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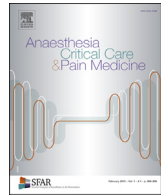
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Original Article

Cost-utility of point-of-care viscoelastic hemostatic assays in the management of bleeding during cardiac surgery: A single-blinded prospective multicenter stepped wedge cluster randomized trial in French context



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ABSTRACT

Background: The IMOTEC study aims to determine whether a point-of-care viscoelastic hemostatic assay (VHA)-guided algorithm is cost-effective for the management of ongoing bleeding.

Methods: Stepped wedge cluster randomized trial, patient blinded, conducted at 16 French academic cardiac surgery centers from 01/2017 to 02/2020. Adults undergoing elective or urgent cardiac surgery with ongoing bleeding were enrolled during 2 successive inclusion periods: 1) transfusion guided on standard hemostasis tests (control period), and 2) transfusion using a VHA-guided algorithm. The primary objective was to estimate the efficiency of VHA based on the 1-year incremental cost-utility ratio (ICUR, primary outcome). Secondary outcomes included transfusion, postoperative complications, duration of stay in-hospital, reintervention, and mortality.

Results: 1095 patients were randomized, and 1044 (95.3%) were analyzed. The mean utility was 0.60 (± 0.30) in the VHA vs. 0.61 (± 0.30) in the control period, adjusted difference, -0.01 [95% CI, -0.09 to 0.07]. The ICUR did not suggest that the VHA-guided algorithm was cost-effective. One-year mortality was 12.0% for VHA and 10.9% for control, Hazard Ratio, 1.69 [95% CI, 0.98–2.89], $P = .06$. The frequency of plasma and platelet transfusions was significantly lower in the VHA compared to the control period (respectively, 48.8% vs. 72.4%, $P < 0.0001$ and 52.3% vs. 74.1%, $P = .0002$), whereas fibrinogen administration was more frequent in the VHA period (58.4% vs. 47.0%, $P = .002$). The median in-hospital length of stay was significantly shorter in the VHA vs. control period: 11.0 days (8.0–18.0) vs. 14.0 (9.0–22.0), $P = .02$.

Conclusions: The ICUR did not suggest that VHA was cost-effective in cardiac surgery patients with ongoing bleeding, compared with standard tests.

Trial registration: Clinical trial submission: November 2, 2016

Registry name: Cost-Utility Analysis of Management of Peri Operative Hemorrhage Following Cardiac Surgery With Cardiopulmonary Bypass (IMOTEC)

ClinicalTrials.gov Identifier: NCT02972684

URL registry: <https://clinicaltrials.gov/study/NCT02972684>

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Key Points

Question

Among cardiac surgery patients with ongoing bleeding, are point-of-care viscoelastic hemostatic assays (VHA) cost-effective, compared with standard coagulation tests?

Findings

In this multicenter, stepped-wedge cluster-randomized controlled trial including 1044 patients, the incremental cost-utility ratio did not suggest that VHA was cost-effective compared with standard coagulation tests.

Meaning

Although VHA was not cost-effective compared with standard tests, decision-makers should consider the reduction of plasma and platelet transfusions, as well as the reduction of the hospital length of stay in the VHA period, to envision a broader use of VHA in cardiac surgery patients.

1. Introduction

Perioperative bleeding is one of the most life-threatening complications of cardiac surgery [1]. Up to one-third of cardiac surgery patients will require perioperative blood transfusion [2]. With 2 million cardiac surgeries performed each year worldwide, bleeding and transfusion represent, therefore, a major economic theme. In the United States and the United Kingdom, 10%–15% of allogenic blood products are used within the context of cardiovascular surgery [3].

Bleeding and blood transfusion are both associated with increased morbidity and mortality, but the causal relationship between transfusion and organ dysfunction is difficult to establish

[4]. Patient Blood Management (PBM) involved preoperative blood mass optimization [5], intraoperative bleeding prevention, and postoperative actions to harness patient physiological reserves [6,7]. Per- and postoperative management of bleeding in association with biological diagnosis is a key point to handle potential severe and multifactorial coagulopathy [8]. The use of standardized algorithms with predefined intervention and point-of-care viscoelastic hemostatic assay (VHA) is proposed to manage coagulopathy [9]. VHA provides a profile of clot formation and dissolution based on the total blood sample. Standard coagulation testing (further referred to as standard tests) is less expensive than VHA, but the time to obtain the results could be longer. Consequently, when results are available, the level and determinants of coagulopathy may have changed, which could lead to delayed or inappropriate administration of hemostatic therapy or transfusion. Moreover, standard tests are performed on platelet-poor plasma, which preclude obtaining a global view of the clotting process.

PBM strategies face economic and organizational barriers [10] such as the cost of VHA testing without specific reimbursement from the French national health insurance. Thus, when comparing VHA and standard tests, documenting the costs and outcomes is important for health system decision-makers. To date, VHA has been reported to reduce major bleeding as well as red blood cell and platelet transfusions when used as a preventive strategy [11]. However, more evidence is needed to envision its implementation in the standard of care, and its impact on the use of healthcare resources should be documented.

The primary objective was to determine the incremental cost-utility of the VHA-guided algorithm for the management of cardiac surgery patients with ongoing bleeding.

2. Methods

2.1. Study design, settings, and ethical considerations

The study protocol was designed by investigators [12], published and approved by the ethics committee of Nantes University Hospital (Comité de protection des personnes of Nantes #2016/05), and was registered at the “Agence Nationale de Sécurité du Médicament et produit de santé” (ANSM ID RCB #2016-A00455-46). The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol and statistical analysis plan are presented in Supplement 1. This was a pragmatic multicenter, single-blind, stepped-wedge cluster-randomized trial (at the center level) involving 16 French academic cardiac surgery centers. Written informed consent to study was obtained by research staff from all participants, either prior to surgery or, if the patient was unable to consent, medical staff could proceed with emergency inclusion. As soon as the patient regained capacity, information was given, and written consent was sought; inclusion in the study was halted if written consent was not obtained or was withdrawn.

2.2. Participants

Patients aged 18 or older, admitted for elective or urgent cardiac surgery with cardiopulmonary bypass, were included in the case of [13]:

- 1 Abnormal bleeding according to both the surgeon and anesthesiologist, or chest drainage >50 mL over 10 min or >1 mL/kg over 30 min, or bleeding delaying sternum closure (*i.e.*, intraoperative inclusion at least 10 min after heparin reversal by protamin).
- 2 Chest drainage > 50 mL over 10 min or >1 mL/kg over 30 min or bleeding requiring urgent surgical reintervention (*i.e.*, inclusion in the intensive care unit).

Patients were not included in case of constitutional hemorrhagic disease, preoperative decision for extracorporeal life support after surgery, uni- or biventricular artificial heart after surgery, refusal of blood transfusion, pregnancy, adult under guardianship, or redo surgery with previous enrollment in the present study.

2.3. Randomization and blinding

Patients could only be included once in the study and stayed blinded to the study period throughout the follow-up period.

