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ORIGINAL RESEARCH ARTICLE

Ticagrelor Removal by CytoSorb® in Patients Requiring Emergent or Urgent Cardiac Surgery: A UK-Based Cost-Utility Analysis

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Abstract

Background Acute coronary syndrome patients receiving dual antiplatelet therapy who need emergent or urgent cardiac surgery are at high risk of major bleeding, which can impair postoperative outcomes. CytoSorb®, a blood purification technology based on adsorbent polymer, has been demonstrated to remove ticagrelor from blood during on-pump cardiac surgery.

Objective The aim of this study was to evaluate the cost utility of intraoperative removal of ticagrelor using CytoSorb versus usual care among patients requiring emergent or urgent cardiac surgery in the UK.

Methods A de novo decision analytic model, based on current treatment pathways, was developed to estimate the short- and long-term costs and outcomes. Results from randomised clinical trials and national standard sources such as National Health Service (NHS) reference costs were used to inform the model. Costs were estimated from the NHS and Personal Social Services perspective. Deterministic and probabilistic sensitivity analyses (PSAs) explored the uncertainty surrounding the input parameters.

Results In emergent cardiac surgery, intraoperative removal of ticagrelor using CytoSorb was less costly (£12,933 vs. £16,874) and more effective (0.06201vs. 0.06091 quality-adjusted life-years) than cardiac surgery without physiologic clearance of ticagrelor over a 30-day time horizon. For urgent cardiac surgery, the use of CytoSorb was less costly than any of the three comparators—delaying surgery for natural washout without adjunctive therapy, adjunctive therapy with short-acting antiplatelet agents, or adjunctive therapy with low-molecular-weight heparin. Results from the PSAs showed that CytoSorb has a high probability of being cost saving (99% in emergent cardiac surgery and 53–77% in urgent cardiac surgery, depending on the comparators). Cost savings derive from fewer transfusions of blood products and re-thoracotomies, and shorter stay in the hospital/intensive care unit.

Conclusions The implementation of CytoSorb as an intraoperative intervention for patients receiving ticagrelor undergoing emergent or urgent cardiac surgery is a cost-saving strategy, yielding improvement in perioperative and postoperative outcomes and decreased health resource use.

1 Introduction

Acute coronary syndrome (ACS) patients receiving dual antiplatelet therapy (DAPT) who need emergent or urgent coronary artery bypass grafting (CABG) are at high risk of major bleeding [1], which can impair the outcome after cardiac surgery. The literature indicates that undergoing cardiac surgery while taking antiplatelet agents is associated with increased bleeding [2, 3] and other adverse events, higher care needs, including duration of surgery and hospital stay, and increased morbidity and mortality. Significant intra- and postoperative bleeding may require the use of blood transfusions such as red blood cells (RBCs), which are strongly associated with long-term morbidity and mortality [4–6]. CABG-related bleeding complications and perioperative coronary events are strongly influenced by the perioperative management of antiplatelet therapy.

Adenosine diphosphate (ADP) receptor inhibitors (also known as $P2Y_{12}$ receptor inhibitors) are recommended either as monotherapy or as part of DAPT for the secondary prevention of cardiovascular events after myocardial infarction

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Key Points for Decision Makers

Intraoperative removal of ticagrelor by CytoSorb® can improve the outcomes for patients who require emergent cardiac surgery, and can reduce the preoperative hospital stay for patients who require urgent cardiac surgery.

Intraoperative removal of ticagrelor by CytoSorb is a cost-saving (dominant) intervention for patients who require emergent and urgent cardiac surgery in the UK.

(MI) or stent implantation. ADP receptor inhibitors include clopidogrel, ticagrelor and prasugrel. According to National Institute for Health and Care Excellence (NICE) [7], ticagrelor is the preferred choice of ADP inhibitor in those with ACS due to it having less response variability than clopidogrel [8, 9] and a better safety profile than prasugrel [10]. The reversal of ticagrelor platelet inhibition has been demonstrated when free drug is removed by binding to monoclonal antibody fragments in preclinical and early clinical studies [11–13].

The major risk of ADP receptor inhibitor use is bleeding; timely discontinuation of these agents must be a consideration when patients are undergoing cardiac surgery or other procedures with an increased bleeding risk. However, withdrawal of these agents may be associated with an increased risk of ischaemic cardiovascular events. NICE provides guidance about when antiplatelet agents should be discontinued before CABG; ticagrelor should be discontinued 3–7 days before surgery [14].

When emergent surgical intervention is called for, including acute cardiovascular events, acute deterioration, or a failed percutaneous coronary intervention (PCI) requiring emergent CABG, the ADP receptor inhibitor (e.g. ticagrelor) will not have been stopped early enough to reduce the bleeding risk. Platelet infusions have been previously recommended in these scenarios, however evidence suggests that platelet transfusions do not counteract the effect of ticagrelor [15].

CytoSorb® (Cytosorbents Corporation, Monmouth Junction, NJ, USA) is an extracorporeal blood purification technology that has been demonstrated to remove ticagrelor from blood and reduce surgical resource use during cardiac surgery [16, 17]. The device consists of a 300 mL cartridge containing small adsorbent polymer beads that permit removal of hydrophobic substances up to a molecular weight of approximately 60 kDa from whole blood by irreversible adsorption. The primary field of application today is the treatment of systemic hyper-inflammatory states, e.g. in refractory septic shock or in endocarditis patients. The technology has been shown to be well tolerated, with a favourable safety profile. The mechanism of action and indications for the use of CytoSorb are expanded on elsewhere [16]. The sorbent cartridge has extended stability and does not require refrigeration, therefore it can be stored in the pharmacy inventory until it is needed for use in surgery. Integration of the device into a cardiopulmonary bypass circuit for intraoperative use in cardiac surgery patients requires only minimal additional accessories and workload, therefore incorporation of the use of the CytoSorb system into the standard practice of care in cardiac surgery could cost effectively improve patient care.

