



Rationale and design of the safe and timely antithrombotic removal - ticagrelor (STAR-T) trial: A prospective, multi-center, double-blind, randomized controlled trial evaluating reductions in postoperative bleeding with intraoperative removal of ticagrelor by the drugsorb™-ATR device in patients undergoing cardiothoracic surgery within 48 hours from last ticagrelor dose

C. Michael Gibson, MD^a, Michael J. Mack, MD^b, Victoria T. Lee, MD^c, David J. Schneider, MD^d, Frank W. Sellke, MD^e, E. Magnus Ohman, MD^f, Vinod H. Thourani, MD^g, Gheorghe Doros, PhD^{a,h}, Hans Kroger, MSc^c, Donald E. Cutlip, MD^a, and Efthymios N. Deliargyris, MD^c *Boston, MA*

Background Ticagrelor is often administered to patients with acute coronary syndromes. However, when these patients require urgent or emergent cardiothoracic (CT) surgery the presence of ticagrelor significantly increases surgical bleeding. The goal of the current trial is to evaluate the effectiveness and safety of the DrugSorb-ATR hemoadsorption device for the intraoperative removal of ticagrelor to reduce postoperative bleeding in the above patient population. The Safe and Timely Antithrombotic Removal - Ticagrelor (STAR-T) Trial is a multi-center, double-blind, randomized, controlled trial enrolling patients who require cardiothoracic surgery on cardiopulmonary bypass (CPB) within 48 hours of last ticagrelor dose.

Methods Subjects will be randomized 1:1 to receive either the DrugSorb-ATR device or an identical sham device during CPB. The study will enroll up to 120 subjects at 20 U.S centers, and the primary outcome is the composite of fatal perioperative bleeding, moderate/severe/massive bleeding according to the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB), and 24 hours chest tube drainage. The components of the composite are hierarchically ranked according to clinical significance and the primary analysis will utilize the Win Ratio method. Percent change in ticagrelor levels before and after CPB (drug removal) will be the key secondary endpoint. An independent Clinical Events Committee will adjudicate all clinical endpoints including safety endpoints relating to postoperative thrombotic events. Subjects will be followed through 30 days after the index operation.

Conclusions The results from STAR-T, if positive, will potentially support FDA market approval for DrugSorb-ATR, and provide a solution to an important unmet clinical need. (Am Heart J 2022;245:19–28.)

From the ^aThe Baim Institute and Harvard Medical School, Boston, MA, ^bBaylor Scott & White Health, Baylor Scott & White Research Institute, Dallas, TX, ^cCytoSorbents Inc, Princeton, NJ, ^dDepartment of Medicine and Cardiovascular Research Institute, University of Vermont, Burlington, VT, ^eDivision of Cardiothoracic Surgery, Alpert Medical School of Brown University, Providence, RI, ^fDuke Clinical Research Institute, Duke Program for Advanced Coronary Disease, Duke University Medical Center, Durham, NC, ^gDepartment of Cardiovascular Surgery, Marcus Valve Center, Piedmont Heart Institute, Atlanta, GA, ^hBoston University School of Public Health, Boston, MA

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Reprint requests: C. Michael Gibson, MD, PERFUSE Study Group, Cardiovascular Division, Department of Medicine, Beth Israel, 20 Overland street, 540, Boston, MA 02215

E-mail address: charlesmichaelgibson@gmail.com.

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Rationale

Ticagrelor is a potent oral platelet P2Y₁₂ inhibitor that antagonizes activation of P2Y₁₂ by adenosine diphosphate (ADP) via reversible binding of the platelet receptor and is frequently used in the management of patients with acute coronary syndrome (ACS) to reduce recurrent thrombotic risk.^{1,2,3} The mean plasma half-life is approximately 7 hours and its pharmacodynamically active primary metabolite AR-C124910XX has a half-life of approximately 9 hours. From 2006 to 2008, the pivotal study of Platelet Inhibition and Patient Outcomes (PLATO) compared the P2Y₁₂ inhibitors ticagrelor and clopidogrel when administered with aspirin and other standard therapy in patients with ACS. Ticagrelor was shown to decrease the rate of cardiovascular death and myocardial infarction (MI) and has since become widely adopted world-wide.⁴

As with any drug that inhibits platelet function, the predominant safety concern with ticagrelor is the increased risk of bleeding which is especially high when patients treated with ticagrelor require surgery. The American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) guidelines (2011, 2013, and 2014) recommend that patients discontinue ticagrelor at least 5 days before elective coronary artery bypass grafting (CABG), while the 2018 European Society of Cardiology / European Association for Cardiothoracic Surgery Guidelines recommends *at least* 72 hours of ticagrelor discontinuation prior to surgery.^{5,6,7,8} Therefore, in aggregate, international practice guidelines recommend that ticagrelor be discontinued between 3 and 5 days prior to CABG.⁹ This is unlike the management of pre-operative Aspirin, which is recommended to be continued during CABG, as benefits are thought to outweigh the bleeding risk.^{5,6,7}

