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Review Article | Peer-Reviewed Article

State of the Art

Contemporary Antithrombotic Drug Removal via Hemoadsorption in Cardiac Surgery

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Abstract

The incidence of severe bleeding in patients treated with dual antiplatelet therapy, including the new P2Y12 inhibitors or new direct oral anticoagulants, who are undergoing urgent cardiac surgery is very high. Novel strategies, including the removal of antithrombotics via intraoperative hemoadsorption, have shown promising results, which are summarized in this holistic review. Overall, current evidence supports antithrombotic removal via hemoadsorption as a potential new therapy in the management of perioperative bleeding risk in patients on antithrombotic medications undergoing cardiopulmonary bypass-assisted cardiac surgery.

Keywords: Cardiac surgery; bleeding; antiplatelets; anticoagulants; hemoadsorption

Introduction

During the last decade, new antithrombotic drugs have been developed and have become frequently used therapies for patients with cardiovascular or other cardiac diseases, as well as for secondary prevention. However, despite their many benefits, including improved survival, these modern antithrombotic drugs carry a well-known risk for bleeding events, which has been clearly described. Moreover, the risk for bleeding is further heightened in patients who need to undergo urgent surgery without sufficient time for the recommended preoperative washout. The current review provides a comprehensive overview on the option of antithrombotic drug removal via hemoadsorption in the field of cardiac surgery [1].

The antiplatelet drug ticagrelor is orally administered and acts as a direct antagonist of the P2Y12 receptor. Ticagrelor binds non-competitively but, in contrast to, e.g., clopidogrel, reversibly to the P2Y12 receptor making it an interesting and perfect target for drug removal. It is indicated for reducing ischemic events in moderate-to-high-risk patients with acute coronary syndrome (ACS), as demonstrated by the PLATO (Platelet Inhibition and Patient Outcomes) trial [2]. Moreover, in patients with prior myocardial infarction, the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) trial also showed the beneficial effects of dual antiplatelet therapy (DAPT), including ticagrelor [3]. Worldwide, a rapid growth in the number of patients taking these medications is expected [4]. As already mentioned, ticagrelor binds reversibly to the receptor, so transfusion of platelets in the scenario of postoperative bleeding is considered inefficient, as the circulating ticagrelor and its active metabolites are likely to directly inhibit the newly administered platelets again [5]. In addition, dialysis is also not a viable option, as ticagrelor is protein-bound.

In the PLATO trial, 10% of the patients required coronary artery bypass graft (CABG) surgery, and, due to the three-day washout period for ticagrelor, they were at a significantly increased risk for bleeding complications in the perioperative period [2, 6]. Consequently, the 2021 ESC/EACTS (European Society of Cardiology/European Association for Cardio-Thoracic Surgery) Guidelines recommended postponing cardiac surgery for at least three days after ticagrelor discontinuation to allow for a sufficient drug washout [7, 8].

The other important class of potent antithrombotic drugs consists of the new direct oral anticoagulants (DOACs), also known as NOACs (non-vitamin K antagonist oral anticoagulants) in German-speaking countries. The DOAC group includes the thrombin inhibitor dabigatran (direct-activated factor II) and the three activated factor X inhibitors rivaroxaban, apixaban and edoxaban. Of those, apixaban and rivaroxaban are currently the most commonly used DOACs worldwide, especially for stroke prevention in patients with non-valvular atrial fibrillation (AF). Due to their ease of use without the necessity of drug monitoring, DOACs have meanwhile become the preferred choice for patients who need oral anticoagulant therapy [9].

The Idea of Antithrombotic Drug Removal from Whole Blood by Hemoadsorption

Around ten years ago, Dr. George Angheloiu showed that iodinated contrast molecules (e.g., iodixanol or iohexol) could be adsorbed by various sorbent beads, including CytoSorb® (CytoSorbents Corporation, Princeton, New Jersey, USA), by up to 95%. These very small particles consist of hydroxy groups that are connected to nitrogen atoms, resulting in a hydrophobic structure (also known as benzene rings). The chemical structure of ticagrelor also contains hydroxyl and nitrogen radicals attached to a similar central hydrophobic ring. This similar structure enables the molecule to link with the styrene copolymers. The molecular weight of ticagrelor is 522.6 Da (daltons). This low molecular weight, in combination with hydrophobicity, results in easy passage into the pores of the porous polymer bead sorbent. Within the bead, ticagrelor and other low-molecular-weight and hydrophobic substances are adsorbed to the internal surface of the polymer. Adsorption is based on a combination of non-polar interactions, hydrogen bonding, and the so-called Van der Waals forces. In 2017, Angheliou et al. published a groundbreaking in-vitro study showing that ticagrelor could be removed via hemoadsorption, both from bovine and human blood, with CytoSorb® having a remarkable removal capacity of >99% [10].

