Cardiac Surgery and Blood Transfusion Products. What Does Really Matter?

Master Thesis in Biostatistics (STA495)

by

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supervised by

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Zurich, August 9, 2017

Acknowledgements

I would like to thank my supervisor, Professor Dr. Reinhard Furrer for his insightful guidance and interest through my thesis. His teaching has been always an inspiration to me.

Also, I would like to dearly thank Dr. Sonja Hartnack for her constant help all this time. Her clinical and statistical input has been proven to be extremely valuable for my thesis.

I would like to show my gratitude to Dr. Christof Hofer, who trusted us with his valuable dataset and for an excellent collaboration.

Lastly, a big thank you to my parents, Dimitris and Vasiliki, as well as my girlfriend Chrysi for their unconditional support and patience through my studies.

Christos Polysopoulos
31.01.2017 Zurich

Thesis summary

In this thesis, we investigate whether the implementation of a new blood coagulation management algorithm had a positive effect in cardiac surgery patients' health at Triemli city hospital during the years 2010 - 2014.

Cardiac patients suffer from blood coagulation disorders during their hospitalization. These disorders are associated with loss of blood, and as a result blood component transfusions are necessary. It is known that transfusions can cause several adverse effects, such as different types of infections and even death. The coagulation management algorithm is designed to provide a tool for practitioners to control blood coagulation related disorders.

Our intention is to use the relatively new methododoly called Additive Bayesian network modelling to come into conclusions about the use of this algorithm. Along with Dr. Sonja Hartnack, the same dataset will be analysed both with Additive Bayesian networks, but also with a more traditional analysis.

This thesis consists of three parts.

First, an overview of the disease, introduction to Additive Bayesian networks and dataset, and conclude to the results and discussion section.

The second part consists of Manuscript I, an analysis performed by Dr. Sonja Hartnack. Basic descriptive statistics and univariable analysis is used along with multicolinearity and variance inflation factors checks.
The first approach consists of a continuity-corrected log transformation of the response and the importance of each predictor in the model is considered in form of R^2 values which is the ratio of the explained to the total variance in regression modelling. Point estimates and 95% confidence intervals are obtained by bootstrapping.
As the response variable contained an excessive amount of zeros, a second approach with a hurdle model was performed with the same predictors. Additionally, to assess the association between potential risk factors and the incidence of infections postoperatively, a generalized linear model with a binomial link and logit function was chosen.

The third part of this thesis consists of Manuscript II, which describes modelling the data with Additive Bayesian networks. This analysis was performed by me, along with Dr. Sonja Hartnack. Two heuristic searches were ran for each period, resulting in 4 different final structures. The first two, describing the multivariate behaviour of blood and coagulation products, and the second two describing patient complications.

All analyses were constatly supervised and assisted by both of my supervisors, Professor Dr. Reinhard Furrer and Dr. Sonja Hartnack.

Contents

Chapter 1

Introduction

1.1 Cardiac surgery and blood coagulation disorders

Cardiovascular surgery is the surgery on the heart or great vessels performed by cardiac surgeons. Frequently, it is done to treat complications of ischemic heart disease, correct congenital heart disease, or treat valvular heart disease from various causes including endocarditis, rheumatic heart disease and atherosclerosis. It also includes heart transplantation.

Coronary artery bypass grafting (CABG) is the most common type of heart surgery. CABG improves blood flow to the heart. Surgeons use CABG to treat people who have severe coronary heart disease (CHD). CHD is a disease in which a waxy substance called plaque builds up inside the coronary arteries. These arteries supply oxygen-rich blood to the heart. Over time, plaque can harden or rupture. Hardened plaque narrows the coronary arteries and reduces the flow of oxygen-rich blood to the heart. This can cause chest pain or discomfort called angina. If the plaque ruptures, a blood clot can form on its surface and can mostly or completely block blood flow through a coronary artery. This is the most common cause of a heart attack. Over time, ruptured plaque also hardens and narrows the coronary arteries.

During CABG, a healthy artery or vein from the body is connected (Figure 1.1), or grafted, to the blocked coronary artery. The grafted artery or vein bypasses the blocked portion of the coronary artery. This creates a new path for oxygen-rich blood to flow to the heart muscle. Surgeons can bypass multiple blocked coronary arteries during one surgery.

In case of cardiac surgery, especially when a life support device is used (Figure 1.2), it often results in increased bleeding due to blood coagulation disorders. Coagulation, also known as clotting is the process by which the blood changes to gel, forming a clot. It can potentially result in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair.

As a result of bleeding, there is an increased need for transfusion of the various blood products, such as fresh frozen plasma, platelets and red blood cells. Whole blood is rarely used for transfusion. Blood component therapy makes clinical sense as most patients need a specific element of blood, and the dose can be optimized.

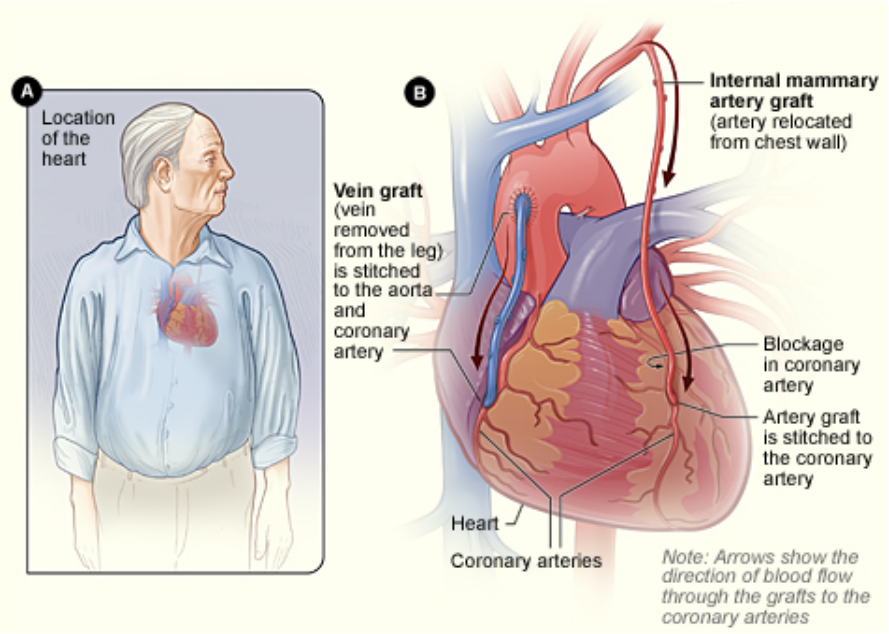

Figure 1.1: Illustration B shows how vein and artery bypass grafts are attached to the heart. Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.

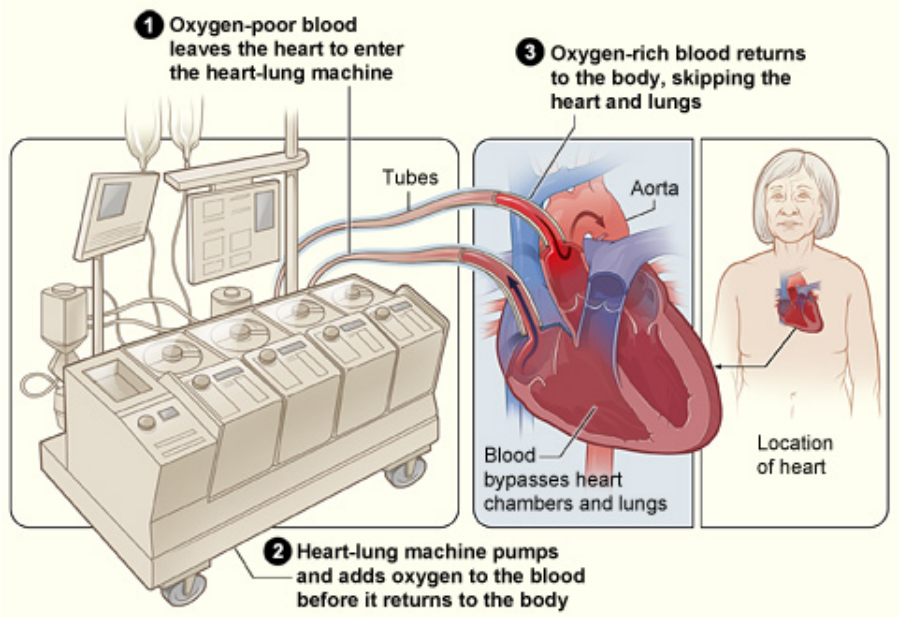

Figure 1.2: Heart and lung machine.
Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.

These coagulation disorders are multifactorial. Preoperative administration of platelet-inhibiting drugs, reduction of coagulation factors, fibrinolysis and platelet dysfunction due to the use of life support device are to be mentioned as the main causes.

Transfusions are associated with several complications that affects patients. Several types of infections such as pulmonary and sepsis, negative transfusion reactions, acute lung injury and eventually mortality.

Doctors, in order to control the adverse effects of transfusions, use functional coagulation tests, such as Thromelastometry and Platelet Aggregometry. These tests allow for timely detection of preoperative coagulation disorders. Coagulation management algorithms based on these tests could possibly reduce perioperative transfusion needs and the negative results associated with it.

1.2 The coagulation management algorithm

In 2012, a coagulation management algorithm (Figure 1.3) was implemented in cardiac surgery patients in Triemli city hospital in Zurich. It has been carefully designed to offer doctors an optimization tool for controlling blood coagulation disorders.
Values from coagulation tests now are been utilized and guidelines based on thresholds have to be followed by practitioners. These thresholds provide suggested doses of clotting products to treat patients.
The algorithm consists of 4 hospitalization periods: Pre-Intervention, Protamine cycle, Post-Intervention A and Post-Intevention B. The column Measurements contains values that result from standard coagulation lab and diagnostic tools. The evaluation stage provides thresholds corresponding to these values. Lastly, column Measures gives the suggested action that a doctor has to follow given the previous evidence.

Standard coagulation lab measurements
Starting from the Pre-Intevention stage, three measurements result from standard coagulation lab tests. Prothrombin time (PT) is the primary assay used in monitoring oral anticoagulant therapy. To produce a result, thromboplastin is added to the blood sample to activate coagulation. This causes a blood clot to form. The time it takes for this clot to form is measured in seconds and is known as Prothrombin time.
In most countries, blood coagulability is typically expressed in a unit known as the Quick value. In this case the measured prothrombin time is expressed in relation to the coagulation time of a healthy person. The value obtained is the precentage of the standard value. In a person not receiving oral anticoagulation medication the normal Quick value is between 70% and 100%.
Fibrinogen, or factor I, is a blood plasma protein that is made in the liver. Fibrinogen is one of 13 coagulation factors responsible for normal blood clotting. When there is an injury and bleeding occurs, the body forms a blood clot through a series of steps. In one of the last steps, soluble fibrinogen is converted into insoluble fibrin threads that crosslink together to form a net that stabilizes and adheres at the injury site until the area has healed.
Platelets (Figure 1.4) are disk shaped cell fragments and 2-4 μm in diameter. Around 150000 and 400000 are present in each cubic millimeter of blood. The inner surface of blood vessels is lined with a thin layer of cells that under normal situations produce messengers that inhibit platelet activation. When this thin layer is injured, collagen is exposed, releasing other factors to the bloodstream which attracts platelets to the wound site. When the platelets are activated, they clump together to form a platelet plug

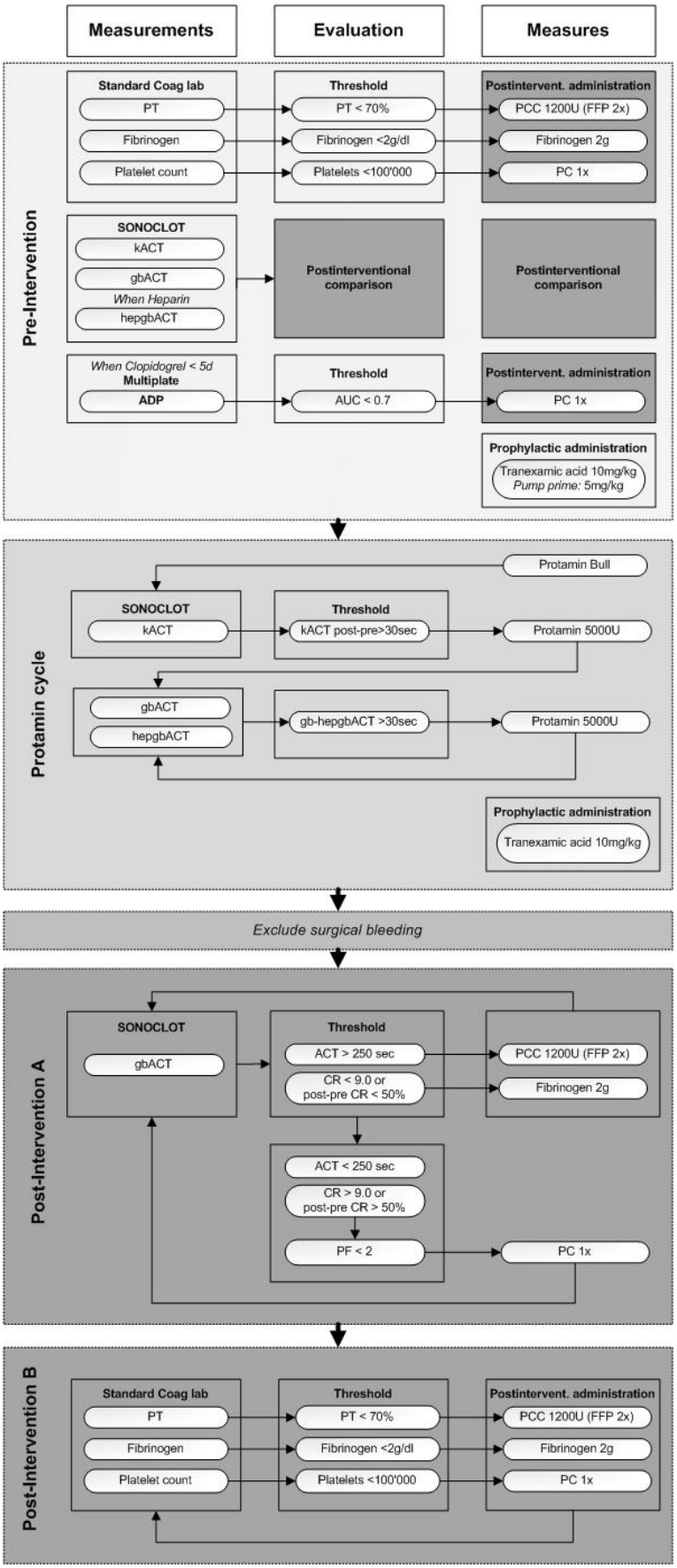

Figure 1.3: The coagulation management algorithm.

releasing their contents. The released contents of the platelets activate other platelets and also interact with other coagulation factors.

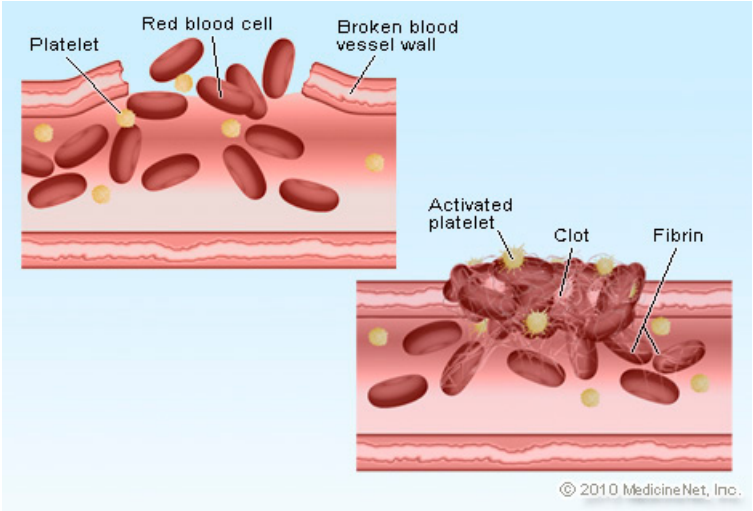

Figure 1.4: Platelet activation @2010 MedicineNet, Inc.

For the measurements mentioned above, thresholds are provided and doses Post-Intervention are suggested to be followed.

Sonoclot measurements in seconds
Sonoclot is a coagulation and platelet function analyzer and is used to monitor activated clotting time (ACT) measured in seconds. Most common activators are kaolin (kACT) and glass bead (gbACT) to initiate contanct activation. During surgery, the ACT is kept above a lower time limit, a limit which most people will not form blood clots.
Clopidogrel is an oral medication that is used to reduce the risk of heart disease and stroke on those patients at high risk. Onset of effects is about 2 hours and lasts for 5 days.
Multiplate ADP tests platelet function in whole blood. This test can be used to diagnose platelet disorders, monitor antiplatelet therapy and is also investigated as a potential predictor of transfusion requirements and bleeding risk in cardiac surgery. Adenosine diphosphate (ADP) is a platelet agonist. When it is added to saline-diluted whole blood in the test cuvette, it stimulates the ADP receptors on platelets, activating the platelets. The activation of the platelets leads to shape change and degranulation, and the released content of the granules further activates the platelets. Activation also induces a conformational change in the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor, giving it high affinity for fibrinogen. Binding of fibrinogen to GPIIb/IIIa receptors leads to platelet-to-platelet bridges and results in platelet aggregation. Area under the curve (AUC) is the most important parameter of this test and is affected by both the height and the slope of the aggregation curve, and is the best overall measure of platelet activity.

