

BMJ Open Cost-effectiveness of point-of-care viscoelastic haemostatic assays in the management of bleeding during cardiac surgery: protocol for a prospective multicentre pragmatic study with stepped-wedge cluster randomised controlled design and 1-year follow-up (the IMOTEC study)

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ABSTRACT

Introduction During cardiac surgery-associated bleeding, the early detection of coagulopathy is crucial. However, owing to time constraints or lack of suitable laboratory tests, transfusion of haemostatic products is often inappropriately triggered, either too late (exposing to prolonged bleeding and thus to avoidable administration of blood products) or blindly to the coagulation status (exposing to unnecessary haemostatic products administration in patients with no coagulopathy). Undue exposure to transfusion risks and additional healthcare costs may arise. With the perspective of secondary care-related costs, the IMOTEC study (Intérêt Médico-économique de la Thrombo-Elastographie, dans le management transfusionnel des hémorragies péri-opératoires de chirurgies Cardiaques sous circulation extracorporelle) aims at assessing the cost-effectiveness of a point-of-care viscoelastic haemostatic assay (VHA: RoTem or TEG)-guided management of bleeding. Among several outcome measures, particular emphasis will be put on quality of life with a 1-year follow-up.

Methods and analysis This is a multicentre, prospective, pragmatic study with stepped-wedge cluster randomised controlled design. Over a 36-month period (24 months of enrolment and 12 months of follow-up), 1000 adult patients undergoing cardiac surgery with cardiopulmonary bypass will be included if a periprocedural significant bleeding occurs. The primary outcome is the cost-effectiveness of a VHA-guided algorithm over a 1-year follow-up, including patients' quality of life. Secondary outcomes are the cost-effectiveness of the VHA-guided algorithm with regard to the rate of surgical reexploration and 1-year mortality, its cost per-patient, its effectiveness with regard to haemorrhagic, infectious, renal, neurological, cardiac, circulatory, thrombotic, embolic complications, transfusion requirements, mechanical

Strengths and limitations of this study

- Study size and design: this is a multicentre (16 academic centres), prospective study with a stepped-wedge cluster randomised controlled design that plans to enrol 1000 adult patients.
- The cost-effectiveness evaluation of a viscoelastic haemostatic assay-based algorithm, with particular emphasis put on quality of life 1 year after cardiac surgery.
- Cost assessment focuses on hospital costs only.
- We did not collect data about patients with ongoing bleeding but not included. This could have introduced a selection bias.
- Quality of life was assessed at hospital discharge, 1, 6 and 12 months but not at baseline, that is, before surgery.

ventilation free-days, duration of intensive care unit and in-hospital stay and mortality.

Ethics and dissemination The study was registered at Clinicaltrials.gov and was approved by the Committee for the Protection of Persons of Nantes University Hospital, The French Advisory Board on Medical Research Data Processing and the French Personal Data Protection Authority. A publication of the results in a peer-reviewed journal is planned.

Trial registration number NCT02972684; Pre-results.

INTRODUCTION

In patients undergoing cardiac surgery, periprocedural significant bleeding is one of the most dreaded complications. Transfusion of allogeneic red blood cells may be necessary

in at least half of the procedures with cardiopulmonary bypass (CPB).^{1 2} Cardiac surgery is one of the leading causes of massive transfusion, including red blood cells and other blood products transfusion.³ Hence, with respect to the number of cardiovascular surgical procedures under CPB (more than 50 000 a year in France⁴), the burden of significant bleeding and transfusion after cardiac surgery is heavy in the high-income countries. In the USA and the UK, 10%–15% of the total amount of allogeneic blood products is used in the cardiovascular surgery setting.^{5 6}

Cardiac surgery-related bleeding and transfusion of blood products are associated with increased morbidity and mortality. Indeed, there is a dose-dependent relationship between the transfusion of red blood cells units and the risk of postoperative cardiac complications, severe infection, acute kidney injury, neurological complications, prolonged ventilatory support, prolonged in-hospital stay and mortality.^{7 8} Of note, these adverse outcomes may be caused not only by the haemorrhage and its consequences (organs ischaemia, protracted CPB, need for surgical reexploration, for example) but also by the blood transfusion itself. Indeed, alongside its undeniable clinical benefits, blood transfusion exposes to infectious, cardiac, pulmonary, neurological or renal adverse effects.^{8 9} Therefore, blood products should be spared not only because they are a rare and expensive resource,^{10–12} but also to prevent transfusion-induced adverse effects.

