Comparison of coagulation monitoring using ROTEM and Sonoclot devices in cardiac surgery A single-centre prospective observational study

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Comparison of coagulation monitoring
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A single-centre prospective observational study

Viscoelastic testing in cardiac surgery

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ABSTRACT

BACKGROUND: Viscoelastic tests (VETs) are recommended during cardiac surgery to monitor coagulation status and guide transfusion. We compared the results of two VETs, the Sonoclot Analyzer and the ROTEM Sigma. Agreement between viscoelastic tests’ subdiagnoses and overall diagnosis severity was assessed. Correlations with conventional coagulation tests (CCT) and the discriminatory potential of numerical VET outputs for transfusion thresholds was determined.

METHODS: Single-centre, prospective observational study in a tertiary academic centre. In fifty adult patients undergoing elective cardiac surgery, parallel Sonoclot, ROTEM and CCT analysis was performed before heparin, or after protamine or coagulation product administration. All patients completed the study, resulting in 139 data points.

RESULTS: Agreement on the severity of coagulation disorders was acceptable (83%), but poor (27%) on the differentiation of the underlying causes. Correlations between ROTEM parameters and CCT were good (post-protamine: FIBTEM A5 ($r^2 = 0.90$ vs fibrinogen) and EXTEM-FIBTEM A5 difference ($r^2 = 0.81$ vs platelet count)). Sonoclot correlated less (Clot Rate ($r^2 = 0.25$ vs fibrinogen) and Platelet Function ($r^2 = 0.43$ vs platelet count)). This was reflected in the discriminatory potential of these parameters as found by linear mixed modelling. We suggest clinically useful grey zones for VET cutoff interpretation.

CONCLUSIONS: ROTEM and Sonoclot accord well on the detection of severity of coagulation dysfunction, but not on the diagnosis of the underlying cause. ROTEM correlated more closely with CCT than Sonoclot. We propose a testing strategy that could lead to a cost-effective approach to the bleeding cardiac surgery patient.

Key words:
Blood Coagulation Tests, Blood Platelets, Cardiopulmonary Bypass, Fibrinogen, Point-of-Care Testing
Introduction

Severe postoperative bleeding is a dreaded but relatively common event after cardiac surgery, with 5-7% experiencing blood loss exceeding two litres.\textsuperscript{1,2} It is associated with increased transfusion rates, morbidity and mortality, as well as increased costs.\textsuperscript{3-7} Excessive bleeding after cardiac surgery is the result of variable degrees of inadequate coagulation, hemodynamic factors and/or suboptimal surgical haemostasis. In order to provide rapid and accurate detection of coagulation abnormalities, numerous point of care coagulation tests have been proposed.\textsuperscript{2,8} Ideally monitoring should be available in both adult and paediatric/neonatal cases.\textsuperscript{9}

We compared two viscoelastic tests (VETs): the Sonoclot® Analyzer (Sienco Inc, Arvada, CO, USA) and the ROTEM® Sigma rotational thromboelastometry (Werfen, Barcelona, Spain).\textsuperscript{10} Both rely on changing physical properties of coagulating whole blood to produce a trace to identify coagulation abnormalities.\textsuperscript{11} In real time, coagulation is visualised, from initiation of fibrin formation to fibrinolysis.\textsuperscript{8,10} Sonoclot uses a vertical continuously vibrating probe (200 Hz) partially immersed in blood. Changes in viscoelastic properties of the clotting blood are reflected by the mechanical impedance. The ROTEM uses a slowly oscillating pin suspended in a cup, which is slowed down by the ongoing coagulation, converted to an amplitude trace. Both devices have advantages and disadvantages. The use of different activators and inhibitors allows multiple parameters to be discerned: Sonoclot uses kaolin or glass bead activated samples, ROTEM offers tissue factor (EXTEM), ellagic acid (INTEM), cytochalasin D (a platelet inhibitor, FIBTEM) and heparinase (HEPTEM) combinations. In EXTEM, FIBTEM and APTEM polybrene inhibits heparin, and all ROTEM analyses use calcium chloride to recalcify the sample. Sonoclot has no onset delay and operates at lower costs\textsuperscript{12}, whereas the ROTEM sigma device has the advantage of being less user-dependent (being semi-automated cartridge-based) that combines four tracks.\textsuperscript{10} It requires 2.7 mL (opposed to 0.36 mL per Sonoclot assay), which may make it less suitable for neonatal cases.\textsuperscript{9} The aim of this study is to compare VETs in patients undergoing cardiac surgery, in order to evaluate diagnostic results, their correlation with traditional coagulation tests and investigate their discriminatory potential for established transfusion thresholds.
Materials and methods

