov/pubmed/37155359
DOI: https://dx.doi.org/10.1097/ALN.0000000000004569

3. Shima M. Current status and future prospects of activated recombinant coagulation factor VIIa, NovoSeven(R), in the treatment of haemophilia and rare bleeding disorders. Ann Hematol. 2023. DOI: 10.1007/s00277-023-05287-2

ABSTRACT: rFVIIa, a human recombinant activated coagulation factor VII, has been used worldwide for more than two decades for the treatment of bleeding episodes and prevention of bleeding in patients undergoing surgery/invasive procedures with congenital haemophilia A or B with inhibitors (CHwI A or B), acquired haemophilia (AH), congenital factor VII deficiency and Glanzmann thrombasthenia (GT), refractory to platelet transfusion. The approved dosage, administration and indication of rFVIIa in the US, Europe and Japan differ, depending on the needs of the patient population and regulatory practices. This review presents an overview of the current status and future prospects, including that from a Japanese perspective, of using rFVIIa in the treatment of approved indications. The efficacy and safety of rFVIIa in the approved indications has been demonstrated in several randomised and observational studies and data from registries. The overall incidence of thrombosis across all approved indications in a retrospective safety assessment of clinical trials and registries, prelicensure studies and postmarketing surveillance studies of rFVIIa use was 0.17%. Specifically, the risk of thrombotic events was 0.11% for CHwI, 1.77% for AH, 0.82% for congenital factor VII deficiency and 0.19% for GT. Emerging non-factor therapies such as emicizumab have changed the treatment landscape of haemophilia A, including preventing bleeding in patients with CHwI. However, rFVIIa will continue to play a significant role in the treatment of such patients, particularly during breakthrough bleeding or surgical procedures.

URL: https://www.ncbi.nlm.nih.gov/pubmed/37391649
DOI: https://dx.doi.org/10.1007/s00277-023-05287-2

4. Yogendrakumar V, Mayer SA, Steiner T, et al. Exploring Hematoma Expansion Shift With Recombinant Factor VIIa: A Pooled Analysis of 4 Randomized Controlled Trials. Stroke. 2023;54(12):2990-8. DOI: 10.1161/STROKEAHA.123.043209

ABSTRACT: BACKGROUND: Hematoma expansion shift (HES) analysis can be used to assess the biological effect of a hemostatic therapy for intracerebral hemorrhage. In this study, we applied HES analysis to individual patient data from 4 randomized controlled trials evaluating rFVIIa (recombinant factor VIIa) 80 mug/kg to placebo. METHODS: We generated polychotomous strata of HES using absolute growth thresholds (</=0/<6/>/=6 mL) and quintiles of percent volume change. The relationship between treatment and HES was assessed using proportional odds models. Differences in subgroups based on baseline volume (>/= or <20 mL), and time from symptom onset to treatment (</= or >2 hours) were explored with testing for interactions. RESULTS: The primary analysis included 721 patients. At 24 hours, 36% (134/369) of rFVIIa-treated patients exhibited no hematoma expansion as compared with 25% of placebo (88/352)-treated patients. Significant expansion (>/=6 mL) was reduced by 10% in those treated with rFVIIa-(adjusted common odds ratio [acOR], 0.57 [95% CI, 0.43-0.75]). An examination of percent change similarly showed a shift across the spectrum of expansion (acOR, 0.61 [95% CI, 0.47-0.80]). In both groups, mild-to-moderate expansion was observed in 38% to 47% of patients, depending on the threshold used. Differences in absolute HES between the rFVIIa and placebo groups were more pronounced in patients with baseline hemorrhage volumes >/=20 mL (acOR, 0.48 [95% CI, 0.30-0.76] versus <20 mL: acOR, 0.67 [95% CI, 0.47-0.95]; P(interaction)=0.02). No treatment interaction in patients treated within 2 or after 2 hours from onset was observed (acOR, 0.42 [95% CI, 0.19-0.91 versus >2 hours: acOR, 0.59 [95% CI, 0.44-0.79]; P(interaction)=0.30). CONCLUSIONS: The association between rFVIIa and hematoma growth arrest is most pronounced in patients with larger baseline volumes but is evident across the full spectrum of treated patients.

URL: https://www.ncbi.nlm.nih.gov/pubmed/37805927
DOI: https://dx.doi.org/10.1161/STROKEAHA.123.043209

5. Ciolek AM, Arnall J, Moore DC, et al. Eptacog Beta for Bleeding Treatment and Prevention in Congenital Hemophilia A and B With Inhibitors: A Review of Clinical Data and Implications for Clinical Practice. Ann Pharmacother. 2022;56(7):831-8. DOI: 10.1177/10600280211049394

ABSTRACT: OBJECTIVE: To review the pharmacology, dosing and administration, safety, clinical efficacy, and role of eptacog beta in the treatment of congenital hemophilia with inhibitors. DATA SOURCES: A literature search of PubMed (1966 to August 2021) was conducted using the keywords eptacog beta, recombinant FVII, and hemophilia. STUDY SELECTION AND DATA EXTRACTION: All relevant published articles and prescribing information on eptacog beta for the treatment of congenital hemophilia with inhibitors were reviewed. DATA SYNTHESIS: Eptacog beta is a novel recombinant activated factor VII (rVIIa) product that demonstrated efficacy in controlling bleeding and associated pain in patients with hemophilia A or B with inhibitors. Eptacog beta has limited Food and Drug Administration-approved and off-label indications compared with other bypassing agents (BPAs; activated prothrombin complex concentrates [aPCC; eptacog alfa]). Eptacog beta costs less than eptacog alfa, but still more than aPCCs. RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE: This review provides insight into the role of eptacog beta for treatment of congenital hemophilia with inhibitors and reviews important health system formulary considerations for available BPAs. CONCLUSIONS: Eptacog beta is more cost-effective than eptacog alfa and, as such, may become the preferred rVIIa formulary product. However, eptacog alfa availability remains necessary for the treatment of disorders where eptacog beta has limited data. aPCC should remain the first-line BPA for the treatment of bleeding in patients with inhibitors with no contraindications to use because of its equivocal efficacy and safety and in light of the magnitude of cost savings associated with this strategy.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34595941
DOI: https://dx.doi.org/10.1177/10600280211049394

6. Kidd B, Sutherland L, Jabaley CS, et al. Efficacy, Safety, and Strategies for Recombinant-Activated Factor VII in Cardiac Surgical Bleeding: A Narrative Review. J Cardiothorac Vasc Anesth. 2022;36(4):1157-68. DOI: 10.1053/j.jvca.2021.03.021

ABSTRACT: As perioperative bleeding continues to be a major source of morbidity and mortality in cardiac surgery, the search continues for an ideal hemostatic agent for use in this patient population. Transfusion of blood products has been associated both with increased costs and risks, such as infection, prolonged mechanical ventilation, increased length of stay, and decreased survival. Recombinant-activated factor VII (rFVIIa) first was approved for

the US market in 1999 and since that time has been used in a variety of clinical settings. This review summarizes the existing literature pertaining to perioperative rFVIIa, in addition to society recommendations and current guidelines regarding its use in cardiac surgery.
URL: https://www.ncbi.nlm.nih.gov/pubmed/33875351
DOI: https://dx.doi.org/10.1053/j.jvca.2021.03.021

