DEPOSITION Statistical Analysis Plan

Decreasing Postoperative Blood Loss by Topical vs. Intravenous Tranexamic Acid in Open Cardiac Surgery (DEPOSITION)

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Background

Postoperative bleeding following cardiac surgery is a major problem, increasing the rates of complications and mortality. Off-label antifibrinolytic therapy has become a mainstay in cardiac surgical procedures for combatting excessive bleeding and minimizing transfusion requirements. Current guidelines from the Society of Thoracic Surgeons (STS) make a Class I (Level A) recommendation for intravenous tranexamic acid (TxA) use as a blood-conservation strategy during cardiac operations. In addition, there is a well-known risk of postoperative seizures associated with intravenous TxA, regardless of the dose used. In the ATACAS trial, anesthesiologists reduced their dosage of TxA at mid-trial to reduce seizures. However, it resulted in similar rates of seizures but with less antifibrinolytic activity and more transfusions. Patients who had seizures had a significant increase in primary outcome and had lengthier stays in ICU and in hospital.[13] Therefore, many anesthesiologists, in order to avoid seizures have lowered their dose of TxA creating resulting in more bleeding with the same seizure risk. The aim of DEPOSITION is to reduce or avoid seizure risk without more bleeding using topical TxA. Proposed benefits of topical (local) compared to intravenous (systemic) TxA delivery include enhanced direct anti-fibrinolytic effects with reduced neurological side effects due to lower systemic levels.

DEPOSITION is a RCT of 3800 patients in patients undergoing on-pump cardiac surgery testing if topical tranexamic acid (intra-pericardial) compared to the usual intravenous tranexamic acid administration would reduce the risk of seizure without increasing red blood cell transfusion? All randomized patients will be included in the main analysis according to the treatment group to which they were allocated by the IVRS (intent to treat analysis). Topical tranexamic acid is the treatment and intravenous tranexamic acid is the control.

1 Data from CRFs

All the data collected from the CRFs are presented in the documents prepared for the DSMB meeting. We use the same Tables numbers in this document. Each variable should be reported in 3 columns: total, intravenous, topical.

2 Baseline Demographics

Baseline demographics and measurement (Table 5) and medical history (Table 6), and Surgery detail in (Table 8a) and (Table 8b) should be provided and tested by treatment group. This will be our TABLE 1 in the manuscript.
We should report Table 8b in a more succinct way: CABG only (with the grafts details LIMA, veins, etc.), Valves only (with details of Aortic Valve, Mitral Valve and Tricuspid valve) and Combination. When time permits, we should do exactly as in Table 8b to include this data in the Appendix section. Table 8c should be done when time permits and will be included in the Appendix section.

3 Enrollment, randomization, and Follow-up

This is the usual Figure with numbers enrolled, randomized, treatment allocation, discontinuation, exclusion, protocol deviation, etc. All our analyses are by ITT.

4 Primary outcome

The **primary outcome** of the trial is the proportion of patients experiencing a seizure (superiority) in Table 14 The primary outcome should be analyzed with the Fischer's exact test as few seizures are expected. Details about history, type, Neuro consultation and death (if any) should be reported as well.

5 Secondary outcome

The **secondary outcome** is the proportion of patients receiving RBC transfusion (non-inferiority) in Table 14. If the results are not-not inferior, a superiority test should be done. Also, these results should be provided for 3 times periods: first day only, second day to end of follow-up and overall. It should be presented as in the documents prepared for the DSMB Table 12.

6 Tertiary outcomes

The tertiary outcomes are all blood products (Table 12), re-operation for bleeding, pericarditis, ICU stay and MACE Table 15 and its individual outcomes.

-All blood products should be analysed as a group (i.e., proportion of patients receiving any blood products) and individually for each blood product (number of "bags" per patient).
- Length of stay in ICU (Table 11) could be skewed and should be analyzed twice, using the median and using the mean.
Step 3, 4, 5 will be grouped in TABLE 2 of the manuscript.

7 Subgroups

Age: (<65, >=65)
Sex: (do we have any patient with "other" gender?)
Type of surgery: (CABG, valves, and all others)
Surgery: elective vs. urgent
Medical history (Stroke, MI, Diabetes (grouped)
It will be Figure 1 of the manuscript as a forest plot.

8 TxA dose, intra-op anticoagulation and surgical times

That data should be provided as in Table 9 and Table 10

9 ICU data

Data reported in Table 11 (except ICU stay already reported in step 6)

10 creatinine, hemoglobin, etc.

