Plasma to red blood cell transfusion ratios in open abdominal aortic surgery: detailed statistical analysis plan

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Background

- Major blood loss is frequent in open repair of ruptured and intact abdominal aortic aneurysm (AAA) as well as in aorto-bifurcated prosthesis insertion due to aortoiliac occlusive disease.
- Major blood loss is associated with death, post-operative complications and coagulopathy.
- Data from randomized trials in trauma patients indicate that a high plasma to red blood cell (RBC) transfusion ratio reduces 30-day mortality(1, 2) (Holcomb 2015, Sperry 2018).
- No randomized trial data are available for the AAA population(3) (Desborough 2015).
- Observational data demonstrate, that a high plasma:RBC transfusion ratio associates to a lower 30 day mortality. However, the reports are based on small cohorts of 78-165 patients(4-7) (Mesar 2017, Montan 2016, Mell 2010, Johansson 2007), short term outcomes and lack information on major adverse events such as cardiac and respiratory.
- The Danish Vascular Registry (DVR), covering 1996-2018, contains data on approx. 4,400 ruptured and 8,200 intact (elective/symptomatic) AAA repairs, and 5,400 open aortoiliac repairs due to occlusive disease. Expected count 1997-2018: 17,000.
- The Danish Transfusion Database (DTDB), covering 1997-2018, contains information on units of RBCs, plasma and platelets transfused. A unique patient identification number (CPR) allows merging of all data set.

Objective

To identify whether resuscitation with a high plasma to RBC ratio associates to improves survival in open abdominal aortic surgery as compared to a low plasma to RBC-ratio.

Material and method

- Population: Open abdominal aortic surgery
- Intervention: “High FFP”: FFP to RBC unit ratio of 2:3 to 3:3 (0.7 - 1.0)
- Comparison: “Low FFP”: FFP to RBC unit ratio of 0:3 to 1:3 (0.0 - 0.3)
- Outcome: All-cause mortality 90 days following surgery

Inclusion criteria:

1. Open abdominal aortic repair of either
    - intact (elective or symptomatic) AAA

- ruptured AAA
- aorto-iliac occlusive disease with the insertion of aorto-bifurcated prosthesis

2. Requiring massive transfusion defined as
   - ≥ 10 units of any blood product[1] transfused on the same date (DTDB)

[1] = Allogeneic packed RBCs, FFP, cryoprecipitate, or platelets.

Cryoprecipitate will account for 4 units of FFP in the FFP:RBC ratio.

Data sources are noted in parenthesis.

Exclusion criteria:

- Surgery time limited to < 50 minutes (DVR)
- No prosthesis inserted (DVR) **AND**

  operation date (DVR) equal to the death date (CPR)

Excluding patients with surgery time less than 50 minutes or cases where no prosthesis has been inserted is expected to minimize survival bias from patients exsanguinating in the operation theater before blood products can be delivered. Intentionally, it may also exclude patients where surgery was considered futile and halted.

Protocol amendment 2020-10-09:

In the original protocol version, patients receiving 6 ≥ RBC units during surgery, or ≥ 15 units within two calendar days, would also fulfill the second inclusion criteria. We have removed these two criteria and confined the definition of massive transfusion (i.e., the second inclusion criteria) to 10 blood products or more transfused on the day of surgery. The old criteria would otherwise introduce bias. First, patients receiving ≥ 6 RBC transfusions during surgery, but less than 10 units total on the same day, could only be included in the low FFP group because the maximal ratio would be 6 RBC : 3 FFP (ratio of 0.5). Two, including patients who received ≥ 15 units within two calendar days, would introduce immortal time bias. These patients would be immortal by definition on the day of surgery, or they would not receive blood products on the 1st postoperative day.

Data sources

CPR, Danish Civil Registration System.
DNPR, Danish National Patient registry.
DVR, Danish Vascular registry.
DPDB, The Danish national Prescription DataBase.

Statistical analysis

Our primary analysis will be a stratified cox regression model.

Stratification

- type of surgery/condition (ruptured AAA vs intact AAA vs aorto-iliac occlusive disease, source: DVR)
- sex (CPR)
- surgical center (Rigshospitalet vs. Gentofte vs. Slagelse vs. Odense vs. Kolding vs. Aarhus vs. Viborg vs. Aalborg, source: DVR)

Covariate adjustment

- calendar time (DVR)
- age (CPR)
- Carlson comorbidity index score (DNPR)
- Priority (Acute vs. Sub-acute vs. Elective, source: DVR)
- Use of anti-thrombotic drugs (DPDB). A covariate of 4 levels:

  The ATC code is noted in parenthesis.

