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POINT-OF-CARE VHA-GUIDED MANAGEMENT OF BLEEDING IN CARDIAC SURGERY: CLINICIANS' COMPLIANCE WITH ALGORITHM, PRELIMINARY CLINICAL RESULTS OF THE IMOTEC STUDY.

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ABBREVIATIONS

AC ……..	Anticoagulant therapy
ACT ……..	Activated Clotting Time
CEC……	Circulation Extra-Corporelle
CHU ……..	Centre Hospitalier Universitaire
CPB ……..	Cardiopulmonary Bypass
CRF ……..	Case Report Form
FFP ……..	Fresh Frozen Plasma
GIHP ……	Groupe d'Intérêt en Hémostase Péri-opératoire
ICU ……..	Intensive Care Unit
Hb ……..	Haemoglobin
PBM ……..	Patient Blood Management
PCC ……..	Prothrombin Complex Concentrate
POC ……..	Point-Of-Care
SC ……..	Standard Care
PAI ……..	Platelet Aggregation Inhibitor
PT ……..	Prothrombin Time
RBC ……..	Red Blood Cells
RCT ……..	Randomised Controlled Trial
ROTEM® ……..	Rotational Thromboelastometry
rVIIa ……..	Recombinant factor VII
TEG® ……..	Thromboelastography
TXA ……..	Tranexamic Acid
VHA ……..	Viscoelastic Haemostatic Assay
X^2 ……..	Chi-2 test

1 TABLE OF CONTENTS

2 ABSTRACT

2.1 BACKGROUND

Cardiac surgery may be associated with bleeding, coagulopathy and haemostatic products need. Transfusion should be administered following lab tests results and consensual triggers [1], but time constraints and clinical judgement may precede this ideal scenario. Transfusion may be differed, exposing patients to prolonged bleeding, or – more likely– unduly triggered, exposing patients to unnecessary transfusion risks. Point-of-care viscoelastic haemostatic assay (VHA) and algorithm guided management of coagulopathy are recommended [2,3]. However, this strategy and clinicians' compliance with algorithm remains unclear [4].

2.2 MATERIAL AND METHODS

The IMOTEC study (Intérêt MédicO-économique des TEsts visco-élastiques dans les hémorragies péri-opératoires de chirurgies Cardiaques sous CEC) was a prospective multicentre pragmatic study, with a stepped-wedge cluster RCT [5]. VHA devices (ROTEM® or TEG®) were successively & randomly installed in 16 participating centres and a bleeding management algorithm promoted, during a 26-month enrolment period. Adult patients undergoing cardiac surgery with cardiopulmonary bypass were included if a post protamine pre-defined significant bleeding occurred. Patients were initially treated according to local Standard Care (group SC), then treatment was guided by VHA tests and bleeding management algorithm (group VHA). Clinical data from one centre, CHU Nantes, were analysed. The VHA device implemented in CHU Nantes was ROTEM®. Clinicians' compliance with algorithm was described for the VHA group. Univariate statistical analysis compared clinical data for the SC group and the VHA group using Mann & Whitney test for continuous or X^2 for nominal data, $p<0.05$.

2.3 RESULTS AND DISCUSSION

From 1/1/17 till 1/3/19, 198 patients were included (144 SC, 54 VHA). ROTEM® was available starting 27/6/18. Population mean age was 66±12 years, 24% were female.

54% of the patients underwent one surgical act only (coronary bypass or valve replacement) with an average CPB duration of 160±124 min. Average bleeding at day 1 was 1078±724mL, 93% of the patients were transfused and 48% needed surgical re-intervention. The average stay in ICU was 6.7±11.2 days.

Statistical difference was found for the proportion of transfused patient (97% in SC vs 83% in VHA, p=0.001). Transfusion requirements for the overall population were 5.4±7.3 RBC, 5.0±5.2 FFP, 1.8±2.3 Platelets. Other haemostatic products administered were fibrinogen (39% of patients), PCC (26%), protamine re-injection (81%) and rVIIa (5%). Statistical difference was found for blood products transfusion during ICU stay (RBC 52% in SC vs 28% in VHA, p=0.002; FFP 55% in SC vs 22% in VHA, p=0.0001; Platelets 43% in SC vs 20% in VHA, p=0.003).

The VHA-guided algorithm recommended the following actions: administer protamine (7.4%), platelets (0%), fibrinogen (3.7%), FFP (20.4%), PCC (7.4%), TXA (5.6%). Clinicians' action was as follows: protamine (72.2%), platelets (46.3%), fibrinogen (48.1%), FFP (57.4%), PCC (27.8%), TXA (3.7%). This led to compliance rates of 25.9% for protamine, platelets 53.7%, fibrinogen 55.6%, FFP 62.9%, PCC 79.6%, TXA 98.1%.

2.4 CONCLUSIONS

Clinicians' action was globally in line with the algorithm's recommendation. However, more haemostatic products were used than actually recommended except for TXA. Compliance rates ranged from 25.9% to 98.1%, suggesting a lack of confidence in the VHA-device and the VHA-guided algorithm. However, there seemed to be less transfusion in the VHA group vs SC group, with statistical difference being found in the ICU blood product transfusion. An analysis of the complete IMOTEC study data remains necessary to assess the efficiency of a VHA-guided management as part of Patient Blood Management (PBM) in cardiac surgery.

3 INTRODUCTION

Massive haemorrhage is classically associated with coagulopathy and higher mortality. A strategy aiming at avoiding coagulopathy tends to reduce mortality. Blood VHA allows a rapid and timely identification of coagulopathy along with enabling an individualised, goal-directed transfusion therapy. Evidence is growing that POC VHA testing may result in fewer transfusions, lesser patient complications, and reduced hospital costs. This is particularly true in cardiac surgery where bleeding is one of the most common complications.

3.1 TRANSFUSION IN CARDIAC SURGERY

Severe bleeding is a major complication of cardiac surgery. It results from multiple factors such as complex surgery, pre-operative antiplatelet and/or anticoagulant treatment, persistence of heparin despite protamine antagonism, consumption and dilution of coagulation factors and platelets [6].

Transfusion therapy is key to manage severe perioperative bleeding [7]. This leads to a high rate of blood products administration in cardiac surgery. The EPICARD II database [8] which aggregated 94,854 patients undergoing cardiac surgery in 2012, 2013 and 2014 in France estimated the rate of RBC transfusion at 35%. Other studies reported that transfusion of RBC may be necessary in at least half of the procedures with CPB [9,10]. Management of massive haemorrhage also necessitates the administration of other blood products and haemostatic products such as FFP with a recommended RBC/FFP ratio of 1/1 or 2/1, early platelets transfusion, fibrinogen, TXA, etc [11].

Transfusion is associated to complications for the patients. These include primarily infectious (respiratory or wound infection or septicaemia), cardiac (ischemic events), or renal adverse effects (with higher need for renal replacement therapy) [12].

Transfusion is associated to high costs for the society. Blood products are a scarce and expensive resource. A high rate of blood products administration is linked to a high cost for the society. In developed countries such as the UK, where more than 30,000 people have heart surgery yearly, it is estimated that up to 15% of total amount of all

RBC is used in cardiac surgery [13]. The transfusion of blood products in cardiac surgery at CHU Nantes, which performs around 1,300 to 1,400 procedures under CPB every year, amounts to over 1 million euros yearly.

Benchmarking transfusion leads to better patient safety and lower costs. A standardisation process to avoid either delayed or unduly triggered administration stimulates awareness of transfusion behaviour, leading to lower transfusion rates [14]. POC VHA and algorithm-guided management of coagulopathy can be part of the standardisation process.

3.2 EFFECTIVENESS OF VHA IN CARDIAC SURGERY

VHA-guided algorithms have proved their effectiveness in cardiac surgery. VHA helps identifying patients who will truly benefit from transfusion and is useful for predicting bleeding tendency after protamine administration [15]. VHA enables early detection of coagulation trouble, which helps reducing the need for blood products and improves morbidity in patients [4,16].

VHA-guided algorithms are recommended for managing coagulopathy. The ROTEM® and the TEG® systems are recommended to help detect, manage and monitor haemostasis during and after cardiac surgery [7].

In the UK, this recommendation is based on a systematic review that included 11 RCTs evaluating ROTEM® and TEG® in cardiac surgery patients [13]. The review points toward a reduction in blood product transfusion by suggesting:

- a significant beneficial effect of the VHA-guided algorithm in reducing the number of patients who received RBC, FFP and platelet transfusion.
- a beneficial effect (with no statistical significance being reached) of the VHA-guided algorithm in reducing the number of patients who received any blood product transfusion and a rVIIa transfusion.
- no difference in the volume of fibrinogen concentrate transfused and in the number of patients who received a PCC transfusion.

The review also points toward a lower number of complications by suggesting:

- a beneficial effect of the VHA-guided algorithm (with no statistical significance being reached) with regards to volume of bleeding, number of patients needing re-operation, and length of stay in ICU.
- no difference was found in mortality and length of hospital stay.

In France, the GIHP proposes to use VHA-guided algorithm in the management of haemorrhage in cardiac surgery once heparin has been neutralised [17].

Despite growing evidence of the interest of VHA-guided algorithm in cardiac surgery, whether VHA allows optimising the use of healthcare resources is still unclear. The aim of the IMOTEC study was to assess the cost-effectiveness of a point-of-care VHA-guided management of patients with ongoing bleeding during cardiac surgery with CPB. Among several outcome measures, particular emphasis was put on quality of life.

The data collected by CHU Nantes were analysed in the form of preliminary clinical results of the IMOTEC study. Particular emphasis was put on transfusion requirement and clinicians' adherence to the proposed VHA-guided algorithm.

4 METHODS

4.1 STUDY DESIGN, POPULATION AND SETTINGS

The IMOTEC research followed a multicentre, prospective, pragmatic, stepped-wedge cluster randomised controlled design [5,18].

Study design: it involved sequential crossover of clusters from control to intervention until all clusters were exposed. Sixteen French academic centres performing yearly from 500 to 1,500 cardiac procedures under CPB were selected. The study aimed at including one thousand patients over a 36-month period (24 months of enrolment and 12 months of follow-up). Recruitment started on 3/1/2017.

Randomisation: it was carried out at the level of the cluster. Indeed, when significant bleeding occurred during a cardiac surgery procedure, time spent in a randomisation process rather than caring for the patient might have been unethical.

Potential biases: the study design could have led to selection biases and confounding effect of time. Possible selection bias is inherent to all cluster trials, with individual recruitment and without blinding of the intervention. Possible confounding effect of time is due to the fact that more clusters were exposed to the intervention towards the end of the study than in its early stages. This implied that the effect of the intervention might have been confounded with any underlying temporal trend.

