Adjusted calculation model regarding heparin and protamine in connection with cardiopulmonary bypass

by

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# Table of contents

Abstract.......................................................................................................................... 1

List of abbreviations ....................................................................................................... 2

Introduction...................................................................................................................... 3

- Heparin ...................................................................................................................... 3
- Activated Clotting Time(ACT) ................................................................................... 4
- Protamine ................................................................................................................... 4
- The HeProCalc program............................................................................................ 5

Aims of study ................................................................................................................... 6

Patients and methods ..................................................................................................... 7

- Methodological considerations ................................................................................. 7
- Selection criteria’s and randomization ...................................................................... 7
- ACT measurement .................................................................................................... 7
- HTC measurement .................................................................................................... 8
- Blood sampling and parameters registered .............................................................. 8
- Cardiopulmonary system ............................................................................................ 9
- The control group ..................................................................................................... 9
- The HeProCalc group ................................................................................................ 9
- Heparin and protamine ............................................................................................. 10
- Statistical methods ................................................................................................... 10

Results ............................................................................................................................ 11

Discussion ...................................................................................................................... 12

- Adjusting doses of protamine .................................................................................. 12
- Less bleeding in the HeProCalc group ..................................................................... 12
- ACT values in the ICU .............................................................................................. 13
- Bolus doses of heparin .............................................................................................. 13
- Identifying sources of bleeding ................................................................................ 13
- Limitations ................................................................................................................. 14

Tables and figures ........................................................................................................... 15

- Table 1. Baseline characteristics ............................................................................. 15
- Table 2. Perioperative data ....................................................................................... 16
- Table 3. Post-operative bleeding and doses of heparin and protamine .................... 17
- Figure 1 ..................................................................................................................... 18
- Figure 2 ..................................................................................................................... 19

Acknowledgements ........................................................................................................ 20

References ...................................................................................................................... 21
Abstract

Background
Heparin dosage during cardiopulmonary bypass (CPB) is commonly calculated from bodyweight. For reversal, traditional protamine dosage is 1.0 to 1.3 mg of protamine/100 units of heparin. With an empirically developed algorithm, the HeProCalc program, heparin and protamine doses are calculated and suggested during the cardiopulmonary bypass procedure. The primary aim of this study was to investigate whether HeProCalc-based dosage of heparin can reduce protamine usage compared with traditional dosage. The secondary aim was to investigate whether HeProCalc-based dosage of protamine will affect the amount of postoperative bleeding.

Patients and methods
We consecutively randomized 40 patients into two groups. In the control group, traditional heparin and protamine dosages based on body weight were given. In the study group the HeProCalc program was used, which calculates the heparin bolus dose from weight, height, and baseline Activated Clotting Time (ACT), calculates eventual additive doses and suggests protamine dose at termination of CPB.

Results
We analyzed the results from 37 patients, after exclusion of 3 patients. Despite equal doses of heparin in both groups, significantly lower doses of protamine were given in the HeProCalc group vs. the control group 211 mg vs. 330 mg (p < 0.001). Postoperative bleeding was lower in the study group 480 ml, vs. 694 ml (p= 0.046).

Conclusions
With the HeProCalc program lower protamine doses than with conventional calculations was sufficient to neutralize heparin after CPB, and also resulted in less postoperative bleeding. The results support previous studies showing an adverse anticoagulant effect of excess protamine doses.
List of abbreviations

CPB  Cardio Pulmonary Bypass
ACT  Activated Clotting Time
HTC  Heparinase Test Cartridge
GFR  Glomerular Filtration Rate
ICU  Intensive Care Unit
ECMO Extra Corporeal Membrane Oxygenation
OR   Operating Room
IU   International Units
**Introduction**

Excess perioperative bleeding and its complications are feared side effects in cardiac surgery. The aetiology of excess bleeding in this patient group is multifactorial, and a large perioperative blood loss will per se promote further bleeding unless proper measures are taken. Also, preoperative medication, activation of inflammatory systems and, maybe most important of all, the need for adequate heparinisation and appropriate reversal of the heparin effect after cardiopulmonary bypass (CPB) is still a challenge in the attempt to improve postoperative haemostatic control.

