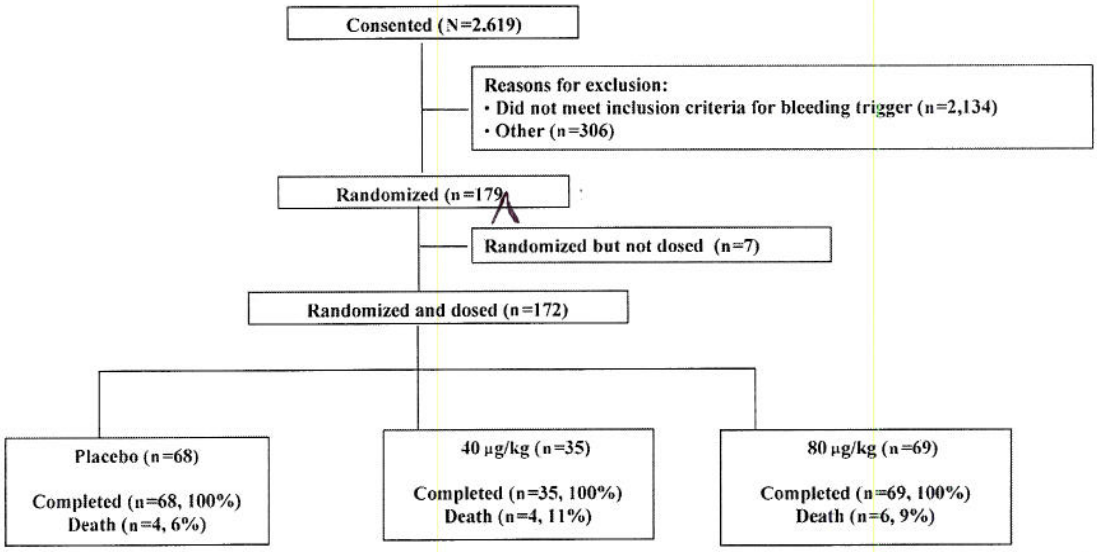

Figure 1. Numbers of patients who consented, were randomized, and completed the study. Of the 7 patients who were randomized but did not receive study drug, 3 were allocated to the placebo group, 3 to the 40 μg/kg group, and 1 to the 80 μg/kg group. In 4 of the 7 patients, the interactive voice response system (IVRS) was called prematurely and was the most common reason for lack of study drug administration. For the remaining 3 patients, there was 1 case each of IVRS called despite not meeting inclusion criterion for bleeding rate, IVRS called but the patient had to go back for reoperation, and IVRS not working.

indicated. We hypothesized that the use of rFVIIa to reduce bleeding in the postoperative setting after cardiac surgery requiring CPB was safe.

Methods

This phase II dose-escalation study was conducted at 30 sites in 13 countries between August 2004 and November 2007. The trial was approved by national, local, and institutional ethics committees and/or review boards as applicable. Written informed consent was obtained before surgery from each patient who met the inclusion criteria (Table I of the online-only Data Supplement).

Patients

Patients eligible for randomization had undergone cardiac surgery requiring CPB and had been admitted to a postoperative care environment (eg, intensive care unit) for at least 30 minutes (stabilization period). Patients were randomized on reaching a prespecified bleeding rate (Table I of the online-only Data Supplement) based on the blood volume obtained from mediastinal drains.

Randomization, Study Monitoring, and Masking

A randomized, double-blind, placebo-controlled trial design was used for each of the individual dose tiers (cohorts). Patients meeting the inclusion criteria were randomized to rFVIIa or placebo. Initially, patients were to be allocated sequentially to 3 cohorts of escalating rFVIIa doses (40, 80, and 160 μg/kg rFVIIa). Cohort 1 comprised 70 patients equally allocated to 40 μg/kg rFVIIa or placebo. Cohort 2 comprised 51 patients randomized 2:1 (80 μg/kg rFVIIa:placebo). Safety and efficacy data were evaluated by a Novo Nordisk Safety Committee and an independent external Data Monitoring Committee at the end of cohort 1, then after every 10 patients randomized in cohort 2a, and every month in cohort 2b. The Data Monitoring Committee had access to all data at the end of each cohort to evaluate the incidence of critical serious adverse events (cSAEs) and advised the sponsor and the Steering Committee if the trial should continue. After completion of the original cohort 2 (cohort 2a), the Data Monitoring Committee recommended duplication of cohort 2 to clarify concerns raised by the data available to the committee. The protocol was amended by including an additional cohort (cohort 2b) with 51 patients randomized 2:1 (80 μg/kg rFVIIa:placebo). At the recommendation of the Steering Committee (masked to treatment allocations), the study was terminated before initiation of cohort 3 (160 μg/kg rFVIIa versus placebo). The committee's advice was based on the data within the expanding cardiac literature in which doses of rFVIIa were in the range of 60 μg/kg.[6,9,10,15]

Patients were randomized through an interactive voice response system and were always assigned to the lowest available randomization number. After randomization, freeze-dried powdered (4.8 mg) rFVIIa or placebo was reconstituted with 8.5 mL sterile water and administered as a bolus injection. To maintain masking within each dose level, an equal volume per body weight of trial product was administered to all patients regardless of treatment group. Physical appearances of the placebo and rFVIIa, either in the freeze-dried form or on reconstitution, were identical. Masking of treatment allocations was maintained until all patient data had been entered and the database was locked.

Transfusion Protocol

No changes to standard practices (eg, anesthesia, surgical practice, CPB, or intensive care) were made until patients reached the prespecified rate of bleeding in a postoperative environment that allowed randomization. At this time, all transfusions except allogeneic red blood cells were discontinued. The transfusion protocol was applied from randomization to day 5 but suspended during reoperations. This protocol is presented as Figure I of the online-only Data Supplement.

End-Point Definitions

The primary end point for the study was the incidence of cSAEs from trial drug administration to day 30. The cSAEs as defined for this trial were death, acute myocardial infarction (ECG evidence of ≥1 new Q waves, left bundle-branch block, or new pathological R waves; troponin T >3.4 μg/L at 48 hours after surgery; or an increase in creatine kinase-MB >30 μg/L at 2 consecutive time points >24 hours after surgery, plus a clinical picture of hemodynamic instability that gives rise to the suspicion of myocardial infarction or graft occlusion), cerebral infarction (new focal neurological deficit, either transient but present >24 hours or permanent), clinically symptomatic pulmonary embolus (clinical signs or suspicion of pulmonary embolus further diagnosed by V/Q scan or postmortem examination; clinical examination is not sufficient for diagnosis), and other clinically symptomatic thrombotic events (signs or suspicion of clinically significant thromboembolic event