In contrast to dialysis where water, small molecules, and hydrophilic substances such as urea, ammonia, or electrolytes are removed via a semipermeable film (approximately 1.5 m^2), the CytoSorb® device is based on the concept of adsorption. Adsorption is a process capable of attracting solid substances to a surface. Therefore, adsorption can remove a range of substances that conventional dialysis cannot. Hemoadsorption by CytoSorb® can remove hydrophobic substances up to 60 kDa, depending on concentration.

DOACs also have a high protein binding capacity and are nondialyzable. This high degree of protein binding is also a factor in their successful adsorption.

Device

The CytoSorb® 300 ml adsorber has a CE marking. It is indicated to remove ticagrelor and rivaroxaban intraoperatively during cardiopulmonary bypass (CPB) as an extracorporeal blood purification therapy. The adsorber consists of a cylindrical cartridge and an endcap assembly that is filled with millions of biocompatible porous polymer beads acting like a sponge. Both endcaps have a standard tubing connector that is compatible with all standard CPB tubing lines.

The beads inside the adsorber are made of a divinylbenzene/polyvinylpyrrolidone copolymer. A single bead, the size of a grain of salt (between 300 and 800 µm), has hundreds of thousands of tightly controlled pores and channels that were created via suspension polymerization. The pores and channels of all beads within a single adsorber provide an effective surface area of >40,000 m^2 to bind hydrophobic molecules between 5 and 60 kDa based on molecular size and surface adsorption.

The CytoSorb® device can be easily and quickly incorporated into the heart-lung machine (HLM) between the membrane oxygenator and the venous reservoir of the HLM (fig. 1). The targeted flow rate through the device should be between 100 and 700 ml/min (usually 500–600 ml/min). The hemoadsorption range and polymer beads selectivity are shown in figure 2.

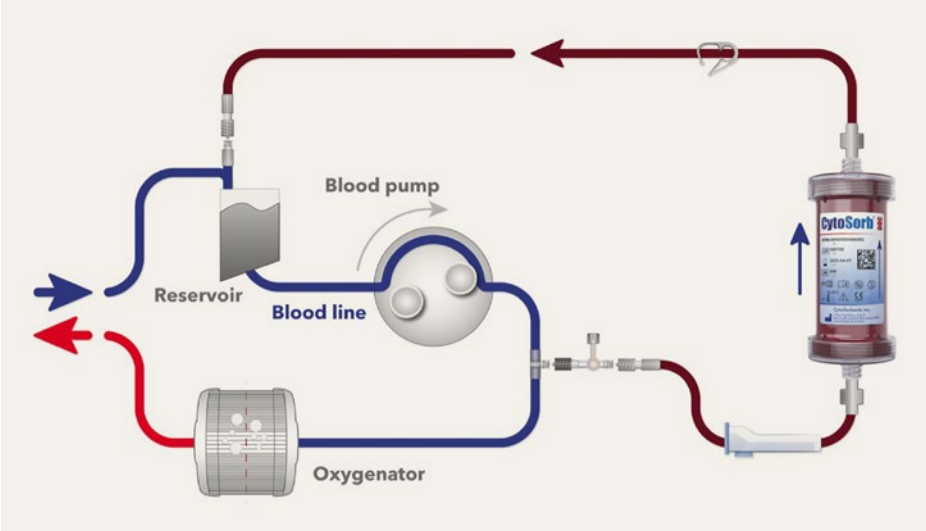

Figure 1: Placement of the CytoSorb® device into the cardiopulmonary bypass circuit.

