Recombinant activated factor VII increases stroke in cardiac surgery: a meta-analysis
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CRD summary
This review evaluated recombinant activated factor VII (rFVIIa) on risk of stroke and need for surgical re-exploration in adult cardiac surgery patients. The authors concluded that rFVIIa could result in a significant increase in stroke and reduced need for surgical re-exploration. Methodological limitations in the included studies suggest that the cautious conclusion and recommendations for practice are justified.

Authors' objectives
To evaluate the impact of recombinant activated factor VII (rFVIIa) on risk of stroke and need for surgical re-exploration in adult cardiac surgery patients.

Searching
PubMed (to December 2010) and eight conference proceedings (2008 to 2010; named in the paper) were searched. Search terms were reported. Reference lists of relevant articles and reviews were scanned and international experts were contacted to identify further studies. There were no language restrictions.

Study selection
Clinical trials that compared rFVIIa with placebo or standard treatment in adult cardiac surgery patients were eligible for inclusion. Studies were excluded if outcome data were missing.

Most studies contained varied cardiac surgery procedures. Intervention dosage varied from 18 to 70ug/kg as a repeatable dose and 90ug/kg as a single dose. Most studies did not have a clear definition of stroke. Primary outcomes assessed were safety in terms of stroke and intervention efficacy for reducing the need for surgical revision for bleeding. Secondary outcomes were death, blood loss and transfusion requirements and the incidence of overall venous and arterial vascular complications (myocardial infarction, stroke and deep vein thrombosis).

Four reviewers independently selected the studies for inclusion.

Assessment of study quality
There was no formally-reported assessment of study quality.

Data extraction
Data were extracted to enable calculation of odds ratios (OR) and 95% confidence intervals (CI). Number needed to harm (NNH) was reported. Authors were contacted for any missing data.

Four reviewers independently extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Odds ratios were pooled in a fixed-effect or random-effects meta-analysis where statistical heterogeneity (measured by Q and I² statistics) was considered high (I²>50%). A funnel plot was used to assess publication bias.

Results of the review
Six trials (470 patients, range 20 to 172) were included in the review. Two trials were randomised, three were propensity-matched and one was a case-matched design. The authors indicated that some trials had poor internal validity.

Use of rFVIIa was associated with a statistically significant increase in rate of stroke (OR 3.69, 95% CI 1.10 to 12.38; six trials, I²=0%; NNH=26). There was no statistically significant difference in the reduction of surgical re-exploration (OR 0.27, 95% CI 0.04 to 1.92; four trials, I²=87%).

A non-statistically significant difference was reported for overall perioperative vascular events (myocardial infarction,
stroke and deep vein thrombosis; six trials, \(I^2=0\%\). There was no difference in mortality (five trials, \(I^2=0\%\)). Further results, which included blood loss and transfusion requirements, were reported in the paper.

There was no evidence of publication bias.

**Authors’ conclusions**

Administration of rFVIIa in cardiac surgery patients could result in a significant increase in stroke and a trend towards a reduced need for surgical re-exploration.

**CRD commentary**

The review question was clear. Inclusion criteria were specified a priori for all aspects apart from outcomes. The search strategy included a major relevant database and several sources of unpublished material. Attempts were made to minimise publication and language biases. The processes of study selection and data extraction included efforts to minimise error and bias. The absence of any formally-reported quality assessment of trials was a limitation of the review; the description of the included designs suggested suboptimal quality (as indicated by the authors). Study details were presented: the number and size of included trials was small; follow-up was reported to be inadequate; and there was evidence of variation and under-reporting of some study characteristics.

The review was generally well conducted. The authors’ cautious conclusion and specific recommendations for practice seem justified.

**Implications of the review for practice and research**

**Practice:** The authors stated that rFVIIa should not be used routinely in cardiac surgery patients. It could be considered cautiously in patients with refractory life-threatening bleeding after other methods to restore haemostasis, rewarming and surgical re-approach had been attempted.

**Research:** The authors stated that sufficiently-powered randomised controlled trials that used intention-to-treat data were needed in this topic area.

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