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RESEARCH

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Direct-acting oral anticoagulant removal by intraoperative hemoadsorption in CABG and/or single valve surgery: interim analysis of the International Safe and Timely Antithrombotic Removal (STAR) registry

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Abstract

Objective Patients on direct-acting oral anticoagulants (DOACs) are at high risk of perioperative bleeding complications. Intraoperative hemoadsorption is a novel strategy to reduce perioperative bleeding in patients on DOACs undergoing non-deferable cardiac surgery. The international STAR-registry reports real-world clinical outcomes associated with this application.

Methods The hemoadsorption device was incorporated into the cardiopulmonary bypass (CPB) circuit and active for the duration of the pump run. Patients on DOACs undergoing CABG and/or single valve surgery before completing the recommended washout were included. Outcome measurements included bleeding events according to standardized definitions and 24-hour chest-tube-drainage (CTD).

Results A total of 62 patients were included from 7 institutions in Austria, Germany, Sweden, and the UK (mean age 69.9 ± 7.5years, 71% male). Approximately half were on apixaban and the other half was split between rivaroxaban and edoxaban with 21% of patients also on aspirin. Surgery occurred at a median time of 28.9 h since the last DOAC dose with single valve surgery accounting for 2/3 of cases. Mean CPB duration was 118.6 ± 46.4 min. Severe bleeding (UDPB ≥ 3) occurred in 4.8%, and BARC-4 bleeding occurred in 3.2% of the patients. Only one patient (1.6%) required reoperation for bleeding control. The mean 24-hour CTD was 771.3 ± 482.79mL. No device-related adverse events were reported.

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Conclusions This interim report of the ongoing STAR-registry shows that, in patients on DOAC undergoing non-deferable CABG and/or single valve surgery, the use of intraoperative hemoadsorption is associated with low rates of severe perioperative bleeding complications. Further prospective studies in larger cohorts are needed to validate the efficacy of this method.

Clinical registration number ClinicalTrials.gov identifier: NCT05077124.

Keywords Hemoadsorption, Antithrombotic removal, Cardiac surgery, CytoSorb, DOAC

Introduction

Antithrombotic drugs are cornerstone treatments for patients with cardiovascular disease [1]. Direct-acting oral anticoagulants (DOACs) are the first-line therapy for millions of patients around the world for lifelong stroke prevention in patients with atrial fibrillation (AF) and for prevention and management of deep vein thrombosis [2–4]. In this context, DOACs have been shown to be safe and effective, but also easier to use since they do not require strict and frequent laboratory monitoring or dose adjustments compared to warfarin. The main safety risk associated with DOACs is increased bleeding, which can be spontaneous or iatrogenic, such as when these patients require urgent or emergency interventions, including cardiac surgery [1].

Current guidelines recommend that DOACs should be discontinued at least 48 h before surgery to minimize the risk of bleeding [5]. However, clinical scenarios often preclude this waiting period, necessitating alternative strategies to reduce the risk of bleeding in cases of non-deferable surgery. Removal of DOACs from the circulation by intraoperative polymer bead hemoadsorption has emerged as a novel strategy to reduce perioperative bleeding in patients on antithrombotic drugs undergoing urgent or emergency on-pump cardiac surgery [6, 7]. The international Safe and Timely Antithrombotic Removal (STAR) registry is designed to collect real-world clinical outcomes associated with this application (NCT05077124).

The current interim analysis of the international STAR Registry reports perioperative bleeding rates in patients on DOACs undergoing non-deferable CABG and/or single valve surgery with the use of intraoperative hemoadsorption.

Methods

The international Safe and Timely Antithrombotic Removal (STAR) registry is designed to collect high-fidelity data on patients who underwent antithrombotic removal (ATR) with CytoSorb® as part of their routine care. Participating centers can include both prospective and retrospective patients depending on the date of ethics approval: patients who received hemoadsorption for ATR as part of their clinical routine prior to the registry's protocol ethics approval are entered as retrospective patients, whereas patients enrolled after ethics approval are entered as prospective. Collected clinical and resource utilization data are entered in an electronic case report form (Medpace Inc., Ohio, Cincinnati, USA). Safety is assessed by collection of definite, probable, or possible device-related investigator-reported adverse events according to the latest ISO 14155:2020 classification. Data collection is done up to 30 days post ATR. The sponsor and funding source of the registry is CytoSorbents Inc., Princeton, NJ, USA. The ongoing registry is designed to enroll up to 1,000 real-world patients undergoing cardiac surgery with intraoperative drug removal by hemoadsorption.