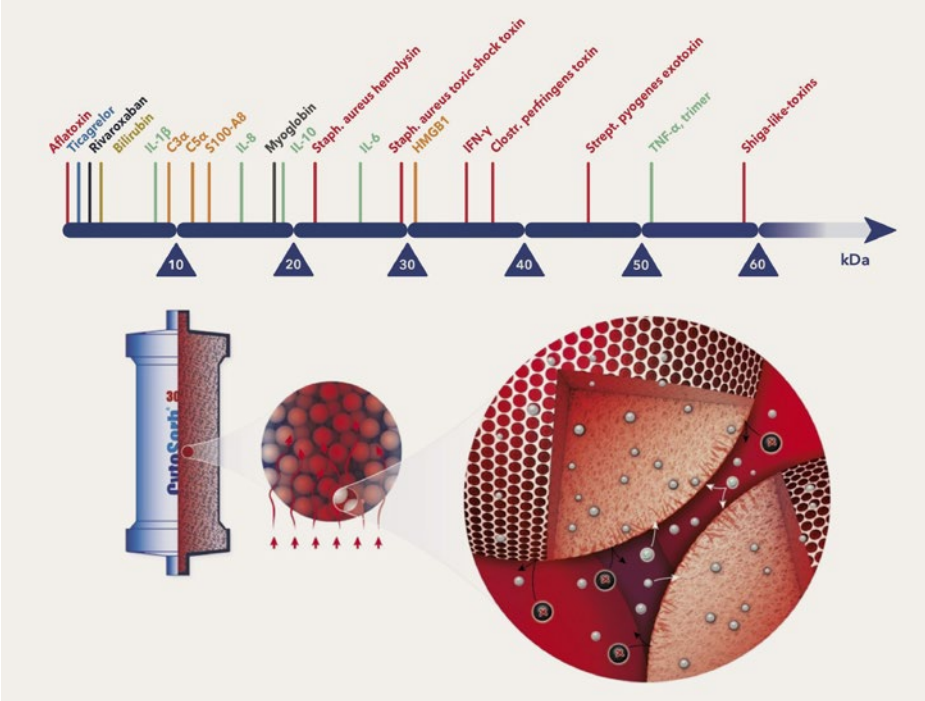

Figure 2: Spectrum of adsorption (upper part) and cartridge filled with highly biocompatible porous polymer beads covered with a divinylbenzene coating (lower part). Each polymer bead is between 300 and 800 µm in size with multiple pores and channels, giving it a large (over 40,000 m^2) effective surface area for binding hydrophobic small- and middle-sized molecules.
C: Complement component; Clostr: Clostridium; HMGB1: High mobility group box 1; IFN-γ: Interferon gamma; IL: Interleukin; Staph: Staphylococcus; TNF-α: Tumor necrosis factor alpha.

Experimental Benchtop Data

In 2022, Tripathi et al. published an in-vitro study evaluating the removal of the antithrombotic drugs apixaban, rivaroxaban, and ticagrelor by the DrugSorb™-ATR (CytoSorbents Corporation, Princeton, New Jersey, USA) hemoadsorption device based on the CytoSorb® technology. The authors used a clinical-scale benchtop recirculation model that was filled with bovine whole blood. Clinically relevant concentrations of all antithrombotic agents were added to the blood and circulated through a 300 ml DrugSorb™-ATR hemoadsorption device at a regulated flow rate of 300 ml/min. The whole setup was designed to mimic clinical routine during CPB [11]. Figure 3 shows the major findings of the in-vitro benchtop drug removal.

To evaluate the drug removal rate, all drug concentrations were measured throughout the entire 360-minute-long experiment. The results were compared to a control setup without an incorporated adsorber. The drug removal rates at 30, 60, 120, and 360 minutes were 81.5%, 96.3%, 99.3%, and >99.8% for apixaban; 80.7%, 95.1%, 98.9%, and >99.5% for rivaroxaban; and 62.5%, 75%, 86.6%, and >95% for ticagrelor (all p <0.0001 compared to the control). In addition to the significant drug removal, the pH of the evaluated blood and other hematological parameters were not significantly influenced by DrugSorb™-ATR when compared to the control setup [11].

Another in-vitro analysis published by Røed-Undlien et al. examined the removal of apixaban from blood by hemoadsorption. Human blood was spiked with apixaban and then circulated in an in-vitro mock circulatory loop with the CytoSorb® adsorber connected. At a constant flow rate of 300 ml/min., a total of 3.1 liters of blood were pumped through the system. Samples were drawn directly before adding apixaban to the circuit and then after 0, 5, 15, 30, 60, and 120 minutes of adsorption. A total of six experiments with the CytoSorb® adsorber column in place as well as four controls without the adsorption were performed. Apixaban levels were measured by an anti-factor Xa activity calibrated for apixaban and, in addition, by ultra-high-performance liquid chromatography mass spectrometry (UPLC-MS), the gold standard for DOAC quantification. The mean apixaban concentration after 30 minutes of adsorption showed a significant reduction from 414.3 to 33 ng/ml (anti-Xa activity method) or 839 to 73 ng/ml using UPLC-MS. After two hours of adsorption, the mean apixaban concentration was less than 2% of the initially added concentration (by both measurement techniques). Finally, thrombin generation was proven to show a maximum effect of adsorption after 60 minutes. Interestingly, the clotting time (measured by thromboelastometry) was close to normal levels after 120 minutes. In the control experiment without the CytoSorb® adsorber, apixaban levels remained unchanged throughout the whole experiment [12].