In this single-centre prospective observational study, the population comprised of fifty consecutive adult patients scheduled for multiple types of cardiac surgery with extracorporeal circulation. No restrictions were imposed concerning the preoperative use of anticoagulants. After institutional board review (Ghent Ethical Committee, BC-08379, 29th September 2020), written informed consent was acquired. Inclusions took place from October to December 2020.

Data collection and patient management

Blood was sampled for parallel analysis by ROTEM, Sonoclot and with conventional coagulation testing (CCT): fibrinogen concentration and platelet count. All samples were drawn from a dedicated lumen of a jugular central line. For each Sonoclot analysis, 0.36 mL of whole blood was directly transferred to the Sonoclot cups by the attending perfusionist. Simultaneously, from the same sampling line, additional blood was collected in citrated tubes (2.7 mL, 3.2% (0.109M) sodium citrate, BD Vacutainer, New Jersey, US) for ROTEM analysis and fibrinogen measurement, and an ethylenediaminetetraacetic (EDTA) tube (4.0 mL, 7.2 mg EDTA, BD Vacutainer, New Jersey, US) for platelet count. Sampling was performed at two predetermined time points: prior to heparin administration and five minutes after protamine administration. If the attending anaesthesiologist deemed it necessary to further correct coagulation after heparin reversal, additional sampling points were created. Possible interventions were one or more of the following: transfusion of coagulation products (pooled platelets, fresh frozen plasma, fibrinogen concentrate or vitamin-K dependent coagulation factors concentrate), additional protamine administration or retransfusion of autologous predonated blood. This resulted in a total of 139 measurement points in fifty patients (ranging from 2 to 5 sampling points per patient). Chest tube drainage was recorded for the first four and twelve postoperative hours.

Tranexaminic acid was administered to all patients before the start of extracorporeal circulation (10 mg.kg⁻¹.hr⁻¹, after a loading dose of 20 mg.kg⁻¹). Before bypass, a loading dose of 300 IU.kg⁻¹ of heparin was administered (Leo, Copenhagen, Denmark). During bypass, repeated Sonoclot measurements were taken to ensure adequate anticoagulation (defined as a Sonoclot ACT >300 seconds and a Clot Rate <6 impedance units). Protamine dose was calculated using Sonoclot ACT based heparin sensitivity analysis.¹³ Clinical
management was unaltered by experimental setup. Study data were collected and managed using REDCap electronic data capture tools hosted at Ghent University Hospital.  

**Coagulation testing and interpretation**

All Sonoclot analyses were performed on a Sonoclot® Analyzer in the operating room using kACT and gbACT kits. For ROTEM analyses, sigma complete+ hep cartridges were used on ROTEM sigma devices. Fibrinogen concentration was measured with the Clauss method (STA-Liquid Fib reagent, STA-R analyser, Diagnostica Stago, Asnières-sur-Seine, France) and platelet count was determined using impedance-based sheath flow direct current detection (Sysmex XE or XN analyser, Sysmex, Fremont, CA). ROTEM, fibrinogen and platelet count measurements were performed in the central clinical laboratory of Ghent University Hospital.

For all 139 measurement points, stored ROTEM and Sonoclot traces were evaluated by two blinded independent assessors. Each had more than 10 years’ experience in clinical Sonoclot use, but (as none are available) no predefined algorithm was used for Sonoclot interpretation. The second assessor provided data for inter-observer reliability assessment.

