The efficacy and safety of human plasma-derived antithrombin in heparin-resistant cardiac surgery patients: A double-blind, placebo-controlled, multicentre study (ATN-108)

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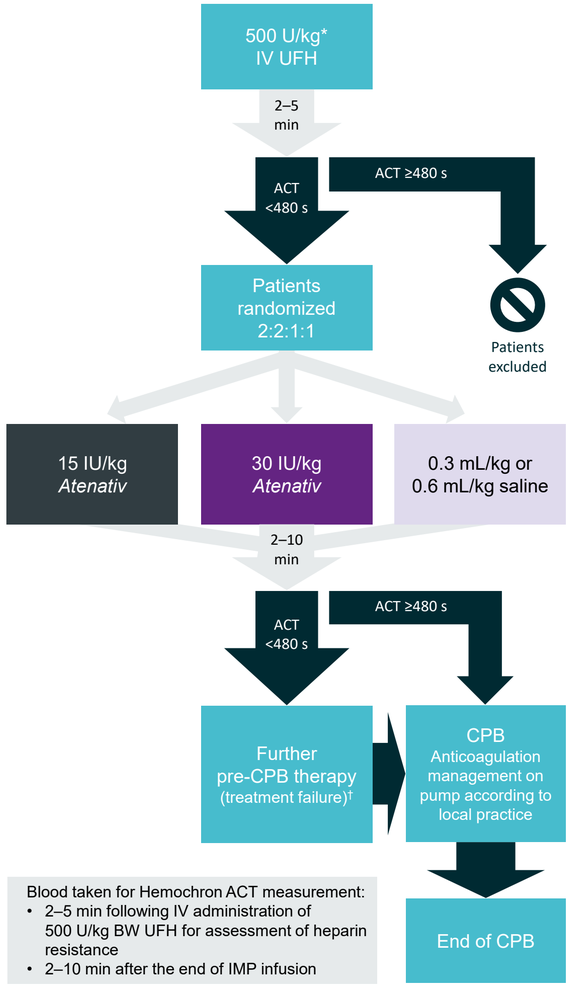
Background and Goal of Study

- Unfractionated heparin (UFH) is the mainstay anticoagulant for patients undergoing cardiopulmonary bypass (CPB); however, up to 26% of these patients experience heparin resistance (defined as an inability to obtain an activated clotting time [ACT] >480 s after administration of 500 U/kg UFH), which is often associated with low antithrombin levels[1,2]
- Antithrombin concentrate, a therapeutic option for treating heparin resistance, is approved in the US for congenital antithrombin deficiency but not for acquired cases
- The ATN-108 study aims to evaluate the efficacy of two doses of antithrombin concentrate (*Atenativ*, Octapharma) versus placebo, in restoring and maintaining heparin responsiveness in adult patients undergoing cardiac surgery necessitating CPB

Materials and Methods

- The ATN-108 study (NCT06096116) is a Phase 3, ongoing, prospective, double-blind, placebo-controlled, three-arm, multicentre study
- The study procedures are outlined in **Figure 1**; heparin-resistant patients (pre-CPB Hemochron ACT <480 s measured 2–5 min following intravenous administration of 500 U/kg UFH) will be randomized to receive a single bolus of either 15 IU/kg or 30 IU/kg *Atenativ*, or saline (0.3 mL/kg or 0.6 mL/kg)
- The need for further pre-CPB therapy to restore heparin responsiveness (i.e., for patients who do not achieve a Hemochron ACT measurement of ≥480 s within 2–10 min after infusion of Atenativ or placebo) will be analysed
- The primary endpoint, the proportion of patients requiring no further therapy containing antithrombin for restoring pre-CPB heparin responsiveness after administration of Atenativ or placebo, and for maintaining it during CPB, will be compared between groups using a one-sided Fisher's Exact Test
- Secondary efficacy and safety endpoints are outlined in **Table 1**, and inclusion and exclusion criteria in **Table 2**

Figure 1. Study Flow



* Possible pre-CPB heparin dosing regimens are outlined below:
1) 500 U/kg BW UFH → Assessment of Heparin Resistance
2) 400 U/kg BW UFH → Hemochron ACT <480 s → 100 U/kg BW UFH → Assessment of Heparin Resistance
3) 300 U/kg BW UFH → Hemochron ACT <480 s → 200 U/kg BW UFH → Assessment of Heparin Resistance
†Following the administration of further corrective therapy (treatment failure), blood will be taken for local ACT measurement and CPB will be initiated at the investigator's discretion
ACT = activated clotting time; BW = body weight; CPB = cardiopulmonary bypass; IU = international units; IMP = investigational medicinal product; IV = intravenous; U = units ; UFH = unfractionated heparin