2.4. Stepped-wedge implementation of VHA

After an initial four-month control period, during which all centers used standard tests (pre-rollout period), the rollout to the intervention period began with the implementation of VHA in group 1 (crossover). The intervention was sequentially repeated every 5 months in Groups 2, 3, and 4 for a total recruitment duration of 24 months (**eMethods 1 in Supplement 2**). Before inclusion, all factors contributing to bleeding (*i.e.*, hypothermia, hypocalcemia, acidosis, anemia, hypo-hypertension) were corrected whenever possible. In both periods, all patients received the same intraoperative care, and surgery was performed according to clinical standards (**eMethods 2 for standard of care in Supplement 2**). During the control period, standard tests abnormalities guided the administration of labile or stable blood products (**See eMethods in Supplement 2**). During the VHA period, in addition to standard tests, blood samples were analyzed with either rotational

thromboelastometry (ROTEM Sigma - Werfen®) in 10 centers or thromboelastography (TEG 6S - Haemonetics®) in 6 centers. Blood products were administered according to a predefined algorithm (previously published) [12] derived from previous publications [14], including VHA, heparin anti-Xa activity, platelet count, prothrombin time, and fibrinogen level (also **eMethods 3 in Supplement 2**). The choice between the two VHA brands and their locations was left to the discretion of each center, and a specific VHA-guided algorithm was applied for each device (*i.e.*, ROTEM Sigma or TEG 6S). [12] Patients were followed from inclusion up to 1 year.

2.5. Outcome

The primary outcome was the incremental cost-utility ratio (ICUR) of the VHA-guided algorithm for the management of ongoing bleeding. It was defined as the difference in costs divided by the difference in Quality-Adjusted Life Years (QALY) at 1 year (in euros per QALY). [15] The costs included intra- and postoperative care (**eMethods 4, 5, and 6 in Supplement 2**). QALYs over 1 year were calculated based on Utilities and the area under the curve approach (**eMethods 7 in Supplement 2**). Utilities were obtained by converting Quality of life into Utilities using the French value set between 0 (deceased patients) and 1 (perfect Health status). [16] Quality of life was measured by telephone call on discharge, 6 months, and 1 year using the EuroQol Five-Dimensions and 3 Level questionnaire (EQ-5D-3L) [16].

Secondary outcomes. Unless otherwise stated, the timeframe was one year. This included the incremental cost-effectiveness ratio (ICER), with effectiveness defined as the ability to avoid 1-year mortality and reintervention after hospital discharge. It also included administration of labile (red blood cell unit, plasma, platelet concentrate) and stable blood products (coagulation factors or fibrinogen), volume of postoperative bleeding, blood cell count, need for surgical reintervention during the initial stay or in the following year, postoperative infection, acute kidney injury or renal replacement therapy, Sequential Organ Failure Assessment (SOFA score) [17], duration of mechanical ventilation, duration of stay in the ICU and in-hospital.

Post hoc exploratory outcomes included: circulatory failure, neurological complications, cardiac arrhythmias, thrombotic or embolic events, and the impact of the location of the VHA device (*i.e.*, operating room, intensive care unit, or laboratory) on blood product transfusion.

2.6. Adherence to the protocol

According to pre-specified rules, adherence to the protocol was determined by comparing the theoretical management of bleeding guided by the VHA algorithm with the actual decision of the attending physician.

2.7. Sample size

Sample size calculations were carried out based on both clinical and economic outcomes. For clinical outcome, with an anticipated 12% rate of surgical reintervention and/or 1-year mortality [18], to detect a 5% absolute reduction with a one-sided alpha-risk of 5% and a power of 80%, 425 patients per arm were required. Sample size was also estimated using Glick's method [19]: with a willingness-to-pay threshold of €50,000/QALY [20], an expected incremental cost of €300 (SD = 1000), and an incremental QALY gain of approximately 0.07 (SD = 0.5), 437 patients per arm were required. For randomization at the center level and considering cluster size, we assumed an intracluster correlation coefficient of 0.001 for in-hospital mortality [21]. Anticipating an average of

60 inclusions per center, we applied an inflation factor (IF) of 1.059 ($IF = 1 + \{Average\ inclusion\ per\ center - 1\} \times 0.001$). Considering a 10% dropout rate, a minimum of 1000 patients needed to be included.

2.8. Statistical analysis

The analysis followed French health authority guidelines, and reporting followed the CHEERS recommendations [22,23]. Differences in costs and Utilities (primary analysis) were analyzed using a linear mixed model. Differences in effectiveness were analyzed using a mixed logistic model. Both models were adjusted for the randomization period as a fixed effect and center as a random effect. The 95% confidence intervals were obtained by bootstrapping, and P-values were based on bootstrap t-tests. Missing data for the primary analysis were handled by multiple imputation (relative efficiency > 99%). The imputation model incorporated

center, period, and baseline covariates (age, sex, body mass index, medical history, and preoperative cardiac status, see **eMethods 8 in Supplemental 2** for further details). ICUR and ICER were calculated by dividing the difference in overall costs between periods by the difference in QALY or avoided events, respectively. Uncertainty in the joint distributions of costs and outcomes was reported using scatter plots and acceptability curves.

Analyses of the secondary outcomes included all randomized patients without imputation for missing data, and 95% CIs were not adjusted for multiplicity. Continuous variables were compared using the unpaired t-test or Mann-Whitney U test, when appropriate. The Shapiro-Wilk test was used to assess normality, and the Fisher-Snedecor test was used to assess homoscedasticity. Continuous and categorical data were analyzed using linear and logistic mixed-effect models, respectively, with adjustment for the center as a random effect and the randomization period as a fixed effect [24]. Time to event data (mortality, length of mechanical