To date, an economic analysis of the cost effectiveness of different strategies for managing patients receiving ticagrelor who need urgent or emergent cardiac surgery has not been performed in the UK. The objective of this study was to evaluate the cost consequence and cost utility of intraoperative removal of ticagrelor using CytoSorb (without the need for a prior washout period) versus usual care among patients requiring emergent or urgent cardiac surgery.

2 Methods

2.1 Model Overview

A de novo decision analytic model was developed to estimate the costs and outcomes in each strategy over 30 days, 5 years, and lifetime time horizons. The model structure was developed based on the treatment pathways. The model was developed by a team that included health economists and physicians specialised in intensive care, with vast experience in CABG. After the first design of the model was accomplished, the model was presented to several cardiovascular and intensive care physicians in the UK for validation, and their suggestions, after reaching consensus with the model development team, were included in the model design.

Outcomes in the model were total costs, total effectiveness (i.e. bleeding complications/re-thoracotomy, number of units of transfused RBCs and platelets, hospital/intensive care unit [ICU] length of stay [LOS], total operating time, and quality-adjusted life-year [QALY]), and incremental cost per QALY gained. All costs and outcomes beyond a 1-year time horizon were discounted at a rate of 3.5% [18].

The model comprised a decision tree followed by a Markov model with three health states (i.e. post-surgery with no RBCs transfused, post-surgery with RBCs transfused, and death). For the long-term analysis, patients could have recurrent MI in the future, of which some could be fatal and have an impact on the estimated QALYs. This has been captured in the model by adjusting the age- and sex-specific mortality rates (obtained from the UK life table) using standardised mortality ratios (SMRs). The SMRs for the first

and subsequent years post-MI are reported in Table 1. The costs and benefits of the first 30 days were calculated in the decision tree, and the costs and consequences after the first 30 days were estimated using the Markov model, which has a cycle length of 12 months (except for the first cycle, which is 11 months). The model structure is illustrated in Fig. 1.

The model was used to simulate the management of two hypothetical cohorts of patients: (1) a cohort of patients who needed emergent cardiac surgery, including patients who had received a loading dose of ticagrelor prior to PCI and who then required emergent CABG because revascularisation could not be achieved by PCI, and those who required emergent cardiac surgery for other reasons; (2) a cohort of patients who were receiving ticagrelor for secondary prevention and who required urgent (but not emergent) cardiac surgery during their current hospital admission. Patients in the second cohort could not be sent home before having the procedure due to the risk of ongoing myocardial ischaemia or infarction [19].

The intervention in both cohorts was intraoperative removal of ticagrelor using CytoSorb, and performing cardiac surgery immediately. The intervention was compared

Table 1 Clinical input parameters

Variables	Base-case	Distribution	Lower limit	Upper limit	Source, year
Without CytoSorb®					
Patients who need transfusion of red blood cells (%)	46.00	Beta	34.13	56.88	Hassan et al., 2019 [17]
Patients who need transfusion of platelet (%)	100.00	Beta	75.00	100.00	Hassan et al., 2019 [17]
Re-thoracotomy rate (%)	36.40	Beta	27.30	45.50	Hassan et al., 2019 [17]
Patients treated with desmopressin (%)	100.00	Beta	75.00	100.00	Hassan et al., 2019 [17]
Total operation time (min)	353.00	Gamma	269.00	437.00	Hassan et al., 2019 [17]
Average LOS in the ICU (days)	3.00	Gamma	2.00	4.00	Hassan et al., 2019 [17]
Average LOS in hospital in each admission (days)	14.00	Gamma	10.00	16.00	Hassan et al., 2019 [17]
Probability of death at 30 days (%)	2.00	Beta	1.54	2.57	Murphy et al., 2007 [5]
With CytoSorb					
Patients who need transfusion of red blood cells (%)	22.00	Beta	16.43	27.38	Hassan et al., 2019 [17]
Patients who need transfusion of platelet (%)	35.00	Beta	25.95	43.25	Hassan et al., 2019 [17]
Re-thoracotomy rate (%)	0.00	Beta	0.00	0.00	Hassan et al., 2019 [17]
Patients treated with desmopressin (%)	66.00	Beta	49.20	82.00	Hassan et al., 2019 [17]
Total operation time (min)	288.00	Gamma	225.00	351.00	Hassan et al., 2019 [17]
Average LOS in the ICU (days)	2.00	Gamma	1.00	3.00	Hassan et al., 2019 [17]
Average LOS in hospital in each admission (days)	11.00	Gamma	9.00	12.00	Hassan et al., 2019 [17]
Probability of death at 30 days (%)	1.19	Beta	0.89	1.48	Murphy et al., 2007 [5]
Other clinical parameters in both groups					
Probability of MI while waiting for physiologic clearance of ticagrelor—only relevant in the comparator arms in the second cohort (%)	1.00	Beta	0.80	1.30	Ferrandis et al., 2012 [20]
SMR for post-MI (first year)	5.84	Fixed	NA	NA	TA236 [22]
SMR for post-MI (subsequent years)	2.21	Fixed	NA	NA	TA236 [22]
Cohort 2 analysis					
HR of death for those who have received transfusion of RBCs compared with those who have not (30 days)	6.70	Log-normal	3.70	15.10	Murphy et al., 2007 [5]
HR of death for those who have received transfusion of RBCs compared with those who have not (30 days–1 year)	2.60	Log-normal	1.70	4.20	Murphy et al., 2007 [5]
HR of death for those who have received transfusion of RBCs compared with those who have not (> 1 year)	1.30	Log-normal	1.10	1.60	Murphy et al., 2007 [5]
Health utility					
Health utility of 'post-surgery, RBCs transfused' health state	0.76	Beta	0.74	0.78	TA420 [7]
Health utility of 'post-surgery, RBCs not transfused' health state	0.76	Beta	0.74	0.78	TA420 [7]
Utility decrements associated with major bleeding complications	−0.0222	Beta	−5.80%	1.40%	Doble et al., 2018 [23]