The ROTEM signatures were classified using a pre-defined in-house algorithm (table I). 15,16 All traces were categorised as one or more of eleven subdiagnoses: normal coagulation, residual heparin effect, hypercoagulability, and mild or severe platelet-based dysfunction, clotting factor-based dysfunction, fibrinogen-based dysfunction or fibrinolysis. 197 subdiagnoses were thus recorded. Results were categorised as severe (any severe compound dysfunction or residual heparin effect) or mild/no dysfunction.

**Statistical analysis**

All analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria. 2020, version 4.0.3), including the lme4 (v1.1-26) package. 17–19 All continuous variables are presented as means ± standard deviations, categorical variables as frequencies and percentages. The primary outcome was the comparability of the diagnoses provided by both VETs, by severity as well as for specific diagnoses. Proportions between paired data were evaluated using McNemar’s test. Severity of last peroperative VET diagnoses was compared to postoperative chest tube drainage. The secondary outcome was the correlation between VET parameters and CCT (fibrinogen concentration and platelet count). Linear regressions were performed in non-clustered data points. To assess goodness-of-fit, $r^2$ coefficients of determination were computed. We used linear mixed modelling (correcting for pseudo-replication at the
patient level) to allow for a component analysis of each parameter, in order to evaluate how well a VET could attribute the cause of coagulation disorder to a fibrinogen- or platelet-based cause. After standardisation, fibrinogen concentration and platelet count were used as fixed effects, and patient as random effect. For the fixed effects, the coefficients and confidence intervals of the regression were plotted as dot-and-whisker plots. Lastly, the discriminatory potential of each monitor for transfusion thresholds was assessed using sensitivity and specificity analyses. We adopted a grey zone approach, where results with a sensitivity or specificity below 0.9 were deemed uncertain.

**Results**

An overview of our cohort’s demographics and operative data is presented in table II.

**Comparing VET diagnoses**

For the viscoelastic global diagnoses, after classification of severity, agreement was 83% (116/139). When comparing postoperative blood loss, expressed as total drained volume 4h and 12h post-surgery, we found a trend towards a statistically significant difference between the Sonoclot groups, but not ROTEM’s (Mann-Whitney U test, 4 hour postoperatively: p= 0.056 for Sonoclot vs p= 0.48 for ROTEM). However, sample size was low in the group with severe VET dysfunction (7 Sonoclot and 8 ROTEM). Results were comparable after twelve hours (p=0.083 for Sonoclot vs p= 0.43 for ROTEM), and in the 2 revisions that occurred (both with a surgical cause identified) both VET’s agreed on normal postoperative coagulation traces.

Agreement between both viscoelastic tests for specific diagnoses was low at 27% (53/197 subdiagnoses). ROTEM tended to more often diagnose fibrinogen-based impairment (64 vs 29 for Sonoclot, McNemar’s test p<0.001), whereas Sonoclot suggested more often a suboptimal thrombocyte contribution (35 vs 19 for ROTEM, McNemar’s test p=0.023). In 61% of normal Sonoclot diagnoses, ROTEM agreed. In 4.6% of normal Sonoclot traces, ROTEM suggested a severe coagulation disorder (75% of which fibrinogen-based). When the Sonoclot signature suggested platelet-based pathology, ROTEM did not agree (8.6% (3/35) of these ROTEM traces suggested platelet-based impairment). Both tests did not tend to agree on the diagnosis of fibrinolysis (albeit not frequent in our population) nor hypercoagulability. Sonoclot signatures were normal in 66% of normal ROTEM traces. Inter-rater reliability of the Sonoclot diagnoses was poor to fair (Cohen’s kappa coefficient
ROTEM diagnoses were directly deduced from the proposed algorithm by two assessors, with full agreement.