The rationale use of blood products includes a bleeding reduction strategy. The early detection and treatment of coagulopathic bleeding should be part of it. Indeed, coagulopathy is an important contributor to bleeding in patients undergoing cardiovascular procedures with CPB.¹³ Such coagulopathy often relates to anticoagulant medications, depletion or dilution of coagulation factors and to their inappropriate consumption after being activated by the interfacing of the blood with the non-endothelial surfaces of the CPB circuit.¹⁴

Point-of-care viscoelastic haemostatic assays (VHA) have been proposed for the early detection of coagulopathy. This point-of-care testing offers, within a few minutes, a global picture of clot formation and dissolution. Conversely, conventional laboratory haemostasis tests (such as prothrombin time, activated partial thromboplastin time or platelet count) have often a too long turn-around time and may fail to identify specific coagulation defects.¹⁵ In addition, conventional laboratory assays are performed on platelet-poor plasma which precludes the analysis of the actual physiological clotting process. Last, since they are performed at 37°C, hypothermia-induced coagulopathy is overlooked by conventional assays.⁵ Hence, conventional assays are often deemed not suitable for the early diagnosis of coagulopathy.⁵ Two consequences may arise from the use of conventional assays. On the first hand, a delayed administration of haemostatic treatments may expose to prolonged bleeding and therefore to avoidable transfusion of blood products. On the other hand, one may be tempted to

administer haemostatic treatments—including blood products (fresh frozen plasma, platelets, cryoprecipitate)—before knowing the coagulation status of the patient with ongoing bleeding, that is, even in patients with no coagulopathy. Such ‘blind approach’ therefore exposes to an undue transfusion of blood products. Thus, for targeted and early correction of coagulopathy, point-of-care haemostatic testing is advocated in order to provide real-time monitoring of the patient’s coagulation.^{6 16} VHA devices using thromboelastography (TEG) or thromboelastometry (ROTEM) are user-friendly techniques which do not require extensive laboratory expertise but only a short training period. Interestingly, VHA testing is widely used for years despite the lack of clearly proven clinical benefit.^{17–19} Of note, the growing evidence in favour of the application of a VHA-guided transfusion strategy, according to single-centre studies,¹⁸ has been recently reinforced by a multicentre randomised controlled trial.²⁰ This Canadian study among patients undergoing cardiac surgery with CPB suggested that implementing point-of-care haemostatic testing within a transfusion algorithm reduces red blood cell transfusions, platelet transfusions and major bleeding. Owing to some limitations of this study, well acknowledged by its authors, and owing to possible publication bias in this topic,¹⁸ robust confirmatory studies are still warranted. Importantly, whether VHA allows optimising the use of healthcare resources is still unclear. Model-based assessments of cost-effectiveness are inherently limited by the need for several assumptions.⁵ Furthermore, for an optimal evaluation of the cost-effectiveness, a long-term follow-up is required, including an assessment of quality of life.

The aim of this study is 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 will be put on quality of life with a 1-year follow-up.

METHODS AND ANALYSIS

Study design

The research will follow a multicentre, prospective, pragmatic, stepped-wedge cluster randomised controlled design.²¹ This design, that is, randomisation at the level of the study centre, has been adopted because it appeared more appropriate than a randomisation at the patient-level. Indeed, when a cardiac surgery-associated periprocedural significant bleeding occurs, the time spent in a randomisation process rather than caring for the patient with ongoing bleeding may appear unethical unless a research staff is dedicated to this purpose on a 24/7 basis, an unrealistic option in a pragmatic multicentre study.

One thousand patients will be included over a 36-month period (24 months of enrolment and 12 months of follow-up). Sixteen French academic centres, performing yearly from 500 to 1500 cardiac procedures under CPB, were selected on the basis of both their potential

recruitment rate and their expertise in cardiac surgery. Recruitment started on 3 January 2017.

