ORIGINAL ARTICLE
ARTIGO ORIGINAL

Rotational thromboelastometry in the perioperative period of cardiac surgeries: cost-effectiveness analysis and budget impact

Tromboelastometria rotacional no período perioperatório de cirurgias cardíacas: custo-efetividade e impacto orçamentário

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Keywords
thrombelastography, blood coagulation, thoracic surgery, biomedical technology assessment, cost-effectiveness evaluation

ABSTRACT

Objective: The transfusion of blood components and blood products in cardiac surgery patients can be guided by protocols based on standard laboratory tests and/or clinical decisions (Standard-of-Care, SOC) or viscoelastic haemostatic assays (VHA). The aim of this study is to evaluate the cost-effectiveness and budget impact of VHAs compared to SOC. **Methods:** A decision tree model was built in TreeAge Pro® 2009. Costs and benefits were taken from the medical literature. The cost-effectiveness was evaluated in a base-case scenario and a worst-case scenario, considering low costs of adverse events. The budget impact was evaluated from data taken from Datasus. Cost data were measured in 2019 USD and outcomes were measured in QALYs. **Results:** VHAs were considered dominant in the base-case scenario and very cost-effective in the worst-case scenario (ICER = $ 1,083.21 USD/QALY). The budget impact analysis varied from a cost-saving result in the base-case scenario to a reasonable increase in cost in the worst-case scenario. Since the total market share of the technology is unlikely, a reasonable estimative for the base-case scenario and the worst-case scenario are about -$275 million USD and $132 million USD, respectively. **Conclusion:** We conclude that the VHAs are cost-effective and should be recommended for the use in the perioperative period of cardiac surgeries, especially for patients with a high risk of hemorrhage or coagulation problems.

Palavras-chave:
tromboelastografia, coagulação sanguínea, cirurgia torácica, avaliação da tecnologia biomédica, avaliação de custo-efetividade

RESUMO

Objetivo: A transfusão de sangue, hemocomponentes e produtos sanguíneos em pacientes submetidos a cirurgia cardíaca pode ser guiada por protocolos baseados em testes laboratoriais padrão e/ou decisão clínica (Standard-of-Care, SOC) ou testes viscoelásticos (TVEs). O objetivo deste estudo é avaliar o custo-efetividade e o impacto orçamentário dos TVEs em comparação com o SOC. **Métodos:** Um modelo de árvore de decisão foi construído em TreeAge Pro® 2009. Os parâmetros de custos e benefícios foram obtidos da literatura médica. A relação custo-efetividade foi avaliada em um cenário-base e no pior cenário, considerando baixos custos de eventos adversos. O impacto orçamentário foi avaliado a partir de dados extraídos do Datasus. Os custos foram avaliados em USD 2019 e os desfechos em AVAQs. **Resultados:** Os TVEs foram considerados dominantes no cenário-base e muito custo-efetivos no pior cenário avaliado (RCEI = 1.083,21 USD/QALY). A análise de im-

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pacto orçamentário variou de um resultado de economia de custos no cenário-base a um aumento razoável no custo no pior cenário. Como a hipótese de que a tecnologia será adotada para toda a demanda do mercado é improvável, estimativas razoáveis para o cenário-base e o pior cenário são de aproximadamente -275 milhões de USD e 132 milhões de USD, respectivamente. **Conclusão:** Concluímos que os VHAs são econômicos e devem ser recomendados para uso no período perioperatório de cirurgias cardíacas, principalmente para pacientes com alto risco de problemas de hemorragia ou coagulação.

Introduction

Cardiovascular diseases (CVDs) have become a major concern in Brazil due to population aging and a high prevalence of chronic diseases, such as diabetes and hypertension (Brasil, 2011; Prince *et al*., 2015; Santos *et al*., 2015; Theme Filha *et al*., 2015; Souza & Peixoto, 2017; Massa *et al*., 2019). Specifically, ischemic heart disease and cerebrovascular diseases were the two main causes of death in 2017, with mortality rates of 80.0 and 56.6 per 100.000 inhabitants, respectively (DANTPS/SVS/MS, 2019). Myocardial revascularization using cardiopulmonary bypass (CPB) with 2 or more grafts was the most common cardiovascular surgery performed between 2009 and 2018 in Brazil (Brasil, 2019). By diverting blood and providing a bloodless surgical field, CPB allows the manipulation of the patient's heart (Souza & Elias, 2006; Braile, 2010). However, the patient who undergoes cardiac surgery, especially with CPB, may experience massive blood losses due to non-surgical causes, surgical causes or coagulation disorders. If not controlled, massive bleeding can contribute to increased patient morbidity and mortality (Miana *et al*., 2004; Whitlock *et al*., 2005; Santos *et al*., 2007; Costa *et al*., 2012; Wikkelsø *et al*., 2016; Lodewyks *et al*., 2018). The control of massive bleeding is achieved through the transfusion of blood, blood products, and blood components.

The transfusion of blood components and blood products such as red blood cells (RBCs), fresh frozen plasma (FFP), fibrinogen, cryoprecipitate, platelets, and coagulation factors can be directed by algorithms based on routine laboratory tests and/or clinical decision (which will be jointly referred to as SOC, Standard-of-Care) or viscoelastic haemostatic assays (VHAs) (Bolliger & Tanaka, 2013; Wikkelsø *et al*., 2016). Although laboratory tests are widely available, the response time with the use of these tests can reach 45 to 60 minutes and the delay in conduct reduces its usefulness in the urgent treatment of coagulopathies (Craig *et al*., 2008; Benes *et al*., 2015; Wikkelsø *et al*., 2016; Wikkelsø *et al*., 2017; Lodewyks *et al*., 2018). It is also argued that the prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests are weak predictors of bleeding in critically ill patients (Lier *et al*., 2013). In addition, studies indicate that 15 to 50% of all allogeneic blood transfusions are inappropriate and the conduct regarding transfusion is highly variable between health services (Görlinger *et al*., 2013).

VHAs have increased their representativeness because of their capacity to distinguish between the most important coagulopathies, such as thrombocytopenia, deficiency of coagulation factors, heparin effect, hypofibrinogenemia and hyperfibrinolysis, and the possibility of a targeted, individualized and timely intervention (Craig *et al*., 2008; Benes, *et al*., 2015). With the use of VHAs close to the patient, the response time can drop to 15 to 20 minutes, with some tests being ready within five minutes (Görlinger *et al*., 2013; Lodewyks *et al*., 2018). The rapid and comprehensive results made VHAs popular to monitor the coagulation in patients undergoing cardiac surgery, liver transplantation and obstetric procedures (Wang *et al*., 2010). In addition to the faster intervention, these tests are associated with a reduction in the amount of allogeneic products used in patients, with potential clinical benefit (Wikkelsø *et al*., 2016; Fahrendorff *et al*., 2017; Serraino & Murphy, 2017; Wikkelsø *et al*., 2017; Lodewyks *et al*., 2018).

Cardiac surgeries are the biggest consumers of blood products (Horvath *et al*., 2013). Transfusion of allogeneic blood products, despite its importance in saving patients' lives, has been associated with adverse outcomes such as increased chance of infections, thromboembolic events, acute kidney injury (AKI), pulmonary complications, sepsis and mortality in patients undergoing surgical procedures (Engoren *et al*., 2002; Dellinger & Anaya, 2004; Murphy *et al*., 2007; Aronson *et al*., 2008; Marik & Corwin, 2008; Glance *et al*., 2011; Bhaskar *et al*., 2012; Santos *et al*., 2013). There is some disagreement in the literature about the causality of this relationship (Murphy *et al*., 2007, 2015; Andrade, 2017; Serraino & Murphy, 2017). Nonetheless, authors suggest that all possible measures to reduce the unnecessary or inappropriate use of allogeneic products should be taken (Görlinger *et al*., 2013).