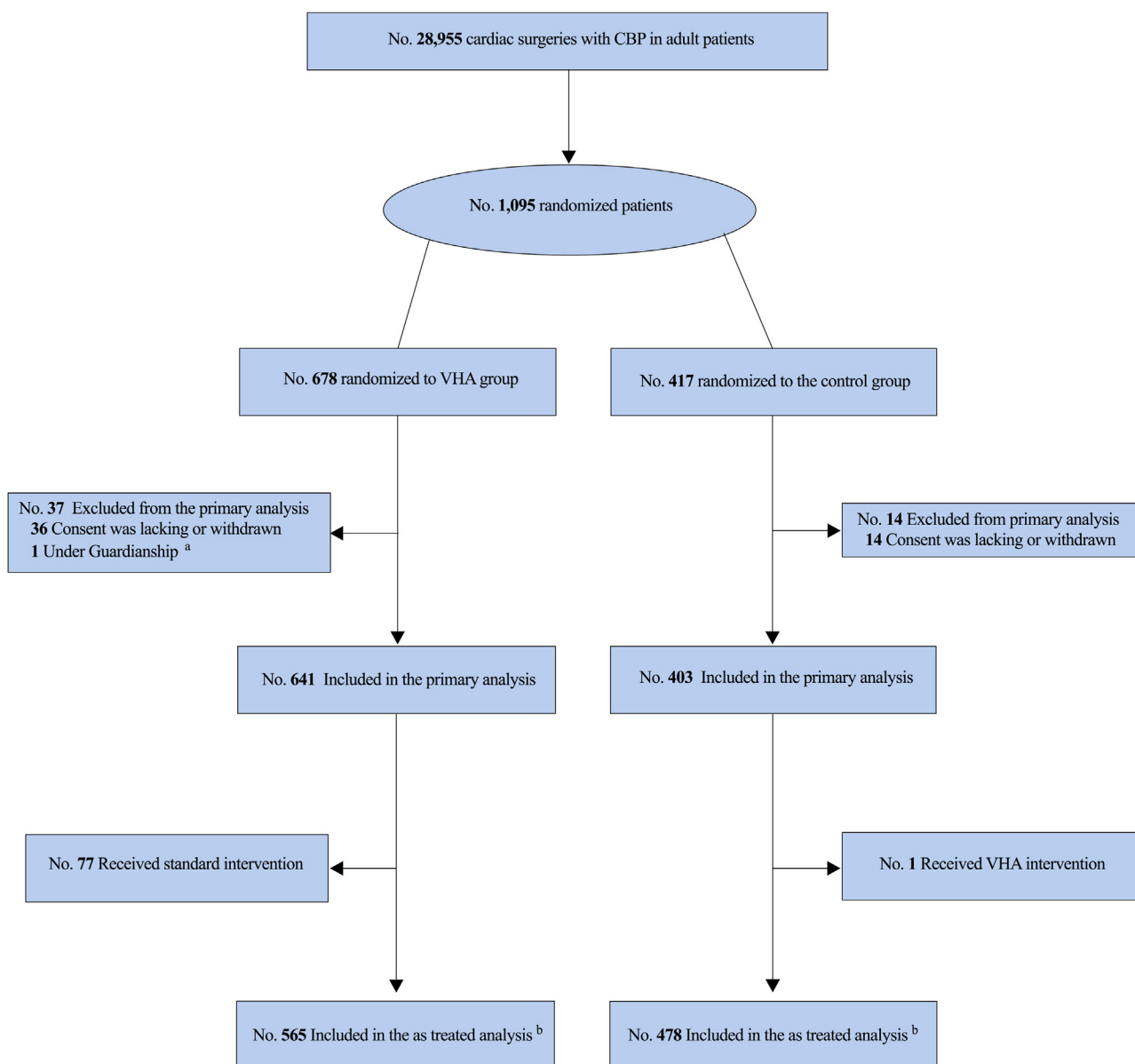


Fig. 1. Screening, randomization, and follow-up of the trial participants.

Legend Fig. 1: CPB: cardiopulmonary bypass, VHA: Viscoelastic hemostatic assay.

^a According to French law.

^b Analysis of each participant according to the intervention they actually received (i.e., 77 patients of the VHA period received standard blood tests and were analyzed with patients of the control period; 1 patient of the control period received VHA intervention and was analyzed with patients of the VHA period).

ventilation, length of stay in the ICU, and in-hospital) were analyzed using a frailty survival model adjusted on the center as a random effect and period as a fixed effect. Data were analyzed using the SAS software (version 9.4; SAS Institute). All tests were 2-tailed, with significance defined at $P < 0.05$.

3. Results

3.1. Study population

A total of 1095 patients were included in the study from January 3, 2017, to March 1, 2019, out of 28,955 adults operated on cardiac surgery during the study period in the 16 study centers (Fig. 1). After randomization, 37 patients from the VHA period (36 lacking consent and one under guardianship) and 14 patients from the control period (lacking consent) were excluded. The primary analysis included 641 patients from the VHA period and 403 patients from the control period. Patient baseline characteristics at randomization are reported in Table 1 (Details of inclusion per center in eTable 1 and eFig. 1 in Supplement 2).

Table 1

Patients demographics and preoperative characteristics in the primary analysis.

	VHA (N = 641)	Missing data No. (%)	Control (N = 403)	Missing data No. (%)	P
Male gender, No. (%)	462 (72.2%)	1 (0.2%)	301 (74.7%)	–	0.37 ^a
Mean age, (\pm SD), years	66.4 (\pm 11.9)	1 (0.2%)	66.0 (\pm 12.5)	–	0.55 ^b
Body mass Index mean (\pm SD), kg/m ² c	26.4 (\pm 5.0)	4 (0.6%)	26.1 (\pm 4.8)	–	0.31 ^b
Euroscore II, mean (\pm SD) d	4.31 (\pm 5.60)	2 (0.3%)	3.92 (\pm 5.15)	–	0.46 ^b
Medical History					
Extra-cardiac arteriopathy, No. (%) e	60 (9.4%)	2 (0.3%)	34 (8.4%)	–	0.60 ^a
Diabetes on insulin, No. (%)	44 (6.9%)	2 (0.3%)	19 (4.7%)	–	0.15 ^a
Chronic pulmonary disease, No. (%) f	43 (6.7%)	2 (0.3%)	27 (6.7%)	–	0.98 ^a
Left Ventricular Ejection Fraction >50%, No. (%)	459 (76.5%)	41 (6.4%)	310 (79.3%)	12 (2.98%)	0.30 ^a
Recent Myocardial Infarction, No. (%) g	33 (5.2%)	2 (0.3%)	24 (6.0%)	–	0.58 ^a
Chronic or hereditary hematological disease, No. (%) h	29 (4.6%)	3 (0.5%)	28 (7.0%)	–	0.10 ^a
Preoperative Status					
Unstable angina, No. (%) i	24 (3.8%)	2 (0.31%)	28 (7.0%)	–	0.02 ^a
Active endocarditis, No. (%) j	53 (8.3%)	–	20 (5.0%)	–	0.04 ^a
Critical preoperative state, No. (%) k	38 (6.0%)	–	19 (4.7%)	–	0.39 ^a
Patient on dialysis, No. (%)	9 (1.4%)	–	8 (2.0%)	–	0.62 ^a
Preoperative Blood tests					
Hemoglobin mean (\pm SD), g/dL	13.2 (\pm 2.0)	40 (6.2%)	13.3 (\pm 2.0)	9 (2.23%)	0.50 ^b
Anemia, No. (%) l	208 (34.6%)	39 (6.1%)	129 (32.8%)	–	0.55 ^a
Platelet count mean (\pm SD), $\times 10^9/L$	218.8 (\pm 76.1)	38 (5.9%)	213.0 (\pm 71.4)	–	0.14 ^b
Platelet count <150 $\times 10^9/L$, No. (%)	97 (16.1%)	38 (5.9%)	61 (15.5%)	–	0.80 ^a
Mean PT (\pm SD), %	86.1 (\pm 14.7)	–	83.0 (\pm 17.8)	–	0.005 ^b
Mean APTT ratio (\pm SD)	1.2 (\pm 0.5)	–	1.10 (\pm 0.3)	–	0.08 ^b
Mean fibrinogen (\pm SD), g/L	3.8 (\pm 1.2)	–	3.81 (\pm 2.4)	–	0.69 ^b
Estimated GFR by Creatinine clearance (MDRD), mean (\pm SD), ml/min/1.73 m ²	77.8 (\pm 32.1)	49 (7.6%)	76.67 (\pm 32.6)	11 (2.73)	0.58 ^b
Preoperative medication in the 5 days before surgery, (%) m					
Antiplatelet therapy before of surgery, No. (%)	264 (41.3%)	2 (0.3%)	178 (44.2%)	–	0.36 ^a
Double antiplatelet therapy before surgery, No. (%)	54 (8.5%)	–	30 (7.4%)	–	0.56 ^a
Anticoagulant therapy before surgery, No. (%)	196 (30.7%)	–	137 (34.0%)	–	0.26 ^a

Abbreviations: **VHA**: viscoelastic hemostatic assay, **SD**: Standard Deviation, **GFR**: Glomerular Filtration Rate, **MDRD**: Modification of Diet in Renal Disease, **PT**: Prothrombin time expressed in % as the ratio of the patient measurement to normal laboratory reference, **APTT**: Activated Partial Thromboplastin Time.