Participants

Patients of 18 years old or older, undergoing cardiac surgery (elective, urgent or emergency surgery) under CPB will be enrolled if they require a haemostasis test because of a periprocedural significant bleeding as defined by at least one of the following criteria:

- ▶ *During the intraoperative period* (at least 10 min after protamine reversal of heparin):
 - i. Bleeding considered abnormal according to the consensus opinion of both the surgeon and the anaesthesiologist.
 - ii. Bleeding through chest drainage exceeding 50 mL over 10 min or exceeding 1 mL kg⁻¹ over 30 min.
 - iii. Bleeding delaying the sternum closure.
- ▶ *During the postoperative period* (at least 30 min after intensive care unit admission) until hospital discharge:
 - i. Bleeding through chest drainage exceeding 50 mL over 10 min or exceeding 1 mL kg⁻¹ over 30 min.

ii. Bleeding requiring urgent surgical reexploration.

Patients will not be included or will be 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 intraoperative CPB, artificial heart, patient's refusal of blood transfusion, pregnancy or adult safeguarding regimen.

Intervention

The intervention will consist in the implementation of a VHA-guided algorithm for the management of bleeding patients undergoing cardiac surgery under CPB (figures 1 and 2). According to the stepped-wedge design, the intervention will be sequentially implemented across four groups of four centres, by steps of 5 months (after an initial period of 4 months in which no centre will be exposed to the intervention). Beforehand, each participating centre will be randomly assigned to one of the four groups. Hence, from the beginning of the 20th month after the beginning of the study, the VHA-guided