When blood circulates outside the human body, efficient anticoagulation is required in order to avoid microscopic clot formation or, in worst case, massive thrombus formation in the CPB circuit, of which the latter is a life-threatening complication. This explains the need for ‘full’ heparinisation during CPB. Furthermore, CPB has several negative effects on blood coagulation caused by shear stress generated by pumps, cardiotomy suction devices, hypothermia and hemodilution, as well as by generalised activation of the complement- and immune system. Hemodilution affects the concentration of platelets, fibrinogen, and other coagulation factors, and hypothermia attenuates the activity of enzymes involved in the coagulation system. Many reactions within the coagulations take place on the surface of platelets, which makes them essential in this context. However, platelets are vulnerable and get activated when in contact with the extracorporeal surfaces of the CPB system, sticking to foreign surfaces and circulating monocytes. Platelet count in circulating blood decreases and remaining platelets are blunted. Altogether, these factors cause a variable disruption of hemostasis during and after CPB \(^1,2\).

**Heparin**

Heparin was discovered in 1916 and its antidote, protamine, was discovered in 1937. These two drugs were used for the first time in 1953 in a patient undergoing cardiac surgery on CPB. Since then, the use of these drugs has continued for more than 6 decades. Adequate doses of heparin are crucial to avoid clot formation in the CPB circuit during the extracorporeal procedure. Furthermore, adequate doses of protamine are necessary to restore normal coagulation after CPB.

The polysaccharide heparin, which is the strongest macromolecular acid in the body, has a molecular weight ranging from 3000 to 40 000 Dalton with a mean mass of approximately 15 000 Dalton. The variating molecular weight between heparin batches also explain why their potency may differ.
In cardiac surgery, heparin is administrated via a central venous line and the maximum activated clotting time (ACT) prolongation is achieved within five minutes. Since heparin is a large molecule with a strong negative charge, extravasal distribution is unlikely to take place. Heparin exerts its effect by inhibiting anti-thrombin III by a thousand times, thereby also depressing effects of activated factors, IX, X, XI, XII, XIII and thrombin 2–3 (Fig 1). The mechanism for elimination of heparin is still uncertain but a part of the drug is eliminated by the reticuloendothelial system (RES), a component of the immune system. Further, some heparin is metabolized by the renal system. Hypothermia is known to delay elimination due to induced decrease in enzyme activity during this condition.

High heparin doses are used in connection with the CPB, and the elimination is dose dependent. The mean half-life for a bolus dose of 400 International Units (IU)/kg is 152 minutes while the mean half-life for 100 IU/kg is approximately 60 minutes 4.

Different methods are used to calculate appropriate heparin doses for safe CPB management. The most common method is calculation of dose from body weight, often using initial doses of heparin between 200–400 IU/kg. Calculations based on Lean Body Mass have been shown to reduce the amount of heparin and protamine by 25% in obese patients 5. Furthermore, dosage based on heparin concentration can be used 6.

**Activated Clotting Time (ACT)**

ACT measures the effect of heparin. This is a test introduced by Hattersley and Blakely in the 1960’s and is considered to be gold standard for analyzing heparin effect in this context. This point of care test, measured in seconds, is based on whole blood. Low ACT levels will, besides trigging the coagulation system, increase the risk of thrombus formation in the CPB circuit. Many studies have been made to define the optimal ACT level for CPB. Even though there is no universal agreement, a minimum of 400 seconds is often referred to as a standard level regarding safety concerns 2. However, a value between 500 and 700 seconds has been associated with lower blood loss compared with ACT < 500 or > 700 seconds. An explanation might be that inadequate heparinisation implies constant consumption of coagulation factors, whereas excessive dosage increases the risk of postoperative heparin rebound 7. Besides heparin, other factors affecting ACT include hemodilution, hypothermia, low platelet count, coagulation deficiencies, and medications such as warfarin, platelet inhibitors, and thrombin inhibitors 1.