4.2 DATA MANAGEMENT AND ETHICS CONSIDERATIONS

Data management: data was collected by investigators on a paper CRF and then entered into a computerised database (eCRF) ruled by the Research Department of Nantes University. The Research Department of Nantes University also monitored recruitment and quality control of the data.

Ethics: the IMOTEC study was conducted in full compliance with the Declaration of Helsinki and its protocol was approved by the Committee for the Protection of Persons of Nantes University Hospital (04/05/2016, number 15/16). The study was registered by the « Agence Nationale de Sécurité du Médicament et produits de santé (ANSM) » (ID RCB number: 2016-A00455-46). It also was registered at Clinicaltrials.gov (NCT02972684 November 23, 2016).

4.3 MANAGEMENT OF BLEEDING ACCORDING TO THE STUDY PHASE

4.3.1 PHASE 1: STANDARD CARE (SC)

Local management of bleeding: Phase 1 or SC corresponded to the pre-intervention observational period. The usual local management of bleeding by the anaesthetist staff was respected. SC was not standardised across the participating centres and VHA was not part of SC.

CHU Nantes local management of bleeding: SC at CHU Nantes included the "FAST" procedure. While time required to obtain haemostasis results often remains a major problem for clinicians dealing with bleeding, the local team implemented in 2014 a rapid laboratory response strategy called the "FAST" procedure. This procedure enables clinicians to obtain haemostasis results such as prothrombin time (PT), anti-Factor Xa,

fibrinogen and platelet count in a very short turnaround time (approximatively 20 minutes), which is a useful guidance for the decision to transfuse blood products [19].

4.3.2 PHASE 2: INTERVENTION (VHA-GUIDED ALGORITHM)

VHA-guided algorithm (figure 1): the intervention consisted in the implementation of a VHA-guided algorithm for the management of severely bleeding patients undergoing cardiac surgery under CPB. Two different algorithms were designed depending on the choice of the VHA device which for one centre was either the ROTEM® or the TEG®. CHU Nantes was equipped with ROTEM® and implemented the ROTEM®-guided algorithm. Algorithm thresholds were derived from previously published algorithms[20,21,22].

Clinicians' management of bleeding: after the implementation of the VHA-guided algorithm, clinicians were encouraged to adopt the algorithm but were not forced to do so, since the IMOTEC study aimed at being pragmatic.

Stepped-wedge design (figure 2): there was a period of 4 months in which none of the sixteen participating centres was exposed to the intervention. Thereafter and according to randomisation, intervention was sequentially implemented across four groups of four centres. Sequential implementation was done after periods of 5 months. CHU Nantes was part of the fourth group (Group 4). As a result, CHU Nantes benefited from the VHA-guided algorithm from the 20th month until the end of the study. This design allowed each participating centre to contribute to both control and intervention data collection.

Patients: they were blinded to their participation in Phase 1 (SC) or Phase 2 (VHA), i.e. they did not know whether VHA-guided algorithm was used. Follow-up period lasted until 12 months after hospital discharge. Follow-up period was not analysed in this work.

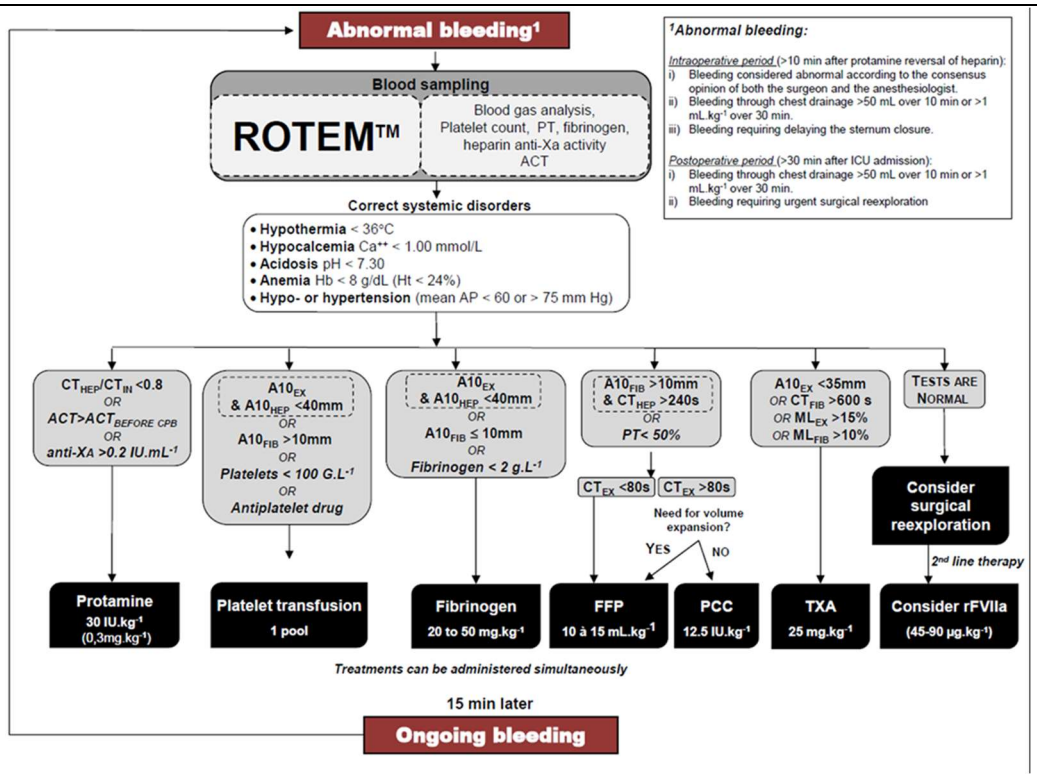

Figure 1: ROTEM®-guided algorithm for bleeding management.

ROTEM® parameters: A10, Amplitude at 10 min; ACT, activated clotting time; AP, arterial pressure; CPB, cardiopulmonary bypass; CT, clotting time; EX, EXTEM; FFP, fresh frozen plasma; FIB, FIBTEM; HEP, HEPTEM; ML, maximum lysis; PCC, prothrombin complex concentrate; PT, prothrombin time; rVIIa, recombinant factor VII; TXA, tranexamic acid.

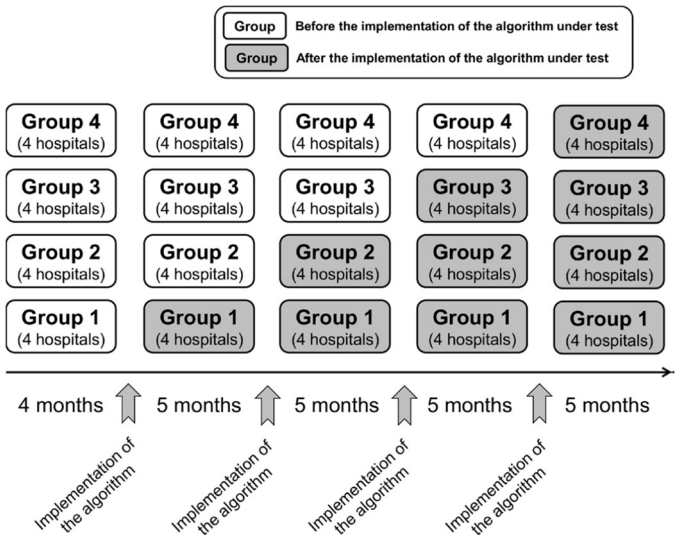

Figure 2: Cluster design.

Each randomisation unit included four centres. White cells represent centres in Phase 1 (SC). Grey cells represent centres in Phase 2 (VHA).

4.4 POINT-OF CARE VHA

Principles of VHA-testing: TEG® and Rotational ROTEM® are two methods of whole blood viscoelastic analysis. The interpretation of the VHA-testing results can help identifying coagulation abnormalities. In cardiac surgery, VHA-testing is of particular interest after the neutralisation of heparin by protamine and the return to normal physiological conditions. VHA-testing is used with a decision algorithm based on validated thresholds [1]. More detailed information is given in supplementary material.

Choice of the VHA device: the latest version of either the ROTEM® (ROTEM Sigma WERFEN) or the TEG® device (TEG6 Haemonetics) was used in the IMOTEC study. It is recognised that their use is easier and that measured parameters closely correlate with those obtained from their predecessor [23,24,25]. The choice of either the ROTEM® or the TEG® device was done by each participating centre before the study began. The type and model of VHA device could not be changed during the study. CHU Nantes opted for the ROTEM® device.

Location of the VHA device: each centre could choose where to locate its own VHA device depending on its local specificities. The VHA device could be located close to the operating room, in the post-operative ICU or even in the laboratory. Location had to be compatible with a similarly short turn-around time. CHU Nantes chose to locate its VHA device close to the operating room. A smart phone application was even developed to get real time results on cell phone and on-site computer allowed real time visualisation of VHA test results.

Professionals involved in VHA testing: the VHA test was performed by the anaesthetic staff or the laboratory team. Its result was interpreted by the anaesthesiologist, who was not forced to comply with the VHA-guided algorithm outcome. Before implementation of the VHA-guided algorithm, clinical and research staff received on-site training. In each centre, maintenance and quality controls of the VHA device was provided by at least two referent persons.

4.5 CPB IN CHU NANTES

Pre-operative patient evaluation: all patients benefitted from a pre-anesthesia consultation. Surgery was performed after proper management of Anticoagulant therapy (e.g. target INR < 1.5 in case of a pre-operative treatment by AVK) and Platelet Aggregation Inhibitor were generally continued.

Monitoring: usual per-operative patient monitoring included five derivations electrocardiograph (ECG), arterial line for invasive systemic arterial pressure, central venous pressure, core body temperature, urine output, pulse oximetry and expired carbon dioxide concentration. There also was a standard monitoring associated with the CPB circuit (continuous Hb rate and Haematocrit level, SvO2, DO2, VO2).

Blood testing: various blood measurements were performed during CPB according to local protocols based on recommended standards of practice. This included sequential measurement of Activated clotting time (ACT Plus Medtronic®) to manage anticoagulation. An ACT over 400 seconds five minutes after initial heparin injection and during CPB was considered good enough to start CPB.

Other considerations: type of CPB circuit priming was not standardised and consisted mostly of crystalloids alone or crystalloids associated with colloids (GeloFusine®). All patients received TXA at the beginning of the procedure, with a total dose of around 35mg.kg^{-1} before and during CPB. Heparin was antagonised by protamine at the end of the procedure on a 1/1 basis, but this was not protocolled. Cell salvage (Cell Saver®) was strongly recommended by the PBM project manager, but it was not systematically used.