**Conventional coagulation tests**

Linear regressions were performed in 50 non-clustered data points to compare predictive value of the different VET parameters. For fibrinogen concentration, regression coefficients show that ROTEM’s FIBTEM A5 gives the most robust estimation of fibrinogen concentration ($r^2 = 0.90$) (figure 1, A-B). We found low coefficient of determination values for the Clot Rate parameter ($r^2 = 0.25$). Pre-heparin correlations were similar ($r^2 = 0.77$ and 0.04 for ROTEM and Sonoclot, respectively). Concerning platelet count, the EXTEM-FIBTEM A5 difference seemed more robust than the Platelet Function as reported by the Sonoclot, with coefficients of determination of 0.81 and 0.43 (figure 1, C-D for post-protamine results). Pre-heparin results were similar ($r^2 = 0.53$ and 0.15 for ROTEM and Sonoclot, respectively).

**Discriminatory potential**

Results of the linear mixed modelling are plotted as distributions, with 0.95 confidence interval represented by their width. Overlap between the fibrinogen and platelet linked distributions of a particular parameter suggest poor discriminatory ability of the suggested parameter. In the fibrinogen-related parameters, both parameters’ coefficient estimates (the product of their standard error and t-value) were statistically associated with fibrinogen concentration, and not with platelet count. The narrow and scattered FIBTEM A5 distributions reflect good discriminatory potential for fibrinogen, with little impact of thrombocyte count (figure 2). Sonoclot’s glass bead Clot Rate’s distributions however shows overlap. For the two thrombocyte-related parameters, modelling indicated that the ROTEM-based parameter was better able to differentiate the contributions of platelet count and fibrinogen concentration (figure 2).

**Classification performance**

Using a sensitivity/specificity-based analysis, multiple proposed thresholds were analysed, according to different guidelines: fibrinogen concentrations of 150 and 200mg.dL⁻¹, and platelet counts of 50, 100 and 150 $10^3$.µL⁻¹. In cases where sensitivity dropped to 0.9 before specificity rose to 0.9, we applied a grey zone approach. In this zone, where sensitivity or specificity was below 90%, formal conclusions cannot be obtained. If sensitivity remained high, a singular cutoff was defined as the maximal sum of sensitivity and specificity. Thus, a maximum of three response classes were obtained: positive,
negative and inconclusive. Results are represented in two-curve plots: ROTEM’s FIBTEM five minute amplitude was able to categorise results based on fibrinogen concentrations of 150mg/dl or 200 mg/dl, with cutoffs of 6.6 and 8.7 respectively. With Sonoclot’s Clot Rate, broad grey zones of 19.5-26.7 and 21.3-32 were obtained (figure 3A). In figure 3B, we plotted sensitivity and specificity in function of the difference between ROTEM’s EXTEM and FIBTEM A5, and found a good ability to categorise platelet count according to proposed thresholds, with no or narrow grey zones (17.1, 29.1 and 33 to 35.9 for thresholds of 50, 100 and 150 \(10^3\cdot\mu\text{L}^{-1}\)). The Platelet Function parameter could confidently categorise low platelet counts (cutoff of 1.1 for 50 \(10^3\cdot\mu\text{L}^{-1}\)), but showed less discriminatory power when the threshold was 100 or 150 \(10^3\cdot\mu\text{L}^{-1}\) (1.8-2.9 and 2.1-4).

Discussion

In fifty adult patients undergoing cardiac surgery, resulting in a total of 139 data points with 197 diagnoses, we compared the ROTEM and Sonoclot. Concerning the detection of severe coagulation disorders (defined as at least one coagulation component interpreted to show severe dysfunction), agreement was good at 83%. This subdivision makes clinical sense, as the therapeutic decision depends on both the severity of testing results and ongoing losses. Often, subpar coagulation is not corrected unless clinically relevant bleeding is suspected. Sonoclot’s, but not ROTEM’s, last peroperative signature trended towards a statistically significant result with postoperative drainage volumes, albeit with low numbers in the group with severe coagulation dysfunction. Agreement on specific results, defined as a classification of eleven diagnoses, was poor at 27%. Differences in underlying operating principles between both VETs may at least in part account for these discrepancies. Moreover, it remains unclear how the interaction of the fibrinogen- and platelet-based components of the global coagulation profile affect the results.