^a Compared with χ^2 tests for categorical variables.

^b Compared with Mann-Whitney test for continuous variables.

^c Body Mass Index: weight/(height)².

^d Euroscore II is a risk model for estimating the predicted in-hospital mortality after cardiac surgery. The score is based on a combination of patient characteristics regarding cardiac- and operation-related factors. It ranges from 0.5 to 100%. A higher score denotes a higher risk of postoperative mortality. [25].

^e Stands for at least one of the following: claudication, carotid occlusion or more than 50% stenosis, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb or carotid arteries.

^f Chronic pulmonary disease defines patients with long-term use of bronchodilators or steroids for lung disease.

^g Defined as myocardial infarction within 90 days.

^h See Supplemental Table 2 for details.

ⁱ Patients presenting angina at rest or requiring nitrates intravenous infusion until arrival in the operating theatre.

^j Patients receiving antibiotic for endocarditis at the time of surgery.

^k Defined as preoperative ventricular tachycardia or fibrillation or aborted sudden death or cardiac massage, ventilation before arrival in the anesthetic room, preoperative intubation support or intra-aortic balloon pump or preoperative acute renal failure (anuria or oliguria <10 ml/h).

^l Defined as a hemoglobin level <130 g/L for males and <120 g/L for females.

^m Details of the interruption or continuation of antiplatelet and anticoagulant therapy are shown in Supplemental eTable 3.

Of the 1044 patients analyzed, 763 (73.1%) were men, with a mean age of 66.3 (\pm 12.2) years and a mean Euroscore II of 4.2 (\pm 5.4) [25]. At baseline, patients from VHA and control periods significantly differed regarding the incidence of unstable angina (respectively 3.8% vs. 7.0%, $P = 0.02$) and active endocarditis (respectively 8.3% vs. 5.0%, $P = 0.04$) (further details on baseline characteristics eTable 2 and eTable 3 in Supplement 2). Participants underwent mainly valvular procedures (69.0%), and 386 (37.7%) underwent combined surgery. Hemorrhagic events occurred in the operating room in 601 patients (57.8%) and/or in the postoperative ICU in 440 patients (42.2%) (Table 2).

3.2. Primary outcome

The total cost per patient and QALY over 1 year were available for 640 (99.9%) and 409 (63.8%) patients in the VHA period, respectively, and 395 (98.0%) and 291 (72.2%) patients in the control period, respectively. In the primary analysis, the mean total cost per patient was €37 097 (\pm €29 316) in the VHA period vs. €39 922 (\pm €29 683) in the control period, adjusted mean difference, -€2 662 [95% CI, -€11 099 to €5 774], $P = 0.39$ after multiple imputation. The mean QALY was 0.60 (\pm 0.30) in the VHA period vs. 0.61 (\pm 0.30) in

Table 2
Surgical settings and hemorrhage characteristics in the primary analysis.

	VHA (N = 641)	Missing data No. (%)	Control (N = 403)	Missing data No. (%)	P
Elective surgery, No. (%)	528 (82.5%)	1 (0.2%)	335 (83.1%)	–	0.79 ^a
Type of surgery					
CABG, No. (%)	238 (37.3%)	2 (0.3%)	149 (37.0%)	–	0.92 ^a
1 CABG	62 (26.1%)		46 (30.9%)		
2 CABG	54 (22.7%)		41 (27.5%)		
3 or more CABG	122 (51.3%)		62 (41.6%)		
Valvular procedure, No. (%)	428 (66.9%)	1 (0.2%)	286 (71.1%)	1 (0.3%)	0.17 ^a
Aortic valve	312 (72.9%)		200 (74.4%)		0.34 ^a
Mitral valve	141 (32.9%)		88 (32.7%)		0.77 ^a
Pulmonary valve	6 (1.4%)		5 (1.9%)		0.76 ^a
Tricuspid valve	41 (9.6%)		49 (18.2%)		0.0006 ^a
Aortic surgery, No. (%)	186 (29.1%)	1 (0.2%)	106 (26.3%)	–	0.34 ^a
Aortic valve-sparing root replacement	11 (5.9%)		5 (4.7%)		0.54 ^a
Bentall surgery	39 (21.0%)		27 (25.5%)		0.69 ^a
Arch	17 (9.1%)		8 (7.6%)		0.49 ^a
Multiple segments	102 (54.8%)		58 (54.7%)		0.51 ^a
Other aortic surgery	28 (15.1%)		21 (19.8%)		0.53 ^a
Isolated CABG, No. (%)	110 (17.2%)	2 (0.3%)	61 (15.1%)	–	0.38 ^a
Single non-CABG procedure, No. (%)	297 (46.%)	2 (0.3%)	180 (44.7%)	–	0.57 ^a
Combined surgery, No. (%)^c	227 (35.7%)	5 (0.8%)	159 (39.6%)	3 (0.7%)	0.19 ^a
2 procedures	189 (83.3%)		109 (68.6%)		
3 procedures	38 (16.7%)		50 (31.5%)		
Surgical management					
Roller pump, No. (%) ^d	419 (66.5%)	11 (1.8%)	316 (80.0%)	8 (2%)	<.0001 ^a
Extracorporeal circulation duration, mean (±SD), min	134.8 (±68.4)	7 (1.1%)	139.5 (±68.9)	2 (0.5%)	0.28 ^b
Cross-clamping duration, mean (±SD), min	94.0 (±47.5)	12 (1.0%)	101.0 (±52.4)	4 (1.0%)	0.03 ^b
Cardioplegia with blood, No. (%) ^e	515 (86.0%)	42 (6.6%)	297 (75.6%)	10 (2.5%)	<.0001 ^a
Use of hypothermia during aortic cross-clamping, No. (%)	208 (32.7%)	4 (0.6%)	103 (25.6%)	–	0.01 ^a
Blood loss prevention strategies					
Blood salvage device use, No. (%)	497 (77.9%)	3 (0.5%)	267 (66.3%)	–	<.0001 ^a
Tranexamic acid, No. (%) ^f	603 (94.4%)	2 (0.3%)	391 (97.3%)	1 (0.3%)	0.03 ^a
Bleeding onset, No (%)					
Intraoperative	354 (55.5%)	1 (0.2%)	247 (61.3%)	1 (0.3%)	0.06 ^a
In the intensive care unit	284 (44.5%)	1 (0.2%)	156 (38.7%)		
First biology after bleeding starts					
Hemoglobin, mean (±SD), g/L	10.3 (±1.8)	–	10.1 (±1.6)	–	0.07 ^b
Platelet count, mean (±SD), × 10 ⁹ /L	138.1 (±63.9)	–	126.7 (±46.3)	–	0.02 ^b
PT, mean (±SD), %	59.3 (±12.6)	–	56.2 (±11.9)	–	<.0001 ^b
APTT ratio, mean (±SD)	1.5 (±2.3)	–	1.4 (±0.6)	–	0.19 ^b
Fibrinogen, mean (±SD), g/L	2.5 (±0.9)	–	2.4 (±0.8)	–	0.28 ^b
Anti-Xa activity, mean (±SD), U/mL	0.2 (±1.0)	–	0.2 (±0.1)	–	0.21 ^b

Abbreviations: VHA: viscoelastic hemostatic assay, CABG Coronary artery bypass graft, PT: Prothrombin time expressed in % as the ratio of patient measurement to the normal laboratory reference, APTT: Activated Partial Thromboplastin Time.