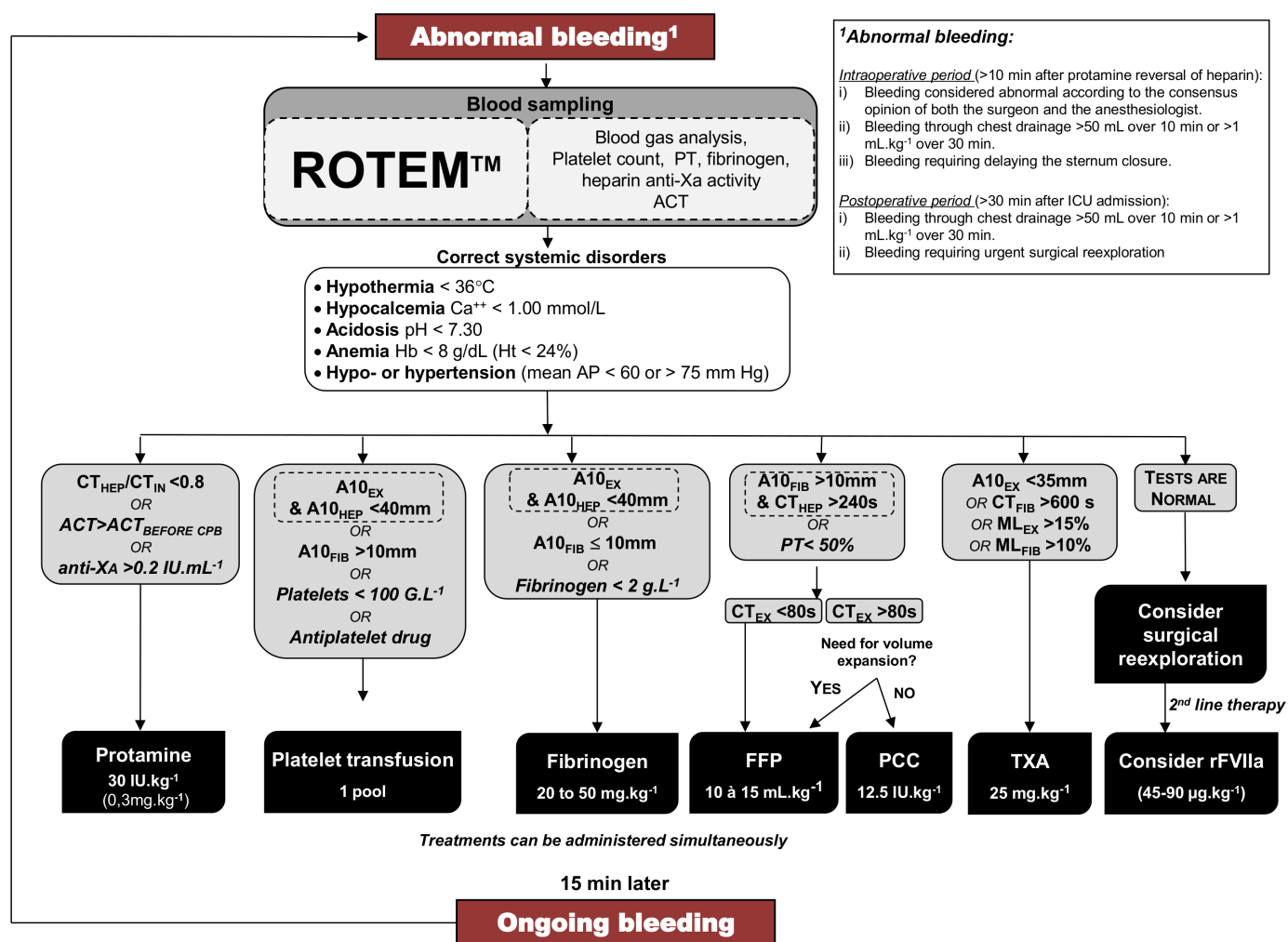


Figure 1 ROTEM-guided algorithm for bleeding management. ROTEM parameters: A10, Amplitude at 10 min; ACT, activated clotting time; AP, arterial pressure; CPB, cardiopulmonary bypass; CT, clotting time; EX, EXTEM; FFP, fresh frozen plasma; FIB, FIBTEM; HEP, HEPTM; ML, maximum lysis; PCC, prothrombin complex concentrate; PT, prothrombin time; rVIIa, recombinant factor VII; TXA, tranexamic acid.