However, in urgent or emergent clinical situations, delay of surgery for ticagrelor washout is not feasible. Data from PLATO demonstrated that approximately 10% of ACS patients required surgical revascularization during the index hospitalization and approximately half of them underwent CABG before the recommended washout period. These patients experienced very high rates of serious surgical and post-surgical bleeding, especially when the operation occurred ≤ 48 hours after the last ticagrelor dose.^{10,11} Over 47% of PLATO subjects who underwent CABG within 1 to 2 days of ticagrelor intake experienced major, life-threatening, or fatal bleeding events. This number was increased to 65.5% in those PLATO subjects who discontinued ticagrelor ≤ 1 day prior to CABG.¹⁰ Platelet transfusions which are routinely used in this setting to manage the excess bleeding are not particularly effective, as also acknowledged in the approved drug labeling.^{12,13} Even when washout is possible in clinically stable patients, there may be an increase in thrombotic risk during this waiting period. "Bridging" of these

patients with short acting intravenous agents (ie, canagrelor or GPIIb/IIIa inhibitors) has previously been proposed, but remains unproven as to whether it actually reduces the risk of major adverse cardiovascular events.¹⁴

Currently, there are no available interventions to address the significant unmet medical need in patients whose clinical condition necessitates cardiothoracic (CT) surgery before adequate washout of ticagrelor. The DrugSorb Anti-Thrombotic Removal (ATR) system been shown to efficiently remove ticagrelor from circulation and can be easily integrated into the cardiopulmonary bypass (CPB) circuit in a parallel fashion (*Figure 1*). DrugSorb was granted Breakthrough Device status by the FDA in April 2020 and the Safe and Timely Antithrombotic Removal - Ticagrelor (STAR-T) is the investigational device exemption (IDE) trial designed to support FDA market approval for this indication.

Objectives

- Demonstrate reductions in postoperative bleeding complications with the intraoperative use of DrugSorb-ATR in patients undergoing CT surgery with CPB ≤ 48 hours since last ticagrelor dose.
- Demonstrate reductions in ticagrelor blood levels (Δ [ticagrelor]) with the intraoperative use of DrugSorb-ATR.
- Establish the safety of the intraoperative use of DrugSorb-ATR in the intended population.

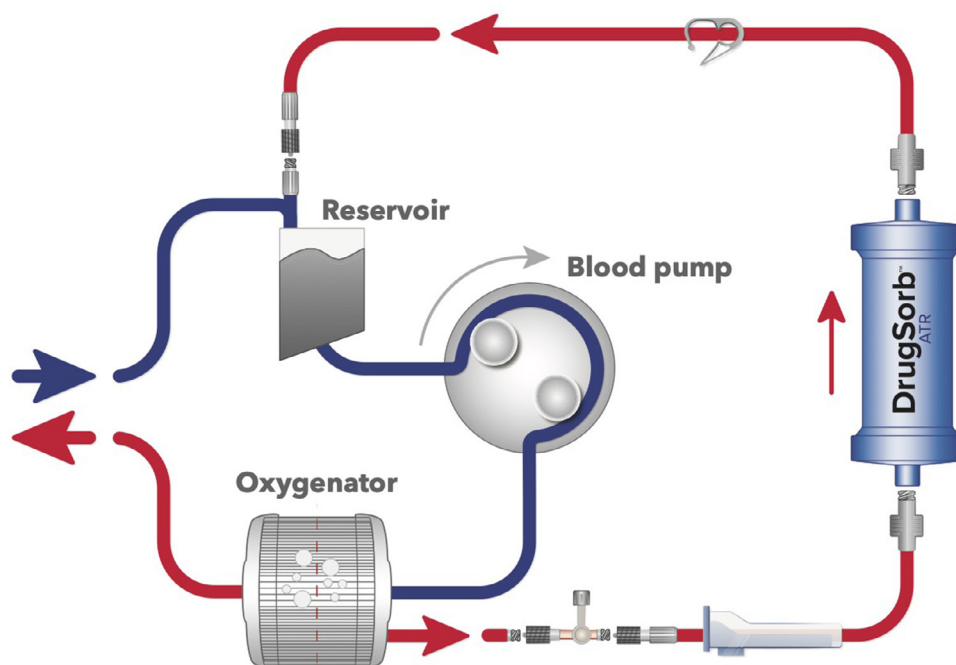
Methods

Trial design

Safe and Timely Antithrombotic Removal - Ticagrelor (STAR-T) is a prospective, multi-center, double-blind, randomized trial to evaluate the safety and effectiveness of DrugSorb-ATR in the reduction of postoperative bleeding by removal of ticagrelor in patients undergoing CT surgery with CPB ≤ 48 hours after the last ticagrelor dose.

