

Intraoperative ticagrelor removal via hemoadsorption during on-pump coronary artery bypass grafting



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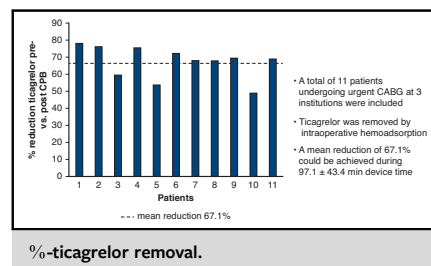
ABSTRACT

Objectives: Patients on ticagrelor undergoing urgent cardiac surgery are at high risk for perioperative bleeding complications. We sought to determine whether intraoperative hemoadsorption could remove ticagrelor and lower circulating drug concentrations.

Methods: The hemoadsorption device was incorporated in the cardiopulmonary bypass (CPB) circuit and remained active for the duration of the pump run. Blood samples were collected before and after CPB. The main objective of the current analysis was to compare mean total plasma ticagrelor levels (ng/mL) at baseline with ticagrelor levels obtained at the end of CPB. Plasma ticagrelor levels were measured at a certified outside laboratory (LabConnect). Data are presented as mean \pm standard deviation.

Results: A total of 11 patients undergoing urgent coronary artery bypass grafting at 3 institutions were included (mean age, 67.9 \pm 9.9 years; 91% male; mean European System for Cardiac Operative Risk Evaluation II of 3.0 \pm 3.3%; range, 0.7%-12.4%). Mean intraoperative hemoadsorption duration was 97.1 \pm 43.4 minutes with a mean flow rate through the device of 422.9 \pm 40.3 mL/min. Mean ticagrelor levels pre-CPB were 103.5 \pm 63.8 ng/mL compared with mean post-CPB levels of 34.0 \pm 17.5 ng/mL, representing a significant 67.1% reduction ($P < .001$). Intraoperative integration of the device was simple and safe without any device-related adverse events reported.

Conclusions: This is the first in vivo report demonstrating that intraoperative hemoadsorption can efficiently remove ticagrelor and significantly reduce circulating drug levels. Whether active ticagrelor removal can reduce serious perioperative bleeding in patients undergoing urgent cardiac surgery is currently being evaluated in the double-blinded, randomized Safe and Timely Antithrombotic Removal-Ticagrelor (STAR-T) trial. (JTCVS Open 2023;15:190-6)



CENTRAL MESSAGE

This is the first in vivo report demonstrating that intraoperative hemoadsorption can efficiently remove ticagrelor and significantly reduce circulating drug levels.

PERSPECTIVE

The removal of ticagrelor from blood has been proven and holds promise to be used in every urgent/emergent patient under ticagrelor treatment. Whether active ticagrelor removal can reduce serious bleeding in patients undergoing urgent cardiac surgery is currently being evaluated in the double-blinded, randomized Safe and Timely Antithrombotic Removal-Ticagrelor (STAR-T) trial.

See Discussion on Page 197.

Ticagrelor is an oral, direct-acting P2Y₁₂ receptor antagonist that binds reversibly and noncompetitively to the P2Y₁₂ receptor at a site distinct from that of the endogenous agonist adenosine diphosphate, making it an allosteric antagonist.¹ Ticagrelor is indicated to reduce recurrent ischemic events in moderate-to-high risk patients with acute

coronary syndromes, as demonstrated by the PLATO (Platelet Inhibition and Patient Outcomes) trial, or following previous myocardial infarction, as demonstrated by the PEGASUS-TIMI 54 trial.¹⁻³

As with any drug that inhibits platelet function, the predominant safety concern with ticagrelor is the increased

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Abbreviations and Acronyms

BARC = Bleeding Academic Research Consortium
 CABG = coronary artery bypass grafting
 CPB = cardiopulmonary bypass

