Recombinant activated factor VII is associated with postoperative thromboembolic adverse events in bleeding after coronary surgery

Aly Makram Habib
Aly Makram Habib

INSTRUCTIONS

We encourage you to use Adobe’s editing tools (please see the next page for instructions). If this is not possible, (i) reply to all and send a list of corrections (in an email or attachment (Word doc or a scan)) listing each change in the following manner: line number, current text, change to be made, or (ii) print out the proof, mark your corrections clearly in black ink, and fax it to +44 (0)1722 323159. Please do not send corrections as track changed Word documents.

Changes should be corrections of typographical errors only. Changes that contradict journal style will not be made.

These proofs are for checking purposes only. They should not be considered as final publication format. The proof must not be used for any other purpose. In particular we request that you do not post them on your personal/institutional web site, and do not print and distribute multiple copies.

Neither excerpts nor all of the article should be included in other publications written or edited by yourself until the final version has been published and the full citation details are available. You will be sent these when the article is published, along with an author PDF of the final article.

1. License to Publish: If you have not already done so, please visit the link in your Welcome email and complete your License to Publish online.

2. Author groups: Please check that all names have been spelled correctly and appear in the correct order. Please also check that all initials are present. Please check that the author surnames (family name) have been correctly identified by pink letters. If this is incorrect, please identify the full surname of the relevant authors. Occasionally, the distinction between surnames and forenames can be ambiguous, and this is to ensure that the authors’ full surnames and forenames are tagged correctly, for accurate indexing online.

3. Missing elements: Please check that the text is complete and that all figures, tables, and their legends are included.

4. Funding: Please provide a Funding statement, detailing any funding received. Remember that any funding used while completing this work should be highlighted in a separate Funding section. Please ensure that you use the full official name of the funding body, and if your paper has received funding from any institution, such as NIH, please inform us of the grant number to go into the funding section. We use the institution names to tag NIH-funded articles so they are deposited at PMC. If we already have this information, we will have tagged it and it will appear as coloured text in the funding paragraph. Please check the information is correct. Figure has been placed as close as possible to its first citation. Please check that it has no missing sections and that the correct figure legend is present.

5. Conflict of interest: All authors must make a formal statement indicating any potential conflict of interest that might constitute an embarrassment to any of the authors if it were not to be declared and were to emerge after publication. Such conflicts might include, but are not limited to, shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product. The following statement has been added to your proof: ‘Conflict of Interest: none declared.’ If this is incorrect please supply the necessary text to identify the conflict of interest.
MAKING CORRECTIONS TO YOUR PROOF

These instructions show you how to mark changes or add notes to your proofs using Adobe Acrobat Professional versions 7 and onwards, or Adobe Reader DC. To check what version you are using go to Help then About. The latest version of Adobe Reader is available for free from get.adobe.com/reader.

DISPLAYING THE TOOLBARS

Adobe Reader DC
In Adobe Reader DC, the Comment toolbar can be found by clicking ‘Comment’ in the menu on the right-hand side of the page (shown below).

Acrobat Professional 7, 8, and 9
In Adobe Professional, the Comment toolbar can be found by clicking ‘Comment(s)’ in the top toolbar, and then clicking ‘Show Comment & Markup Toolbar’ (shown below).

The toolbar shown below will then be displayed along the top.

USING TEXT EDITS AND COMMENTS IN ADOBE

This is the quickest, simplest and easiest method both to make corrections, and for your corrections to be transferred and checked.

1. Click Text Edits
2. Select the text to be annotated or place your cursor at the insertion point and start typing.
3. Click the Text Edits drop down arrow and select the required action.

You can also right click on selected text for a range of commenting options, or add sticky notes.

SAVING COMMENTS

In order to save your comments and notes, you need to save the file (File, Save) when you close the document.

DO NOT MAKE ANY EDITS DIRECTLY INTO THE TEXT, USE COMMENTING TOOLS ONLY.
Author Query Form

Journal: Interactive CardioVascular and Thoracic Surgery
Article Doi: 10.1093/icvts/ivy067
Article Title: Recombinant activated factor VII is associated with postoperative thromboembolic adverse events in bleeding after coronary surgery
First Author: Aly Makram Habib
Corr. Author: Aly Makram Habib

AUTHOR QUERIES – TO BE ANSWERED BY THE CORRESPONDING AUTHOR

The following queries have arisen during the typesetting of your manuscript. Please click on each query number and respond by indicating the change required within the text of the article. If no change is needed please add a note saying “No change.”