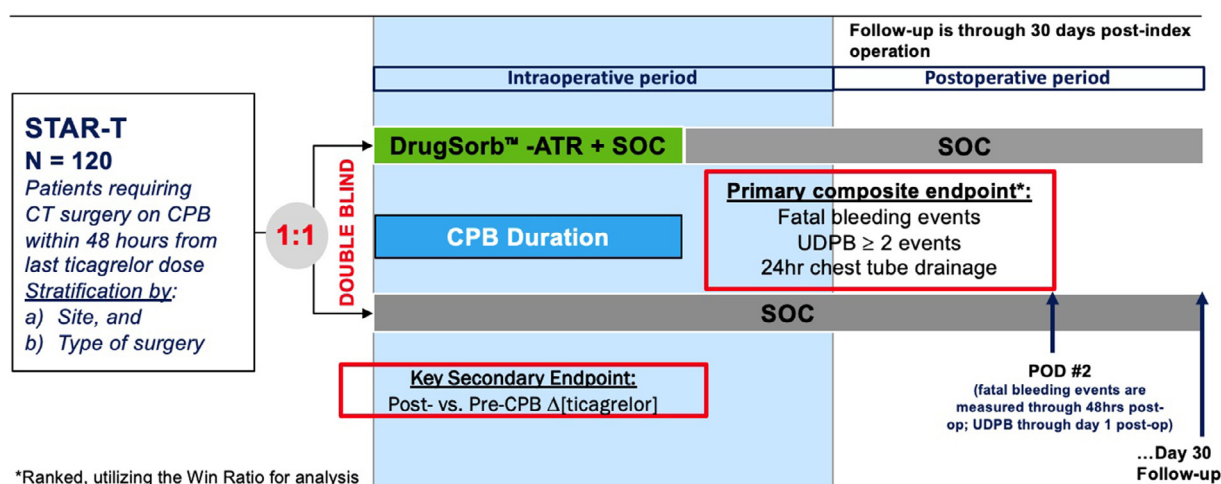
A total of 120 subjects at approximately 20 U.S centers will be randomized in a 1:1 fashion to either standard of care (SOC) or SOC plus intraoperative DrugSorb-ATR (*Figure 2*). Subjects will be stratified before randomization according to (1) investigational site, and (2) planned type of cardiothoracic operation. Stratification by operation will distinguish cases of isolated CABG (irrespective of number of grafts) from all other eligible CT surgeries including mixed cases (e.g., CABG+MVR, CABG+AVR, etc.). Pre-randomization stratification will ensure that any potential confounding effects from differing institutional practices (ie, operative technique, transfusion protocols) and differential impact of the type of operation (ie, CPB duration and duration of device exposure, bleeding risk) are balanced between the randomized groups.

Figure 1



Standard integration of DrugSorb-ATR within a CPB circuit: DrugSorb is integrated as a parallel shunt circuit to the main CPB circuit. Blood flow intake to the parallel circuit is after the pump in the main CPB circuit, and blood flow return from the parallel circuit is to the blood reservoir in the main CPB circuit.

Figure 2



Design Overview: STAR-T U.S. Pivotal Trial: SOC=standard of care. One-to-one randomization is to the investigational treatment (SOC + ticagrelor removal with DrugSorb during CPB) vs control (SOC alone). The primary effectiveness endpoint is a hierarchical composite of a full spectrum of bleeding events through 48 hours post-operation. Ticagrelor resumption is recommended after this time. The key secondary endpoint is a drug removal endpoint, as less circulating ticagrelor is presumed to be the mechanism for reduced bleeding.

Table 1. Allowed and disallowed antithrombotic medications

Medication	Allowed/Disallowed	Timing
Aspirin	Allowed	At all times
Ticagrelor	Allowed	≤48 h prior to surgery
Clopidogrel	Disallowed	≤7 d prior to surgery
Prasugrel	Disallowed	≤7 d prior to surgery
Cangrelor	Disallowed	≤4 h prior to surgery
Tirofiban	Disallowed	≤8 h prior to surgery
Eptifibatide	Disallowed	≤8 h prior to surgery
Abciximab	Disallowed	≤5 d prior to surgery
Argatroban	Disallowed	≤4 h prior to surgery
Bivalirudin	Disallowed	≤2 h prior to surgery
Heparin	Allowed	At all times
Low molecular weight heparin (e.g., enoxaparin) and fondaparinux	Allowed	At all times
Direct oral anticoagulants (e.g., apixaban, rivaroxaban, dabigatran, and edoxaban)	Disallowed	≤5 d prior to surgery
Warfarin	Disallowed	Any recent use unless INR <1.5

Postoperative bleeding will be evaluated by a hierarchical composite primary endpoint as detailed in [Figure 2](#), and further below.