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risk of spontaneous bleeding or iatrogenic bleeding with invasive medical procedures. In PLATO, up to 10% of patients required surgical revascularization and were at significantly increased risk of perioperative bleeding complications when coronary artery bypass grafting (CABG) was performed within 3 days of the last ticagrelor dose.^{2,4} Accordingly, for patients on ticagrelor requiring cardiothoracic surgery, the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines recommend postponing surgery for at least 3 days after ticagrelor discontinuation to allow for drug washout.^{5,6} Discontinuation, however, of antiplatelet therapy in these settings has been associated with an increase in ischemic complications, and therefore “bridging” strategies with different P2Y₁₂ antagonists have been proposed.⁷

However, in patients who need to proceed to surgery before completing the necessary washout, there are no available strategies to mitigate the bleeding risk.^{4,8,9} Specifically, platelet transfusions are not particularly effective in ticagrelor-associated bleeding since the reversible mode of binding renders new platelets also vulnerable to inhibition, and studies have shown that platelet reactivity remained unchanged following transfusion of platelets.¹⁰⁻¹² The aim of the present study was to determine the ability of the CytoSorb 300-mL device (CytoSorbents) to actively remove ticagrelor intraoperatively and lower circulating drug concentrations in patients undergoing on-pump CABG.

METHODS

Patients

The current analysis was conducted from patients who were recruited in 2 company-sponsored trials designed to investigate the ticagrelor-removal capabilities of the device. Both studies were initiated shortly before the onset of the pandemic and subsequently were unable to continue enrollment due to the pandemic-related research restrictions and staffing shortages at the participating institutions. Accordingly, both studies were terminated early due to enrollment futility. The combined number of 11 patients enrolled and their available drug-level data were used for this analysis. The present study enrolled patients on ticagrelor in a prospective fashion who underwent nondeferable CABG surgery at the Department of Cardiac Surgery, Asklepios Heart Center Hamburg, Germany; the Department of Cardiac Surgery, Royal Infirmary Hospital, Aberdeen, Scotland, United Kingdom; or the Department of Cardiothoracic Surgery,

Royal Infirmary of Edinburgh, Edinburgh, Scotland. Eligible participants for this study met all the following criteria: (1) age ≥ 18 years; (2) treated with ticagrelor; (3) on-pump CABG ≤ 48 hours following the last dose of ticagrelor; and (4) written informed consent. Exclusion criteria included (1) index surgery > 48 hours after last dose of ticagrelor; (2) cardiopulmonary resuscitation; (3) any preoperative coagulopathy; (4) sepsis (according to Sepsis 3.0 definition); (5) malignant tumor; (6) left ventricular ejection fraction $< 20\%$; (7) history or presence of significant pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, neurologic, or psychiatric disease; (8) presence of end-stage renal disease or currently receiving renal-replacement therapy; (9) history of major organ transplantation; (10) in acute sickle cell crisis or (11) requiring concurrent immunosuppressive therapy, with the exception of corticosteroids, or those who are profoundly immunosuppressed; and (12) women of childbearing potential with a positive pregnancy test performed during the current admission or who are lactating. The study complies with the Declaration of Helsinki and was performed according to ethics committee approval; all patients provided written informed consent for publication of study data (Central German Ethics committee Hamburg, Germany: number: #PV7329 from November 26, 2020, and central National Institutes of Health ethics committee UK: National Institute for Health and Care Research Clinical Research Network Reference: SURG 42128, Integrated Research Application System (IRAS) number: 264064 from October 1, 2018).

Device

The CytoSorb 300-mL device bears a Conformité Européenne conformity marking and is indicated for removal of ticagrelor intraoperatively during cardiopulmonary bypass (CPB) as an extracorporeal blood purification therapy. The cartridge consists of a cylinder and end-cap assembly filled with biocompatible porous polymer beads. Each end-cap has a standard blood tubing connector that is compatible with standard CPB tubing lines.