Despite this controversy, recent systematic reviews have shown some interesting advantages in terms of final outcomes with the use of VHAs during various types of procedures, including cardiac surgeries, but the result is not stable throughout the studies (Wikkelsø *et al*., 2016; Fahrendorff *et al*., 2017; Serraino & Murphy, 2017; Lodewyks *et al*., 2018). We conducted a systematic review and found some advantages for patients with the use of the VHAs. Specially, mortality (3.4% vs. 6.8%; RR = 0.50, 95% CI = 0.26-0.96, p-value = 0.04; I^2 = 1%, p-value = 0.40; 689 patients, seven studies; fixed-effects model) and the risk of acute kidney failure seem to be reduced in clinical relevant levels (10.5% vs. 17.6%; RR = 0.56, 95% IC = 0.36-0.87, p-value = 0.009; I^2 = 0%, p-value = 0.43; 449 participants, five studies; fixed-effects model).

The costs of cardiac surgeries are significant for the public system in Brazil (Siqueira *et al*., 2017; Stevens *et al*., 2018). An estimative show that the cost of cardiac surgeries in Brazil is

between 15,675.81 to 24,994.18 USD, depending on the severity of the case (Titinger *et al.*, 2015). Despite being more efficacious for the management of transfusions, the VHA-based protocols are expected to add an extra cost to the procedure. So, in many health services, transfusion is still guided by SOC. Given the apparent relevance of the technology for patients undergoing surgical procedures, the objective of this work is to evaluate the cost-effectiveness and budget impact of the use of VHAs compared to the SOC in patients undergoing cardiac surgery in the Brazilian public health system.

Methods

Cost-effectiveness analysis

A decision tree model was built in TreeAge Pro® 2009 to assess the cost-effectiveness relationship between VHA-guided or SOC-guided transfusions. In this model, four categories of variables were used: the *probability* of occurrence of events, *volumes* of blood products transfused, *costs* of hospital treatment, treatment of adverse events and allogeneic blood transfusion and treatment *outcomes*. The perspective of the health system was adopted, as recommended by the Brazilian guidelines on pharmacoeconomic analysis (Brasil, 2009, 2014b). This assessment followed the principles of the CHEERS report (Husereau *et al.*, 2013).

Intervention

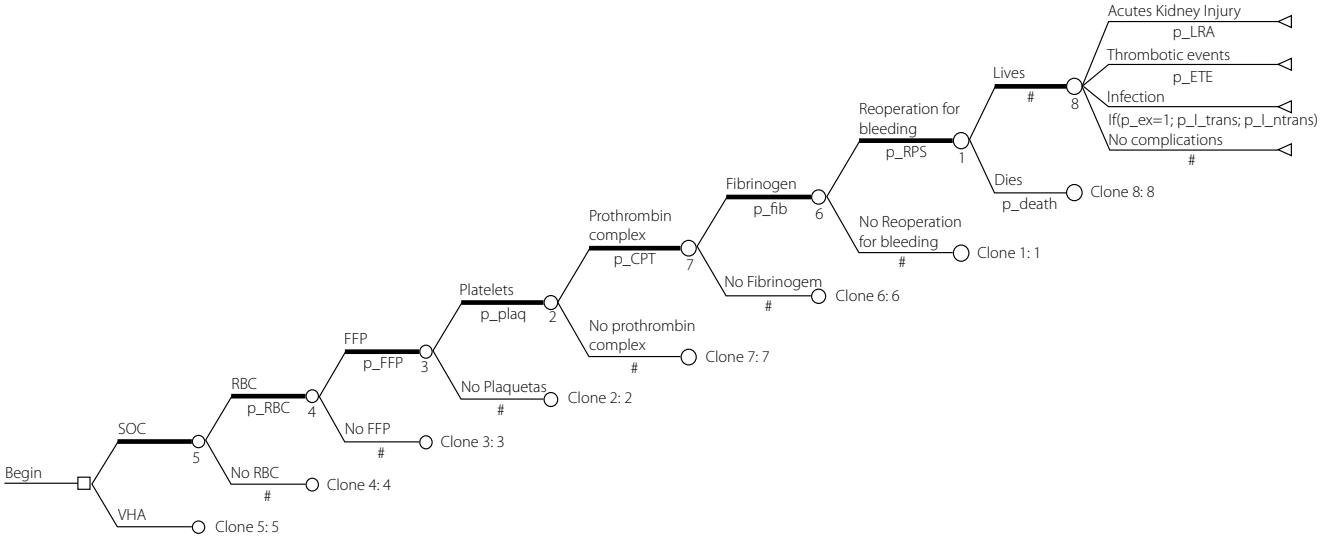
Two devices are most commonly recommended to perform VHAs: (i) thromboelastography (TEG®; Haemoscope Corporation, Niles, IL, USA), which was described in 1948 (Hartert, 1948; Luddington, 2005; and (ii) rotational thromboelastometry (ROTEM®; Tem Innovations, GmbH, Munich, Germany), which is a modification of the thromboelastography method that emerged in the 1990s (Luddington, 2005; Tem International GmbH, 2016). The principle of these tests is the change in blood viscoelastic properties during clot formation. The firmer the clot, the greater the force opposing the rotation or vibration movement of the device (Simioni *et al.*, 2008; Keene *et al.*, 2013; Benes, *et al.*, 2015; Görlinger *et al.*, 2016; Tem International GmbH, 2016; Zamper *et al.*, 2017). The VHA used in this economic evaluation was the ROTEM®.

Comparator

The VHAs were compared to the SOC, which is composed of standard laboratory tests and/or clinical decisions. The most common routine laboratory tests for coagulation control are prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time (ACT), platelet count (CP), and plasma fibrinogen concentration (CFP) (Whiting *et al.*, 2015). As said before, the SOC procedures vary a lot between health services (Görlinger *et al.*, 2013).

Model

The patients in the model enter one of the treatment groups and may or may not receive transfusions of RBC, FFP or platelets, or need to use fibrinogen or prothrombin complex. Patients may also undergo reoperation due to bleeding. After this, patients may live or die and, if they survive, they might have complications associated with the procedure, such as acute kidney injury, thromboembolic event or infection, or they might not suffer complications (Figure 1). The hypothetical cohort was constructed considering patients undergoing cardiac procedures with data from a previous meta-analysis conducted by the same research group (Supplementary Materials – Appendix 1). Each patient in the VHA group was considered to have been tested three times during the perioperative period and each test consisted of four trials: EXTEM, INTEM, FIBTEM and HEPTEM (Whiting *et*



SOC: Standard-of-Care; VHA: viscoelastic haemostatic assay; RBC: red blood cell; FFP: fresh frozen plasma.

Figure 1. Schematic model.

al., 2015) (Supplementary Materials – Appendix 2). In the SOC group, the tests performed were prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time (ACT), platelet count (PC), and plasma fibrinogen concentration (PFC) (Whiting *et al.*, 2015) and it was considered that they were performed only once during the procedure.

Probabilities

Data on the probabilities of transfusion of RBC, FFP, platelets, fibrinogen and prothrombin complex, as well as the probabilities of death, reoperation from bleeding, acute kidney injury, and thromboembolic events, were taken from our meta-analysis. Data not available, such as the risk of infection, were derived from other studies published in the literature and duly explained and referenced (Supplementary Materials - Appendices 3). The risk of infection was estimated from a retrospective population-based study in the United Kingdom (Murphy *et al.*, 2007). The data by Murphy *et al.* (2007) specifically address the risk of infections generated by the transfusion of RBCs. Patients who had infections, after being treated, were considered to have the same life expectancy as other patients who had no complications. These infections refer to patients who did not die as a result of the procedure within a short-term follow-up.