Eligibility criteria

Inclusion criteria:

1. Males and females aged ≥18;
2. Written full informed consent;
3. Cardiothoracic surgery on CPB ≤48 hours from the last dose of ticagrelor.

Exclusion criteria:

1. Any cardiothoracic surgery >48 hours after last dose of ticagrelor;
2. Heart-lung transplant procedures;
3. Procedures for ventricular assist device;
4. Underlying bleeding diathesis, including:
 - Heparin induced thrombocytopenia
 - Peri-operative platelet count < 50,000 μ /L
 - Hemophilia
 - INR > 1.5
5. Prohibited concomitant antithrombotic medications ([Table 1](#));
6. Acute sickle cell crisis;
7. Known allergy to any of the device components;
8. Subjects with active (untreated) systemic infection;
9. Subjects with a history of major organ transplantation and those currently receiving immunosuppressive medication (corticosteroids excluded) or who are profoundly immune suppressed;
10. Women of childbearing potential with a positive pregnancy test performed during the current admission or who are lactating;
11. Subjects with life expectancy of <30 days;
12. Inability to comply with the requirements of the trial protocol;

13. Treatment with an investigational drug or device within 30 days prior to surgery;
14. Subjects with previous enrollment in this trial.

Informed consent must be obtained before inclusion of a patient in the trial, in accordance with the Declaration of Helsinki. Consent forms will comply with FDA regulations and be approved by the Institutional Review Board (IRB) of each participating investigational site. Where allowed by the participating study site and their IRB, assent for study participation may be provided by a legally authorized representative (LAR) if the patient is unable to provide their own consent at the time of surgery. If initial study consent is provided by a LAR, the subject will be re-consented once he or she has regained capacity.

Study endpoints

Effectiveness

The primary endpoint is a hierarchical composite of: (1) Fatal perioperative bleeding occurring within 48 hours, (2) Incidence of “moderate,” “severe,” or “massive” bleeding events based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPb ≥2) classification ([Table II](#)) and (3) 24-hour chest tube drainage (CTD) volume (mL). The UDPb classification is a standardized bleeding definition that was specifically designed by experts to capture bleeding after cardiac surgery and is based on 9 criteria occurring either during the operation or during the first postoperative day.¹⁵

The key secondary endpoint will be the change in blood concentration of ticagrelor when comparing pre-versus postoperative levels (Δ [ticagrelor]) as measured by mass spectroscopy. This will be reported as percent (%) difference, and quantifies the ticagrelor-removal ability of DrugSorb. This key secondary endpoint will establish the relationship between ticagrelor removal and

Table II. Bleeding class according to the universal definition of perioperative bleeding in adult cardiac surgery

Class	Sternal closure delayed	Postoperative chest tube blood loss within 12 h (mL)	pRBC (units)	FFP (units)	PLT (units)	Cryoppt	PCCs	rFVIIa	Reexploration/tamponade
0	No	<600	0*	0	0	No	No	No	No
1	No	601-800	1	0	0	No	No	No	No
2	No	801-1,000	2-4	2-4	Yes	Yes	Yes	No	No
3	Yes	1,001-2,000	5-10	5-10	N/A	N/A	N/A	No	Yes
4	N/A	>2,000	>10	>10	N/A	N/A	N/A	Yes	N/A

Class 0 = Insignificant; Class 1 = Mild; Class 2 = Moderate; Class 3 = Severe; Class 4 = Massive; pRBC = packed red blood cells; FFP = fresh frozen plasma; PLT = platelet concentrates; Cryoppt = Cryoprecipitate; PCCs = prothrombin complex concentrates; rFVIIa = recombinant activated factor VII; N/A = not applicable

* For purposes of UDPB, PRBC, PLT, FFP, and Cryoppt transfusions are counted beginning **at chest closure**. PCC and rFVIIa transfusions are counted beginning **at the start of the procedure**. Prophylactic/preoperative transfusion of blood products and factor concentrates do not contribute to UDPB.

decreased postoperative bleeding (ie, less drug = less bleeding).

Additional secondary endpoints are as follows, including individual components of the composite primary endpoint:

- 24-hour CTD volume (mL)
- Total platelet transfusions during the index hospitalization (volume and units)
- Total packed red blood cell (pRBC) transfusions during the index hospitalization (volume and units)
- Total UDPB events by class
- All surgical re-explorations for excess bleeding during the index hospitalization
- Total fatal perioperative bleeding events (occurring within 48 hours post-index operation).