HR hazard ratio, *MI* myocardial infarction, *NA* not applicable, *RBCs* red blood cells, *SMR* standardised mortality ratio, *LOS* length of stay, *ICU* intensive care unit

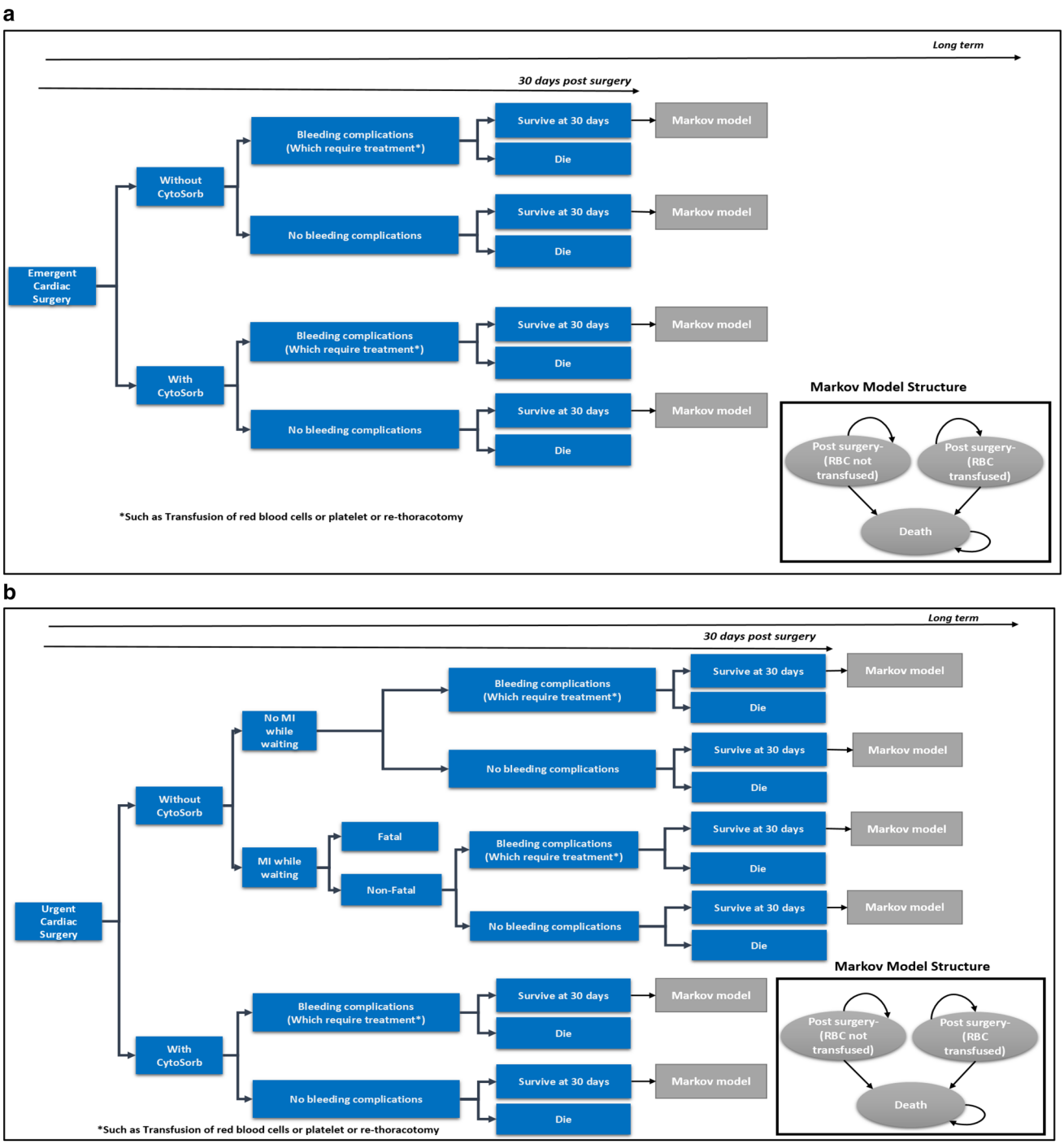

Fig. 1 Model structure: **a** modeling cohort 1; **b** modeling cohort 2. *MI* myocardial infarction, *RBC* red blood cells

with the relevant current standard of care in each cohort. In cohort 1, CytoSorb was compared with the usual standard of care where an emergent cardiac surgery was performed without waiting for physiologic clearance of ticagrelor. The intervention in cohort 2 was compared with three different comparators: (1) delaying surgery until the recommended amount of time passes for physiologic clearance of ticagrelor, which could be associated with a small increase in the risk MI, estimated at approximately 1% while the patient was waiting for surgery [20]; (2) delaying surgery until the recommended amount of time passes physiologic clearance of ticagrelor, while providing a short-acting antiplatelet as

adjunctive therapy; and (3) delaying surgery until the recommended amount of time passes for physiologic clearance of ticagrelor, while providing a low-molecular-weight heparin as adjunctive therapy.

2.2 Model Inputs

A series of targeted searches were conducted on the NICE website and of existing clinical guidelines to identify values for the input parameters. The Cochrane pyramid of evidence was considered to select the evidence to inform the model where possible. We converted all the reported rates into probabilities using the formula ($p = 1 - \exp(-rt)$), where p = probability of an event, r = reported rate and t = time [21].

2.2.1 Clinical Inputs

Clinical inputs were incidence of bleeding complications/re-thoracotomy, number of units of transfused RBCs and platelets, hospital/ICU LOS, total operating time, mortality rates, and incidence of MI while waiting for physiologic clearance of ticagrelor (Table 1). In cohort 2, patients wait for physiologic clearance of ticagrelor, and surgery will be conducted when ticagrelor is cleared from the blood, therefore it was assumed that the postoperative outcomes in terms of bleeding rates, operation time, and hospital stay were the same in the intervention and comparator arms.