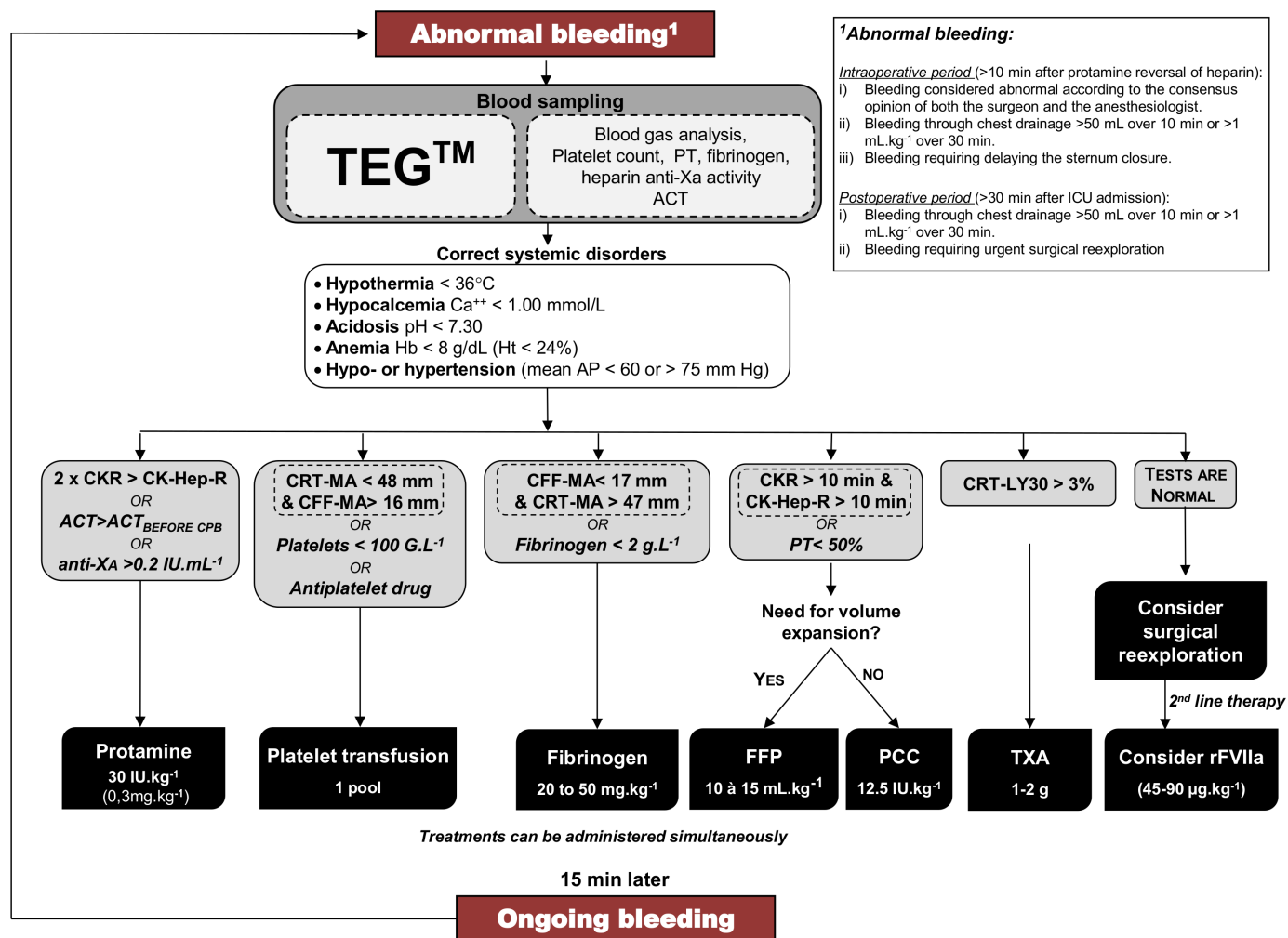


Figure 2 TEG-guided algorithm for bleeding management. ACT, activated clotting time; CFF MA, citrated functional fibrinogen maximum amplitude; CKR, citrated kaolin test reaction time; CK-HEP, R citrated kaolin heparinase test reaction time; CPB, cardiopulmonary bypass; CRT LY30, citrated rapid TEG lysis at 30 min; CRT MA, citrated rapid TEG maximum amplitude; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PT, prothrombin time; rVIIa, recombinant factor VII; TEG parameters: CPB, cardiopulmonary bypass; TXA, tranexamic acid.

algorithm will be implemented in all centres (figure 3). Since data collection will occur during both the preinterventional and the interventional study phase, each centre will contribute both control and intervention observations. Patients will be followed up until hospital discharge and at 1, 3 and 12 months after inclusion. Patients will be blinded to the use of either the tested VHA-guided algorithm (intervention) or the usual local management of bleeding by the anaesthetist medical staff (control).

Point-of care viscoelastic haemostatic assays

Two VHA devices are similarly recommended for point-of-care use in the setting of cardiac surgery: the ROTEM and the TEG.⁵ The latest version of either the ROTEM (RoTem Sigma (WERFEN) or the TEG device (TEG6 Haemonetics) will be used in the present study. Indeed, these new versions are associated with greater ease of use and the measured parameters closely correlate with those obtained from their predecessor.²²⁻²⁴ The choice of either the RoTem Sigma or the TEG6 Haemonetics has been

left to the discretion of each participating centre before the beginning of the study. Once chosen, the type and model of VHA device will be the same, for each centre, throughout the study. The device will be placed in the more convenient location, with respect to the specificities of each centre: in the operating room, the postoperative intensive care unit or even the laboratory if the latter is compatible with a similarly short turn-around time. Hence, VHA will be performed by the anaesthetic or the laboratory team. Either way, the anaesthesiologist will interpret the VHA data. Within 2 months before the implementation of the VHA-based algorithm (figures 1 and 2), clinical and research staff will receive on-site training. In each centre, maintenance and quality controls of the VHA device will be provided by at least two referent persons.

Management of bleeding according to the study phase

In the preintervention observational period, the usual local management of bleeding by the anaesthetist staff

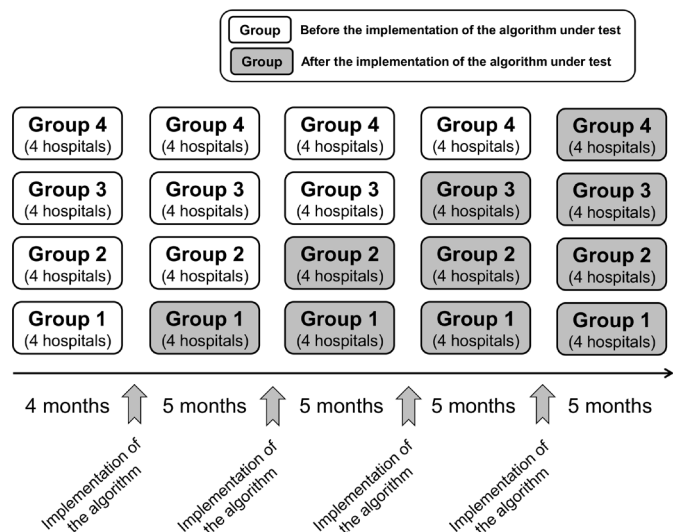


Figure 3 The IMOTEC study cluster design. Each randomisation unit (U1, U2 ...) includes four institutions following the protocol for a same time period. White cells represent units using standard local haemorrhage management without visco-haemostatic assay (VHA). Grey cells represent units using the VHA-guided algorithm for haemorrhage management.