^a Compared with χ^2 test for categorical variables.

^b Compared with Student's *t*-test for continuous variables.

^c Combined surgery included several cardiac interventions that required opening of the pericardium, such as CABG, valve repair or replacement, aortic replacement, structural defect repair, maze procedure, or resection of a cardiac tumor.

^d Centrifugal pump was the alternative to the roller pump to ensure cardiopulmonary bypass.

^e Crystalloid cardioplegia was used in 84 (14.02%) patients in the VHA vs. 96 (24.43%) in the control period.

^f Details of the doses are provided in **Supplement eTable 3**.

the control period, adjusted mean difference -0.01 [95% CI, -0.09 to 0.07], $P = .77$ after multiple imputations (Table 3). The as-treated analysis did not show any significant differences between the periods (eTable 4, Supplement 2 for complete case analyses). Based on these results, the point estimate of the ICUR of VHA was €266 200 per QALY. The joint distribution of costs and QALYs is represented in the cost-utility scatter plots in Fig. 2A for the primary analysis and Fig. 2B for the as-treated population. The cost-utility acceptability curves are shown in eFig. 2, and the fluctuation of Utilities over 1 year in eFig. 3, Supplement 2.

3.3. Secondary outcomes

One year after randomization, 79 (13.7%) patients in the VHA period vs. 58 (15.6%) in the control period needed reintervention after hospital discharge, adjusted OR, 0.89 [95% CI, 0.50–1.58], $P = 0.67$. In the VHA period, the 1-year mortality rate was 12.0% vs. 10.9% in the control period, adjusted HR, 1.69 [95% CI, 0.98–2.89],

$P = 0.06$. There was no difference in effectiveness between the VHA period and the control period, respectively 77.4% vs. 76.2%, adjusted mean difference, 1.07 [95% CI, -5.77 to 7.91], $P = 0.38$. The ICER of VHA is represented in the cost-effectiveness scatter plot in Fig. 2C for the primary analysis and in Fig. 2D for the as-treated population. The point estimate of the ICER was -€248 875, indicating the likelihood that the VHA strategy could be both cost-saving and outcome-improving. The incidence of plasma and platelet concentrate transfusions was significantly lower in the VHA than that in the control period, respectively 48.8% vs. 72.4%, adjusted OR, 0.32 [95% CI, 0.21 to 0.50], $P < 0.0001$, and 52.3% vs. 74.1%, adjusted OR, 0.36 [95% CI, 0.23 to 0.56], $P = 0.0002$. The percentage of patients who received fibrinogen was significantly higher in the VHA than in the control period, respectively 58.4% vs. 47.0%, adjusted OR, 2.10 [95% CI, 1.38–3.20], $P = 0.0020$. According to the universal definition for perioperative bleeding (UDPB) classification [26], hemorrhage in the first 24 h was rated as severe in 420 (65.6%) patients in the VHA period and 296 (73.5%) in the

Table 3
Primary outcome over 1-year and secondary outcomes.

	VHA (N = 641)	Missing data No. (%)	Control (N = 403)	Missing data No. (%)	Mean difference or Odds Ratio or Hazard ratio	P
Primary Outcome^a						
Total cost per patient over 1-year period, ^b mean (SD), euros, primary analysis						
Without multiple imputation	37 087 (±29 322)	1 (0.2%)	39 937 (±29 709)	8 (2.0%)	MD -2641 [-9357 to 6648]	0.41 ^c
With multiple imputation	37 097 (±29 316)	-	39 922 (±29 683)	-	MD -2662 [-11 099-5774]	0.39 ^c
Total cost per patient over 1-year period, mean (±SD), euros, as-treated analysis	36 861 (±28 887)		39 820 (±30 207)		MD -3003 [-11 137-5130]	0.35 ^c
Utility over 1-year, mean QALY, mean (±SD), primary analysis ^d						
Without multiple imputation	0.60 (±0.31)	232 (36.2%)	0.64 (±0.28)	112 (27.8%)	MD -0.057 [-0.130 to 0.054]	0.33 ^c
With multiple imputation	0.60 (±0.30)	-	0.61 (±0.30)	-	MD -0.01 [-0.09 to 0.07]	0.77 ^c
Utility over 1-year, mean QALY, mean (±SD), as treated analysis	0.60 (±0.30)		0.60 (±0.30)		MD 0.004 [-0.078 to 0.085]	0.92 ^c
Secondary Outcome						
Effectiveness over 1-year period, cases avoided no (%) ^e						
Primary analysis	496 (77.4%)	-	307 (76.2%)	-	MD 1.07 [-5.77 to 7.91]	0.38 ^f
As treated analysis	441/565 (78.0%)	-	360/478 (75.3%)	-	MD 2.02 [-4.70 to 8.75]	0.34 ^f
Reintervention during initial hospital stay, No. (%)	212 (33.3%)	4 (0.6%)	151 (37.6%)	1 (0.3%)	OR 0.81 [0.53-1.26]	0.33 ^f
Reintervention after hospital discharge up to 1 year, No. (%)	79 (13.7%)	65 (10.1%)	58 (15.6%)	30 (7.4%)	OR 0.89 [0.50-1.58]	0.67 ^f
One-year mortality, No. (%)	77 (12.0%)	-	44 (10.9%)	-	HR 1.69 [0.98-2.89]	0.06 ^g
Transfusion per- and postoperatively up to 1 year ^h						
Labile blood products, No (%)						
No transfusion, patient, No (%)	110 (17.2%)		19 (2.5%)		OR 3.45 [1.53-7.78]	0.006 ^f
Packed red blood cells, patient, No (%)	463 (72.5%)		325 (80.9%)		OR 0.86 [0.52-1.41]	0.52 ^f
Mean number of packed red blood cells, unit (± SD)	4.49 ± 5.60		5.00 ± 6.68			0.96 [*]
Fresh Frozen Plasma, patient, No (%)	312 (48.8%)		291 (72.4%)		OR 0.32 [0.21 to 0.50]	<0.0001 ^f
Mean number of Fresh Frozen Plasma, unit (± SD)	2.91 ± 4.68		3.80 ± 4.33			0.18 [*]
Platelet concentrates, patient, No (%)	333 (52.3%)	4 (0.6%)	298 (74.1%)	1 (0.3%)	OR 0.36 [0.23 to 0.56]	0.0002 ^f
Mean number of Platelet concentrates, unit, (± SD)	3.45 ± 5.05		1.93 ± 2.03			0.14 [*]
Stable blood products, No. (%) (et le nombre exact cumulé)						
Fibrinogen concentrate, patient, No (%)	373 (58.4%)		189 (47.0%)		OR 2.10 [1.38-3.20]	0.002 ^f
Prothrombin complex concentrate, patient, No (%)	127 (19.9%)		105 (26.1%)		OR 1.02 [0.64-1.61]	0.93 ^f
Activated recombinant factor VII, patient, No (%)	18 (2.8%)		14 (3.5%)		OR 0.82 [0.25-2.67]	0.73 ^f
Mean volume of retransfusion after blood salvage, mL, (±SD)	785.8 (±604.0)	-	796.9 (±780.3)	-	MD -32.26 [-217.21-152.68]	0.73 ^c
No transfusion of any labile or stable blood products, No (%)	67 (10.5%)	2 (0.3%)	18 (4.5%)	1 (0.3%)	OR 1.95 [0.79-4.84]	0.14 ^f
Postoperative complications						
Postoperative bleeding						
In the first 12 -hs, mean (±SD), mL	782.1 (±614.9)	22 (3.4%)	810.2 (±546.1)	4 (1.0%)	MD -60.74 [-187.24-65.76]	0.35 ^c
In the first 3-days, mean (±SD), mL	1459.9 (±1163.3)	18 (2.8%)	1583.9 (±1235.0)	3 (0.7%)	MD -197.88 [-455.29-59.52]	0.13 ^c
Bleeding classification according UDBP, n (%) ⁱ						
Class 2 moderate	176 (27.5%)		80 (19.9%)		OR 1.53 [1.10-2.13]	0.01 ^f
Class 3 severe	420 (65.6%)		296 (73.5%)		OR 0.69 [0.52 to 0.91]	0.008 ^f
Class 4 massive	42 (6.6%)		26 (6.5%)		OR 1.02 [0.61 to 1.69]	0.94 ^f
ICU-acquired infection, No. (%)						
Respiratory infection	127 (19.9%)	4 (0.6%)	83 (20.7%)	1 (0.3%)	OR 0.87 [0.53 to 1.43]	0.56 ^f
Bacteremia	88 (13.8%)		58 (14.4%)		OR 0.95 [0.54 to 1.68]	0.85 ^f
Catheter related infection	28 (4.4%)		22 (5.5%)		OR 1.12 [0.59 to 2.59]	0.77 ^f
Urinary tract infection	9 (1.4%)		13 (3.2%)		OR 0.38 [0.11 to 1.39]	0.13 ^f
Surgical site infection	20 (3.1%)		19 (4.7%)		OR 0.23 [0.07 to 0.79]	0.02 ^f
Invasive fungus infection	16 (2.5%)		11 (2.7%)		OR 1.88 [0.59 to 6.03]	0.26 ^f
Acute kidney injury, No (%) ^j						
KDIGO 1 ^j	4 (0.6%)		3 (0.8%)		OR 0.43 [0.10 to 1.86]	0.24 ^f
KDIGO 2	242 (41.9%)	64 (10.0%)	179 (45.8%)	12 (15.9%)	OR 0.77 [0.51 to 1.17]	0.21 ^f
KDIGO 3	120 (20.8%)		79 (20.2%)		OR 0.97 [0.58 to 1.61]	0.91 ^f
Renal replacement therapy during initial stay, No. (%)	79 (13.7%)		58 (14.8%)		OR 0.75 [0.41 to 1.39]	0.34 ^f
Renal replacement therapy up to 1-year postoperatively, No. (%)	43 (7.5%)		42 (10.7%)		OR 0.67 [0.31 to 1.44]	0.28 ^f
Renal replacement therapy during initial stay, No. (%)	68 (10.7%)	4 (0.6%)	49 (12.2%)	1 (0.3%)	OR 0.82 [0.44 to 1.52]	0.50 ^f
Renal replacement therapy up to 1-year postoperatively, No. (%)	32 (5.6%)	70 (10.9%)	22 (5.9%)	30 (7.4%)	OR 0.67 [0.28 to 1.58]	0.33 ^f