In each strategy, the patients may or may not experience bleeding complications, a cardiac event (e.g. MI) or death. Depending on the events experienced during this initial pathway, patients will move to the relevant health states in the Markov model: 'post-surgery, no RBCs transfused', 'post-surgery, RBCs transfused', and 'dead.' The risk of death in the Markov model was adjusted for whether the patients had received RBC transfusion or not. Mortality rates at 30 days and long-term following cardiac surgery were obtained from a UK-based study conducted by Murphy et al. [5] (Table 1).

2.2.2 Utilities

In order to estimate the QALYs gained by different strategies, it is necessary to quality-adjust the period of time the average patient is alive in the model using an appropriate health utility weight. The health utility weights were based on the values that have been assessed and verified by the NICE external review teams in the previous NICE technology appraisal guidance on 'Ticagrelor for preventing atherothrombotic events after myocardial infarction' (TA420) [7]. The utilities are based on the EuroQol-5 Dimension (EQ-5D) questionnaire. The EQ-5D score can be negative and ranges from (−0.594 to 1) when the UK value set is used to convert the 5-digit codes from the EQ-5D questionnaire to utility scores. If a value set from another country is used, the range would be slightly different but could still take negative values. Utility decrements of −0.022 have been reported for major bleeding in a previous systematic review of quality-of-life studies [23]. This disutility was applied for the proportion of patients who experienced bleeding complications for the period they were in hospital. To simplify the model, it was assumed that patients in the 'post-surgery, RBCs not transfused' and 'post-surgery, RBCs transfused' health states will have the same heath utility of 0.76, as reported in Table 1.

2.2.3 Costs

Costs were estimated from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The NHS perspective includes treatment costs such as General Practitioner (GP) visits, hospital admissions, medicine costs, and costs of managing adverse events caused by treatment, while the PSS perspective includes services for those with special needs due to old age or physical or mental disability. The following costs were included: cost of initial intervention (i.e. CABG and CytoSorb); cost of reoperation/re-thoracotomy; transfusion of RBCs, platelets and/or desmopressin; costs of hospital stay (including ICU and general ward); and costs of other complications, including fatal and non-fatal MI. Costs were in UK pound sterling (£) and adjusted, where needed, to the 2018 price year.

The cost of CABG surgery was calculated based on the average theatre time in each strategy, as well as the hospital LoS. The average operation times were obtained from the study by Hassan et al. [17], i.e. 288 and 353 min in the CytoSorb and non-CytoSorb arms, respectively. The average cost of operating theatre time in the UK was assumed to be £20 (£8.80–£28.70) per minute (£525/h for cardiology, and £1722/h for emergency surgeries) [24, 25]. Additional costs for procedures and interventions that are required because of bleeding complications, such as transfusions of RBCs or platelets and re-thoracotomy, were taken into account. The unit costs of these are reported in Table 2. For the second cohort (i.e. patients who needed urgent cardiac surgery), in the base-case analysis it was assumed that patients stayed in hospital for 5 days while waiting for the physiologic clearance of ticagrelor [14, 26].

2.3 Analysis

The cumulative estimates of costs and effectiveness were estimated using Monte Carlo simulation (10,000 iterations) for the intervention and comparators for both cohorts separately. Deterministic and probabilistic sensitivity analyses (PSAs) were conducted to explore the uncertainty surrounding the results. The deterministic sensitivity analysis was

Table 2 Cost inputs

Variable	Base-case value	Distribution	Lower limit	Upper limit	Source
Cost of interventions					
Unit cost of operating theatre per min (£)	20.00	Gamma	8.80	28.70	NHS [25, 27]
Unit cost of postoperative hospital stay in the ICU (£)	1449.40	Gamma	1087.00	1811.70	NHS reference cost 2017/2018 [28]
Unit cost of postoperative hospital stay in cardiac the ward (£)	305.00	Gamma	228.80	381.30	NHS reference cost 2017/2018 [28]
Cost of CytoSorb [materials and labour costs] (£)	1500.00	Fixed	NA	NA	Cytosorbents
Pre-CABG					
Unit cost of bed days while waiting for physiologic clearance of ticagrelor (£)	305.00	Gamma	228.80	381.30	NHS reference cost 2017/2018 [28]
Average number of hospital bed days while waiting for physiologic clearance of ticagrelor	5.00	Gamma	3.00	7.00	NHS Digital 2017/2018 and Sousa-Uva et al., 2014 [14]
Patients who will be discharged home while waiting for physiologic clearance of ticagrelor (%)	0.00	Fixed	NA	NA	Assumption
Cost of cangrelor and tirofiban (£)	205.00	Gamma	153.75	256.25	British National Formulary [29]
Cost of LMWH (£)	30.30	Gamma	22.70	37.84	British National Formulary [29]
Cost of blood clotting test (£)	3.60	Gamma	2.72	4.53	Inflated to 2018 [30]
Cost of bleeding					
Transfusion of RBCs [unit] (£)	129.00	Gamma	96.70	161.20	NHS Blood and Transplant
Transfusion of platelets [unit] (£)	185.90	Gamma	139.40	232.30	NHS Blood and Transplant
Cost of administering blood per unit (£)	50.70	Gamma	38.00	63.40	Stokes, 2018, inflated to 2018 [38]
Cost of administering platelets per unit (£)	60.00	Gamma	45.00	75.00	Stokes, 2018, inflated to 2018 [38]
Unit cost of re-thoracotomy (£)	4800.00	Gamma	2100.00	6888.00	Assumed to require 4 h of theatre time
Unit cost of treatment with desmopressin (£)	13.16	Fixed	NA	NA	British National Formulary [29]
Cost of health states					
Annual cost of post-surgery health states (£)	2010.20	Gamma	1959.00	2061.50	Walker et al., 2016, inflated to 2018 [31]

CABG coronary artery bypass graft, *ICU* intensive care unit, *LMWH* low-molecular-weight heparin, *NA* not applicable, *RBCs* red blood cells

used to test the impact of varying key parameter values used in the base-case analysis; several variations to the base-case were analyzed, i.e. assuming no cardiac events and mortality during the washout period, assuming no difference in mortality between model arms, assuming no difference in hospital LOS (post-surgery), assuming no differences in operation time, and assuming a time horizon of 5 years and lifetime.