7. Batsuli G, Tran DQ, Young G, et al. Real-World Data of the Hemostatic Efficacy of Recombinant Human Factor VIIa Eptacog Beta for Acute Bleeding Events in Patients with Hemophilia a and B with Inhibitors. Blood. 2021;138(Supplement 1):4246-. DOI: 10.1182/blood-2021-152981
ABSTRACT: Introduction: Activated prothrombin complex concentrate (FEIBA, Takeda) and recombinant factor VIIa (rFVIIa, Novoseven, NovoNordisk) remain the primary bypassing agents (BPA) available for bleeding management in patients with hemophilia and inhibitors. Eptacog beta [rFVIIa-B, Coagulation factor VIIa (recombinant)-jncw, Sevenfact, HEMA Biologics & LFB] is a recombinant human FVIIa approved by the FDA in 2020 for the treatment of acute bleeding events in adult and adolescent patients ≥12 years old with hemophilia A or B with inhibitors. rFVIIa-B demonstrated hemostatic efficacy of 86% in a phase 3, randomized cross-over study of 465 mild/moderate bleeding events in 27 patients with hemophilia A and B with inhibitors. The purpose of this study is to report real-world data on the hemostatic efficacy of rFVIIa-B for acute bleeding management in patients with hemophilia A and B with inhibitors. Methods: This is a retrospective chart-review of individuals ≥12 years of age with severe hemophilia A (factor VIII <1%) or hemophilia B (factor IX <1%) with an active inhibitor from 3 U.S. hemophilia treatment centers who utilized rFVIIa-B for acute bleed management. Results: Seven bleeds were treated among the 3 patients identified. Patient characteristics and bleeding events are summarized in Table 1. The 3 patients were 12, 13, and 31 years of age. Two patients had hemophilia A and 1 patient had hemophilia B. The 2 patients with hemophilia A were on emicizumab prophylaxis per standard dosing regimens for bleeding prevention. The individual patient with hemophilia B had a history of anaphylaxis at inhibitor development and received on-demand BPA for acute bleeding events. All 7 bleeds consisted of hemarthroses with the knee being the primary site in 57% of the bleeds. Five of the 7 bleeds (71%) received a severe bleeding dose of 210-225 microgram per kilogram (mcg/kg) for the initial rFVIIa-B dose followed by 70-75 mcg/kg for subsequent doses. Final dosing regimens were dependent on available vial sizes. rFVIIa-B resulted in complete resolution of all bleeds (100%) at a median of 4 doses (range 1-8 doses) and a median of 24 hours (range 3-48 hours). There were no failures in bleeding resolution following treatment. No adverse events with infusions were reported including infusion-related reactions, hypersensitivity reactions, thrombosis, or thrombotic microangiopathy. Conclusions: Administration of rFVIIa-B in the real-world setting appears to demonstrate hemostatic efficacy in a cohort of pediatric and adult patients with hemophilia A and B with inhibitors and may serve as an alternative human rFVIIa therapy for the management of acute bleeds in this population. Further post-marketing studies are warranted to expand the indication to younger children (<12 years of age) and to continue to monitor drug efficacy and adverse events in a larger population of patients over time including individuals on non-factor therapies such as emicizumab. [Formula presented] Disclosures: Batsuli: Bio Product Laboratory: Honoraria; Kedrion: Honoraria. Tran: HEMA Biologics: Honoraria. Young: Apcintex, BioMarin, Genentech/Roche, Grifols, Novo Nordisk, Pfizer, Rani, Sanofi Genzyme, Spark, Takeda, and UniQure: Consultancy; Genentech/Roche, Grifols, and Takeda: Research Funding. Sidonio: Guardian Therapeutics: Consultancy; Octapharma: Consultancy, Research Funding; Catalyst: Consultancy; Pfizer: Consultancy; Takeda: Consultancy, Research Funding; Biomarin: Consultancy; Novo Nordisk: Consultancy; Bayer: Consultancy; Genentech: Consultancy, Research Funding.
URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02371158/full
DOI: https://dx.doi.org/10.1182/blood-2021-152981

8. Chang Z, Chu X, Liu Y, et al. Use of recombinant activated factor VII for the treatment of perioperative bleeding in noncardiac surgery patients without hemophilia: A systematic review and meta-analysis of randomized controlled trials. Journal of Critical Care. 2021;62:164-71.
ABSTRACT: Purpose: To evaluate the efficacy and safety of perioperative use of recombinant activated factor VII (rFVIIa) in noncardiac patients. Material(s) and Method(s): We searched electronic databases for randomized controlled trials (RCTs) that involved the use of rFVIIa through December 13, 2019 in noncardiac patients without hemophilia. Two investigators extracted the related data and assessed the quality of the included trials. Result(s): Eleven RCTs examining 993 perioperative patients were ultimately included. The use of rFVIIa did not decrease all-

cause mortality (RR:0.90; 95% CI:0.50,1.64; I² = 0.0%; P = 0.738), shorten the length of ICU (SMD:-0.15; 95% CI:-0.47,0.17; I² = 0.0%; P = 0.346) or hospital (SMD:0.42; 95% CI:-0.05,0.89; I² = 0.0%; P = 0.078) stay, or increase incidence of the thromboembolic events (RR:1.30; 95% CI:0.70,2.41; I² = 0.0%; P = 0.403) among perioperative patients. However, individual RCT analyses showed that the use of rFVIIa could reduce the volume of blood loss (including prostatic cancer, severe acute pancreatitis (SAP), and spinal disease) and the transfusion of RBCs (including prostatic cancer, SAP, and spinal disease) and FFP (SAP) in a subset of perioperative patients. Publication bias was not present. Conclusion(s): For perioperative hemorrhagic patients, rFVIIa-based hemostatic therapy showed no effect on mortality, ICU or hospital LOS, or the rate of thromboembolic events, although it appears to decrease blood loss and reduce the need for blood product transfusion in a subset of patients. Copyright © 2020 Elsevier Inc.
URL: https://pubmed.ncbi.nlm.nih.gov/33385773/
DOI: https://doi.org/10.1016/j.jcrc.2020.12.009

9. Cotter E, Sharma A, Campton A, et al. Very low-dose recombinant Factor VIIa administration for cardiac surgical bleeding reduces red blood cell transfusions and renal risk: a matched cohort study. Blood Coagulation and Fibrinolysis. 2021;32(7):473-9.
ABSTRACT: Outcomes following administration of very-low-dose recombinant activated factor VIIa (vld-rFVIIa) for cardiac surgical bleeding remain debatable. We sought to determine the association of vld-rFVIIa and adverse surgical outcomes. Retrospective, cohort matching of patients undergoing cardiac surgery who received vld-rFVIIa (median 13.02 microg/kg) for perioperative bleeding were matched to cardiac surgical patients who had bleeding and received standard of care for bleeding without Factor VIIa administration. Of the 362 matched patients (182 in each group), patients who received rFVIIa required significantly less red blood cell transfusions [median 3 units (range 0 - 60, IQR = 4 units) versus 4 units (range 2-34, IQR = 4 units); P = 0.0004], decreased length of hospital stay (median 8 versus 9 days; P = 0.0158) and decreased renal risk (P < 0.0001). Incidence of renal failure, postoperative infection, postoperative thrombosis, prolonged ventilation, total ICU hours and 30-day mortality were not different between the two groups. Vld-rFVIIa for cardiac surgical bleeding was associated with decreased red blood cell transfusion, renal risk and length of hospital stay without increased thromboembolism or mortality when compared to patients who had cardiac surgical bleeding and received standard of care without Factor VIIa.
URL: https://pubmed.ncbi.nlm.nih.gov/34650021/
DOI: https://doi.org/10.1097/mbc.0000000000001079