AQ1: Please check that all names have been spelled correctly and appear in the correct order. Please also check that all initials are present. Please check that the author surnames (family name) have been correctly identified by a pink background. If this is incorrect, please identify the full surname of the relevant authors. Occasionally, the distinction between forenames (first names) and surnames can be ambiguous, and this is to ensure that the authors’ full first names and surnames are tagged correctly, for accurate indexing online. Please also check all author affiliations. **ok**

AQ2: Please provide department name (if any) for affiliations ‘a, d and e’ and also check whether the affiliation details are Ok as set. **ok**

AQ3: Please check whether the address details, tel number, extension number and email address of the corresponding author are OK as set. **ok**

AQ4: Please note that per journal style a separate abbreviation section is not allowed. Hence, the section has not been retained, while the expansions have been utilized in the article. Please check. **ok**

AQ5: Please check whether the keywords are OK as set. **ok**

AQ6: Please spell out ‘DDAVP’ (if necessary) provided in artwork of Figure 1. **ok**

AQ7: Figures have been placed as close as possible to their first mention in the text. Please check that the figures are accurately placed in the text, that the images are correct, and that they have the correct caption and citation. **ok**

AQ8: Please note that references have been renumbered as to make them sequential order. Please check. **ok**

AQ9: Please check whether the edit made to the sentence ‘In Supplementary Material …’ is appropriate. **ok**

AQ10: Please check whether the supplementary material citations are OK as set. **ok**

AQ11: Please check whether the addition of section head ‘Limitations’ is appropriate. **ok**

AQ12: Please provide a Funding statement, detailing any funding received. Remember that any funding used while completing this work should be highlighted in a separate Funding section. Please ensure that you use the full official name of the funding body, and if your paper has received funding from any institution, such as NIH, please inform us of the grant number to go into the funding section. We use the institution names to tag NIH-funded articles so they are deposited at PMC. **ok**

AQ13: All authors must make a formal statement indicating any potential conflict of interest that might constitute an embarrassment to any of the authors if it were not to be declared and were to emerge after publication. Such conflicts might include, but are not limited to, shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product. The following statement has been added to your proof: ‘Conflict of Interest: none declared’. If this is incorrect please supply the necessary text to identify the conflict of interest. **ok**

AQ14: Please check whether the article title is OK as given in Ref. [14]. **ok**
Recombinant activated factor VII is associated with postoperative thromboembolic adverse events in bleeding after coronary surgery

Aly Makram Habib, Antonio Maria Calafiore, Marco Cargoni, Massimiliano Foschi and Michele Di Mauro

Abstract

OBJECTIVES: To evaluate the impact of recombinant activated factor VII (rFVIIa) administration on thromboembolic adverse events (TAEs) in coronary artery bypass grafting (CABG) surgery patients showing postoperative bleeding.

METHODS: From January 2004 to May 2015, 180 CABG surgery patients with postoperative bleeding were included in the study. All patients were managed conservatively and 81 (45%) also received rFVIIa.

RESULTS: Ten patients developed new TAEs (5.6%), 15 (8.3%) were re-explored, 4 (2.2%) had postoperative dialysis and 6 (3.3%) died by day 30 postoperation. Among those with TAEs, 7 experienced cerebrovascular accidents, 2 had myocardial infarction and 1 had pulmonary embolism. A multivariable regression model confirmed rFVIIa as the only independent factor associated with the development of TAEs (odds ratio 6.19, 95% confidence interval 1.197–31.996; \(P = 0.0296\)). Fifteen (8.3%) patients were re-explored for bleeding according to our management protocol. No variables to predict the need for re-exploration were identified by the regression model. Chest tube output was statistically significantly lower in patients who received rFVIIa from 3 h \([1.9 (Q1–Q3 1.7–2.1) \text{ml/kg/h vs } 3.2 (Q1–Q3 3–3.4) \text{ml/kg/h}, P = 0.000]\) through to 12 h after admission \([0.6 (Q1–Q3 0.5–0.6) \text{ml/kg/h vs } 0.7 (Q1–Q3 0.6–0.9) \text{ml/kg/h}, P = 0.000]\).