PSA was also performed and was used to map the parameter uncertainty. To conduct the PSA, probabilistic distributions were assigned to each input variable in the model and were used to randomly select new values within their plausible range. The distributions for each variable are included in Table 2. Each new randomly sampled set of values was used in the model and the new results were recorded. This process was repeated for 10,000 iterations to produce a distribution of results from the model. The probability of being cost saving represents the percentage of iterations within the PSA where the incremental cost was negative.

3 Results

Total and incremental costs, QALYs, incremental cost-effectiveness ratios (ICERs), and the probability that each strategy is cost effective at different willingness-to-pay (WTP) thresholds are presented in Table 3. Probabilistic results from the Monte Carlo simulation, in the form of cost-effectiveness scatter plots and cost-effectiveness acceptability curves, are presented in electronic supplementary Figs. S1–S4.

3.1 Base-Case Analysis (30-Day Time Horizon)

For cohort 1, over a 30-day time horizon, intraoperative removal of ticagrelor using CytoSorb was less costly (£12,933 vs. £16,874) and more effective (0.06201 vs. 0.06091 QALYs), therefore it was a dominant strategy compared with the usual standard of care where emergent surgery is performed without waiting for physiologic clearance of ticagrelor. The main cost savings came from a lower overall cost of intervention and lower cost of transfusion of

red blood cells and platelet and re-thoracotomy (Table 4). Results from the Monte Carlo simulation showed that the CytoSorb intervention had a more than 99% probability of being cost effective at a £20,000 WTP threshold and cost saving (cost-effectiveness acceptability curves and scatter plots are reported in the electronic supplementary material).

For cohort 2, over a 30-day time horizon, intraoperative removal of ticagrelor using CytoSorb was less costly (£12,912, £12,939, £12,954 vs. £12,959, £13,200, £13,030, respectively) than any of the comparators, i.e. delaying CABG for physiologic clearance without adjunctive therapy, adjunctive therapy with short-acting antiplatelet agents, or adjunctive therapy with low-molecular-weight heparin (LMWH). The main cost savings came from shorter hospital stay for clearance of ticagrelor prior to the surgery (Table 4). Intraoperative removal of ticagrelor using CytoSorb was more effective than waiting for physiologic clearance of ticagrelor (0.0625 vs. 0.0623 QALYs), and almost equally effective as using an adjunctive therapy. Intraoperative removal of ticagrelor using CytoSorb was therefore a dominant strategy in all of these cases (Table 3). The results from the Monte Carlo simulation showed that CytoSorb intervention had a 53–77% probability of being cost effective at a £20,000 WTP threshold.

3.2 Sensitivity Analyses

Different deterministic sensitivity and scenario analyses were conducted to explore different time horizons, as well as relevant assumptions in the model structure. Full results

Table 3 Base-case probabilistic results over a 30-day time horizon

Base-case probabilistic results	Without CytoSorb®	With CytoSorb®
Cohort 1 (comparator: no physiologic clearance)		
Cost (£)	16,874	12,933
Incremental cost (£)	−3941	
QALYs	0.06091	0.06201
Incremental QALYs	0.0011	
ICER (£; ΔCost/ΔQALYs)	Dominant	
Probability of being cost-effective with £20,000 WTP thresholds (%)	99.68	
Probability of being cost saving (%)	99.63	
Cohort 2 (comparator: physiologic clearance)		
Cost (£)	12,959	12,912
Incremental cost (£)	−47.00	
QALYs	0.06234	0.06250
Incremental QALYs	0.00017	
ICER (£; ΔCost/ΔQALYs)	Dominant	
Probability of being cost-effective with £20,000 WTP thresholds (%)	53.11	
Probability of being cost saving (%)	51.06	
Cohort 2 (comparator: physiologic clearance + short-acting antiplatelet)		
Cost (£)	13,200	12,939
Incremental cost (£)	−261.00	
QALYs	0.06247	0.06249
Incremental QALYs	0.000013	
ICER (£; ΔCost/ΔQALYs)	Dominant	
Probability of being cost-effective with £20,000 WTP thresholds (%)	77.20	
Probability of being cost saving (%)	77.02	
Cohort 2 (comparator: physiologic clearance + LMWH)		
Cost (£)	13,030	12,954
Incremental cost (£)	−77	
QALYs	0.06248	0.06249
Incremental QALYs	0.000014	
ICER (£; ΔCost/ΔQALYs)	Dominant	
Probability of being cost-effective with £20,000 WTP thresholds (%)	57.06	
Probability of being cost saving (%)	56.91	

QALYs quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *WTP* willingness to pay, *LMWH* low-molecular-weight heparin