**Protamine**

When CPB is ended, normal coagulation is facilitated by neutralization of heparin with protamine, a polycationic protein derived from salmon sperm. Heparin, with a strong negative
charge, binds ionically to protamine. Protamine both neutralizes heparin and exerts a mild anticoagulant effect, which is independent of heparin. Few drugs are as non-toxic as heparin in high doses when CPB is used. However, this does not apply for protamine. Adverse reactions such as severe hypotension due to release of histamine from mast cells, high pulmonary arterial pressure, and other anaphylactic reactions, e.g. bronchospasm are well known. Administration of excess doses may also have a deleterious effect on coagulation, including platelet dysfunction, down regulation of thrombin generation by inhibition of factor V, and weakened clot structure. Commonly, a fixed dose of 1.0 to 1.3 mg of protamine is used to neutralize each 100 IU of given heparin. This dose does not account for heparin elimination and might result in an excess of circulating protamine. Protamine titration or a low dose protamine regime after termination of CPB has been suggested by The Society of Thoracic Surgeons and The Cardiovascular Anesthesiologists in their guidelines regarding blood conservation clinical practice. The half-life of protamine is approximately five minutes and it has nearly completely disappeared from the circulation within 20 minutes.

**The HeProCalc program**

The HeProCalc computer program was invented by Per Srisophon Stensved, perfusionist at the Department of Cardiothoracic Surgery, Karolinska University Hospital. The program is designed to optimize dosage of heparin and protamine taking into account both the patient’s body surface area and the baseline ACT value. All ACT values measured during CPB are continuously inserted in the computer program as well as additional heparin doses and temperature of the arterial line of the CPB circuit to calculate the optimal protamine dose at the termination of CPB. During CPB, the computer program presents the calculated ACT value, heparin consumption/minute and calculated total heparin amount present in the circulation as well as in IU/kg.
Aims of study

The aims of this study were:

- To investigate whether HeProCalc-based dosage of heparin can reduce protamine usage compared with traditional dose calculation based on body weight.

- To investigate whether HeProCalc-based dosage of protamine will affect the amount of postoperative bleeding.
Patients and methods

Methodological considerations
Recently, the HeProCalc program was used clinically for over six months at the Department of Cardiothoracic Surgery, Karolinska University Hospital. With hindsight, a study was requested to investigate whether this program could ameliorate dosage of anticoagulation and its appropriate reversal without affecting the postoperative bleeding. Since the program has been continuously improved during this period, it was not considered useful to perform a retrospective study. By performing a randomized controlled trial we minimized bias.

Selection criteria's and randomization
The regional Human Research Ethics Committee in Stockholm, Sweden approved the study. After informed consent, we randomized 40 consecutive adult patients into two groups, a control group and a study group, the HeProCalc group. All patients were scheduled for elective or urgent cardiac surgery on CPB due to cardiovascular and/or valve diseases at Karolinska University Hospital, Stockholm. Patients with diagnosed HIT, Heparin Induced Thrombocytopenia, were indirectly excluded, since these patients will be anti-coagulated in other ways than with heparin. Emergency patients, who could not leave an informed consent, were also excluded.
Patients undergoing surgery with planned hypothermia below 34 °C were not included since the influence of hypothermia on coagulation might would confuse the interpretation of the results. All patients were given tranexamic acid during the operation. However, patients on clopidogrel with active inhibition on platelet aggregation according to point-of-care testing with Plateletworks ® (Helena Lab, Beaumont, USA) were not randomized since, in this department, these patients are treated with aprotinin instead of tranexamic acid. The random assignment was conducted using unmarked envelopes, each containing a protocol indicating HeProCalc or control group, that the perfusionist in charge of the patient drew in conjunction with preparations for the operation.

ACT measurement
We used the Kaolin-reagent based Medtronic High Range Activated Clotting Time Cartridges for measuring activated clotting time with the Medtronic ACT Plus® System. Fresh whole blood from an arterial line was used for the analyses. The cartridge consists of two channels with a plunger that falls through the blood sample. When fibrin is formed, the fall-rate of the plunger decreases and the rate is measured with an optical sensor. The endpoint of the test is the plug formation. The clotting times, measured in seconds for each channel, as well as the average times, are presented.
**HTC measurement**

To identify remaining heparin after injection of a calculated dose of protamine, we used the Medtronic High Range Heparinase Cartridges (HTC) analysed with the Medtronic ACT Plus® System. This analysis is also conducted on fresh whole blood. The cartridge consists of two channels of which one contains purified bacterial heparinase that rapidly destroys any heparin left in the blood by enzymatic cleavage of linkages at the anti-thrombin III binding site. The amount of heparinase present in the channel will neutralize 6 units of heparin /ml of blood. The other channel in the cartridge is a standard high-range ACT. The heparinase channel will show a clotting time reflecting the ACT value of unheparinized blood while the standard ACT channel will identify the eventual presence of heparin.