Table 1. Study Endpoints

Primary Endpoint
The percentage of patients requiring no further therapy containing antithrombin (i.e., FP or other antithrombin concentrates) for restoring pre-CPB heparin responsiveness after administration of *Atenativ* or placebo, and for maintaining it during CPB
Secondary Endpoints: Efficacy Parameters
The amounts of further therapy containing antithrombin needed for restoring pre-CPB heparin responsiveness after administration of *Atenativ* or placebo, and for maintaining it during CPB
The change in ACT values following infusion of each of the *Atenativ* doses and placebo
The change in antithrombin plasma levels following infusion of each of the *Atenativ* doses and placebo
Heparin usage following the infusion of each of the *Atenativ* doses and placebo
The number of units of FP transfused for reasons other than restoring or maintaining heparin responsiveness, both intraoperatively and postoperatively, as well as cumulatively
Postoperative use of antithrombin concentrates for reasons other than restoring heparin responsiveness
Transfusion of other allogeneic blood products (e.g., RBCs, platelets, cryoprecipitate), both intraoperatively and postoperatively, as well as cumulatively
Administration of coagulation factor concentrates (e.g., fibrinogen concentrate, PCC, factor XIII concentrate and recombinant activated factor VII), both intraoperatively and postoperatively, as well as cumulatively
Administration of other haemostatic-relevant therapies (e.g., tranexamic acid, protamine), both intraoperatively and postoperatively, as well as cumulatively
Chest tube drainage volume at 24 h after the start of *Atenativ* or placebo infusion, and total chest tube drainage volume until discharge or 7 days after surgery, whichever comes first
Reoperation for bleeding, including description of the cause of bleeding (surgical vs. non-surgical)
Cell saver volume until the end of surgery
Secondary Endpoints: Safety Parameters
Incidence of AEs in the three study groups
Standard haematological parameters (i.e., RBC count, WBC count, haemoglobin levels, hematocrit, and platelet count) following *Atenativ* or placebo infusion, after the end of CPB, at the end of surgery, and at 24 h after the start of *Atenativ* or placebo infusion
Survival status

ACT = activated clotting time; AE = adverse event; CPB = cardiopulmonary bypass; FP = frozen plasma; PCC = prothrombin complex concentrate; RBC = red blood cell; WBC = white blood cells

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria
1. Planned cardiac surgery with CPB
2. Heparin-resistant patients: pre-CPB Hemochron ACT <480 s in the measurement performed between 2 and 5 min following IV administration of 500 U/kg BW UFH
3. Patients ≥18 and ≤85 years of age
4. Freely given written or electronic informed consent
5. In female patients of childbearing potential, a pre-existing negative pregnancy test within 14 days prior to surgery
Exclusion Criteria
Receiving or have received one or more of the following medications within the specified time frames prior to the start of the surgery: warfarin (within 3 days); direct oral anticoagulants (within 2 days); ticlopidine (within 14 days); prasugrel (within 7 days); clopidogrel (within 5 days); ticagrelor (within 5 days); glycoprotein IIb/IIIa antagonist (within 1 day)
Pre-existing coagulopathy, a history of bleeding problems or a laboratory-diagnosed bleeding disorder (e.g., von Willebrand disease, platelet disorder)
Renal insufficiency, defined as serum creatinine level >1.5 mg/dL
Known hypersensitivity or allergic reaction to antithrombin or any of the excipients in *Atenativ*, i.e., human albumin, sodium chloride, acetyl tryptophan and caprylic acid
History of anaphylactic reaction(s) to blood or blood components
Refusal to receive transfusion of blood or blood-derived products
Current participation in another interventional clinical trial with an investigational medicinal product or previous participation in the current trial
Treatment with any investigational medicinal product within 30 days prior to screening visit

ACT = activated clotting time; BW = body weight; CPB = cardiopulmonary bypass; IV = intravenous; UFH = unfractionated heparin

Results and Discussion

- ATN-108 is planned to start in Q2 2024 and will be conducted across approximately 20 sites in Europe and the United States
- Target enrolment is approximately 120 patients
- The overall study duration will be approximately two years, with completion anticipated in Q3 2026
- The end of the study is defined as the date of completion of the last study visit of the last patient participating in the study

Conclusion

- The results will assess the efficacy and safety of antithrombin concentrate in restoring and maintaining heparin responsiveness in adult patients undergoing CPB for cardiac surgery

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1. Chen Y, et al. *J Cardiothorac Vasc Anesth* 2022;36(11):4150-60; 2. Levy JH, et al. *J Thromb Haemost* 2024;22(4):1249–1257.