Table 4 Base-case deterministic results over a 30-day time horizon

Cost and outcome per patient	Without CytoSorb®	With CytoSorb®	Δ Incremental
Cohort 1: 30-day time horizon (comparator: no physiologic clearance)			
Cost of presurgery resource use per patient (£)	0.00	0.00	0.00
Cost of intervention per patient (£)	14,764.00	12,904.00	−1859.00
Cost of transfusion of red blood cells per patient (£)	164.00	79.00	−85.00
Cost of transfusion of platelet per patient (£)	380.00	94.00	−286.00
Cost of re-thoracotomy per patient (£)	1747.00	0.00	−1747.00
Cost of desmopressin per patient (£)	13.00	9.00	−5.00
Total costs of bleeding complications per patient (£)	2304.00	181.00	−2123.00
Total costs per patient at 30 days (£)	17,068.00	13,085.00	−3982.00
Costs after 30 days per patient (£)	0.00	0.00	0.00
Total costs per patient (£)	17,068.00	13,085.00	−3982.00
Number of transfusions of red blood cells (units) per patient	0.91	0.44	−0.47
Number of transfusions of platelet (units) per patient	1.55	0.38	−1.16
Number of patients who need re-thoracotomy per patient	0.36	0.00	−0.36
Cohort 2: 30-day time horizon (comparator: physiologic clearance)			
Cost of presurgery resource use per patient (£)	1572.00	0.00	−1572.00
Cost of intervention per patient (£)	11,373.00	12,904.00	1531.00
Cost of transfusion of red blood cells per patient (£)	78.00	79.00	1.00
Cost of transfusion of platelet per patient (£)	93.00	94.00	1.00
Cost of re-thoracotomy per patient (£)	0.00	0.00	0.00
Cost of desmopressin per patient (£)	9.00	9.00	0.00
Total costs of bleeding complications per patient (£)	180.00	181.00	1.00
Total costs per patient at 30 days (£)	13,125.00	13,085.00	−39.00
Costs after 30 days per patient (£)	0.00	0.00	0.00
Total costs per patient (£)	13,125.00	13,085.00	−39.00
Number of transfusions of red blood cells (units) per patient	0.44	0.44	0.00
Number of transfusions of platelet (units) per patient	0.38	0.38	0.00
Cohort 2: 30-day time horizon (comparator: physiologic clearance + short-acting antiplatelet)			
Cost of presurgery resource use per patient (£)	1751.00	0.00	−1751.00
Cost of intervention per patient (£)	11,402.00	12,904.00	1503.00
Cost of transfusion of red blood cells per patient (£)	79.00	79.00	0.00
Cost of transfusion of platelet per patient (£)	94.00	94.00	0.00
Cost of re-thoracotomy per patient (£)	0.00	0.00	0.00
Cost of desmopressin per patient (£)	9.00	9.00	0.00
Total costs of bleeding complications per patient (£)	181.00	181.00	0.00
Total costs per patient at 30 days (£)	13,333.00	13,085.00	−248.00
Costs after 30 days per patient (£)	0.00	0.00	0.00
Total costs per patient (£)	13,333	13,085.00	−248.00
Number of transfusions of red blood cells (units) per patient	0.44	0.44	0.00
Number of transfusions of platelet (units) per patient	0.38	0.38	0.00
Cohort 2: 30-day time horizon (comparator: physiologic clearance + LMWH)			
Cost of presurgery resource use per patient (£)	1576.00	0.00	−1576.00
Cost of intervention per patient (£)	11,402.00	12,904.00	1503.00
Cost of transfusion of red blood cells per patient (£)	79.00	79.00	0.00
Cost of transfusion of platelet per patient (£)	94.00	94.00	0.00
Cost of re-thoracotomy per patient (£)	0.00	0.00	0.00
Cost of desmopressin per patient (£)	9.00	9.00	0.00
Total costs of bleeding complications per patient (£)	181.00	181.00	0.00
Total costs per patient at 30 days (£)	13,159.00	13,085.00	−73.00
Costs after 30 days per patient (£)	0.00	0.00	0.00

Table 4 (continued)

Cost and outcome per patient	Without CytoSorb®	With CytoSorb®	Δ Incremental
Total costs per patient	13,159.00	13,085.00	− 73.00
Number of transfusions of red blood cells (units) per patient	0.44	0.44	0.00
Number of transfusions of platelet (units) per patient	0.38	0.38	0.00

LMWH low-molecular-weight heparin

from these analyses are reported in Tables 5 and 6 and Fig. 2. Within cohort 1, the estimated total costs per patient using a 5-year horizon were £22,127 versus £25,899 for intraoperative removal of ticagrelor using CytoSorb and the usual standard of care, respectively. The total estimated QALYs per patient over this time period were 3.4140 and 3.3344, respectively. Over a lifetime time horizon, the total costs were £34,131 versus £37,263 for intraoperative removal of ticagrelor using CytoSorb and the usual standard of care, respectively. The total estimated QALYs per patient over this time period were 7.9462 and 7.6250, respectively. Over 5-year and lifetime time horizons, intraoperative removal of ticagrelor using CytoSorb was a dominant strategy compared with the usual standard of care. Intraoperative removal of ticagrelor with CytoSorb also remained a dominant strategy compared with usual care when varying several assumptions of the model, i.e. assuming no difference in operation time, assuming no difference in hospital LOS, assuming no difference in ICU LOS, and assuming no difference in mortality due to transfusion of RBCs. In each case, intraoperative removal of ticagrelor with CytoSorb was less expensive and more effective.

In cohort 2, over a lifetime time horizon, intraoperative removal of ticagrelor with CytoSorb was a cost-effective strategy compared with each comparator, i.e. delaying the CABG while waiting for physiologic clearance of ticagrelor without adjunctive therapy, and a dominant strategy when compared with delaying the CABG while waiting for physiologic clearance of ticagrelor with adjunctive therapy of short-acting antiplatelet agents, or with adjunctive therapy

Table 5 Results from the deterministic scenario analysis—cohort 1

Base-case probabilistic results	Without CytoSorb®	With CytoSorb®	Δ Incremental
Assuming a time horizon of 5 years			
Cost (£)	25,899	22,127	− 3771
QALYs	3.3344	3.4140	0.0797
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming a lifetime time horizon			
Cost (£)	37,263	34,131	− 3132
QALYs	7.6250	7.9462	0.3212
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming no differences in operation time (30-day time horizon)			
Cost (£)	17,068	14,385	− 2682
QALYs	0.0600	0.0619	0.0019
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming no difference in hospital LOS (post-surgery) [30-day time horizon]			
Cost (£)	17,068	14,000	− 3067
QALYs	0.0600	0.0619	0.0019
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming no difference in ICU LOS (post-surgery) [30-day time horizon]			
Cost (£)	17,068	14,230	− 2838
QALYs	0.0600	0.0619	0.0019
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming no difference in mortality due to transfusion of RBCs (lifetime time horizon)			
Cost (£)	38,546	34,754	− 3792
QALYs	8.1096	8.1815	0.0719
ICER (£; ΔCost/ΔQALYs)	Dominant		

QALYs quality-adjusted life-years, *ICERs* incremental cost-effectiveness ratio, *LOS* length of stay, *ICU* intensive care unit, *RBCs* red blood cells