4.6 PARTICIPANTS

Patients of 18 years old or older, undergoing cardiac surgery (elective, urgent or emergency surgery) under CPB were enrolled if they required a haemostasis test because of a per-procedural or post-operative significant bleeding as defined by at least one of the following criteria:

During the intra-operative period:

(at least 10 min after protamine reversal of heparin)

- Bleeding considered abnormal according to the consensus opinion of both the surgeon and the anaesthesiologist.
- Bleeding through chest drainage exceeding 50 mL over 10 min or exceeding 1 $mL.kg^{-1}$ over 30 min.
- Bleeding delaying the sternum closure.

During the post-operative period until hospital discharge:

(at least 30 min after ICU admission)

- Bleeding through chest drainage exceeding 50 mL over 10 min or exceeding 1 $mL.kg^{-1}$ over 30 min.
- Bleeding requiring urgent surgical re-exploration.

Exclusion criteria: patients were not included or were excluded in case of previous enrolment in this study, constitutional haemorrhagic disease (haemophilia A or B or von Willebrand disease), need for extracorporeal circulatory support aside from intra-operative CPB, artificial heart, patient's refusal of blood transfusion, pregnancy or adult safeguarding regimen.

Consent: informed consent was obtained from the patient (or his next of kin, if the patient was incapable) by the medical staff, before surgery. Emergency inclusions without consent prior to surgery were possible. In that case, investigators had to collect consent afterwards, from the the patient's next of kin or from the patient himself if he had regained his ability to consent.

4.7 OUTCOMES

4.7.1 PRIMARY OUTCOME

The IMOTEC study: its primary outcome was the estimation of the cost-effectiveness of the VHA-guided algorithm [5].

CHU Nantes preliminary results: the primary outcome in our study of preliminary clinical results was clinicians' compliance with the VHA-guided algorithm. Parameters of the first VHA test of each patient included in Phase 2 (VHA) led to a recommendation for administering haemostatic products or not. This recommendation was benchmarked with the clinicians' decision to administer haemostatic products or not as recommended by the algorithm.

- Clinicians' compliance with the VHA-guided algorithm ("complied") meant that the algorithm's recommendation to administer or not a specific blood product was followed.
- In the opposite way, when clinicians did not follow the algorithm's recommendation (e.g. they administered a specific blood product while the algorithm did not conclude to do so, or they did not while the algorithm concluded to do so), their action was classified as "did not comply".

4.7.2 SECONDARY OUTCOMES

Secondary outcomes mostly corresponded to those of the IMOTEC study [5]. They aimed at assessing the effectiveness of the VHA-guided algorithm during hospitalisation with regard to the following criteria:

- transfusion requirements (RBC, coagulation factors and other blood products).
- postoperative bleeding volume.
- need for surgical re-exploration.
- occurrence of postoperative infection, acute kidney injury (including the need for renal replacement therapy), circulatory failure, thrombotic or embolic complications.
- duration of ICU and in-hospital stay.

Our preliminary analysis of clinical results did not include the 1-year trial follow-up period of the IMOTEC study. In this one-year follow-up period, data such as quality of life and postoperative complications were collected by phone by a clinician or a study nurse at 1, 6 and 12 months after each patient's cardiac surgery.

4.8 STATISTICAL ANALYSIS

Adherence to the treatment: clinicians' compliance with the VHA-guided algorithm was described for the VHA group. In fact, the results of each VHA test were captured on the case report forms (CRFs), which allowed adherence to the treatments to be evaluated.

Clinical data: data collected during Phase 1 (SC) and Phase 2 (VHA) was compared with appropriate statistical tests. A univariate statistical analysis compared clinical data for the two groups. A Mann & Whitney test was performed for continuous data. A X^2 was used for nominal data. Statistical difference meant that $p<0.05$ with an α risk at 5%.

5 RESULTS

5.1 PROGRESS OF THE STUDY

Recruitment period was extended by 2 months and lasted from 1/1/17 till 1/3/19. Over this time period, 198 patients were included (144 in SC, 54 in VHA-group) **(figure 3)**. ROTEM® was available in CHU Nantes starting on 27/6/18. Preliminary results were available for in-hospital data only. Follow-up data was not included.

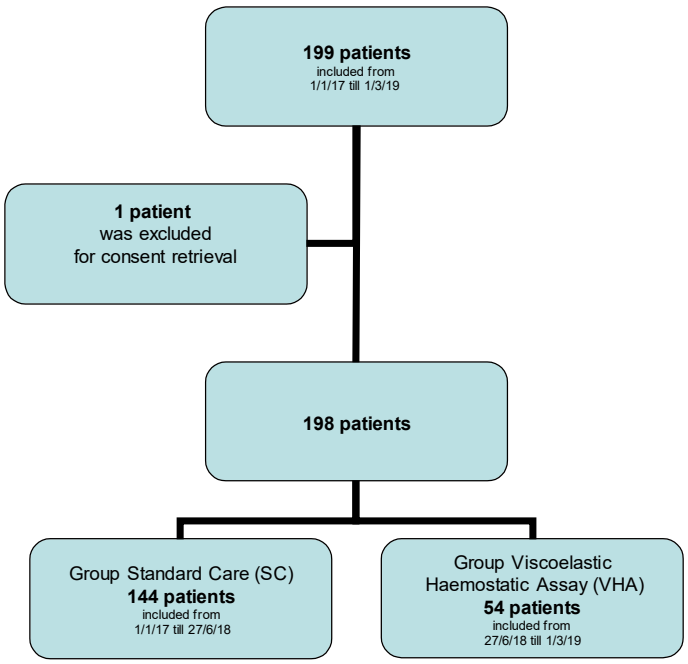

Figure 3: Flow chart.

Patients were split into two groups: SC and VHA

5.2 STUDY POPULATION

Study population was analysed based on existing bleeding risk factors. Predictors of bleeding in cardiac surgery typically include patients' characteristics before surgery such as gender, age, renal failure, body surface index, as well as type of surgery and degree of emergency. Biological haemostatic issues such as pre-operative haemostatic treatment, pre-operative coagulation status, and changes induced by extracorporeal circulation were also considered.

5.2.1 *DEMOGRAPHICS*

Gender and Age (table 1): demographics were comparable between SC group and VHA group except for gender. Statistical difference was found for sex ratio (p=0.015) with more female in VHA group than SC group (37.0% vs 19.4%). No other statistical difference was found. Mean age was 65.9±11.8 years with no statistical difference between the two groups (SC 66.3±11.8 years, VHA 64.7±11.7 years). Over one third of the patients were between 70 and 80 years old (71 patients representing 35.9% of total).

Body Mass Index and Body Surface Index (table 2): 39.4% of the patients had a Body Mass Index (BMI) comprised between 20 and 25 kg/m2 (SC 39.6%, VHA 38.9%) and 29.8% had a Body Surface Index of less than 1.8m2 (SC 29.2%, VHA 31.5%).

ASA class and Euroscore II (table 3): 66.2% of the patients had an ASA score of 3 (SC 67.4%, VHA 63.0%). About one third of the patients had a Euroscore II of less than 1.5% (All 31.3%, SC 31.9%, VHA 29.6%).

	SC		VHA		All		p
Number of patients							
	144	73%	54	27%	198	100%	
Age (years)							
Mean +/- s. deviation	66,3 +/- 11,8		64,7 +/- 11,7		65,9 +/- 11,8		ns
Gender							
Female	**28**	**19,4%**	**20**	**37,0%**	**48**	**24,2%**	**p=0,015**
Male	116	80,6%	34	63,0%	150	75,8%	

Table 1: Mean age ± standard deviation (years) and gender.

	SC		VHA		All	
Number of patients						
	144	73%	54	27%	198	100%
BMI						
<20 kg/m2	6	4,2%	4	7,4%	10	5,1%
<25 kg/m2	57	39,6%	21	38,9%	78	39,4%
<30 kg/m2	54	37,5%	16	29,6%	70	35,4%
<35 kg/m2	20	13,9%	10	18,5%	30	15,2%
>= 35 kg/m2	7	4,9%	3	5,6%	10	5,1%
Body surface index						
<1.8m2	42	29,2%	17	31,5%	59	29,8%
<1.9m2	31	21,5%	9	16,7%	40	20,2%
<2.0m2	21	14,6%	9	16,7%	30	15,2%
<2.10m2	26	18,1%	11	20,4%	37	18,7%
>= 2.10m2	24	16,7%	8	14,8%	32	16,2%

Table 2: Body mass index (BMI) and body surface index.

	SC		VHA		All	
Number of patients						
	144	73%	54	27%	198	100%
ASA class						
1	3	2,1%	0	0,0%	3	1,5%
2	5	3,5%	4	7,4%	9	4,5%
3	97	67,4%	34	63,0%	131	66,2%
4	37	25,7%	12	22,2%	49	24,7%
5	0	0,0%	2	3,7%	2	1,0%
n.a.	2	1,4%	2	3,7%	4	2,0%
Euroscore II						
< 1.5%	46	31,9%	16	29,6%	62	31,3%
< 3.0%	43	29,9%	12	22,2%	55	27,8%
< 6.0%	32	22,2%	14	25,9%	46	23,2%
< 10.0%	11	7,6%	2	3,7%	13	6,6%
>= 10.0%	4	2,8%	5	9,3%	9	4,5%
n.a.	8	5,6%	5	9,3%	13	6,6%

Table 3: ASA class and Euroscore II.

5.2.2 PRE-OPERATIVE BIOLOGICAL STATUS

Anaemic status (table 4 and 5): Quantitative analysis found a statistical difference in pre-operative Hb rate (SC 13.7±1.6 g/dL, VHA 13.2±1.7 g/dL, p=0.037). 25.3% of men had an Hb rate lower than 13g/dL (25.0% SC, 26.5% VHA) and 18.8% of female had an Hb rate lower than 12g/dL (7.1% SC, 35.0% VHA).

Renal failure (table 6 and 7): 45.5% of the patients had a Cockroft Clearance (CC) between 50 and 85 mL/min (SC 47.2%, VHA 40.7%). This glomerular filtration rate category used in Euroscore II corresponded to stages G2 and G3a of the KDIGO classification (respectively: "mildly decreased" and "mildly to moderately decreased" glomerular filtration rate). Quantitative analysis found a statistical difference in pre-operative Creatinine level (SC 90.9±29.7 µmol/L, VHA 89.9±46.9 µmol/L, p=0.026).