10. Escobar M, Castaman G, Boix SB, et al. The safety of activated eptacog beta in the management of bleeding episodes and perioperative haemostasis in adult and paediatric haemophilia patients with inhibitors. Haemophilia. 2021;27(6):921-31. DOI: 10.1111/hae.14419
ABSTRACT: INTRODUCTION: Haemophilia patients with inhibitors often require a bypassing agent (BPA) for bleeding episode management. Eptacog beta (EB) is a new FDA-approved recombinant activated human factor VII BPA for the treatment and control of bleeding in haemophilia A or B patients with inhibitors (>/=12 years of age). We describe here the EB safety profile from the three prospective Phase 3 clinical trials performed to date. AIM: To assess EB safety, immunogenicity and thrombotic potential in children and adults who received EB for treatment of bleeding and perioperative care. METHODS: Using a randomized crossover design, 27 subjects in PERSEPT 1 (12-54 years) and 25 subjects in PERSEPT 2 (1-11 years) treated bleeding episodes with 75 or 225 mug/kg EB initially followed by 75 mug/kg dosing at predefined intervals as determined by clinical response. Twelve PERSEPT 3 subjects (2-56 years) received an initial preoperative infusion of 75 mug/kg (minor procedures) or 200 mug/kg EB (major surgeries) with subsequent 75 mug/kg doses administered intraoperatively and post-operatively as indicated. Descriptive statistics were used for data analyses. RESULTS: Sixty subjects who received 3388 EB doses in three trials were evaluated. EB was well tolerated, with no allergic, hypersensitivity, anaphylactic or thrombotic events reported and no neutralizing anti-EB antibodies detected. A death occurred during PERSEPT 3 and was determined to be unlikely related to EB treatment by the data monitoring committee. CONCLUSION: Results from all three Phase 3 trials establish an excellent safety profile of EB in haemophilia A or B patients with inhibitors for treatment of bleeding and perioperative use.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34636112
DOI: https://dx.doi.org/10.1111/hae.14419

11. Baral P, Cotter E, Gao G, et al. Characteristics Associated With Mortality in 372 Patients Receiving Low-Dose Recombinant Factor VIIa (rFVIIa) for Cardiac Surgical Bleeding. J Cardiothorac Vasc Anesth. 2019;33(8):2133-40. DOI: 10.1053/j.jvca.2019.01.047

ABSTRACT: OBJECTIVE: Activated recombinant factor VII (rFVIIa) has been used to treat cardiac surgical bleeding in an off-label manner. This observational report analyzes the outcomes with use of a low dose and early administration of rFVIIa for cardiac surgical bleeding. DESIGN: A retrospective, observational study. SETTING: Single-center, tertiary care cardiothoracic surgical setting. PARTICIPANTS: A total of 6,862 patients underwent cardiac surgery from January 2012 to January 2018. Of those, 372 patients received rFVIIa perioperatively. INTERVENTIONS: An institutional policy directed low-dose, incremental aliquots of intravenous rFVIIa (0.5-1 mg). Characteristics and outcomes were compared among patients who survived (n = 328) and patients who died (n = 44). MEASUREMENTS AND MAIN RESULTS: The median dose of rFVIIa was low at 13.29 mug/kg. Higher doses were given to patients who died (15.79 mug/kg v 12.99 mug/kg; p = 0.0133). Patients who died received more blood and component transfusions (median 9 products in those who died v 6 products in survivors; p = 0.0022), although the median transfusion requirement for all patients was 6 units per patient. The rate of reoperation was not different in the 2 groups. Mortality was associated with emergent/urgent surgical procedures (p = 0.0282), type of surgical procedure with aortic procedures being highest risk (p = 0.0014), cardiogenic shock (p = 0.0028), postoperative renal failure (p = 0.0035), postoperative cardiac arrest (p = 0.0006), and ischemic stroke (p = 0.0084). CONCLUSION: Mortality after life-threatening cardiac surgical bleeding treated with rFVIIa was more common in aortic procedures and emergent and urgent surgeries. Lower doses of rFVIIa than previously reported may achieve bleeding cessation because overall blood component transfusions were low in this cohort.

URL: https://www.ncbi.nlm.nih.gov/pubmed/30772178
DOI: https://dx.doi.org/10.1053/j.jvca.2019.01.047

12. Diaz R, Almeida P, Alvarez M, et al. Life-Threatening Pulmonary Hemorrhage Responds to Recombinant Factor VIIa: A Case Series in South Florida Hospitals. Cureus. 2019;11(11):e6202. DOI: 10.7759/cureus.6202

ABSTRACT: Intravenous recombinant activated Factor VIIa (rFVIIa) is approved as a hemostatic agent for only a few bleeding disorders. Since the first reported case of off-label use for rFVIIa in 1999, off-label use far exceeds the use for approved conditions. The endobronchial administration of rFVIIa to control alveolar hemorrhage has been published in only a few case reports. Herein we report a case series of endobronchial rFVIIa use for life-threatening pulmonary hemorrhage at two institutions in south Florida.

URL: https://www.ncbi.nlm.nih.gov/pubmed/31890404
DOI: https://dx.doi.org/10.7759/cureus.6202

13. Feih JT, Juul JJ, JR GR, et al. Adequacy of hemostatic resuscitation improves therapeutic efficacy of recombinant activated factor VII and reduces reexploration rate for bleeding in postoperative cardiac surgery patients with refractory hemorrhage. Ann Card Anaesth. 2019;22(4):388-93. DOI: 10.4103/aca.ACA_108_18

ABSTRACT: BACKGROUND: Excessive bleeding and surgical reexploration are common complications that increase the risk of multi-organ failure and prolonged hospitalization after cardiac surgery. Off-label use of recombinant activated factor VII (rFVIIa) is a recommended treatment for refractory bleeding. OBJECTIVE: The objective of the study is to determine if the adequacy of hemostatic resuscitation enhances the efficacy of rFVIIa. METHODS: This retrospective, observational, cohort study included patients who received rFVIIa for refractory postoperative bleeding after cardiac surgery. Patients were divided into two groups based on the presence or absence of adequate coagulation resuscitation before rFVIIa administration, defined as international ratio (INR) </=1.5, platelet count >/=100 K/mL, and fibrinogen >/=200 mg/dL. The failure of rFVIIa treatment was defined as surgical reexploration within 24 h, thoracostomy drainage >400 mL/h within 6 h or transfusion of additional blood products or another rFVIIa dose within 6 h after initial rFVIIa dose. RESULTS: Of the 3833 patients, screened who underwent cardiothoracic surgery procedures, 58 patients received rFVIIa for refractory postoperative bleeding. Successful hemostasis with rFVIIa was more likely in patients who were adequately resuscitated compared with those who were not (20 [71.4%] vs. 10 [33.3%], respectively; P = 0.0046). Multiple logistic regression analysis indicated that patients who were adequately resuscitated before rFVIIa were less likely to fail treatment (odds ratio, 0.16; 95% confidence interval [0.04-0.62]; P = 0.007). CONCLUSIONS: The therapeutic efficacy of rFVIIa is dependent on the adequacy of hemostatic resuscitation; restoration of normal serum fibrinogen, INR, and platelet counts >100 K/mL

may provide an adequate substrate for rFVIIa to be effective in managing refractory postoperative cardiac surgical bleeding.
URL: https://www.ncbi.nlm.nih.gov/pubmed/31621674
DOI: https://dx.doi.org/10.4103/aca.ACA_108_18