  1) None vs.
  2) Anti-platelet therapy
     - acetylsalicylic acid (B01AC06) or
     - dipyridamole (B01AC07, eg. persantin or asasantin)
  3) Anti-platelet therapy "thienopyridines-like drugs"
     - clopidogrel (B01AC04) or
     - ticagrelor (B01AC24, eg. Brilique) or
     - prasugrel (B01AC22, eg. Efient)

     Comment: patients prescribed thienopyridines in combination with aspirin will be included in this "thienopyridine anti-platelet group 3"
  4) Anti-coagulant therapy
     - Vitamin K antagonists (B01AA, eg. warfarin or phenprocoumon (B01AA04)

- Low-molecular weight heparine (B01AB01-10)
- Direct thrombin inhibitors (B01AE, eg. Pradaxa/Dabigatran)
- Direct factor Xa inhibitors (B01AF, eg. Rivaroxaban/Xarelto)

  Comment: patients prescribed both anticoagulant- and antiplatelet therapy and will be included in this "Anti-coagulant group 4"

Additional analyses

1. Stratify the population into 4 groups according to the total transfusion requirement
    a. patients receiving $\leq$10 units of any blood product < 24 hrs or 11-15 units < 48 hrs. *vs.*
    b. patients receiving 11-15 units of any blood product < 24 hrs. or 16-20 units < 48 hrs. *vs.*
    c. patients receiving 16-20 units of any blood product < 24 hrs. or 21-25 units < 48 hrs. *vs.*
    d. patients receiving more than 20 units of any blood product < 24 hrs. or more than 25 units < 48 hrs.
2. Outcome predicted by a joint function (general interaction) of total plasma transfusion and total blood cell transfusion will be assessed in an exploratory way by inspection and by agnostic modelling in the mold of Multivariate Adaptive Regression Splines (MARS) and recursive partitioning, i.e. Classification And Regression Trees (CART).
3. Redefine intervention and control group as 4^{th} and 1^{st} quartile of FFP:RBC ratio. Initially, we will divide the population into 4 groups according to quartiles and compared the population below 1^{st} quartile with the population above the 4^{th} quartile, which will define the low vs. the high FFP group, resp. However, to allow for stratification for operation type (ruptured AAA *vs.* intact AAA *vs*. occlusive disease) it may be necessary to adjust the percentile cut to retain power in the analyses. For instance, the population may be cut according to tertiles, or, if there is sufficient data, cut by quintiles (5 groups) or deciles (10 groups).
4. Confine the population to patient with blood loss above 50 % of total blood volume (calculated by Naddler's equation accounting for sex, weight and height). If height and weight are not available, the registered blood loss must exceed 2 L in females and 2.5 L in males.
5. Adjusting exclusively for calendar year, sex, age, Charlson's comorbidity index score, and center (ie, excluding priority and antithrombotic therapy).

Missing data

We won't have missing data on total units of blood products transfused as this is an inclusion criterion. All remaining covariates are discrete, and we will include missing data as a separate parameter (factor level).

Statistical significance level

We will apply Bonferroni adjustment of the significance level to control for multiple testing. With one primary and four secondary outcomes, only a P value below 0.01 (0.05/5) will be considered statistically significant. A P value between 0.01 and 0.05 will be considered borderline significant.

Outcomes

Primary outcome

1. 90-day all-cause mortality

Secondary outcomes

2. 30-day all-cause mortality
3. 1-year all-cause mortality
4. Death or any major adverse event at 90-days (DNPR):
    A. Major adverse cardiovascular events "MACE" [ICD10-codes]
        - acute myocardial infarction [DI21.0-23.9, DT817Y2]
        - stroke [DI60-64.9, DT817Y1] (and DVR)
        - non-fatal cardiac arrest [DI460]
    B. Major adverse respiratory events
        - Adult respiratory distress syndrome [DJ80]
        - pulmonary edema [DJ81]
        - pulmonary embolism [DI26, DT817D]
    C. Major adverse vascular event
        - bowel ischemia [DK550C-H] (and DVR)
        - vascular reoperation for deep rebleeding or thrombus or embolus [KPWE, KPWG], lower-limb fasciotomy [KNGM09, KNHM09, KNFM09] or explorative laparotomy [KJAH00] (and DVR)

- major lower limb amputation [KNE-HQ] (and DVR)
- acute limb ischemia requiring intervention (DVR)

D. Other

- renal replacement therapy [BJFD, DZ992] (and DVR)
- AB0-incompatibility reaction [DT803]
- Rhesus-incompatibility reaction [DT804]
- Hemorrhage and hematoma complicating a procedure, not elsewhere classified [T810, DT810G, DT810E]

5. Days alive outside hospital within 90 days (DNPR and CPR).

Figure 1. Time overlap of registries

*Not all centers go back to 1997.