Protamine cycle
In the second panel of Figure 1.3 the use of Protamine is described. During the hospitalisation period, an initial dosis of protamine (Protamine Bull) is given to patients to reverse the effects of heparin. Heparin acts as an anticoagulant factor. It is used to

decrease the clotting ability of the blood and help prevent harmful clots from forming in blood vessels.
Patients who remain hospitalized for days and are unable to move, are at a greater risk of forming clots. Thus, different activation times in seconds (ACT) are monitored and protamine is given accordingly.

Post Intervention A, B
After surgery, clotting of the blood is keep monitored. Sonoclot tests are again performed to assess activation clotting time (ACT), clotting rate (CR) and platelet function (PF). As the healing process has already begun, the suggested doses provided now are Prothrombin complex concentrate (PCC), Fibrinogen and platelet concentrate (PC).

Implementing the algorithm
Before the implementation of this algorithm, doctors would act independently and take a decision based on their expert knowledge and experience. Now every doctor has to follow this strict procedure through out the treatment period of a patient. The algorithm aims to reduce the in-between variation of the doctor's decisions and establish a powerful tool for managing coagulation disorders.

1.3 Goal of Thesis

The goal of this project can be expanded in to two branches related to the people involved . Questions of clinical nature were asked by Dr. Christof Hofer. His primary interest was to test whether the implementation of the algorithm had a positive impact on patients' health. Therefore, the following primary questions should be answered.

1. Was the need of transfusion and clotting products reduced by introducing the coagulation management algorithm?

2. Was there a reduction to patients' complications?

Taking into consideration the two treatment periods, the number of coagulation and blood products will be compared. Same for the patients' complications, in form of hospital mortality, infections, length of hospitalisation and many more.
A statistically significant lower number of products used and less complications in the period after the implementation will show if the algorithm is indeed working.

Methodology-wise, our interest lies in modelling such a vast and complex dataset, with a large number of predictors. A new methodology will be used, called Additive Bayesian networks (ABN) and it will be introduced in the next section. Questions regarding this methodoly involve:

1. How Additive Bayesian network modelling will perform with a large number of variables.

2. Choosing the right search algorithm.

3. Avoid overfitting.

4. Discover the best structure represented by a directed acyclic graph.

Chapter 2

Statistical Methods

Through out this thesis Additive Bayesian networks (ABN) have been used to model the data. Based on the classical Bayesian networks, ABNs provide the user a powerful tool to discover dependencies among variables under the generalized linear modelling frame. For more information visit http://www.r-bayesian-networks.org.

2.1 Bayesian networks

2.2 Definition

Bayesian networks (Pearl, 1988) are a graphical representation of a multivariate joint probability distribution that exploits the dependency structure of distributions to describe them in a compact and natural manner (Friedman and Koller, 2003).

2.3 Components of a Bayesian network

A Bayesian network comprises of two parts. The network structure $\boldsymbol{S}$ and the model parameters $\boldsymbol{\theta}$.
The network structure is represented by a Directed Acyclic Graph (DAG). Each variable in the DAG is called node, and the lines connecting the nodes are called arcs. The arcs provide the marginal and conditional dependencies in the variable domain.

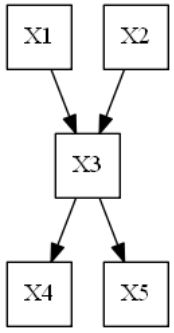

Figure 2.1: The structure.

The local probabilities are given based on the parents of each node. The parents of a node $pa(X_j)$ are its predecessors, or simply the nodes that come before it. For example in Figure 2.1 the parents of node X_3 are X_1 and X_2. X_1 and X_2 are independent of the rest of the nodes so no parents are present.
Given the structure and the model parameters, as the definition of Bayesian networks suggests, we can obtain the join probability of the structure $\boldsymbol{S}$. The joint probability of $\boldsymbol{X}$ is the product of all the local arcs in the structure:

$$P(\boldsymbol{X}) = \prod_{j=1}^{n} P(X_j|pa(X_j)).$$

2.3.1 A popular example

One of the most common applications in Bayesian networks literature is the A.L.A.R.M. network (Beinlich et al., 1989). The initials stand for A Logical Alarm Reduction Mechanism and is a diagnostic application that implements an alarm message system for patient monitoring. It calculates probabilitites for a differential diagnosis based on available evidence.

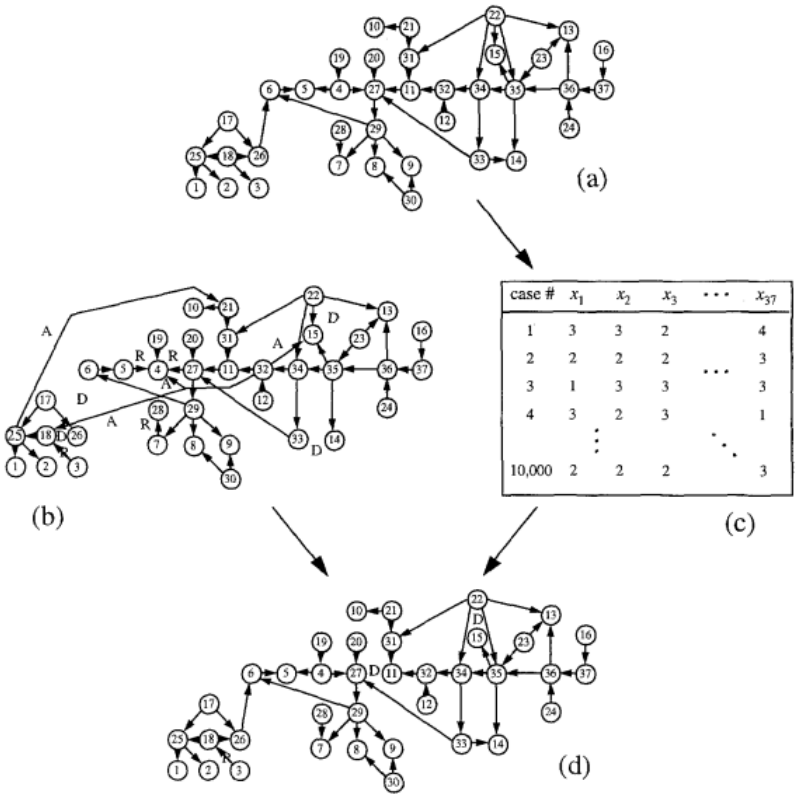

Figure 2.2: The A.L.A.R.M. network.

The medical knowledge is encoded as in Figure 2.2a with 8 diagnoses, 16 findings and 13 intermediate variables. Diagnoses and other qualitative information are at the top level of the network. These variables have no predecessors and they are assumed to be mutually independent a priori.

Figure 2.2a is the true network where is used in literature to create a database of cases as in Figure 2.2c. Since we are under the Bayesian framework, a prior belief about the network is encoded in Figure 2.2b. These two sources of information, prior belief and database, allow us to *learn* one or more Bayesian networks presented in Figure 2.2d.
To appreciate the effectiveness of the method, we observe that the learned Bayesian network in Figure 2.2d is very close to the true network Figure 2.2a. Given the evidence from the database, the prior belief of the investigator was corrected and led to an accurate respresentation of the true network.

2.4 Additive Bayesian networks

2.4.1 Description

Additive Bayesian networks modelling (ABN) is a new technique which extends the previous methodology to generalized linear models. The nodes in the structure are not just variables anymore, but each node represents a generalized linear model. The previous conditional probabilities are replaced with linear additive contributions of the variables in the link function space.
Figure 2.3 represents an ABN with 5 variables. Let nodes X_1, X_2, X_5, denoted by a square to be binary and X_3, X_4 denoted by a cirle to be continuous. Also, let $P(X_i = 1) = 1 - P(X_i = 0)$ and μ_i the mean of X_i for $i = 3, 4$.

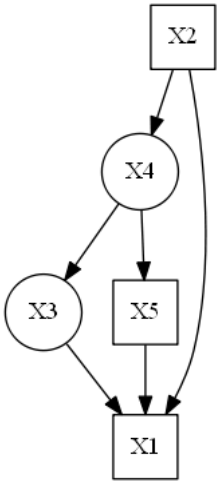

Figure 2.3: A simple ABN.

X_2 is independent of the other nodes. As it is a binary node the interpretation corresponds to a logistic regression model with no covariates:

$$\log\{\pi_2/(1-\pi_2)\} = \beta_{2,0}.$$

The continuous node X_4 is conditionally dependent upon X_2 so the mean:

$$\mu_4 = \beta_{4,0} + \beta_{4,1}X_2.$$

For the node with the most parents, X_1, given that is a binary node and dependent upon X_2, X_3, X_5 we have:

$$\log\{\pi_1/(1-\pi_1)\} = \beta_{1,0} + \beta_{1,1}X_2 + \beta_{1,2}X_3 + \beta_{1,3}X_5.$$

Additive Bayesian networks were implemented in R with the package `abn` which currently supports three types of variables: continuous, binary and count data.

2.4.2 Learning the structure

Previously, the basic structure of an Additive Bayesian network was introduced. Our objective is to identify a network that represents the data sufficiently well and at the same time not being overly complex. Theoretically, we could search all possible node structures resulting from the combination of nodes and select the one that represents the data the best.
This is computationally not possible because of the vast space of all possible structures. It has been shown that the number of combinations grow more than exponentially in the number of nodes.

Table 2.1: Possible DAGS given the number of nodes.

Nodes	1	2	3	4	5	...	21
DAGS	1	3	25	543	29281	...	10^{80}

Table 2.1 shows the extreme growth of all possible DAGS given a set of nodes. For one node, we can obtain maximum one possible DAG. For two nodes X_1, X_2, the first would be a structure with $X_1 \leftarrow X_2$, the second would be $X_1 \rightarrow X_2$ and the third is simply the empty network with no arcs connecting the nodes.
Allowing all nodes to connect with eachother, it is not possible to search for the best DAG. An immediate solution for this computational problem is to restrict some of the arcs between nodes before begining the search. In this way we can decrease the number of combinations that we can search from.

After restricting the number of possible structure down to a sensible number, it is now time to introduce a method that allows us to select the one that is more likely to generate the original data in hand. To achieve this we use what are called score based functions. A desired property of these score based functions is decomposability, which states that the total score of a structure can be expressed as the sum of individual nodes scores. More precisely:

$$Score(D,S) = \sum_{j=1}^{n} Score(X_j, Pa_j, D).$$

Now being under the Bayesian framework, a possible candidate for this score is marginal likelihood. With marginal likelihood we can assess the goodness of fit for a structure S.

Thus, we have

$$P(S|D) = \frac{P(S)P(D|S)}{P(D)},$$

where, $P(D)^{-1}$ is the normalization constant which does not depend on S, $P(S)$ is the prior of a structure S and $P(D|S)$ the marginal likelihood of the structure given the data D. We assume that all possible structures are equally plausible to be selected, so the comparison of structures collapses to the comparison of the marginal likelihoods $P(D|S)$ as given by

$$P(D|S) = \int_{\beta_A} P(D|S, \beta_A)\pi(\beta_A|S)d\beta_A,$$

where, β_A the parameters of the model and $\pi(\beta_A|S)$ the prior probability over the parameters conditioned over S.

2.4.3 Search algorithm

Using the previously introduced score functions to uncover the best structure for our data, it is essential, to define an algorithm to search among all possible structures. The statistical R package `abn` offers two options of algorithms for different occasions.
Exact search (Koivisto and Sood, 2004) is mainly used when there is only a handful of variables. It performs an exaustive search across node orderings to identify a globally best structure. Then bootstrapping is used to control for overfitting. As exact search was not an option for us, because of the size of the dataset, and we will not get into detail on this text.
The algorithm that fitted our needs the best was the heuristic search (Heckerman et al., 1995). Heuristic search is used when the size of the dataset does not allow for an exact search and identifies a locally best DAG, starting from a initial random structure. This process is performed multiple times, each time starting from a different initial DAG. At the end we summarize the results and obtain the final structure. The algorithm is described next, along with the method to *prune* the excessive arcs.
Before introducing the steps of the algorithm, it is important to define three search operators:

- **Arc addition**: Add a single arc between two nodes.
- **Arc deletion**: Remove a single arc between two nodes.
- **Arc reversal**: Reverse the direction of a single arc.

The search algorithm uses the three operators iteratively to reveal the DAG with the largest score:

- Let $\boldsymbol{op(S, E)}$ the result of applying a legal operation $\boldsymbol{E}$ to the DAG.
- The DAG and $\boldsymbol{op(S, E)}$ differ only by 1 arc.

1. Let $\boldsymbol{S}$ be an initial structure.

2. Repeat:
   - Calculate $\boldsymbol{\Delta(E)}$ for each possible legal operation E.
   - Let $\boldsymbol{\Delta^* = max_E \Delta(E)}$ and $\boldsymbol{E^* = argmax_E \Delta(E)}$.
   - If $\boldsymbol{\Delta^* > 0}$ then
   - Set $\boldsymbol{S = op(S, E^*)}$.
3. Until $\boldsymbol{\Delta^* \leqslant 0}$.

Each time, the algorithm starting from an initial random DAG, applies all legal operations on the structure until there is no change in the marginal likelihood $\boldsymbol{\Delta}$. A legal operation $\boldsymbol{E}$ must not result into a cyclic arc pattern. This search is ran n times, resulting to n locally best DAGS.

2.4.4 Control for overfitting

Having run n heuristic searches, then the next challenge is to summarise the results from the n local structures. A single robust structure is constructed from the majority concensus structure, in other words, only the arcs present in at least 50% of the local structures are kept and the rest are discarded.

Chapter 3

The Dataset

3.1 Introduction

For all cardiac surgery patients at Triemli city hospital a database is maintained for quality assurance. In this database, sociodemographic, disease-release and perioperative data are filled routinely.

The dataset consisted of two periods, the period before the implementation of the coagulation management algorithm and after the implementation of it with a total of 1754 patients.

Inclusion Criteria: All patients to whom a cardiac surgery in Triemli City hospital was carried out between the years 2010-2014.

Exclusion Criteria: None

Two periods: The years 2010-2011 are characterized as the before period including 839 patients and 2013-2014 with 915 patients. The datapoints of year 2012 were not used as this period is considered to be the learning phase of the algorithm.

3.2 Data related problems

The initial dataset contained a substancial amount of missing values in certain variables. As `abn` package is not performing with incomplete datasets, these variables had to be removed. Complete case analysis was made for the rest variables.

Additionally, extreme values were observed in the basic clinical measurements during a preliminary analysis of the data. It made sense to ask whether these values were to be trusted for analysis. After consulting with Dr. Christof Hofer, it was concluded that many observations were not valid. For example, a BMI of 3000 was found. That would correspond to a person weighing around 10 tons.

After locating all the invalid observations and the indeces were obtained the dataset had to be corrected. The doctor had to go back to the initial database and look for the correct datapoints. The correction of the dataset was a time consuming procedure which lasted around two months since the start of the project.

3.3 Description

The initial dataset contained around 100 working variables. In this section we are going to describe the dataset in a compact way considering the large number of variables.

Table 3.1: Basic demographics.

		Before (n = 839)	**After** (n = 915)	P
Patient				
F/M ratio	*n(%)*	211/628 (34.0)	200/715 (28.0)	0.116
Age	*Years*	66.6±11.0	66.4±10.9	0.652
BMI	kg/m^2	27.3±4.73	27.0±4.2	0.208
LVEF	%	54.3±13.3	55.6±13.0	0.045
HYPER	*n (%)*	607 (72.3)	650 (71.0)	0.580
DMins	*n (%)*	85 (10.1)	68 (7.4)	0.055

In Table 3.1 we can see some basic demographic variables of the patients for the two periods. We observe substancially more males than females with mean age to be 66 years old and higher than the normal weight limit (BMI). Left ventricular ejection fraction (LVEF) represents how good the heart pumps with a lower threshold to be 50%. Patients with hypertension c(HYPER) tend to undergo a cardiac surgery as can be seen by the frequencies. Also, a small number of patients had diabetes (DMins) and insulin was administered.

Table 3.2: Variable clusters.

Pre-op Medication ASA, Heparin	Coagulation Products Fibrinogen, Prothrombin Complex
Pre-op Lab Creatinine, Hematocrit	General post-op outcomes Myocardial Infarction, Cerebrovascular Insult
Interventions Aortic Valve, Cardio Pulmonary Bypass	Infections Pulmonary, Sepsis
Interventional times Duration of anesthesia / Operation	Post-op times ICU / Hospital Length of Stay
Allogeneic Transfusions Red Blood Cells, Fresh Frozen Plasma Platelets	Mortality ICU / Hospital

Table 3.2 presents part of the variables in a compact manner. This clustering was done by Dr. Christof Hofer based on the nature of each variable. Some examples are given of what kind of variables each cluster contains. Allogeneic transfusions and coagulation products are of primary interest. Also, as a secondary endpoint we consider Infections and Mortality cluster.

The initial 100 variable dataset was reduced to 54 variables for the before period and 47 variables for the after period. This reduction was necessary from a technical point of view as mentioned before. After an aggreement with the Dr. Christof Hofer non importand

variables and partially separated binary variables were removed. We were also able to aggregate some preoperation and postoperation count data to one total summation.

Chapter 4

Results

In this section we present results in form of DAGS accompanied with regression coefficients for the two periods. For both searches, the maximum number of parents allowed was 4 due to computational limitations.

4.1 Before period DAG

In Figure 4.1 the final DAG of the blood and coagulation products is presented. This DAG results from the bigger DAG with 54 nodes. The variables of importance are graphically subseted and only direct links between them are kept. The blue nodes, except node FFREE are poisson regression models and the parents of each node the covariates with the corresponding coefficients.