14. Gladstone DJ, Aviv RI, Demchuk AM, et al. Effect of Recombinant Activated Coagulation Factor VII on Hemorrhage Expansion Among Patients With Spot Sign-Positive Acute Intracerebral Hemorrhage: The SPOTLIGHT and STOP-IT Randomized Clinical Trials. JAMA Neurol. 2019;76(12):1493-501. DOI: 10.1001/jamaneurol.2019.2636
ABSTRACT: IMPORTANCE: Intracerebral hemorrhage (ICH) is a devastating stroke type that lacks effective treatments. An imaging biomarker of ICH expansion-the computed tomography (CT) angiography spot sign-may identify a subgroup that could benefit from hemostatic therapy. OBJECTIVE: To investigate whether recombinant activated coagulation factor VII (rFVIIa) reduces hemorrhage expansion among patients with spot sign-positive ICH. DESIGN, SETTING, AND PARTICIPANTS: In parallel investigator-initiated, multicenter, double-blind, placebo-controlled randomized clinical trials in Canada ("Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy [SPOTLIGHT]) and the United States (The Spot Sign for Predicting and Treating ICH Growth Study [STOP-IT]) with harmonized protocols and a preplanned individual patient-level pooled analysis, patients presenting to the emergency department with an acute primary spontaneous ICH and a spot sign on CT angiography were recruited. Data were collected from November 2010 to May 2016. Data were analyzed from November 2016 to May 2017. INTERVENTIONS: Eligible patients were randomly assigned 80 mug/kg of intravenous rFVIIa or placebo as soon as possible within 6.5 hours of stroke onset. MAIN OUTCOMES AND MEASURES: Head CT at 24 hours assessed parenchymal ICH volume expansion from baseline (primary outcome) and total (ie, parenchymal plus intraventricular) hemorrhage volume expansion (secondary outcome). The pooled analysis compared hemorrhage expansion between groups by analyzing 24-hour volumes in a linear regression model adjusted for baseline volumes, time from stroke onset to treatment, and trial. RESULTS: Of the 69 included patients, 35 (51%) were male, and the median (interquartile range [IQR]) age was 70 (59-80) years. Baseline median (IQR) ICH volumes were 16.3 (9.6-39.2) mL in the rFVIIa group and 20.4 (8.6-32.6) mL in the placebo group. Median (IQR) time from CT to treatment was 71 (57-96) minutes, and the median (IQR) time from stroke onset to treatment was 178 (138-197) minutes. The median (IQR) increase in ICH volume from baseline to 24 hours was small in both the rFVIIa group (2.5 [0-10.2] mL) and placebo group (2.6 [0-6.6] mL). After adjustment, there was no difference between groups on measures of ICH or total hemorrhage expansion. At 90 days, 9 of 30 patients in the rFVIIa group and 13 of 34 in the placebo group had died or were severely disabled (P = .60). CONCLUSIONS AND RELEVANCE: Among patients with spot sign-positive ICH treated a median of about 3 hours from stroke onset, rFVIIa did not significantly improve radiographic or clinical outcomes. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT01359202 and NCT00810888.
URL: https://www.ncbi.nlm.nih.gov/pubmed/31424491
DOI: https://dx.doi.org/10.1001/jamaneurol.2019.2636

15. Loddo A, Cornacchia S, Cane FL, et al. Prophylaxis of peripartum haemorrhage using recombinant factor VIIa (rfVIIa) in pregnant women with congenital factor VII deficiency: A case report and literature review. Eur J Obstet Gynecol Reprod Biol. 2019;235:77-80. DOI: 10.1016/j.ejogrb.2019.02.017
ABSTRACT: Congenital factor VII deficiency is a rare autosomal recessive disorder associated to different haemorrhagic manifestations. Labour and delivery may cause bleeding risk in patients with this coagulation deficit, thus it is appropriate to clarify whether prophylaxis of peripartum haemorrhage is necessary. To date, there are very few cases in scientific literature which report the management of women with congenital factor VII deficiency during labour, and a consensus for prophylaxis does not exist. In this manuscript we present the management of a 35 years old woman with factor VII deficiency, treated with recombinant factor VIIa before delivery, without haemorrhagic complications either for the woman and for the infant. Therefore, we present a review of similar cases managed with a peripartum prophylaxis with recombinant factor VIIa, and discuss its usefulness and effectiveness, in view of the severity of the deficit and the doses used.
URL: https://www.ncbi.nlm.nih.gov/pubmed/30831446
DOI: https://dx.doi.org/10.1016/j.ejogrb.2019.02.017

16. Meeks SL, Leissinger CA. The evolution of factor VIIa in the treatment of bleeding in haemophilia with inhibitors. Haemophilia. 2019;25(6):911-8. DOI: 10.1111/hae.13845
ABSTRACT: The use of activated factor VII (FVIIa) for the treatment of bleeding events in haemophilia patients with inhibitors was first reported over 30 years ago. Since then clinical trials, registries, case series, real-world experience and an understanding of its mechanism of action have transformed what was originally a scientific curiosity into one of the major treatments for inhibitor patients, with innovative therapeutic regimens, dose optimization and individualized care now widely practiced. Given current understanding and use, it might be easy to forget the years of clinical research that led up to this point; in this review, we lay out changes based on broad eras of rFVIIa use. These eras cover the original uncertainty associated with dosing, efficacy and safety; the transformation of care ushered in with its widespread use; and the optimization and individualization of patient care and the importance of specialized support provided by haemophilia treatment centres. Today with the introduction of novel prophylactic agents such as emicizumab, we once again find ourselves dealing with the uncertainties of how best to utilize rFVIIa and newer investigational variants such as marzeptacog alfa and eptacog beta; we hope that the experiences of the past three decades will serve as a guide for this new era of care.
URL: https://www.ncbi.nlm.nih.gov/pubmed/31489759
DOI: https://dx.doi.org/10.1111/hae.13845

17. Shayeb AM, Su Y, Kang G, et al. Efficacy and Safety of Recombinant Activated Factor VII Off-label Use in a Pediatric Hematology/Oncology Cohort. Journal of Pediatric Hematology/Oncology. 2019;41(2):E72-E8.
ABSTRACT: Background: Recombinant activated factor VII (rFVIIa) has been used off-label to treat or prevent severe bleeding in patients for whom conventional treatments are unsuccessful. However, studies in children remain limited. Procedure: To examine the efficacy and safety of rFVIIa, we performed a retrospective analysis of rFVIIa off-label use in a pediatric hematology/oncology cohort at a single center from 2006 to 2014. Result(s): Of 58 patients identified, 46 (79.3%) received rFVIIa to treat bleeding and 12 (20.7%) to prevent bleeding. Thirty-three (71.7%) patients had life-threatening bleeding. In the treatment group, 63.0% patients were responders (ie, bleeding decreased or stopped) and 37.0% were nonresponders (ie, bleeding did not change). Blood products usage was similar between responders and nonresponders. After rFVIIa administration, prothrombin time, partial thromboplastin time and lactate were significantly lower, but fibrinogen was significantly higher in responders than nonresponders. Venous thromboembolism developed in 5.2% (3/58) patients, but its relation to rFVIIa remains unclear. Responders had significantly lower mortality than nonresponders (17.2% vs. 82.4%, P<0.0001). Conclusion(s): rFVIIa controlled most bleeding events in this cohort, despite predominance of life-threatening bleeding, suggesting good efficacy. Venous thromboembolism rate was low. Further studies are warranted to identify predictors of favorable response to rFVIIa in similar patients.
URL: https://pubmed.ncbi.nlm.nih.gov/30608491/
DOI: https://doi.org/10.1097/mph.0000000000001379

18. Smith JE, Watts S, Spear AM, et al. Nebulised recombinant activated factor VII (rFVIIa) does not attenuate the haemorrhagic effects of blast lung injury. Journal of the Royal Army Medical Corps. 2019;165(1):51-6.
ABSTRACT: INTRODUCTION: Primary blast lung injury causes intrapulmonary haemorrhage. A number of case reports have suggested the efficacy of recombinant activated factor VII (rFVIIa) in the treatment of diffuse alveolar haemorrhage from a range of medical causes, but its efficacy in blast lung is unknown. The aim of this study was to investigate whether nebulised rFVIIa attenuates the haemorrhagic effects of blast lung injury in an animal model. METHOD(S): Terminally anaesthetised rabbits subjected to blast lung injury were randomised to receive either rFVIIa or placebo via a nebuliser. The primary outcome was the level of blood iron-transferrin complex, a marker of the extent of blast lung injury, analysed using low temperature electron paramagnetic resonance spectroscopy. RESULT(S): Blast exposure led to a significant fall in iron-bound transferrin in both groups of animals (p<0.001), which remained depressed during the study. There were no significant differences in iron-transferrin between the rFVIIa and placebo treatment groups over the duration of the study (p=0.081), and there was no trend towards elevated iron-transferrin in the rFVIIa-treated group once drug treatment had started. There was suggestive evidence of systemic absorption of rFVIIa given via the inhaled route. CONCLUSION(S): A single dose of nebulised rFVIIa did not attenuate pulmonary haemorrhage in a rabbit model of blast lung injury. As there was some

evidence of systemic absorption, the inhaled route does not avoid the concern about potential thromboembolic complications from administration of rFVIIa. Copyright © Crown copyright (2018), Dstl.
URL: https://pubmed.ncbi.nlm.nih.gov/30420554/
DOI: https://doi.org/10.1136/jramc-2018-001029