Outcomes

To calculate the clinical benefit of the technology, we used the population's life expectancy adjusted for complications. Thus, the results of the models were initially measured in terms of life-years gained (LYG). The life expectancy of patients with acute kidney injury was estimated based on the median survival observed in a study that evaluated the impact of the recovery of renal function on long-term mortality after coronary artery bypass grafting (Mehta *et al.*, 2010). The median age of patients in the study was 65 years (IQR = 57-73). The median survival of patients who had and did not have acute kidney injury was extracted from the Kaplan-Meyer curve using the Engauge Digitizer® 12.0. It was assumed that patients who had a nosocomial infection and did not die had the same life expectancy as individuals who did not have this event. The life expectancy of individuals who experienced thromboembolic events was estimated based on another specific study for individuals who experienced ischemic stroke (AVEi) (Brønnum-Hansen *et al.*, 2001). In the study, about 72% of patients survived a stroke for more than 27 days, unlike the case of AKI in which few patients die at the beginning of the follow-up period (Mehta *et al.*, 2010). In 10 years, the risk of death was about 76%. As in-hospital and short-term mortality is considered in the model, the 10-year survival time was used to estimate the life expectancy of patients who had a thromboembolic event and survived. The life expectancy data used is available in Supplementary Materials – Appendix 4.

Quality of life data from patients undergoing cardiac surgery are available in the literature (Oddershede *et al.*, 2014; Heiskanen *et al.*, 2016; Izawa *et al.*, 2018). Izawa *et al.* (2018) examined age-related differences in health-related utility using the SF-6D scale in patients five months after cardiac surgery. They observed scores of 0.72 ± 0.14 in middle-aged patients and 0.71 ± 0.10 in elderly patients. These values are very close to the scores found by Oddershede *et al.* (2014) using the EQ-5D-3L. They found values of 0.72 (SD = 0.20; n = 233) and 0.73 (SD = 0.16; n = 149) for patients in the estimation group and the validation group, respectively. Heiskanen *et al.* (2016) found utility values of 0.795 (0.765-0.826), in the baseline, and +0.053 (0.017-0.088) after 12 months. Given the proximity of the numbers, we decided to adopt a conservative approach and assume the value found by Oddershede *et al.* (2014) for being the largest sample among the three studies, which is roughly equivalent to the study by Izawa *et al.* (2018) who is the most recent. Disutility values were used in long-term adverse events. These disutilities were specifically applied to cases of thrombotic events and acute kidney injury since it was considered that individuals who had an infection and did not die had the same outcome as individuals who did not have complications. These data were taken from a WHO report on the disabilities used in the Global Burden of Disease (World Health Organization, 2018). In this way, outcomes were measured in quality-adjusted life-years (QALYs). The data on utility and disutility used in the models are available in Supplementary Materials – Appendix 5 and 6.

Costs

The costs with the equipment and its supplies were derived from a proposal made by the company that represents the product in Brazil (Biomig Brasil), varying by 20% for more or less for the sensitivity analysis. A triangular distribution was used for the probabilistic sensitivity analysis, which only represents that there is a greater probability that the value will be close to that provided by the company. It is not an attempt to estimate a distribution for the variable. The costs were estimated from the perspective of the public health system, considering the company's proposal to work with the ROTEM® Delta System 4-channel equipment in commodate with a minimum monthly purchase of $7,242.88 PPP-USD in supplies. In commodate, there are no costs associated with the maintenance or depreciation of the equipment.

The cost of the cardiac procedure was estimated from a study of the literature for the public health system in Brazil (Titinger *et al.*, 2015). In the study, the cost is calculated from the patient's risk at low (34% of patients, 13,093.01 USD), moderate (39% of patients, 16,829.63 USD) and high (27% of patients, 20,876.06 USD). As data on mean and standard deviation for the procedures, in general, were not provided and the number of patients in each group is relatively close, instead of a gamma distribution, a triangular distribution

was used with the most likely value equal to the cost of the procedure in a moderate patient and the minimum and maximum costs equal to a 20% variation in this cost, adjusted to the value in PPP-USD (2019). The cost of reoperation for bleeding was not found directly in the literature. However, a study carried out in the USA estimated that the incremental cost of reoperation for bleeding is between 63 and 179% of the cost of the procedure (Gunnarsson *et al.*, 2015). Thus, the same value of the cardiac procedure was used to parameterize a triangular distribution with a more likely value equal to the value of the procedure.

The costs of thromboembolic events were estimated based on the cost of treating a stroke, as this is the event most reported by the studies that measured thrombotic complications (Shore-Lesserson *et al.*, 1995; Girdauskas *et al.*, 2010; Paniagua *et al.*, 2011; Weber *et al.*, 2012). About 45% of the direct costs of AVEi in the first year are associated with hospital treatment (Bergman *et al.*, 1995). Thus, the cost associated with the AVEi was estimated based on a study conducted in Brazil that evaluated the costs related to hospital treatment, considering the average and standard deviation data ([5,020 USD, SD = 3,065 USD (Safanelli *et al.*, 2019). The cost of treating AKI was estimated based on data from a cost-effectiveness study carried out in Brazil for a 5-year time horizon (Ramirez *et al.*, 2017).

No data were found on the treatment costs of cardiac surgery patients who had nosocomial infections in Brazil. Thus, the cost of nosocomial infections was estimated based on a study conducted in a philanthropic hospital in Belo Horizonte, Brazil. The study provided data on the median and interquartile range (Nangino *et al.*, 2012). The costs associated with platelet concentrate, RBCs and FFP were estimated from the Hemominas Foundation's table of products and services [ordinance no. 251/2019 (Hemominas, 2019)] and varied by 20% for more and less in a triangular distribution, and the volumes found in the previous meta-analysis (Supplementary Materials – Appendix 7). The costs associated with fibrinogen and prothrombin complex were estimated from the average value reported in the Price Panel of the Ministry of Planning. Individuals who needed fibrinogen and prothrombin complex were considered to have used a unit. The costs used in the model are available in Supplementary Materials – Appendix 8 and 9. Data in BRL was converted to USD using the OECD Purchase Parity Power conversion rate (2.071 in 2019).

Data analysis

Most of the studies that provided data for this assessment were conducted in patients with age close to the median age of this population. In cases where the confidence interval of the analysis was not reported or there was no way to calculate it, a triangular distribution with a 20% variation in relation to the point estimate was considered, as previously stated. The cost-effectiveness assessment was carried out using the expected value approach (Arrow & Lind, 1970). The outcome was reported in QALYs. A univariate sensitivity analysis was performed on the number of tests performed and on the cost variables of RBCs, FFP, platelets, fibrinogen, prothrombin complex, routine laboratory tests, ROTEM® tests and reoperation for bleeding. The result is reported in the form of a tornado diagram. The model variables were adjusted as distributions as instructed by Briggs *et al.* (2006), except when explicitly indicated, and a probabilistic sensitivity analysis (PSA) was conducted to assess the uncertainty in transition probabilities, costs and treatment outcomes through the simulation of 10,000 iterations. To determine the result of the study, various threshold values were considered (Pichon-Riviere et al., 2017; Santos *et al.*, 2018, 2019). No discount rate was applied since the intervention was performed during a surgical procedure; *i. e.*, it is a one-off event that is not chronic or repetitive. The costs of outcomes that are chronic were incorporated into the model from the perspective of total treatment cost at present value.

The VHAs were associated with a statistically significant reduction in mortality, risk of acute kidney injury, transfused red cell volume, risk of platelet transfusion, risk of FFP transfusion, and volume of FFP transfusion and a non-statistically significant advantage in terms of risk of reexploration for bleeding, risk of RBC transfusion, the volume of platelets transfused, use of fibrinogen, use of prothrombin complex, use of factor VIIa, length of hospital stay or length of ICU stay (data from our own meta-analysis). Therefore, the higher the cost of adverse events is, the more the VHAs would be favored. Not to risk overestimating the cost of such adverse events, we conducted a secondary one-way sensitivity analysis dividing the costs of adverse events from 1 to 10. These values were chosen for convenience. We believe that a 10 times reduction in the costs of adverse events is already high enough to leave no doubt about the results.