	SC	VHA	All	
Hb (g/dL)				
N. of cases	143,0	54,0	197,0	
Minimum	9,0	9,3	9,0	
Maximum	17,0	17,0	17,0	
Median	13,8	13,4	13,8	
Mean	**13,7**	**13,2**	**13,6**	**p=0,037**
Standard deviation	1,6	1,7	1,6	

Table 4: Pre-operative Hb level (g/dL).

	SC		VHA		All	
Number of patients	144		54		198	
Female n=	28	19,4%	20	37,0%	48	24,2%
Hb < 12g/dL	2	7,1%	7	35,0%	9	18,8%
Hb > 12g/dL	26	92,9%	13	65,0%	39	81,3%
Male n=	116	80,6%	34	63,0%	150	75,8%
Hb < 13g/dL	29	25,0%	9	26,5%	38	25,3%
Hb > 13g/dL	87	75,0%	25	73,5%	112	74,7%

Table 5: Anaemic status according to gender (Hb rate g/dL).

	SC		VHA		All	
Number of patients						
	144	73%	54	27%	198	100%
Creatinine Clearance						
n.a.	2	1,4%	1	1,9%	3	1,5%
< 50 mL/min	15	10,4%	5	9,3%	20	10,1%
50 < CC < 85 mL/min	68	47,2%	22	40,7%	90	45,5%
> 85 mL/min	59	41,0%	26	48,1%	85	42,9%

Table 6: Pre-operative Cockcroft-Gault Creatinine Clearance (CC, mL/min).

	SC	VHA	All	
Creatinin level (µmol/L)				
N. of cases	143,0	54,0	197,0	
Minimum	44,3	49,0	44,3	
Maximum	317,0	328,0	328,0	
Median	86,0	78,5	84,0	
Mean	**90,9**	**89,9**	**90,7**	**p=0,026**
Standard deviation	29,7	46,9	40,1	

Table 7: Pre-operative Creatinine level (µmol/L).

5.2.3 SURGERY

Type of surgery: groups were comparable with regards to type of surgery except that there was less aortic surgery in the SC group compared with VHA (SC 22.2%, VHA 46.3%, p=0.001). 28.3% of the patients underwent two surgical acts such as coronary bypass and valve replacement (SC 26.4%, VHA 33.3%) and 17.7% underwent three surgical acts (SC 19.4%, VHA 13.0%).

Degree of emergency (table 8): rescue surgery accounted for 13.6% of all interventions (SC 12.5%, VHA 16.7%).

	SC		VHA		All		p
Number of patients							
	144	73%	54	27%	198	100%	
Degree of emergency							
Rescue	18	12,5%	9	16,7%	27	13,6%	ns
Planned	126	87,5%	45	83,3%	171	86,4%	ns
Aortic surgery							
No	112	77,8%	29	53,7%	141	71,2%	
Yes	**32**	**22,2%**	**25**	**46,3%**	**57**	**28,8%**	**p=0,001**
Number of surgical acts							
Coronary bypass only	15	10,4%	7	13,0%	22	11,1%	ns
1 excl. coronary bypass	63	43,8%	22	40,7%	85	42,9%	ns
2	38	26,4%	18	33,3%	56	28,3%	ns
3	28	19,4%	7	13,0%	35	17,7%	ns

Table 8: Type of surgery: degree of emergency, aortic surgery and number of surgical acts. Statistical test used: Chi-2.

5.2.4 BIOLOGICAL HAEMOSTATIC PARAMETERS

Pre-operative coagulation status (table 9): no statistical difference was found between the two groups. 14.6% of the patients had a PT lower than 70% (SC 13.9%, VHA 16.7%), and 18.7% had a platelet count lower than 150G/L (SC 19.4%, VHA 16.7%).

Pre-operative haemostatic treatment (table 10): no statistical difference was found between the two groups. 31.3% of the patients had no haemostatic treatment (SC 27.8%, VHA 40.7%. There was a higher rate of patients on Platelet Aggregation Inhibitor (PAI) treatment only in the SC group vs VHA group but this was not statistically different (SC 39.6%, VHA 29.6%). 23.2% of the patients were treated with on Anticoagulant therapy (AC) alone (SC 25.0%, VHA 18.5%). 8.6% of the patients were on both PAI and AC (SC 7.6%, VHA 11.1%).

Changes induced by CPB (table 11): Aortic clamping times were also similar with an average of 107±49 min (SC 105±51, VHA 111±46). Average CPB duration was 160±124 min (SC 158±135, VHA 169±92).

Cell salvage (table 12): 42.4% of the patients benefited from cell salvage with a statistical difference being found between the groups (SC 38.2%, VHA 53.7%, p=0.049).

	SC		VHA		All	
Number of patients						
	144	73%	54	100%	198	
PT						
<70%	20	13,9%	9	16,7%	29	14,6%
>= 70%	120	83,3%	43	79,6%	163	82,3%
n.a.	4	2,8%	2	3,7%	6	3,0%
Hb						
< 12 g/dL	18	12,5%	9	16,7%	27	13,6%
>= 12 g/dL	125	86,8%	43	79,6%	168	84,8%
n.a.	1	0,7%	2	3,7%	3	1,5%
Platelet count						
< 150 G/L	28	19,4%	9	16,7%	37	18,7%
>= 150 G/L	115	79,9%	45	83,3%	160	80,8%
n.a.	1	0,7%	0	0,0%	1	0,5%

Table 9: Pre-operative coagulation status: PT, Hb rate and platelet count.

	SC		VHA		All	
Number of patients						
	144	73%	54	27%	198	
Preoperative haemostatic treatment						
No haemostatic treatment	40	27,8%	22	40,7%	62	31,3%
PAI only	57	39,6%	16	29,6%	73	36,9%
AC only	36	25,0%	10	18,5%	46	23,2%
PAI and AC	11	7,6%	6	11,1%	17	8,6%

Table 10: Pre-operative haemostatic treatment: PAI and AC.

	SC	VHA	All	
N. of patients	144	54	198	
Aortic clamping time (min)				
Minimum	27	20	20	
Maximum	421	240	421	
Mean	**105**	**111**	**107**	**ns**
Standard deviation	51	46	49	
CPB duration (min)				
Minimum	35	57	35	
Maximum	1503	444	1503	
Mean	**158**	**169**	**160**	**ns**
Standard deviation	135	92	124	

Table 11: CPB parameters: aortic clamping times and CPB duration (minutes).

	SC		VHA		All		p
N. of patients	144	73%	54	27%	198		
Cell Saver®							
No	89	61,8%	25	46,3%	114	57,6%	
Yes	55	38,2%	29	53,7%	84	42,4%	**p=0,049**

Table 12: Use of cell salvage during CPB.

5.2.5 *INCLUSION CRITERIA*

There was a higher proportion of patients' inclusions in the operating room in the VHA group (SC 59%, VHA 81% p=0.003). Amongst all inclusion criteria, significant statistical difference was found for bleeding delaying the sternum closure (SC 29.2%, VHA 68.5%, p<10-4) **(table 13)**.

	SC		VHA		All		p	test
Number of patients								
	144	73%	54	27%	198	100%		
Bleeding delaying the sternal closure								
No	102	70,8%	17	31,5%	119	60,1%		
Yes	**42**	**29,2%**	**37**	**68,5%**	**79**	**39,9%**	**p<10-4**	Chi-2

Table 13: Inclusion criteria: bleeding delaying the sternal closure.

5.3 OUTCOMES

Results showed that more haemostatic products were used in the VHA group than recommended by the algorithm, suggesting that clinicians did not totally comply with the algorithm. However, there was less administration of blood products in the VHA group vs SC.

5.3.1 *PRIMARY OUTCOME*

VHA-guided algorithm conclusion: the algorithm called for additional protamine injection in 7.4% of the cases, fibrinogen 3.7%, and TXA 5.6%. Platelet transfusion was never recommended by the VHA-guided algorithm. PCC or FFP were recommended in 7.4% and 20.4% of the cases respectively.

Clinicians' decision: clinicians actually administered additional protamine in 72.2% of the cases, fibrinogen 48.1%, and TXA 3.7%. Platelet transfusion was used in 46.3% of the cases. PCC was done in 27.8% of the cases and FFP transfusion 57.4%.

Clinicians' compliance (table 14 and figure 4): results showed that clinicians did not totally comply with the VHA-guided algorithm conclusions. Compliance rate was 25.9% for additional protamine and 50% or over for other products (platelets 53.7%, fibrinogen 55.6%, FFP 62.9%, PCC 79.6%, TXA 98.1%).

	Protamine	Platelets	Fibrinogen	FFP	PCC	TXA
VHA-guided algorithm conclusion						
DO	4	0	2	11	4	3
	7,4%	0,0%	3,7%	20,4%	7,4%	5,6%
DON'T	50	54	52	43	50	51
	92,6%	100,0%	96,3%	79,6%	92,6%	94,4%
Clinicians' decision						
DONE	39	25	26	31	15	2
	72,2%	46,3%	48,1%	57,4%	27,8%	3,7%
NOT DONE	15	29	28	23	39	52
	27,8%	53,7%	51,9%	42,6%	72,2%	96,3%
Clinicians' compliance						
COMPLIED	14	29	30	34	43	53
	25,9%	53,7%	55,6%	62,9%	79,6%	98,1%
DID NOT COMPLY	40	25	24	20	11	1
	74,1%	46,3%	44,4%	37,1%	20,4%	1,9%

Table 14: VHA-guided algorithm's recommendation, clinicians' action and compliance with algorithm.

"COMPLIED" meant VHA-guided algorithm recommended to administer a specific blood product ("DO") and the clinician actually did ("DONE") or the VHA-guided algorithm recommended not to administer a specific blood product ("DON'T") and the clinician actually did not ("NOT DONE").
"DID NOT COMPLY" meant VHA-guided algorithm recommended to administer a specific blood product ("DON'T") and the clinician actually did ("DONE") or the VHA-guided algorithm recommended not to administer a specific blood product ("DON'T") and the clinician actually did ("DONE").