A value out of range in the heparinase channel indicates that other factors than heparin, such as low levels of fibrinogen, platelet dysfunction, or dilution of the sample, is causing the high ACT-value. However, it is very important that the cartridge temperature is correct. Therefore, the analysis has to be preceded by 3-5 minutes, when the cartridges are warmed. The heparinase analysis is heparin-specific and will not reveal other reasons for compromised coagulation. To avoid errors in measurement the ACT Plus® System was cleaned prior to every patient to eliminate the risk of blood contaminating the light path.

**Blood sampling and parameters registered**

We recorded age, sex, length, weight, creatinine, calculated Glomerular Filtration Rate (GFR) 13, haemoglobin, platelet count, prothrombin complex-values, and preoperative anticoagulation treatment for all patients. Basic information was collected from the patient's records. Perioperatively, lowest bladder temperature was noted as well as transfusion of red blood cells, plasma or platelets per- and postoperatively. The preoperative blood loss was noted as well as postoperative blood loss from drains until the following morning. We also documented type of surgery, perioperative fluid balance, duration of operation, and time on CPB.

Baseline ACT was collected prior to induction of anaesthesia. HTC and ACT analyses were conducted at 3 occasions, namely 3 minutes after protamine administration in the operating room (OR), then 1 and 3 hours, respectively, following arrival to the intensive care unit (ICU). When interpreting the data, a difference of more than 30 seconds between the HTC and the ACT was set as a definition of residual heparin in the sample. An additional protamine dose of 50 mg was given if the test indicated that the sample contained heparin.

Postoperative day 1, the ICU nurse documented postoperative blood loss from drains, number of transfusions and if the patients had undergone a reoperation due to bleeding.
**Cardiopulmonary system**

We used Sorin’s open cardiopulmonary bypass system with a hard shell venous reservoir, Revolution® centrifugal pump and the phosphoryl choline (PH.I.S.I.O) coated PrimOx™ oxygenator, primed with RingerAcetat, 1100-1500 ml, Mannitol, 15%, 250 ml and heparin 5000 IU.

**The control group**

Patients randomized to the control group received the traditional dose of 400 IU of heparin/ kg bodyweight. We analysed ACT after 3 minutes, and if ACT was < 480 seconds, an additive dose of heparin, decided by the perfusionist, was given. ACT was then analysed every 30 minutes or more often if ACT value was volatile. Extra doses of heparin were given at the preference of the perfusionist. After finishing CPB, protamine was given at a ratio of 1.0-1.3 mg/100 IU of heparin, thus allowing additional protamine to reverse extra heparin given during CPB. Of the total protamine amount, decided by the anaesthetist, the last 50 mg of protamine was administrated after the residual, heparin-containing blood from the CPB-circuit had been infused. After HTC analysis any additional protamine was administered at the surgeon’s or anaesthetist’s preference.

**The HeProCalc group**

With the HeProCalc computer program, the initial dose of heparin was calculated from an empirically produced algorithm that includes data of the patient’s height, weight, and baseline ACT. In this study the target ACT was 550 seconds, thereby allowing for a slight decrease of ACT in case the onset of ECC was delayed. ACT was analysed 3 minutes after the given heparin bolus dose to ensure an appropriate ACT level before initiating CPB. The program also suggested eventual extra doses of heparin.

During CPB all ACT values and additional heparin doses were registered in the program, which calculated if any additional heparin doses were to be given to keep ACT above 480 second for the next 15-20 minutes, except approximately 15 minutes before end of CPB when we allowed the ACT to fall below 480 seconds. After weaning from CPB, the program calculated an appropriate protamine dose based on all ACT values, total amount of heparin and heparin consumption. In the same way as for the control group, the last 50 mg of the calculated protamine dose was administrated after the residual, heparin-containing blood from the CPB-circuit had been infused. Any additional protamine after a following HTC analysis was calculated by the program.