Clinical Data

Two studies by Hassan et al. reported significant improvements in various clinically important outcomes by hemoadsorption using the CytoSorb® device during CPB in patients treated with ticagrelor or rivaroxaban and requiring urgent or emergency cardiac surgery, including acute type A aortic dissections as well [13, 14]. The initial study examined the outcomes of intraoperative hemoadsorption in emergency (predominantly) isolated CABG surgery in patients treated with either ticagrelor or rivaroxaban. These patients were compared to a non-randomized control group. The authors showed a significantly shorter overall

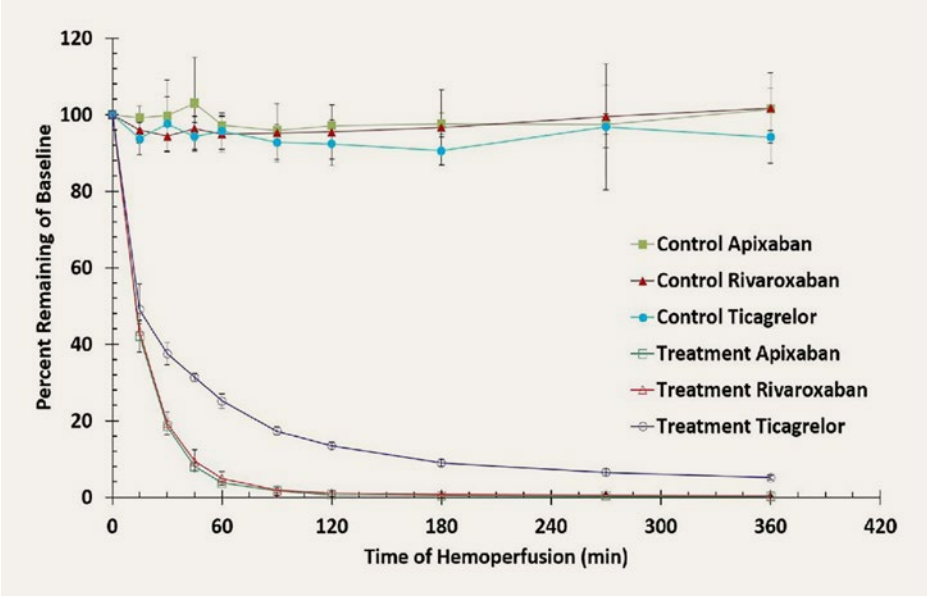

Figure 3: Percent removal of ticagrelor, rivaroxaban, and apixaban. Results represent mean ± standard deviation, n = 5, [11].