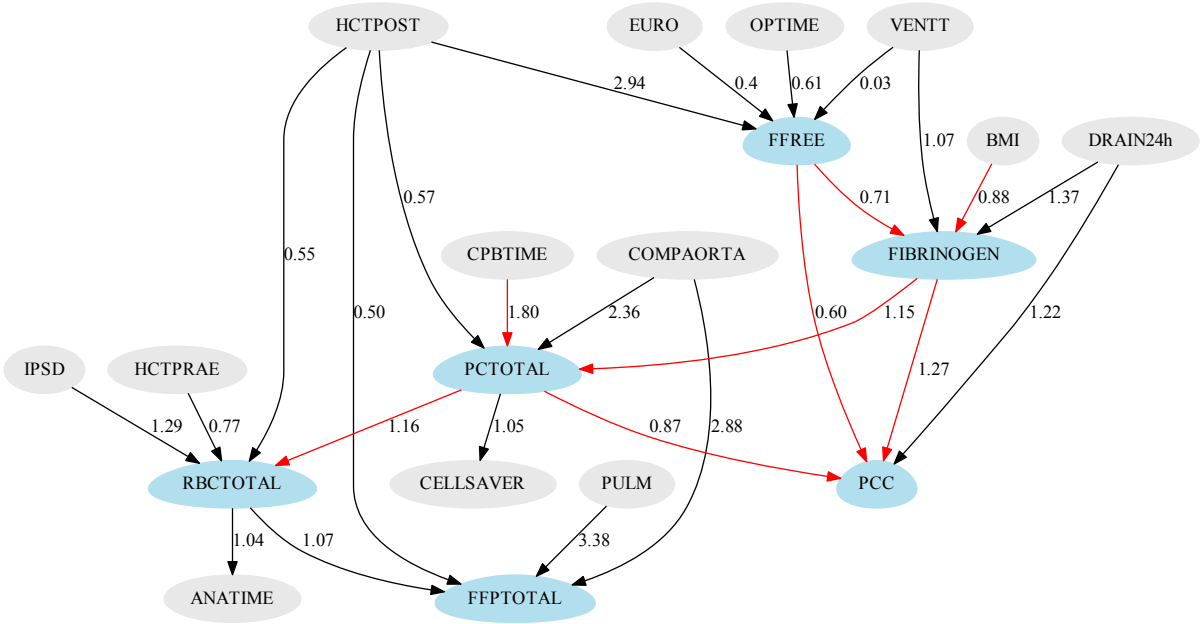

Figure 4.1: Before period blood-coagulation products DAG.

Interpeting these coefficients correspond to a normal generalized linear model. For exam-

ple, FFPTOTAL node represents the total count of fresh frozen plasma units that was given to a patient. An arc is connecting FFPTOTAL to HYPER with a coefficient of 8.93. We would say the expected count of fresh frozen plasma units is 9 times higher to patients with hypertension.
Node FFREE is a binary variable which dichotomize the patients into two groups, one group that was free of transfusion and the other group not free of transfusion. We observe a connection to Euroscore (EURO) and the coefficient to be 0.43. Euroscore is a preoperative score that predicts perioperative mortality. The odds of a patient of been free of transfusion decrease by 0.57 for each point increase in Euroscore.

4.2 After period DAG

Figure 4.2 shows the DAG for the after period for the blood and coagulation products. This DAG was again subsetted from the bigger DAG of 47 variables. Interpretation of the coefficient can be made again in the same way as in the previous DAG.
As noticed, the two DAGs for the two different time periods did not result into the same models. Given that, they are not directly comparable. The arcs that are denoted with red color are the common arcs that were presented in the two periods. But again, these common arcs cannot be compared to test the efficacy of the coagulation algorithm.

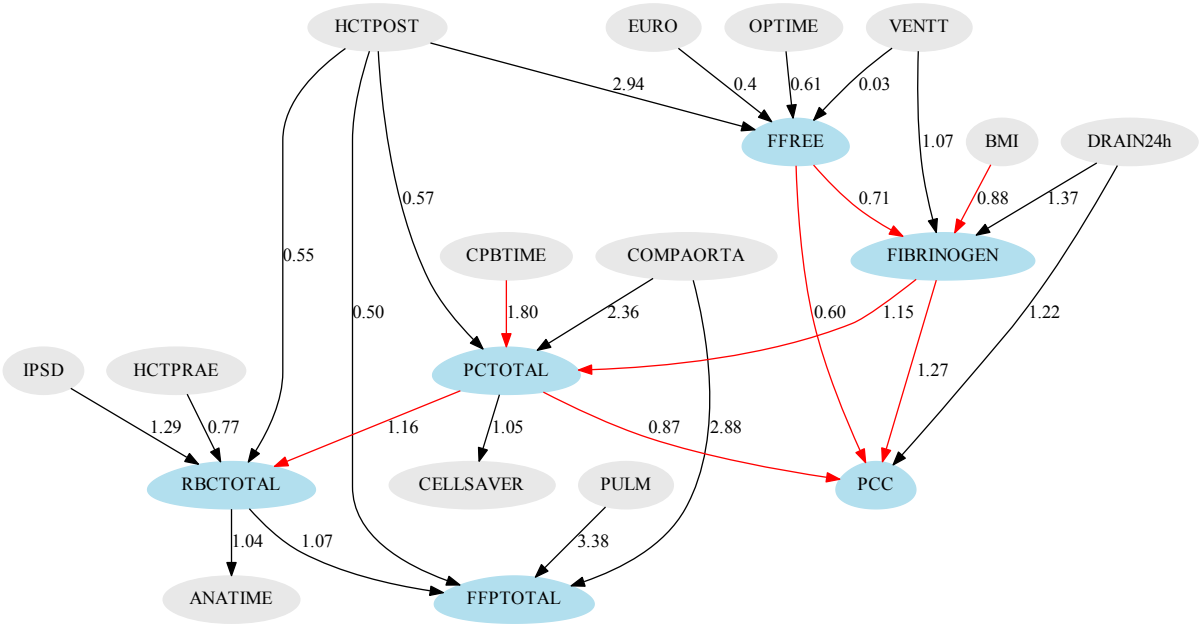

Figure 4.2: After period blood-coagulation products DAG.

We prefer to focus on how the structure changed, and not just compare coefficients. The coefficients along with 95% credible intervals for the two periods are available to Dr. Christof Hofer to make clinical inference.

Chapter 5

Discussion

Final structures

The models for the two periods resulted to different DAG structures. Thus, direct comparison of the two periods cannot be made. The red arcs are presenting the common arcs in the DAGs between the two periods. Also, these common arcs cannot be compared. Given these results, we cannot draw coclusions regarding the use of the algorithm in terms of model coefficients.

A more interesting approach would be to investigate how the structure changed from one period to another. Carefully controlling for the differences between models, is the total number of arcs reduced after the use of the algorithm?

It is also worth wondering why we ended up with different structures when using the same variable domain. Computational limitations did not allow us to increase the limit of parents above 4. A larger number of parents could possibly result to more similar structures, with intersecting local arcs in nodes between periods. In that situation comparison would be possible.

Could possibly the two period cohorts were heterogeneous and not been comparable sets of observations? Different demographic characteristics could have led to this result.

As mentioned before, partially separated binary nodes were removed from the model. The choice of parameter prior led to posteriors not integrating to unity. After cleaning up these binaries, the two periods had different number of variables that could be used for modeling. That is also a candidate of the above results.

Limitations of ABN

The amount of variables in our dataset forced us to limit the search to only 4 variables and not use the superior exact search. Even with only 4 parents and around 50 variables in each model, an ad-hoc use of `abn`'s heuristic search had to be performed. Each single run of a heuristic search algorithm was taking an excessive amount of time. Adding an additional parent to the search, R would crash lacking memory resources. It would not be possible without a server cluster to finish the analysis. Limiting the search to a small number of parents we might have lost important information through the process.

Additionally, blood and clotting products that were coded as count data, were overdispersed and that lead to extremely narrow credible intervals. Currently, there is no way

to deal with this problem, as `abn` package does not support a wide range of distributions.

Overfitting After obtaining 170 locally best structures with the heuristic approach, a summary based on the 50% majority concensus was performed. The distribution of the frequencies was an inversed bell curve showing that the strong arcs would appear even if we would have used a more strict threshold as a cutoff value.

Further research on ABN

While exact search with a small number of variables is well established, when there is more than a handfull of variables in the dataset, problems would start to appear. A more in depth documentation on heuristic search would be extremely useful, while methods of dimension reduction before implementing ABNs should be introduced at the same time. Further investigation is needed in order to deal with problems such as the zero inflated poisson counts that were mentioned before.

Conclusion

While Additive Bayesian network modelling performs extremely well under a very specific framework, that is a small number of variables following certain distributions and available computational resources, more light needs to be shed in more complicated cases like ours. We, as users of R and statistics need to spread the word around this new methodology. It can provide solution to the neverending question of multivariable vs multivariate analysis under the traditional framework of generalized linear models.

Bibliography

I. Beinlich, H. Suermondt, R. Chavez, and G. Cooper. *The ALARM monitoring system: A case study with two probabilistic inference techniques for belief networks. In Proceedings of the Second European Conference on Artificial lntelligence in Medicine, London.* Springer Verlag, Berlin, 1989. 9

N. Friedman and D. Koller. Being Bayesian about network structure. A Bayesian approach to structure discovery in Bayesian networks. *Machine Learning*, 50:95–125, 2003. 8

D. Heckerman, D. Geiger, and M Chickering. Learning bayesian networks. The combination of knowledge and statistical-data. *Machine Learning*, 20:197–243, 1995. 12

M. Koivisto and K. Sood. Exact bayesian structure discovery in bayesian networks. *Journal of Machine Learning Research*, 5:549–573, 2004. 12

J. Pearl. *Probabilistic Reasoning in Intelligent Systems.* Morgan Kaufmann, San Francisco, California, 1988. 8

Appendix A

Supplemental Information

A.1 Abbreviations and definitions

Abbr	Expanded-Explained
BMI	Body mass index
LVEF	Left ventricular ejection fraction
COLD	Chronic obstructive lung disease
KREAprae	creatinine pre-operation
GOTprae	Liver enzyme pre-operation
GPRprae	Liver enzyme pre-operation
LDHprae	Liver enzyme pre-operation
DMins	Diabetes Insulin
DMoral	Diabetes oral medication
ASA	Acetylsalicylic Acid Aspirin
CLOP	Clopidogrel at Operation
ALTCt	Other antiplatelet drugs at operation
ExASA	All antiplatelet drugs at operation
DUAL	Dual antiplatelet therapy at operation
LIQ	Heparin Liquemin pre operation
STATUS	urency of operation
CABG	Coronary artery bypass grafting
CABGno	Number of Coronary artery bypass grafting
AKE	Aortic valve replacement
COMP	Composite Graft
COMB	Combined procedures
MKR	Mitral valve replacement
AORTA	Aortic graft
OTHER	Other operations
ReDO	Re-operation after previous cardiac operation
CPB	Cardiopulmonary bypass
CONV	Convertion to CPB
VALVE	Different cardiac valves
OPTIME	Duration of operation
ANATIME	Time anaesthetized
CPBTIME	Time needed for cardiopulmonary bypass
CROSSTIME	TIme of aortic cross clamping
INRPRAE	Prothrombin paramemeter coagulation pre operation
APTTPRAE	Activated partial thromboplastin time pre operation
FIBPRAE	Fibrinogen level pre operation
ATPRAE	Activated prothrombplastin time pre operation
TCPRAE	platelet count pre operation
HCTPRAE	Hematocrit pre operation
kACTPRAE	Kaolin activated clotting time pre operation
gbACTPRAE	glass bead activated clotting time pre operation
CRPRAE	Clot rate pre operation
PFPRAE	Platelet function pre operation
FIBPOST	Fibrinogen level post operation

Abbr	Expanded-Explained
TCPOST	Platelet count post peration
kACTPOST	Kaolin Activation clotting time post operation
gbACTPOST	glass bead activated clotting time post operation
CRPOST	Clot rate post operation
PFPOST	Platelet function post operation
RBCTOTAL	Red blood cells given in total
PCTOTAL	Platelet concentrate given in total
FFPTOTAL	Fresh frozen plasma given in total
ICU	Intensive care unit
FCOP	Fibrinogen given during operation
FCIP	Fibrinogen given in ICU
PCCOP	Prothrombin complex concentrate given during operation
PCCIPS	Prothrombin complex concentrate given in ICU
DRAIN12H	Blood in drainage 12hours post operation
FFREE	Patient having received no blood products
FIB	Fibrinogen given
PCC	Prothrombin complex concentrate given
RETHX	Open thorax again
NEURO	Neurological problem
INFARCTION	Post operation myocardial infarction
IABP	Intra aortic balloon pump
RRT	Renal replacement therapy
EXTD	Time to extubatin in days
VENTT	Ventilation time in hours
IPSCH	ICU length of stay
LOScorr	Hospital length of stay
ICUMO	ICU mortality
POMO	Post op mortality
HOMO	hospital mortality
INFTOTAL	Total infections
KATH	Catheter associated infections
PULM	Pulmonary Infection
STERNAL	Sternal infection
HWI	Urinary tract infection
SEPSIS	Sepsis

A.2 Complete structures for the two periods

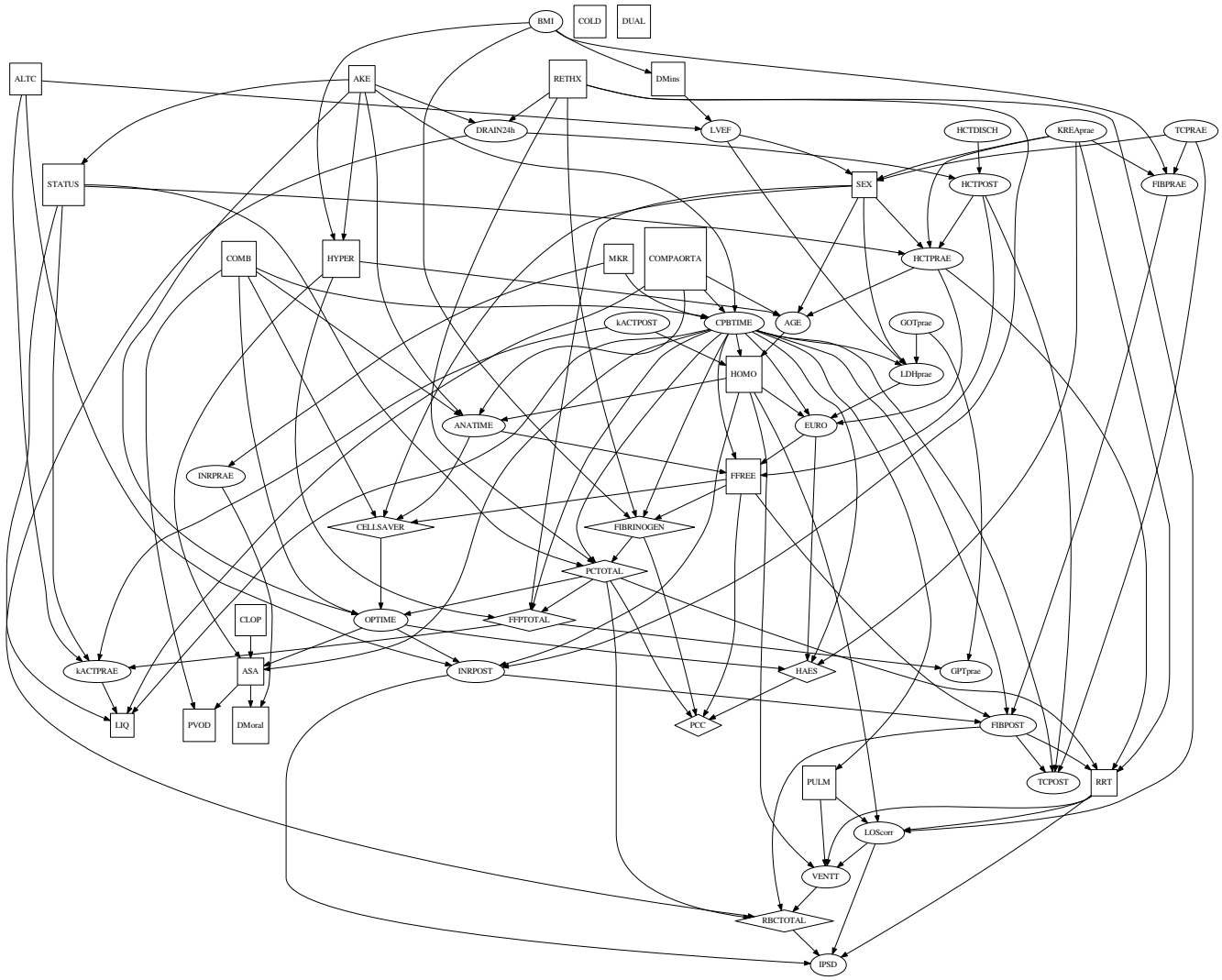

Figure A.1: Complete final DAG for the before period.