19. Chu T, Tang Y, Wang H, et al. Efficacy of recombinant factor VIIa for severe bleeding complicated by platelet transfusion refractoriness in patients with hematologic malignancies. Thromb Res. 2017;160:14-8. DOI: 10.1016/j.thromres.2017.10.015
ABSTRACT: INTRODUCTION: Severe bleeding with platelet transfusion refractoriness (PTR) is a common complication associated with reduced survival in patients with hematologic malignancies. The present study aimed to evaluate the efficacy of recombinant factor VIIa (rFVIIa) for severe bleeding complicated by PTR. MATERIALS AND METHODS: Sixty-four patients suffering from severe bleeding with PTR hospitalized in our center between September 2012 and December 2016 were enrolled in this study. Thirty-two patients received rFVIIa (rFVIIa group) and other conventional hemostatic treatments, while the other 32 patients received conventional hemostatic treatments other than rFVIIa (control group). RESULTS: The baseline parameters of patients before treatment were similar in both groups. The total response rates to hemostatic treatment at 24h and 48h were significantly higher in the rFVIIa group compared with the control group (p=0.014, p=0.020, respectively). Significantly more patients in the rFVIIa group achieved complete responses (CR) at 24h (p=0.031), 48h (p=0.039), and 72h (p=0.021) compared with the control group. The bleeding score (p=0.029), time to control bleeding (p=0.034), and activated partial thromboplastin time (p=0.021) after hemostatic treatment were significantly lower in the rFVIIa group compared with the control group. Patients who achieved a CR to rFVIIa had a significant survival advantage compared with those with a partial response/no response (p=0.020). No complications with venous or arterial thromboembolism were observed during treatment. CONCLUSIONS: rFVIIa may provide effective and safe hemostasis in patients suffering from severe bleeding and PTR.
URL: https://www.ncbi.nlm.nih.gov/pubmed/29080548
DOI: https://dx.doi.org/10.1016/j.thromres.2017.10.015

20. Di Minno MND, Ambrosino P, Myasoedova V, et al. Recombinant Activated Factor VII (Eptacog Alfa Activated, NovoSeven(R)) in Patients with Rare Congenital Bleeding Disorders. A Systematic Review on its Use in Surgical Procedures. Curr Pharm Des. 2017;23(7):1125-31. DOI: 10.2174/1381612822666161230143612
ABSTRACT: In the absence of definite guidelines in the area, we have carried a systemic review to provide a thorough overview concerning the efficacy and safety of recombinant activated factor VII (rFVIIa, NovoSeven(R), Novo Nordisk A/S, Bagsvaerd, Denmark) in patients with Glanzmann's thrombasthenia (GT) and FVII deficiency, undergoing surgical procedures. PubMed, Web of Science, Scopus and EMBASE databases was employed for the search. Three multicenter registries were identified: the Glanzmann's Thrombasthenia Registry (GTR), the Seven Treatment Evaluation Registry (STER), and a German post-marketing surveillance registry (the WIRK study). In addition, data from 10 case-series and/or single-center experiences have been summarized. We have found that the following; perioperatively, the hemostatic effectiveness of rFVIIa was high in GT patients and in those with FVII deficiency undergoing both minor and major surgical procedures. Moreover, in all studies, rFVIIa was well tolerated. Thus, the current evidence shows an optimal perioperative safety/efficacy profile of rFVIIa in the setting of these rare bleeding disorders, and provides the rationale for further studies aimed at evaluating the optimal perioperative anti-hemorrhagic prophylaxis with rFVIIa in GT and in FVII deficient patients.
URL: https://www.ncbi.nlm.nih.gov/pubmed/28034354
DOI: https://dx.doi.org/10.2174/1381612822666161230143612

21. Ducore J, Lawrence JB, Simpson M, et al. Safety and dose-dependency of eptacog beta (activated) in a dose escalation study of non-bleeding congenital haemophilia A or B patients, with or without inhibitors. Haemophilia. 2017;23(6):844-51.
ABSTRACT: Introduction: Varying initial doses of activated eptacog beta (recombinant human FVIIa, rhFVIIa) may provide therapeutic options when treating bleeding in patients with congenital haemophilia who have developed inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX). This study evaluated escalated doses of a new rhFVIIa product as a prelude to selecting the doses for clinical efficacy evaluation in haemophilia patients. Aim(s): To assess the safety, pharmacokinetics, and laboratory pharmacodynamics of 3 doses of rhFVIIa in non-bleeding

patients with congenital haemophilia A or B with or without inhibitors. Method(s): Adult male patients (18-75 years old) with congenital haemophilia A or B (with or without inhibitors) received infusions of rhFVIIa at doses of 25, 75 or 225 mug/kg body weight. Ten patients were treated at each dose level, and each patient received 2 different dose levels. Descriptive methods were used to analyse the data. Result(s): Administration of rhFVIIa at all doses was well tolerated. Pharmacokinetic analyses showed that peak FVIIa plasma levels (C<inf>max</inf>) were approximately proportional to dose and correlated well with peak thrombin generation. Total AUC<inf>0-inf</inf> also was approximately dose proportional. Clot formation and duration correlated with FVIIa activity. Repeat doses did not produce an immunological response. Conclusion(s): In the first dose-escalation study of rhFVIIa to support product registration, eptacog beta at doses of 25, 75, and 225 mug/kg was pharmacodynamically active and well tolerated in non-bleeding patients with congenital haemophilia A or B. Copyright © 2017 The Authors. Haemophilia Published by John Wiley & Sons Ltd.
URL: https://pubmed.ncbi.nlm.nih.gov/28984010/
DOI: https://doi.org/10.1111/hae.13357

22. Lentz SR, Rangarajan S, Karim FA, et al. The potential correlation between patient-reported symptoms and the use of additional haemostatic medication for joint bleeding in haemophilia patients with inhibitors: a post hoc exploratory analysis of recombinant activated factor VII data from the ADEPT2 trial. Blood Coagul Fibrinolysis. 2017;28(3):224-9. DOI: 10.1097/MBC.0000000000000584
ABSTRACT: : Haemophilia treatment guidelines advocate early home-based treatment of acute bleeds. In the ADEPT2 trial, data were collected on the home treatment of bleeds with recombinant activated factor VII (rFVIIa) in haemophilia patients with inhibitors and self-reported bleeding-related symptoms. A total of 93% of all bleeds, and 91.5% of joint bleeds, were treated successfully with one to three doses of 90 mug/kg rFVIIa. However, some patients self-administered additional haemostatic medication (AHM) up to 48 h after the first rFVIIa treatment. The aim of this trial was to investigate the relationship between patient-reported symptoms, time to treatment initiation, and the use of AHM. A post hoc analysis was conducted on 177 joint bleeds and the patient-reported categorical symptoms of pain, swelling, mobility, tingling, and warmth, and the pain visual analogue scale (VAS) score. Analyses were descriptive and used logistic regression modelling. Complete symptom data were available for 141, 136, and 129 joint bleeds at 0 or 1, 3, and 6 h, respectively. Pain and pain VAS assessments were the best predictors of AHM use. Patients who self-administered AHM had higher mean pain VAS scores at each time point; both pain and pain VAS scores declined over time. Time to treatment initiation was an independent predictor for AHM use. Higher initial pain scores and longer time to treatment were the best predictors for administration of AHM. The observation that some patients chose to self-infuse in the face of declining levels of pain warrants further study to better understand the reasons behind patient decision-making.
URL: https://www.ncbi.nlm.nih.gov/pubmed/27427786
DOI: https://dx.doi.org/10.1097/MBC.0000000000000584