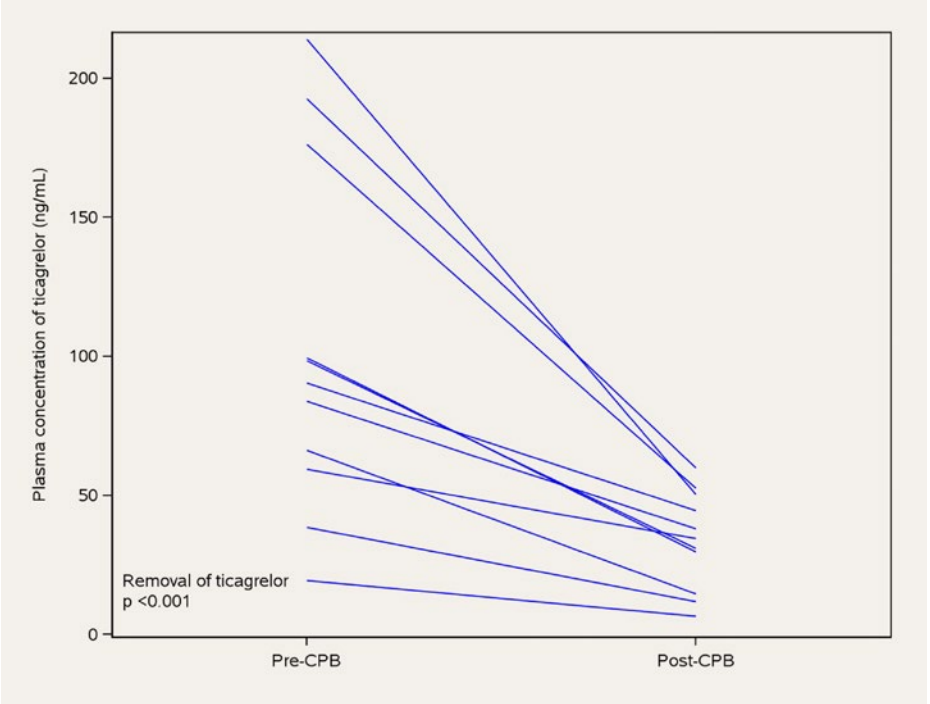

Figure 4: Plasma concentration of ticagrelor (ng/ml) before and after cardiopulmonary bypass (CPB) for each individual patient.

operation time (skin-to-skin) in the CytoSorb® group despite the fact that the CPB durations were similar in both groups, as well as lower chest tube drainage (CTD), less red blood cell use, and fewer platelet transfusions. A significantly higher rate of postoperative revisions as well as a significantly longer intensive care unit and hospital stay were observed in the control group without intraoperative hemoadsorption. Moreover, Hassan et al. showed better intraoperative bleeding control when the CytoSorb® adsorber was added to the HLM [13]. The authors concluded that the intraoperative use of hemoadsorption with CytoSorb® could significantly reduce postoperative bleeding and recommended the routine use of this adjunctive technique in urgent or emergent patients undergoing cardiac surgery while being treated with ticagrelor or rivaroxaban. In their most recently published second analysis, the same group of authors evaluated the clinical and bleeding outcomes of patients presenting with acute type A aortic dissections on recent antithrombotic therapy. Even in this high-risk group of patients, the authors were able to validate their previous beneficial results for the use of intraoperative hemoadsorption. In their analysis, the overall skin-to-skin time was again significantly reduced in the treatment group, and, most importantly, they reported zero rethoracotomies in the treatment group compared to two rethoracotomies (18.9%) among patients without the use of the adsorber. Moreover, more platelet transfusions were needed in patients without intraoperative hemoadsorption. Therefore, the authors concluded that the use of intraoperative hemoadsorption in patients presenting with an acute aortic dissection pretreated with antithrombotic drugs is beneficial and could improve outcomes [14].

Another trial investigated the off-label use of intraoperative removal of apixaban with hemoadsorption. In this three-site case-controlled study, twelve consecutive patients undergoing cardiac surgery with the CytoSorb® adsorber integrated into the HLM while on concomitant therapy with apixaban, prescribed mostly for AF, were compared to the next 13 consecutive similar patients who were operated on without the use of CytoSorb®. Preoperative mean daily dose of apixaban was significantly higher in the hemoadsorption group (8.5±2.4 vs 5.6±2.2 mg, p = 0.005), while time since last the apixaban dose was longer in the control group (1.3±0.9 vs 0.6±1.2 days, p <0.001). The authors reported that there were no BARC-4 (Bleeding Academic Research Consortium) bleeding events and no rethoracotomies in the treatment group compared with three and one, respectively, in the control