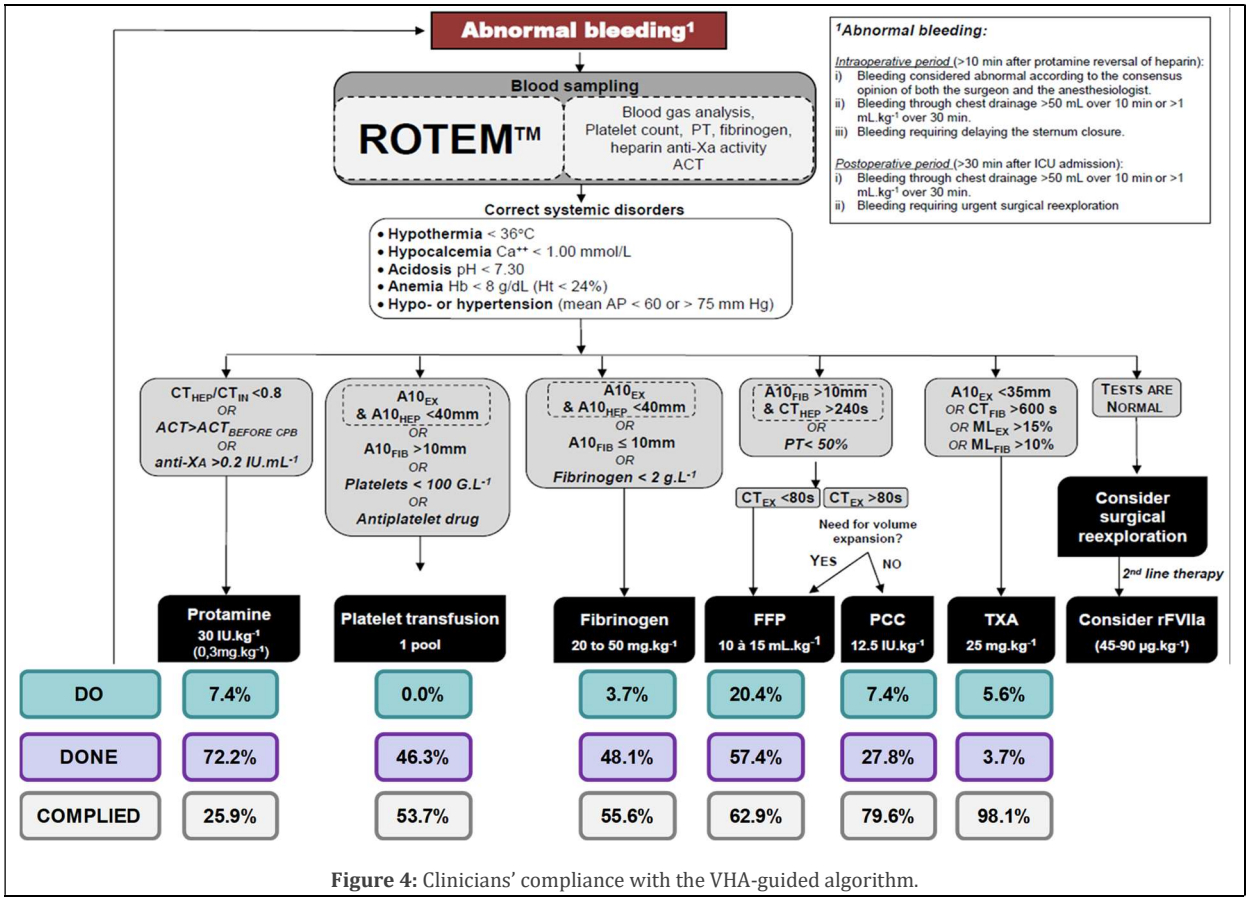

Figure 4: Clinicians' compliance with the VHA-guided algorithm.

5.3.2 *SECONDARY OUTCOMES: TRANSFUSION REQUIREMENTS*

Statistical difference was found for the proportion of transfused patient (97% in SC vs 83% in VHA, p=0.001). **(Figure 5)**

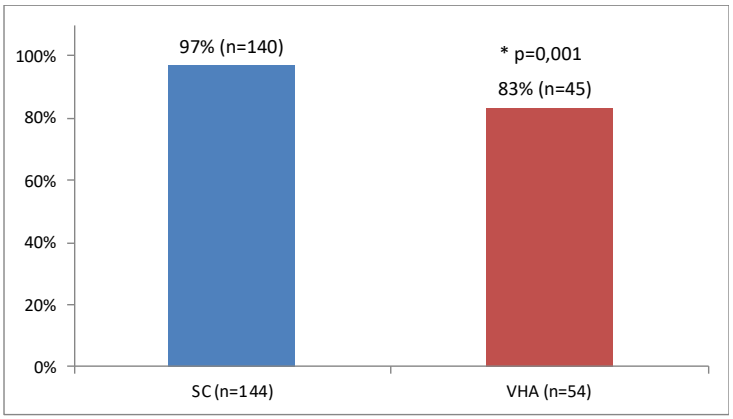

Figure 5: Proportion of transfused patients in SC group and VHA group (RBC, FFP and platelets).

Transfusion requirements by product type (all locations):

- **RBC (table 15):** an average of 5.6 units per patient was transfused during hospital stay in the SC group vs 4.9 in the VHA group.
- **FFP (table 16):** an average 5.2 units per patient was transfused during hospital stay in the SC group vs 4.6 in the VHA group.
- **Platelets (table 17):** an average 1.8 units per patient was transfused during hospital stay in the SC group vs 1.8 in the VHA group.
- **Other haemostatic products (table 18):** 26% of patients received PCC, 39% fibrinogen, 16% TXA, 81% protamine re-injection, 5% rVIIa.

RBC	SC	VHA	All	
1. Operating room				
Number of units	208	105	313	
Average per patient	1,4 ± 2,1	1,9 ± 4,0	1,6 ± 2,7	ns
2. ICU				
Number of units	221	54	275	
Average per patient	1,5 ± 2,1	1,0 ± 1,9	1,4 ± 1,9	p=0,018
3. Hospitalisation unit				
Number of units	380	105	485	
Average per patient	2,6 ± 6,8	1,9 ± 3,4	2,4 ± 6,0	ns
Total : hospital stay				
Number of units	809	264	1073	
Average per patient	5,6 ± 7,5	4,9 ± 6,8	5,4 ± 7,3	ns

Table 15: Number of units, average number of units, and standard deviation of RBC transfused per patient in the three different locations (Operating Room, ICU and Hospitalisation Unit).

FFP	SC	VHA	All	
1. Operating room				
Number of units	358	167	525	
Average per patient	2,5 ± 3,3	3,1 ± 5,0	2,6 ± 3,8	ns
2. ICU				
Number of units	306	55	361	
Average per patient	2,1 ± 2,6	1,0 ± 2,4	1,8 ± 2,6	p<10-4
3. Hospitalisation unit				
Number of units	83	25	108	
Average per patient	0,6 ± 2,2	0,5 ± 1,6	0,5 ± 2,0	ns
Total : hospital stay				
Number of units	747	247	994	
Average per patient	5,2 ± 4,6	4,6 ± 6,6	5,0 ± 5,2	ns

Table 16: Number of units, average number of units, and standard deviation of FFP transfused per patient in the three different locations (Operating Room, ICU and Hospitalisation Unit).

Platelets	SC	VHA	All	
1. Operating room				
Number of units	129	57	186	
Average per patient	0,9 ± 1,1	1,1 ± 1,6	0,9 ± 1,3	ns
2. ICU				
Number of units	84	15	99	
Average per patient	0,6 ± 0,8	0,3 ± 0,6	0,5 ± 0,7	p=0,005
3. Hospitalisation unit				
Number of units	48	25	73	
Average per patient	0,3 ± 1,2	0,5 ± 1,6	0,4 ± 1,3	ns
Total : hospital stay				
Number of units	261	97	358	
Average per patient	1,8 ± 1,9	1,8 ± 3,1	1,8 ± 2,3	ns

Table 17: Number of units, average number of units, and standard deviation of Platelets transfused per patient in the three different locations (Operating Room, ICU and Hospitalisation Unit).

Other haemostatic products	SC		VHA		All		
N. of patients	154		44		198		
PCC							
No	109	76%	38	70%	147	74%	ns
Yes	35	24%	16	30%	51	26%	ns
Fibrinogen							
No	93	65%	27	50%	120	61%	ns
Yes	51	35%	27	50%	78	39%	ns
TXA							
No	115	80%	51	94%	166	84%	ns
Yes	29	20%	3	6%	32	16%	ns
Protamine re-injection							
No	28	19%	10	19%	38	19%	ns
Yes	116	81%	44	81%	160	81%	ns
rVIIa							
No	137	95%	51	94%	188	95%	ns
Yes	7	5%	3	6%	10	5%	ns

Table 18: Number of patients who were administered PCC, Fibrinogen, TXA, additional protamine and rVIIa during total hospital stay.

Transfusion requirements in the ICU only (table 19): we found statistical difference for the transfusion of RBC (SC 1.5±2.1 unit, VHA 1.0±1.9 unit, p=0.018) as well as FFP (SC 2.1±2.6 unit, VHA 1.0±2.4 unit, p<10-4) and platelets (SC 0.6±0.8 unit, VHA 0.3±0.6 unit, p=0.005).

	SC	VHA	All	
RBC				
N. of cases	144,0	54,0	198,0	
Minimum	0,0	0,0	0,0	
Maximum	11,0	9,0	11,0	
Median	1,0	0,0	0,0	
Mean	**1,5**	**1,0**	**1,4**	**p=0,018**
Standard deviation	2,1	1,9	1,9	
FFP				
N. of cases	144,0	54,0	198,0	
Minimum	0,0	0,0	0,0	
Maximum	14,0	14,0	14,0	
Median	2,0	0,0	0,0	
Mean	**2,1**	**1,0**	**1,8**	**p<10-4**
Standard deviation	2,6	2,4	2,6	
Platelets				
N. of cases	144,0	54,0	198,0	
Minimum	0,0	0,0	0,0	
Maximum	4,0	2,0	4,0	
Median	0,0	0,0	0,0	
Mean	**0,6**	**0,3**	**0,5**	**p=0,005**
Standard deviation	0,8	0,6	0,7	

Table 19: Number of units, average number of units, and standard deviation of RBC, FFP and Platelets transfused per patient in the Intensive Care Unit.

Transfusion requirements by location (all products):

- **Operating room (table 20):** no statistical difference was found except for fibrinogen. More fibrinogen was administered in the VHA group (SC 19.4%, VHA 44.4%, p=0.001).
- **ICU (table 21):** statistical difference was found for RBC, FFP, platelets, PCC and additional protamine. More RBC units were transfused in the SC group (SC 52.1%, VHA 27.8%, p=0.002), more FFP were transfused in the SC group (SC 54.9%, VHA 22.2%, p<10-4), more platelets were transfused in the SC group (SC 43.1%, VHA 20.4%, p=0.003), more PCC was administered in the SC group (SC 9.0%, VHA 0.0%, p=0.021), more protamine was administered in the SC group (SC 54.9%, VHA 31.5%, p=0.004).
- **Hospitalisation unit (table 22):** no statistical difference was found for blood products and transfusion.