Safety

The primary safety endpoint is the good clinical practice (GCP)-level assessment of adverse events (AEs) during the 30-day follow-up period.

Additional safety endpoints include:

- Thirty-day cardiac mortality
- Thirty-day all-cause mortality
- Postoperative stroke during the index hospitalization
- Postoperative myocardial infarction (MI) during the index hospitalization
- Urgent postoperative coronary revascularization during the index hospitalization
- Serious device-related AEs (as assessed by the Investigator, based on reported theoretical risks associated with device use).

These safety endpoints include standard components of MACE (major adverse cardiac events) and will allow risk assessment of any potential thrombotic rebound that might occur following ticagrelor removal. To reduce this risk, and in accordance with standard guidelines, *subjects will remain on aspirin* through-out the study duration. All ACS subjects or those with recent coronary stent

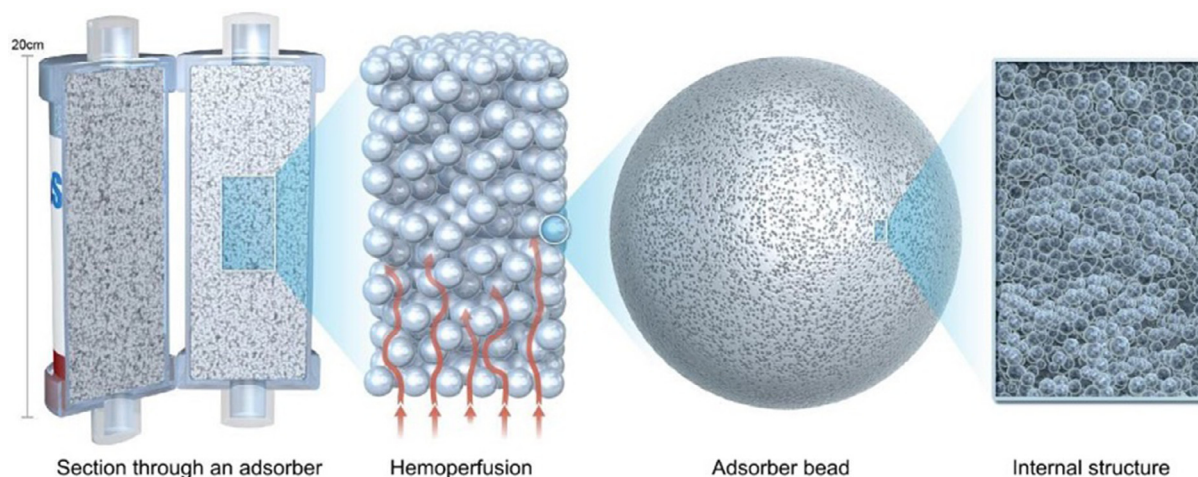
placement will *resume DAPT on post-operative day #1*, barring any clinical concern for significant bleeding. Concomitant antithrombotic medications will be tracked for all subjects through-out the course of the study.

All adverse events will be closely monitored and assessed for severity and potential relatedness to the device and/or the surgical procedure. The study blind may be broken in the event of a possible unanticipated adverse device effect (UADE), or other serious adverse event if doing so is necessary to make informed decisions about clinical care. An independent group of physicians who are not involved in the trial and are subject matter experts will act as the Clinical Events Committee (CEC). This committee will be selected and managed by the Baim Institute for Clinical Research (formerly known as the Harvard Clinical Research Institute). The CEC will be responsible for the adjudication of clinical effectiveness and safety endpoints that occur throughout the 30-day follow-up period, according to pre-specified standardized definitions.

A Data Safety Monitoring Board (DSMB) comprised of 3 clinicians and 1 biostatistician with relevant clinical/medical experience will be charged with ensuring overall safety of the subjects enrolled in the trial. The DSMB will also provide oversight of the planned interim analysis (discussed in detail below). The Center for Interventional Cardiovascular Research and Clinical Trials at the Icahn School of Medicine at Mount Sinai will be responsible for selection and management of the DSMB.