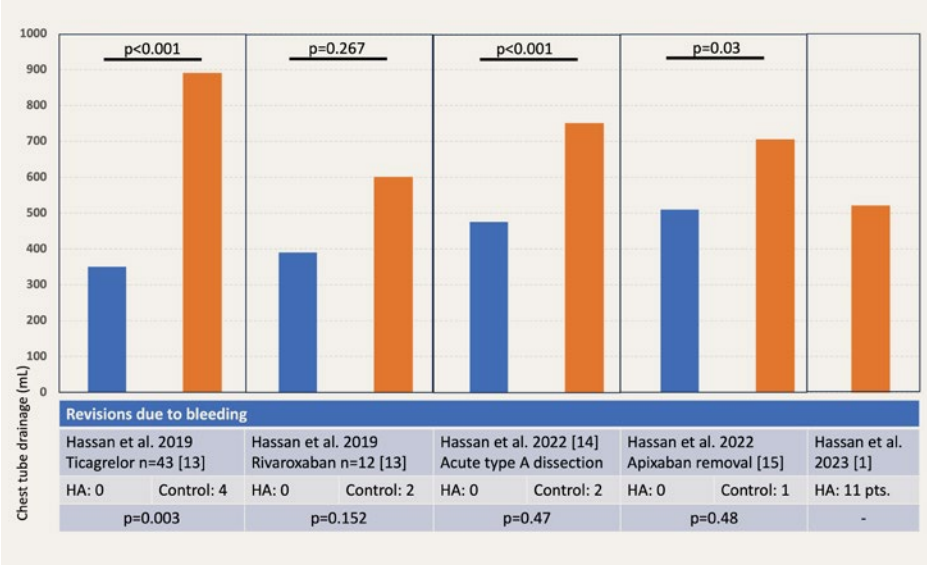

Figure 5: Chest tube drainage and surgical reexploration rates.
HA: Health Authority.

Healthcare System			
Overall Cost Saving vs Standard of Care	$3,434	£3,941	€4,200 ± 1,100
Reference	Cohen BG et al., Am J Cardiovasc Drugs 2023; epub	Javanbakht M et al., PharmacoEconomics Open 2020; 4:307-319	Hassan et al., presented at ESC Congress, August 2022

Figure 6: Potential cost savings by intraoperative hemoadsorption as published in three different countries.

group. Postoperative 24-hour CTD volume was significantly lower in the CytoSorb® group (510±152 vs 893±579 ml, p = 0.03). This was the first study to show that intraoperative hemoadsorption can improve outcomes in patients on apixaban undergoing urgent or emergency on-pump cardiac surgery by mitigating the risk of perioperative bleeding complications [15].

Until recently, the beneficial effects of antithrombotic removal by intraoperative hemoadsorption had been only shown in clinical data and in-vitro analyses. However, newly published data has also confirmed the in-vivo removal of ticagrelor [1]. This multicenter international evaluation included eleven prospective patients on ticagrelor undergoing urgent CABG surgery. The CytoSorb® adsorber was incorporated into the HLM and remained active for the whole pump-run. Before starting and at the end of the CPB period, blood samples were drawn to measure the mean ticagrelor levels. The time interval (preoperative washout period) between the last ticagrelor intake and surgery was 48 hours, and the mean intraoperative hemoadsorption duration was 97 minutes. The mean flow rate through the device was 422 ml/min. The mean ticagrelor levels before CPB were 103 ± 63.8 ng/ml compared to 34.0±17.5 ng/ml after CPB, resulting in a significant reduction of 67.1% (p <0.001) as illustrated in figure 4. No reoperations for bleeding were performed, and no BARC-4 bleeding events occurred. The median CTD over the first postoperative day was 520 ml (375–930 ml). The integration of CytoSorb® into the extracorporeal circuit was described by the authors as simple and safe, without any device-related adverse events reported [1]. Figure 5 summarizes the major clinical findings (surgical revision and CTD) for the above-mentioned literature.

Moreover, two recent holistic reviews by Jackson et al. and Matejic-Spasic et al. specifically evaluated hemoadsorption for the removal of ticagrelor and DOACs in the setting of cardiac surgery, also giving an overview on antithrombotics [16, 17]. Both publications comprehensively assessed all aspects of CytoSorb® therapy, and they also elaborated on its ability to remove excessive levels of cytokines to attenuate the cytokine storm.

Until recently, the clinical application of antithrombotic removal by hemoadsorption in cardiac surgery has been almost exclusively performed in on-pump cases with integration

into the CPB circuit. However, recently, Mair et al. published a first reference case on the use of CytoSorb® with the direct hemoperfusion pump PUR-01 (Nikkiso Co., Ltd., Tokyo, Japan) during urgent off-pump coronary artery bypass (OPCAB) surgery. Mair et al. presented a 74-year-old patient on DAPT with both ticagrelor and aspirin® [18]. The stand-alone hemoperfusion device pumped for 221 minutes to eliminate ticagrelor from whole blood. Over the duration of the pump-run, a total blood volume of 39.04 liters circulated through the CytoSorb® adsorber. The postoperative course was uneventful, and the patient showed a quick recovery. At six-week follow-up, the patient presented without any cardiac-related symptoms. Since this initial case, the group has used the same setup and concept on three other DAPT patients requiring urgent or emergent OPCAB surgery. For the whole cohort, the surgical procedures were not complicated by any noteworthy perioperative bleeding, no patient required a reintervention, and the postoperative courses were uneventful. However, it should be noted that using the CytoSorb® adsorber for ticagrelor removal outside CPB is not covered in the current instructions for use (IFU).