In both groups, patients were given a bolus dose of 1-2 grams of tranexamic acid after induction of anaesthesia, followed by a continuous infusion of 0.5-1 g per hour during surgery.
**Heparin and protamine**

Heparin and protamine were obtained from Leo Pharmaceutica (Copenhagen, Denmark), protamine at a concentration of 1400 anti-heparin IU/ml (corresponding to 10 mg/ml) and heparin at a concentration of 5000 IU/ml.

**Statistical methods**

To describe baseline characteristics means and standard deviations were used for continuous variables and frequencies and percentages for categorical variables. Continuous variables were compared using the Mann-Whitney test and categorical variables were compared using Fisher's exact test. All reported p-values are 2-sided, and p < 0.05 was set as the threshold for statistically significant findings. From prior clinical experience we estimated a 150 mg difference in protamine dose between traditional regime and HeProCalc regime. Assuming a power of 0.80 and a significance level of 0.001, a study sample of 20 patients in each group was needed. Stata version 13.1 (StataCorp LP, College Station, TX) and R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for data management and statistical analysis.
Results

Of 40 randomized patients, 3 were excluded from the final analysis. Two of them had to be cooled below 34°C, since surgical complications made it necessary to decrease the CPB flow rate. The third excluded patient needed ECMO treatment after CPB because of severe bleeding caused by surgical complications, which resulted in massive transfusions including multiple doses of coagulation factors. Of the remaining 37 patients, one patient in the control group was re-operated within the first 24 hours due to an arterial bleeding. All measured ACT values, in both groups, were above 400 seconds during CPB.

As shown in Table 1 there was no demographic baseline differences between the two groups. Furthermore, there were no significant differences with respect to duration of surgery, time on CPB, perioperative bleeding and fluid balance as depicted in Table 2. Table 3 summarises the mean heparin and protamine doses, as well as mean postoperative bleeding in both groups. No significant difference was found in mean total amount of heparin between the HeProCalc group and the control group (43333 IU vs. 40526 IU, p = 0.359). However, the mean total amount of protamine was significantly lower in the HeProCalc group (211 mg vs. 330 mg, p < 0.001). Mean postoperative bleeding was lower in the HeProCalc group (480 ml, vs. 694 ml p= 0.046). Overall, 4 patients in the HeProCalc group received some type of transfusion (red blood cells, plasma or platelets) during surgery vs. 2 patients in the control group. Postoperatively, 4 patients in each group received some type of transfusion. There were no significant differences in ACT values between the two groups at any sampling occasion (Figure 2). To attain ACT > 480 seconds prior to start of CPB, extra heparin had to be added in 8 of the 18 (44%) patients in the HeProCalc group compared with 2 of 19 (10%) in the control group. The total additional amount of heparin was 75000 IU heparin in the HeProCalc group versus 15000 IU in the control group. Mean ACT after the initial bolus dose of heparin was 514 seconds in the HeProCalc group versus 621 seconds in the control group (p=0.0127). However, in the HeProCalc group 4 patients did not reach an ACT value above 400 seconds after the initial bolus dose of heparin, while in the control group all patients obtained an ACT above 400 seconds.

One patient in the control group was reoperated due to surgical bleeding. After excluding this patient, repeated analysis regarding postoperative bleeding showed that the mean postoperative blood loss was 480 ml in the HeProCalc group vs. 649 ml in the control group (p=0.0736).
Discussion

In this randomized controlled study, the total amount of protamine as well as postoperative blood loss was significantly lower in the HeProCalc group.

It is a well-known fact that heparin has to be used to achieve adequate anticoagulation during CPB in order to prevent thrombus formation in the CPB-circuit, a complication that might be lethal. The use of heparin also contributes to the delicate haemostatic situation after CPB even though the specific antidote protamine is used to reverse the anticoagulant effect of heparin. During the last decades, different methods have been used to calculate the appropriate heparin dose. Traditionally, and most common, the calculation has been based on body weight, often resulting in initial doses of heparin between 200-400 IU/kg. For protamine, the reversal dose of 1.0 to 1.3 mg of protamine for every 100 IU of heparin has been assumed to neutralize the heparin effect. A drawback with protamine is its possible side effects related to allergic reactions, caused by an antigen-antibody response, which may result in a severe anaphylactic reaction. Nevertheless, in cardiac surgery that includes CPB, protamine reversal is unavoidable after full heparinisation. On the other hand, excessive protamine is known to possibly enhance further bleeding by impairing platelet function, down regulating of thrombin generation and weakening of clot structure. The traditional way of dosing heparin and protamine may be questioned, and studies have tried to define optimal ACT levels for CPB, where a minimum value of 400 seconds is mostly used. An ACT value between 500 and 700 seconds has been associated with lower blood loss compared with ACT levels < 500 or > 700 seconds. The higher blood loss associated with an ACT level <500 seconds may be explained by increased consumption of coagulation factors, whereas excessive dosage with ACT-levels >700 seconds may increase the risk of bleeding after reversal with protamine because of heparin rebound.