The polymer beads are composed of a divinylbenzene/polyvinyl pyrrolidone co-polymer, and each bead has hundreds of thousands of tightly controlled pores and channels that are generated via suspension polymerization. Each polymer bead is between 300 and 800 μm in size and the pores and channels provide a large (40,000 m^2) effective surface area for binding hydrophobic molecules between 5 and 60 kDa based on pore capture (size) and surface adsorption.¹³

Ticagrelor has a molecular weight of 522.6 Daltons and easily passes into the pores of the polymer, where it adsorbs onto the internal polymer surface through a combination of nonpolar interactions, hydrogen bonding, and Van der Waals forces. The device was incorporated into the CPB circuit between the oxygenator and the venous reservoir (Figure 1). The target flow rate through the device was 450 to 550 mL/min (up to 15%-20% of a typical flow rate in CPB).

Laboratory Parameters

Blood was drawn at the following time periods to test drug levels: $t = 0$ (before start of CPB) and $t = 1$ (after end of CPB). Blood was placed into dipotassium ethylenediaminetetraacetic acid vials (BD) and processed by centrifuging at $4000 \times g$ at 4°C for 10 minutes. The resulting plasma was stored at -80°C until drug concentration analysis could be performed by protein precipitation using reversed-phase liquid chromatography with tandem mass spectrometry. Analysis of plasma ticagrelor concentrations (ng/mL) was performed by an independent laboratory (LabConnect).

Outcome Measures

The primary end point of the study was the percentage of ticagrelor reduction after, compared with before, CPB. Secondary end points included serious bleeding events and 24-hour chest tube drainage. Bleeding events were evaluated according to the standardized BARC (Bleeding Academic Research Consortium) criteria that specifically include a distinct classification for bleeding within 48 hours of CABG (ie, BARC type 4:

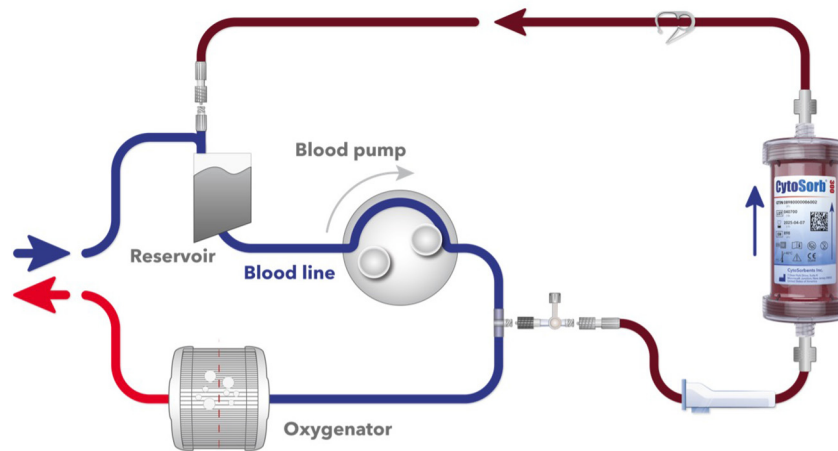


FIGURE 1. Implantation of the CytoSorb device into the cardiopulmonary bypass circuit.

defined as perioperative intracranial bleeding within 48 hours, or reoperation for the purpose of controlling bleeding, or transfusion of 5 units of whole blood or packed red blood cells within 48 hours, or chest tube output greater than 2000 mL within 24 hours). Safety of the device was assessed by investigator-reported adverse events including severity and relatedness classifications.

Statistical Analysis

Data were analyzed using SAS, version 9.2, software (SAS Institute). Continuous variables are expressed as mean ± standard deviation and were compared using the Student *t*-test. Plasma ticagrelor levels and chest tube drainage are presented as median and interquartile range. Categorical data are expressed as number of patients and frequencies.