Table 3 (Continued)

	VHA (N = 641)	Missing data No. (%)	Control (N = 403)	Missing data No. (%)	Mean difference or Odds Ratio or Hazard ratio	P
Circulatory failure, No. (%) ^k	199 (31.3%)	5 (0.8%)	109 (27.1%)	1 (0.3%)	OR 1.25 [0.80 to 1.94]	0.30 ^f
Cardiac arrhythmias, No. (%) ^l	275 (43.2%)	4 (0.6%)	181 (45.0%)	1 (0.3%)	OR 1.02 [0.68 to 1.54]	0.91 ^f
Neurological complications, No. (%) ^m	80 (12.6%)	4 (0.6%)	50 (12.4%)	1 (0.3%)	OR 1.22 [0.66 to 2.26]	0.50 ^f
Thrombotic or embolic complications, No. (%) ⁿ	22 (3.5%)	5 (0.8%)	20 (5.0%)	1 (0.3%)	OR 0.42 [0.14 to 1.26]	0.11 ^f
Postoperative outcome						
Mechanical ventilation duration, median (IQR), days	0.6 (0.3 to 1.0)	3 (0.5%)	0.7 (0.4 to 1.2)	–	HR 1.10 [0.91 to 1.33]	0.32 ^g
Length of stay in the ICU, median (IQR), days	4.0 (2.0 to 6.0)	3 (0.5%)	4.0 (2.0 to 8.0)	1 (0.3%)	HR 1.21 [1.00 to 1.46]	0.046 ^g
In-hospital length of stay, median (IQR), days	11.0 (8.0 to 18.0)	3 (0.5%)	14.0 (9.0 to 22.0)	1 (0.3%)	HR 1.26 [1.04 to 1.53]	0.02 ^g
Mortality in the ICU, n (%)	37 (5.8%)	–	23 (5.7%)	–	HR 1.32 [0.78–2.23]	0.29 ^g

VHA: Viscoelastic hemostatic assay, **SD:** Standard deviation, **IQR:** Interquartile range, **MD:** Mean Difference, **OR:** Odds Ratio, **HR:** Hazard Ratio, **ICU:** intensive care unit, **QALY:** Quality-Adjusted Life Year, **UDPB:** Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery, **KDIGO:** Kidney Disease Improving Global Outcomes.

^a The primary outcome was the estimation of the incremental cost-utility ratio of the VHA algorithm for ongoing bleeding during or after cardiac surgery. The incremental cost-utility ratio was calculated by dividing the difference between the overall cost of the VHA and the control periods and the difference between the QALY of the VHA and control periods. The incremental cost-utility ratio is expressed in euros per QALY. Also see the complete case analysis in **Supplemental eTable 4**.

^b See details for cost calculation in **Supplemental eTable 4**.

^c Linear mixed model adjusted for the randomization period as fixed effect and center as random effect with Period 1 as the reference (*i.e.*, standard blood tests). Costs and utility uncertainty were estimated using bootstrapping methods (see **Supplemental eTable 4** for unadjusted analysis).

^d Utility was estimated based on patients' quality of life during 1-year postoperatively according to the EuroQol Five-dimensions and 3 Level version (EQ-5D-3 L) auto-administered questionnaire (see details in **Supplemental eTable 4**). Length and quality of life were expressed as quality-adjusted life-years (QALY). The measure of the disease burden ranged from 0 (death) to 1 (perfect health). For instance, a mean QALY of 0.6 means that the patient lived 0.6 years with a perfect health status after surgery.

^e The number (%) of patients alive at 1-year follow-up without reintervention following hospital discharge (*i.e.*, avoided events). Reintervention included thoracic surgery whatever the cause (*i.e.*, infection, pleural or pericardial effusion).

^f Logistic mixed model adjusted for the randomization Period as fixed effect and center as random effect with Period 1 as the reference (*i.e.*, standard blood tests). See **Supplemental eTable 4** for unadjusted analysis.