Adjusting doses of protamine

Previous studies have indicated that lower doses of protamine than conventional may be sufficient to fully reverse the heparin effect. Protamine is an antidote to heparin, but the drug itself does not promote coagulation. On the contrary, and independent of heparin, protamine may exert a mild anticoagulant effect. Therefore, by different mechanisms as aforementioned, though not always affecting ACT, redundant protamine doses may enhance further bleeding.

Less bleeding in the HeProCalc group

The difference in mean postoperative bleeding between the two groups was statically significant with 480 ml in the HeProCalc group vs. 694 ml in the control group.
(p= 0.046). This difference of 200 ml may seem negligible, but in the perspective of deciding whether to transfuse or not, it could make a difference for some patients. Furthermore, any measure that may reduce transfusions can be regarded as essential, since transfusions have been associated with impaired clinical outcome 14. However, the size of this randomized study was too small to draw any conclusions regarding effects on transfusion rates. A larger study could possibly clarify whether or not the HeProCalc program may have a significant impact on postoperative transfusion requirements. After excluding the reoperated patient in the control group from the analysis, there was no significant difference between the groups regarding postoperative bleeding (p=0.074). However, the result still indicates that patients in the study group tended to bleed less.

**ACT values in the ICU**

ACT values were sometimes elevated in both groups in the analyses performed in the ICU, as shown in Figure 2. The parallel HTC testing with heparinase excluded that the slight increases in ACT were caused by remaining heparin. Thus, the prolonged ACT in the ICU may instead be explained by loss of coagulation factors due to bleeding, damaged platelets, or low fibrinogen levels on account of consumption during CPB. Furthermore, hemodilution during and after CPB lowers the concentration of platelets and coagulation factors, and thus also affect ACT values in the ICU 15.

**Bolus doses of heparin**

In this study additional heparin doses were more frequent in the HeProCalc group in order to attain acceptable ACT values before CPB. The disadvantage of giving additional heparin must be weighed against risk of excessive ACT values if the program were to be modified to a higher target-ACT. Although the target-ACT was set to 550 seconds the mean value turned out to be 513 seconds in the HeProCalc group. Moreover, 4 patients in this group did not reach an ACT value above 400 seconds after the initial bolus dose of heparin, while in the control group all patients obtained an ACT above 400 seconds. It may be argued that, provided the patient is haemodynamically stable, a potential delay of a few minutes before initiating CPB, after obtaining adequate ACT with additional heparin, is in general not associated with any risks. However, if there is a need for an urgent start of CPB, it is probably safer to administer a larger initial bolus dose to avoid a possibly too low ACT response.

**Identifying sources of bleeding**

The aetiology of bleeding after CPB is versatile, and blood loss itself might maintain further bleeding unless proper treatment is initiated. If lack of protamine can be ruled out as a source of bleeding, how can other reasons for this feared complication be identified in an accessible way?
Random administration of extra protamine will often not be advantageous to the patient and, further, other beneficial interventions may be delayed. To determine the optimal treatment, other analyses than ACT/HTC, e.g. thromboelastography could be performed, since the HTC is heparin-specific and will not indicate other reasons for a prolonged clotting time.

In summary, the result of this study indicates that lower protamine doses than traditionally given do not result in aggravated bleeding. On the contrary, despite a 35 % reduction in mean protamine dose in the HeProCalc group, these patients bled significantly less postoperatively than the patients in the control group, with equal total amounts of heparin in both groups. Data from this study support previous studies \(^{16-18}\) that advocate a low dose protamine regime in order to avoid the possible drawbacks of the drug.