Ethical statement

This registry complies with the Declaration of Helsinki. National central or local approvals of respective Ethics committees were granted for the STAR registry according to local regulations (complete list of all ethics available within the Supplement). Written consent for data collection was obtained before or after surgery from prospective patients and was waived for retrospective patients.

Inclusion criteria

CytoSorb® utilization for antithrombotic removal and informed consent for prospective registry participation. The CE-marked CytoSorb adsorber was used as part of routine clinical care.

Exclusion criteria

Use of CytoSorb® for a purpose other than antithrombotic removal.

Patients

This interim analysis of the STAR Registry included all enrolled patients undergoing ATR for DOAC removal with intraoperative hemoadsorption during CABG and/or single valve surgery.

Hemoadsorption therapy

Antithrombotic removal via hemoadsorption therapy was performed with the CytoSorb® adsorber (CytoSorbents Inc., Princeton, NJ, USA). The device is based on a proprietary extracorporeal blood purification and is

CE-mark approved to remove ticagrelor and rivaroxaban during on-pump cardiac surgery. The cartridge is filled with highly biocompatible, porous polymer beads covered with a divinylbenzene coating and can be easily integrated into various extracorporeal circuits, such as e.g., continuous renal replacement therapy, extracorporeal membrane oxygenation (ECMO), or cardio-pulmonary bypass (CPB), as shown in Fig. 1. Each polymer bead is between 300 µm and 800 µm in size and has pores and channels, giving it a large (> 40,000 m^2) effective surface area for binding hydrophobic small and medium-sized molecules up to 60 kDa of molecular weight [8]. DOACs have a molecular weight ranging between ~ 400–600 Daltons [9] and can therefore easily pass into the pores of the beads and readily adsorb onto the internal polymer surface through a combination of non-polar interactions, hydrogen bonding, and van der Waals forces.

Outcome measures

Perioperative bleeding complications were evaluated according to two standardized bleeding definitions: (a) *B*leeding *A*cademic *R*esearch *C*onsortium (BARC), and (b) *U*niversal *D*efinition of *P*erioperative *B*leeding (UDPB). Additional outcomes included 24-hour chest tube drainage (CTD), blood product transfusions, re-operation for bleeding, and in-hospital mortality. Safety of the device was assessed by investigator-reported adverse device events, including severity and related classifications (**Supplement**).

Results

For the present analysis, a total of 62 patients on DOACs were included from 7 institutions in Austria, Germany, Sweden, and UK. All patients underwent on-pump isolated CABG and/or single valve surgery and received intraoperative hemoadsorption as part of their clinical routine.

Baseline characteristics are presented in Table 1. Patients on all 4 available DOACs (rivaroxaban, apixaban, edoxaban and dabigatran) were included; however, almost half of the patients were on apixaban, approximately one-quarter each were on rivaroxaban and edoxaban, and only few were on dabigatran (Fig. 2). The washout period from the last DOAC dose (median 28.9 h [Q1: 24.0, Q3: 50.9]) was less than 48 h in all patients (Table 1). Patients with either longer or shorter washout periods according to the overall cohort's median and interquartile range for washout did not differ in terms of demographics or bleeding outcomes according to the UDPB ($p = 0.562$) or BARC-4 ($p = 1.000$) definition (See Fig. 3).

Procedural and postoperative outcomes are summarized in Table 2. A total of 23 patients underwent isolated CABG and 39 underwent single valve surgery, of whom 16 received concomitant CABG surgery. The duration of CPB (a direct measure also of hemoadsorption device exposure) and aortic cross clamp duration were 118.6 ± 46.4 and 80.9 ± 32.8 min, respectively (See Table 3).