	SC		VHA		All		Chi-2
	144	73%	54	27%	198	100%	
All products							
No	31	21,5%	6	11,1%	37	18,7%	
Yes	113	78,5%	48	88,9%	161	81,3%	ns
RBC							
No	70	48,6%	30	55,6%	100	50,5%	
Yes	74	51,4%	24	44,4%	98	49,5%	ns
FFP							
No	63	43,8%	26	48,1%	89	44,9%	
Yes	81	56,3%	28	51,9%	109	55,1%	ns
Platelets							
No	66	45,8%	28	51,9%	94	47,5%	
Yes	79	54,9%	26	48,1%	105	53,0%	ns
Fibrinogen							
No	116	80,6%	30	55,6%	146	73,7%	
Yes	**28**	**19,4%**	**24**	**44,4%**	**52**	**26,3%**	**p=0,001**
TXA							
No	134	93,1%	53	98,1%	187	94,4%	
Yes	10	6,9%	1	1,9%	11	5,6%	ns
PCC							
No	120	83,3%	38	70,4%	158	79,8%	
Yes	24	16,7%	16	29,6%	40	20,2%	ns
Protamine sulfate supplement							
No	87	60,4%	21	38,9%	108	54,5%	
Yes	57	39,6%	33	61,1%	90	45,5%	ns
rVIIa							
No	139	96,5%	51	94,4%	190	96,0%	
Yes	5	3,5%	3	5,6%	8	4,0%	ns

Table 20: Haemostatic and blood products administered in the operating room: all type of products (RBC, FFP, Platelets, fibrinogen, TXA, PCC, protamine, rVIIa)..

	SC		VHA		All		
	144	73%	54	27%	198	100%	
All products							
No	37	25,7%	31	57,4%	68	34,3%	
Yes	107	74,3%	23	42,6%	130	65,7%	
RBC							
No	69	47,9%	39	72,2%	108	54,5%	
Yes	**75**	**52,1%**	**15**	**27,8%**	**90**	**45,5%**	**p=0,002**
FFP							
No	65	45,1%	42	77,8%	107	54,0%	
Yes	**79**	**54,9%**	**12**	**22,2%**	**91**	**46,0%**	**p<10-4**
Platelets							
No	82	56,9%	43	79,6%	125	63,1%	
Yes	**62**	**43,1%**	**11**	**20,4%**	**73**	**36,9%**	**p=0,003**
Fibrinogen							
No	116	80,6%	49	90,7%	165	83,3%	
Yes	28	19,4%	5	9,3%	33	16,7%	ns
TXA							
No	127	88,2%	52	96,3%	179	90,4%	
Yes	17	11,8%	2	3,7%	19	9,6%	ns
PCC							
No	131	91,0%	54	100,0%	185	93,4%	
Yes	**13**	**9,0%**	**0**	**0,0%**	**13**	**6,6%**	**p=0,021**
Protamine sulfate supplement							
No	65	45,1%	37	68,5%	102	51,5%	
Yes	**79**	**54,9%**	**17**	**31,5%**	**96**	**48,5%**	**p=0,004**
rVIIa							
No	142	98,6%	53	98,1%	195	98,5%	
Yes	2	1,4%	1	1,9%	3	1,5%	ns

Table 21: Haemostatic and blood products administered in the ICU: all type of products (RBC, FFP, Platelets, fibrinogen, TXA, PCC, protamine, rVIIa).

	SC		VHA		All		
	144	73%	54	27%	198	100%	
All products							
No	62	43,1%	31	57,4%	93	47,0%	
Yes	82	56,9%	23	42,6%	105	53,0%	
RBC							
No	66	45,8%	31	57,4%	97	49,0%	
Yes	78	54,2%	23	42,6%	101	51,0%	ns
FFP							
No	128	88,9%	49	90,7%	177	89,4%	
Yes	16	11,1%	5	9,3%	21	10,6%	ns
Platelets							
No	126	87,5%	47	87,0%	173	87,4%	
Yes	18	12,5%	7	13,0%	25	12,6%	ns
Fibrinogen							
No	144	100,0%	54	100,0%	198	100,0%	
Yes	0	0,0%	0	0,0%	0	0,0%	ns
TXA							
No	141	97,9%	54	100,0%	195	98,5%	
Yes	3	2,1%	0	0,0%	3	1,5%	ns
PCC							
No	142	98,6%	54	100,0%	196	99,0%	
Yes	2	1,4%	0	0,0%	2	1,0%	ns
Protamine sulfate supplement							
No	138	95,8%	54	100,0%	192	97,0%	
Yes	6	4,2%	0	0,0%	6	3,0%	ns
rVIIa							
No	144	100,0%	54	100,0%	198	100,0%	
Yes	0	0,0%	0	0,0%	0	0,0%	ns

Table 22: Haemostatic and blood products administered in the Hospitalisation unit: all type of products (RBC, FFP, Platelets, fibrinogen, TXA, PCC, protamine, rVIIa).

5.3.3 SECONDARY OUTCOMES: COMPLICATIONS

Post-operative bleeding volume (table 23 and figure 6): a significant statistical difference was found in bleeding volume at H12, D+1 and D+2 after intervention (H12 : SC 953.6±491.2mL, VHA 716.2±666.9mL, p<10-4 ; D+1 : SC 1115.4±576.6mL, VHA 975.6±869.9mL, p=0.005 ; D+1 : SC 1470.0±742.3mL, VHA 1293.8±977.3mL, p=0.011).

Need for surgical re-exploration (table 24): 48.5% of the patients needed re-intervention (SC 51.4%, VHA 40.7%) and no statistical difference was found between the two groups.

Other complications excluding death (table 25): the occurrence of circulatory failure, acute kidney injury (including the need for renal replacement therapy), post-operative infection, thrombotic or embolic complications was not found to be statistically different between the two groups.

Duration of ICU stay (table 26): no statistical difference was found. The average ICU stay was 6.7±11.2 days (SC 6.0±9.7 days, VHA 8.4±14.5 days).

Death during in-hospital stay (table 27): no statistical difference was found between the two groups. Thirteen patients died in total, thereof 9 in the SC group and 4 in the VHA group (SC 6.3%, VHA 7.4%).

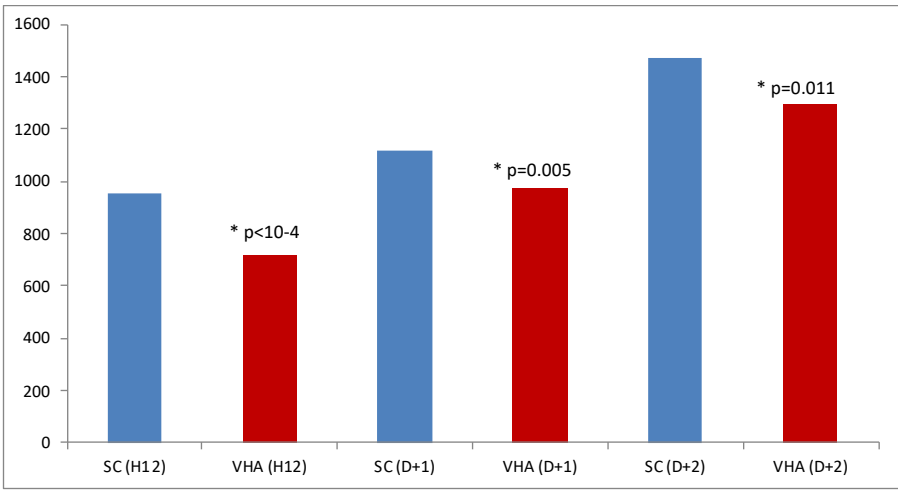

Figure 6: Complications: post-operative bleeding volume (mL) after 12 hours (H12), day 1 (D+1) and day 2 (D+2).

	SC	VHA	All	
Bleeding volume H12				
N. of cases	144,0	52,0	196,0	
Minimum	160,0	150,0	150,0	
Maximum	2630,0	3840,0	3840,0	
Median	905,0	485,0	825,0	
Mean	**953,6**	**716,2**	**890,6**	**p<10-4**
Standard deviation	491,2	666,9	560,9	
Bleeding volume D+1				
N. of cases	143,0	52,0	195,0	
Minimum	170,0	190,0	170,0	
Maximum	2950,0	5280,0	5280,0	
Median	1040,0	690,0	980,0	
Mean	**1115,4**	**975,6**	**1078,1**	**p=0,005**
Standard deviation	576,6	869,9	724,2	
Bleeding volume D+2				
N. of cases	140,0	48,0	188,0	
Minimum	140,0	250,0	140,0	
Maximum	4280,0	5840,0	5840,0	
Median	1332,5	990,0	1260,0	
Mean	**1470,0**	**1293,8**	**1425,0**	**p=0,011**
Standard deviation	742,3	977,3	818,8	

Table 23: Complications: post-operative bleeding volume (mL) after 12 hours (H12), day 1 (D+1) and day 2 (D+2): average volume, minimum, maximum and standard deviation.

).

	SC		VHA		All	
	144	73%	54	27%	198	
Reintervention						
No	69	47,9%	32	59,3%	101	51,0%
Yes	74	51,4%	22	40,7%	96	48,5%

Table 24: Complications: need for surgical re-exploration.

	SC		VHA		All	
	144	73%	54	27%	198	
Circulatory failure						
No	109	75,7%	45	83,3%	154	77,8%
Yes	35	24,3%	9	16,7%	44	22,2%
Dialysis						
No	126	87,5%	44	81,5%	170	85,9%
Yes	18	12,5%	10	18,5%	28	14,1%
Infection						
No	108	75,0%	39	72,2%	147	74,2%
Yes	35	24,3%	15	27,8%	50	25,3%
Thrombotic event						
No	136	94,4%	49	90,7%	185	93,4%
Yes	7	4,9%	5	9,3%	12	6,1%

Table 25: Other complications: circulatory failure, dialysis, infection, thrombotic event.

	SC		VHA		All	
	144	73%	54	27%	198	
ICU stay						
Days	6,0		8,4		6,7	
+/- days	9,7		14,5		11,2	

Table 26: Length of ICU stay (days).

	SC		VHA		All	
	144	73%	54	27%	198	
Death						
No	135	93,8%	50	92,6%	185	93,4%
Yes	9	6,3%	4	7,4%	13	6,6%

Table 27: In-hospital mortality.

6 DISCUSSION

6.1 STUDY LIMITS

Small group: the IMOTEC study included 1,098 patients. Patients enrolled by CHU Nantes added to a total of 198, thereof 54 were included in Phase 2 (VHA group). This relatively small sample size might have led to ignore some differences between the two groups.