23. Wang M, Lawrence JB, Quon DV, et al. PERSEPT 1: a phase 3 trial of activated eptacog beta for on-demand treatment of haemophilia inhibitor-related bleeding. Haemophilia. 2017;23(6):832-43. DOI: 10.1111/hae.13301
ABSTRACT: INTRODUCTION: Haemophilia A or B patients with inhibitors have been treated with FVIIa-containing bypassing agents for over 20 years. However, due to uncertainty regarding dose response and thrombotic risk, the use of a gradual, titrated, minimal dosing strategy remains prevalent, potentially hampering early haemostasis. AIM: Evaluate the dose-dependent efficacy, safety and immunogenicity of activated eptacog beta (rhFVIIa), a new recombinant inhibitor bypassing agent for the treatment of bleeding episodes (BEs). METHODS: A Phase 3, randomized, cross-over study of initial dose regimens (IDRs) in 27 bleeding congenital haemophilia A or B subjects with inhibitors was conducted to evaluate on-demand treatment of mild/moderate BEs. Intravenous 75 mug/kg or 225 mug/kg initial doses with 75 mug/kg subsequent doses by schedule were administered until clinical response. RESULTS: The primary endpoint was sustained clinical response within 12 hours, determined by a composite of objective and pain measures. In the 75 mug/kg IDR, 84.9% (95% CI; 74.0%, 95.7%) of mild/moderate BEs at 12 hours were successfully treated compared to 93.2% (95% CI; 88.1%, 98.3%) treated in the 225 mug/kg IDR. Efficacy between the IDRs was statistically different (P<.020) in mild/moderate bleeding episodes. Both IDRs were well tolerated with no detectable immunogenic or thrombotic responses to rhFVIIa or host cell proteins. CONCLUSION: The dose-dependent efficacy seen in this study supports individualizing the initial dose of eptacog beta to optimize

clinical response. By reducing uncertainty, the PERSEPT 1 results should increase the adoption of early haemostasis as a treatment goal for clinicians who treat haemorrhage in the inhibitor population.
URL: https://www.ncbi.nlm.nih.gov/pubmed/28776894
DOI: https://dx.doi.org/10.1111/hae.13301

24. Young G, Escobar MA, Pipe SW, et al. Safety and efficacy of recombinant activated coagulation factor VII in congenital hemophilia with inhibitors in the home treatment setting: A review of clinical studies and registries. Am J Hematol. 2017;92(9):940-5. DOI: 10.1002/ajh.24811
ABSTRACT: Self-administration of factor and bypassing agents by persons with hemophilia in the home setting is recommended to facilitate earlier intervention after bleeding episodes. The objective of this review was to summarize recombinant activated coagulation factor VII (rFVIIa) safety and efficacy data from clinical trials and patient registries documenting use in the home treatment setting in people with congenital hemophilia with inhibitors (CHwI). A total of 16 studies and registries were identified for inclusion; 14 evaluated on-demand treatment of acute bleeding episodes (865 patients, 9024 bleeding episodes) and 2 evaluated use for secondary prophylaxis (108 patients, 42,861 prophylaxis days). In the on-demand studies, efficacy was consistently high (81%-96%), and thrombotic events were uncommon (n = 3). In the secondary prophylaxis studies, rFVIIa was associated with a 45% to 59% reduction in bleeding episodes and no thrombotic events. These data support the clinical practice of administering rFVIIa in patients in the home treatment setting after initiation under a physician's care.
URL: https://www.ncbi.nlm.nih.gov/pubmed/28589615
DOI: https://dx.doi.org/10.1002/ajh.24811

25. Baker MS, Diab KJ, Graham Carlos W, et al. Intrapulmonary Recombinant Factor VII as an Effective Treatment for Diffuse Alveolar Hemorrhage: A Case Series. Journal of Bronchology and Interventional Pulmonology. 2016;23(3):255-8.
ABSTRACT: Background:The diffuse alveolar hemorrhage (DAH) syndrome is a life-threatening pulmonary complication related to systemic vasculitides, posthematopoietic stem cell transplantation, drugs, or toxins. Once DAH develops, the mortality rate is as high as 50% to 80%. Initial treatment consists of high-dose steroids and supportive measures, including mechanical ventilation. We present a case series of 6 patients treated with intrapulmonary recombinant factor VIIa (rFVIIa) to treat refractory DAH. Method(s):Six patients with DAH were treated with intrapulmonary instillation of rFVIIa. Doses were divided equally between the right and the left lungs. Doses were 30, 50, or 60 mcg/kg and frequencies varied from a single administration to repeated doses on subsequent days on the basis of the clinical response. All patients received high-dose steroids, and 4 also received an aminocaproic acid infusion. Result(s):Intrapulmonary rVFIIa treated DAH effectively in 5 of 6 patients. Doses used were smaller and less frequent than those described previously. Conclusion(s):Intrapulmonary factor VII is an effective adjunctive treatment for DAH. We achieved treatment success with both smaller and less frequent doses than those described previously. This may be a good therapeutic option for DAH, particularly when standard therapies have failed or bleeding is immediately life threatening. It is possible that intrapulmonary rFVIIa could save costs, while improving the intensive care unit length of stay. Further prospective studies are needed to assess the optimal dose and frequency for adequate therapeutic efficacy.
URL: https://pubmed.ncbi.nlm.nih.gov/27261934/
DOI: https://doi.org/10.1097/lbr.0000000000000286

26. Faranoush M, Abolghasemi H, Mahboudi F, et al. A Comparison of Efficacy Between Recombinant Activated Factor VII (Aryoseven) and Novoseven in Patients With Hereditary FVIII Deficiency With Inhibitor. Clin Appl Thromb Hemost. 2016;22(2):184-90. DOI: 10.1177/1076029614555902
ABSTRACT: INTRODUCTION: This study compared the efficacy of Aryoseven with Novoseven to control bleeding episodes in patients with hemophilia A with inhibitors. METHODS: Sixty-six patients were randomized into 2 groups, with 4 consecutive block randomization. These groups received Aryoseven and Novoseven dosages of 90 to 120 mug/kg intravenously every 2 hours. RESULTS: Median (interquartile range) level of factor VIII (FVIII) inhibitor in groups A and B was 15.0 and 19.0 Bethesda Unit (BU) preadministration. Bleeding onset in group A was 1246 +/- 1104 minutes and in group B was 2301 +/- 1693 minutes (P = .311). The Kavakli global response scores and treatment success rate was comparable in both the groups. The side effects in groups A (9.7%) and B (2.9%)

were comparable. CONCLUSION: Biosimilar recombinant activated FVII is found to be as effective as Novoseven in the treatment of acute joint bleeding in patients with hemophilia with inhibitors. Its usage will decrease the gaps in hemophilia.
URL: https://www.ncbi.nlm.nih.gov/pubmed/25343955
DOI: https://dx.doi.org/10.1177/1076029614555902

27. Hollis AL, Lowery AV, Pajoumand M, et al. Impact on postoperative bleeding and cost of recombinant activated factor VII in patients undergoing heart transplantation. Ann Card Anaesth. 2016;19(3):418-24. DOI: 10.4103/0971-9784.185523
ABSTRACT: BACKGROUND: Cardiac transplantation can be complicated by refractory hemorrhage particularly in cases where explantation of a ventricular assist device is necessary. Recombinant activated factor VII (rFVIIa) has been used to treat refractory bleeding in cardiac surgery patients, but little information is available on its efficacy or cost in heart transplant patients. METHODS: Patients who had orthotopic heart transplantation between January 2009 and December 2014 at a single center were reviewed. Postoperative bleeding and the total costs of hemostatic therapies were compared between patients who received rFVIIa and those who did not. Propensity scores were created and used to control for the likelihood of receiving rFVIIa in order to reduce bias in our risk estimates. RESULTS: Seventy-six patients underwent heart transplantation during the study period. Twenty-one patients (27.6%) received rFVIIa for refractory intraoperative bleeding. There was no difference in postoperative red blood cell transfusion, chest tube output, or surgical re-exploration between patients who received rFVIIa and those who did not, even after adjusting with the propensity score (P = 0.94, P = 0.60, and P = 0.10, respectively). The total cost for hemostatic therapies was significantly higher in the rFVIIa group (median $10,819 vs. $1,985; P < 0.0001). Subgroup analysis of patients who underwent redo-sternotomy with left ventricular assist device explantation did not show any benefit for rFVIIa either. CONCLUSIONS: In this relatively small cohort, rFVIIa use was not associated with decreased postoperative bleeding in patients undergoing heart transplantation; however, it led to significantly higher cost.
URL: https://www.ncbi.nlm.nih.gov/pubmed/27397445
DOI: https://dx.doi.org/10.4103/0971-9784.185523