^g Survival frailty model adjusted for the randomization Period as a fixed effect and center as a random effect with Period 1 as the reference (*i.e.*, standard blood tests). The events considered for the survival models were extubation, discharge from intensive care unit, or hospitalization. Unlike death, these are "positive" events for the patient; Hazard Ratio is therefore interpreted as follows: HR > 1 indicates that patients in the VHA period have a shorter duration of intubation or hospitalization than patients in the reference period.

^h Transfusion during initial hospitalization and the following year. Mean number of labile blood products were calculated among patients receiving transfusion.

ⁱ Classification based on 9 events occurring during surgery or the first postoperative day: delayed sternal closure, postoperative chest tube output in the first 12 h after chest closure, transfusion of packed red blood cells, plasma, platelets, use of prothrombin complex concentrates, fibrinogen or recombinant activated factor VII, and surgical reintervention. Finally, the total score defines 5 classes of severity of perioperative bleeding (*i.e.*, class 0 insignificant, class 1 mild, class 2 moderate, class 3 severe, class 4 massive). [26].

^j Acute kidney disease was classified according to the increase in serum creatinine level postoperatively compared with the preoperative period. KDIGO 1, 2 and 3 refer to a respective increase of 1.5–1.99 times (1), 2–2.99 times (2) and 3 times or more (3) baseline serum creatinine. [42] The initiation of renal replacement therapy was classified as KDIGO 3. The worse serum creatinine level 1-year postoperatively was considered.

^k Patient requiring inotropic agent for 12 h or more postoperatively.

^l The onset of atrial fibrillation/flutter or sustained ventricular arrhythmia 1-year postoperatively.

^m Any significant postoperative neurologic disorder including confusion, seizure, and strokes up to 1-year follow-up.

ⁿ Includes pulmonary embolism, limb ischemia, or coronary or graft occlusion up to 1-year postoperatively.

control period, adjusted OR, 0.69 [95% CI, 0.52 to 0.91], $P = 0.008$. The incidence of acute kidney injury and renal replacement therapy during ICU stay did not differ between periods. The median duration of mechanical ventilation did not differ between periods. The median in-hospital length of stay was significantly shorter in the VHA period: 11.0 days (8.00–18.00) vs. 14.0 (9.00–22.00) in the control period, adjusted HR, 1.26 [95% CI, 1.04–1.53], $P = 0.02$. Mortality in the ICU was not different between periods: 5.8% in the VHA vs. 5.7% in the control period, HR, 1.32 [95% CI, 0.78–2.23], $P = 0.29$ (other secondary outcomes in **eTable 4** and **eTable 5**, **Supplement 2**). The average adherence rate for the VHA-guided algorithm was 72.9% (**eTable 6**).

4. Discussion

In this multicenter, single-blind, stepped-wedge cluster-randomized controlled trial, the ICUR did not suggest that the VHA-guided algorithm was cost-effective for the management of intra- or postoperative bleeding compared with standard tests, with a large uncertainty in the distribution of differences in costs and outcomes. Although VHA led to a significant reduction in plasma and platelet transfusions, the lack of difference between periods

for transfusion-related costs can be explained by the significant increase in fibrinogen administration in the VHA period. Patients in the VHA period had shorter in-hospital lengths of stay than those in the control period, without a difference in 1-year mortality.

Single-center studies [27,28], as well as meta-analyses [29,30], have reported controversial results regarding the ability of VHA to reduce transfusion. In 2016, guidelines recommended (Grade IC) using VHA to guide individualized hemostatic intervention in case of perioperative bleeding [31]. Accordingly, a primary outcome with a medico-economic dimension was chosen to assess whether these guidelines could also help to reduce health costs.

Our results follow the same trends as the Karkouti et al. trial in which VHA was used as a preventive strategy, reducing major bleeding, red blood cell units, and platelet transfusion [11]. In the present study, the high incidence of reintervention compared with recent literature [32] may come from selection bias since participants presented with significant bleeding on inclusion (*i.e.*, more than 75% presented severe or massive bleeding, and 91% received at least one labile or stable blood product). In the control period, standard hemostatic testing coupled with the recommendation of ratio-driven transfusion of labile blood products at the time of the study could have led to unnecessary plasma or platelet transfusions [6,9]. On the other hand, VHA provides a comprehen-

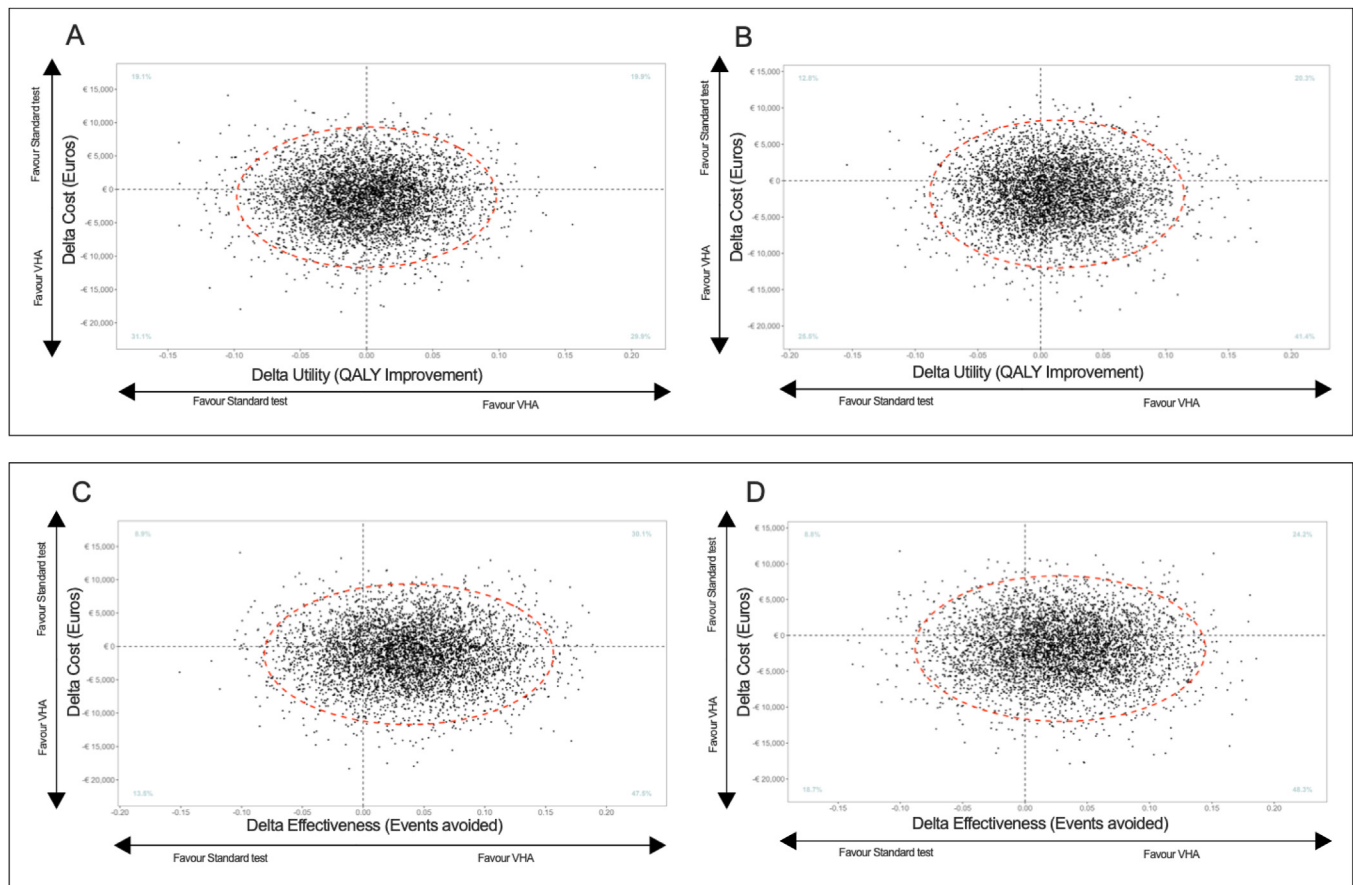


Fig. 2. Primary outcome and effectiveness.