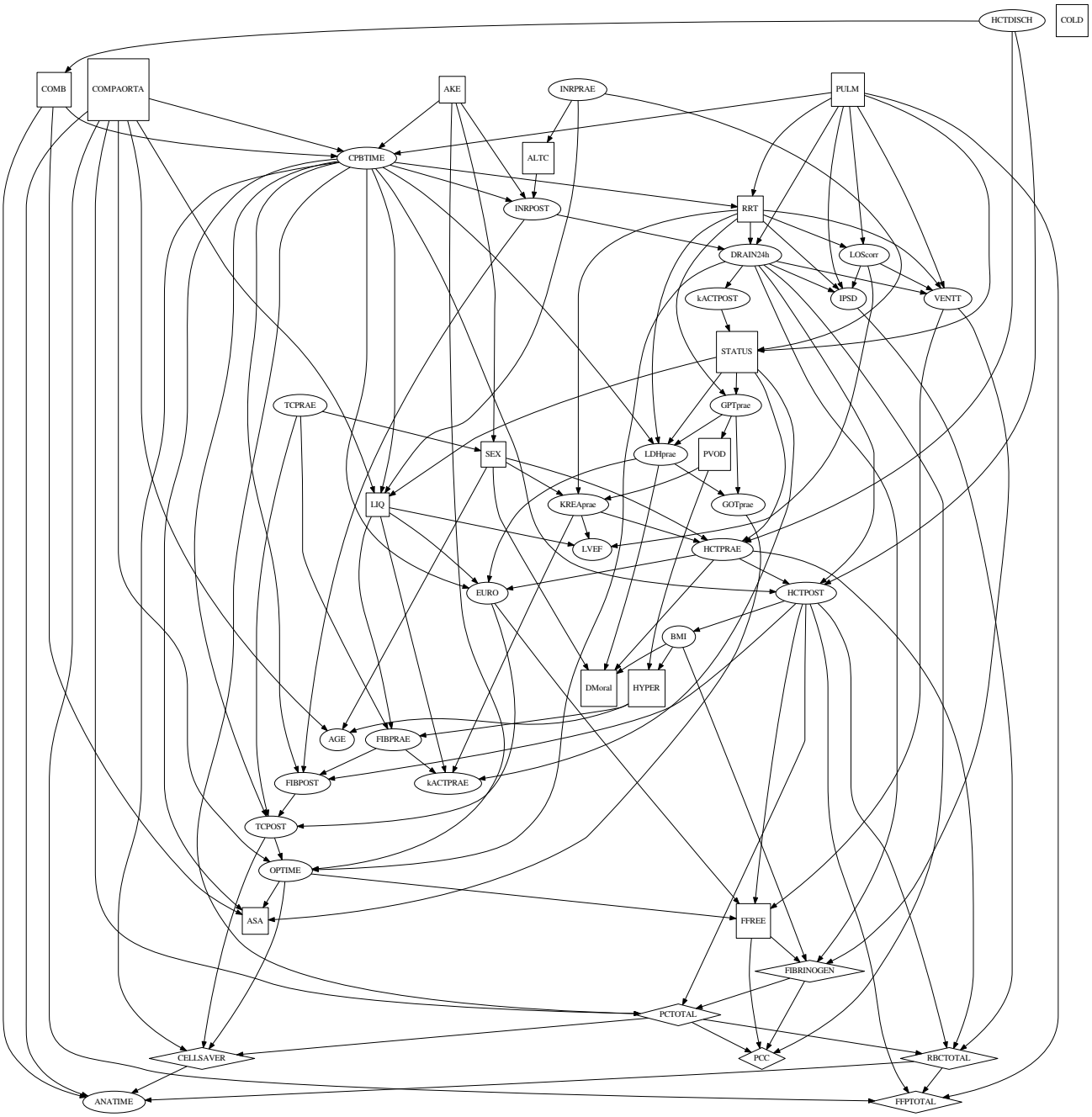

Figure A.2: Complete final DAG for the after period.

Appendix B

Manuscript I

Impact of a Sonoclot based Coagulation Management Algorithm on Allogeneic Blood Transfusion and Outcome in Cardiac Surgery

Christoph K. Hofer, Sonja Hartnack, Renate Behr, Christos Polysopoulos, Andreas Zollinger, Michele Genoni, Reinhard Furrer, Omer Dzemali

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Patient cohorts before and after implementing a Sonoclot based Coagulation Management Algorithm on Allogeneic Blood Transfusion and Outcome in Cardiac Surgery

A Quality Control Study

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Study number: NCTXXX

Funding and conflicts of interests: There is no funding and there are no conflicts.

Article word count (exclusive of abstract and references):

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ABSTRACT

Background:

Implementing coagulation management algorithms based on Point-of-care testing devices (i.e. thromboelastography (TEG) and rotational thromboelastometry (ROTEM)) have been shown to be benefial, both in terms of reducing transfusion rates and occurrence of adverse patient outcomes. Information on implementing a Sonoclot based coagulation management algorithm is scarce.

Methods:

Observational study comparing the transfusion rates of red blood cells (RBC) and patient adverse outcomes in two cohorts before (2009 to 2011) and after (2013 to 2015) implementation of a Sonoclot based coagulation management algorithm in 1754 patients undergoing different types of cardiac surgery. The effect of cohort and 19 predictors on transfusion of RBC was assessed by relative R^2-values obtained by bootstrapping and a hurdle regression model, comprising a binomial and a Poisson count component. Association of predictors with post-operative infections was assessed with a logistic regression model.

Results:

The proportion of patients not receiving allogenic blood products increased from 32.1 % (95 % CI [28.9 to 35.3] %) prior to 63.2 % (95 % CI [59.9 to 66.3] %) after implementing a Sonoclot coagulation management algorithm. While proportions of patients receiving RBC and PLT both decreased from 64.1 % (95 % CI [60.8 to 67.4]) to 33.4 (95 % CI [30.4 to 36.6]) and 34.7 (95 % CI [31.5 to 38.0]) to 16.1 (95 % CI [13.7 to 18.6]), respectively, the proportion of patients receiving fresh frozen plasma was increased from 2 % (95 % CI [1.2 to 3.2] to 9.9 % (95 % CI [8.1 to 12.1]). If

patients received any allogenic blood product, solely the median of RBC units received decreased from four to three units after implementing the coagulation management algorithm. A significant decrease in renal replacement therapy from 12.4 % (95% CI [10.2 to 14.8]) to 7.9 % (95% CI [6.2 to 9.8]), in pulmonary from 15.5 % (95% CI [13.1 to 18.1] to 7.1 % (95 % CI [5.5 to 9.0]) and urinary infections from 4.0 % (95 % CI [2.8 to 5.6] to 1.3 % (95 % CI [0.7 to 2.3] was detected.

Conclusion:

The implementation of a Sonoclot based coagulation management algorithm was found to be beneficial for both a reduction in transfusion rates and a decrease in renal replacement therapies and post-operative infections.

KEYWORDS

Sonoclot, point-of-care devices, visco-elastic measurement, coagulation, cardio-pulmonary bypass, heparin, bleeding, cardiac surgery, risk factors infection, RBC transfusion needs

INTRODUCTION

Bleeding and the associated transfusion of blood products is a major concern in patients undergoing cardiac surgery. Both, bleeding and transfusion have been shown to be independent risk factors for increased postoperative morbidity and mortality in this patient group resulting in increased hospital costs. The relationship between RBC and post-operative infections remains elusive with controversial findings [1–8].

A wide range of guidelines on peri-operative blood transfusion exist, which may rather reflect expert opinion than evidence-based decision-making [9]. Typically, transfusion rates of red blood cells (RBC) are larger when management of bleeding is at the clinician's discretion [3,10]. When a liberal transfusion strategy with the same thresholds for both gender is followed, women may have a higher transfusion rate and be presumably over transfused [11]. Transfusion rates differ markedly in different hospital settings even after adjusting for patient characteristics and operative data [12]. In the past years an increasing number of PBM (patient blood management) initiatives have been published [13,14], indicating that transfusions can be reduced while patient outcome is maintained or even ameliorates [15–19].

Different studies in the last decade demonstrated that the point-of-care (POC) coagulation management algorithms based on viscoelastic measurement techniques, predominantly the thrombelastometry (ROTEM) and thrombelastography (TEG) combined with platelet function tests i.e. blood impedance aggregometry (Multiplate) are associated with a reduction of transfusion requirements and therefore in decrease morbidity (such as transfusion associated adverse events or cerebrovascular insults) and mortality [10], [3,20–22]. However, so far no coagulation management algorithm using another viscoelastic measurement technique, the

SONOCLOT analyzer, has been published. Based on our experience with this technique in different studies and the daily practice for more than ten years we developed and implemented a SONOCLOT based algorithm in cardiovascular surgery predominantly for the use of specific coagulation factors (fibrin concentrate and prothrombin complex concentrate) [23–25].

Aim of this quality control study was to assess if patient cohorts before and after implementing an coagulation management algorithm differed in the transfusion of blood products, the administration of coagulation factors and the related outcome while adjusting for potential risk factors.

MATERIAL AND METHODS

Study setting and patient population

Patient and procedure related data of cardiac surgery procedures at the Triemli City Hospital, Switzerland are recorded since 2007 in a dedicated database (Dendrite system) with the approval of the institutional research ethics board (Kantonale Ethikkommission Zurich, Switzerland; KEK Nr. StV 1-2007 SPUK Chirurgie) and patient informed consent. The full range of cardiac surgical interventions except heart transplantation are performed in this hospital: The off-pump approach is used for routine coronary artery bypass grafting. The main types of heart surgery performed include coronary artery bypass grafting (CABG), aortic valve procedures (av), mitral valve procedures (mv), combined procedures (comb) and aortic procedures (ao). When conversion to cardio-pulmonary bypass (CPB) is required, the beating heart technique under normothermia is applied. Open-heart surgery is done on CPB under moderate hypothermia (28 to 32 °C). Data analysis focusing on coagulation

management using a dedicated algorithm in the present quality control study was done for 1754 out of 2199 consecutive patients undergoing cardiac surgery after additional ethics board approval (Kantonale Ethikkommission Zurich, Switzerland; KEK-ZH-Nr. 2015-0633, BASEC Nr. 2015-00038) comprising the prior cohort from 2009 to 2011 and the post cohort from 2013 to 2015.

Red blood cell transfusion

Anesthesia and intensive care were performed according to standardized protocols. Fluid management was done with lactated Ringer's solution (Laboratory Dr. Bichsel AG, Switzerland) and synthetic colloids (Physiogel balanced, B. Braun Medical AG, Melsungen, Germany). Red blood cells (RBC) were transfused intraoperatively at hematocrit (HCT) levels below 25% (preserved left ventricular function) or below 28% (left ventricular function ≤ 30%, emergency operations), respectively.

Prealgorithm coagulation management

Based on standard activated clotting time (kaolin, kACT). Detailed technical aspects of Sonoclot technology have been described previously [23].

Coagulation management algorithm

The concept is depicted in figure 1 and described in [24,25].

Outcome parameters

Primary outcome parameters: the amount of red blood cells given (in units) per patient.

116 Secondary outcome parameter: incidence of post-op infections.

117

118 ***Statistical analysis***

119 All analyses were performed with the software package R [26], version 3.3.3. To
120 compare patient-related demographic, pre-, peri- and postoperative data prior and
121 post implementation of the coagulation management algorithm ($cm_{algorithm}$),
122 descriptive statistics and univariable analysis were performed. Based on the format
123 and distribution of the data, either Fisher's exact test, t-tests or Wilcoxon rank sum
124 test were applied. To quantify a significant difference between the two patient cohorts
125 either an odds ratio with a 95 % confidence interval, a 95 % confidence interval for
126 the difference between the means, or a 95 % confidence interval for the difference
127 between medians is given. The latter one was obtained by 10'000 bootstraps with the
128 package boot [27] using the percentile approach.
129 To assess if the two cohorts prior and post implementing the $cm_{algorithm}$ differed
130 significantly in their amount of red blood cells given, while controlling for other
131 potential influential factors, two different approaches were chosen. First, after a
132 continuity-corrected log-transformation of the units of red blood cells given, the
133 following predictors were included in the analysis: prior or post implementation of
134 $cm_{algorithm}$, procedure time in minutes representing the time anaesthetized, five
135 different types of surgery (cabg, av, mv, comb and comp), elective or emergency
136 procedures (coded in 0 and 1), conversion to cardio-pulmonary-bypass with no (0)
137 and yes (1), left-ventricular ejection fraction (LVEF) in %, administration of heparin
138 preoperative with no (0) and yes (1) [LIQ], acetylsalicylic acid given preoperatively
139 with no (0) and yes (1) [ASA], administration of clopidogrel preoperatively with no (0)
140 and yes (1) [CLOP], administration of other platelet inhibitors with no (0) and yes (1)

[ALTC], body mass index (BMI), age in years, sex, preoperative hematocrit, preoperative platelets in 10^9/l, international normalized ratio (INR), preoperative activated partial thromboplastin time (aPTT) in sec, preoperative fibrinogen in mg/dl, preoperative creatinine in µmol/l and preoperative alanine-aminotransferase in IU/l. To check for multicollinearity, variance inflation factors were assessed with the R package usdm [28]. Subsequently, only predictors with values below two were included in the analysis. The aim of this first analytical approach was to describe the "relative importance" or association of each of the predictors regarding the amount of red blood cells given. The importance of each of the predictors in the model was considered in form of a R^2 value that is the ratio of the explained to the total variance in linear regression models. The relative R^2 value refers to the ratio of the explained variance of the respective predictor to the total variance explained by the model. Point estimates and 95% confidence intervals for relative R^2 values were obtained by bootstrapping (10'000 bootstraps) using the R package relaimpo [29] with both either including the respective predictor first or last.

Since the number of red blood cells given contained an excess of zeros, in a second analytical approach, with the same predictors, a hurdle model using the package pscl [30] was chosen and its goodness-of-fit metrics (i.e. AIC and BIC) compared to other types of generalized models such as Poisson or negative binomial regression.

Furthermore, to assess the association between potential risk factors and the incidence of infections postoperatively, a generalized linear model with a binomial link and logit function was chosen and performed with the R package MASS [31].

RESULTS

Descriptive statistics and univariable comparisons between the two patient cohorts

Patient-related demographic data, as well as preoperative medication and standard lab values of 1754 patients without missing values undergoing cardiac surgery before and after implementation of the $cm_{algorithm}$ are summarized in Table 1. With regard to sex, age, BMI, and EUROScore no significant differences were detected between the prior and post cohort. LVEF was found to be significantly increased for the cohort after $cm_{algorithm}$ implementation with a 95% CI of the difference of [0.03 to 2.5] %. Within the four different types of preoperative medication recorded, aspirin salicylic acid, heparin, clopidogrel or other platelet inhibitors and, only clopidogrel was found to be given significantly less often in the post cohort with an OR of 0.48 (95% CI [0.32 to 0.70]).

Concerning preoperative lab values creatinine, INR and haematocrit were found to be significantly increased in the post cohort with 95 % confidence intervals of differences in medians of [2 to 6] µmol/l and [0 to 0.02] INR and a 95 % confidence interval of difference in means of [0.17 to 1.13] %, respectively. In contrast, Alanine-Aminotransferase and platelets were significantly decreased in the post cohort compared to the prior cohort with corresponding 95 % confidence intervals of their differences in medians of [1 to 4] IU/l and [0 to 16] times 10^9/l. Activated partial thromboplastin time and fibrinogen did not differ significantly between the two cohorts.

The interventional times, i.e. duration of anaesthesia, operation time and CPB time, were all significantly reduced in the post cohort (table 2) with the respective 95% confidence intervals of difference in cohort medians of [15 to 35], [20 to 35] and [-14 to 75] minutes. In contrast, the cross clamp time did not differ significantly between the two cohorts. The proportion of emergency procedures was significantly higher before implementing the $cm_{algorithm}$ with an OR of 1.4 (95% CI [1.07 to 1.75]). Neither the proportion of conversion nor the proportions of the different types of cardiac

193 surgeries including the number of CABG differed significantly between the two
194 cohorts (table 2).
195
196 Regarding transfusions (table 3), significantly less ml of cell saver was re-transfused
197 in the post cohort with a 95 % confidence interval of difference in medians of [50 to
198 135]. Similarly, the proportion of patients having received any RBC versus none was
199 significantly decreased in the post cohort with an OR of 0.28 (95% CI [0.23 to 0.34]).
200 In patients who received RBC, significantly less units of RBC were administered in
201 the post cohort with median of three units compared to four units in the prior cohort
202 with 95 % confidence intervals of the medians of [2 to 6] for both cohorts. The
203 proportion of patients with FFP was significantly increased in the post cohort with an
204 OR of 5.3 (95 % CI [3.1 to 9.6]), the proportions of patients with platelet transfusions
205 were significantly reduced with an OR of 0.36 (95 % CI of [0.28 to 0.45]). In patients
206 which received either fresh frozen plasma or platelets there was no significant
207 difference found between the two cohorts. The proportion of patients who did not
208 receive any allogenic transfusion was significantly increased with an associated OR
209 of 3.6 (95 % CI [3.0 to 4.4]). For the other coagulation products, fibrinogen and
210 prothrombin complex C, the proportions of patients receiving these were significantly
211 reduced after implementing the $cm_{algorithm}$ with corresponding ORs of 0.45 (95 % CI
212 [0.38 to 0.57]) and of 0.44 (95 % CI [0.35 to 0.54]), respectively. The group medians
213 did not differ for these two products between these two cohorts.
214 With respect to postoperative outcomes (table 4), the proportion of re-explored, of
215 patients with myocardial infarction or with cerebrovascular insults did not differ
216 significantly between the two cohorts. In contrast, the proportion of patients with renal
217 replacement therapy was significantly reduced in the after cohort with an OR of 0.6
218 (95% CI [0.43 to 0.84]). Similarly, the proportion of patients with an infection was

219 significantly reduced in the after cohort with an OR of 0.39 (95% CI [0.29 to 0.52]). In
220 decreasing order pulmonary, urinary, sternal, sepsis and catheter associated
221 infection were recorded, only the first two were significantly reduced in the post
222 cohort.
223 The duration of mechanical ventilation was significantly reduced in the patient cohort
224 after implementation of the $cm_{algorithm}$ with a 95% confidence of the difference in
225 medians of [2 to 3]. The length of stay in ICU or in hospital was significantly
226 increased after implementing $cm_{algorithm}$ with a 95 % CI of the difference in medians
227 less than a day and of [0 to 2] days. Mortality in ICU or in hospital did not differ
228 significantly in both patient cohorts.
229
230 ***Factors associated with amount of RBC given***
231 *Relative importance*: We used a bootstrap approach to determine relative R^2 values
232 of each predictor. Here, the implementation of the $cm_{algorithm}$ was found - in all models
233 including only one of the three interventional times each - to rank between the ranks
234 two to four 4 out of 20 predictors. The first four ranks of the most important predictor
235 were in all models taken by the variables interventional times, haematocrit, type of
236 surgery and cohort. Still the total amount of variance explained by the model was
237 only approximately 40 % (Figure 2).
238 *Hurdle model*: Based on AIC and BIC, the model best fitting the data was a hurdle
239 model with a negative binomial component to model counts of the units of blood cells
240 given and a hurdle component to model the zeros (i.e. no red blood cells given)
241 versus larger counts by a binomial distribution. In this regression model, the
242 magnitude of the p values associated with the predictors was found to be in
243 accordance with the results of the relative importance approach (supplementary file).
244 More predictors are significantly associated with the zero hurdle component, i.e.

having received any number of blood cells versus none compared to the count component.