will be respected, as standard care. Importantly, in none of the participating centres VHA is part of standard care. Standard care may differ across the participating centres and will be thoroughly analysed and described. After the implementation of the tested intervention (VHA-guided algorithm), clinicians will be encouraged to adopt the algorithm in all patients with ongoing bleeding but will not be forced to do so, since this study aimed at being pragmatic. In this algorithm (figures 1 and 2), the thresholds for VHA-derived data stem from previously proposed algorithms.^{25–27}

Outcomes

For primary and secondary outcomes, the time horizon will be 1 year.

Primary outcome

The primary outcome measure for this trial will be the estimation of the cost-effectiveness of the VHA-guided algorithm.

In each group (standard care or VHA-guided algorithm), effectiveness will focus on patients' quality of life during a 1-year follow-up. Length and quality of life after cardiac surgery will be expressed as quality-adjusted life year (QALY).²⁸ Quality of life will be assessed using the EuroQol EQ-5D-3L questionnaire.^{29 30}

Cost calculation will include all the hospital-related costs over a 1-year period, including a detailed costing of using ROTEM or TEG (see the Calculation of costs section).

The analysis will follow the French Health Authority and the Consolidated Health Economic Evaluation Reporting Standards guidelines on economic evaluation in healthcare.^{31 32}

Secondary outcomes

- Additional evaluation of the cost-effectiveness of our VHA-guided algorithm: effectiveness will be assessed via a composite criterion based on surgical reexploration and 1-year mortality. Costs over a 1-year period will be calculated as for the primary outcome.
- Analysis of the financial impact of the VHA-guided algorithm at the patient level, performed according to the guidelines from the international society for pharmacoeconomics and outcomes research task force on good research practices.³³ Costs over a 1-year period will be calculated as for the primary outcome.
- Assessment of the effectiveness of the VHA-guided algorithm during hospitalisation with regard to transfusion requirements (number of units of red blood cells, 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, cardiac arrhythmias, neurological complications, thrombotic or embolic complications, number of mechanical ventilation free-days, duration of ICU and in-hospital stay and 1-year mortality.
- Analysis of the impact of the type of VHA device (ROTEM or TEG) and of its location (operating theatre, ICU or laboratory) on its cost-effectiveness and effectiveness.

Trial follow-up

Quality of life (assessed at hospital discharge, at 1, 6 and 12 months after cardiac surgery), postoperative complications and use of hospital resources (such as consultations, emergency room visits, hospital admissions) will be obtained by collection of data during the initial hospital stay and then by telephone call from a clinician or a study nurse, at 1, 6 and 12 months after cardiac surgery. In addition, a double checking of the use of hospital-related resources after the initial discharge will be made via hospital databases.

Statistical analysis

Calculation of costs

Costs will be calculated over 1 year. Owing to the impact of a significant bleeding on the use of hospital resources (ICU and in-hospital length of stay, for instance), the perspective chosen for the estimation of costs will be hospital (secondary care)-related costs. Primary care-related costs will not be analysed. The rates for the hospital stay will be calculated with respect to the Diagnosis Related Groups. Whenever possible, we will evaluate the costs more precisely than simply systematically using the national health insurance reimbursement scale. A micro-costing approach will be adopted. For instance, reagents for haemostatic treatment, blood products and coagulation factors concentrates will be valued at the actual price paid by the institutions. The possible wastage of reagents will be taken into account.

Equipment and maintenance costs will be included as well as labour costs.

Then, the extra cost of VHA with respect to the average cost of conventional haemostatic techniques will be estimated.