When comparing VET parameters with conventional coagulation tests (CCT), ROTEM correlated better. The comparison with fibrinogen concentration has previously been investigated by Espinosa’s group in ROTEM and Sonoclot (70 data points) and they deemed Sonoclot less suitable than ROTEM. In our setup, we were able to confirm these lower correlation coefficients. This was also reflected in each parameters discriminatory potential as evidenced by linear mixed modelling. For platelet count, post-protamine
correlations in our dataset were good for ROTEM’s EXTEM-FIBTEM A5 difference \( (r^2 = 0.81) \), and reasonable for Sonoclot’s Platelet Function \( (r^2 = 0.43) \). This was again reflected in their discriminatory potential. It should be noted that the Platelet Function parameter of the Sonoclot is ill-defined, and it’s precise determination not disclosed. Care has to be taken when directly comparing VET and CCT results. It is unclear what the precise contribution of count and function is to VET parameters.

Importantly, ROTEM uses citrated samples. Over- or under-filling of the citrate tube may cause pre-analytic error (although the investigators were attentive to this aspect) and citrate in itself can cause some artifacts due to its anti-aggregating effect on platelets. Recalcification of citrated blood allows for exclusive thrombin generation via the contact pathway in absence of a coagulation activator. Studies comparing citrated versus fresh blood samples when using ROTEM and Sonoclot indicated significant differences: a hypercoagulable response was noted with citrated blood. Correcting the ROTEM platelet parameter from amplitudes to elasticity, as some groups propose, yielded similar results. Due to the cubic relation between the EXTEM-FIBTEM absolute amplitude difference and it’s elastic counterpart, this correction has minimal effect in the low range. As it is this range that is clinically most valuable, and the elastance measurement is not readily available bedside, we decided not to incorporate this measurement.

Importantly, with sensitivity and specificity analysis, we defined useful grey zones with regard to transfusion thresholds. The first cutoff represents a sensitivity below 0.9, representing a clinically unacceptable uncertainty to correctly identify patients below the threshold. When specificity rises above 0.9, the second cutoff is created. Thus, when the parameter value is situated in the intermediary grey zone, further testing is warranted. This equips the clinician with a more nuanced interpretation of the viscoelastic test results.

**Hybrid testing**

As the operational costs of the Sonoclot Analyzer are 20% of ROTEM’s, a cost-effective hybrid testing approach can be suggested. A Sonoclot result in the grey zone would prompt further ROTEM testing, as uncertainty persists as to the specific cause of the coagulation disorder. When the results do not reach these lower grey zone limit, Sonoclot suggests targeted transfusion. This should be interpreted with caution, as in this setup only the specificity regarding fibrinogen concentration and platelet count was assessed. Other causes, e.g. severe residual heparin leading to an uninterpretable Sonoclot signal, should be excluded. When imposing a fibrinogen concentration of 150mg.dl\(^{-1}\) and a platelet
count of $100 \cdot 10^3 \mu L^{-1}$ as cutoffs, in 68% of our sampling points the Sonoclot provided a reliable therapeutic suggestion both concerning platelet- and fibrinogen-based coagulation disorders (with a sensitivity and specificity larger than 0.9). Solely looking at the costs associated with the diagnostic device, in our study cohort, this approach would have resulted in a significant cost reduction of 48% (as opposed to a ROTEM-first approach). It should be noted that in some situations the additional time needed for performing both tests in series may be unacceptable. Thus, in cases with a clinically known high a priori chance of bleeding, an early ROTEM approach is suggested. In retrospect, this would have been the case in 10/50 patients, reducing the cost reduction to 38%. The precise cutoff values of the Sonoclot’s grey zone should be validated in a larger, preferably multi-centre population. It should be noted that reduction can also be attained on the level of the required blood volume needed for sampling, which can be of interest in neonatal cases.