Budget impact analysis

According to the Ministry of Health's guideline, the cost of treating a disease consists of multiplying the population that would potentially benefit from the technology by the cost of the alternatives (Brasil, 2014a). The difference between these costs indicates the incremental budget impact. The budgetary impact analysis was carried out from the perspective of the budget holder, in this case, the public health system, like the cost-effectiveness analysis. As directed by the Ministry of Health, all direct costs related to technology for the payer were incorporated into the analysis (Brasil, 2014a). This includes differences in terms of the cost of adverse events and supplies used. The valuation was based on the company's minimum of $7,242.88 USD minimum monthly purchase. In this way, the equipment can be supplied by commodate and there is no need to incorporate the equipment, maintenance

and depreciation costs to the analyses. The analyses were made by scenario, to make the report as clear as possible. The VHAs market share was varied between 10 and 100% with 10% jumps.

The decision tree used to evaluate the cost-effectiveness was adjusted to calculate the budget impact for the population of cardiac surgery patients with micro-simulation in a 5-year time horizon. The values for the five years were calculated at present value, there was no adjustment for the discount rate. The assessment of the number of cardiac procedures performed in Brazil was calculated using Datasus, a government-maintained database. Data on the number of approved cardiovascular surgeries were obtained between 2008 and 2018 (Supplementary Materials – Appendix 10). The projection data for the years 2020 to 2024 was calculated using simple linear regression. The data fit was good (R^2 = 0.945; Supplementary Materials – Appendix 11).

Results

Cost-Effectiveness Analysis

ROTEM® was considered dominant over SOC in the base case scenario. It was associated with a lower cost ($25,440.07 USD vs. $26,421.44 USD) and higher effectiveness (8.262 QALYs vs. 7.829 QALYs; Table 1). The tornado diagram of the deterministic sensitivity analysis showed that the number of assays done during the perioperative period is the most influential variable to the ICER, followed by the cost of the procedure, cost of treatment of AKI, cost of reoperation for bleeding and the costs of the ROTEM® assays. Nevertheless, none of these variables turned the ICER positive; *i. e.* in all evaluated scenarios in this sensitivity analysis, ROTEM® is dominant to the SOC (Figure 2). The PSA showed strong robustness in the analysis (93.35% of the iterations fell on the forth quadrant; higher effectiveness and lower cost). A small proportion of the iterations fell in the first quadrant (higher effectiveness and higher cost; 6.26%). 5.95% fell in the area below a threshold of 0.5 GDP per capita/QALY (4,460.40 in 2018; data from the World Bank) and 0.31% over this threshold (Figure 3).

As can be seen, a good part of the most influential variables to the ICER is associated with the costs of adverse events. The one-way sensitivity analysis considering the division of the costs of adverse events between 1 and 10 showed that, in group, they could turn the ICER positive when this divisor is higher than ≅2.55 (Figure 4). Independently, even if the divisor is set to ten, the ICER would be equal to $1,083.21 USD/QALY; that is, ROTEM® would still be considered cost-effective when compared to any previously suggested threshold [Materiais Suplementares – Apêndice 12; (Santos *et al.*, 2018, 2019)].

Table 1. Cost-effectiveness table of VHAs compared to SOC with outcomes measured in QALYs

Technology	Cost (BRL)	Incremental cost (BRL)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	CER (BRL/QALY)	ICER (BRL/QALY)
VHA	$25,440.07		8.262		3079 $/E	
SOC	$26,421.44	$981.36	7.829	-0.433	3375 $/E	(Dominated)

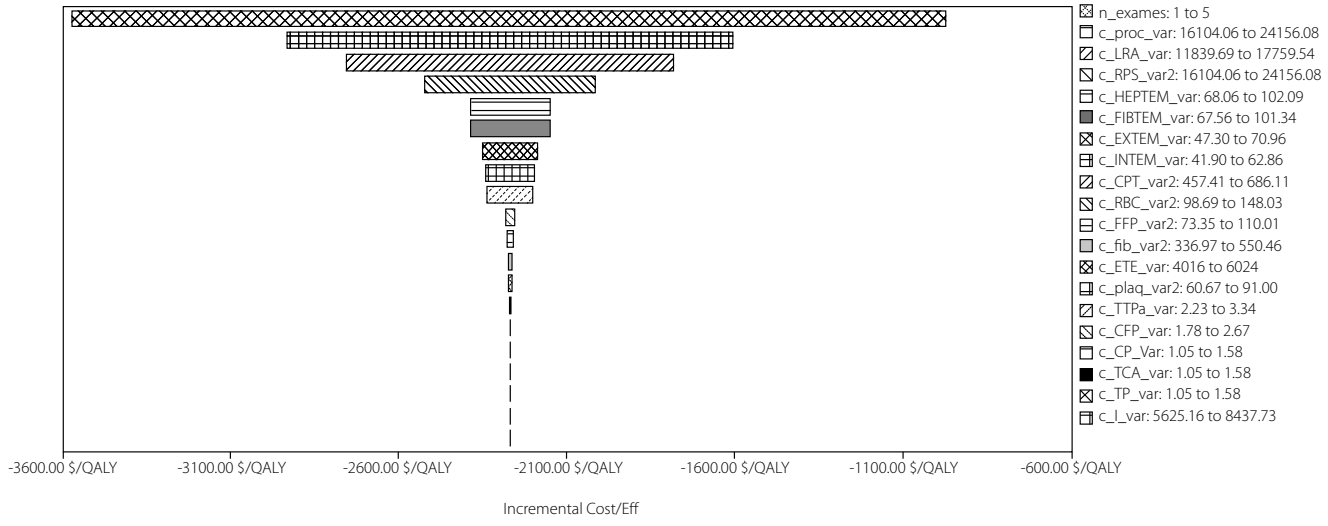


Figure 2. Tornado diagram of the cost-effectiveness ratio varying costs variables and number of exams order by impact on the ICER.

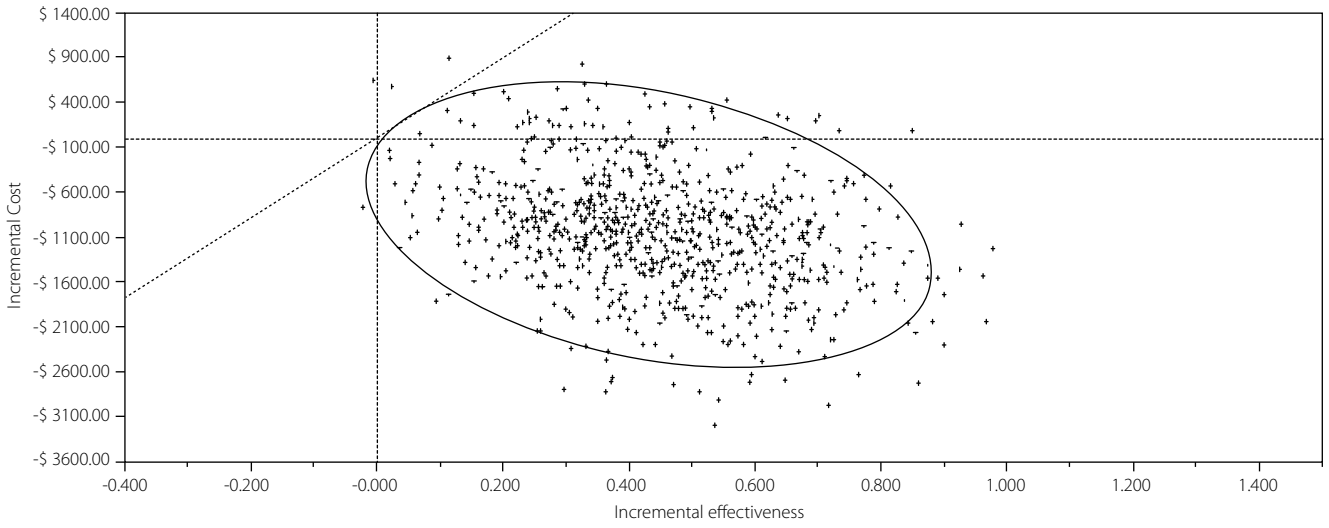


Figure 3. Incremental cost-effectiveness scatterplot between the VHA and SOC with outcomes measured in QALY and the threshold defined at zero.