Risk factors for infection post-OP

Resulting from a logistic regression model the following predictors were found to be highly significantly associated with an infection post-operatively: implementation of $cm_{algorithm}$ (OR of 2.5 with a 95% CI [1.8 to 3.6]) and RBC transfusion with an OR of 1.12 (95% CI of [1.07 to 1.17]). Significantly associated were BMI, anesthesia time, creatinine, age and conversion to CPB (table 5).

DISCUSSION

Within the context of quality control and patient safety, this observational study aimed at comparing patient cohort before and after implementing a coagulation algorithm with regard to the amount of RBC given and post-operative outcomes. The proportion of patients which received RBC, PLT, fibrinogen and PCC was significantly decreased after implementation of the coagulation algorithm. In contrast, more patients received FFP after implementing the coagulation management algorithm. However, among the patients which received the specific blood products, the median amount did not differ between both cohorts with the exception of RBC where the median amount was four and three in the prior and post cohort, respectively. The decrease in RBC and PLT is in line with a number of studies showing beneficial effects of PBM [9,16,17,22,32,33], but an increase in the proportions of patients receiving FFP from 2 to 9.9%, while the median did not alter between the two cohort, is an unexpected finding.

The individual effects of a number of potentially interrelated predictors on RBC administration are difficult to disentangle in a regression model. Still, based on two different statistical approaches, relative R^2-values and a hurdle model, the difference

between the two cohorts was found to be significantly associated with the transfusion of RBC. The hurdle regression model, with a binomial as well as a count component, allows to differentiate, if the predictors are significantly with the binomial component (transfusion of RBC: yes or no) or with the amount of RBC units given. We chose the hurdle model to deal appropriately with an excess of zeros and over dispersion. Based on the hurdle model, it became evident that 12 out of 19 predictors are significantly associated with the transfusion of RBC, but only six with the amount of RBC given. Longer procedural times, no coagulation management algorithm implemented, lower pre-operative haematocrit, increasing age, lower BMI, higher pre-operative creatinine, being an emergency surgery, being female, conversion to CBP, pre-operative Alanin-Aminotransferase, and higher pre-operative INR were all associated with a significantly higher odds to receive RBC. Regarding the count component, only procedural times, pre-operative haematocrit, BMI, emergency procedure and conversion were significantly associated, in the same direction as the binomial component, with the amount of RBC units given. Additional in the count component, higher LVEF values were associated with a lower amount of RBC units given.

Although the two cohorts differ significantly in a number of variables, most of the detected differences are clinically not considered relevant. Notable exceptions are Clopidogrel, which is administered significantly less often in the post cohort as well as the procedural times and the number of emergency surgeries, which are all reduced in the post cohort. This study is an observational study comprising observations from patient data collected in two different time periods. With the aim to assess the relative effect of each predictor, we decided not to use any approach involving matching or propensity scores.

Comparing the two cohorts, re-exploration rate, myocardial infarction, cerebro-vascular insults did not differ significantly. In contrast, renal replacement therapy, pulmonary and urinary infection occurred significantly less often after implementing a coagulation management algorithm. Other types of infection (i.e. sternal, catheter associated and sepsis) occurred also less often, but were not significant, presumably due to small sample size.

The beneficial effect of cohort, with the post cohort performing better than the prior cohort, could be due to a number of reasons: the coagulation management algorithm itself, but presumably also other changes in the two time periods which may have occurred. Still in the context of quality control and patient safety, we are confident that despite differences in the patient characteristics in the two cohorts, that the reduction in transfusion and subsequently costs, while improving with regard to patient safety (infections) are true and not spurious findings. Other reasons explaining, the beneficial effects on transfusion need and outcomes, may be an increased awareness of transfusion behaviour due to implementing a new coagulation management algorithm [15,34].

LEGENDS TO FIGURES

Figure 1

Title:

Coagulation management algorithm based on Sonoclot in cardiac surgery

Footnote:

ACT = Activated clotting time, ADP = Adenosine Diphosphate, AUC = Area under the curve, CR = Clot rate, FFP = Fresh frozen plasma, gbACT = glass bead-activated

clotting time, hepgbACT= glass bead-activated clotting time with heparinase. kACT = kaolin-activated clotting time, PC = Platelet concentrate, PCC = Prothrombin complex concentrate, PF = Platelet function, PT = Prothrombin time

Figure 2

Title:

Risk factors for perioperative RBC administration. Here the relative R^2-values, the ratio of the explained variance of the respective predictor to the total variance explained by the model obtained by bootstrapping are shown.

Footnote:

ALAT = Alanin-Aminotransferase, aPTT = Activated Partial Thromboplastin Time, ASA = Aspirin Salicylate Acid, BMI = Body mass index, CPB = Cardiopulonary bypass, HCT = Hematocrit, INR = International Normalized Ratio, LVEF = Left Ventricular Ejection Fraction

Table 1: Patient characteristics and preoperative standard lab values

		Before (n = 839)	**After** (n = 915)	P
Patients				
F/M ratio	*n/n (%)*	211/628 (25.1)	200/715 (21.8)	0.114[F]
	95% CI	[22.2;28.2]	[19.2;24.7]	
Age in years	*median (IQR)*	68 (60,70)	68 (59,75)	0.652[T]
BMI in *kg/m²*	*median (IQR)*	26.6 (24.2,29.7)	26.5 (24.2,29.4)	0.208[T]
LVEF in %	*median (IQR)*	60 (47,65)	60 (50,65)	0.044[T]
EUROScore	*median (IQR)*	6 (3,8)	6 (4,8)	0.984[T]
Preoperative Medication				
ASA	*n (%)*	535 (63.8)	588 (64.3)	0.842[F]
	95% CI	[60.4;67.0]	[61.1;67.4]	
Clopidogrel	*n (%)*	82 (9.8)	45 (4.9)	< 0.001[F]
	95% CI	[7.8;12.0]	[3.6;6.5]	
Other platelet inhibitors	*n (%)*	121 (14.4)	133 (14.5)	0.999[F]
	95% CI	[12.1;17.0]	[12.3;17.0]	
Heparin	*n (%)*	153 (18.2)	173 (18.9)	0.759[F]
	95% CI	[15.7;21.0]	[16.4;21.6]	
Preoperative Lab				
Creatinine *umol/lit*	*median (IQR)*	77 (67,89)	81 (70,96)	< 0.001[W]
ALAT in *IU/lit*	*median (IQR)*	23 (16,33)	20 (15,31)	< 0.001[W]
INR	*median (IQR)*	1.02 (0.98,1.08)	1.03 (0.99,1.09)	0.044[W]
aPTT in *sec*	*median (IQR)*	31 (29,39)	31 (29,36)	0.471[W]
Fibrinogen in *mg/dl*	*median (IQR)*	367 (304,440)	358 (304,416)	0.067[W]
Platelets in *10^9/lit*	*median (IQR)*	215 (181,263)	209 (172,246)	< 0.001[W]
HCT in %	*median (IQR)*	40 (37,43)	41 (38,43)	0.006[T]

ALAT = Alanin-Aminotransferase, aPTT = Activated Partial Thromboplastin Time, ASA = Aspirin Salycilate Acid, BMI = Body mass index, F/M ratio = Female/Male ratio, HCT = Hematocrit, INR = International Normalized Ratio, LVEF = Left Ventricular Ejection Fraction

[F] = Fisher's exact test, [T] = t-test, [W] = Wilcoxon rank sum test

Table 2: Operation related data

		Before (n = 839)	**After** (n = 915)	P
Interventional times				
Anesthesia time in min	*median (IQR)*	390(335,450)	370(324,420)	<0.001[W]
Surgery time in min	*median (IQR)*	250(210,300)	225(180,270)	<0.001[W]
CPB time in min	*median (IQR)*	68(0,125)	56(0,114)	0.039[W]
Interventions				
Emergency procedures	*n (%)*	182 (21.7)	154 (16.8)	0.011[F]
	95% CI	[18.9,24.6]	[14.5,19.4]	
CABG	*n (%)*	412 (49.1)	479 (52.3)	0.181[F]
	95% CI	[45.7,52.5]	[49.0,55.6]	
Conversion rate	*n (%)*	30 (3.6)	39 (4.3)	0.539[F]
	95% CI	[2.4,5.1]	[3.0,5.8]	
AV procedures	*n (%)*	165 (19.7)	156 (17.0)	0.174[F]
	95% CI	[17.0,22.5]	[14.7,19.6]	
MV procedures	*n (%)*	55 (6.5)	56 (6.1)	0.768[F]
	95% CI	[5.0,8.4]	[4.6,7.9]	
Combined procedures	*n (%)*	156 (18.6)	151 (16.5)	0.258[F]
	95% CI	[16.0,21.4]	[14.1,19.1]	
Aortic procedures	*n (%)*	108 (12.3)	103 (11.8)	0.769[F]
	95% CI	[10.1,14.7]	[9.8,14.1]	

AV = Aortic Valve, CABG = Coronary Artery Bypass Grafting, CPB = Cardio-Pulmonary Bypass, [F] = Fisher's exact test, [W] = Wilcoxon rank sum test

Table 3: Transfusions

		Before (n = 839)	After (n = 915)	P
Autologous transfusions				
Cell saver re-transfusion in ml	*median (IQR)*	520 (330,700)	430 (300,700)	<0.001[W]
Allogenic transfusions				
RBC				
Patients with RBC	n (%)	538 (64.1)	306(33.4)	<0.001[F]
	95% CI	[60.8,67.4]	[30.4,36.6]	
If RBC received	*median (IQR)*	4(2,6)	3(2,6)	0.027[W]
FFP				
Patients with FFP	n (%)	17(2.0)	91(9.9)	<0.001[F]
	95% CI	[1.2,3.2]	[8.1,12.1]	
If FFP received	*median (IQR)*	4(2,4)	4(2,8)	0.306[W]
PLT				
patient with PLT	n (%)	291(34.7)	147(16.1)	<0.001[F]
	95% CI	[31.5,38.0]	[13.7,18.6]	
If PLT received	*median (IQR)*	2(1.5,2.0)	2(1,3)	0.809[W]
Free of transfusion	*n (%)*	269 (32.1)	578 (63.2)	<0.001[F]
	95% CI	[28.9,35.3]	[59.9,66.3]	
Other coagulation products				
patient with Fib	n(%)	506(60.3)	379(41.4)	<0.001[F]
	95% CI	[56.9,63.4]	[38.2,44.7]	
If Fib received	*median (IQR)*	2(2,4)	2(2,4)	0.180[W]
PCC in *U/patient*				
patient with PCC	n(%)	343(40.9)	213(23.3)	<0.001[F]
	95% CI	[37.5,44.3]	[20.6,26.1]	

If PCC received	*median (IQR)*	1200(600,1200)	1200(600,1800)	0.264[W]

FFP = Fresh Frozen Plasma, PLT = Platelet Concentrate, PCC = Prothrombin Complex Concentrate, RBC = Red Blood Cells

[F] = Fisher's exact test, [W] = Wilcoxon rank sum test

Table 4: Postoperative Outcome

		Before (n = 839)	**After** (n = 915)	P
General				
Re-exploration rate	*n (%)*	68 (8.1)	67 (7.3)	0.591[F]
	95% CI	[6.4,10.2]	[5.7,9.2]	
Myocardial infarction	*n (%)*	12 (1.4)	14 (1.5)	0.999[F]
	95% CI	[0.7,2.5]	[0.8,2.5]	
Cerebrovascular Insult	*n (%)*	19 (2.3)	11 (1.2)	0.098[F]
	95% CI	[1.4,3.5]	[0.06,2.1]	
Renal replacement therapy	*n (%)*	104 (12.4)	72 (7.9)	0.002[F]
	95% CI	[10.2,14.8]	[6.2,9.8]	
Infection				
Pulmonary	*n (%)*	130 (15.5)	65 (7.1)	<0.001[F]
	95% CI	[13.1,18.1]	[5.5,9.0]	
Catheter associated	*n (%)*	9 (1.1)	4 (0.4)	0.164[F]
	95% CI	[0.5,2.0]	[0.1,1]	
Sternal	*n (%)*	18 (2.1)	12 (1.3)	0.200[F]

	95% CI	[1.3,3.7]	[0.7,2.3]	
Urinary	*n (%)*	34 (4.0)	12 (1.3)	<0.001[F]
	95% CI	[2.8,5.6]	[0.7,2.3]	
Sepsis	*n (%)*	19 (2.3)	11 (1.2)	0.098[F]
	95% CI	[1.4,3.5]	[0.6,2.1]	
Infection total	*n (%)*	177(21.1)	86 (9.4)	<0.001[F]
	95% CI	[18.4,24.0]	[7.6,11.5]	
Postoperative times				
Duration of mech. Ventilation in h	*median (IQR)*	7(5,15)	5(4,8)	<0.001[W]
ICU length of stay in d	*median (IQR)*	1(0.67,1.67)	1(1,1.67)	<0.001[W]
Hospital length of stay in d	*median (IQR)*	8(6,11)	8(7,12)	<0.001[W]
Mortality				
ICU < 24h	*n (%)*	19 (2.3)	15 (1.6)	0.388[F]
	95% CI	[1.4,3.5]	[0.9,2.7]	
ICU Total	*n (%)*	24 (2.9)	18 (2.0)	0.274[F]
	95% CI	[1.8,4.2]	[1.2,3.1]	
Hospital stay	*n (%)*	45 (5.4)	35 (3.8)	0.137[F]
	95% CI	[3.9,7.1]	[2.7,5.3]	

ICU = Intensive Care Unit

[F] = Fisher's exact test, [W] = Wilcoxon rank sum test

Table 5: Risk factors for postoperative infections

Predictors	odds ratio	95% CI	p
No algorithm	2.535	[1.813 to 3.572]	**<0.001**
RBC transfusion	1.118	[1.074 to 1.167]	**<0.001**
BMI	1.053	[1.018 to 1.088]	**0.002**
Anesthesia time	1.002	[1.001 to 1.004]	**0.005**
Preop creatinine	1.004	[1.001 to 1.008]	**0.008**
Age	1.025	[1.006 to 1.045]	**0.012**
Conversion to CPB	2.115	[1.057 to 4.025]	**0.027**
Platelet inhibitors	1.488	[0.997 to 2.197]	**0.049**
Preop platelet count	0.998	[0.995 to 1.000]	0.063
Preop fibrinogen level	1.001	[1.000 to 1.003]	0.076
Preop ALAT	1.003	[0.999 to 1.007]	0.113
Preop INR	1.017	[0.991 to 1.041]	0.139
Type of surgery*			0.232
Clopidogrel	0.719	[0.389 to 1.267]	0.270
EURO Score	1.035	[0.967 to 1.107]	0.315
PCC administration	1.000	[0.9999 to 1.0003]	0.316
Preop HCT	0.986	[0.956 to 1.018]	0.376
Sex	1.171	[0.805 to 1.693]	0.406
ASA intake	0.885	[0.623 to 1.260]	0.494
Fibrinogen administration	0.973	[0.896 to 1.053]	0.496
Preop aPTT	1.001	[0.997 to 1.005]	0.531
Emergency procedures	0.874	[0.551 to 1.369]	0.562
LVEF	1.003	[0.991 to 1.016]	0.594

ALAT = Alanin-Aminotransferase, aPTT = Activated Partial Thromboplastin Time, ASA = Aspirin Salicylate Acid, AV = Aortic valve, BMI = Body mass index, CPB = Cardiopulonary bypass, HCT = Hematocrit, INR = International Normalized Ratio, LVEF = Left Ventricular Ejection Fraction, MV = Mitral valve, PCC = Prothrombin Complex Concentrate, *based on a likelihood-ratio test