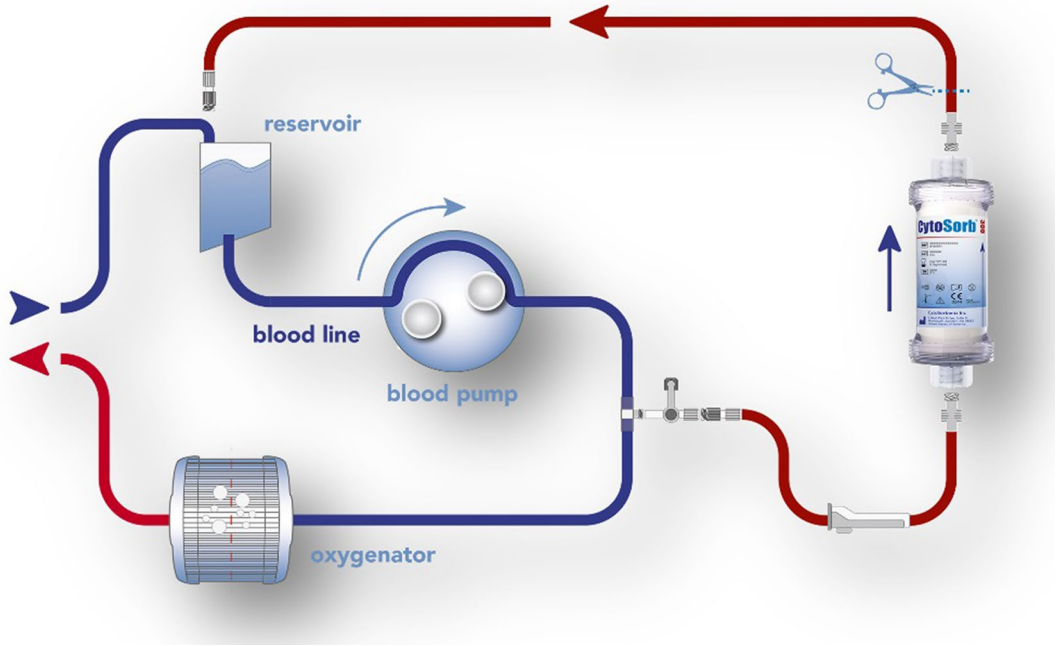

Fig. 1 Hemoadsorption device (CytoSorb®) incorporated in the cardiopulmonary (CPB) circuit. The device remained active for the duration of the CPB-run

Table 1 Demographics

Variable	Isolated CABG or single valve surgery *n* = 62
Age, years	69.9 ± 7.5
Gender, male	44 (71.0%)
Weight, kg	84.8 ± 18.9
Acetylsalicylic acid use before surgery	13 (21.0)
Acute coronary syndrome	17 (27.4%)
Atrial fibrillation	56.7% (34/60)
History of deep vein thrombosis	7.1% (4/56)
Prior Stroke	6.7% (4/60)
Current smoker	39.3% (11/28)
Time since last dose of DOAC, hours	28.9 (24.0, 50.9)
NYHA functional class III/IV	61.3% (19/31)
Hypertension	52 (85.2%)
Diabetes	20 (32.3%)
Hyperlipidemia	42.4% (25/59)
Prior myocardial infarction	11.5% (7/61)
Peripheral artery disease	6.8% (4/59)
Renal dysfunction (creatinine > 1.3 mg/dL / failure (dialysis))	31.1% (19/61)
Hepatic Impairment	6.8% (4/59)
Prior sternotomy	6.6% (4/61)
EuroSCORE-II, %	6.9 ± 12.8

Data are presented as number (%), or % (n/N), mean±SD or median (Q1, Q3)

NYHA - New York Heart Association, EuroSCORE - European System for Cardiac Operative Risk Evaluation