Table 6 Results from the deterministic scenario analysis—cohort 2

Base-case probabilistic results	Without CytoSorb®	With CytoSorb®	Δ Incremental
Assuming a lifetime time horizon (comparator: physiologic clearance)			
Cost (£)	34,116	34,131	+15
QALYs	7.9257	7.9462	0.0205
ICER (£; ΔCost/ΔQALYs)	722.94		
Assuming a lifetime time horizon (comparator: physiologic clearance + short-acting antiplatelet)			
Cost (£)	34,375	34,131	−244
QALYs	7.9445	7.9462	0.0017
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming a lifetime time horizon (comparator: physiologic clearance + LMWH)			
Cost (£)	34,200	34,131	−69
QALYs	7.9445	7.9462	0.0017
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming no risk of MI while waiting for natural washout of ticagrelor (comparator: physiologic clearance) [lifetime time horizon]			
Cost (£)	34,174	34,131	−43
QALYs	7.9462	7.9462	0.0000
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming no risk of MI while waiting for natural washout of ticagrelor (comparator: physiologic clearance + short-acting antiplatelet) [lifetime time horizon]			
Cost (£)	34,379	34,131	−248
QALYs	7.9462	7.9462	0.0000
ICER (£; ΔCost/ΔQALYs)	Dominant		
Assuming no risk of MI while waiting for natural washout of ticagrelor (comparator: physiologic clearance + LMWH) [lifetime time horizon]			
Cost (£)	34,205	34,131	−74
QALYs	7.9462	7.9462	0.0000
ICER (£; ΔCost/ΔQALYs)	Dominant		

QALYs quality-adjusted life-years, *ICERs* incremental cost-effectiveness ratio, *LMWH* low-molecular-weight heparin, *MI* myocardial infarction

with LMWH. When assuming no MI while waiting for physiologic clearance of ticagrelor, intraoperative removal of ticagrelor with CytoSorb remained a dominant strategy against all three comparators because it remained less expensive (£34,131 vs. £34,174, and £34,379 and £34,205, respectively), with equal efficacy.

The results for the one-way sensitivity analyses (Tornado diagram) are presented in Fig. 2 and electronic supplementary Figs. S5–S7. This diagram depicts the sensitivity of the base-case result to changes in individual input values that are varied one at a time while keeping all other inputs at their initial values. For cohort 1, the results from the Tornado diagram showed that ± 25% changes on the following inputs had the biggest impacts (± 9.4 to ± 44.3%) on the estimated total cost savings, i.e. total operation time, average LOS (days) in the hospital and ICU, cost of the operating theatre and ICU, and cost of re-thoracotomy, whereas for cohort 2, the input parameters with the highest impact on the estimated cost savings were the average number of hospital bed days while waiting for physiologic clearance of ticagrelor, and the cost of CytoSorb device implementation and percentage of patients who will not be discharged home while waiting for physiologic clearance of ticagrelor. Threshold analyses were conducted to explore the relationship between the cost of implementation of the CytoSorb device and total cost savings (electronic supplementary Figs. S8–S11). The results for cohort 1 indicate that using CytoSorb was a cost-saving strategy as long as the cost of CytoSorb implementation was less than £5482. The corresponding number for cohort 2 was £1539. We conducted additional analyses and compared CytoSorb versus all comparators simultaneously, and the results are reported in the supporting materials (electronic supplementary Table S1 and Figs. S12–S14).

4 Discussion

A review of the economic literature did not find any existing studies relevant to the management of patients who are taking an ADP receptor inhibitor (e.g. ticagrelor, clopidogrel, etc.) who require urgent or emergent cardiac surgery, including following a failed PCI. Thus, to our knowledge, this is the first economic evaluation of an intervention to manage the risks of bleeding for patients taking ticagrelor who require urgent or emergent cardiac surgery in the UK. The results suggest that intraoperative removal of ticagrelor by CytoSorb is a cost-saving (dominant) intervention for the management of patients who require emergent cardiac surgery upon admission or following a failed PCI, and for patients requiring an urgent CABG.

Ticagrelor removal by CytoSorb was found to be cost saving, both for short (30-day) and longer (5-year and lifetime) time horizons. While there is an initial cost for the CytoSorb technology, meaningful clinical benefit and cost savings are gained because of the reduced bleeding complications and LOS relative to the various comparators. The CytoSorb intervention was also cost saving when varying significant assumptions of the base-case analysis, e.g. operation time, hospital LOS, blood component transfusions, and mortality rate. For those patients who need urgent cardiac surgery,

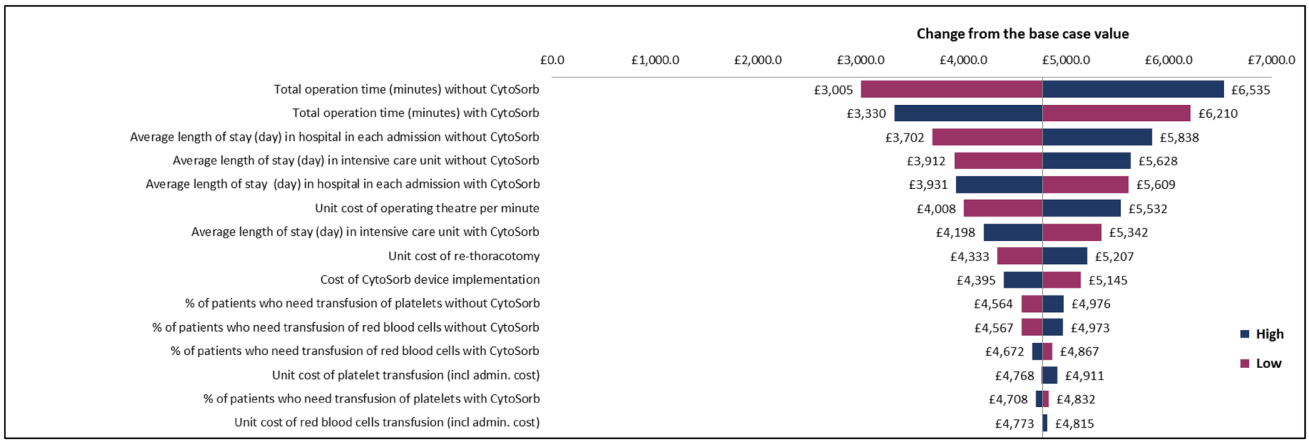

Fig. 2 Impact on the estimated NMB of changing the input parameters by ± 25% (base-case NMB = £4770) [cohort 1: 30-day time horizon]. *NMB* net monetary benefit, *incl* including, *admin* administration