Data reported in Table 13

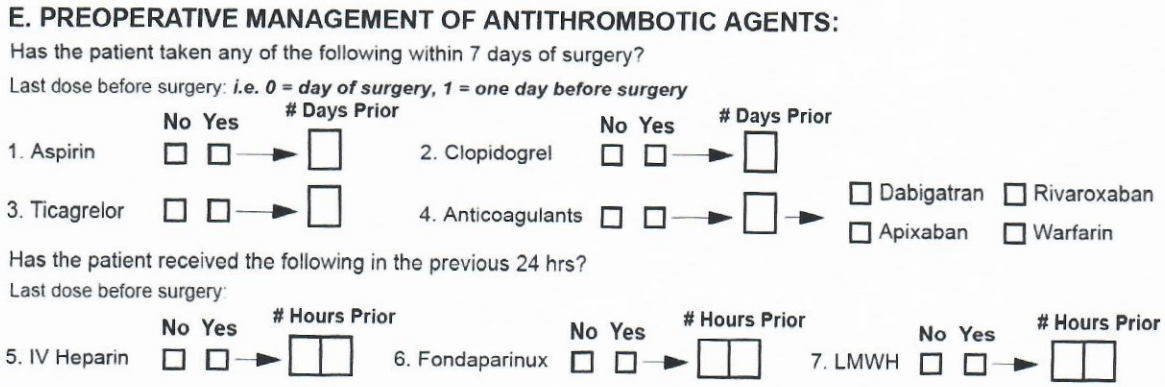
11 Other tertiary outcomes

Data reported in Table 15 not already reported

12 Pre-op antiplatelets and anti-coagulants.

This is more complicated. There are 7 medications to analyze but we should analyze No4 "anticoagulants" as a group rather than separately for each (dabi, riva, api and warfarin) at this stage. They were seldom used.

Each of these 7 medications have a different metabolism and the time to stop them before surgery varies accordingly. We should test yes/no first and then look if timing of last dose has an effect. The outcome to test should be the number of "bags" for each blood product. This is more work to be done but it is a kind of subgroup-quality control.



13 Dose of TXA tertiles and possible interactions

The dose of TxA used is an important covariate that we need to examine, especially for the **intravenous** dose. There is a wide variation in the intravenous dose (2 grams to 10 grams) given by anesthesiologists and we may find different results with different dosages.

So far in our blinded data for **intravenous** TxA, the total mean dose is 3.7 g with a median of 4 g (2.4, 5.0 for Q1, Q3) and corresponding to a total mean dose 45.5 mg/kg and with a median of 45.5 mg/kg (28.4, 58.8 for Q1, Q3) as well. The average weight is 83.4 kg.
I propose to divide the intravenous dose in tertiles of 0 to 3.0 grams, 3.01 to 5.0 grams, 5.01 grams and more. We should also look at tertiles of 0 to 36 mg/kg, 36.01 to 60 mg/kg, and 60.01 mg/kg and more. There is a close correlation in these numbers as grams or mg/kg.

The dose of **topical** TxA used is a wide variation (1 grams to 10 grams) as well. The TxA is provided to surgeons as a syringe of 5 grams. Surgeons will give a syringe or two for a maximum of 10 grams. The data is skewed and likely regrouped around 5 grams and 10 grams.

So far in our blinded data for **topical** TxA, the total mean dose is 6.7 g with a median of 5.0 g (5.0, 10.0 for Q1, Q3) and corresponding to a total mean dose 83.3 mg/kg and with a median of 69.4 mg/kg (57.7, 108.7 for Q1, Q3).
I am not sure that tertiles would work here and maybe it should be analyzed as 0 to 5 grams and more than 5 grams. I would appreciate your input here.

Then we should analyze the primary and secondary outcomes for each set of tertiles (or halves) with the appropriate statistical tests. These analyses should be done in grams and in mg/kg. This is more work but some anesthesiologists work in grams, others in mg/kg and this data will be asked by reviewers. These analyses may justify a paper on their own or be the TABLE 3 of the manuscript.

The hypotheses are:
1-Lower dose of TxA are associated with higher rate of blood transfusions than larger dose. This is an issue debated amongst anesthesiologists. We should prove or disprove this correlation.
2-Higher dose of TxA are associated with higher rate of seizures. This is an issue also debated amongst anesthesiologists. We should prove or disprove this correlation.

14 Analyses per site

We should analyse the primary outcome (few events however) and the secondary outcomes and assess for interaction between sites and outcomes. A forest plot should be generated for the secondary outcome.

15 Analysis per blood type

We should analyze the secondary outcome (% of patients transfused) and the number of RBC "bags" per each blood type regardless of the treatment group (both together). This will be in the appendix section.

16 MACE and bleeding: possible interaction

MACE may be increased due to bleeding. We should test MACE (composite) per bleeding (secondary outcome) and look for a possible treatment interaction.

17 Recruitment per site

Table 1 showing recruitment per site. Will be in the Appendix section.

18 Primary and secondary outcomes per site

Primary and secondary outcomes per site and per treatment group. Will be in the Appendix section.