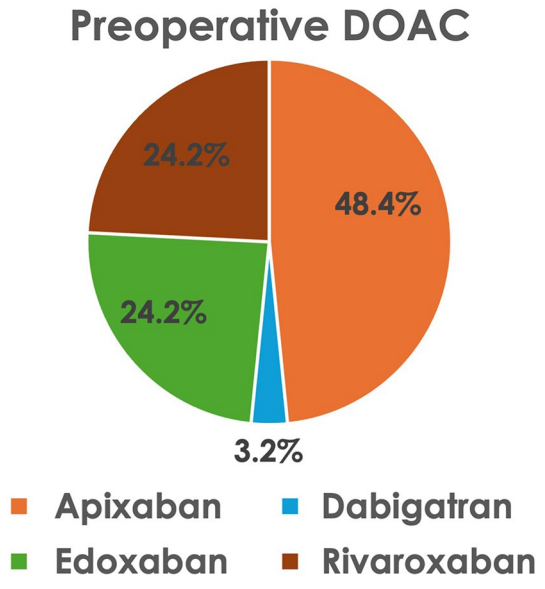

Fig. 2 Type of DOAC drug

Serious postoperative bleeding complications were infrequent and included one re-operation for bleeding control, one case of CTD > 2 L and one patient receiving 8 units of fresh-frozen plasma. These events resulted in rates of 4.8% and 3.2% according to the UDPB and BARC-4 definitions, respectively. Mean 24-hour CTD was 771.3 ± 482.79mL with 10 patients exceeding 1 L (16.1%) and 1 patient exceeding 2 L (1.6%).

Packed red blood cells (pRBC) were not transfused during the first postoperative day in 75.8% of the patients. Platelets and fresh frozen plasma were administered in 12.9% and 9.7% of the patients, respectively.

Mortality at 30 days in the overall cohort was 6.5% (4/62) and all deaths were unrelated to bleeding. There were no device-related adverse events reported by investigators.

Discussion

This interim analysis from the ongoing international STAR registry reports rates of serious perioperative bleeding complications in patients on DOACs undergoing non-deferable on-pump CABG and/or single-valve surgery with intraoperative hemoadsorption. The main observation of this report is that the intraoperative use of a hemoadsorption device resulted in low rates of serious perioperative bleeding complications in patients on DOACs undergoing isolated CABG and/or single valve surgery before completing the recommended washout period. In addition, participating investigators reported that incorporation of intra-operative hemoadsorption in their routine surgical protocol was simple and safe since there were no device-related adverse events observed.

Tens of millions of patients are on DOACs worldwide and a significant number of them will require urgent surgical intervention during the course of their therapy [1, 2, 10]. In such a scenario, high perioperative bleeding rates of up to 23% have been reported [2]. Accordingly, current guidelines recommend that patients discontinue DOACs at least 48 h prior to surgery whenever possible with even longer periods required for patients with renal insufficiency [1, 5, 11].

The CytoSorb hemoadsorption device (CytoSorbents, Inc., Princeton, NJ, USA) has been shown to effectively remove all DOACs from blood in the in-vitro setting [7]. CytoSorb is currently CE mark approved for clinical use for removal of cytokines, myoglobin, bilirubin, ticagrelor and rivaroxaban and can be easily integrated into any extracorporeal hemoperfusion circuit such as cardiopulmonary bypass, extracorporeal membrane oxygenation, continuous renal replacement therapy/continuous venovenous hemofiltration or simple hemoperfusion [12]. CytoSorb is meanwhile used in various clinical settings in cardiac surgery [13].

The international STAR Registry is designed to capture high-fidelity data with the use of CytoSorb for antithrombotic removal in everyday clinical practice [6]. The current analysis focused on bleeding outcomes after CABG and/or single valve surgery in order to minimize any impact on postoperative bleeding by more complex