CONCLUSIONS: rFVIIa for the treatment of post-CABG bleeding resulted in increased incidence of TAEs in spite of rapid control of bleeding. Hence, rFVIIa should only be used in such patients within a very narrow range of suitable patients and with extreme caution.

Keywords: Thromboembolic adverse events • Coronary artery bypass grafting • Recombinant activated factor VII • Post-surgical bleeding • Retrospective analysis

INTRODUCTION

Postoperative bleeding occurs in 3–5% of cases following cardiac surgery [1]. Failure of the haemostatic pathways is the major cause, in addition to surgical bleeding. Life-threatening postoperative bleeding may persist in spite of transfusions and medical therapy, and re-exploration may be required [2]. Three to four percent of patients undergoing coronary artery bypass grafting (CABG) surgery require re-exploration for bleeding, which may cause a 2- to 3-fold increase in mortality [3].

Recombinant activated factor VII (rFVIIa) was originally developed to treat bleeding in patients with haemophilia A or B [4]. There are reports [5–7] describing the efficacy and safety of rFVIIa in cardiac surgery but there is limited information regarding its use in CABG. On the contrary, many cardiac surgery studies and meta-analyses [8–12] report some thromboembolic adverse events (TAEs), such as stroke, myocardial infarction (MI), pulmonary embolism (PE), deep venous thrombosis or any other arterial thrombosis, even though the CABG population has not been explored in detail.

Hence, the aim of the present retrospective study is to evaluate the possible impact of rFVIIa administration on TAEs in a CABG population presenting postoperative bleeding.

PATIENTS AND METHODS

The study was conducted in the Cardiac Surgical Intensive Care Unit (CSICU), King Faisal Heart Center, King Faisal Specialist Hospital and
Research Center, Riyadh, Saudi Arabia. Retrospectively, the medical charts of all adult patients who had undergone CABG surgery between January 2004 and May 2015 were screened to identify those who had postoperative bleeding. Postoperative bleeding was defined as chest tube bleeding of 3 mL/kg/h or greater for 2 or more consecutive hours after admission to the CSICU from the operating room. The study protocol was approved by the institutional research centre and ethics committee (RAC # 2121076). As this was a retrospective chart review study, informed consent was waived by the ethical committee.

PATIENTS

Inclusion criteria

All patients in CSICU who underwent CABG surgery between January 2004 and May 2015 and experienced postoperative bleeding were included in the study.

Exclusion criteria

Patients aged less than 18 years old, with a primary coagulation defect, who received rFVIIa in the operating room, pregnant females, or those requiring a mechanical circulatory support device or extracorporeal membrane oxygenation were excluded.

Management of postoperative bleeding in the cardiac surgical intensive care unit and use of recombinant activated factor VII

According to the intraoperative protocol, all patients received a 20-mg/kg tranexamic acid bolus followed by 5 mg/kg/h during the operation and until skin closure. After the bypass, protamine was given to reverse the residual effects of heparin, aiming at an activated clotting time of 120–140 s.

Figure 1 shows the management of postoperative bleeding in our CSICU. Exclusion of surgical causes of bleeding requiring re-exploration (cardiac tamponade, mediastinal haematoma or huge haemothorax) was performed by clinical examination, haemodynamic monitoring, chest X-ray and bedside echocardiography, and finally by consulting the attending cardiac surgeon. Two doses of rFVIIa were commonly used in our CSICU: a full dose (90–120 μg/kg) or a half dose (40–50 μg/kg). The decision to administer rFVIIa was made after discussion between the intensive care unit and surgical teams regarding the options for further treatments, the risks associated with rFVIIa administration, the likelihood of re-exploration, and the haemodynamic state, according to the protocol reported in Fig. 1.

Baseline assessment and data collection

Demographic and clinical data, as well as all the information to calculate EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) [14], were obtained for each patient. Smoking was defined as current smoker or those who ceased smoking in the month previous to surgery.