**Limitations**

First, the use of the HeProCalc algorithm for more than six months before the study was started may have made physicians and perfusionists more inclined to use lower doses of protamine in the control group compared with those used before the introduction of the HeProCalc computer program. If this was to be true, the difference in protamine dosages between the two groups may have been underestimated.

Second, changes were made in the HeProCalc computer program after the power calculation for this study. These changes may explain why the results differ from the power calculations.

Third, whereas ACT/HTC testing was restricted to six perfusionists in the OR, the tests were performed by many more nurses in the ICU. Therefore, risk of incorrect measurements is probably slightly higher in the ICU. Optimally, one could have restricted the number of participating nurses in the ICU.

It could be argued that a possible difference in molecular weight between heparin batches might have influenced the outcome of the study, but the randomized design should have prevented this possibility.
# Tables and figures

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
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<th>Control group</th>
<th>HeProCalc</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Percent of study population</td>
<td></td>
<td></td>
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<tr>
<td>Age, years</td>
<td>63.9 (10.4)</td>
<td>69.0 (10.7)</td>
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<tr>
<td>Female sex</td>
<td>3 (16%)</td>
<td>5 (28%)</td>
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<tr>
<td>Weight, kg</td>
<td>80.0 (13.5)</td>
<td>77.7 (12.6)</td>
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</tr>
<tr>
<td>Height, cm</td>
<td>174 (8.0)</td>
<td>173 (8.5)</td>
<td>0.615</td>
</tr>
<tr>
<td>Body Surface Area, m²</td>
<td>1.9 (0.2)</td>
<td>1.9 (0.2)</td>
<td>0.770</td>
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<tr>
<td>Estimated GFR, mL/min/1.73 m²</td>
<td>86 (33)</td>
<td>76 (27)</td>
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<td>Haemoglobin, g/l</td>
<td>135 (16)</td>
<td>131 (13)</td>
<td>0.513</td>
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<td>Platelets, x 10⁹</td>
<td>206 (58)</td>
<td>218 (56)</td>
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<td>Prothrombin complex, INR</td>
<td>1.1 (0.2)</td>
<td>1.0 (0.1)</td>
<td>0.318</td>
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<td>Baseline ACT, seconds</td>
<td>143 (22)</td>
<td>138 (18)</td>
<td>0.378</td>
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<tr>
<td>Aspirin</td>
<td>12 (63%)</td>
<td>14 (78%)</td>
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<td>Warfarin</td>
<td>4 (21%)</td>
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<td>0.105</td>
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<td>Procedure</td>
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<tr>
<td>CABG</td>
<td>6 (32%)</td>
<td>5 (28%)</td>
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<tr>
<td>Aortic valve replacement</td>
<td>4 (21%)</td>
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<tr>
<td>Other</td>
<td>9 (47%)</td>
<td>7 (39%)</td>
<td>0.769</td>
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Mean and standard deviation or number of patients and percentage.
GFR = glomerular filtration rate, CABG = Coronary artery bypass grafting. ACT= Activated Clotting Time
<table>
<thead>
<tr>
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<th>HeProCalc</th>
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<tr>
<td>Number of patients</td>
<td>19</td>
<td>18</td>
<td></td>
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<tr>
<td>Duration of surgery, min</td>
<td>212 (82)</td>
<td>213 (61)</td>
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<td>Cardiopulmonary bypass time, min</td>
<td>104 (49)</td>
<td>103 (35)</td>
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<td>Perioperative fluid balance, ml</td>
<td>1893 (957)</td>
<td>1893 (1127)</td>
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<td>Bleeding during surgery, ml</td>
<td>556 (426)</td>
<td>485 (241)</td>
<td>0.927</td>
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Mean and standard deviation
<table>
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<td>Number of patients</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Heparin total, IE</td>
<td>40526 (10560)</td>
<td>43333 (12891)</td>
<td>0.359</td>
</tr>
<tr>
<td>Protamine, mg</td>
<td>330 (61)</td>
<td>211 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postop bleeding, ml</td>
<td>694 (334)</td>
<td>480 (229)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Mean and standard deviation
Figure 1. Heparin acts by potentiating anti-thrombin³.
Figure 2. Activated Clotting Time (ACT) as measured at four different occasions in unheparinized blood in the HeProCalc group vs. the control group. Baseline ACT was collected prior to induction of anaesthesia.
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References