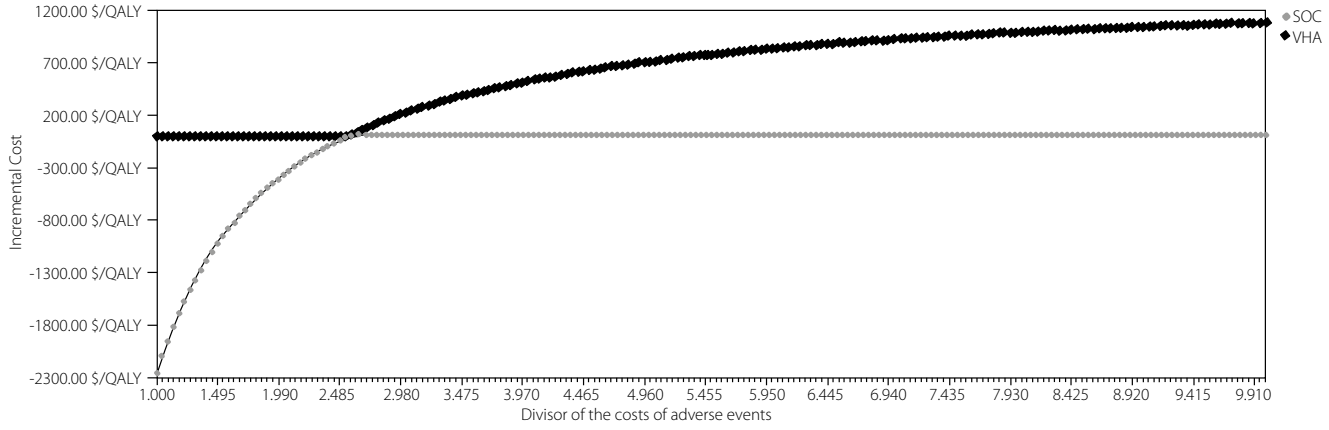


Figure 4. One-way sensitivity analysis considering that the costs of adverse event might not be totally imputed to the technologies and varying the divisor between 1 and 10.

Budget impact analysis

The results here are presented in two tables, considering the divisor of the cost of adverse events equal to 1 (base case scenario) and to 10 (worst case scenario). Table 2 shows the results of the base case scenario. As expected, the VHA would provide savings varying between -$90,237,868.62 and -$902,378,686.20 for a market share of 10% and 100%, respectively, in five years. If the market share of the technology increased steadily absolute 10% per year, the budget impact would be a saving of -$274,933,128.34 in five years.

Table 3 shows the result of the worst-case scenario considered. In this scenario, the budget impact would be between $43,187,031.69 and $431,870,316.85 for a market share of 10% and 100%, respectively, in five years. If the market share of the technology increased steadily absolute 10% per year, the budget impact would be $131,624,071.34 in five years.

Discussion

The efficiency analysis presented data favorable for the recommendation of the technology. The ICER showed dominance for ROTEM® in the base case scenario and cost-effectiveness in the worst-case scenario compared to any previously suggested threshold. In the base case scenario, the VHA is very cost-saving (around -$902 million USD). In the worst-case scenario, it has a maximum budget impact of about $432 million USD. These scenarios with 100% market share are very unlikely, though. A more reasonable estimative for the base case scenario and the worst-case scenario are about -$275 and $132 million USD, respectively.

Health Technology Assessment agencies around the world have previously evaluated the cost-effectiveness of protocols based on VHAs in comparison to protocols based

Table 2. Incremental budget impact of the VHA for cardiac procedures considering the total costs of adverse events

Market Share ROTEM	2020	2021	2022	2023	2024	Total
0.1	-$17,250,860.53	-$17,451,222.50	-$18,149,388.72	-$18,600,327.69	-$18,786,069.18	-$90,237,868.62
0.2	-$34,501,721.06	-$34,902,445.01	-$36,298,777.43	-$37,200,655.38	-$37,572,138.35	-$180,475,737.24
0.3	-$51,752,581.59	-$52,353,667.51	-$54,448,166.15	-$55,800,983.08	-$56,358,207.53	-$270,713,605.86
0.4	-$69,003,442.12	-$69,804,890.02	-$72,597,554.87	-$74,401,310.77	-$75,144,276.70	-$360,951,474.48
0.5	-$86,254,302.65	-$87,256,112.52	-$90,746,943.58	-$93,001,638.46	-$93,930,345.88	-$451,189,343.10
0.6	-$103,505,163.19	-$104,707,335.03	-$108,896,332.30	-$111,601,966.15	-$112,716,415.06	-$541,427,211.72
0.7	-$120,756,023.72	-$122,158,557.53	-$127,045,721.02	-$130,202,293.85	-$131,502,484.23	-$631,665,080.34
0.8	-$138,006,884.25	-$139,609,780.04	-$145,195,109.73	-$148,802,621.54	-$150,288,553.41	-$721,902,948.96
0.9	-$155,257,744.78	-$157,061,002.54	-$163,344,498.45	-$167,402,949.23	-$169,074,622.59	-$812,140,817.58
1	-$172,508,605.31	-$174,512,225.05	-$181,493,887.16	-$186,003,276.92	-$187,860,691.76	-$902,378,686.20

Table 3. Incremental budget impact of the VHA for cardiac procedures considering the costs of adverse events divided by ten

Market Share ROTEM	2020	2021	2022	2023	2024	Total
0.1	$8,235,621.49	$8,413,328.88	$8,634,957.27	$8,858,699.95	$9,044,424.09	$43,187,031.69
0.2	$16,471,242.98	$16,826,657.76	$17,269,914.53	$17,717,399.91	$18,088,848.19	$86,374,063.37
0.3	$24,706,864.47	$25,239,986.64	$25,904,871.80	$26,576,099.86	$27,133,272.28	$129,561,095.06
0.4	$32,942,485.96	$33,653,315.52	$34,539,829.07	$35,434,799.81	$36,177,696.38	$172,748,126.74
0.5	$41,178,107.45	$42,066,644.40	$43,174,786.33	$44,293,499.76	$45,222,120.47	$215,935,158.43
0.6	$49,413,728.94	$50,479,973.28	$51,809,743.60	$53,152,199.72	$54,266,544.57	$259,122,190.11
0.7	$57,649,350.43	$58,893,302.16	$60,444,700.87	$62,010,899.67	$63,310,968.66	$302,309,221.80
0.8	$65,884,971.92	$67,306,631.04	$69,079,658.13	$70,869,599.62	$72,355,392.76	$345,496,253.48
0.9	$74,120,593.41	$75,719,959.93	$77,714,615.40	$79,728,299.57	$81,399,816.85	$388,683,285.17
1	$82,356,214.90	$84,133,288.81	$86,349,572.67	$88,586,999.53	$90,444,240.95	$431,870,316.85

on SOC (Craig *et al.*, 2008; Whiting *et al.*, 2015). Whiting *et al.* (2015) made an indirect assessment of the effect of reducing the volume of transfusion with clinical outcomes of patients based on data of strong associations presented in the literature. With that, they concluded the "probable" cost-effectiveness of the procedure. For the cardiac surgery model, savings of £43 GBP were observed with the use of ROTEM®, £79 GBP with the use of TEG®, and £132 GBP with the use of the Sonoclot Analyzer (Whiting *et al.*, 2015). The results found in Scotland are similar (Craig *et al.*, 2008). The analysis of the scenarios suggested that VHAs remain cost-effective, except in two cases: when the number of tests per year is small or when VHAs are used as a complement to routine tests and not as substitutes (Craig *et al.*, 2008; Whiting *et al.*, 2015). These results are in consonance with ours, however, they were obtained from assumptions made based on intermediate outcomes, like the risk of transfusions. We used final outcomes and intermediate outcomes for our analysis.