Figure 1

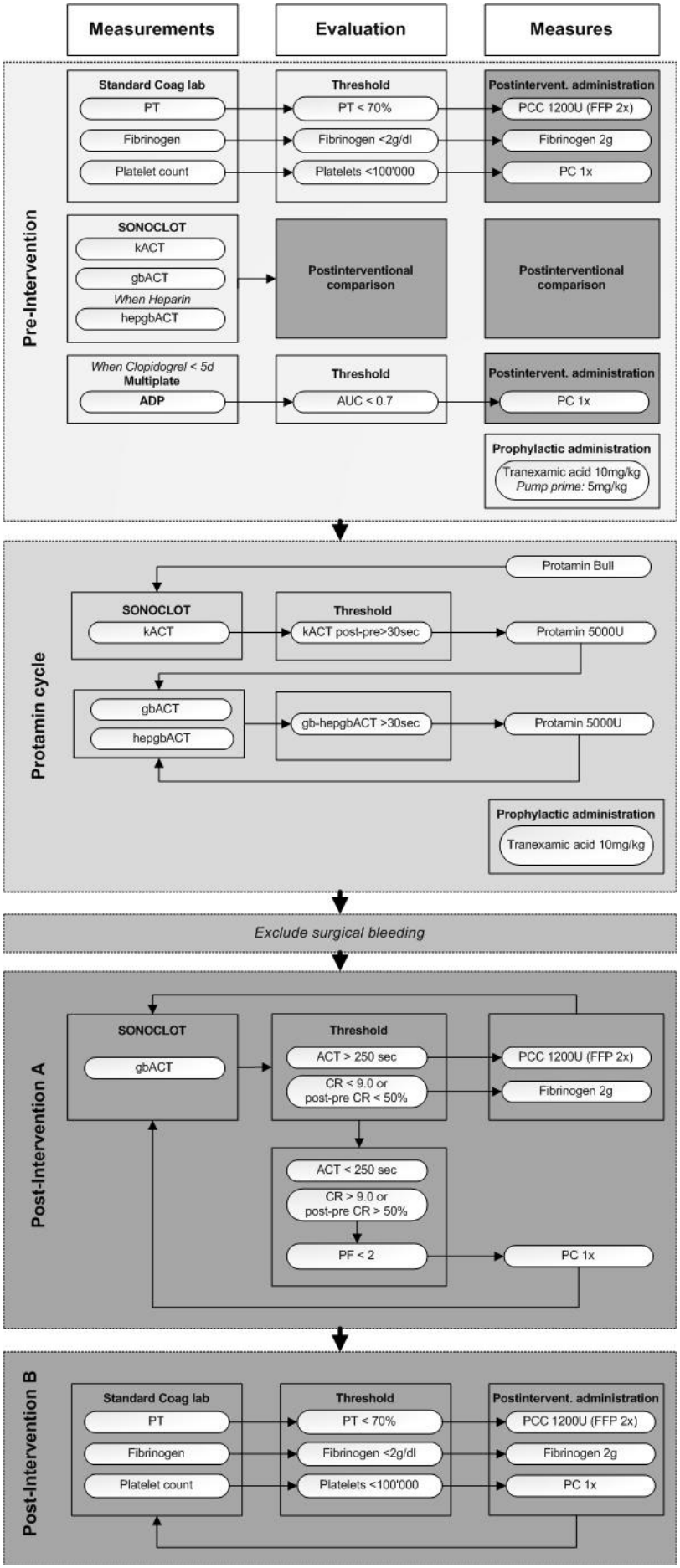
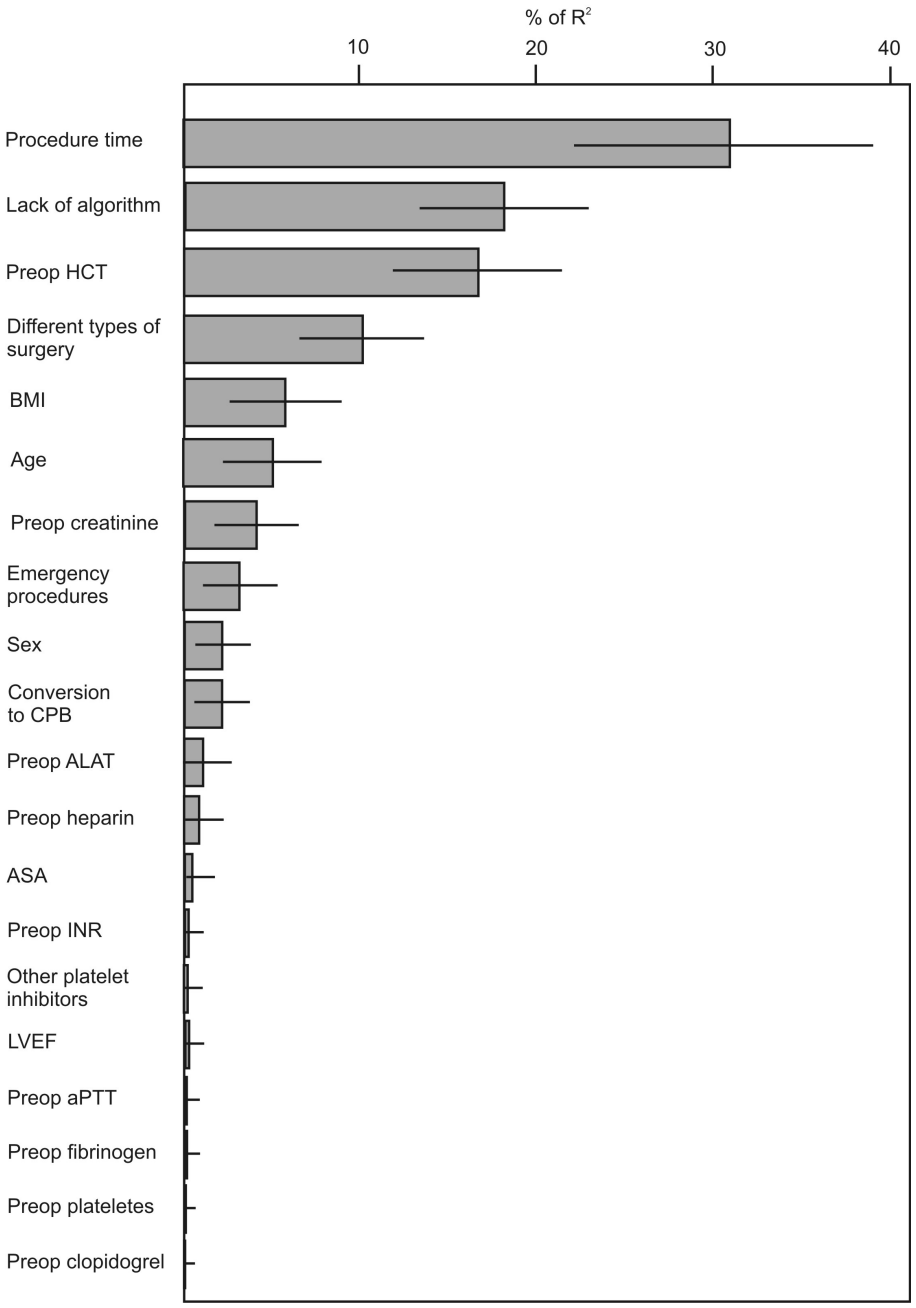

Measurements
Evaluation
Measures
Pre-Intervention
Standard Coag lab
PT
Fibrinogen
Platelet count
Threshold
PT < 70%
Fibrinogen <2g/dl
Platelets <100'000
Postintervent. administration
PCC 1200U (FFP 2x)
Fibrinogen 2g
PC 1x
SONOCLOT
kACT
gbACT
When Heparin
hepgbACT
Postinterventional comparison
Postinterventional comparison
When Clopidogrel < 5d
Multiplate
ADP
Threshold
AUC < 0.7
Postintervent. administration
PC 1x
Prophylactic administration
Tranexamic acid 10mg/kg
Pump prime: 5mg/kg
Protamin cycle
Protamin Bull
SONOCLOT
kACT
Threshold
kACT post-pre>30sec
Protamin 5000U
gbACT
hepgbACT
gb-hepgbACT >30sec
Protamin 5000U
Prophylactic administration
Tranexamic acid 10mg/kg
Exclude surgical bleeding
Post-Intervention A
SONOCLOT
gbACT
Threshold
ACT > 250 sec
CR < 9.0 or post-pre CR < 50%
PCC 1200U (FFP 2x)
Fibrinogen 2g
ACT < 250 sec
CR > 9.0 or post-pre CR > 50%
PF < 2
PC 1x
Post-Intervention B
Standard Coag lab
PT
Fibrinogen
Platelet count
Threshold
PT < 70%
Fibrinogen <2g/dl
Platelets <100'000
Postintervent. administration
PCC 1200U (FFP 2x)
Fibrinogen 2g
PC 1x

Figure 2


% of R²
10
20
30
40
Procedure time
Lack of algorithm
Preop HCT
Different types of surgery
BMI
Age
Preop creatinine
Emergency procedures
Sex
Conversion to CPB
Preop ALAT
Preop heparin
ASA
Preop INR
Other platelet inhibitors
LVEF
Preop aPTT
Preop fibrinogen
Preop plateletes
Preop clopidogrel

REFERENCES

1. Stokes EA, Wordsworth S, Bargo D, Pike K, Rogers CA, Brierley RCM, Angelini GD, Murphy GJ, Reeves BC: Are lower levels of red blood cell transfusion more cost-effective than liberal levels after cardiac surgery? Findings from the TITRe2 randomised controlled trial. *BMJ Open* 2016, 6:e011311.

2. Engoren M, Brown RR, Dubovoy A: A retrospective analysis of the effect of blood transfusion on cerebral oximetry entropy and acute kidney injury. *Perfusion* 2017, 32:35-43.

3. Fahrendorff M, Oliveri RS, Johansson PI: The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products - A systematic review and meta-analysis. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2017, 25:39.

4. Helgason D, Helgadottir S, Viktorsson SA, Orrason AW, Ingvarsdottir IL, Geirsson A, Gudbjartsson T: Acute kidney injury and outcome following aortic valve replacement for aortic stenosis. *Interactive Cardiovascular and Thoracic Surgery* 2016, 23:266-272.

5. Koster A, Zittermann A, Börgermann J, Knabbe C, Diekmann J, Schirmer U, Gummert JF: Transfusion of 1 and 2 units of red blood cells does not increase mortality and organ failure in patients undergoing isolated coronary artery bypass grafting. *European Journal of Cardio-Thoracic Surgery: official journal of the European Association for Cardio-thoracic Surgery* 2016, 49:931-936.

6. Leahy MF, Hofmann A, Towler S, Trentino KM, Burrows SA, Swain SG, Hamdorf J, Gallagher T, Koay A, Geelhoed GC, Farmer SL: Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. *Transfusion* 2017, 57:1347-1358.

7. Stone GW, Clayton TC, Mehran R, Dangas G, Parise H, Fahy M, Pocock SJ: Impact of major bleeding and blood transfusions after cardiac surgery: analysis from the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial. *American Heart Journal* 2012, 163:522-529.

8. Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD: Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007, 116:2544-2552.

9. Ad N, Holmes SD, Patel J, Shuman DJ, Massimiano PS, Choi E, Fitzgerald D, Halpin L, Fornaresio LM: The impact of a multidisciplinary blood conservation protocol on patient outcomes and cost after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2017, 153:597-605.e1.
10. Avidan MS: Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. *British Journal of Anaesthesia* 2004, 92:178-186.
11. Gombotz H, Schreier G, Neubauer S, Kastner P, Hofmann A: Gender disparities in red blood cell transfusion in elective surgery: a post hoc multicentre cohort study. *BMJ open* 2016, 6:e012210.
12. Magruder JT, Blasco-Colmenares E, Crawford T, Alejo D, Conte JV, Salenger R, Fonner CE, Kwon CC, Bobbitt J, Brown JM, Nelson MG, Horvath KA, Whitman GR: Variation in Red Blood Cell Transfusion Practices During Cardiac Operations Among Centers in Maryland: Results From a State Quality-Improvement Collaborative. *The Annals of tThoracic Surgery* 2017, 103:152-160.
13. Meybohm P, Froessler B, Goodnough LT, Klein AA, Muñoz M, Murphy MF, Richards T, Shander A, Spahn DR, Zacharowski K: "Simplified International Recommendations for the Implementation of Patient Blood Management" (SIR4PBM). *Perioperative medicine (London, England)* 2017, 6:5.
14. Spahn DR: Patient Blood Management: the new standard. *Transfusion* 2017, 57:1325-1327.
15. Mehra T, Seifert B, Bravo-Reiter S, Wanner G, Dutkowski P, Holubec T, Moos RM, Volbracht J, Manz MG, Spahn DR: Implementation of a patient blood management monitoring and feedback program significantly reduces transfusions and costs. *Transfusion* 2015, 55:2807-2815.
16. Verdecchia NM, Wisniewski MK, Waters JH, Triulzi DJ, Alarcon LH, Yazer MH: Changes in blood product utilization in a seven-hospital system after the implementation of a patient blood management program: A 9-year follow-up. *Hematology (Amsterdam, Netherlands)* 2016, 21:490-499.
17. Weber CF, Görlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, Cohn LH, Zacharowski K: Point-of-Care Testing A Prospective, Randomized Clinical Trial of Efficacy in Coagulopathic Cardiac Surgery Patients. *Anesthesiology* 2012, 117:531-547.

18. Meybohm P, Herrmann E, Steinbicker AU, Wittmann M, Gruenewald M, Fischer D, Baumgarten G, Renner J, van Aken HK, Weber CF, Mueller MM, Geisen C, Rey J, Bon D, Hintereder G, Choorapoikayil S, Oldenburg J, Brockmann C, Geissler RG, Seifried E, Zacharowski K: Patient Blood Management is Associated With a Substantial Reduction of Red Blood Cell Utilization and Safe for Patient's Outcome: A Prospective, Multicenter Cohort Study With a Noninferiority Design. *Annals of Surgery* 2016, 264:203-211.
19. Geissler RG, Rotering H, Buddendick H, Franz D, Bunzemeier H, Roeder N, Kwiecien R, Sibrowski W, Scheld HH, Martens S, Schlenke P: Utilisation of blood components in cardiac surgery: a single-centre retrospective analysis with regard to diagnosis-related procedures. *Transfusion medicine and hemotherapy: offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie* 2015, 42:75-82.
20. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP, Pinto R, Scales DC: Point-of-Care Hemostatic Testing in Cardiac Surgery: A Stepped-Wedge Clustered Randomized Controlled Trial. *Circulation* 2016, 134:1152-1162.
21. Serraino GF, Murphy GJ: Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. *British Journal of Anaesthesia* 2017, 118:823-833.
22. Shen L, Tabaie S, Ivascu N: Viscoelastic testing inside and beyond the operating room. *Journal of Thoracic Disease* 2017, 9:S299-S308.
23. Ganter MT, Monn A, Tavakoli R, Klaghofer R, Zollinger A, Hofer CK: Kaolin-based activated coagulation time measured by sonoclot in patients undergoing cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia* 2007, 21:524-528.
24. Dzemali O, Ganter MT, Zientara A, Graves K, Behr R, Genoni M, Hofer CK: Evaluation of a New Sonoclot Device for Heparin Management in Cardiac Surgery. *Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis* 2017, 23:20-26.
25. Bischof DB, Ganter MT, Shore-Lesserson L, Hartnack S, Klaghofer R, Graves K, Genoni M, Hofer CK: Viscoelastic blood coagulation measurement with Sonoclot predicts postoperative bleeding in cardiac surgery after heparin reversal. *Journal of Cardiothoracic and Vascular Anesthesia* 2015, 29:715-722.

26. R Core Team: *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/
27. Canty A, Ripley B: *boot: Bootstrap R (S-Plus) Function S*; 2016. https://CRAN.R-project,org/package=boot
28. Babak Naimi: *usdm: Uncertainty analysis for species distribution models*; 2015. https://CRAN.R-project.org/package=usdm
29. Grömping U: Relative importance for linear regression in R: The package relaimpo. *Journal of Statistical Software* 2006, 17:1-27.
30. Zeileis A, Kleiber C, Jackman S: Regression models for count data in R. *Journal of Statistical Software* 2008, 27. http://www.jstatsoft.org/v27/i08/
31. Venables WN, Ripley BD: *MASS. Modern Applied Statistics with S.* New York: Springer. http://www.stats.ox.ac.uk/pub/MASS4
32. Karkouti K, McCluskey, Stuart A., Callum, Jeannie, Freedman J, Selby R.: Timoumi T, Debashis R, Rao V: Evaluation of a Novel Transfusion Algorithm Employing Point-of-care Coagulation Assays in Cardiac Surgery. *Anesthesiology* 2015, 122:560-570.
33. Wikkelsø A, Wetterslev J, Møller AM, Afshari A: Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. *Anaesthesia* 2017, 72:519-531.
34. Brouwers C, Hooftman B, Vonk S, Vonk A, Stooker W, Te Gussinklo WH, Wesselink RM, Wagner C, Bruijne MC de: Benchmarking the use of blood products in cardiac surgery to stimulate awareness of transfusion behaviour. Results from a four-year longitudinal study. *Netherlands heart journal: monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation* 2017, 25:207-214.

Appendix C

Manuscript II

Complex dependencies between potential risk factors, blood products given and postoperative infections in patients with cardiac surgery analysed with additive Bayesian networks.