Health Economy Data

Since all clinical studies to date have shown significant reductions in the need for revisions due to bleeding, transfusions, and duration of hospital stay, two publications have reported on the cost-effectiveness of intraoperative hemoadsorption. Moreover, a study from Hamburg, Germany, compared the economic effects of intraoperative hemoadsorption in ACS patients (n = 72) with former patients (n = 22) without intraoperative hemoadsorption by bootstrap analysis [26]. They resulted in cost savings of 4.200 ± 1.100 euros. A cost-utility analysis from the United Kingdom (UK) by Javanbakht et al. evaluated CytoSorb® for the intraoperative removal of ticagrelor compared to standard care in patients undergoing emergent or urgent cardiac surgery [19]. The authors showed that intraoperative removal of ticagrelor by CytoSorb® could save about 4,000 pounds over a 30-day time period due to less consumption of blood products, lower rethoracotomy rates, and a shorter length of stay in the emergency surgical setting. The National Institute of Health Care Excellence in the UK published advice on the use of intraoperative hemoadsorption in cardiosurgical cases under antithrombotics (https://www.nice.org.uk/advice/mib249). In addition to this, a recently published paper estimated the cost-effectiveness and budget impact of using CytoSorb® intraoperatively compared to standard practice for reducing the risk of perioperative bleeding during and after CABG surgery from the healthcare sector's perspective in the United States of America (USA). The authors interpreted the results both as incremental cost-effectiveness ratios and as net monetary benefits at a distinctive cost-effectiveness threshold of 100,000 United States dollars (USD) per quality-adjusted life year (QALY). The authors showed that the intraoperative use of CytoSorb® was superior for all evaluated cohorts. Patients with less than 24 hours of preoperative washout in the device arm gained a total of 0.017 QALYs combined with savings of 1748 USD, for a net monetary benefit of 3434 USD. Based on their probabilistic sensitivity analyses, the intraoperative use of CytoSorb® had a 91% likelihood of being superior for patients with less than 24 hours of washout and a 99% likelihood of being cost-effective at a 100,000 USD/QALY threshold. Cohen et al. concluded that intraoperative hemoadsorption is a superior strategy compared with standard therapy for CABG patients on ticagrelor with less than two days of washout time. Hence, this novel and innovative device could easily be used for cardio-surgical patients on ticagrelor treatment to provide better clinical outcomes with lower overall healthcare costs [20]. Figure 6 exemplifies the cost savings published so far from three different international analyses [19, 20, 26].

Guidelines

The latest update on the management of severe perioperative bleeding, the Guidelines from the European Society of Anesthesiology and Intensive Care, provided an evidence-based set of recommendations to help ensure clinical management of patients with perioperative bleeding. A group of experts has met and revised the existing guidelines to incorporate new evidence. In the specific section on antithrombotics, the following recommendation was made for patients undergoing cardiac surgery: "In patients on ticagrelor or rivaroxaban undergoing emergency cardiac/aortic surgery on CPB, haemoadsorption may be considered as an adjuvant therapy to reduce bleeding complications. 2C" [21]. It has to be acknowledged that this recommendation is currently rated as 2C, meaning weak recommendation/low-quality of evidence.

Discussion

To summarize, perioperative bleeding complications related to antithrombotic medications in cardiosurgical settings are currently a serious and recent problem, owing to the increasing popularity of these agents. There seems to be an unmet need for safe and effective solutions, such as drug removal by extracorporeal hemoadsorption techniques.

To date, the most investigated method for mitigating the risk of major bleeding and/or bleeding complications during or after cardiac surgery has been to allow enough time for natural drug washout or metabolism prior to the surgical procedure. The relevance of a medication-tailored delay after discontinuation of the antiplatelet therapy and relevant perioperative clinical outcomes was evaluated for the first time in the post-hoc analysis of the PLATO trial, which evaluated the efficacy and safety of ticagrelor and clopidogrel in patients with ACS undergoing CABG, and has since been confirmed in subsequent literature [2, 17, 22].

The EACTS, in collaboration with the European Association of Cardiothoracic Anesthesiology (EACTA), released the 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery [23], which recommended a delay in surgery for at least 72 hours after cessation of ticagrelor therapy and at least 48 hours after DOAC discontinuation in patients undergoing non-emergent cardiac surgery. For DOACs especially, it was stated that an even longer interval of drug washout may be necessary, especially for patients with impaired kidney function. The same recommendations were given by the ESC [4] and the European Heart Rhythm Association [9]. Similarly, a three- or two-day interruption strategy for DAPT or DOAC therapy, respectively, has been endorsed by the societies based in the USA [7, 24].