Selection bias: the intervention was not blinded to the clinicians. As a result, this study faced a selection bias. Such bias is inherent to all cluster trials, with individual recruitment and without blinding of the intervention.

Confounding effect of time: more clusters were exposed to the intervention towards the end of the study than in its early stages. An underlying temporal trend might have been overlooked.

6.2 COMPARABILITY BETWEEN THE TWO GROUPS

6.2.1 PRE-OPERATIVE DATA

Pre-operative data for the VHA and the SC group were widely comparable in terms of demographics, biological status, surgery type and haemostatic parameters.

Demographics: population mean age was 66±12 years, 66% had an ASA score of 3 and 59% had a Euroscore II of less than 3%. We found statistical difference for gender with more female in the VHA group compared to the SC group (37.0% vs 19.4%, p=0.015). Female gender is usually associated with a higher risk of bleeding in cardiothoracic surgery [26,27].

Biological status: quantitative analysis found a statistical difference in pre-operative Creatinine level (SC 90.9±29.7 µmol/L, VHA 89.9±46.9 µmol/L, p=0.026). Such difference in pre-operative Creatinine levels was not clinically relevant. Other data was comparable between the two groups. Quantitative analysis also found a statistical difference in pre-operative Hb rate (SC 13.7±1.6 g/dL, VHA 13.2±1.7 g/dL, p=0.037). In

the same way, such difference was not clinically relevant. If it was, it was noted that a lower Hb rate is usually associated with a higher risk of bleeding [26,27,28]. The lower Hb rate in the VHA group might be linked to gender (37.0% female in the VHA group vs. 19.4% in the SC group).

Type of surgery: there was less thoracic aortic surgery in the SC group compared with VHA (SC 22.2%, VHA 46.3%, p=0.001). Aortic surgery is usually associated with higher risk of bleeding [29].

Haemostatic parameters: the two groups were comparable with regards to pre-operative PT level or platelet count. No statistical difference was found either with regards to pre-operative haemostatic treatments.

6.2.2 INTRA-OPERATIVE DATA

Changes induced by CPB: CPB procedure was homogeneous across the two groups and our statistical analysis found no difference in per-intervention parameters such as ACT levels, CPB duration or aortic clamping.

Inclusion criteria: there was a higher proportion of patient inclusions in the operating room in the VHA group (SC 59%, VHA 81% p=0.003). In other words, after implementation of the VHA-device, there were comparatively less inclusions in the post-operative period. There was no straight-forward explanation other than ICU clinicians' inclination to change their practices by using the VHA-device in its early phase of implementation. This might have been driven by the location chosen for the VHA-device. In fact, ICU clinicians' bleeding management using the VHA-device required one person to leave the unit, go to the operating room and perform the test, which was probably considered as non-practical. We also noted that bleeding delaying the sternum closure amounted for about two thirds of patient inclusions in the VHA group (SC 29.2%, VHA 68.5%, p<10-4). This might be explained by the fact that intra-operative inclusions, which were higher compared to post-operative inclusions, were less likely to be done according to the chest drainage criteria.

6.3 PRIMARY OUTCOME: CLINICIANS' COMPLIANCE WITH THE ALGORITHM

More of every product was actually administered by clinicians compared with the VHA-guided algorithm recommendation, meaning compliance rate appeared to be low except for PCC (79.6%) and TXA (98.1%). The VHA-guided algorithm scarcely recommended to re-inject those products, and these were effectively scarcely used by clinicians in their bleeding management.

Compliance rate was 25.9% for protamine re-injection: 72.2% of the patients received additional protamine in the VHA group whereas the VHA-guided algorithm recommended to do so in just about 7.4% of the cases. Protamine is readily and easily available in the operating room and the ICU. Clinicians might have taken the decision to re-inject protamine without even waiting for the first VHA-guided algorithm results.

Compliance rate was 50% or over for other products: platelets 53.7% (never recommended, done in 46.3% of the cases), fibrinogen 55.6% (recommended 3.7%, done 48.1%), FFP 62.9% (recommended 20.4%, done 57.4%).

There were probably two main reasons to explain these compliance rates: first, the need to act as quickly as possible, and then the complexity of changing practice.

The need to act quickly: when severe bleeding occurs, clinicians may be tempted to act before even getting the first results of biological tests, even if they are obtained in less than 10 minutes. This might have led to order and then administer blood products in excess compared to the VHA-guided algorithm recommendation. CHU Nantes also implemented in 2014 a so-called "FAST" procedure which enables clinicians to get biological results such as PT or platelet count in a timely fashion. The "FAST" procedure and its results interpretation by the clinician was part of SC and may have competed with the newly-proposed VHA-device.

The complexity of changing practices: even with clinicians' awareness of the potential to apply improved practice, numerous barriers needed to be overcome. Despite the user-friendly VHA-device implemented in CHU Nantes, a training period was still necessary for instance. Key successful components of changing practices were well-described in a recent case study analysis of the implementation of a bleeding management quality initiative in an Australian cardiac surgery unit[30]. Clinical leadership

and an appropriately skilled project manager were identified as being key components for driving changes. CHU Nantes fulfilled this requirement: in addition to being main investigator for the IMOTEC study, there was a multidisciplinary dedicated team for the project. On top of this and as part of Group 4, CHU Nantes benefited from the VHA-device for about 8 months from 27/6/2018 until 1/3/2019. Clinicians were therefore only at the beginning of the learning curve for this new procedure.

6.4 SECONDARY OUTCOMES: LESS TRANSFUSION

RBC, FFP and platelets: Statistical difference was found for the proportion of transfused patient (SC 97%, VHA 83%, p=0.001). Overall, there seemed to be less administration of blood products in the VHA group vs SC: 4.9 RBC units vs 5.6, 4.6 FFP units vs 5.2, and 1.8 Platelet vs 1.8. This was consistent with previous studies, although we noted that cell salvage was more frequent in the VHA group (SC 38.2%, VHA 53.7%, p=0.049). This tendency was statistically significant in the ICU for all three products (RBC: SC 52%, vs VHA 28%, p=0.002 ; FFP: SC 55%, VHA 22%, p=0.0001 ; Platelet : SC 43%, VHA 20%, p=0.003).

A recent meta-analysis by Deppe et al. in 2016 summarised 17 studies published in cardiac surgery. This study included 8,332 patients and provided a comparison between a VHA-guided group and a SC group (ROTEM® 78.3%, SC 21.7% of patients). A reduction in transfusion support was observed in the VHA-guided arm (OR=0.63, 95% CI 0.56–0.71). This reduction mainly concerned the administration of FFP (OR=0.31, 95% CI 0.13–0.74) [31].

These results were consistent with another meta-analysis published by Bolliger et al. in 2013 (12 studies were analysed, thereof 7 RCTs) [32] as well as the Wikkelsø et al. study published in 2016 (17 studies, 1,493 patients, 96% of which in cardiac surgery, equal distribution between TEG® and ROTEM®). The Wikkelsø et al. analysis showed a significant reduction in transfusion of RBC (RR: 0.86, 95% CI 0.79–0.94), FFP (RR: 0.57, 95% CI 0.33–0,96) and Platelet (RR: 0.73; 95% CI: 0.60–0.88) with the use of VHA [33].

A RCT by Karkouti et al. in 2016 (12 Canadian centres, 7,402 patients) was conducted in two phases: SC and then use of ROTEM® with an algorithm. The use of ROTEM® was

associated with a reduction in transfusion of RBC (RR: 0.91, 95% CI: 0.85–0.98, P=0.02), Platelet (RR: 0.77; 95% CI: 0.68–0.87, P<0.001), but not of FFP [4].

Other coagulation factors and products: a statistical difference was found for fibrinogen administration in the operating room (SC 19%, VHA 44%, p=0.002). Over-administration of fibrinogen in the VHA group was consistent with the Bolliger et al. findings in 2013 (OR=1.56, 95% CI 1.29–1.87) [32]. This might be due to a focus on A10 FIBTEM by clinicians without taking into account A10 EXTEM.

6.5 SECONDARY OUTCOMES: LESS COMPLICATIONS

Less bleeding: the VHA-guided algorithm was associated with less bleeding in the post-operative period. In fact, a statistical significant difference was found in bleeding volume at H12, D+1 and D+2 after intervention (H12 : SC 953.6±491.2mL, VHA 716.2±666.9mL, p<10-4 ; D+1 : SC 1115.4±576.6mL, VHA 975.6±869.9mL, p=0.005 ; D+1 : SC 1470.0±742.3mL, VHA 1293.8±977.3mL, p=0.011). This was consistent with the Karkouti et al. study in which ROTEM® monitoring was associated with a significant reduction in major bleeding [4].

Other complications during hospital stay: no statistical difference was found between the two groups with regards to length of ICU stay, length of in-hospital stay, rate of surgical re-exploration, the occurrence of circulatory failure, acute kidney injury (including the need for renal replacement therapy), post-operative infection, thrombotic or embolic complications.

Our relatively small sample might have not allowed finding a statistical difference as less transfusion is expected to be associated with less morbidity. In the 2016 Deppe et al. meta-analysis [31], a number of clinical outcomes were significantly improved in the VHA-group: reduction in thromboembolic events, re-exploration due to post-operative bleeding, and incidence of acute kidney injury. However, ROTEM® monitoring had no impact on complications or length of hospitalisation in the Karkouti et al. study [4].

Mortality: no statistical difference was found between the two groups for in-hospital mortality. This might be due to the small sample size. In fact, the Deppe et al. meta-analysis demonstrated a significant reduction in mortality in the VHA group (RR: 0.52,

95% CI 0.28–0.95). The reduction in mortality was still significant when VHA-guided algorithms were compared to standard laboratory testing guided algorithms (RR: 0.36, 95% CI 0.16–0.84). The Karkouti et al. study [4] found no difference in mortality using ROTEM®.

Impact of the "FAST" procedure: in the Weber et al. 2012 study [20], POC testing reduced patient exposure to allogenic blood products and provided significant benefits with respect to clinical outcomes: there was significant difference in RBC transfusion rate in the conventional compared with the POC group [5 (4;9) versus 3 (2;6) units [median (25 and 75 percentile)], P<0.001]. The "FAST" procedure, which is part of SC in CHU Nantes, allowed clinicians to obtain conventional haemostatic parameters almost as quickly as the ROTEM® device. This could have diminished the chances to find statistical differences between the two groups.