Ethics

The trial is conducted under a United States Investigational Device Exemption (IDE) approval by the granted the Food and Drug Administration (FDA) on July 2, 2021 and in accordance with the FDA Breakthrough Designation granted on April 20, 2020. Accordingly, the trial will adhere to standards of research ethics in accordance with applicable FDA regulations and IRB requirements. Funding for the research and creation of this paper was provided in its entirety by the STAR-T trial sponsor, Cy-

Figure 3

DrugSorb-ATR Device: Each adsorber bead has hundreds of thousands of tightly controlled pores & channels, removing molecules based on pore capture/size exclusion, and hydrophobic adsorption. Concentration gradient influences speed of removal, with more rapid removal occurring at higher circulating drug concentrations.

tosorbents Inc. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Trial registration # [The ClinicalTrials.gov registry [NCT04976530]]

Treatment, trial duration, and schedule of events

The investigational treatment will be intraoperative use of the DrugSorb-ATR system, which will be limited to the duration of CPB. The DrugSorb-ATR system comprises of a hemoperfusion cartridge filled biocompatible polymer beads, a pre-packaged tubing set for CPB integration, and a flow detector to ensure device flow in the targeted range. Removal of substances from blood is based on pore capture and surface adsorption within those channels (Figure 3). Hydrophobic substances with molecular weight under ~60 KDa are preferentially removed. Accordingly, DrugSorb-ATR can efficiently remove ticagrelor from circulating blood.

Trial follow-up will be through 30 days after the index operation, to monitor occurrence of adverse events and survival. EuroScore II and Society of Thoracic Surgeons (STS) Risk Scores will be obtained at the time of enrollment for baseline risk analysis. Blood sampling for the key secondary effectiveness (drug removal) endpoint will be done immediately pre-CPB and within 30 minutes of coming off CPB. Serial sampling will also occur every 30 minutes for the first 2 hours of CPB, to allow for exploratory pharmacokinetic assessment of intraoperative ticagrelor concentrations via the area under the concentration curve (AUC). Subjects will undergo sched-

uled trial assessments from screening to final follow-up, as detailed in the *Schedule of Assessments* (provided in the Appendix, Table IV [Supplemental]).

Methods to minimize bias and blinding procedures

The trial employs both a randomized, double-blind design and independent adjudication of study endpoint by a Clinical Events Committee as measures of minimizing bias. As part of the study blinding procedure, subjects randomized to SOC without DrugSorb (ie, control) will receive a *sham* device in the operating room. The *sham* devices are identical in appearance to an active DrugSorb-ATR device, but are sealed, inactive, and cannot unintentionally be put online within the CPB circuit. The perfusionist will be unblinded to the subject's assignment to administer the appropriate treatment. The operating surgeons, operating room staff, anesthesiologist, site clinical research staff, postoperative care staff, and the sponsor will remain blinded to each subject's randomization assignment for the full duration of the study.

Statistical methods

Sample size estimations. A sample size of 114 evaluable subjects is required for the powered assessment of the primary endpoint based on the assumed treatment effect sizes for each of the 3 endpoint components. A summary of effect size assumptions and resultant power for the proposed sample size is provided in Table III, below. Where possible, effect size assumptions were driven by data from real-world use of the device (under CE Mark in the European Union).¹⁶ Otherwise, data from the literature on differences in bleeding outcomes between patients with partial ticagrelor washout (3-5 days, representing the DrugSorb cohort) versus minimal or no tica-

Table III. Win ratio effect size assumptions with power and sample size estimates

n Per Group	Effect Size						Power
	Component #1		Component #2		Component #3		
	Fatal Bleeding		UDPB (Class ≥ 2)		24hr CTD		
	TreatmentEvent	ControlEvent	TreatmentEvent	ControlEvent	TreatmentMean (SD)	ControlMean (SD)	
57	3.0%	3.0%	24.3%	40.5%	480 (253)	800 (253)	99.7%

Notes: n, number; UDPB, Universal Definition of Perioperative Bleeding; CTD, chest tube drainage (volume [mL]). Component #1 minimum rates of 3.0% assumed as a conservative approach. Component #2 rates based on Russo et al. (2019), however, with a discount applied to bring the Treatment arm up to ~40% reduction on the Control arm.¹⁷ Component #3 rates based on Hassan et al. (2019), however, with a discount applied to bring the Treatment arm up to ~40% reduction on the Control arm.¹⁶

grelor washout (<3 days, representing the control cohort) prior to cardiac surgery was used to infer anticipated effect size.¹⁷ Allowing for 5% attrition, a total of 120 subjects will be randomized. The target sample size was calculated via an iterative simulation process with programming code available from Redfors et. al.¹⁸

The primary effectiveness endpoint will be evaluated using the Win Ratio method of analysis for a hierarchical composite endpoint based on the Finkelstein-Schoenfeld test with 3 components ranked in order of clinical importance: (1) fatal bleeding events occurring ≤ 48 hours post-index procedure; (2) UDPB class ≥ 2 bleeding events; and (3) 24-hour CTD.^{19,20} The Win Ratio assigns “wins,” losses,” or “ties” in sequential comparisons between treatment and control arm subjects according to the hierarchical order of the components.²⁰ A Win Ratio greater than 1.0 favors the treatment arm; when the lower bound of a 95% confidence interval (CI) around the ratio exceeds 1.0, the treatment is shown to be statistically superior to control at $\alpha = 0.05$.