Authors

Complex dependencies between potential risk factors, blood products given and postoperative infections in patients with cardiac surgery analysed with additive Bayesian networks

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24

25**Abstract**

26Background:

27Methods:

28Results:

29Conclusions:

30

31**Keywords**

32

33

INTRODUCTION

Blood transfusion rates are particularly high in cardiac surgeries [1,2]. A high variability in red blood cell (RBC) transfusion exists even after adjustment for patient demographic data, comorbidity and operative data [3]. Next to increased costs, transfusion-related adverse outcomes including raised major concerns [4]. A randomised trial comparing restrictive transfusion cut-off for haemoglobin (<7.5 g/dl) and liberal (<9g/dl) one, showed no clear difference in cost-effectiveness and QALYS [5]. Transfusion of one or two units of RBC did not affect mortality in patients undergoing isolated coronary artery bypass graft (CABG) [6]. This finding was also substantiated by a systematic review [7]. However, in patients with acute coronary syndrome, transfusion of ≥4 units RBC after CABG was found to be strongly associated with mortality [8]. Differences when assessing the impact of red blood cell transfusion on mortality can explained partially by differences in observational versus randomised clinical trials [9].

Typically, adverse outcomes in patients undergoing cardiac surgery are significantly associated with a triad of factors: patient related demographic data including co-morbidities, operation-related patient data and transfusion-related patient data.

Prediction models for postoperative pneumonia, the most prevalent of all-hospital-acquired infections after CABG surgery, included a number of patient demographic and comorbidity data as well as peri-operative data [10,11] and transfusion-related data, esp. RBC were found to impact pneumonia rates after CABG [12]. Amongst patient demographic data, BMI was found to be significantly associated with pulmonary morbidity [13]. Deep sternal wound infections were found to be associated with transfusion of ≥ 4 units of RBC and chronic infections [14]. Post-operative infection has been found to be associated with a high-risk profile [15] and with RBC transfusion [16].

Renal replacement therapy after aortic dissection was shown to be associated with preoperative creatinine level, cardiopulmonary bypass time and amount of red blood cells transfused intra-operatively [17] and with pre-operative co-morbidities and intra-operative data [18]. Acute kidney injury after aortic valve replacement was found to be associated with RBC transfusion, obesity and prolonged cardiopulmonary bypass times [19]. Similarly, in a matched case-control study, RBC transfusion as found to be associated with acute kidney injury [20].

A number of so-called patient blood management (PBM) initiatives, aiming at reducing transfusion rates and improving patient outcome have been published [21–26]. The ESA (European Society of Anaesthesiology) has officially endorsed a practical implementation guide for hospitals to support PBM in the EU [27]. In the US, PBM programs were reported in 37.8% US AABB hospitals in 2013 [28].

Coagulation management algorithms based on point-of-care (POC) viscoelastic testing resulted in reduced transfusion rates of RBC, plasma and platelets compared to clinical judgement combined with conventional laboratory tests [29–33]. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have been described to reduce the proportions of patients receiving allogenic blood products [34]. Additionally, the overall mortality was found to be decreased, but the quality of evidence based on the available studies was considered to be low [34]. Another review indicated no additional benefit in important clinical outcomes beyond reduction in transfusion rates [35]. In a randomized clinical trial, solely the RBC transfusion rates were found to be reduced [36]. In a single-center cohort study, first line administration of coagulation factor concentrates combined with POC testing gave evidence for a decrease in allogenic blood transfusions and adverse events [37].

A lack of understanding on how transfusion might be related to morbidity and mortality becomes evident, i.e. the effect of patient related data, with patients displaying different

predicted risks of mortality and the role of RBC and other allogeneic blood transfusion, while the latter was hypothesized to be secondary to the former [38]. When aiming to reduce hospital-related costs and improving patient outcome in an evidence-based approach, one encounters the difficulty to disentangle the single effects of transfusion procedures, operation data, as well as patient demographic data including co-morbidities in cardiac surgeries. The relationship between these risk factors represent a complex interaction, which is poorly understood [39].

In the context of risk factor analysis, traditional regression approaches including logistic, linear and Poisson regression are widely used and well-known to clinicians. Amongst the most widely reported measurements for statistical associations between a potential risk factor and a dichotomous outcome, e.g. needing or not a renal replacement therapy after cardiac surgery are odds ratios (OR) resulting from logistic regression models. Based on the scale of the potential risk factor, e.g. binary meaning absence (0) or presence (1) of pre-existing renal impairment or continuous, e.g. creatinine in mg/dl, an odds ratio of 2 is interpreted as the odds receiving renal replacement therapy is twice as high in patients with pre-existing renal impairment compared to those without. Similarly, for a continuous predictor, each unit increase in mg/dl creatinine, the odds of receiving renal replacement therapy would be increased by two. Likewise, if the outcome is continuous, the effect of a binary predictor, would be the difference in means (e.g. classical t-test) and the effect of a continuous predictor is assessed in the form of a regression coefficient, describing the effect of a one unit increase in the predictor on the outcome. Furthermore, in the context of Poisson regression, where the outcome are counts, e.g. units of RBC transfused intraoperatively, a binary predictor being an emergency or an elective surgery, is interpreted on the multiplicative scale. More precisely, an odds ratio of 4 for being an emergency versus an elective case, would indicate that the units of RBC transfused are four times higher in elective cases.

Classical, frequentist regression approaches, including p-values and confidence intervals, originate from experimental settings developed by pioneers like Ronald Fisher in the first half of last century. In this setting, it is assumed, that the investigator is able to control for all factors leading to a potentially balanced data set. This assumption would imply for a risk factor study, that the numbers of patients presenting specific risk factors, e.g. being smokers or not, is the same in males and females or in diabetic and non-diabetic individuals, or in emergency and elective surgeries. While having clearly its merits in many fields of clinical epidemiology, the classical frequentist regression approach including many different predictors in observational studies is actually questionable for a number of reasons [40,41]. The frequent (mis-)use of p-values to assess clinical significance and subsequently claim evidence has been deployed for a long time by statisticians [37,42]. In the context of the so-called reproducibility crisis, classical medical data analysis relying on p-values and hypothesis testing is continuously criticized [43]. A radical decision to ban all p-values in publications was taken by the *Journal Basic and Applied Social Psychology* [44]. Recently, the ongoing debate led to a formal statement of the American Statistical Association aiming at "clarifying several widely agreed upon principles underlying the proper use and interpretation of the p-value" [45].

Two technical aspects are worth mentioning when analysing observational data assessing the effect of multiple potential risk factors or predictors on outcomes like amount of blood products administered and occurrence of infections postoperatively associated. First, finding the best model or deciding which predictor should actually be included in a multivariable analysis can be challenging and overfitting, e.g. finding spurious – non reproducible – significant associations, is an ever present issue [46] in regression analysis. Although being described a long time ago, Simpson's paradox, consisting of finding an effect or trend between groups, which disappears or may even be reversed once groups are combined,

continues to be involved in biased and misleading results [47]. Second, in studies aiming at assessing the effect of implementing coagulation management algorithm, most often there are a number of relevant outcomes: e.g. amount of different blood products given, incidence of different types of infections post-operatively, myocardial infarction, cerebrovascular insults, length of hospital or ICU stay and mortality. In consequence, an analysis, allowing not only for including multiple predictors (multivariable) but simultaneously multiple outcomes (multivariate), is warranted. Performing a PubMed literature research using the following MeSH terms (cardiac, surgery, blood, transfusion, risk, factor, infection) yields 36 publications from 2010 onwards. A number of papers uses matching [14,38,48] or propensity scores [15,16,49] to obtain groups of patients which are balanced with regard to some characteristics. The downside from this approach is, that it is no longer possible to assess the effect of these variables, being potentially a risk factor, which have been used for matching on the outcome of interest. Although in several papers out of the 36 papers found, different clinical outcomes are explicitly mentioned as research interest, typically each clinical outcome is analysed separately by – depending on the data format – multivariable regressions. One attempt is made to capture the information contained in several outcome variables of interest by composite end points [50], thus leading to a reduction in dimension.

Most clinicians use regularly Bayesian reasoning, not only in the form of predictive values as a direct application of Bayes theorem, but also in clinical decision making [51]. Still the vast majority of risk factor studies uses frequentist approaches as evidenced by the 36 publications found. With increased computational power, complex Bayesian analyses relying on Monte Carlo Markov chain simulations became possible. Bayesian network analysis, a form of graphical modeling, has mainly been developed in the context of machine learning and computing science [52–54] . Although the underlying theoretical concepts of Bayesian

network modeling have been well established [55], this type of modeling is rarely seen in risk factor studies.

One special case of Bayesian network analysis, the so-called additive Bayesian network (ABN) analysis can be understood as a multivariate regression with all variables being potentially statistically dependent, thus offering a far richer modelling framework compared to multivariable regression [56]. Results of ABN analysis are displayed in the form of graphical models, so called directed acyclic graphs (DAG). They consist of nodes, which are the variables – with no difference made between predictors and outcomes – and arcs connecting them. While nodes from which arcs start to reach another node are names parents, those nodes which receive arcs from another are named children. The resulting DAG is a graphical representation of statistical associations between variables. Similarly to generalized linear models, it is possible to quantify the association or effect size between to variables. Performing an analysis with ABN comprises two steps. First, including all variables of interest and then, based on the data at hand, obtain a so-called globally optimal model. Optimal means here that the number of potential parents is subsequently increased, meaning that the complexity of the model is increased, while the marginal log-likelihood is used as a measure of goodness-of-fit criterion [57]. In a subsequent assessment the posterior density of each variable and dependency upon another variable will be assessed. The aim of this check is to assure, that not only the globally best model was determined, but also that each variable included contains enough information to be included. The second step consists of relying on bootstrap approaches to handle appropriately overfitting and subsequently remove arcs, which are found in less than 50 % of the bootstraps.

In contrast to classical Bayesian networks, ABNs do not rely on expert opinion and use only uninformative priors to find the best graphical representation of the data. This approach relieves the clinical data analyst from separating different categories of clinical outcomes for

analysis, while presumably the same data generating mechanisms (e.g. patient characteristics, intervention-related data) actually may explain a the joint occurrence of a number of different clinical relevant outcomes (e.g. amount of different blood products given, infections, renal replacement therapy, myocardial infarction, length of stay in hospital or ICU and moratlity).

For this study we used data analysed previously with classical multivariable frequentist methods (Hofer, pers. communication). The data were collected within a quality control study the impact of implementing a coagulation management algorithm [58,59]. Assuming complex relationships between patient demographic data including comorbidities and pre-medication, patient data generated during surgery with administration of different blood products and the occurrence of a number of adverse events in patients undergoing cardiac surgery, the aim was to assess if applying additive Bayesian network modeling would allow to disentangle the effects of single factors simultaneously.

MATERIAL and METHODS

Database

The two sets of data (before and after implementation of a coagulation management algorithm) comprised 90 variables including demographic data, preoperative medication, lab values, data recorded during surgery and afterwards, number of types of blood products received and a number of different complications as well as length of hospital stay and mortality. A detailed description of all variables is given in the annex. After plausibility checks and data cleaning 1754 patients were included in the analysis. The initial number of 90 variables was reduced to 54 for each period, after assessing the computational difficulties related to the size of the dataset. The reduction of the dataset was based on several criteria. Less important variables were removed after agreement, as well as partially separated binary

206factors. Lab and diagnostic tool measurements at patient level, taken before and after surgical 207operation were aggregated into one. Indications such as diabetes, with two separate binary 208factors for oral and insulin medication, now are considered as one. Similarly, patients with 209cardiac insufficiency in the past or present, ICU mortality and mortality during hospitalisation 210period are reduced two one variable.

211

212*Analysis*

213First to find an optimal DAG, the maximal number of parents of each node was subsequently 214increased from 1 to 9 and marginal log-likelihood, assessing the goodness-of-fit was utilised 215to determine the globally best model with the optimal number of parents. To discover the 216optimal structure, a heuristic algorithm was used. Starting from a random starting structure 217created by adding arcs randomly to an empty network, the algorithm performs a stepwise 218search for an improved network, where three stepwise operations are possible: i) add an arc; 219ii) remove an arc; iii) reverse an arc. The stepwise search is subject to a number of conditions, 220first only moves that do not generate a cycle are permitted, secondly, a parent limit is imposed 221which fixes the maximum number of parents which each child node can have, and thirdly, it is 222possible to ban or retain arcs. This heuristic algorithm was ran multiple times, each time 223starting from an initial random DAG resulting to a local optimum structure. After gathering all 224locally best DAGs, the majority consensus is extracted, in other words, only associations 225appeared 50% of the times were kept. Excess arcs were discarded.

226 Next to posterior densities, which should look bell-shaped and integrate to one, the AUC 227(area under the curve) of all posterior densities was also assessed. (add data separation here?) 228Subsequently 10’000 bootstraps were run and the final DAGS for both cohorts contain only 229arcs which were retrieved in at least 50% of the bootstraps.

The results will be presented in the form of DAGS. (Add likelihood equivalence: direction of arcs).

RESULTS

Possible up to 4 parents, 54 variables, data separation, memeory

It was possible to obtain DAGS for both patient cohorts separately.

In Figure 1 and 2 the Markov blankets, jointly shown for all variables describing the administration of five different blood products given during surgery or in intensive care unit (RBC, platelets, fresh frozen plasma prothrombine complex C, fibrinogen and absence of any allogeneic blood prodcuct) as well as the complications post-OP (renal replacement therapy, infection, re-thoracotomy, mortality and neurological sequelae) for both patient cohorts are shown.

Prior cohort blood products

RBC: Was found to be linked to six other variables. With more units of RBC transfused, the the drained volume 24 h post-Op increased. RBC transfusion rates increased jointly with transfusion of paltelets. There was a positive association between hours of ventilation and RBC transfused. Furthermore both endogeneous fibrinogen and kaolin-activated clotting time, with (more) RBC transfused being associated with a lower fibrinogen concentration and longer kaolin-activated clotting times.

PCtotal: The amount of platelets transfused was linked to ten variables. Next to a positive association with RBC, transfusion of platelets was also positively associated with fresh frozen plasma and fibrinogen. Patients with higher platelet counts before surgery received less platelets. Both longer surgery and anaesthesia times were associated with more platelets transfused. Patients with emergencies compared to elective surgeries received more platelets. Similarly, patients with re-opening of the thorax received more platelets. Receiving more platelets was also associated with a higher odds for renal replacement therapy and a higher mortality.

FFPTotal: Fresh frozen plasma given in total is linked to 6 variables. Higher fresh frozen plasma was given to male patients with hypertension, as well as it had a positive association with cardiopulmonary bypass time and kaolin activated time in seconds prior the operation.

Fibrinogen: Units of Fibrinogen given in total is linked to 6 variables. A negative association was found for higher values of BMI and patients who did undergo a transfusion of the blood products. An increased amount of Fibrinogen was given to patients with a re opening of the thorax operation , as well as it was positively connected with higher cardiopulmonary bypass times, Prothrombin complex concentrates and platelets given in total.

PCC: Prothrombin complex concentrate given in total was linked to 4 variables. Higher expected counts of Prothrombin complex concentrate found to be assoaciated with higher number of units of platelets and fibrinogen, as well as for patients that had an aortic valve replacement procedure. Patients free of any blood transfusion product are expected to have a lower number of Prothrombin complex concentrate units given.

FFREE: Patients that were free of allogenic blood products transfusions. FFREE was linked to 9 variables in total. The odds of a patient being free of transfusion had a negative association with increased anaesthesia time, cardiopulmonary bypass time, Euroscore, number

of units of Prothrombin complex concentrate, Fibrinogen, Cellsaver(patient's own blood re transfused) and postoperative measurement of endogenous Fibrinogen. Additionally, a negative association was found between being free of transfusion and having an Infection or a re opening of the thorax procedure. Last, free of transfusion patients were found to have higher post operative hematocrit value.

Prior complications

RRT: Renal replacement therapy was connected with 6 variables. Increased odds are associated with increased values for pre operative endogenous creatinine value and total platelets given, while decreased odds for higher values of post operative endogenous Fibrinogen values.

Infection: Several indications of infections. Linked to 5 variables. Includes pulmonary, sternal, catheter, urinary and sepsis. The odds of patients having an infection of several types was increased by age and anaesthesia time while patients with no transfusion of the blood products had lower odds of infection. Positive association was also found with length of stay at the hospital and ventilation time.

RE-THX: Re opening of the thorax. 5 connections were discovered. Positive association of patients with re opened thorax was found with 24h drainage, platelet units given, post operation International normalized ratio (INR) score and Fibrinogen given. The odds for patients with re opened thorax are decreased if they are free of transfusion.

MORT: Mortality either in ICU or during hospitalisation is connected to 6 other variables. The odds of mortality are associated with increased age and platelet in units given. Positive association also found with ventilation time and post operative kaolin activated time while a negative one with length of stay and International normalized ratio (INR) score.

Neurocerebro: Neurological problem specific to cerebral palsy was connected only to Euroscore with higher odds for increased scores.

Post cohort blood products

RBC: Red blood cells units given in total was connected to 6 variables. A positive relationship was found for increased platelets and fresh frozen given in units, while higher number of red blood cells is expected for increased number of days spent in intensive care. Red blood cells are also associated positively with mortality.

Pctotal: Platelet units given in total were connected with 7 variables. Increased units of platelets are expected to be given to patients with a re opening of the thorax operation, a renal replacement therapy and operation at the great vessels and aorta. Positive association was also found with cardio pulmonary bypass time in seconds, Fibrinogen given, red blood cells given and cellsaver (patient's own blood re-transfusion)

FFPTotal: Fresh frozen plasma was connected to 4 variables. More plasma is expected to be given to patients with a re opening of the thorax procedure and surgery of the great vessels and aorta. A positive association was found with red blood cells while patients with lower hematocrit after operation are expected to have less fresh frozen plasma transfused.