RESULTS

Baseline and Operative Characteristics

From November 2019 through January 2022, 11 patients on ticagrelor underwent on-pump CABG at the 3 participating centers. The time interval between surgery and last ticagrelor dose was ≤48 hours in all cases. All patients were also on 75 to 100 mg of aspirin daily. Preoperative baseline characteristics of the patients are outlined in Table 1. Mean age was 67.9 ± 9.9 years, and 91% of the patients were male. The mean European System for Cardiac Operative Risk Evaluation II for the total population was 3.0 ± 3.3% (range, 0.7%-12.4%). Table 2 represents the intraoperative characteristics. All patients underwent isolated CABG surgery with a mean intraoperative CPB duration of 97.1 ± 43.4 minutes and a mean flow rate of 422.9 ± 40.3 mL/min through the device.

End Points

Results of the primary end point of %-ticagrelor removal are presented in Figure 2. Mean ticagrelor levels pre-CPB were 103.5 ± 63.8 ng/mL (median, 90.4 ng/mL) compared with mean post-CPB levels of 34.0 ± 17.5 ng/mL (median 34.6 ng/mL), representing a statistically significant reduction of 67.1% (*P* < .001), which is shown in Figure E1.

Secondary end points are presented in Table 2. In summary, there were no re-operations performed for bleeding and no BARC-4 bleeding events occurred. Median chest tube drainage over 24 hours was 520 mL (375-930 mL). All sites reported that the intraoperative integration of the device was

TABLE 1. Baseline characteristics

Variable	N = 11
Age, y	67.9 ± 9.9
Sex, male	10 (91.0)
BMI, kg/m ²	29.3.9 ± 4.0
CABG indication	11 (100.0)
Last ticagrelor dose	
90 mg	10 (91.0)
180 mg	1 (9.0)
Urgency	
Urgent	10 (91.0)
Emergent	1 (9.0)
Acute infarction	6 (54.5)
IABP insertion preoperative	1 (9.0)
EuroSCORE II, %	3.0 ± 3.3
LV function, %	50.8 ± 8.0
Systemic hypertension	8 (72.7)
COPD	3 (27.3)
Hyperlipidemia	9 (81.8)
Diabetes, oral	8 (72.7)
Laboratory parameters	
Creatinine, μmol/L	98.8 ± 18.6
Platelets, /nL	243.0 ± 56.6
Fibrinogen, g/L	4.8 ± 1.1

Data are presented as number (%) or mean ± standard deviation. *BMI*, Body mass index; *CABG*, coronary artery bypass grafting; *IABP*, intra-aortic balloon pump; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *LV*, left ventricular; *COPD*, chronic obstructive pulmonary disease.

TABLE 2. Intraoperative and postoperative bleeding data

Variable	N = 11
Intraoperative	
Intraoperative device time, min	97.1 ± 43.4
Device flow rate, mL/min	422.9 ± 40.3
Operation time (skin-to-skin)	269.1 ± 76.7
RBC, overall units in 11 patients	2
Platelets, overall units in 11 patients	1
FFP, overall units in 11 patients	3
Postoperative	
Revision due to bleeding	0 (0.0)
>5 RBC/48 h	0 (0.0)
Intracranial bleeding	0 (0.0)
>2000 mL/24 h	0 (0.0)
BARC-4 bleeding events	0 (0.0)
Chest tube drainage volume/24 h, mL	520 (375-930)
RBC within 24 h, overall units in 11 patients	11
Platelets within 24 h, overall units in 11 patients	1
FFP within 24 h, overall units in 11 patients	3

Data are presented as number (%) or mean ± standard deviation. RBC, FFP, and platelets are shown in units. Chest tube drainage is presented as median and interquartile range. RBC, Red blood cell; FFP, fresh-frozen plasma; BARC, Bleeding Academic Research Consortium.

simple and safe, and there were no device-related adverse events reported.

Overall mortality was 18.2% (2/11). One patient died on postoperative day 2 due to complications from cardiogenic shock and myocardial infarction immediately following explantation of a pre-operatively implanted intra-aortic balloon pump (European System for Cardiac Operative Risk Evaluation II, 12.4%; left ventricular function, 35%) without any thromboembolic history. The second fatality was the result of pulmonary embolism that occurred on hospital day 11. The site investigator classified the death as unrelated to the CytoSorb device and related to prolonged immobilization during the hospitalization.