The key secondary effectiveness endpoint is a drug removal assessment. Due to highly variable baseline ticagrelor blood levels in enrolled subjects, percent change from baseline will be analyzed as opposed to observed values. The percent change in pre-CBP versus post-CBP ticagrelor blood levels will be measured using blood samples at those time periods, and evaluation of drug concentration will be with mass spectroscopy.

Change from baseline in blood concentration of ticagrelor is defined as:

$$\frac{\text{pre} - \text{CPB}[\text{ticagrelor}]_{\text{blood}} - \text{post} - \text{CPB}[\text{ticagrelor}]_{\text{blood}} * 100\%}{\text{pre} - \text{CPB}[\text{ticagrelor}]_{\text{blood}}}$$

Benchtop studies of drug removal by the DrugSorb-ATR device demonstrate that ticagrelor removal exceeds 50% and can reach ~70% after 45 min of hemoabsorption at flow rates of between 100 and 700 mL/min [CytoSorbents R&D data: not yet published]. Based on these benchtop studies, a conservative estimate of 40% reduction in blood concentration of ticagrelor between pre- and post- DrugSorb-ATR removal is expected, with a standard deviation of 40%, in the treatment arm. The wide standard deviation accounts for potential intraoperative fluid shifts and other confounding variables. Min-

imal change is expected in the control arm. A 2-sample *t* test will be used to evaluate the difference between treatment arms.

With a sample size of 114 subjects, power for the key secondary endpoint is estimated at >99.9% based on a 2-sample *t* test assuming equal variance and a 2-sided alpha of 0.05. This overall trial size is designed to provide adequate power (>90%) for the composite primary and key secondary effectiveness endpoints at both the final analysis as well as at planned interim analysis, which would take place at 70% study completion. During this time the DSMB will perform an interim evaluation for possible early study termination for *overwhelming efficacy* based on pre-specified stopping rules outlined in the protocol, DSMB charter and statistical analysis plan.

The primary analysis population of the trial is the Intent-to-Treat (ITT) Population, comprising all randomized subjects. A modified Intent-to-Treat (mITT) Population will include all randomized subjects who undergo the index surgical procedure and receive a study device. So long as the mITT and ITT populations are not identical, the primary analyses of the trial will be performed additionally on the mITT population. The Per Protocol Population (PP) will include all mITT subjects who have no major protocol deviations. Primary and key secondary effectiveness analyses on the PP population and will be considered supplementary. The Safety Analysis Population will include all enrolled subjects treated with a device.

Discussion

To date, there are no available options to manage the high bleeding risk of patients on ticagrelor undergoing cardiothoracic surgery, given that platelet transfusions cannot fully restore platelet function. This is due to the reversible nature of ticagrelor's binding to the P2Y₁₂ receptor that allows for inhibition of freshly transfused platelets.¹² While clinical testing is underway for a monoclonal antibody reversal agent, results of the single-arm phase 3 trial are yet unknown, and timing of commercial availability remains uncertain. Therefore, the only currently recommended approach is to delay surgery for at

least 3 to 5 days to allow for ticagrelor washout, with the risk of additional clinical events (including thrombotic complications) during this period as well as increased hospital costs. However, that is not an option when surgery cannot be delayed, exposing patients to a very high risk of bleeding. Intraoperative removal of ticagrelor by the DrugSorb-ATR system may provide a novel solution to reduce the high risk of bleeding in ticagrelor treated patients proceeding to surgery.

The double-blind, randomized STAR-T trial will determine whether DrugSorb-ATR reduces postoperative bleeding by actively removing ticagrelor during on-pump CT surgery in patients operated within 48 hours of their last dose. The primary endpoint has been designed to cover the full spectrum of postoperative bleeding complications ranging from fatal bleeding (most severe) to excess 24-hour CTD (least severe). This endpoint also includes moderate, severe, and massive perioperative bleeding events as defined by the UDPB classification system. Data from the CAPITAL Registry demonstrated a 40.5% incidence of at least moderate bleeding (UDPB ≥ 2) when patients underwent CABG <72 hours after last ticagrelor dose. This is contrasted with a <20% incidence of such bleeding events in patients who were able to undergo longer wash-out periods.¹⁷ Severity of bleeding is expected to be even higher in those undergoing surgery <48 hours after last ticagrelor dose. Importantly, it has been demonstrated that higher classification within the UDPB is correlated with higher 30-day mortality rates. Analysis of one sample population demonstrated 30-day mortality rates of >22% in patients with UDPB ≥ 3 , ~7% in patients with UDPB = 2, and <1.5% in patients with UDPB = 0 to 1.¹⁵

Statistical analysis of the primary endpoint employs the Win Ratio method which is increasingly being employed in cardiovascular device trials (detailed below). Evaluation of treatment effect will focus on the early postoperative period, since bleeding events that occur in temporal proximity to the index procedure are most likely to be modifiable by the intervention. Of note, in keeping with standard clinical practices, trial subjects with ACS or recent coronary stent placement will be re-started on ticagrelor (or the treating physician's choice agent for DAPT) on postoperative day #1 if there is no concern for active or ongoing bleeding.