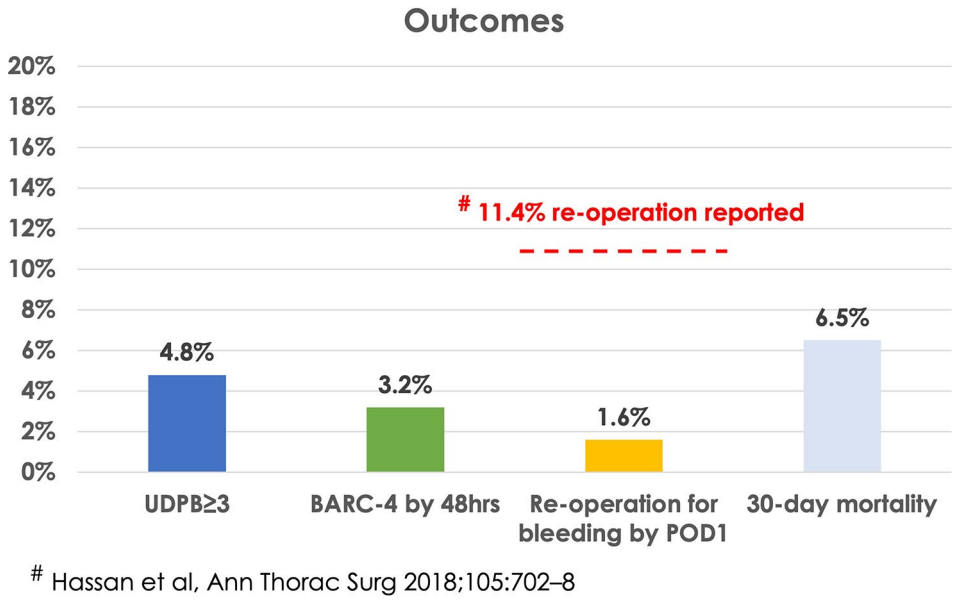

Fig. 3 Perioperative outcomes according to UDPB and BARC-4, the surgical revision rate and 30-day mortality

Table 2 Procedural & postoperative outcomes

Outcome parameters	Isolated CABG or single valve surgery *n* = 62
Procedural	
Operation duration, hours	3.8 ± 1.2
CPB time (device exposure), min.	118.6 ± 46.4
ACC time, min.	80.9 ± 32.8
Isolated CABG surgery	23 (37.1)
Single valve surgery	39 (62.9)
Single valve surgery and concomitant CABG surgery	16/39
Cerebral perfusion performed	0 (0)
Postoperative	
24-hour CTD, mL	771.3 ± 482.79
0-600mL	44.6%
601-800mL	19.6%
801-1,000mL	17.9%
1,001–2,000mL	16.1%
>2,000mL	1.6%
UDPB ≥ 3, %	4.8
BARC-4 within 48 h	3.2
Re-operation for bleeding at any time, %	1.6
Re-operation for bleeding by POD1, %	1.6
ICU-stay, hours	70.8 (26.2, 163.0)
Hospital stay, days	13 (9, 17)
30-day mortality, %	6.5

Data are presented as number (%), mean±SD or median (Q1, Q3)

CPB - cardiopulmonary bypass, ACC - aortic cross clamp, CTD - chest tube drainage, BARC - Bleeding Academic Research Consortium, UDPB – Universal Definition of Perioperative Bleeding, POD – postoperative day

Table 3 Blood product consumption (until postoperative day 1)

Variable	Isolated CABG or single valve surgery *n* = 62
Patients receiving pRBC transfusion	15 (24.2)
pRBC units	2.5 ± 1.6
Patients receiving platelet transfusion	8 (12.9)
platelet units	2.3 ± 1.6
Patients receiving FFP transfusion	6 (9.7)
FFP units	5.2 ± 2.9

Data are presented as number (%) or mean±SD. pRBC - packed red blood cells, FFP - fresh frozen plasma

surgery (i.e. aortic surgery or multiple valve procedures). In a recently published first analysis of the STAR registry, all types of surgery were analyzed, including complex aortic surgery, heart transplantation or combination procedures, resulting in higher UDPB and BARC-4 bleeding rates compared with the current analysis, which was intended to evaluate the impact of the device on antithrombotic related bleeding without any potential confounding due to the additional bleeding risk associated with more complex and higher risk procedures [6]. Consistent with global prescribing trends, patients in the STAR Registry were more frequently on apixaban followed by rivaroxaban and edoxaban. The overall median time from last dose to surgery in our cohort was 28.9 h, which is substantially shorter than the guideline recommendation of at least 48 h [5]. However, surgeons routinely report that their standard washout period is longer as many of their elderly patients have concomitant renal or hepatic disease, resulting in slower drug metabolism and washout. It is worth noting that in a previous analysis

of cardiac surgery patients on DOACs, a longer withdrawal period, particularly in patients with reduced renal function, was essential for safe on-pump cardiac surgery [14]. The authors concluded that, despite official recommendations, patients should not be considered for elective cardiac surgery within 10 days of stopping DOAC treatment [14]. The current report was representative of an all-comer population that included approximately 1/3 of patients with some degree of renal insufficiency and to a certain extent, liver disease. Of note, for dabigatran compared to other DOACs, renal excretion is the dominant elimination pathway, but all DOACs are eliminated to a certain extent by the renal pathway as mentioned by Chen et al. All DOAC therapies are eliminated by the kidneys to varying degrees, and changes in renal clearance must be taken into account when dosing these agents. Dabigatran has the highest fraction eliminated renally at 80%, of its clearance pathway, followed by edoxaban, rivaroxaban, apixaban, and betrixaban: 50%, 35%, 27%, and 11%, respectively [15].