Advantages of our setup include the large study population of fifty patients, more than previously reported studies. They represented a good cross-section of our cardiac surgery population. All viscoelastic traces were blinded before interpretation and interpreted by two independent assessors. Nevertheless, this observational setup presents with its limitations. Sonoclot interpretation was solely based on expert opinion. No predefined algorithm was followed, as to the best of our knowledge, such an algorithm is not available. Inter-observer variability was large. This is a reflection of real-life Sonoclot use, where the interpretation of the signature shape tends to be more user-dependent than the numerical ROTEM output. A more objective, numerical description of the Sonoclot signature may provide a sounder approach, but currently only Activated Clotting Time, Clot Rate and Platelet Function are reported. Second, comparing CCT measurements with functional VET measurements has its limitations. CCT are widely used as they are inexpensive, but they may mask essential global in-vivo clotting information that could be provided by viscoelastic measurements. VET’s allow for an assessment of total clot strength, as opposed to clot initiation. As such, they are increasingly being incorporated in guidelines. Nonetheless, different VET parameters showed close correlation with conventional measurements, and many used transfusion thresholds are at least partially based on conventional coagulation measurements. Lastly, in this observational setup we did not have access to external reference for residual heparin effect, clotting factor efficiency or hyperfibrinolysis, which would have made the setup more powerful.
Conclusions

ROTEM and Sonoclot accorded well on the detection of the severity of coagulation dysfunction, but not in the specification of the underlying cause. Correlations with conventional coagulation tests were higher in ROTEM than in Sonoclot parameters. Using a grey zone approach could lead to a more cost-effective approach to the bleeding cardiac surgery patient.
WHAT IS KNOWN

• Viscoelastic coagulation testing is recommended during cardiac surgery, but
  multiple devices are available

• Head-to-head comparisons are scarce: we compared ROTEM and Sonoclot devices

WHAT IS NEW

• Diagnostic accordance was high for severity of coagulation disorder, but not for
  specific diagnoses

• ROTEM correlated better with fibrinogen concentration and platelet counts

• Based on sensitivity and specificity analysis, we propose a grey zone approach to
  interpretation of viscoelastic testing
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Conflicts of interest — The authors declare that they have no conflict of interest regarding the material discussed in the manuscript.

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Authors’ contributions — M Vandenheuvel, C Van Gompel, F De Somer, KMJ Devreese and P Wouters contributed to the study conception and design. Material preparation and data collection was performed by M Vandenheuvel, C Van Gompel, K Vandewiele, F De Somer, P De Kesel and KMJ Devreese. Data analysis and interpretation of data was performed by M Vandenheuvel, C Van Gompel and P Wyffels. M Vandenheuvel and C Van Gompel, drafted the work and all authors revised it critically. All authors read and approved the final manuscript.

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**TABLES**

**Table I — Classifying ROTEM diagnoses**

<table>
<thead>
<tr>
<th>Impairment</th>
<th>ROTEM cutoffs</th>
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<tr>
<td>Residual heparin effect</td>
<td>CT&lt;sub&gt;INTEM&lt;/sub&gt; &gt;200s and CT&lt;sub&gt;HEPTEM&lt;/sub&gt; / CT&lt;sub&gt;INTEM&lt;/sub&gt; &lt;0.8</td>
</tr>
<tr>
<td>Platelet-based</td>
<td>A&lt;sub&gt;5EXTEM&lt;/sub&gt; - A&lt;sub&gt;FIBTEM&lt;/sub&gt; ≤ 25mm</td>
</tr>
<tr>
<td>mild</td>
<td>A&lt;sub&gt;5EXTEM&lt;/sub&gt; - A&lt;sub&gt;FIBTEM&lt;/sub&gt; ≤ 16mm</td>
</tr>
<tr>
<td>severe</td>
<td>CT&lt;sub&gt;EXTREM&lt;/sub&gt; ≥ 90s</td>
</tr>
<tr>
<td>clotting factor-based</td>
<td>CT&lt;sub&gt;EXTREM&lt;/sub&gt; ≥ 100s</td>
</tr>
<tr>
<td>Fibrinogen-based</td>
<td>A&lt;sub&gt;5FIBTEM&lt;/sub&gt; 5-8mm</td>
</tr>
<tr>
<td>mild</td>
<td>A&lt;sub&gt;5FIBTEM&lt;/sub&gt; 16mm</td>
</tr>
<tr>
<td>severe</td>
<td>M&lt;sub&gt;L&lt;/sub&gt;EXTEM/INTEM &gt;15%</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>M&lt;sub&gt;L&lt;/sub&gt;EXTEM/INTEM &gt;25%</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>M&lt;sub&gt;C&lt;/sub&gt;EXTREM ≥ 70mm</td>
</tr>
</tbody>
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CT: clotting time, A5: 5 minute amplitude, ML: maximal lysis, MCF: maximal clot firmness