The use of composite primary endpoints is common in randomized trials evaluating cardiovascular therapies. However, conventional statistical methods for analysis have a major weakness: clinical severity of the different components within the endpoint are not taken into account, and may instead be masked by time-to-first-occurrence.¹⁸ In contrast, the Win Ratio, a method inspired by the Finkelstein-Schoenfeld Test, employs hierarchical assessment of the individual components of the composite endpoint according to clinical signifi-

cance.^{20,19} The general principle is formation of subject-to-subject pairs in which every treatment subject is compared to each control subject, and "wins" versus "losses" are assigned based on who has the better outcome within the pair. Components of the composite endpoint are compared within every pair by descending order of importance, and only instances in which the outcome is the same for both subjects in the pair (e.g., "ties") would they proceed to comparison in the next component of lesser severity. The Win Ratio is not restricted to composites of a single variable type, and as such was deemed well-suited to evaluating STAR-Ts primary effectiveness measure, which incorporates both continuous, and categorical outcomes. The ranked nature of the Win Ratio also elegantly addresses potential competing risks within this study. Statistical experts have recommended supplementation of the Win Ratio analysis with conventional analyses of each component within the composite endpoint, which will also be employed here.¹⁸

Of note, a small number of trials have already utilized the Finkelstein - Schoenfeld Method for primary outcomes analysis in the setting of medical devices,^{21,22} and several ongoing trials for cardiac implantable devices are utilizing the Win Ratio as the pre-defined method for evaluating the primary composite endpoint [TAVR-UNLOAD (NCT02661451), RELIEVE-HF (NCT03499236), CARILLON (NCT03142152), and ACTIVE (NCT03016975); available for review on <https://clinicaltrials.gov>]. However, STAR-T is the first of its kind to utilize the Win Ratio for analysis of outcomes in a pivotal medical device trial meant to support regulatory clearance in a non-cardiac and non-implantable device.

The STAR-T trial is the first randomized controlled trial evaluating the utility of intraoperative ticagrelor removal for the reduction in perioperative bleeding. The strengths of this study include its randomized, double-blind, design, which in addition to allowing direct comparison of clinical bleeding outcomes, also allows robust safety evaluation. STAR-T utilizes a novel approach to analysis of a primary composite endpoint with the Win Ratio, which prioritizes clinical severity of each component. This allows the primary endpoint of the study to include a broad spectrum of outcomes, while addressing potential competing risks among the components. While the current study is in the specific setting of cardiothoracic surgery, future studies may be indicated to investigate benefit of DrugSorb-ATR for ticagrelor removal in additional clinical settings.

In conclusion, STAR-T is a prospective, randomized, double-blind, controlled trial that aims to determine if there is a reduction in postoperative bleeding complications with use of DrugSorb-ATR for intraoperative ticagrelor removal in patients undergoing cardiothoracic surgery ≤ 48 hours since last ticagrelor dose.

Authors' contribution

C. Michael Gibson: Methodology, Resources, Writing - review & editing, Supervision, Michael J. Mack: Methodology, Resources, Writing - review & editing, Supervision, Victoria T. Lee: Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Project administration, David J. Schneider: Methodology, Resources, Writing - review & editing, Frank W. Sellke: Methodology, Resources, Writing - review & editing, E. Magnus Ohman: Methodology, Resources, Writing - review & editing, Vinod H. Thourani: Methodology, Resources, Writing - review & editing, Gheorghe Doros: Methodology, Resources, Writing - review & editing, Hans Kroger: Methodology, Resources, Writing - original draft, Writing - review & editing, Donald E. Cutlip: Writing - review & editing, Efthymios N. Deliargyris: Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- Efthymios N. Deliargyris, MD, Victoria T. Lee, MD, and Hans Kroger, MSc, are employees of CytoSorbents Inc.
- The Baim Institute (with which authors C. Michael Gibson, MD, Gheorghe Doros, PhD, and Donald E. Cutlip, MD are affiliated) received unrestricted grant support for this study.
- C. Michael Gibson, MD, Michael J. Mack, MD, David J. Schneider, MD, Frank W. Sellke, MD, E. Magnus Ohman, MD, and Vinod H. Thourani, MD are members of the STAR-T clinical trial Executive Committee.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ahj.2021.10.188](https://doi.org/10.1016/j.ahj.2021.10.188).

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