Operative data included: type of surgical procedure, cardiopulmonary bypass time (CPB), cross-clamping time and circulatory arrest time. Laboratory values were recorded at hospital admission for: haemoglobin, prothrombin time, activated partial thromboplastin time, international normalized ratio, creatinine level, electrolyte levels, bilirubin level, white blood cell counts and platelet counts.

Outcome measures

TAEs were defined as cerebrovascular accidents (CVAs) [15], MI [16], PE [17], deep venous thrombosis or arterial thrombosis. Screening for TAE was performed daily by physical examination. When TAE was suspected, the confirming diagnosis was achieved by coloured duplex ultrasonography for the suspected affected site, trans-thoracic echocardiography, brain computed tomography (CT) scan or magnetic resonance imaging, pulmonary angiogram or CT angiogram and laboratory blood tests. A further brain CT scan was repeated after 48 h if there were no findings from the first scan but the clinical signs of TAEs were still present.

Statistical analysis

Descriptive statistics for the continuous variables are reported as mean ± standard deviation for parametric data while non-parametric data are presented as median and 25th and 75th percentiles. In Supplementary Material, Table S1, normal distribution is reported. Categorical variables are summarized as frequencies and percentages. Comparison between the rFVIIa group and the conventional treatment group was done by Student’s independent t-test or Mann–Whitney U-test for continuous variables, while categorical variables were compared using Fisher’s exact test. To determine the variables associated with TAEs and re-exploration in post-CABG bleeding patients, we conducted standard univariable and multivariable logistic regression analyses for each outcome. A threshold of P-value ≤0.3 was chosen in the univariable models to select variables for the multivariable models. The discrimination and calibration of the final models were tested by receiver operating characteristic curve analysis and Hosmer–Lemeshow Test, respectively. Statistical analyses of the data were done using the software packages SAS version 9.4 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA) and IBM SPSS (Statistical Package for the Social Sciences, IBM, Armonk, New York, USA) version 23 for Microsoft Windows.

RESULTS

Demographic and important laboratory data for the patients who received rFVIIa compared to the conventional treatment group are presented in Table 1. EuroSCORE II and white blood counts were statistically significantly higher in the conventional treatment group compared to the rFVIIa group. Seventeen percent of all patients were taking an oral anticoagulant prior surgery. All of them were shifted to low- or high-molecular-weight heparin 5 days before surgery. Heparin was stopped 12 h before surgery. For emergency cases, high international normalized ratio was reversed to <1.5 using fresh frozen plasma before surgery. Around 92.8% of patients received antiplatelet drugs before surgery: all of these patients received aspirin and 16 (8.9%) patients received an adenosine diphosphate receptor blocker in addition to aspirin. In all patients but emergency cases, antiplatelet drugs were discontinued 5 days before surgery. All emergency cases received aspirin and 2 of them also received adenosine diphosphate receptor blockers.
Thromboembolic events occurred in 10 (5.6%) patients, 15 (8.3%) were re-explored, 4 (2.2%) had postoperative dialysis and 6 (3.3%) patients died by 30 days postoperation (Tables 2–4).

Thromboembolic adverse events

Seven patients had CVA, 2 had MI and 1 had PE (Tables 3 and 4). Five predictors for TAEs were identified through univariable analysis: the use of rFVIIa, female sex, isolated CABG surgery (with no additional valve surgery), preoperative left ventricular ejection fraction lower than 40% and preoperative dialysis (Supplementary Material, Table S2). Multivariable regression model confirmed rFVIIa to be the only independent factor associated with the development of TAEs (Table 5). Two of the CVA patients had hemiplegia but they were able to recover acceptable mobility after 4 months. Three patients had mono-paresis that was completely recovered in a few weeks. The remaining 2 patients had some disorientation.
Two patients experienced MI as confirmed by echo- and electrocardiogram, along with significant troponin release. Coronary angiography was carried out, which revealed a new obstruction in the obtuse marginal artery in 1 patient and in 5 the left anterior descending artery in the second one, both distally to the anastomoses. Percutaneous coronary intervention stenting was successfully performed in both cases with clinical and functional improvement, and they were successfully discharged.

The patient who developed PE showed significant hypoxia with echocardiographic signs of right ventricular strain after the rFVIIa dose. Pulmonary CT angiogram revealed an obstruction in the right middle lobar pulmonary artery. The patient received thrombolytic therapy and showed a considerable clinical improvement. A further pulmonary CT scan, 24 h afterwards, showed partial opening of the occluded artery so the patient was transferred to the ward.