6.6 CONCLUSION

Clinicians' action was globally in line with the VHA-guided algorithm's recommendation. However, more haemostatic products were used than actually recommended except for TXA supplemental administration. Compliance rates ranged from 25.9% to 98.1%, suggesting a lack of confidence in the VHA-device and the VHA-guided algorithm.

Although clinicians did not fully comply with the algorithm, there seemed to be less transfusion of blood products in the VHA group with a statistical difference even being found in the ICU.

VHA-guided algorithm might be of interest for reducing transfusion needs when managing bleeding during cardiac surgery but it is difficult to distinguish the impact of VHA-guided algorithm from that of an overall trend to rationalise the indication for transfusion. Various PBM initiatives are being carried out in CHU Nantes such as increasing use of cell salvage (Cell Saver®) or dedicated pre-operative PBM consultation. All are coordinated by a dedicated PBM project manager. These initiatives participate to clinicians' increased awareness of the need for transfusion savings.

Preliminary results of the IMOTEC study suggest that the indication for transfusion based on point-of-care VHA monitoring and a defined algorithm is associated with lower transfusion. An analysis of the complete IMOTEC study data remains necessary to assess the efficiency of a VHA-guided management as part of PBM in cardiac surgery.

7 SUPPLEMENTARY MATERIAL

7.1 TEG® AND ROTEM® PRINCIPLES

Thromboelastography (TEG®) and Rotational Thromboelastometry (ROTEM®) are two methods of whole blood viscoelastic analysis. In both TEG® and ROTEM®, a sample of whole blood is placed into a small cup and a pin is suspended within the sample. The sample is rotated and as the blood begins to clot, the increase in viscosity is relayed through sensors on the pin that are graphically transmitted [34].

- In a TEG® analysis, whole blood is placed within a cup that is rotated gently while a thin wire tension probe is suspended within the sample.
- ROTEM® **(figure 7)** is very similar to TEG®, but instead of the cup being spun within the cuvette, it is the sensor probe itself that rotates within the sample. This method generates less vibration and mechanical disturbances.

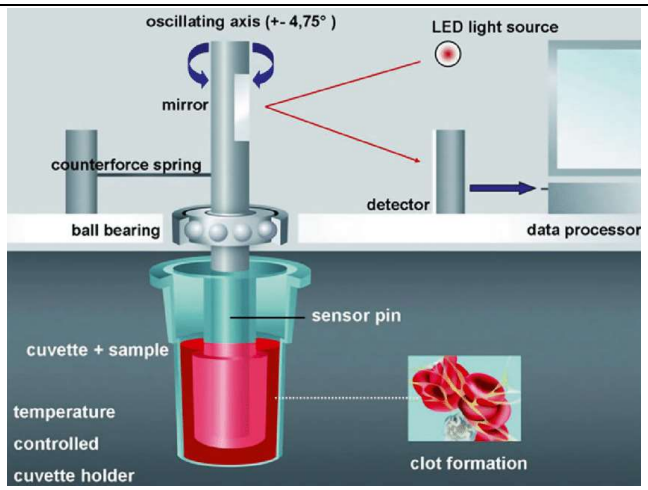

Figure 7: Measuring principle of ROTEM.

Courtesy of Klaus Görlinger, Tem International

7.2 TEG® AND ROTEM® GRAPHICS ANALYSIS

The graphics **(figure 8)** which are transmitted can be measured. Their interpretation can help identifying coagulation abnormalities.

- **In the early phase** of the clotting cascade, the blood sample is in liquid form and there is no resistance to the suspended pin during rotation. This is represented as a flat line.
- **Clot formation** begins once thrombin levels are high enough, leading to an increase in amplitude. Once clot formation has started, there is a kinetic action of platelet and fibrin interaction. As a result, the clot gains strength until a maximum.
- **Fibrinolysis** which is part of normal physiology then follows, allowing the clot to be broken down.

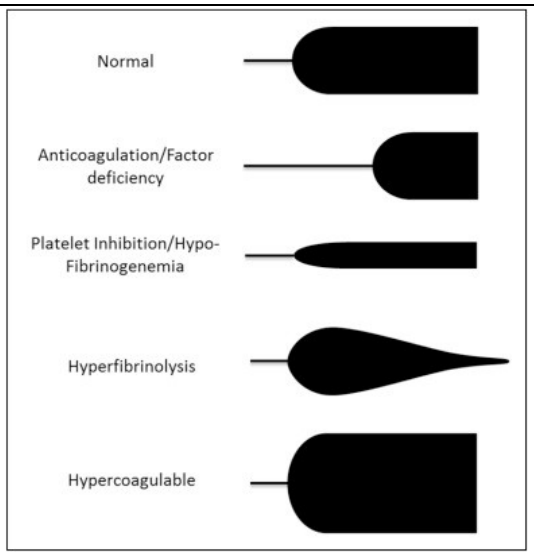

Figure 8: graphics transmitted by TEG® and ROTEM®, and their broad interpretation.

7.3 TEG® AND ROTEM® PARAMETERS

The most relevant parameters given by TEG® and ROTEM® from a clinical standpoint are listed below **(table 28 and figure 9)**. They have been widely studied over time, allowing to drawing VHA-guided algorithms for the management of bleeding [20,21,22].

Time from test initiation to 2 mm above baseline	R	Clotting Time (CT)	Prolongation may indicate a deficiency of coagulation factors, or presence of anticoagulants
Time from 2 mm above baseline to 20 mm above baseline	K	Clot Formation Time (CFT)	Representative of the kinetics of clot formation. Can be an early indicator of clot deficiency or hypercoagulability
Alpha angle	α	α	Prolongation suggests platelet dysfunction or deficiency and fibrinogen deficiencies; shortening may indicate hypercoagulability
Amplitude at time X	A30, A60, etc.	A5, A10, etc.	Clot strength at given time during the analysis. Values at these times are often used as "transfusion triggers"
Clot Lysis at time X	CL30, CL60	LY30, LY45, LY60, etc.	Indication of fibrinolysis and potential need for anti-fibrinolytics

Table 28: TEG® and ROTEM® most important parameters.

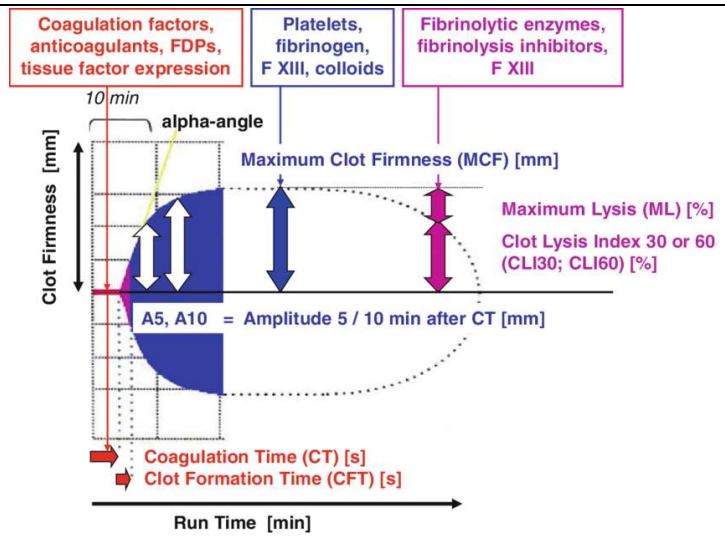

Figure 9: ROTEM® trace displaying clinically relevant parameters.

FDPs = fibrin(ogen) split products, K Görlinger, Tem International

7.4 ROTEM SIGMA®

The ROTEM Sigma® **(figure 10)** which was implemented in CHU Nantes starting on 27/6/18 provides information on a patient's coagulation status within about 10 minutes. The ROTEM Sigma® analyser measures kinetic changes in the clot elasticity of whole blood samples. Through measurement of clot status parameters, quantitative and

qualitative assessment is offered. Analysis is performed at the point of care (CHU Nantes chose to locate the device close to the operating room) and provides essential information about hyper-fibrinolysis, coagulopathies caused by dilution, substitution of fibrinogen, factors or platelet substitution, as well as heparin or protamine dosage control.

The addition of activators and inhibitors to a whole blood sample allow for targeted analysis of specific components of the coagulation cascade, generating various graphics:

- **INTEM C:** assessment of clot formation, fibrin polymerization and fibrinolysis via the intrinsic pathway
- **EXTEM C:** assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway
- **FIBTEM C:** analysis without platelets; qualitative assessment of fibrinogen status
- **APTEM C:** in-vitro fibrinolysis inhibition; assessment of the possible effect of anti-fibrinolytic drugs
- **HEPTEM C:** specific detection of heparin when compared with INTEM C via heparin neutralisation

Figure 10: ROTEM Sigma® device.

The device provides a whole blood diagnosis of coagulopathies to optimise patient blood management in major surgeries such as cardiac surgery.

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9.2 FIGURES

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Titre de Thèse : POINT-OF-CARE VHA-GUIDED MANAGEMENT OF BLEEDING IN CARDIAC SURGERY: CLINICIANS' COMPLIANCE WITH ALGORITHM, PRELIMINARY CLINICAL RESULTS OF THE IMOTEC STUDY

Evaluation de l'application d'un algorithme basé sur les tests visco-élastiques pour la gestion des hémorragies en chirurgie cardiaque ; résultats préliminaires de l'étude IMOTEC

RESUME

La chirurgie cardiaque peut se compliquer de saignement et de coagulopathie pour lesquelles l'administration de produits hémostatiques et la transfusion sont souvent nécessaires. Les tests visco-élastiques (TVE) associés à un algorithme guidant le traitement font l'objet de recommandations. L'étude IMOTEC (Intérêt MédicO-économique des TVE dans les hémorragies péri-opératoires de chirurgies Cardiaques sous CEC) comparait la prise en charge habituelle à un traitement guidé par un algorithme basé sur les résultats de TVE (ROTEM® ou TEG®). Entre le 1/1/17 et le 1/3/19, 198 patients ont été inclus par le CHU de Nantes dont 54 avec le TVE (ROTEM®). Les actions hémostatiques prises par les cliniciens étaient en accord avec la proposition de l'algorithme, même si elles se sont avérées plus nombreuses que recommandé. Une analyse de l'ensemble des données de l'étude serait nécessaire pour déterminer si la stratégie TVE + algorithme est efficiente.

MOTS-CLES

CHIRURGIE CARDIAQUE, TRANSFUSION, TESTS VISCO-ÉLASTIQUES, ROTEM®, HÉMORRAGIE PER-OPERATOIRE

KEY WORDS

CARDIAC SURGERY, TRANSFUSION, VISCOELASTIC HAEMOSTATIC ASSAY, ROTEM®, SEVERE PERIOPERATIVE BLEEDING