Fibrinogen: Fibrinogen units given in total are linked to 5 variables. Patients who were free of transfusion received less Fibrinogen while re opening of the thorax procedure increases the units of Fibrinogen given. At the same time, a positive association was found with the volume drained 24h, prothrombin complex concentrate in units and platelets given.

PCC: Prothrombin complex concentrate in units was linked with 4 variables. Patients with cardiac insufficiency present or in the past as well as patients free of any transfusion of the

various blood products are expected to have lower units of Prothrombin complex concentrate given in total.

FFREE: Patients free of transfusion of the various blood products was connected to 6 variables. The odds of being free of transfusion are increased with higher values of post operative hematocrit value. Increased operation times in seconds, Euroscore, Fibringen units and platelet units given decrease the odds of a patients being free of transfusion. Lastly, the odds are decreased if a patient suffering from types of infection.

Post complications

RRT : Renal replacement therapy is linked to 6 variables. The odds of a patients having a renal repalcement therapy are decreased for those being free of transfusions, while the odds are increased with higher values of pre operative creatinine and platelet units given as well as for increased length of stay in hospital, days spent in ICU and ventilation time.

Infection : Several indications of infections. Includes pulmonary, sternal, katheter, urinary and sepsis. A positive association between length of stay at the hospital was found, while the odds of infections were decreased for patients free of transfusion.

RE-THX : Re opening of the thorax procedure is linked to 8 variables.The odds of re opening of the thorax procedure were increased for higher values of kaolin activated time in seconds while the odds were decreased for patients with peripheral vascular occlusive disease. Positive associations were also found with drainage 24h, fresh frozen plasma given in units, fibrinogen given in units, ventilation time, days spent at ICU and mortality.

MORT ; Mortality during hospitalisation period or in ICU was connected to 6 variables. Positive links between mortality and age, re opening of the thorax procedure, red blood cells

given in total, ventilation time and days spent in ICU were found. Mortality odds were decreased for patients who received clopidrogel, an inhibitor that prevent blood clots and strokes – heart attacks.

Neurocerebro: Neurological problem specific to cerebral palsy was linked only to Euroscore with higher values uncover neurological problems.

Discussion

This study aimed to gain insights into the complex relationsships between the triad of factors: patient related demographic data including co-morbidities, operation-related patient data and transfusion-related patient data. It was possible to obtain dags with up to four parents, thus presumably not the complete complexity was covered. Still within this approach 54^4 potential different DAGS were searched, thus offering a richer modelling framework compared to classical frequentist approaches with are limited to a single outcome variable.

A number of associations founds are to be expected, e.g. higher 24 h drained volume with an increase in transfusion rates and with re-thoracotomy or longer procedural times being associated with higher odds for infections, higher pre-Op Euro-Scores

While RBC was not found to be associated to infection in both patient cohorts, transfusion rates of RBC were associated to mortality. Still, different explanations are possible. Critical-ill patients will have a higher chance to die and/or RBC transfusion rates are associated with a higher risk to die [38].. Ventilation-associated pneumonia has been described [60].

This analysis also highlighted the role of ventilation hours being positively associated with higher mortality, longer hospital stay and higher odds for renal replacement therapy and infection.

Using additive Bayesian network modeling is an innovative and promising approach to gain insights into complex relationsships.

References

1. Beguin C, Closon M-C, Vandekerckhove P, Baele P: **Concentration of transfusion resources on a few pathologies and a few patients: analysis of the comprehensive in-hospital patient database**. *Transfusion* 2007, **47**:217-227.

2. Geißler G, Franz D, Buddendick H, Krakowitzky P, Bunzemeier H, Roeder N, van Aken H, Kessler T, Berdel W, Sibrowski W, Schlenke P: **Retrospective analysis of the blood component utilization in a university hospital of maximum medical care**. *Transfusion Medicine and Hemotherapy* 2012, **39**:129-138.

3. Magruder JT, Blasco-Colmenares E, Crawford T, Alejo D, Conte JV, Salenger R, Fonner CE, Kwon CC, Bobbitt J, Brown JM, Nelson MG, Horvath KA, Whitman GR: **Variation in red blood cell transfusion practices during cardiac operations among centers in Maryland: Results from a state quality-improvement collaborative**. *The Annals of Thoracic Surgery* 2017, **103**:152-160.

4. Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD: **Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery**. *Circulation* 2007, **116**:2544-2552.

5. Stokes EA, Wordsworth S, Bargo D, Pike K, Rogers CA, Brierley RCM, Angelini GD, Murphy GJ, Reeves BC: **Are lower levels of red blood cell transfusion more cost-effective than liberal levels after cardiac surgery? Findings from the TITRe2 randomised controlled trial**. *BMJ open* 2016, **6**:e011311.

6. Koster A, Zittermann A, Börgermann J, Knabbe C, Diekmann J, Schirmer U, Gummert JF: **Transfusion of 1 and 2 units of red blood cells does not increase mortality and organ failure in patients undergoing isolated coronary artery bypass grafting**. *European journal of Cardio-Thoracic Surgery* 2016, **49**:931-936.

3977. Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L, Hickner A, Rogers
398 MAM: **Health care-associated infection after red blood cell transfusion: a systematic**
399 **review and meta-analysis**. *JAMA* 2014, **311**:1317-1326.
4008. Stone GW, Clayton TC, Mehran R, Dangas G, Parise H, Fahy M, Pocock SJ: **Impact of**
401 **major bleeding and blood transfusions after cardiac surgery: analysis from the**
402 **Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial**.
403 *American Heart Journal* 2012, **163**:522-529.
4049. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JAC, Murphy GJ: **Indications for**
405 **red blood cell transfusion in cardiac surgery. A systematic review and meta-analysis**.
406 *The Lancet Haematology* 2015, **2**:e543-e553.
40710. Strobel RJ, Liang Q, Zhang M, Wu X, Rogers MAM, Theurer PF, Fishstrom AB,
408 Harrington SD, DeLucia A3, Paone G, Patel HJ, Prager RL, Likosky DS: **A**
409 **Preoperative risk model for postoperative pneumonia after coronary artery bypass**
410 **grafting**. *The Annals of Thoracic Surgery* 2016, **102**:1213-1219.
41111. Allou N, Bronchard R, Guglielminotti J, Dilly MP, Provenchere S, Lucet JC, Laouénan
412 C, Montravers P: **Risk factors for postoperative pneumonia after cardiac surgery and**
413 **development of a preoperative risk score**. *Critical Care Medicine* 2014, **42**:1150-1156.
41412. Likosky DS, Paone G, Zhang M, Rogers MAM, Harrington SD, Theurer PF, DeLucia A,
415 Fishstrom A, Camaj A, Prager RL: **Red blood cell transfusions impact pneumonia**
416 **rates after coronary artery bypass grafting**. *The Annals of Thoracic Surgery* 2015,
417 **100**:794-800; discussion 801.
41813. Devarajan J, Vydyanathan A, You J, Xu M, Sessler DI, Sabik JF, Bashour CA: **The**
419 **association between body mass index and outcome after coronary artery bypass**
420 **grafting operations**. *European Journal of Cardio-Thoracic Surgery* 2016, **50**:344-349.
42114. Cutrell JB, Barros N, McBroom M, Luby J, Minhajuddin A, Ring WS, Greilich PE: **Risk**
422 **factors for deep sternal wound infection after cardiac surgery: Influence of red**

blood cell transfusions and chronic infection. *American Journal of Infection Control* 2016, **44**:1302-1309.

15. Robich MP, Sabik JF, Houghtaling PL, Kelava M, Gordon S, Blackstone EH, Koch CG: **Prolonged effect of postoperative infectious complications on survival after cardiac surgery**. *The Annals of Thoracic Surgery* 2015, **99**:1591-1599.

16. Mazzeffi M, Gammie J, Taylor B, Cardillo S, Haldane-Lutterodt N, Amoroso A, Harris A, Thom K: **Healthcare-associated infections in cardiac surgery patients with prolonged intensive care unit stay**. *The Annals of Thoracic Surgery* 2017, **103**:1165-1170.

17. Wu H-B, Ma W-G, Zhao H-L, Zheng J, Li J-R, Liu O, Sun L-Z: **Risk factors for continuous renal replacement therapy after surgical repair of type A aortic dissection**. *Journal of Thoracic Disease* 2017, **9**:1126-1132.

18. Muralidhar K, Bhagyashri K, Guptha R, Hegde N, Ahmed I, Vincent L: **Determinants of renal replacement therapy after adult cardiac surgery**. *Asian Cardiovascular & Thoracic Annals* 2013, **21**:533-538.

19. Helgason D, Helgadottir S, Viktorsson SA, Orrason AW, Ingvarsdottir IL, Geirsson A, Gudbjartsson T: **Acute kidney injury and outcome following aortic valve replacement for aortic stenosis**. *Interactive Cardiovascular and Thoracic Surgery* 2016, **23**:266-272.

20. Engoren M, Brown RR, Dubovoy A: **A retrospective analysis of the effect of blood transfusion on cerebral oximetry entropy and acute kidney injury**. *Perfusion* 2017, **32**:35-43.

21. Spahn DR: **Patient blood management: the new standard**. *Transfusion* 2017, **57**:1325-1327.

22. Meybohm P, Herrmann E, Steinbicker AU, Wittmann M, Gruenewald M, Fischer D, Baumgarten G, Renner J, van Aken HK, Weber CF, Mueller MM, Geisen C, Rey J, Bon D, Hintereder G, Choorapoikayil S, Oldenburg J, Brockmann C, Geissler RG, Seifried E,

449 Zacharowski K: **Patient blood management is associated with a substantial reduction**
450 **of red blood cell utilization and safe for patient's outcome: A prospective,**
451 **multicenter cohort study with a noninferiority design**. *Annals of Surgery* 2016,
452 **264**:203-211.
45323. Leahy MF, Hofmann A, Towler S, Trentino KM, Burrows SA, Swain SG, Hamdorf J,
454 Gallagher T, Koay A, Geelhoed GC, Farmer SL: **Improved outcomes and reduced costs**
455 **associated with a health-system-wide patient blood management program: a**
456 **retrospective observational study in four major adult tertiary-care hospitals**.
457 *Transfusion* 2017, **57**:1347-1358.
45824. Verdecchia NM, Wisniewski MK, Waters JH, Triulzi DJ, Alarcon LH, Yazer MH:
459 **Changes in blood product utilization in a seven-hospital system after the**
460 **implementation of a patient blood management program: A 9-year follow-up**.
461 *Hematology (Amsterdam, Netherlands)* 2016, **21**:490-499.
46225. Mehra T, Seifert B, Bravo-Reiter S, Wanner G, Dutkowski P, Holubec T, Moos RM,
463 Volbracht J, Manz MG, Spahn DR: **Implementation of a patient blood management**
464 **monitoring and feedback program significantly reduces transfusions and costs**.
465 *Transfusion* 2015, **55**:2807-2815.
46626. Geissler RG, Rotering H, Buddendick H, Franz D, Bunzemeier H, Roeder N, Kwiecien
467 R, Sibrowski W, Scheld HH, Martens S, Schlenke P: **Utilisation of blood components**
468 **in cardiac surgery: a single-centre retrospective analysis with regard to diagnosis-**
469 **related procedures**. *Transfusion Medicine and Hemotherapy* 2015, **42**:75-82.
47027. Directorate-General for health and Food Safety Health Programme: *Supporting Patient*
471 *Blood Management (PBM) in the EU.* B-1049 Brussels: Luxembourg Publications Office
472 of the European Union; 2017.

28. Whitaker B, Rajbhandary S, Kleinman S, Harris A, Kamani N: **Trends in United States blood collection and transfusion: results from the 2013 AABB blood collection, utilization, and patient blood management survey**. *Transfusion* 2016, **56**:2173-2183.

29. Shen L, Tabaie S, Ivascu N: **Viscoelastic testing inside and beyond the operating room**. *Journal of Thoracic Disease* 2017, **9**:S299-S308.

30. Weber CF, Görlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, Cohn LH, Zacharowski K: **Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients**. *Anesthesiology* 2012, **117**:531-547.

31. Fahrendorff M, Oliveri RS, Johansson PI: **The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products - A systematic review and meta-analysis**. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2017, **25**:39.

32. Bollinger D, Tanaka KA: **Ponit-of-Care coagulation testing in cardiac surgery**. *Seminars in Thrombosis and Hemostasis*, **43**:386-396.

33. Avidan MS: **Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery**. *British Journal of Anaesthesia* 2004, **92**:178-186.

34. Wikkelsø A, Wetterslev J, Møller AM, Afshari A: **Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis**. *Anaesthesia* 2017, **72**:519-531.

35. Serraino GF, Murphy GJ: **Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis**. *British Journal of Anaesthesia* 2017, **118**:823-833.

49736. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP, Pinto R,
498 Scales DC: **Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge**
499 **clustered randomized controlled trial**. *Circulation* 2016, **134**:1152-1162.
50037. Görlinger K, Dirkmann D, Hanke A, Kamler M, Kottenberg E, Thielmann M, Jakob H,
501 Peters J: **First-line therapy with coagulation factor concentrates combined with**
502 **point-of-care coagulation testing is associated with decreased allogenic blood**
503 **transfusion in cardiovascular surgery**. *Anesthesiology* 2011, **115**:1179-1191.
50438. Paone G, Herbert MA, Theurer PF, Bell GF, Williams JK, Shannon FL, Likosky DS,
505 Prager RL: **Red blood cells and mortality after coronary artery bypass graft surgery:**
506 **an analysis of 672 operative deaths**. *The Annals of Thoracic Surgery* 2015, **99**:1583-9;
507 discussion 1589-90.
50839. Arias-Morales CE, Stoicea N, Gonzalez-Zacarias AA, Slawski D, Bhandary SP,
509 Saranteas T, Kaminiotis E, Papadimos TJ: **Revisiting blood transfusion and predictors**
510 **of outcome in cardiac surgery patients: a concise perspective**. *F1000Research* 2017,
511 **6**.
51240. Ioannidis JPA: **Why most published research findings are false**. *PLoS Medicine* 2005,
513 **2**:e124.
51441. Nuzzo Regina: **Scientific method: Statistical errors**. *Nature* 2014, **506**:150-152.
51542. Goodman S: **A dirty dozen: twelve p-value misconceptions**. *Seminars in Hematology*
516 2008, **45**:135-140.
51743. Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG:
518 **Statistical tests, P values, confidence intervals, and power: a guide to**
519 **misinterpretations**. *European Journal of Epidemiology* 2016, **31**:337-350.
52044. Peng R: **The reproducibility crisis in science. A statistical counterattack**. *Significance*
521 2015, **12**:30-32.
52245. Trafimow D, Marks M: **Editorial**. *Basic and Applied Social Psychology* 2014, **37**:1-2.

52346. Wasserstein RL, Lazar NA: **The ASA's statement on p -values. Context, process, and**
524 **purpose**. *The American Statistician* 2016, **70**:129-133.
52547. Babyak MA: **What you see may not be what you get: a brief, nontechnical**
526 **introduction to overfitting in regression-type models**. *Psychosomatic Medicine* 2004,
527 **66**:411-421.
52848. Simpson EH: **The interpretation of interaction in contingency tables**. *Journal of the*
529 *Royal Statistical Society, Series B* 1951, **13**:238-241.
53049. Ad N, Holmes SD, Patel J, Shuman DJ, Massimiano PS, Choi E, Fitzgerald D, Halpin L,
531 Fornaresio LM: **The impact of a multidisciplinary blood conservation protocol on**
532 **patient outcomes and cost after cardiac surgery**. *The Journal of Thoracic and*
533 *Cardiovascular Surgery* 2017, **153**:597-605.
53450. Cappabianca G, Mariscalco G, Biancari F, Maselli D, Papesso F, Cottini M, Crosta S,
535 Banescu S, Ahmed AB, Beghi C: **Safety and efficacy of prothrombin complex**
536 **concentrate as first-line treatment in bleeding after cardiac surgery**. *Critical Care*
537 *(London, England)* 2016, **20**:5.
53851. Wu B, Wang Y, Wang C, Cheng Y, Rong R: **Intraoperative platelet transfusion is**
539 **associated with increased postoperative sternal wound infections among type A**
540 **aortic dissection patients after total arch replacement**. *Transfusion Medicine (Oxford,*
541 *England)* 2014, **24**:400-405.
54252. Gill CJ, Sabin L, Schmid CH: **Why clinicians are natural bayesians**. *British Medical*
543 *Association* 2005, **330**:1080-1083.
54453. Friedman N, Koller D: **Being Bayesian about network structure. A Bayesian**
545 **approach to structure discovery in Bayesian networks**. *Machine Learning* 2003,
546 **50**:95-125.
54754. Heckerman D, Geiger D, Chickering DM: **Learning Bayesian networks: the**
548 **combination of knowledge and statistical data**. *Machine Learning* 1995, **20**:197-243.

54955. Koivisto, M., Sood, K.: **Exact Bayesian structure discovery in Bayesian networks**.
550 *Journal of Machine Learning Research*, **5**:549-573.
55156. Tierney, L., Kadane, Joseph B.: **Accurate Approximations for Posterior Moments and**
552 **Marginal Densities**. *Journal of the American Statistical Association* 1986, **81**:82-86.
55357. Lewis FI, Ward MP: **Improving epidemiologic data analyses through multivariate**
554 **regression modelling**. *Emerging Themes in Epidemiology* 2013, **10**:4.
55558. Hortal J, Giannella M, Pérez MJ, Barrio JM, Desco M, Bouza E, Muñoz P: **Incidence**
556 **and risk factors for ventilator-associated pneumonia after major heart surgery**.
557 *Intensive Care Medicine* 2009, **35**:1518-1525.
558