Author's response to reviews

Title: Activated coagulation time vs. intrinsically activated modified rotational thromboelastometry in assessment of hemostatic disturbances and blood loss after protamine administration in elective cardiac surgery: analysis from the clinical trial (NCT01281397)

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Author's response to reviews:

Editors in chief
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Dear Editors in Chief,

On behalf of all co-authors allow me to thank you for the extraordinary review, which has contributed to the improvement of our manuscript.

Our working group has carefully examined the reviewers' comments, and herein we provide point-by-point answers in response to these comments.

This manuscript presents exploratory analysis from a clinical trial NCT01281397. Trial was designed in prospective observational fashion. The aim of trial was to assess possibility of point-of-care hemostatic devices (rotational thromboelastometry and multiple electrode aggregometry) to predict excessive bleeding in elective cardiac surgery. Parameters of rotational thromboelastometry and multiple electrode aggregometry were obtained perioperatively at three time points and respective values were correlated with observed key endpoints such as chest tube discharge and transfusion requirements. Patients (n=148) undergoing elective cardiac surgery procedures requiring CPB between July 2010 and January 2011 were prospectively studied. Criteria for excluding patients from the group of subjects were: age younger than 18 years, urgent
procedure, patients with off-pump cardiac surgical procedure, administration of antiplatelet agents other than and clopidogrel, patients with inaccurate antiplatelet therapy administration documentation, urgent surgery, and patients requiring surgical exploration for excessive bleeding due to obvious surgical bleeding with a bleeding vessel identified. Initially, a trial was supposed to include 400 patients. However, during study period our research group decided to perform interim analysis after approximately every 50 patients. After 148 patients enrolled, interim analysis revealed positive results in regard to primary hypothesis that point of care tests for assessment of platelet function and viscoelastic blood properties may predict bleeding in cardiac surgery patients. Thus, considering costs and positive results we decide to terminate study because our primary hypothesis was confirmed much earlier than our primary estimation was.

Patients requiring surgical reexploration for excessive bleeding were supposed to be excluded from study if bleeding vessel would be identified during reexploration. Reexploration per se was not exclusion criteria, in particular if no exact surgical cause of bleeding was present suggesting hemostatic disorder. Please note that study was prospective observational and during study period hemostatic management was based on consensus opinion between consultant anesthesiologist and cardiac surgeon. During study period, no surgical reexploration for bleeding was performed. It is obvious that chest tube output is consisted of both “surgical” and “hemostatic disorder” origin. However, without surgical reexploration performed it is impossible to detect whether some proportion of patients was actually bleeding predominantly due to surgical cause. At our center, surgical reexploration is being performed for each case with suspicion to surgical cause of bleeding.

CTO was determined as study’s primary outcome. To estimate blood loss, we meticulously documented CTO, in first 24 postoperative hours and divided it by patient’s weight. Drainage loss was assessed after completion of a 30-min stabilization period. Blood loss during the stabilization period was not included in the definition of postoperative hemorrhage. Such loss may be caused by postural changes when transferring the patient from the operating room table to the bed or because of fluid in the pleural or mediastinal cavity, which may have arisen from the rinsing with water as an attempt to achieve surgical hemostasis. Intraoperative and postoperative transfusion requirements (PRBC in mL, FFP in mL, fibrinogen cryoprecipitate in grams and platelet concentrates in units) were determined as study’s secondary outcome. Surgical reexploration of the mediastinum for excessive bleeding was noted, along with any surgical explanation for the bleeding. Although some authors offer definitions of abnormal blood loss [16], we decided to make our own definition in order to adapt the volume of postoperative CTO to our study cohort. We believe that such a definition makes the most reliable correlation, and is not distorted to different perfusionistic, surgical and anesthetic techniques described by other authors. Postoperative CTO was recorded and divided by the patient’s weight. Patients were characterized as bleeders if their 24 h CTO (ml/kg) exceeded 75th percentile of distribution. Hemostatic impairment after CPB is complex in nature due to many components of the hemostatic system involved in. In addition to
insufficient surgical hemostasis, bleeding after CPB may be induced by many abnormalities in the coagulation system. Blood loss through these tubes is the sum of coagulopathic bleeding and surgical bleeding from wound edges. Unfortunately, it is impossible to differentiate bleeding volume according to surgical or coagulopathic cause.

Antifibrinolytics are routinely used at our center at two time points, (1) at the induction of anesthesia and (2) after protamine administration. There are conflicting data published recently on this issue. Al-Lawati et al recently showed that antifibrinolytics were not able to prevent excessive postoperative bleeding in group of patients who underwent CABG with preoperative aspirin administration. In contrast to, Shi et al showed tranexamic acid to be beneficial in terms of reduced blood loss, major bleeding and reduced transfusion outcome in patients who were exposed to CLO within 7 days before surgery. The same authors obtained the same results in patients undergoing CABG without preoperative clopidogrel and aspirin cessation.

Since all patients received tranexaminic acid in the same dose and at the same time we assume that all patients were well balanced in respect to possible effects of tranexaminic acid. Even if correlations between POC hemostatic tests and bleeding outcome might be distorted in some degree by tranexaminic acid, the possible role of tranexaminic acid should not be overestimated. Aside from tranexaminic acid, there are several factors that influence correlations between POC hemostatic devices and chest tube outcome such as prospective noninterventional studies such as ours. Despite the fact that patients were recruited in study, patients were regularly treated according to our center transfusion management. All procoagulant blood components administered perioperatively, certainly affected correlations in way that correlations were probably attenuate as well as sensitivity/specificity values in bleeding prediction estimation model. This is ubiquitous shortcoming of all prospective observational studies. Please note that ideal research setting would not be ethically accepted since patients were supposed to receive the best current available hemostatic protocol in respective center.

The study was designed as prospective observational trial. Transfusion management of procoagulant blood components was not changed during the study and patients received procoagulant blood components either according to predetermined criteria or according to attending anesthesiologist preference. Administration of fibrinogen concentrate and platelet concentrate was left to anesthesiologist discretion. All patients were treated by the same group of consultant anesthesiologists.

It is well known that CPB alters the hemostatic balance and predisposes cardiac surgery patients to increased risk of excessive bleeding. Pathophysiology of excessive bleeding after CPB has been described by Green et al. There are several factors related to CPB that contribute to onset of hemostatic disorder such as: foreign surface contact, consumption of clotting factors, platelet activation and dysfunction and fibrinolysis. In addition to, hemostatic impairment during CPB arises in some extent from systemic hypothermia that induces kinetic slowing of coagulation, kinin and kalikrein activation, platelet function and fibrinolysis. The fact that hypothermia tends to increase bleeding in the
cardiosurgical patients has been intuitively recognized by cardiac surgeons despite scarce evidence available at the beginning. Canine studies have shown that hypothermia causes thrombocytopenia and activates fibrinolytic system. Those results were confirmed in normal volunteers both in vitro and in vivo suggesting that adequate rewarming strategy may reduce the need for less safe alternative such as transfusion of procoagulant blood components.

Discussion section, in particular the part addressing the possible role of TEM in transfusion management, has been shortened.

Conclusion within Abstract is shortened with aim to stay focused on the scope of investigation.

Abstract/Results section has been changed in line with reviewer suggestions. Tables are changed as suggested by reviewer. Figures are merged into one. Manuscript published by Galeone et al has been included into discussion.

Minor typewriting mistakes have been changed.

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