A study published by Hassan et al. analyzed 25 consecutive patients on apixaban who underwent cardiac surgery, 13 with CytoSorb and 12 without. In their analysis, the preoperative washout interval was 0.6 ± 1.2 days in the CytoSorb vs. 1.3 ± 0.9 days in the control group ($p < 0.001$). Despite the shorter washout interval, the authors concluded that no BARC-4 bleeding complications did occur in the CytoSorb group and chest tube drainage was significantly lower [10].

The bleeding rates observed in the current analysis (UDPB ≥ 3: 4.8% and BARC-4: 3.2%) are similar to rates observed among patients not on DOACs and compare favorably to rates of bleeding complications reaching 23% that have been reported in the literature for patients on DOACs [2]. In addition, we observed a low surgical revision rate of 1.6% compared to a recent analysis by Hassan et al., who reported a surgical revision rate of 11.4% (4/35) in a cohort of DOAC-treated patients undergoing cardiac surgery prior to recommended washout compared to less than 2% in the control group [16]. In the current literature, incidence of surgical revision in DOAC patients varies between 6.28% and 11.8% [14, 17].

By adopting checklists for hemostasis and a dedicated algorithm for surgical preoperative planning in elective cases, bleeding rates can be further reduced [18]. Similarly, the same authors reported an increased red blood cell (RBC) transfusion rate of 39.5% in DOAC patients compared to less than 20% in controls [16]. Therefore, the results of the present analysis, with less than 2% of surgical revisions and 24.2% of patients receiving RBC transfusion, are almost comparable to control patients not on DOACs, suggesting a significantly lower incidence of major postoperative bleeding complications with the use of intraoperative hemoadsorption.

To date, only a few studies with smaller single-center cohorts have been published on this topic. Only one study reported bleeding outcomes in isolated CABG patients with prior rivaroxaban treatment. The authors reported no surgical revisions in the CytoSorb treated group ($n = 7$) compared to 2 surgical revisions in the control group ($n = 5$). All patients treated with rivaroxaban and the use of adsorption showed a significant reduction in drug levels in the anti-factor Xa assay [16]. In another observational case series from 2 centers, the use of intraoperative hemoadsorption in patients on apixaban undergoing different types of cardiac surgery (there were no BARC-4 bleeding events and no surgical revisions in the CytoSorb group compared with 3 and 1 in the control group [10].

It is also noteworthy that no serious device-related adverse events were observed. This important observation is consistent with other published reports and may provide an important advantage for hemoadsorption over the use of reversal agents that may be associated with serious thrombotic complications in this setting. Moreover, DOAC reversal agents are expensive: Andexanet al.pha ranges from $10,000 to $12,000, idarucizumab from $5,000 to $6,000 [2]. Specifically, for andexanet al.fa, the approved reversal agent for apixaban and rivaroxaban, there are published reports of significant intraoperative complications associated with heparin reversal and resistance during CPB and high risk for thrombotic postoperative complications. Various reports [19–22] warn about the off-label use of andexanet al.fa in CPB-assisted cardiac surgery due to the anticipated development of heparin resistance and anticoagulant rebound. Similarly, a Direct Healthcare Professional Communication letter issued by the European Medicines Agency advises against the use of this reversal agent prior to heparinization since it causes unresponsiveness to the anticoagulant effects of heparin [23]. A recently published comment discussed the problems associated with reversal agents such as andexanet al.pha and the authors concluded that it seems advisable to avoid preoperative administration of andexanet al.pha in cardiothoracic procedures involving the use of a heart–lung machine; they also mentioned alternative methods for eliminating DOACs, such as hemoadsorption [24]. Intraoperative hemoadsorption is increasingly recognized as a valid alternative with a favorable safety profile and recently the latest ESAIC guidelines for the management of major perioperative bleeding [25] include a Class 2 C recommendation for the use of hemoadsorption as an adjunct in patients on ticagrelor or rivaroxaban undergoing emergency cardiac/aortic surgery on cardiopulmonary bypass to reduce bleeding complications. Moreover, Mair et al. recently published their experience with off-pump

CABG and antithrombotic removal by using a standalone hemoperfusion pump intraoperatively [26].