DISCUSSION

The current study aimed to determine whether intraoperative hemoadsorption can actively remove ticagrelor in patients undergoing urgent or emergent cardiac surgery with cardiopulmonary bypass. There are 3 main observations from the current study: First, intraoperative hemoadsorption was able to significantly reduce circulating plasma ticagrelor levels. Second, there were no serious perioperative bleeding events (BARC-4) among these high-risk patients. Finally, use of the hemoadsorption device was simple and safe without any device-related adverse events reported.

The current study is the very first in vivo demonstration of significant reductions in ticagrelor concentrations with intraoperative hemoadsorption. Published benchtop models have previously shown that ticagrelor can be efficiently removed from blood via hemoadsorption.^{14,15} Previous reports from our group have also shown that the use of

intraoperative hemoadsorption can significantly reduce bleeding complications in patients on ticagrelor or rivaroxaban undergoing non-deferable cardiac surgery.¹⁶⁻¹⁸ The present study extends the observations from the benchtop models and provides the mechanistic link for the significant reductions in perioperative bleeding observed in clinical practice.

Thus far, the clinical use of a hemoadsorption to remove ticagrelor in cardiac surgery has been limited to on-pump cases only with integration into the CPB circuit. Just recently, Mair and colleagues¹⁹ presented their experience on 4 patients with the new apheresis machine PUR-01 (Nikkisio Co, Ltd) to intraoperatively remove ticagrelor during off-pump coronary artery bypass grafting surgery.

Benchtop data show that ticagrelor, apixaban, and rivaroxaban are all removed efficiently from blood by the device and that, in less than 60 minutes, their concentrations drop below the therapeutic range.^{14,15,20} The Society of Thoracic Surgeons practice guidelines recommend a minimum 3 days of ticagrelor washout,²¹ based on the high bleeding rates reported in patients operated within 48 hours of the last dose.² Pharmacokinetics of ticagrelor also suggest that about 48 hours of washout would be required for a similar drop in circulating as measured in our study.²² In the present study, the 67% reduction in ticagrelor levels was observed with a mean device exposure of 97 minutes, establishing that efficient ticagrelor removal to lower levels below therapeutic concentrations can be achieved in standard CABG operations. This is also corroborated by the absence of any serious bleeding complications, even though all patients were operated on an urgent or emergent basis in under 48 hours from the last dose of ticagrelor. Importantly, in all cases, integration of the device was reported as simple and safe without any device-related adverse events. It should be acknowledged, however, that in one case a fatal pulmonary embolism occurred 11 days postoperatively, which seemed to be related to immobilization, during the coronavirus disease 2019 pandemic. It also should be acknowledged that the CytoSorb 300-mL device was initially designed to remove cytokines and to attenuate the so-called cytokine storm.¹³ Meanwhile, drug elimination through active removal has been evaluated extensively.²³

The current study focused on removal of ticagrelor from human blood (plasma). Of note, a huge variety of proteins within the adsorptive spectrum can also be removed. A recently published study by Piskovatska and colleagues²⁴ reported on broad-spectrum removal of a wide range of molecules eliciting endothelial damage and retarded wound healing by hemoadsorption. Moreover, Jansen and colleagues²⁵ could prove that the immunological response was not altered by hemoadsorption.