Main analyses

The value of the VHA-guided algorithm will be determined with respect to (1) the extra cost related to the VHA-guided algorithm and (2) its potentially beneficial impact on both quality and quantity of life lived after cardiac surgery. For this latter point, QALY, the commonly used generic measure of disease burden,³¹ will be used. The overall cost difference between the standard management and the VHA-guided algorithm will be assessed via the calculation of the incremental cost-effectiveness ratio, expressed as € per QALY³¹:

$$ICER = \frac{C_{\text{algorithm}} - C_{\text{standardmanagement}}}{QALY_{\text{algorithm}} - QALY_{\text{standardmanagement}}}$$

where $C_{\text{algorithm}}$ is the cost of the management with the VHA-guided algorithm, $C_{\text{standardmanagement}}$ is the cost associated with the standard management, QALY is the quality-adjusted life-years for patients.^{29–31} To refine the 95% CI of these parameters, the bootstrapping technique will be used. We will compare the result to the usually applied thresholds of €50 000–100 000/QALY and calculate the probability of cost-effectiveness from the bootstrapped probabilistic sensitivity analysis.

Considering the primary endpoint, an intention-to-treat analysis will be performed. First a complete case analysis will be performed based on the population for whom all cost and effectiveness data are available. Secondly, after imputation of missing data, an intention-to-treat analysis will be performed in the whole population. Considering secondary endpoints, analyses will follow the same methodology.

Since the test results will be captured on the case report forms (CRFs), adherence to the treatments indicated by the algorithm will be evaluated.

Data collected during the preintervention and the intervention phases will be compared with appropriate tests: χ^2 tests for binary or nominal outcomes data and Student's tests for continuous measures. In-hospital and 1-year mortality rates will be determined for these two phases, via a linear mixed-effects model. In this model, the study centre will be a random factor whereas the study phase will be a fixed factor. Hospital length of stay, ICU length of stay, mechanical ventilation-free days will be analysed using Cox proportional-hazards models. Subgroup analyses will be performed with respect to the severity of the bleeding³⁴ or to the location of the VHA device.

All analyses will be conducted by a statistician according to this prespecified statistical analysis plan.

Sample-size calculation

With the standard management of bleeding during cardiac surgery, the rate of surgical reexploration and/

or 1-year mortality is estimated to be 12%.^{35 36} To detect a 5% absolute difference in this rate, 425 patients per arm would be required with a randomisation at the individual level, that is, a total of 850 patients, with an alpha risk of 5% and a power of 80%. Owing to the randomisation at the hospital level, the intracluster correlation coefficient (ICC) and the average cluster size should be taken into account. We assumed an ICC of 0.001 according to a previous work reporting this ICC for in-hospital mortality in patients with heart failure.³⁷ We also assumed that, based on the recruitment capacities of the 16 participating centres, the inclusion of an average of 60 patients per centre would be a realistic goal. We then determined that an inflation factor of 1.059 should be applied to the above-mentioned total number of 850 patients (inflation factor = $1 + (n - 1)\rho$ where $n=60$ and $\rho=0.001$). Assuming a drop-out rate of 10%, a minimum of 1000 patients will be included in this study.

Of note, the sample size calculation has been based on clinical outcomes, mostly for ethical reasons: the clinical outcome takes priority over the efficiency of the allocation of healthcare resources. Hence, we input the above mentioned sample size into Glick's formula.³⁸ Thus, this sample size will allow testing for the existence of a difference of €300 and 0.05 or 0.04 QALYs at the €50 000 and €100 000/QALY thresholds between standard management and VHA-guided algorithm, respectively.

Data management, monitoring and quality control

Data will be collected by investigators on a paper CRF and then entered into a computerised database (eCRF) ruled by the Research Department of Nantes University Hospital, in accordance with the current protocol and regulations guarantying the anonymity of the patient.

Recruitment will be monitored by the Research Department of the University Hospital of Nantes. Investigators will receive a newsletter on a quarterly basis. Recruitment will be analysed after 9 and 15 months to identify unforeseen issues and motivate centres to reach the recruitment goal.

Quality control of the data will be carried out by the Research Department of Nantes University Hospital. In each study centre, on-site data monitoring every 12 months will be performed (total of four visits per centre). Clinical Research Associates will have access to patients' medical files and CRFs. Unscheduled inspections could also be undertaken.

Patient and public involvement

Patients or public were not involved in the development of the research question, the study design or the assessment of the burden of the intervention. However, reducing the need for allogeneic transfusion and ensuring its safety is part of a national plan of high priority in France.

ETHICS AND DISSEMINATION

The study will be conducted in full compliance with the Declaration of Helsinki. The study protocol was approved

by the Committee for the Protection of Persons of Nantes University Hospital (04/05/2016, number 15/16). The study has been registered by the « Agence Nationale de Sécurité du Médicament et produits de santé (ANSM) » (ID RCB number: 2016-A00455-46).