28. Bonanno L, Badeaux J, Devlin R. The incidence of thromboembolism formation following the use of recombinant factor VIIa in patients suffering blunt force compared to penetrating trauma: a systematic review protocol. JBI Database System Rev Implement Rep. 2015;13(2):125-35. DOI: 10.11124/jbisrir-2015-1744
ABSTRACT: Review question/objective This review aims to identify the incidence of thromboembolism formation in patients suffering traumatic injuries after receiving recombinant factor VIIa. To achieve this objective, the following question will be addressed. In both civilian and combat trauma patients 15 years or older that have received intravenous recombinant factor VIIa, is there a difference in the incidence of thromboembolism formation between injuries sustained from blunt force trauma compared to injuries sustained from penetrating trauma? Inclusion criteria Types of participants This review will consider studies of participants who are: 15 years and older suffering blunt force trauma and penetrating trauma injuries, and civilian and combat trauma injuries. Patients suffering burn injuries, a combination of blunt force and penetrating trauma and those patients with a combination of blunt force trauma and penetrating trauma and those on pharmacological anticoagulation will be excluded from this review. Types of intervention(s)/phenomena of interest The incidence of thromboembolism formation associated with rFVIIa administration including: control (non-recombinant factor VIIa and recombinant factor VIIa in blunt force trauma populations control (non-recombinant factor VIIa and recombinant factor VIIa in penetrating trauma populations in both control and recombinant factor VIIa, usual care will be administered to include packed red blood cells, fresh frozen plasma, platelets and crystalloid solutions. Types of outcomes Criteria used to determine a diagnosis of thromboembolism may differ based on varying guidelines. Criteria used in each study reviewed will be considered in an assessment of heterogeneity between studies. Diagnosis of thromboembolism formation will be confirmed by the following: Deep venous thrombosis high-sensitivity D-dimer assay ultrasound. Pulmonary embolism ventilation-perfusion scan computerized tomography pulmonary angiography.
URL: https://www.ncbi.nlm.nih.gov/pubmed/26447038
DOI: https://dx.doi.org/10.11124/jbisrir-2015-1744

29. Di Minno G. Eptacog alfa activated: a recombinant product to treat rare congenital bleeding disorders. Blood Rev. 2015;29 Suppl 1:S26-33. DOI: 10.1016/S0268-960X(15)30005-9
ABSTRACT: Glanzmann's thrombasthenia (GT) and congenital factor VII deficiency (FVII CD) are rare autosomal recessive bleeding disorders: GT is the most frequent congenital platelet function disorder, and FVII CD is the most common factor-deficiency disease after haemophilia. The frequency of these disorders in the general population ranges from 1:500,000 to 1:2,000,000. Because GT and FVII CD are both rare, registries are the only approach possible to allow the collection and analysis of sufficient observational data. Recombinant activated factor VII (rFVIIa, eptacog alfa activated) is indicated for the treatment of acute bleeding episodes and for surgery coverage in patients with GT who are refractory to platelets and have antiplatelet or anti-human leukocyte antigen (HLA) antibodies, and for the prevention and treatment of bleeding in patients with FVII CD. This article summarises published data on the mechanism of action and use of rFVIIa in these disorders from two international, prospective, observational registries: the Glanzmann's Thrombasthenia Registry (GTR) for GT; and the Seven Treatment Evaluation Registry (STER) for FVII CD. Haemostatic effectiveness rates with rFVIIa were high across all patients with GT and those with FVII CD, and treatment with rFVIIa in the GTR and STER registries was well tolerated. The GTR and the STER are the largest collections of data in GT and FVII CD, respectively, and have expanded our knowledge of the management of these two rare bleeding disorders.
URL: https://www.ncbi.nlm.nih.gov/pubmed/26073366
DOI: https://dx.doi.org/10.1016/S0268-960X(15)30005-9

30. Lavigne-Lissalde G, Aya AG, Mercier FJ, et al. Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial. J Thromb Haemost. 2015;13(4):520-9. DOI: 10.1111/jth.12844
ABSTRACT: BACKGROUND: Case reports on recombinant human factor VIIa (rhuFVIIa) use in women with severe postpartum hemorrhage (PPH) showed encouraging results, but no randomized controlled trial (RCT) is available. PATIENTS AND METHODS: Eighty-four women with severe PPH unresponsive to uterotonics were randomized to receive one early single rhuFVIIa infusion (n = 42) or standard care (no rhuFVIIa; n = 42). The primary efficacy outcome measure was the reduction of the need for specific second-line therapies, such as interventional hemostatic procedures, for blood loss and transfusions. The primary safety outcome measure was the number of deaths and thrombotic events during the 5 days following rhuFVIIa infusion. RESULTS: rhuFVIIa was associated with a reduction in the number of patients who needed second-line therapies compared with controls (standard care). Specifically, 39/42 (93%) patients in the standard care arm received second-line therapies and 22/42 (52%) patients in the rhuFVIIa arm (absolute difference, 41%; range, 18-63%; relative risk RR, 0.56 [0.42-0.76]). The delivery mode (vaginal or Cesarean section) did not affect the primary outcome. No death occurred. Two venous thrombotic events were recorded in the rhuFVIIa arm: one ovarian vein thrombosis and one deep vein thrombosis with a non-severe pulmonary embolism. CONCLUSION: This open RCT in women with severe PPH refractory to uterotonics shows that rhuFVIIa reduces the need for specific second-line therapies in about one in three patients, with the occurrence of non-fatal venous thrombotic events in one in 20 patients.
URL: https://www.ncbi.nlm.nih.gov/pubmed/25594352
DOI: https://dx.doi.org/10.1111/jth.12844

31. Matino D, Makris M, Dwan K, et al. Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors. Cochrane Database Syst Rev. 2015;2015(12):CD004449. DOI: 10.1002/14651858.CD004449.pub4
ABSTRACT: BACKGROUND: In people with haemophilia, therapeutic clotting agents might be recognised as a foreign protein and induce anti-factor VIII antibodies, known as 'inhibitors'. Drugs insensitive to such antibodies, either recombinant or plasma-derived, are called factor VIII 'by-passing' agents and used for treatment of bleeding in people with inhibitors. OBJECTIVES: To determine the clinical effectiveness of recombinant factor VIIa concentrate compared to plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors. SEARCH METHODS: We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Coagulopathies Trials Register which comprises references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.Date of the most recent search of the Group's Coagulopathies Trials Register: 23 September 2015. SELECTION CRITERIA: Randomised and quasi-randomised controlled clinical trials comparing recombinant factor VIIa concentrate to

human plasma-derived concentrates (high-dose human or recombinant factor VIII or factor IX concentrate; non-activated prothrombin complex concentrates; activated prothrombin complex concentrates) in people with haemophilia. Comparisons with animal-derived products were excluded. DATA COLLECTION AND ANALYSIS: Two authors independently assessed the trials (eligibility and risk of bias) and extracted data. No combined meta-analyses were performed due to the unavailability of outcomes and comparisons common to the included trials. MAIN RESULTS: A total of 15 trials were identified, two of which (with data for a total of 69 participants) were eligible for analysis. Both trials showed methodological flaws and did not show superiority of one treatment over the other. Both the treatments showed that recombinant factor VIIa and activated prothrombin complex concentrate appeared to have a similar haemostatic effect in both trials, without increasing thromboembolic risk. AUTHORS' CONCLUSIONS: Based on the separate analysis of the two available randomised trials, recombinant factor VIIa and activated prothrombin complex concentrate were found to be similar in efficacy and safety. However, there is a need for further, well-designed, adequately-powered, randomised controlled trials to assess the relative benefits and risks of using recombinant factor VIIa compared to human plasma-derived concentrates in people with haemophilia with inhibitors. It is advisable that researchers in the field define commonly agreed objective outcome measures in order to enable the pooling of their results, thus increasing the power of comparisons. To date, data could not be combined in a formal meta-analysis. For the same reason reporting concordant and discordant pairs in cross-over trials is recommended.
URL: https://www.ncbi.nlm.nih.gov/pubmed/26677005
DOI: https://dx.doi.org/10.1002/14651858.CD004449.pub4