Our data show that intraoperative hemoadsorption therapy can effectively reduce circulating plasma ticagrelor concentration and support the hypothesis that this

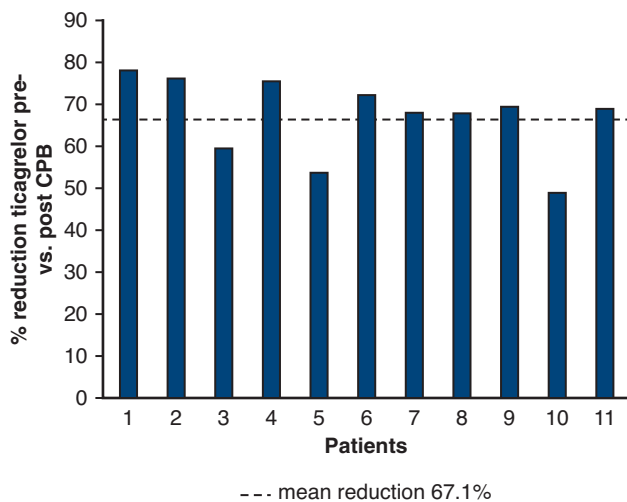


FIGURE 2. % ticagrelor reduction pre- and post-CPB for each individual patient. CPB, Cardiopulmonary bypass.

intervention may also mitigate the risk of perioperative bleeding. The hypothesis of whether ticagrelor removal can reduce serious perioperative bleeding in patients undergoing urgent cardiac surgery is currently formally tested in the pivotal, double blind, randomized Safe and Timely Antithrombotic Removal–Ticagrelor (STAR-T) trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04976530) Identifier: NCT04976530).²⁶

Limitations

Our study has 4 limitations that have to be considered when interpreting the results. First, this was a relatively small cohort for the purpose of evaluating clinical outcomes especially for clinical bleeding events; however, since the primary end point was drug removal, the power is considered adequate, especially considering that the investigated effect was observed consistently in all subjects. Second, the absence of a control arm does not allow comparison of the kinetics of active drug removal with baseline elimination; however, the known pharmacokinetics of ticagrelor suggest that passive elimination would be nowhere close to the 67% reduction observed after 97 minutes of device exposure.^{27,28} Third, comprehensive platelet function testing results were not available to accurately determine the impact of the residual ticagrelor on platelet aggregation following CABG surgery. Fourth, there is a lack of data on the removal of other proteins within the spectrum of adsorption that could have clinical implications.

CONCLUSIONS

In conclusion, intraoperative hemoadsorption effectively reduces circulating ticagrelor plasma concentration in patients undergoing nondeferable on-pump CABG. This intervention has the potential to improve on the current standard of care by allowing timely surgery while reducing the high risk of perioperative bleeding. Whether ticagrelor removal

can reduce serious perioperative bleeding in patients undergoing urgent cardiac surgery is currently being evaluated in the pivotal, double-blind, randomized STAR-T trial.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: <https://www.aats.org/resources/ticagrelor-removal-with-intraoperative-polymer-bead-hemo-adsorption-in-patients-undergoing-urgent-coronary-artery-bypass-grafting>.



Conflict of Interest Statement

Daniel Wendt and Efthymios N. Deliargyris are both full-time employees of CytoSorbents. Kambiz Hassan, Stephan Geidel, Robert F. Storey, and Michael Schmoedel received speaker honoraria and travel grants from CytoSorbents. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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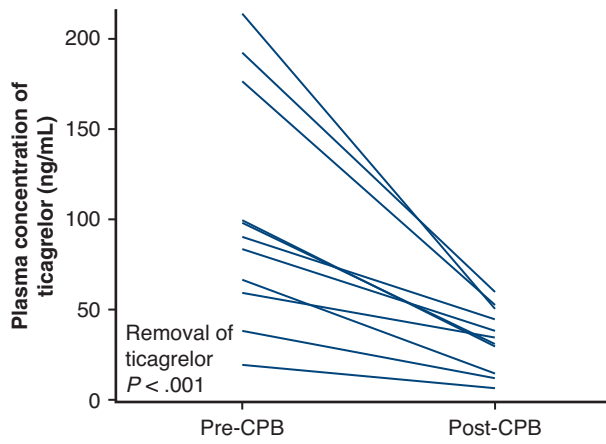


FIGURE E1. Plasma concentration of ticagrelor (ng/mL) pre- and post-CPB for each individual patient. *CPB*, Cardiopulmonary bypass.