Legend Fig. 2: Incremental Cost-Utility and Cost-effectiveness 1 year after surgery of the VHA intervention.

VHA: Viscoelastic hemostatic assay, **QALY:** Quality-Adjusted Life Year, **Delta cost:** difference between overall cost of VHA period and control period **Delta utility:** the difference of QALY between the VHA and the control period, **Delta effectiveness:** difference between the effectiveness of the VHA and the control period.

These scatter plots represent the incremental cost-utility ratio (**2A**, primary analysis and **2B**, as treated analysis) and incremental cost-effectiveness ratio (**2C**, primary analysis and **2D**, as treated analysis) of the VHA intervention for each participant. This plane shows cases in which VHA was respectively more expensive and less effective (top left), more effective but more expensive (top right), cheaper but less effective (bottom left), and cheaper and more effective (bottom right). The intersection between the vertical and horizontal lines represents the comparator (*i.e.*, control period). Events avoided refers to patients without death and surgical reintervention 1-year postoperatively. The red circle represents 95% of the replications.

sive view of clot development and dissolution, which enables the specific targeting of coagulation defects. Saving transfusion also raises the possibility of a reduction in transfusion-related organ dysfunction [33] or transfusion-associated circulatory overload [34], which could explain the reduction in hospital length of stay in the VHA period.

The equivalence of legacy (*i.e.*, TEG5000 and ROTEM Delta) and the latest versions remains a matter of debate today, and whether older algorithms validated on earlier versions can be used for TEG6s and ROTEM Sigma is questionable. However, recent publications confirm that new platforms deliver valid results even if some thresholds need to be validated [35,36]. To increase the transposability of our results, we chose to use the latest versions because of the fully automated cartridge-based assay. In the same way, we chose to combine the data of thromboelastometry and thromboelastography, since current guidelines recommend using VHA for bleeding management in cardiac surgery regardless of the device [6,9].

Several points should be considered when interpreting these results. 1) Although missing data were handled by multiple imputations, we cannot exclude these altered results of the primary outcome. 2) Because patients were included intraoperatively, a 1-year follow-up cannot appreciate the fluctuation of EQ-5D-3L compared with the preoperative period. 3) Surgery

accounted for more than half of the total cost per patient, whereas transfusion accounted for less than 15%. 4) The heterogeneity for some of the baseline characteristics could be explained by the randomization at a center level and the Step Wedge design. It generated significant heterogeneity in the length of control and VHA periods between centers. The significantly higher proportion of tricuspid valve procedures in the control period can be explained by a longer duration of the control period in a center with a high volume of tricuspid procedures. The same applies to Hydroxyethyl starch priming and Protamin/Heparin ratio, and may have hindered the potential benefits of the VHA technique [37,38]. However, randomization at a center level enhanced ethical acceptability and feasibility because patients were included during ongoing bleeding. 5) The adhesion rate could be explained by the complexity of the dual management of transfusion during bleeding while interpreting VHA results. The different locations of VHA testing between centers (*i.e.*, at bedside or in the laboratory) may have caused heterogeneous turnaround time, which could also alter adherence to the algorithm. 6) Since the study was conducted in France, the specific characteristics of the healthcare system may limit the validity of the medico-economic findings in the U.S. or international settings. 7) When the trial was designed, methodological guidelines for SW-CRT did not advise including the time effect in the sample size calculation, which could overestimate the

power [39,40]. Since then, new approaches have also included the time parameter [41].

5. Conclusion

The ICUR at 1-year did not suggest that VHA-guided management was cost-effective in cardiac surgery patients with ongoing bleeding, compared with standard tests.

However, from a patient blood management perspective, the reduction of plasma and platelet transfusions, as well as the shorter length of in-hospital stay for patients in the intervention period should be considered to the use of VHA point-of-care technique and algorithm in cardiac surgery centers.

CRedit authorship contribution statement

Dr. Mickael Vourc'h, Pr. Bertrand Rozec and Dr. Jean-Christophe Rigal had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dr. Mickael Vourc'h, Pr. Bertrand Rozec, Dr. Jean-Christophe Rigal, Dr. Elodie Boissier, Dr. Karim Lakhal.

Data acquisition: All authors participated in data collection and acquisition.

Data analysis and interpretation: Mickael Vourc'h, Pr. Bertrand Rozec, Dr. Jean-Christophe Rigal, Dr. Elodie Boissier, Dr. Karim Lakhal.

Drafting of the manuscript: Mickael Vourc'h, Pr. Bertrand Rozec, Dr. Jean-Christophe Rigal, Dr. Elodie Boissier, Dr. Karim Lakhal.

Critical revision of the manuscript for important intellectual content: All of the authors.

Statistical analysis: Morgane Pere.

Funding obtained: Pr. Bertrand Rozec, Dr. Jean-Christophe Rigal.

Administrative, technical or material support: All of the clinician authors.

Study supervision: Pr. Bertrand Rozec, Dr. Jean-Christophe Rigal, and Dr. Elodie Boissier.

Ethical statement

The study protocol was designed by investigators, published and approved by the ethics committee of Nantes University Hospital (Comité de protection des personnes #2016/05) and was registered at the "Agence Nationale de Sécurité du Médicament et produit de santé" (ANSM ID RCB #2016-A00455-46). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Previous presentation

None.

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The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; The sponsor did not have the right to veto publication or to decide which journal the manuscript was submitted.

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Declaration of competing interest

Dr. Vourc'h declares personal fees from MSD, Pfizer, Baxter, and Grants from Fisher Paykel outside the submitted work. Pr. Rozec declares having received personal fees from LFB, Aguetant, Nordic Pharma, i-Sep. Dr. Rigal declares consulting fees from Vifor, research grants from i-Sep, congress support from Edwards and Fresenius outside the submitted work. Dr. Karim Lakhal declares having received consulting fees from Philips and congress registration support from Pfizer, Advanz Pharma/Correvio, and AOP Health. Dr. Diane Zlotnik declares personal fees from i-Sep and LFB. Dr. Veronique Wurtz declares personal fees from Stago. Other authors declare that they have no conflict of interest involving the work under consideration for publication.

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The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; The sponsor did not have the right to veto publication or to decide which journal the manuscript was submitted.

Appendix A. Collaborators and additional contributions

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Data Sharing Statement: see Supplement 3.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.accpm.2025.101704>.

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