It is very unlikely, given the results observed in our meta-analysis and other previously published studies, that this technology is not effective. A recent systematic review published by the Cochrane Collaboration reported that VHAs reduce mortality (7.4% vs. 3.9%; RR = 0.52; 95% CI = 0.28-0.95; I^2 = 0%; p-value = 0.033; 8 studies; 717 participants; low level of evidence), the proportion of patients receiving RBC (RR = 0.86; 95% CI = 0.79-0.94; p-value = 0.001; I^2 = 0%; 10 studies; 832 participants; low level of evidence), FFP (RR = 0.57; 95% CI = 0.33-0.96; p-value=0.034; I^2 = 86%; 8 studies; 761 participants; low level of evidence), platelets (RR = 0.73; 95% CI = 0.60-0.88; p-value = 0.0012; I^2 = 0%; 10 studies; 832 participants; low level of evidence) and the risk of dialysis-dependent kidney failure (RR = 0.46; 95% CI = 0.28-0.76; p-value = 0.0028; I^2 = 0%; three studies; 200 patients) (Wikkelsø *et al.*, 2016; Wikkelsø *et al.*, 2017). Other subsequent reviews, however, showed less favorable results for the technology (Fahrendorff *et al.*, 2017; Serraino & Murphy, 2017; Lodewyks *et al.*, 2018).

Wikkelsø *et al.* (2016) included different populations to be able to demonstrate a significant benefit in terms of mortality with the use of VHAs. The problem with the demonstration of some of the beneficial effects of the VHAs seems to

be the small samples included in the randomized controlled trials. Even clinically relevant improvements in final outcomes, such as mortality, could be difficult to demonstrate if the optimal information size is not achieved. Mortality is the most important final outcome included in all these meta-analyses. Another five systematic reviews assessed mortality outcomes. None of them reported statistically significant advantage with the use of VHA at a 5% significance level, but most of them suffer from imprecision associated to small sample sizes and short follow-up periods (Deppe *et al.*, 2016; Fahrendorff *et al.*, 2017; Serraino & Murphy, 2017; Lodewyks *et al.*, 2018; Li *et al.*, 2019). Some of them were able to demonstrate statistically significant results at a 10% significance level (Fahrendorff *et al.*, 2017; Serraino & Murphy, 2017). An important distinction here is that cardiac patients with high risk of bleeding or coagulopathies seem to be the most favored by the intervention in terms of short-term mortality [6.6% vs. 20.6%; RR = 0.33, 95% CI = 0.12-0.91, p-value = 0.03; I^2 = 0%, p-value = 0.34; two studies, 144 patients; random-effects model; (Santos *et al.*, 2020)]. Another difficulty associated to the demonstration of relevant clinical results is the highly variable transfusion protocols used in different health services (Görlinger *et al.*, 2013).

All previous meta-analysis found in the literature demonstrated significant advantages in terms of AKI (Deppe *et al.*, 2016; Wikkelsø *et al.*, 2016; Serraino & Murphy, 2017; Wikkelsø *et al.*, 2017). The advantage for VHAs in the risk of reoperation for bleeding was only showed by meta-analyses that included observational studies, which would be expected since their samples are much bigger (Bolliger & Tanaka, 2013; Deppe *et al.*, 2016; Li *et al.*, 2019). What is odd is that the relative risks are much more favorable for the VHAs in these studies [0.42 to 0.67 vs. 0.75 to 0.82; (Bolliger & Tanaka, 2013; Deppe *et al.*, 2016; Wikkelsø *et al.*, 2016; Serraino & Murphy, 2017; Wikkelsø *et al.*, 2017; Li *et al.*, 2019)]. The results on the risk of transfusion are also much more favorable for the VHAs in meta-analysis that included observational studies (Bolliger & Tanaka, 2013; Deppe *et al.*, 2016; Wikkelsø *et al.*, 2016; Serraino & Murphy, 2017; Wikkelsø *et al.*, 2017; Lodewyks *et al.*, 2018; Li *et al.*, 2019). There might be an overutilization of blood, blood products and blood components in the SOC group in observational studies. Since we might not be sure, we chose to use only data from randomized controlled trials in our meta-analysis. This "extra" advantage of the VHAs in meta-analyses that include observational studies is not seen for the mortality outcome (Deppe *et al.*, 2016; Wikkelsø *et al.*, 2016; Fahrendorff *et al.*, 2017; Serraino & Murphy, 2017; Wikkelsø *et al.*, 2017; Lodewyks *et al.*, 2018; Li *et al.*, 2019).

All models are simplifications of reality and, therefore, decisions about the essential elements of an assessment must be made to ensure that a model is useful for decision making (Briggs *et al.*, 2006). Complications resulting from the procedure or transfusions were not separated and were considered to have occurred within the hospitalization period, being attributed according to the result of the meta-analysis within each treatment arm. In incremental terms, it provides an assessment of how much has been gained in terms of clinical outcomes with the use of technology. The entire cost of treatment and loss of survival time associated with complications were considered within the arm of each technology. Considering the limitation of the minimum purchase of $7,242.88 USD per month for supplies in commodate situations, the model is only valid if the technology is used in at least 8 patients per month, considering that the assays will be performed three times during the perioperative period. The cost data for adverse events were estimated from the medical literature. The LRA cost data were taken from the economic modeling study by Ramirez *et al.* (2017) from the perspective of the Supplementary Health System in Brazil over a five-year time horizon due to the lack of more precise data. Some cost data were estimated from triangular distributions due to a lack of data on mean and standard deviation to generate a normal or gamma distribution. The assumption adopted that the risk of infection is due to RBC only, which could be estimated from the study Murphy *et al.* (2007), may not be true. However, this assumption is quite conservative, given that the RR of platelet and plasma transfusion favor the intervention a lot. A patient could use more than one vial of prothrombin complex or fibrinogen. But, since we did not have the average consumption in the literature, we assumed one unit per patient. This is a conserved assumption given that it favors the SOC as well. The economic evaluation was carried out only considering ROTEM®. However, no important difference has been demonstrated between TEG® and ROTEM®. The effect of both seems similar in relation to the outcomes (Wikkelsø *et al.*, 2016; Fahrendorff *et al.*, 2017; Serraino & Murphy, 2017; Wikkelsø *et al.*, 2017; Lodewyks *et al.*, 2018; Li *et al.*, 2019). The cost associated with TEG®, though, is lower than the costs of ROTEM®. That way, considering the costs of ROTEM® as VHA is also a conservative approach (Whiting *et al.*, 2015).

Conclusion

A recent systematic review states that, currently, the benefits shown by VHAs are not sufficient to allow a recommendation for incorporation (Lodewyks *et al.*, 2018). We respectfully disagree. Deppe *et al.* (2016) argue that the use of viscoelastic tests leads to a balanced transfusion regimen, decreases the amount of transfused products and can lead to a decrease in the rate of clinical complications. The authors also state and we agree that longer studies may be necessary to definitively demonstrate the effects of VHAs on mortality. Nevertheless, we would argue that (i) this is a technology that has been proven to be efficacious for final and intermediate outcomes by different meta-analyses (Deppe *et al.*, 2016; Wikkelsø

et al., 2016; Fahrendorff *et al*., 2017; Serraino & Murphy, 2017; Wikkelsø *et al*., 2017; Lodewyks *et al*., 2018; Li *et al*., 2019), (ii) has been found cost-saving by different studies (Craig *et al*., 2008; Whiting *et al*., 2015), and (iii) has no adverse effects for patients. If this technology is not to be recommended, what is? Therefore, we conclude that the VHAs are cost-effective and should be recommended for the use in the perioperative period of cardiac surgeries, especially for patients with a high risk of hemorrhage or coagulation problems.