Median CSICU, hospital length of stay (LOS) and postoperative mechanical ventilator days were 4 (Q1–Q3 3–5), 8 (Q1–Q3 7–9) and 2.5 (Q1–Q3 2–3) days, respectively. The patients developing TAEs had significantly higher CSICU, hospital LOS and mechanical ventilator days (8 (Q1–Q3 5.8–9.3) vs 4 (Q1–Q3 3–5), P = 0.000, [19.5 (Q1–Q3 17.5–21.3) vs 8 (Q1–Q3 7–9) P = 0.000] and [5 (Q1–Q3 3.8–6.3) vs 2 (Q1–Q3 2–3), P = 0.000] days, respectively. None of them died within the first month postoperation.

### Bleeding

Fifteen (8.3%) patients were re-explored for bleeding according to our management protocol. rFVIIa, female sex, preoperative diastolic, preoperative anticoagulation treatment, emergency surgery, redo surgery, EuroSCORE II and CPB time in minutes were identified as predictors for re-exploration in the univariable analysis (Supplementary Material, Table 3). However, multivariable analysis failed to confirm any of them as independent predictors of re-exploration (Table 6).

### Table 1: rFVIIa group versus Conventional treatment group on admission

<table>
<thead>
<tr>
<th>Demographic</th>
<th>rFVIIa (81)</th>
<th>Conventional (99)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>53 (48.5–58.5)</td>
<td>53 (50–595)</td>
<td>0.571</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>48 (59.3)</td>
<td>54 (54.5)</td>
<td>0.549</td>
</tr>
<tr>
<td>BMI*</td>
<td>31.6 ± 6.3</td>
<td>32 ± 5.8</td>
<td>0.692</td>
</tr>
<tr>
<td>Pre-operative comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>18 (22.2)</td>
<td>22 (22.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>28 (34.6)</td>
<td>36 (36.4)</td>
<td>0.876</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>32 (39.5)</td>
<td>33 (33.3)</td>
<td>0.437</td>
</tr>
<tr>
<td>Dialysis, n (%)</td>
<td>7 (8.6)</td>
<td>10 (10.1)</td>
<td>0.802</td>
</tr>
<tr>
<td>LVEF &lt;40%, n (%)</td>
<td>38 (46.9)</td>
<td>46 (46.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>6 (7.4)</td>
<td>9 (9.1)</td>
<td>0.790</td>
</tr>
<tr>
<td>IE, n (%)</td>
<td>5 (6.2)</td>
<td>12 (12.1)</td>
<td>0.207</td>
</tr>
<tr>
<td>OVA, n (%)</td>
<td>14 (17.3)</td>
<td>20 (20.2)</td>
<td>0.703</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>0.450</td>
</tr>
<tr>
<td>DVT, n (%)</td>
<td>4 (4.9)</td>
<td>2 (2)</td>
<td>0.411</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td>13 (16)</td>
<td>18 (16.2)</td>
<td>0.843</td>
</tr>
<tr>
<td>Antiplatelet, n (%)</td>
<td>77 (95.1)</td>
<td>91 (90.9)</td>
<td>0.389</td>
</tr>
<tr>
<td>EuroSCORE II*</td>
<td>6.9 (6.1–8.3)</td>
<td>8.3 (6.4–9.7)</td>
<td>0.016</td>
</tr>
<tr>
<td>Operative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency, n (%)</td>
<td>8 (9.9)</td>
<td>6 (6.1)</td>
<td>0.407</td>
</tr>
<tr>
<td>Redo surgery, n (%)</td>
<td>24 (29.6)</td>
<td>26 (26.3)</td>
<td>0.621</td>
</tr>
<tr>
<td>Surgery type, n (%)</td>
<td>50 (61.7)</td>
<td>(59.6)</td>
<td>0.878</td>
</tr>
<tr>
<td>Isolated CABG</td>
<td>31 (38.3)</td>
<td>40 (40.4)</td>
<td></td>
</tr>
<tr>
<td>Valve + CABG</td>
<td>100 (84–121)</td>
<td>112 (92–120)</td>
<td>0.082</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)*</td>
<td>81 (62.5–120)</td>
<td>90 (71–101)</td>
<td>0.151</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/l)*</td>
<td>8.6 (8.3–9.3)</td>
<td>8.7 (8–9)</td>
<td>0.063</td>
</tr>
<tr>
<td>WBC (×10⁹/l)*</td>
<td>11.6 (11.5–11.8)</td>
<td>12.2 (11.9–12.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>Platelets (×10⁹/l)*</td>
<td>160.9 × 10⁹</td>
<td>163.8 × 15.9</td>
<td>0.142</td>
</tr>
<tr>
<td>aPTT (s)*</td>
<td>41 (40–43)</td>
<td>41 (39–43)</td>
<td>0.081</td>
</tr>
<tr>
<td>INR*</td>
<td>1.3 (1.1–1.4)</td>
<td>1.2 (1.1–1.3)</td>
<td>0.116</td>
</tr>
<tr>
<td>ACT (s)*</td>
<td>121 (119–123)</td>
<td>120 (118–123)</td>
<td>0.057</td>
</tr>
<tr>
<td>Urea (mmol/l)*</td>
<td>9 (8–10)</td>
<td>9.6 (9–10)</td>
<td>0.091</td>
</tr>
<tr>
<td>Creatinine (μmol/l)*</td>
<td>152 (146–155)</td>
<td>152 (149–156)</td>
<td>0.090</td>
</tr>
<tr>
<td>Glucose (mmol/l)*</td>
<td>12 (10–13)</td>
<td>12.5 (11–13)</td>
<td>0.126</td>
</tr>
<tr>
<td>Lactate*</td>
<td>3.1 (2.7–3.4)</td>
<td>2.8 (2.5–3.4)</td>
<td>0.118</td>
</tr>
</tbody>
</table>