one might argue that patients in the CytoSorb group have to wait before undergoing urgent surgery due to the non-availability of the operation theatre, however it seems very unlikely that an urgent CABG surgery would be postponed in order to perform surgery on an elective (i.e. non-urgent) cardiac surgery patient. In addition, the decision on whether to postpone surgery of either the urgent patient or the scheduled elective patient is multifactorial, including both of the patients' comorbidities and expected outcomes. Important to note, CytoSorb can actually help hospitals to run more efficiently, especially if the availability of beds in cardiac wards is constrained.

CytoSorb is easy to implement into an existing surgical workflow. Hassan et al. [17] described the experience of St. George Hospital (Hamburg, Germany) using CytoSorb adsorption during emergent open-heart operations in patients receiving treatment with coagulation-active substances: "The handling of installation had been straightforward and optimal flow conditions could be achieved". This indicates that CytoSorb utilisation during emergent or urgent cardiovascular surgeries does not require significant deviation from the routine surgical workflow. The benefits and cost-savings of the CytoSorb intervention will outweigh any potential small costs for its implementation.

This economic analysis was mainly informed by results from an observational clinical study [17] with relatively small sample sizes. However, this is the only study that investigates the impact of using CytoSorb on patient outcomes and has reported all the bleeding complication-related resource use for the economic model; the mechanism of action for ticagrelor removal has been demonstrated in independent studies [16]. We identified three other relevant studies [32–34], each with a decent sample size, but only one of those studies reports blood product transfusion rates [34] by time after the discontinuation of ticagrelor. Furthermore, none of those studies have reported all the related health resource use by time after the discontinuation of ticagrelor. We conducted a wide range of probabilistic and deterministic sensitivity analyses to address the uncertainty of the inputs that were obtained from the study by Hassan et al. [17].

Using the results from both Hansson et al. [34] and Hassan et al. [17] to compare the number of units of RBCs and platelets transfused with and without CytoSorb, show that the values used in the economic model (from Hassan et al. [17]) is a conservative estimate of the number of blood product transfusions that can be averted. Unfortunately, similar data on other types of health resource use are not available for comparison. However, it should be noted that the average reported LOS in the ICU is 2–3 days in the studies by both Hansson et al. [34] and Holm et al. [32]. This value is comparable with the values reported by Hassan et al. [17]. In general, despite the small sample size in the study by Hassan et al. [17] we believe the results of this study provide realistic estimates of the potential health resource use savings. This estimation will benefit from further prospective evaluation.

The primary value of this study is that it presents the first evaluation of the costs and benefits for the implementation of a new technology that can mitigate the risks for patients taking ticagrelor who require cardiovascular surgery. This analysis considers two groups of patients who exhibit high healthcare resource use: patients who require an emergent surgery and are therefore at high risk of bleeding and associated complications, and patients who could wait for the physiologic elimination of ticagrelor but would be at risk of ischaemic complications. Prolonged hospitalization puts patients at risk for nosocomial infections, which are associated with significant morbidity and mortality, which would further increase the financial burden on the health

care system [35–37]. Further studies in larger patient cohorts will be of value in refining the trend toward decreased risks of re-thoracotomy for CytoSorb-treated patients, as observed in the study by Hassan et al. [17].

This model explores the likely cost effectiveness of CytoSorb on both short (30-day) and long (5-year and lifetime) time horizons. It also allows for the consideration of various structural assumptions of the model. Across a broad range of patients, time horizons, and structural assumptions, the use of CytoSorb for the removal of ticagrelor during cardiovascular surgery was consistently found to be both less expensive and more effective than the current standard of care and other plausible comparators. The main limitations of this work stem from the availability of data to guide the parameterisation of the model. Despite the small sample size and retrospective analysis of the study by Hassan et al. [17], which was used to inform the clinical input parameters for the model, Hassan et al. found a large effect size that supports the plausibility of the results of this analysis. Additionally, a wide range of both probabilistic and deterministic sensitivity analyses to explore various assumptions of the model, both in terms of the parameter values and structural assumptions, found no change in the overall conclusions of the analysis.

5 Conclusions

CytoSorb is a blood purification technology, using adsorbent polymer, that allows removal of ticagrelor from blood both in vitro, and in clinical experience during cardiac surgery. The technology is easy to implement into an existing surgical workflow as an intraoperative intervention for patients undergoing cardiovascular surgery while taking ticagrelor, and is a cost-saving strategy, yielding improvement in perioperative and postoperative outcomes and decreased health resource use.

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Author Contributions MJ and MT were responsible for developing and populating the economic model and drafting the final version of this paper. All authors provided inputs for the model, and read and approved the final version of the manuscript.

Data Availability Statement The authors declare that all of the data supporting the findings of this study are available either within the article or within the electronic supplementary material.

Compliance with Ethical Standards

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Conflict of interest Fabian Degener, Daniel Adam, Franziska Preissing, Jörg Scheier are employees of CytoSorbents Europe GmbH, Berlin, Germany and Eric Mortensen is employee of CytoSorbents Corporation, Monmouth Junction, NJ, USA. Suzanne F. Cook is a consultant to CERobs LLC and CytoSorbents. Mehdi Javanbakht, Miranda Trevor, Mohsen Rezaei Hemami, Kazem Rahimi and Michael Branagan-Harris have no conflicts of interest to declare that are directly relevant to the content of this article. Device Access received funds from Cytosorbents during the conduct of this study.

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