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APPENDICES

1. Characteristics of participants in the primary studies included

Randomized Controlled Trial	Viscoelastic Haemostatic Assay	N	Conditions	Country	Hemorrhage or coagulopathy as an inclusion criterion?	Age range	Mean age	Proportion of males (%)	Mean BMI	ASA score	euroSCORE
Ak *et al.*, 2009	TEG	224	C	Turkey	No	NA	64.5	86.5	NA	NA	2.9
Avidan *et al.*, 2004	TEG	210	C	United Kingdom	No	NA	64	78	27.55	NA	NA
Cao *et al.*, 2015[1]	TEG	60	O	China	Yes	NA	NA	NA	NA	NA	NA
Cui *et al.*, 2010	TEG	31	C	China	No	NA	38.36	NA	NA	NA	NA
De Pietri *et al.*, 2016	TEG	60	H	Italy	Yes	18 a 80	58.2	63.3	NA	NA	NA
Girdauskas *et al.*, 2010	ROTEM	56	C	Germany	No	>18	61.64	57.55	27.26	NA	NA
Gonzalez *et al.*, 2015	TEG	111	T	USA	Yes	>18	39.51	70.21	25.70	NA	NA
Karkouti *et al.*, 2016	ROTEM	7402	C	Canada	No	NA	67	74.96	NA	NA	NA
Kempfert *et al.*, 2011[1]	ROTEM	104	C	Germany	Yes	NA	67.2	NA	NA	NA	7
Khalaf Adeli *et al.*, 2017[1]	ROTEM	80	C	Iran	No	NA	NA	NA	NA	NA	NA
Kultufan Turan *et al.*, 2006	ROTEG	40	C	Turkey	No	NA	NA	NA	NA	NA	NA
Lehmann *et al.*, 2019	ROTEM	26	C	Germany	Yes	≥18	70.75	67	NA	NA	5.5
Nakayama *et al.*, 2015	ROTEM	100	C	Japan	No	3 to 28 months	11.5 months	64	16.3	NA	NA
Nuttall *et al.*, 2001	TEG	92	C	USA	Yes	≥30	68.5	72.6	27.4	NA	NA
Paniagua *et al.*, 2011[1]	ROTEM	22	C	Spain	Yes	≥18	NA	NA	NA	NA	NA
Royston & Von Kier, 2001	TEG	60	C	United Kingdom	No	21 A 83	NA	NA	NA	NA	NA
Schaden *et al.*, 2012	ROTEM	30	Q	Austria	No	17 A 87	52.75	60	26.8	NA	NA
Shore-Lesserson *et al.*, 1999	TEG	105	C	USA	No	49.5 A 81.6	52.75	57.69	NA	NA	NA
Wang *et al.*, 2010	TEG	28	H	Taiwan	No	38.8 A 63.8	65.8	64.28	24.2	NA	NA
Weber *et al.*, 2012	ROTEM	100	C	Germany	Yes	≥18	71	62	26	3	6.7
Westbrook *et al.*, 2009	TEG	60	C	Australia	No	NA	63.65	70.25	NA	NA	NA

C: cardiac procedures; H: hepatic procedures; Q: burned victims procedures; O: orthopedic procedures; Ob: obstetric procedures; T: trauma patient procedures. [1] Full text unavailable.

2. Cost of supplies to perform ROTEM tests on cardiac patients considering that the equipment will be provided by commodatum

Tests	Reagents needed per test	Number of tests	Unit cost (USD)	Total Cost (USD)	Reference
INTEM	INTEM, STARTEM, cup/pin e 2 pipette tips	3	52.38	157.14	Company proposal and (Whiting *et al.*, 2015)
EXTEM	EXTEM, STARTEM, cup/pin e 2 pipette tips	3	59.130	177.39	
FIBTEM	FIBTEM, EXTEM, cup/pin e 3 pipette tips	3	84.45	253.34	
APTEM	APTEM, EXTEM, cup/pin e 3 pipette tips	0	85.074	0	
HEPTEM	HEPTEM, INTEM, cup/pin e 3 pipette tips	3	83.06	249.18	
Total				**837.05**	

3. Distribution of transition probabilities

Name	Description	Distribution	r	n	References
p_death_VHA	Probability of death with the use of VHAs.	Beta	12	350	Own meta-analysis
p_death_soc	Probability of death with the use of SOC	Beta	23	339	Own meta-analysis
p_RBC_VHA	Probability of transfusion of RBCs with the use of VHAs.	Beta	2025	4306	Own meta-analysis
p_RBC_soc	Probability of transfusion of RBCs with the use of SOC.	Beta	1887	4003	Own meta-analysis
p_FFP_VHA	Probability of transfusion of FFP with the use of VHAs.	Beta	1024	4269	Own meta-analysis
p_FFP_soc	Probability of transfusion of FFP with the use of SOC.	Beta	906	3969	Own meta-analysis
p_plaq_VHA	Probability of transfusion of platelets with the use of VHAs.	Beta	1036	4306	Own meta-analysis
p_plaq_soc	Probability of transfusion of platelets with the use of SOC.	Beta	1090	4003	Own meta-analysis
p_LRA_VHA	Probability of acute kidney injury with the use of VHAs.	Beta	24	228	Own meta-analysis
p_LRA_soc	Probability of acute kidney injury with the use of SOC.	Beta	39	221	Own meta-analysis
p_ETE_VHA	Probability of thrombotic events with the use of VHAs.	Beta	5	156	Own meta-analysis
p_ETE_soc	Probability of thrombotic events with the use of SOC.	Beta	5	149	Own meta-analysis
p_RPS_VHA	Probability of reoperation for bleeding with the use of VHAs.	Beta	36	444	Own meta-analysis
p_RPS_soc	Probability of reoperation for bleeding with the use of SOC.	Beta	48	443	Own meta-analysis
p_I_trans	Probability of infections in patients that received RBCs.	Beta	596	4842	(Murphy *et al.*, 2007)
p_I_ntrans	Probability of infections in patients that did not receive RBCs.	Beta	141	3674	(Murphy *et al.*, 2007)
p_CPT_VHA	Probability of use of prothrombin complex with the use of VHAs.	Beta	26	91	Own meta-analysis
p_CPT_soc	Probability of use of prothrombin complex with the use of SOC.	Beta	52	95	Own meta-analysis
p_fib_VHA	Probability of fibrinogen use in patients who used VHAs.	Beta	53	77	Own meta-analysis
p_fib_soc	Probability of fibrinogen use in patients who used SOC.	Beta	56	79	Own meta-analysis

4. Distributions of patients' life expectancy data depending on complications

Variable	Description	Distribution	Min	Most likely	Max	References
o_LRA	Life expectancy of patients with acute kidney injury.	Triangular	8.7	10.9	13.1	(Mehta *et al.*, 2010)
o_ETE	Patients' life expectancy after a thromboembolic event.	Triangular	8	10	12	(Brønnum-Hansen *et al.*, 2001)
o_I	Patients' life expectancy after nosocomial infection.	Triangular	9.8	12.3	14.8	(Mehta *et al.*, 2010)
o_SC	Life expectancy of patients without complications.	Triangular	9.8	12.3	14.8	(Mehta *et al.*, 2010)

5. Distribution of quality of life of patients who have undergone cardiac surgery

Variable	Description	Distribution	$\bar{x}$	SE	References
o_qol	Quality of life of patients after uncomplicated cardiac surgery	Normal	0.72	0.01310244	(Oddershede *et al.*, 2014)