*Median (25–75 percentile).

Variables with parametric distribution presented as mean ± SD and P-value is calculated through independent t-test.

ACT: activated clotting time; AF: atrial fibrillation; aPTT: activated partial thromboplastin time; BMI: body mass index; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CVA: cerebrovascular accidents; DVT: deep venous thrombosis; EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; Hb: haemoglobin; HTN: hypertension; IE: infective endocarditis; IHD: ischaemic heart disease; INR: International normalized ratio; LVEF: left ventricular ejection fraction; PE: pulmonary embolism; rFVIIa: recombinant activated factor VII; WBC: whit blood count.

and speech problems. Two patients experienced MI as confirmed by echo- and electrocardiogram, along with significant troponin release. Coronary angiography was carried out, which revealed a new obstruction in the obtuse marginal artery in 1 patient and in the left anterior descending artery in the second one, both distally to the anastomoses. Percutaneous coronary intervention stenting was successfully performed in both cases with clinical and functional improvement, and they were successfully discharged.

The patient who developed PE showed significant hypoxia with echocardiographic signs of right ventricular strain after the rFVIIa dose. Pulmonary CT angiogram revealed an obstruction in the right middle lobar pulmonary artery. The patient received thrombolytic therapy and showed a considerable clinical improvement. A further pulmonary CT scan, 24 h afterwards, showed partial opening of the occluded artery so the patient was transferred to the ward.

Median CSICU, hospital length of stay (LOS) and postoperative mechanical ventilator days were 4 (Q1–Q3 3–5), 8 (Q1–Q3 7–9) and 2.5 (Q1–Q3 2–3) days, respectively. The patients developing TAEs had significantly higher CSICU, hospital LOS and mechanical ventilator days (8 (Q1–Q3 5.8–9.3) vs 4 (Q1–Q3 3–5), P = 0.000, [19.5 (Q1–Q3 17.5–21.3) vs 8 (Q1–Q3 7–9) P = 0.000] and [5 (Q1–Q3 3.8–6.3) vs 2 (Q1–Q3 2–3), P = 0.000] days, respectively. None of them died within the first month postoperation.