Just recently, a group from Oslo published their experience with intraoperative hemoadasorption in 8 emergent apixaban-treated patients presenting with acute type-A aortic dissection. Røed-Undlien and colleagues were able to prove a significant removal of apixaban by intraoperative hemoadsorption as reflected by a significant decrease in apixaban concentrations. Interestingly the authors reported that 50% of the patients received 2,000IE of prothrombin complex concentrate (PCC) and one patient received recombinant activated factor VII (rFVIIa). Intraoperative administration of factor VII per se represents a severe bleeding event as per the UDPB definition. Of note, no surgical revisions have been reported by the authors [27].

In conclusion, these interim results from the ongoing International Safe and Timely Antithrombotic Removal (STAR) Registry show lower rates of major bleeding compared to historical cohort rates in patients on DOACs undergoing cardiac surgery before completion of the recommended washout period. Hemoadsorption appears to be a feasible, safe and potentially effective solution for reducing perioperative bleeding in this patient population.

Limitations

Our study has some major limitations that must be considered when interpreting the results. First, since the current dataset is derived from a single-arm observational registry, a DOAC control group (without adsorber use) is missing. Therefore, definitive conclusions about the effectiveness of the device cannot be made, but only contextualized with existing literature. Second, although the current analysis reflects the largest dataset on this topic, it is still limited by the fairly small number of patients and therefore results should be interpreted with the appropriate caution. Third, safety reporting was not according to GCP-level assessment of all adverse events, but rather via investigator surveillance and oversight for device related adverse events. Fourth, coagulation testing (anti-factor Xa or thromboelastometry) was not performed and therefore specific analyses based on the preoperative degree of anticoagulant DOAC effect cannot be performed. Finally, local institutional transfusion policies may have had an impact on the overall administration of blood products. Future larger studies also including control patients will be required to validate the preliminary results presented in this report to better define the efficacy of intraoperative hemadsorption to reduce perioperative bleeding in these patients.

Abbreviations

ACC	Aortic Cross Clamp
BARC	Bleeding Academic Research Consortium
CABG	Coronary Artery Bypass Grafting
CPB	Cardio-pulmonary bypass
CTD	Chest tube drainage
DOAC	Direct-acting oral anticoagulants
ECMO	Extracorporeal membrane oxygenation
ESAIC	European Society of Anaesthesiology and Intensive Care
STAR	Safe and Timely Antithrombotic Removal
UDPB	Universal Definition of Perioperative Bleeding

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-024-03326-1.

Supplementary Material 1

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Author contributions

Data akquisition was performed (reflecting all local principal investigators) by: M.S., M.T., K.V., T.E., N.M., K.H., A.L., S.L., G.M., R.S. Data cruration and analysis was performed by: M.S., M.T., M.S., D.W., E.D., R.S.The main manuscript was written by M.S., M.T., D.W., E.D., R.S. and all authors reviewed the manuscipt including substantial contributions. Figure were prepared by D.W.

Data availability

Data availabilityThe data underlying this article were provided by CytoSorbents Inc., Princeton, NJ, USA. Data will be shared on request to the corresponding author with permission of CytoSorbents.

Declarations

Competing interests

Michael Schmoeckel, Matthias Thielmann, Kambiz Hassan, Stephan Geidel, Sandra Lindstedt, received speaker honoraria and travel fees. Marijana Matejic-Spasic, Daniel Wendt are full-time employees of CytoSorbents Europe GmbH, Berlin, Germany, Efthymios Deliargyris is a full-time employee of CytoSorbents Inc., Princeton, NJ, USA. Robert Storey reports institutional research grants/support from Cytosorbents and AstraZeneca; and personal fees from Alfasigma, AstraZeneca, Boehringer Ingelheim/Lilly, Chiesi, Cytosorbents, Daiichi Sankyo, Idorsia, Novartis, Novo Nordisk, Pfizer, PhaseBio and Tabuk.

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