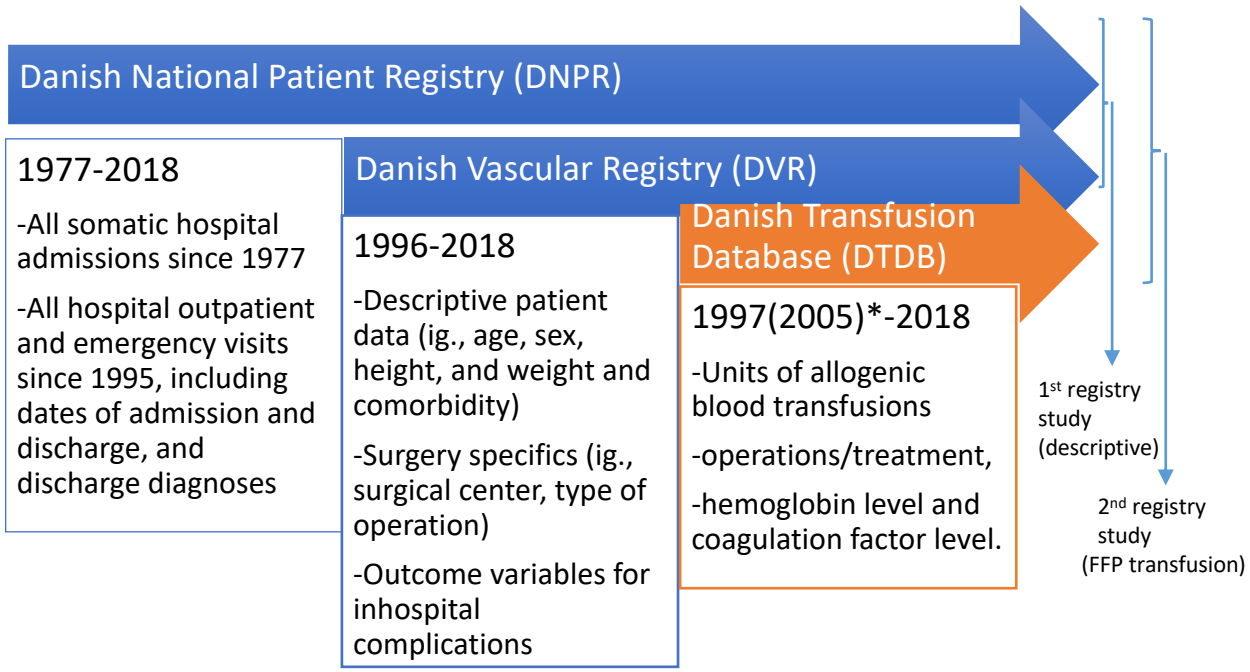
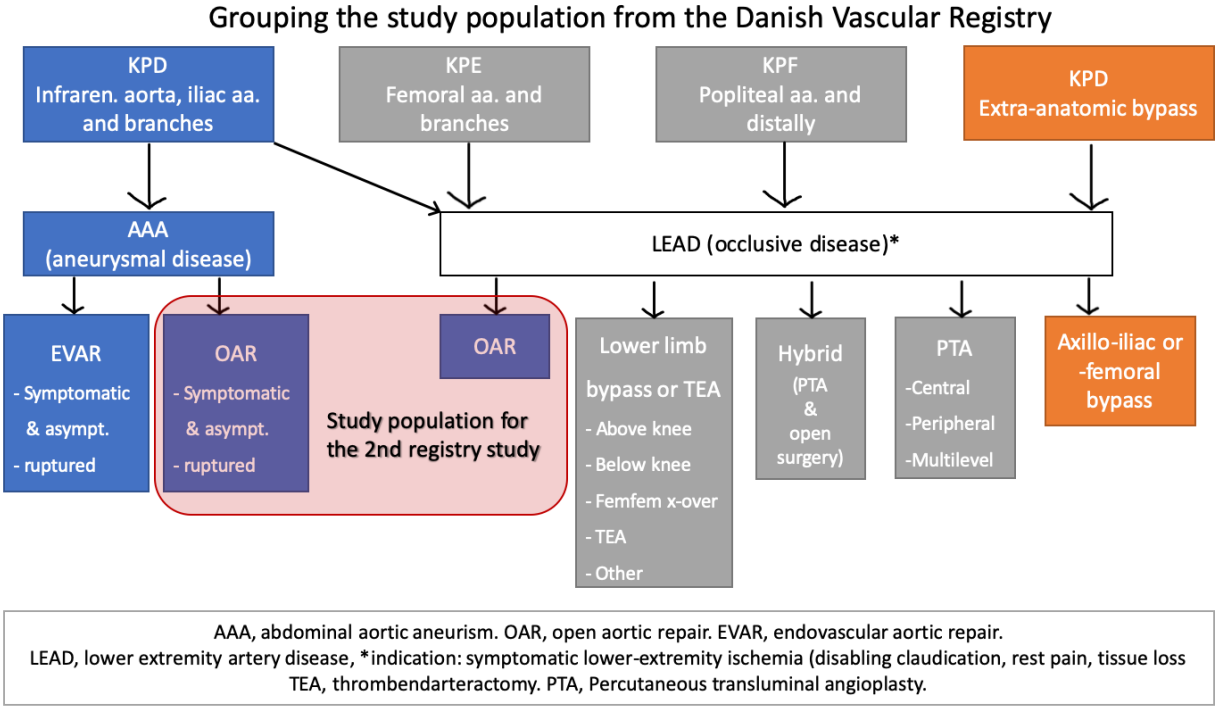


Figure 2. Grouping the study population.



AAA, abdominal aortic aneurism. OAR, open aortic repair. EVAR, endovascular aortic repair.
LEAD, lower extremity artery disease, *indication: symptomatic lower-extremity ischemia (disabling claudication, rest pain, tissue loss
TEA, thrombendarteractomy. PTA, Percutaneous transluminal angioplasty.

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