### Bleeding

Fifteen (8.3%) patients were re-explored for bleeding according to our management protocol. rFVIIa, female sex, preoperative diastolic, preoperative anticoagulation treatment, emergency surgery, redo surgery, EuroSCORE II and CPB time in minutes were identified as predictors for re-exploration in the univariable analysis (Supplementary Material, Table 3). However, multivariable analysis failed to confirm any of them as independent predictors of re-exploration (Table 6).
DISCUSSION

In this retrospective analysis, rFVIIa was found to be the only independent predictor of the development of TAEs, which was associated with significantly higher CSICU and hospital LOS. Von Heymann et al. [6] was the first to report the use of rFVIIa for a case of refractory bleeding after a redo CABG with no TAEs detected. Many data analyses and systemic reviews [7, 8, 18, 19] have evaluated rFVIIa safety in general post-cardiac surgery populations, including CABG patients, with mixed results. These reports did not advise its prophylactic use as it did not improve mortality but can raise the risk for thromboembolic events.

A higher incidence of TAEs was found in the rFVIIa group compared to the conventionally treated group, and this result is in agreement with other studies [20–23]. However, our TAE rate seems to be similar to the rate reported in the literature for patients who did not receive rFVIIa [22, 23]. An interesting point has to be emphasized in our series: most of the patients (72%) received a full dose (90–120 mg/kg) exceeded the lowest dose reported in the literature.

The incidence of TAEs in this report was higher in CABG patients (9.9%) compared to the general cardiac surgery population receiving rFVIIa (5.5–5.9%) [20, 21]. Conversely, the TAE rate in the conventionally treated CABG group who did not receive rFVIIa (2%) was comparable to that reported in the general population (2.4%) [20]. However, the mechanisms underlying this difference in terms of TAEs between the CABG population and the general cardiac surgery population are not clear and deserve further investigation.

The European Multicentre Study on Coronary Artery Bypass Grafting (E-CABG) [24] should be able to provide us with more details about the use of rFVIIa after isolated CABG and its relationship with the development of stroke, MI, and other TAEs. Furthermore, as shown by Mayer et al. [22], the majority of the newly developed TAEs in this report were CVA (70%). Moreover, A.M. Habib et al. / Interactive CardioVascular and Thoracic Surgery 5
Ponschab et al. [23] showed that the use of rFVIIa was associated with an increased rate of stroke in the rFVIIa group compared to the control arm. In this study, 20.4% of the study population had preoperative CVA, which increases their risk for another CVA. In addition, carotid duplex was only performed preoperatively in selected patients.

Regarding bleeding, our results are in agreement with other published studies [25, 26]. The chest tube output continued to be significantly higher in the conventional treatment group until 9–12 h after the admission. A decrease in surgical re-exploration for bleeding was found in the rFVIIa group [27, 28]. A meta-analysis of 5 clinical trials assessing a total of 298 patients revealed no significant decrease in surgical re-exploration for bleeding [25]. In 2011, this same group showed [23] that the use of rFVIIa was associated with an insignificant reduction in terms of surgical re-exploration rate. Surprisingly, Chapman et al. [29], who retrospectively analysed the safety profile and efficacy of rFVIIa used for bleeding following cardiac surgery, showed that the rFVIIa group had a higher rate of re-operation for bleeding (11% vs 4%) and also required increased traditional blood product administration.

Conclusions

Post-CABG bleeding patients treated with rFVIIa exhibited significantly rapid control of chest tube bleeding and fewer blood product transfusions. However, rFVII was the only independent predictor identified for the development of TAEs.

Our results showed that rFVIIa is an effective treatment to control persistent bleeding in the postoperative cardiac surgery setting. However, because of the risk of serious complications, we advise restricting its use to the following situations:

1. Correction of core temperature.
2. Correction of coagulation factors including calcium (we strongly recommend the use of a thromboelastogram to guide transfusions).
3. Reversal of heparin by protamine to achieve an activated clotting time of 120–140 s.
4. Exclusion of surgical bleeding with maximum available efforts including clinical criteria (Barret-Boyes), bedside echocardiogram, and others.

rFVIIa should not be used as an alternative to re-exploration nor by surgeons to buy some time before re-exploration. It is advised to avoid its use in patients bleeding post-CABG and extra-corporeal membrane oxygenation patients.

Further prospective randomized studies are needed to clarify the safety of rFVIIa in these patients. Meanwhile, the use of rFVIIa in such patients should be with extreme caution.

Supplementary Material

Supplementary material is available at ICVTS online.

Conflict of interest: none declared.

References