The anonymity of the patients will be guaranteed and only authorised individuals can access the patients' health information.

The patient (or his next of kin, if the patient is incapable) written informed consent will be obtained by the medical staff, before surgery. In the event of an emergency surgery, it is expected that the patient could not be able to consent for this study. Emergency inclusion will therefore be possible but investigators are then committed to collect the consent of the patient's next-of-kin and to collect a posteriori the consent of the patient himself if he regained ability to consent. The patient (or his next-of-kin in the event of inability to consent), will be informed of the right to refuse use of the data. In any case, the informed consent will be recorded in the patient's medical file and an information note reminding the patient's rights is handed to the patient (or his next of kin). The findings of the study will be communicated to the patient on his request. Recruitment information will be regularly shared with participating centres. Each centre will have access to its own data set.

The study is registered at Clinicaltrials.gov (NCT02972684 November 23, 2016).

The results will be published in an international peer-reviewed journal.

DISCUSSION

Progress of the study

After 2 years of recruitment, 1058 patients have been enrolled. The planned recruitment period of 2 years has been extended by 2 months for the following reasons. First, one centre could not initially perform the 1-year follow-up, which is required for our primary outcome. About 50 patients could therefore not be analysed. Second, 3 months before the end of initial recruitment period, we were concerned with an imbalance in the rate of inclusions between the two study phases: substantially more patients were included in the observational phase (before the implementation of the algorithm under test) than in the interventional phase (after its implementation). Owing to the stepped-wedge cluster design of this study, simply extending the interventional phase allowed to guarantee that the number of patients recruited during the interventional phase will not be lower than expected. Since after 2 years, 528 and 530 patients were included in the observational and the interventional phase, respectively, extending the recruitment period was retrospectively probably not necessary but has contributed to increase the power of our study.

Strengths of this study

This is a multicentre (16 academic centres), prospective study with a stepped-wedge cluster randomised controlled design. More than 1000 adult patients have been enrolled. Furthermore, we adopted a pragmatic approach for this study: anaesthesiologists were encouraged to guide their management with the VHA-guided algorithm (during the interventional phase) but not forced to do so. In addition, multicentre data collected during the observational phase will provide useful information about current practices. Last, and most importantly, this study will not only assess the effectiveness of a VHA-based algorithm but also thoroughly evaluate its cost-effectiveness, with particular emphasis put on quality of life 1 year after cardiac surgery.

Study limitations

First, since management of the patient with ongoing bleeding will be guided by VHA results, only the patient will be blinded to the assigned strategy (standard or VHA-guided).

Second, primary care-related costs will not be analysed and the estimation of costs will solely include hospital costs. In other words, use of out-of-hospital resources such as visits to general practitioners will be overlooked. However, owing to the important impact of a significant bleeding on the use of hospital resources (ICU and in-hospital length of stay, for instance), we believe that the major part of healthcare-related costs will be captured in our study.

Third, during the interventional phase, as adopting the VHA-guided algorithm was encouraged but was not mandatory, some patients with ongoing bleeding may not be included. Since we did not collect data about non-included patients, the estimation of the magnitude of this potential selection bias is not possible.

Fourth, the choice of the device (ROTEM or TEG) was left to the centre. This may be source of bias. Since National Institute for health and Care Excellence (NICE) guidelines do not favour one of these devices over the other,⁵ since both of them are on the market, and since some physicians may find one device more convenient than the other, we prioritised the pragmatic character of our study by leaving the choice of the device to the participating centres rather than imposing one. Of note, collecting data about these two devices will allow the specific analysis and comparisons of the respective performance of ROTEM-guided and the TEG-guided algorithm. Other potential sources of bias will be specifically analysed, such as the location of the device (laboratory or operating room).

Finally, quality of life will be assessed at hospital discharge, at 1, 6 and 12 months but not at baseline, that is, before surgery. However, given the large sample size, we assume that randomisation will balance the baseline levels of quality of life.

The 1-year follow-up period and the data analyses will precede the publication of the results of this study.

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Contributors Conception and design: J-CR, EB, V-PR, ID-Z, BR. Analysis and interpretation of data: not applicable (study protocol). Drafting the article or revising it critically for important intellectual content: J-CR, EB, KL, V-PR, ID-Z, BR.

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