Patients presenting with urgent or emergent nondeferrable surgery cannot wait for natural metabolism or washout of antithrombotics. Hemoadsorption therapy with CytoSorb®, which bears CE marking, has been shown to reduce the levels of rivaroxaban, apixaban, and ticagrelor, with off-label use possible for apixaban, edoxaban, and dabigatran. For antithrombotic removal, the cartridge is incorporated into the CPB circuit but can be easily integrated and connected into other extracorporeal circuits, such as continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) to remove e.g., cytokines. Removal of antithrombotics by intraoperative hemoadsorption has a durable effect (as shown by both in-vitro and in-vivo data) and comes with proven safety, as no adverse device-related events have been reported so far. The therapy has the potential to be used in clinical settings other than HLM-assisted cardiac surgery antithrombotic removal, such as trauma, neuro-,

or orthopedic surgery using various platforms (CRRT, ECMO, etc., currently off-label).

A newly published state-of-the-art review in the European Heart Journal summarized the current practice in the "reversal and removal of oral antithrombotic drugs in patients with active or perceived imminent bleeding" [25]. The authors elaborated on the common practices for nonspecific reversal, which has been done for decades, such as administering fibrinogen, fresh frozen plasma or prothrombin complex concentrates. The second consideration for treatment is reflected by specific reversal of antithrombotic drugs by new factor Xa inhibitors (andexanet alfa) among others. Another and new treatment option that has been mentioned for the first time is the adsorption of antithrombotic drugs from the blood by an adsorber [25]. Indeed, this new, easy and cost-effective way of drug removal should be evaluated in large, randomized control trials in the future.

Three major trials are currently evaluating the effect of intraoperative antithrombotic removal. The "family name" of these investigations is Safe and Timely Antithrombotic Removal of ticagrelor (T) or rivaroxaban and apixaban (D, standing for DOACs), hence the names STAR-T (ClinicalTrials.gov, NCT04976530), and STAR-D (ClinicalTrials.gov, NCT05093504). The STAR-T trial finalized enrollment in July 2023. A "close cousin" under the same acronym is the STAR registry (ClinicalTrials.gov, NCT05077124) which summerizes real-world clinical data and associated clinical outcomes with the use of CytoSorb® for the removal of antithrombotic agents.

Future Considerations

Hemoadsorption is safe and represents an easy-to-use single solution for multiple antithrombotic drugs and has already shown significant clinical benefits. It is expected that in the near future, new indications and further evidence might justify antithrombotic drug removal outside of cardiac surgery, e.g., in trauma or neurosurgery.

Limitations

Nevertheless, it has to be mentioned that unintentional removal of other drugs may occur in patients being treated for antithrombotic drug removal and that clinical management in those situations is up to the discretion of the treating physician and according to recommendations included in the device's IFU.

Conclusion

It has been shown that the incidence and prevalence of major bleeding in cardio-surgical patients on DAPT or DOACs is high since the overall cohort of surgical patients on antithrombotics has rapidly increased in recent years. Therefore, there is an unmet clinical need for potential solutions for patients on antithrombotics requiring urgent surgery. As a result, reversal agents for DOACs or for ticagrelor have recently been launched, but the usefulness of such agents in the non-elective cardio-surgical setting remains limited due to their high costs and/or potential incompatibility with heparin-based anticoagulation. In contrast to pharmacological reversal agents, it has been shown that intraoperative hemoadsorption can be a universal and cost-effective method to mitigate perioperative bleeding complications. Contemporaneous evidence implies that intraoperative drug removal via hemoadsorption might be the new method of choice for the management of perioperative bleeding complications in cardio-surgical patients who are on concurrent antithrombotic treatment.

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Conflict of Interest Statement

DW received speaker honoraria until the end of 2021 from CytoSorbents GmbH, Berlin, Germany and is a full-time employee of CytoSorbents.
EN is a shareholder and a full-time employee of CytoSorbents.
SG received honoraria for presentations on medical congresses and support for traveling from CytoSorbents GmbH, Berlin, Germany.

Author Contributions

DW, END & SG: Substantial contributions to the conception or design of the work and drafting the work or reviewing it critically for important intellectual content and final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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