**Table II — Patient demographics and perioperative data**

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>66.2 (10.5)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>35 / 15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.7 (15.7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (9)</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>27.0 (4.4)</td>
</tr>
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Preoperative ongoing anticoagulation:
- None                       | 30.0 %   |
- Acetylsalicylic acid      | 56.0 %   |
- Ticagrelor                | 4.0 %    |
- Clopidogrel               | 16.0 %   |
- Vitamin K agonists        | 0.0 %    |
- Direct oral anticoagulants (DOAC) | 4.0 % |
- Unfractionated heparin    | 2.0 %    |
- Therapeutic LMWH          | 0.0 %    |
- Prophylactic LMWH         | 2.0 %    |

Preoperative laboratory results:
- Haemoglobin (g/dl)        | 13.7 (2.0) |
- Platelet count (.10<sup>3</sup>.µL<sup>-1</sup>) | 232 (62)   |
- Fibrinogen concentration (mg/dl) | 368 (84) |
- INR (%)                   | 1.02 (0.11) |
<table>
<thead>
<tr>
<th>Type of surgery:</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>- Isolated CABG</td>
<td>40%</td>
</tr>
<tr>
<td>- Single valve surgery</td>
<td>18%</td>
</tr>
<tr>
<td>- Multiple valve surgery</td>
<td>12%</td>
</tr>
<tr>
<td>- Combined CABG and valve surgery</td>
<td>8%</td>
</tr>
<tr>
<td>- Aortic surgery</td>
<td>18%</td>
</tr>
<tr>
<td>- Heart transplantation</td>
<td>2%</td>
</tr>
<tr>
<td>- Transapical resection</td>
<td>2%</td>
</tr>
</tbody>
</table>

| Aortic cross clamp time (min)                        | 60.1 (27.0) |
| ECC time (min)                                       | 104 (40)    |
| Use of separated suction (%)                         | 48%         |
| Total heparin dose (IU)                              | 29088 (9000) |
| Total protamine dose (mg)                            | 141 (43)    |
| Autologous retransfusion in OR (yes / no)            | 32% / 68%   |
| Red cell transfusion** (yes / no)                    | 30% / 70%   |
| Fresh frozen plasma transfusion** (yes / no)         | 20% / 80%   |
| Platelet transfusion** (yes / no)                    | 16% / 84%   |
| Concentrated clotting factor administration** (yes / no) | 12% / 88% |
| Fibrinogen administration** (yes / no)               | 4% / 96%    |
| Drained volume when leaving OR (mL)                  | 91 (108)    |
| Drained volume 4 hours postoperatively (mL)          | 375 (326)   |
| Drained volume 12 hours postoperatively (mL)         | 649 (549)   |
| Need for operative revision, (yes / no)              | 4%*** / 96% |

* values expressed as mean (SD) or %. ** 12 first postoperative hours. *** all surgical cause confirmed
TITLES OF FIGURES

Figure 1
**Correlations for selected viscoelastic parameters** with fibrinogen concentration (A,B) and platelet count (C,D) (post protamine samples).

Figure 2
**Dot-and-whisker plot of selected VET parameters** for fibrinogen concentration and platelet count. Coefficient estimates from each linear mixed model are presented as distributions with 0.95 confidence interval as width.

Figure 3
**Comparing sensitivity and specificity over the range of parameter results.** A: Results for a detection threshold of a fibrinogen concentration of 150mg/dl are shown on the left, and of 200mg/dl on the right. B: Results for a detection threshold of thrombocyte count of 50, 100 and 150 $10^3\mu L^{-1}$. 