32. Payani N, Foroughi M, Dabbagh A. The Effect of Intravenous Administration of Active Recombinant Factor VII on Postoperative Bleeding in Cardiac Valve Reoperations; A Randomized Clinical Trial. Anesth Pain Med. 2015;5(1):e22846. DOI: 10.5812/aapm.22846
ABSTRACT: BACKGROUND: Postoperative bleeding after cardiac reoperations is among the most complicating problems, both for the physicians and for the patients. Many modalities have been used to decrease its adverse effects and the need for blood products administration. OBJECTIVES: In a randomized double-blinded clinical trial of redo cardiac valve surgery in adult, the effect of active recombinant factor VII (rFVIIa) on postoperative bleeding was compared with placebo. Chest tube drainage was used for comparison of bleeding between the two groups. PATIENTS AND METHODS: Two groups of 18 patients undergoing redo valve surgeries were treated and compared regarding chest tube drainage, need for blood products, prothrombin time (PT), partial thromboplastin time (PTT), hemoglobin and hematocrit, platelet count, and international normalized ratio (INR) in first 24 hours after surgery. Bleeding was assessed at 3rd, 12th, and 24th hour after operation. In rFVIIa group, 40 microg/kg of AryoSeven was administered before end of surgery and same volume of normal saline was administered as placebo in the control group. RESULTS: Study groups showed no difference regarding baseline variables. Three patients in rFVIIa group (16.67%) and 13 in placebo group (72.23%) received blood products ($P < 0.01$). Chest tube blood drainage at 24th hour after operation was 315 +/- 177 mL in rFVIIa group and 557 +/- 168 mL in control group ($P = 0.03$). At third and 12th hour after operation, the difference was not statistically significant ($P = 0.71$ and $P = 0.22$, respectively). Postoperative ICU stay was not different; while extubation was longer in the placebo group (352 +/- 57 vs. 287 +/- 46 minutes; $P = 0.003$). CONCLUSIONS: Our study demonstrated the efficacy of rFVIIa in controlling postoperative bleeding in redo cardiac valve surgeries regarding subsequent blood loss and transfusion requirement; however, outcome results remains to be defined.
URL: https://www.ncbi.nlm.nih.gov/pubmed/25789239
DOI: https://dx.doi.org/10.5812/aapm.22846

33. Pemmaraju N, Sasaki K, Johnson D, et al. Successful Treatment of Intracranial Hemorrhage with Recombinant Activated Factor VII in a Patient with Newly Diagnosed Acute Myeloid Leukemia: A Case Report and Review of the Literature. Front Oncol. 2015;5:29. DOI: 10.3389/fonc.2015.00029
ABSTRACT: Intracranial hemorrhage (ICH) is a common complication in acute myeloid leukemia (AML) patients with an incidence rate of 6.3% (1). Bleeding disorders related to disseminated intravascular coagulation (DIC) are common complications in AML cases (2). Recombinant activated Factor VII [rFVIIa (NovoSeven((R)))] is approved for the treatment of bleeding complications with FVIII or FIX inhibitors in patients with congenital FVII deficiency. Use of rFVIIa for the treatment of acute hemorrhage in patients without hemophilia has been successful (3, 4). Herein, we describe the successful use of rFVIIa in a patient with acute ICH in the setting of newly diagnosed AML.

URL: https://www.ncbi.nlm.nih.gov/pubmed/25717439
DOI: https://dx.doi.org/10.3389/fonc.2015.00029

34. Santagostino E, Escobar M, Ozelo M, et al. Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors. Blood Rev. 2015;29 Suppl 1:S9-18. DOI: 10.1016/S0268-960X(15)30003-5
ABSTRACT: The availability of recombinant activated factor VII (rFVIIa, eptacog alfa activated) has greatly advanced the care of patients with haemophilia A or B who have developed inhibitors against the infused replacement factor. Recombinant FVIIa is licensed for the on-demand treatment of bleeding episodes and the prevention of bleeding in surgery or invasive procedures in patients with congenital haemophilia with inhibitors. This article attempts to review in detail the extensive evidence of rFVIIa in congenital haemophilia patients with inhibitors. Patients with acute bleeding episodes are best treated on demand at home, to achieve the short- and long-term benefits of rapid bleed control. Key prospective studies have shown that rFVIIa achieves consistently high efficacy rates in the management of acute (including joint) bleeds in inhibitor patients in the home treatment setting. Substantial post-approval data from key registries also support the on-demand efficacy profile of rFVIIa established by the prospective clinical trials. The availability of rFVIIa has allowed major surgery to become a reality for inhibitor patients. Studies in key surgery, including orthopaedic procedures, have found that rFVIIa provides consistently high efficacy rates. Importantly, the wealth of data does not raise any unexpected safety concerns surrounding rFVIIa use; this is likely because rFVIIa is a recombinant product with a localised mechanism of action at the site of vascular injury. In summary, rFVIIa is established as an effective and well-tolerated first-line treatment for on-demand bleeding control and bleed prevention during minor and major (including elective orthopaedic) surgery in inhibitor patients. Use of rFVIIa has been a major step towards narrowing the gap in outcomes between inhibitor patients and non-inhibitor patients.
URL: https://www.ncbi.nlm.nih.gov/pubmed/26073369
DOI: https://dx.doi.org/10.1016/S0268-960X(15)30003-5

Search Details & History

Date range filter: 2015-2023
Limits: English, Review Articles, Clinical Trials
Sources searched: Cochrane Library, Embase (OVID), MEDLINE (Ovid), TRIP Pro

Search history:

OVID Databases

Embase, Ovid MEDLINE(R)

#	Searches	Results
1	*Factor VIIa/	3566
2	*recombinant blood clotting factor 7a/	2695
3	(niastase or aryoseven or cevenfacta or coagil-vii or eptacog alfa or eptacog alfa pegol or eptacog alpha or eptacog beta or hemaryo or marzaa or marzeptacog alfa or marzeptacog alpha or novo seven or novoseven or oreptacog alfa or oreptacog alpha or sevenfact or vatreptacog alfa or vatreptacog alpha).ti.	502
4	(((FVII or FVIIa or FVII-A or factor-7 or factor-7a factor-7-a or factor-vii or factor-viia or factor-vii-a or factor-seven or factor-seven-a) adj2 (concentrate? or concentration? or	4802

	infusion? or intravenous or replacement or recombinant or supplement* or transfusion?)) or rFVII or rFVIIa or rFVII-a).ti.	
5	(factor adj2 ("7" or "7A" or "7-A" or VII or VIIA or VII-A or seven or seven-A) adj2 (concentrate? or concentration? or infusion? or intravenous or replacement or recombinant or supplement* or transfusion?)).ti.	4111
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17	limit 16 to english language	1292
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19	limit 18 to yr="2015 -Current"	199

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