6. Disutility variables used in the model

Variable	Description	$\bar{x}$	References
o_qol_LRA	Disutility associated with acute kidney injury.	0.104	WHO methods and data sources for global burden of disease estimates 2000-2016 in Chronic kidney disease (stage IV)
o_qol_ETE	Disutility associated with thromboembolic events.	0.070	WHO methods and data sources for global burden of disease estimates 2000-2016 in Stroke: long-term consequences, moderate
o_qol_I	Disutility associated with infections.	0	Oddershede *et al.* (2014)

7. Distribution of transfused volume variables

Variable	Description	Distribution	$\bar{x}$	SE	References
v_RBC_VHA	Volume of RBCs transfused in patients using VHAs.	Normal	1.416	0.2676	(Shore-Lesserson *et al.*, 1999)
v_RBC_soc	Volume of RBCs transfused in patients using SOC.	Normal	1.9	0.3289	(Shore-Lesserson *et al.*, 1999)
v_FFP_VHA	Volume of FFP transfused in patients using VHAs.	Normal	0.133	0.0723	(Shore-Lesserson *et al.*, 1999)
v_FFP_soc	Volume of FFP transfused in patients using SOC.	Normal	0.804	0.2378	(Shore-Lesserson *et al.*, 1999)
v_plaq_VHA	Volume of platelets transfused in patients using VHAs.	Normal	0.1	0.0379	(Shore-Lesserson *et al.*, 1999)
v_plaq_soc	Volume of platelets transfused in patients using SOC.	Normal	0.244	0.0653	(Shore-Lesserson *et al.*, 1999)

8. Distribution of the cost analysis variables of the exams and adverse events

Variable	Description	Distribution	Min	Most likely	Max	References
c_INTEM	Unit cost of INTEM®	Triangular	41.90	52.38	62.86	Biomig Materiais Médico-Hospitalares Ltda.
c_EXTEM	Unit cost of EXTEM®	Triangular	47.30	59.13	70.96	Biomig Materiais Médico-Hospitalares Ltda.
c_FIBTEM	Unit cost of FIBTEM®	Triangular	67.56	84.47	101.34	Biomig Materiais Médico-Hospitalares Ltda.
c_HEPTEM	Unit cost of HEPTEM®	Triangular	68.06	85.07	102.09	Biomig Materiais Médico-Hospitalares Ltda.
c_TP	Unit cost of the PT test	Triangular	1.05	1.32	1.58	SigTap; procedure 02.02.02.014-2
c_TTPa	Unit cost of the aPTT test	Triangular	2.23	2.79	3.34	SigTap; procedure 02.02.02.013-4
c_TCA	Unit cost of the ACT test	Triangular	1.05	1.32	1.58	SigTap; procedure 02.02.02.007-0
c_CP	Unit cost of the PC test	Triangular	1.05	1.32	1.58	SigTap; procedure 02.02.02.002-9
c_CFP	Unit cost of the PFC test	Triangular	1.78	2.22	2.67	SigTap; procedure 02.02.02.029-0
c_I	Cost of treatment of infections	Triangular	5625.16	7031.44	8437.73	(Nangino *et al.*, 2012)
c_LRA	Cost of treatment of acute kidney injury	Triangular	11839.69	14799.61	17759.54	(Ramirez *et al.*, 2017)
c_proc	Cost of cardiac procedures	Triangular	16104.06	20130.07	24156.08	(Titinger *et al.*, 2015)
c_RPS	Cust of reoperation for bleeding	Triangular	16104.06	20130.07	24156.08	(Gunnarsson *et al.*, 2015; Titinger *et al.*, 2015)
c_RBC	Cost of RBC units	Triangular	98.69	123.36	148.03	Hemominas, 2019
c_FFP	Cost of FFP units	Triangular	73.35	91.68	110.01	Hemominas, 2019
c_plaq	Cost of platelet units	Triangular	60.67	75.84	91.00	Hemominas, 2019
c_CPT	Cost of prothrombin complex unit	Triangular	457.41	571.76	686.11	Ministry of Planning, search carried out on 11/29/2019, via price panel, for the last 180 days.
c_fib	Cost of fibrinogen unit	Triangular	366.97	458.72	550.46	Ministry of Planning, search carried out on 11/29/2019, via price panel, for the last 180 days.

*Data from the Ministry of Health's price panel were obtained from the website paineldepreços.planejamento.gov.br/.

9. Distribution of cost of thromboembolic events

Variable	Description	Distribution	α	λ	References
c_ETE	Cost of treatment of thromboembolic events	Gamma	525.7782	0.1047367	(Safanelli *et al.*, 2019)

10. Population undergoing cardiac surgery in Brazil per year, according to data from Datasus

SUS hospital procedures - by place of stay – Brazil
AIH approved by Year attendance
Procedure group: 04 Surgical procedures
Organization form: 040601 Cardiovascular surgery, 040603 Interventional cardiology
Period: Jan/2008-Sep/2019

Year of service	AIH_approved	Reference
2008	113,819	Ministry of Health
2009	122,380	Ministry of Health
2010	128,739	Ministry of Health
2011	138,254	Ministry of Health
2012	144,990	Ministry of Health
2013	148,149	Ministry of Health
2014	152,840	Ministry of Health
2015	152,775	Ministry of Health
2016	156,196	Ministry of Health
2017	160,595	Ministry of Health
2018	164,882	Ministry of Health
2019	171,089	Estimated by linear regression
2020	175,472	Estimated by linear regression
2021	179,856	Estimated by linear regression
2022	184,239	Estimated by linear regression
2023	188,623	Estimated by linear regression
2024	193,006	Estimated by linear regression
Total	2,675,904	

Fonte: Ministry of Health - SUS Hospital Information System (SIH/SUS)

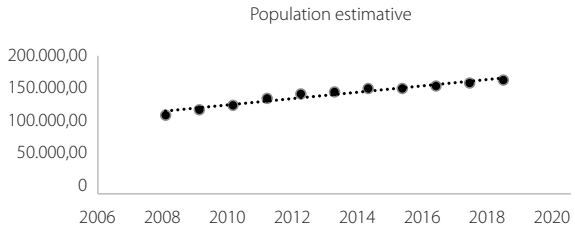
11. Linear regression data used to estimate the population undergoing cardiac procedures

Regression statistics	
Multipl R	0.971932384
R^2	0.944652558
Adjusted R^2	0.937734128
Standard Error	3407.287727
Observations	10

ANOVA

	df	SS	MS	F	Significance F	
Regression	1	1585193051	1585193051	136,5414599	2,6248E-06	
Residual	8	92876877,22	11609609,65			
Total	9	1678069928				
	Coefficient	**Standard Error**	**t Stat**	**P-value**	**Lower 95%**	**Upper 95%**
b	-8679056.915	755325.0889	-11.49049203	2.98188E-06	-10420839.69	-6937274.137
a	4383.430303	375.1300325	11.68509563	2.6248E-06	3518.378897	5248.481709

Formula: ax+b



12. Comparison of the ICER with various cost-effectiveness thresholds previously proposed

Parameter	Value in USD	Would VHAs be cost-effective at this threshold?
3 GDP per capita/QALY[a]	26,762.40	Yes
1.05 GDP per capita/QALY[a]	9,366.84	Yes
1 GDP per capita/QALY[a]	8,920.80	Yes
0.62 GDP per capita/QALY[a]	5,530.90	Yes
0.5 GDP per capita/QALY[a]	4,460.40	Yes
50,000 USD/QALY	50,000.00	Yes
20,000 BRP/QALY[b]	29,027.58	Yes
CER of the SOC	3,079	Yes

[a] GDP per capita taken from the World Bank data in http://data.worldbank.org/indicator/NY.GDP.PCAP.CD. [b] Converted with the OCDE Purchase Power Parity rate (2019). CER: cost-effectiveness ratio; SOC: Standard-of-care; QALY: quality-adjusted life year.

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